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Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes*

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Aim: To assess the addition of sitagliptin to ongoing metformin therapy in patients with type 2 diabetes who were inadequately controlled [haemoglobin A_{1c} (HbA_{1c}) 7–11%] on metformin monotherapy.
Methods: Patients (n = 273) on metformin (≥1500 mg/day) were randomized to receive the addition of once-daily placebo, sitagliptin 100 mg or rosiglitazone 8 mg in a 1 : 1 : 1 ratio for 18 weeks. The efficacy analysis was based on the all-patients-treated population using an analysis of co-variance with change in HbA_{1c} from baseline as the primary endpoint.
Results: The mean baseline HbA_{1c} was 7.7% for the entire cohort. After 18 weeks, both active add-on therapies led to greater improvements in HbA_{1c} from baseline: −0.73% for sitagliptin ($p < 0.001$ vs. placebo) and −0.79% for rosiglitazone compared with −0.22% for placebo. No difference was observed between the sitagliptin and rosiglitazone treatments (0.06% [95% confidence interval (CI): −0.14 to 0.25]). The proportion of patients achieving an $HbA_{1c} < 7\%$ was greater with sitagliptin (55%) and rosiglitazone (63%) compared with placebo (38%). Body weight increased from baseline with rosiglitazone (1.5 kg) compared with body weight reduction with sitagliptin (−0.4 kg) and placebo (−0.8 kg). The difference in body weight between the sitagliptin and rosiglitazone groups was 1.9 kg (95% CI: 1.3–2.5). In a prespecified analysis, the proportion of patients experiencing a greater than 3-kg increase in body weight was 21% in the rosiglitazone group compared with 2% in both the sitagliptin and placebo groups. Both active treatments were generally well tolerated, with no increased risk of hypoglycaemia or gastrointestinal adverse events compared with placebo.
Conclusions: In this 18-week study, the addition of sitagliptin was effective and well tolerated in patients with type 2 diabetes inadequately controlled with metformin monotherapy. Treatment with sitagliptin produced similar reductions in HbA_{1c} compared with the addition of rosiglitazone.

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Introduction

In patients with type 2 diabetes, optimal glycaemic control is often not achieved and/or maintained with a single antihyperglycaemic agent [1–3]. Because of the progressive decline in beta-cell function, many patients with type 2 diabetes require additional antihyperglycaemic agents to manage continued or progressively worsening hyperglycaemia [4]. Metformin is the most commonly used oral antihyperglycaemic agent, both as monotherapy and in combination with other agents [5,6]. Metformin acts primarily by reducing hepatic

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glucose output [5–7]. Combining metformin with oral antihyperglycaemic agents that act through distinct and complementary mechanisms may target more of the pathophysiological defects of type 2 diabetes and potentially lead to greater therapeutic effects.

Dipeptidyl peptidase-4 (DPP-4) inhibitors target the incretin axis and represent a novel therapeutic approach for the treatment of type 2 diabetes [8]. DPP-4 inhibitors prevent the enzymatic degradation and inactivation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), the major incretins involved in glucose homeostasis [9]. Sitagliptin, an oral, once-daily and highly selective DPP-4 inhibitor, lowers glucose concentrations through increases in intact (active) GLP-1 and GIP concentrations, which, in a glucose-dependent manner, enhance insulin release and reduce glucagon secretion in patients with type 2 diabetes [10]. In clinical trials, the addition of sitagliptin to ongoing metformin therapy or the initiation of the two agents simultaneously produced clinically meaningful improvements in glycaemic control and markers of beta-cell function in patients with type 2 diabetes [11–14]. Furthermore, the addition of sitagliptin to metformin did not attenuate the weight loss usually observed with metformin, was not associated with an increased risk of hypoglycaemia or gastrointestinal adverse experiences and led to small but positive effects on the lipid profile [13].

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor-γ agonists, lower glucose concentrations by increasing peripheral insulin sensitivity [15]. Rosiglitazone, a TZD, is used as monotherapy, but is also commonly used in combination with metformin [6,16]. When added to metformin, rosiglitazone improved glycaemic control and measures of insulin sensitivity and beta-cell function [17]. However, the addition of rosiglitazone was associated with body weight gain, an increased incidence of oedema and increased low-density lipoprotein cholesterol (LDL-C) levels in this study [17].

Because both sitagliptin and rosiglitazone target mechanisms that are complementary to metformin, the present 18-week study assessed the efficacy and tolerability of the addition of sitagliptin or rosiglitazone compared with the addition of placebo to ongoing metformin therapy in patients with type 2 diabetes and inadequate glycaemic control.

Patients and Methods

Patients

Men and women with type 2 diabetes (18–75 years of age) who were taking metformin monotherapy at a stable dose of ≥1500 mg/day for at least 10 weeks prior to the screening visit and had inadequate glycaemic control [defined by a haemoglobin A_{1c} (HbA_{1c}) level ≥7 and ≤11%] were recruited for the study. Patients were excluded if they had type 1 diabetes, insulin use within 8 weeks of the screening visit, any contraindications for use of TZDs or metformin, impaired renal function (creatinine clearance <60 ml/min), alanine aminotransferase (ALT) or aspartate aminotransferase levels more than twofold the upper limit of normal or a fasting glucose value >270 mg/dl prior to randomization. Throughout the study, patients received counselling on exercise and a weight maintenance diet consistent with American Diabetes Association recommendations.

Patients provided written informed consent. The protocol was reviewed and approved by the appropriate committees and authorities and performed in accordance with the Declaration of Helsinki.

Study Design

This was a multinational, double-blind, randomized, parallel-group study. Patients who met all entry criteria at the screening visit entered a 2-week single-blind, placebo run-in period. Patients with adequate compliance during this run-in period had baseline measurements and were randomized in a 1 : 1 : 1 ratio to one of the following once-daily treatment groups: placebo, sitagliptin 100 mg or rosiglitazone 8 mg for 18 weeks.

Study Endpoints

Efficacy Assessments

HbA_{1c}, fasting plasma glucose (FPG), fasting serum insulin, fasting serum proinsulin and fasting plasma lipids were measured at baseline and during the study. Proinsulin/insulin ratio and homeostasis model assessment of beta-cell function (HOMA-β) were calculated to assess beta-cell function [18,19]. HOMA of insulin resistance (HOMA-IR) was calculated to assess insulin resistance [18].

A standard meal tolerance test (MTT) was administered at baseline (prior to the first dose of study medication) and at week 18. Patients were required to finish the meal [one nutrition bar and one nutrition drink (total content ≈460 kcal; 75 g carbohydrate, 9 g fat and 18 g protein)] within 15 min. The morning dose of metformin was taken just prior to the start of the MTT at baseline and at week 18. At baseline, on-treatment study drug was taken after the completion of the MTT (i.e. 2 h after the start of the meal), while at week 18, it was taken 30 min prior to the start of

the MTT. Blood was collected at 0 and 2 h from the meal start for determination of 2-h postprandial plasma glucose (PPG), insulin and C-peptide levels as well as glycaemic excursion from the 0-h time point to the 2-h time point of the MTT (i.e. incremental 2-h PPG).

Safety Assessments

Data on adverse experiences, physical examinations, vital signs and body weight were collected. All adverse experiences were rated by investigators for intensity and relationship to study drug. Laboratory evaluations included blood chemistry, haematology and urinalysis.

Laboratory measurements were performed at a central laboratory (PPD Global Central Labs, LLC, Zaventem, Belgium) that was blinded to the patients' treatment assignments. 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). Plasma triglyceride (TG) was measured by enzymatic determination of glycerol (Roche Diagnostics). Plasma total cholesterol (TC) was quantified enzymatically (Roche Diagnostics). After selective removal of apolipoprotein B-containing lipoproteins by heparin and manganese chloride precipitation for high-density lipoprotein (HDL) isolation, plasma HDL cholesterol (HDL-C) was quantified enzymatically (Roche Diagnostics). LDL-C was calculated using the Friedewald equation [20]. For data presented in conventional units, the following SI conversion factors may be used: to convert glucose values to mmol/l, multiply by 0.0551; to convert insulin values to pmol/l, multiply by 6; to convert C-peptide values to nmol/l, multiply by 0.331; to convert cholesterol to mmol/l, multiply by 0.02586 and to convert TGs to mmol/l, multiply by 0.01129.

Statistical Analysis

Efficacy analyses were based on the all-patients-treated population consisting of all randomized patients who received at least one dose of study drug and who had both a baseline and at least one postbaseline measurement. An analysis of co-variance (ANCOVA) model compared treatment groups for continuous efficacy parameters, focusing on change from baseline at week 18, with baseline values as a co-variate. Missing data were handled using the last observation carried forward method. From the ANCOVA model, least squares (LS) mean change (or per cent change) from baseline at week 18 along with 95% confidence intervals (CI) were calculated for each efficacy endpoint across groups. The study was designed to determine superiority of sitagliptin vs. placebo. To assess between-group differences, inferential testing with p values was prespecified to compare changes in the sitagliptin and placebo groups. The rosiglitazone arm was included for estimation purposes only. Differences in LS mean change (or per cent change) and 95% CI were calculated to estimate the between-group differences for the comparison between rosiglitazone and placebo groups or between rosiglitazone and sitagliptin groups. A p value of ≤ 0.05 was considered statistically significant.

The proportion of patients achieving $HbA_{1c} < 7\%$ was compared among groups using a logistic regression analysis. Prespecified subgroup analyses for the primary efficacy endpoint (HbA_{1c}) were performed to explore whether treatment effects were consistent within subgroups, which included gender, age ($<$ or $\geq$65 years), race, baseline body mass index (BMI), baseline HbA_{1c} and known duration of type 2 diabetes.

Safety and tolerability analyses were based on the all-patients-as-treated population, that is, patients who received at least one dose of study medication. Clinical adverse experiences of special interest included hypoglycaemia, oedema and gastrointestinal-related adverse experiences (specifically, abdominal pain, nausea, vomiting and diarrhoea). Changes in body weight were analysed using the ANCOVA model described above. Additionally, the proportion of patients experiencing at least a 3-kg increase in body weight was prespecified for analysis.

Results

Demographics and Baseline Characteristics

Of the 486 patients who were screened, 273 were randomized to study treatments (figure 1). The baseline demographic, anthropometric and disease characteristics of the randomized patients were similar across the treatment groups (table 1). For the entire study population, the average known duration of diabetes was 4.9 years (range: 0.2–19.0 years), average baseline HbA_{1c} was 7.7% (range: 5.4–11.1%; 71% of patients had a baseline $HbA_{1c} < 8\%$) and the average baseline FPG was 158 mg/dl. Of these patients, 59% had a secondary diagnosis of hypertension and 42% had hypercholesterolaemia/dyslipidaemia. The proportion of patients discontinuing the 18-week study was low in all

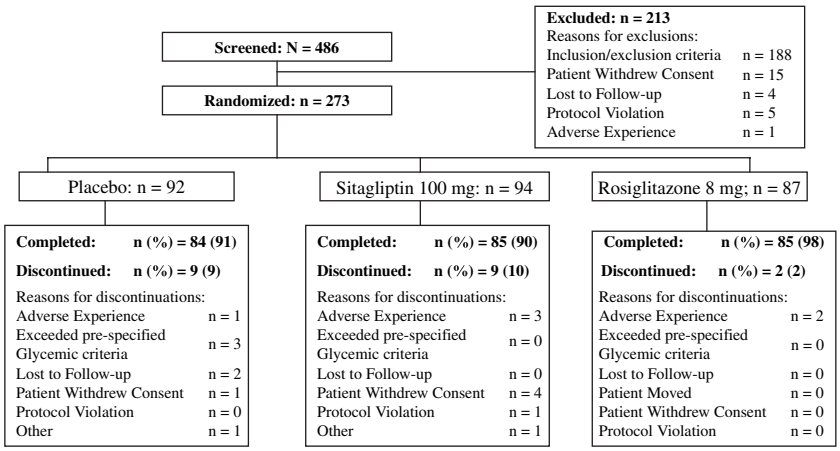

Fig. 1 Overall disposition of screened and randomized patients.

groups, but slightly higher in the sitagliptin and placebo groups compared with the rosiglitazone group (figure 1). Mean compliance (±s.d.) as assessed by tablet counts averaged across groups was 99.7% (±4.4).

Efficacy

At week 18, the addition of once-daily sitagliptin produced a significant ($p \leq 0.001$) reduction from baseline in HbA_{1c} compared with the addition of placebo (table 2); the placebo-subtracted LS mean (95% CI) change from baseline in HbA_{1c} was −0.51% (−0.70 to −0.32). In comparison, the placebo-subtracted change from baseline in HbA_{1c} was −0.57% (−0.76 to −0.37) in the rosiglitazone group. The difference in HbA_{1c} change from baseline was small and not clinically meaningful between the rosiglitazone and sitagliptin groups (table 2). HbA_{1c} decreased in the sitagliptin group relative to placebo during the first 12 weeks of treatment and then remained generally stable through 18 weeks, whereas the change in the rosiglitazone group fell progressively over the 18-week treatment period (figure 2A).

The proportion of patients achieving an $HbA_{1c} < 7\%$ was significantly ($p = 0.006$) greater in the sitagliptin

Table 1 Baseline demographics and disease characteristics

Parameter	Placebo (n = 92)	Sitagliptin 100 mg q.d. (n = 94)	Rosiglitazone 8 mg q.d. (n = 87)
Age (years)	55.3 ± 9.3	55.2 ± 9.8	54.8 ± 10.5
Sex, n (%)			
Male	54 (59)	52 (55)	55 (63)
Female	38 (41)	42 (45)	32 (37)
Race, n (%)			
Caucasian	56 (61)	57 (61)	51 (59)
Asian	36 (39)	36 (38)	33 (38)
Others	0 (0)	1 (1)	3 (3)
Body weight (kg)	84.6 ± 16.5	83.1 ± 17.1	84.9 ± 18.5
Body mass index (kg/m^2)	30.0 ± 4.5	30.3 ± 4.7	30.4 ± 5.5
Known duration of type 2 diabetes (years)	5.4 ± 3.7	4.9 ± 3.5	4.6 ± 4.0
HbA_{1c}, % (range)	7.7 ± 0.9 (5.4–10.3)	7.8 ± 1.0 (6.1–11.1)	7.7 ± 0.8 (6.3–11.1)
HbA_{1c} distribution at baseline, n (%)			
<8%	65 (71)	70 (74)	59 (68)
8 to <9%	17 (18)	13 (14)	21 (24)
≥9%	10 (11)	11 (12)	7 (8)
FPG (mg/dl)	160.0 ± 37.4	157.5 ± 31.4	156.9 ± 31.6

FPG, fasting plasma glucose; HbA_{1c}, haemoglobin A_{1c}.
Data are expressed as mean ± s.d. or frequency n (%).

Table 2 Fasting glycaemic efficacy endpoints

Parameter	Placebo	Sitagliptin 100 mg q.d.	Rosiglitazone 8 mg q.d.
HbA_{1c} (%), n	88	91	87
Baseline	7.68 ± 0.88	7.75 ± 0.99	7.73 ± 0.81
Week 18	7.47 ± 1.05	7.01 ± 0.86	6.94 ± 0.75
Change from baseline	−0.22 (−0.36 to −0.08)	−0.73 (−0.87 to −0.60)	−0.79 (−0.92 to −0.65)
Difference from placebo	—	−0.51 (−0.70 to −0.32)*	−0.57 (−0.76 to −0.37)
Difference from sitagliptin	—	—	−0.06 (−0.25 to 0.14)
FPG (mg/dl), n	89	92	87
Baseline	160.0 ± 38.0	157.2 ± 30.7	156.9 ± 31.6
Week 18	165.4 ± 50.2	145.8 ± 35.3	132.8 ± 29.9
Change from baseline	6.1 (−0.8 to 13.1)	−11.7 (−18.6 to −4.9)	−24.5 (−31.6 to −17.5)
Difference from placebo	—	−17.8 (−27.6 to −8.1)*	−30.6 (−40.6 to −20.7)
Difference from sitagliptin	—	—	−12.8 (−22.6 to −3.0)
Fasting insulin (μIU/ml), n	76	79	73
Baseline	13.8 ± 9.2	14.7 ± 9.9	15.1 ± 9.6
Week 18	13.8 ± 8.3	14.5 ± 8.6	11.2 ± 8.8
Change from baseline	−0.3 (−1.7 to 1.2)	−0.2 (−1.6 to 1.2)	−3.7 (−5.2 to −2.2)
Difference from placebo	—	0.0 (−2.0 to −2.1)	−3.4 (−5.5 to −1.4)
Difference from sitagliptin	—	—	−3.5 (−5.5 to −1.4)
Fasting proinsulin (pmol/l), n	76	78	74
Baseline	24.2 ± 16.1	29.9 ± 24.8	27.6 ± 23.8
Week 18	24.0 ± 19.1	23.9 ± 20.1	16.3 ± 10.3
Change from baseline	−1.8 (−4.9 to 1.3)	−4.6 (−7.7 to −1.5)	−11.1 (−14.3 to −7.9)
Difference from placebo	—	−2.8 (−7.7 to 1.7)	−9.3 (−13.7 to −4.8)
Difference from sitagliptin	—	—	−6.5 (−10.9 to −2.1)
Proinsulin/insulin ratio†, n	75	78	73
Baseline	0.33 ± 0.15	0.35 ± 0.25	0.32 ± 0.17
Week 18	0.30 ± 0.15	0.29 ± 0.17	0.28 ± 0.17
Change from baseline	−0.03 (−0.06 to 0.01)	−0.05 (−0.08 to −0.02)	−0.04 (−0.08 to −0.01)
Difference from placebo	—	−0.02 (−0.07 to 0.03)	−0.01 (−0.06 to 0.03)
Difference from sitagliptin	—	—	0.01 (−0.04 to 0.05)
HOMA-β, n	76	78	71
Baseline	62.2 ± 53.7	62.8 ± 42.9	62.6 ± 36.8
Week 18	55.4 ± 32.5	72.1 ± 51.5	71.0 ± 74.2
Change from baseline	−6.9 (−16.8 to 3.0)	9.4 (−0.4 to 19.2)	8.4 (−1.9 to 18.7)
Difference from placebo	—	16.3 (2.3 to 30.3)**	15.3 (1.0 to 29.6)
Difference from sitagliptin	—	—	−1.0 (−15.2 to 13.2)
HOMA-IR, n	76	78	71
Baseline	5.4 ± 4.0	5.7 ± 4.3	5.9 ± 4.2
Week 18	5.8 ± 4.4	5.2 ± 3.6	3.7 ± 3.1
Change from baseline	0.3 (−0.4 to 1.0)	−0.5 (−1.1 to 0.2)	−2.1 (−2.8 to −1.4)
Difference from placebo	—	−0.7 (−1.7 to 0.2)	−2.4 (−3.4 to −1.4)
Difference from sitagliptin	—	—	−1.6 (−2.6 to −0.7)

FPG, fasting plasma glucose; HbA_{1c}, haemoglobin A_{1c}; HOMA-β, homeostasis model assessment of beta-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; LS, least squares.

Baseline and week 18 data are expressed as mean ± s.d.; change from baseline = LS mean change from baseline (95% CI); difference from placebo or difference from sitagliptin results = between-group difference in LS mean change from baseline (95% CI).

*$p \leq 0.001$ for sitagliptin vs. placebo; **$p \leq 0.05$ for sitagliptin vs. placebo.

†The insulin concentration was converted to pmol/l for calculation of the proinsulin/insulin ratio.

group (55%) compared with the placebo group (38%). Similar findings to sitagliptin were observed with rosiglitazone (63%) relative to placebo [difference (95% CI) in proportions between the rosiglitazone and sitagliptin groups = 8% (−6 to 22)]. Treatment effects were generally consistent in subgroups defined by demographic (gender, age and race) and anthropometric (BMI) characteristics and by known duration of type 2 diabetes. Patients with a baseline HbA_{1c} above the median (7.5%) tended to have a greater HbA_{1c} response to the active treatments. Patients with a baseline $HbA_{1c} \leq 7.5\%$ had placebo-subtracted HbA_{1c} reductions of −0.46% (95% CI: −0.63 to −0.28) and −0.41% (−0.58 to −0.23) in the sitagliptin and rosiglitazone groups, respectively,

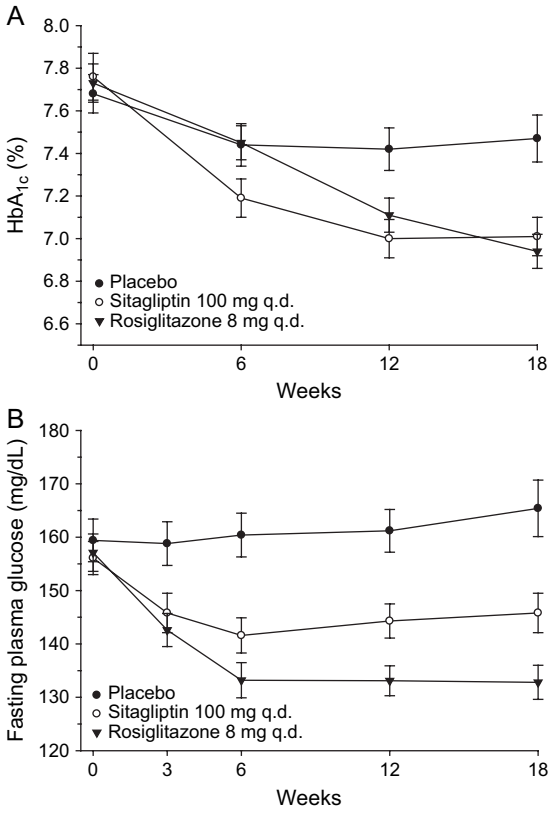

Fig. 2 Haemoglobin A_{1c} (HbA_{1c}) (A) and fasting plasma glucose (B) over time (mean ± s.e.).

compared with reductions of −0.63% (−1.02 to −0.24) and −0.78% (−1.17 to −0.39), respectively, in patients with a baseline $HbA_{1c} > 7.5\%$.

The addition of sitagliptin led to a significant ($p \leq 0.001$) reduction from baseline in FPG compared with placebo; a greater reduction relative to placebo was observed with rosiglitazone than was seen with sitagliptin (table 2). The FPG profile over time showed that the maximal reduction in FPG was achieved by week 6 with sitagliptin, followed by a slight increase that parallelled the slight rise observed in the placebo group (figure 2B). For rosiglitazone, the maximal effect on FPG was observed at week 6 and remained stable through week 18.

Both sitagliptin and rosiglitazone produced similar increases in HOMA-β compared with placebo (table 2). Rosiglitazone provided numerically greater reductions in HOMA-IR relative to placebo or sitagliptin, while the changes with sitagliptin were similar to those observed with placebo (table 2). Rosiglitazone lowered fasting serum insulin and proinsulin relative to placebo or sitagliptin, but the change in the proinsulin/insulin ratio was similar across treatments (table 2).

The addition of sitagliptin led to a significant ($p \leq 0.001$) reduction from baseline in 2-h PPG compared with placebo (table 3). The 2-h PPG change from baseline was greater with rosiglitazone compared with placebo or sitagliptin (table 3). Because the change in FPG from baseline influences the 2-h PPG results, the change from baseline in 2-h incremental PPG (i.e. difference between 0 and 2-h time points of MTT) was assessed. Both sitagliptin and rosiglitazone produced greater reductions in 2-h incremental PPG from baseline relative to placebo, but no difference was observed between rosiglitazone and sitagliptin treatments (table 3). Treatment with sitagliptin increased 2-h postmeal insulin and C-peptide relative to both placebo and rosiglitazone, with no differences observed between rosiglitazone and placebo (table 3).

All treatments increased LDL-C, with a decrease relative to placebo observed with sitagliptin and an increase relative to placebo observed with rosiglitazone (table 4). For TGs, sitagliptin provided a small reduction relative to baseline, while an increase from baseline was observed with placebo and a greater increase with rosiglitazone. HDL-C was increased in the sitagliptin and rosiglitazone groups, with a larger effect observed with rosiglitazone. TC and non-HDL-C were increased in all treatment groups, but the effect with sitagliptin was lower compared with the placebo or rosiglitazone groups (table 4). The changes in TC and HDL-C led to greater improvement in the TC/HDL-C ratio with sitagliptin relative to placebo and rosiglitazone.

Safety

There was a modestly higher overall incidence of clinical adverse experiences for sitagliptin (39%) and rosiglitazone (44%) relative to placebo (30%) (table 5). No meaningful differences were observed among the sitagliptin, rosiglitazone and placebo groups with respect to the incidences of serious clinical adverse experiences and drug-related clinical adverse experiences. There were three clinical adverse experiences leading to discontinuation: one patient in the placebo group (arthralgia, considered by the investigator as not drug related) and two patients in the sitagliptin group (coronary artery disease, considered as not drug related, and peripheral coldness, considered as drug related). The incidences of both hypoglycaemia and predefined gastrointestinal adverse experiences were similar among groups (table 5). The incidences of specific adverse experiences were similar among the sitagliptin, rosiglitazone and placebo groups, with the most commonly reported clinical adverse experiences being upper

Table 3 Efficacy endpoints following a meal tolerance test

Parameter	Placebo	Sitagliptin 100 mg q.d.	Rosiglitazone 8 mg q.d.
2-h PPG (mg/dl), n	78	80	76
Baseline	220.1 ± 63.2	221.8 ± 48.0	224.4 ± 57.7
Week 18	216.1 ± 72.1	186.5 ± 46.8	172.0 ± 51.2
Change from baseline	−4.9 (−16.0 to 6.1)	−35.4 (−46.3 to −24.5)	−51.3 (−62.5 to −40.1)
Difference from placebo	—	−30.5 (−46.0 to −15.0)*	−46.4 (−62.1 to −30.7)
Difference from sitagliptin	—	—	−15.9 (−31.6 to −0.3)
2-h Incremental PPG (mg/dl), n	73	77	75
Baseline	61.1 ± 44.2	66.6 ± 36.5	69.7 ± 42.8
Week 18	52.0 ± 42.1	42.0 ± 31.4	41.8 ± 36.9
Change from baseline	−12.2 (−20.2 to −4.3)	−24.1 (−31.8 to −16.4)	−25.4 (−33.2 to −17.5)
Difference from placebo	—	−11.9 (−23.0 to −0.8)**	−13.2 (−24.3 to −2.0)
Difference from sitagliptin	—	—	−1.3 (−12.2 to 9.7)
2-h Postmeal insulin (μIU/ml), n	75	79	72
Baseline	60.6 ± 36.7	65.2 ± 43.0	64.0 ± 47.1
Week 18	54.3 ± 34.2	68.4 ± 50.5	51.0 ± 33.2
Change from baseline	−7.2 (−13.9 to −0.5)	3.8 (−2.6 to 10.3)	−12.8 (−19.6 to −6.0)
Difference from placebo	—	11.0 (1.7 to 20.3)**	−5.6 (−15.1 to 3.9)
Difference from sitagliptin	—	—	−16.6 (−26.0 to −7.3)
2-h Postmeal C-peptide (ng/ml), n	76	79	72
Baseline	9.7 ± 3.3	9.9 ± 4.2	9.1 ± 3.3
Week 18	8.9 ± 3.3	10.3 ± 3.8	8.6 ± 3.2
Change from baseline	−0.8 (−1.3 to −0.2)	0.5 (0.0 to 1.1)	−0.6 (−1.2 to −0.1)
Difference from placebo	—	1.3 (0.5 to 2.1)*	0.1 (−0.7 to 0.9)
Difference from sitagliptin	—	—	−1.2 (−2.0 to −0.4)

LS, least squares; PPG, postprandial plasma glucose.
Baseline and week 24 data are expressed as mean ± s.d.; change from baseline = LS mean change from baseline (95% CI); difference from placebo or difference from sitagliptin results = between-group difference in LS mean change from baseline (95% CI).
*$p \leq 0.001$ vs. placebo; **$p \leq 0.05$ vs. placebo.

respiratory tract infection (4.3, 4.6 and 1.1%, respectively) and nasopharyngitis (4.3, 3.4 and 3.3% respectively). As expected, oedema was seen with the same incidence in the sitagliptin and placebo groups, but at a higher incidence in the rosiglitazone group (1.1, 1.1 and 4.6% respectively).

The overall incidence of laboratory adverse experiences was modestly increased in the sitagliptin (7.4%) and rosiglitazone (9.2%) groups compared with placebo (3.3%). Similar incidences of drug-related laboratory adverse experiences were observed with sitagliptin (1.1%), rosiglitazone (2.3%) and placebo (1.1%) treatment. Three patients discontinued because of a laboratory adverse experience: one in the sitagliptin group (increased blood glucose, considered by the investigator as drug related) and two in the rosiglitazone group (both for increased blood creatinine, both considered as not drug related). No serious laboratory adverse experiences were reported. The most commonly reported laboratory adverse experience was increased blood glucose (5.3% for sitagliptin, 1.1% for rosiglitazone and 0% for placebo).

For haematology parameters, no clinically relevant differences were observed between sitagliptin and placebo. For rosiglitazone, decreases from baseline of −0.55 g/dl in haemoglobin, −1.78% in haematocrit and $-0.25 \times 10^6/mm^3$ in red blood cell count were observed at week 18. For blood chemistry parameters, no clinically relevant differences were observed between sitagliptin and placebo. For rosiglitazone, decreases from baseline of −10.1 IU/l in serum alkaline phosphatase and of −4.8 IU/l in serum ALT were observed at week 18. There were no clinically meaningful changes in vital signs in any treatment group.

After 18 weeks, there were small mean decreases from baseline in body weight in the sitagliptin [LS mean change from baseline (95% CI) = −0.4 (−0.8 to 0.0)] and placebo [−0.8 (−1.2 to −0.4)] groups, with no significant difference between groups. In contrast, treatment with rosiglitazone increased body weight from baseline [1.5 kg (1.0–1.9)], leading to greater between-group differences relative to placebo [2.3 kg (1.7–2.9)] and sitagliptin [1.9 kg (1.3–2.5)]. In a prespecified analysis, the proportion of patients experiencing a greater than 3-kg increase in body weight was 21% in the rosiglitazone group compared with 2% in both the sitagliptin and placebo groups. A progressive rise in body weight from

Table 4 Fasting lipid endpoints

Parameter	Placebo	Sitagliptin 100 mg q.d.	Rosiglitazone 8 mg q.d.
LDL-C (mg/dl), n	83	86	85
Baseline	95.6 ± 30.8	95.4 ± 30.8	99.2 ± 29.4
Week 24	108.4 ± 33.6	104.6 ± 35.1	119.6 ± 37.6
Mean per cent change from baseline	16.7 (10.2 to 23.3)	11.4 (5.0 to 17.8)	26.2 (19.7 to 32.7)
Difference from placebo	—	−5.3 (−14.5 to 3.9)	9.5 (0.2 to 18.7)
Difference from sitagliptin	—	—	14.8 (5.7 to 23.9)
TC (mg/dl), n	83	86	85
Baseline	173.0 ± 34.5	174.8 ± 35.9	180.4 ± 33.9
Week 24	190.4 ± 33.6	182.9 ± 39.5	206.6 ± 49.1
Mean per cent change from baseline	11.3 (7.4 to 15.1)	4.9 (1.1 to 8.7)	16.4 (12.6 to 20.2)
Difference from placebo	—	−6.3 (−11.8 to −0.9)**	5.1 (−0.3 to 10.6)
Difference from sitagliptin	—	—	11.5 (6.0 to 16.9)
HDL-C (mg/dl), n	83	86	85
Baseline	43.5 ± 10.5	43.9 ± 11.6	42.2 ± 10.0
Week 24	44.1 ± 12.1	45.7 ± 13.4	45.7 ± 10.5
Mean per cent change from baseline	1.8 (−1.3 to 4.9)	4.3 (1.2 to 7.3)	9.2 (6.1 to 12.2)
Difference from placebo	—	2.5 (−1.8 to 6.8)	7.4 (3.1 to 11.7)
Difference from sitagliptin	—	—	4.9 (0.6 to 9.2)
TG (mg/dl), n	83	86	85
Baseline	171.1 ± 73.3	177.8 ± 80.7	201.6 ± 126.2
Week 24	191.5 ± 111.1	163.3 ± 74.0	199.8 ± 108.4
Mean per cent change from baseline	11.9 (3.9 to 19.9)	−4.8 (−12.7 to 3.1)	13.1 (5.2 to 21.1)
Difference from placebo	—	−16.7 (−27.9 to 5.5)**	1.2 (−10.1 to 12.6)
Difference from sitagliptin	—	—	17.9 (6.7 to 29.2)
Non-HDL-C (mg/dl), n	83	86	85
Baseline	129.2 ± 34.3	130.9 ± 35.1	138.2 ± 34.6
Week 24	146.2 ± 34.3	137.2 ± 38.2	160.9 ± 50.0
Mean per cent change from baseline	15.7 (10.3 to 21.2)	5.4 (0.1 to 10.8)	20.2 (14.8 to 25.6)
Difference from placebo	—	−10.3 (−18.0 to −2.7)**	4.5 (−3.2 to 12.2)
Difference from sitagliptin	—	—	14.8 (7.2 to 22.4)
TC/HDL-C ratio, n	83	86	85
Baseline	4.2 ± 1.1	4.2 ± 1.2	4.5 ± 1.3
Week 24	4.6 ± 1.3	4.2 ± 1.3	4.7 ± 1.6
Mean per cent change from baseline	11.3 (6.6 to 16.0)	1.6 (−3.1 to 6.2)	8.6 (3.9 to 13.2)
Difference from placebo	—	−9.7 (−16.3 to −3.2)**	−2.7 (−9.4 to 3.9)
Difference from sitagliptin	—	—	7.0 (0.4 to 13.6)

HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; LS, least squares; TC, total cholesterol; TG, triglyceride.
Baseline and week 24 data are expressed as mean ± s.d.; mean per cent change from baseline = LS mean per cent change from baseline (95% CI); difference from placebo or difference from sitagliptin results = between-group difference in LS mean per cent change from baseline (95% CI).
*$p \leq 0.001$ for sitagliptin vs. placebo; **$p \leq 0.05$ for sitagliptin vs. placebo.

baseline was observed in the rosiglitazone group over 18 weeks, whereas the small weight loss observed in the sitagliptin and placebo groups was evident by week 6 (figure 3).

Discussion

In this study, the addition of once-daily sitagliptin led to clinically meaningful reductions in HbA_{1c} in patients with type 2 diabetes and inadequate glycaemic control on metformin monotherapy. The addition of sitagliptin treatment enabled more than half of these patients with mild-to-moderate baseline hyperglycaemia to achieve the HbA_{1c} target of <7%. This placebo-controlled study also included a rosiglitazone arm to provide information relative to a commonly used add-on antihyperglycaemic agent. After 18 weeks, the change in HbA_{1c} was not meaningfully different between the sitagliptin and rosiglitazone arms. This agrees with the findings of a recently published trial in which sitagliptin or the sulphonylurea, glipizide, led to the same mean reduction in HbA_{1c} after 1 year when treatment was added to patients with inadequate glycaemic control on metformin monotherapy [12]. In the current study, patients with higher baseline HbA_{1c} levels experienced greater reductions in HbA_{1c} with both active treatments, an effect consistently shown with other antihyperglycaemic agents [21].

Table 5 Clinical AE summary

Number (%) of patients	Placebo (n = 91)	Sitagliptin 100 mg q.d. (n = 94)	Rosiglitazone 8 mg q.d. (n = 87)
One or more AEs	27 (30)	37 (39)	38 (44)
Drug-related AEs†	8 (9)	10 (11)	9 (10)
Serious AEs	5 (5)	5 (5)	5 (6)
Drug-related SAEs†	1 (1)	0 (0)	0 (0)
Discontinued because of AEs	1 (1)	2 (2)	0 (0)
Discontinued because of drug-related AEs	0 (0)	1 (1)	0 (0)
Discontinued because of SAEs	0 (0)	1 (1)	0 (0)
Discontinued because of drug-related SAEs	0 (0)	0 (0)	0 (0)
Special AEs of clinical interest			
Hypoglycaemia	2 (2)	1 (1)	1 (1)
Oedema	1 (1)	1 (1)	4 (5)
All gastrointestinal AEs	8 (9)	8 (9)	6 (7)
Diarrhoea	1 (1)	3 (3)	3 (3)
Nausea	2 (2)	1 (1)	1 (1)
Abdominal pain	1 (1)	0 (0)	1 (1)
Vomiting	1 (1)	1 (1)	1 (1)

AE, adverse experience; SAE, serious adverse experience.
†Considered by the investigator to be drug related.

Although a plateau in HbA_{1c} levels was not evident at the end of the study (i.e. at 18 weeks) in the rosiglitazone group, the maximal mean reduction in FPG was reached at 6 weeks and remained constant through 18 weeks. Because HbA_{1c} reflects glycaemic control over a 2- to 3-month period, the sustained mean reduction in FPG from weeks 6–18 suggest that the nadir for HbA_{1c} was most likely established at 18 weeks for rosiglitazone in the present study. Consistent with this finding, the maximal efficacy of once-daily rosiglitazone 8 mg on HbA_{1c} was reached at 18 weeks in a previously reported 26-week, placebo-controlled, add-on to metformin study [17].

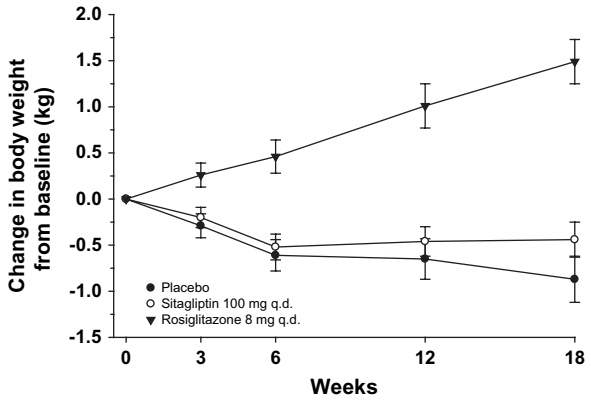

Fig. 3 Change in body weight from baseline (mean change ± s.e.).

In this study, similar reductions in HbA_{1c} levels were seen in the sitagliptin and rosiglitazone treatment groups. Both active treatments lowered FPG and 2-h PPG relative to placebo, but the changes were greater with rosiglitazone. For 2-h PPG, the difference between the sitagliptin and rosiglitazone treatment groups was attributable to the lower FPG seen with rosiglitazone, in that the changes in the incremental 2-h PPG, which reflects the actual glycaemic excursion following a meal, were similar between the active treatments. This suggests that sitagliptin resulted in improvement in hyperglycaemia during other intervals of the day or night. Future studies are needed to compare the 24-h glucose profiles with treatment with both agents.

Sitagliptin increased postmeal insulin and C-peptide levels in the present study, which is consistent with the glucose-dependent effects on incretin-mediated insulin release [22]. Moreover, HOMA-β, a marker of beta-cell function, was also increased in the sitagliptin group relative to placebo. Previous studies have shown that sitagliptin improved beta-cell function as assessed by HOMA-β [13] and the C-peptide minimal model [11]. Collectively, these data show that sitagliptin improves beta-cell function and beta-cell responsiveness to glucose. Rosiglitazone has also been reported to improve beta-cell function [17], consistent with the improvement in HOMA-β observed with rosiglitazone relative to placebo in the current study.

The reduction in HOMA-IR with rosiglitazone is consistent with its mechanism of action of improving peripheral insulin sensitivity [23], while the neutral effect on HOMA-IR observed with sitagliptin in the current study has previously been reported [13].

Weight gain is typically observed with rosiglitazone treatment as monotherapy or as add-on to metformin therapy [1,17]. In the present study, body weight was increased by approximately 2 kg with rosiglitazone relative to the other treatments. Moreover, more than 20% of patients experienced at least a 3-kg increase with rosiglitazone. The progressive increase in body weight observed in this 18-week study has been reported with rosiglitazone monotherapy with long-term treatment [1]. On the other hand, DPP-4 inhibitors have been shown generally to be weight neutral [9]. In this and another study [13], sitagliptin added to metformin therapy produced a small reduction in body weight from baseline that was not different from the addition of placebo to metformin. This suggests that sitagliptin does not interfere with the weight loss typically observed with metformin [7], despite the improvement in glucose control.

In a previous study, the addition of sitagliptin to metformin produced small but statistically significant improvements in lipid parameters relative to placebo [13]. In the present study, in patients with average baseline LDL-C levels below 100 mg/dl, an increase in LDL-C from baseline was observed in the placebo group and in both active treatment groups. However, sitagliptin treatment led to a slight numerical improvement in LDL-C relative to placebo, while an increase in LDL-C was seen with rosiglitazone relative to the other treatments. Similar trends were observed with other lipid parameters, including TC, TG and non-HDL-C. HDL-C was increased with all treatments, with the largest increase observed in the rosiglitazone group. Sitagliptin treatment led to improvements in the TC/HDL-C ratio relative to the other treatments. Collectively, the addition of sitagliptin resulted in a more favourable lipid profile compared with placebo and rosiglitazone in this study.

Consistent with earlier studies [13,17], the addition of sitagliptin or rosiglitazone to metformin-treated patients was generally well tolerated, with a very low incidence of hypoglycaemia that was similar to that observed in the placebo group. The addition of sitagliptin or rosiglitazone to ongoing metformin therapy did not lead to an increase in the incidence of gastrointestinal-related adverse experiences, which are commonly reported with treatment with metformin [7]. Although infrequent, the incidence of oedema was higher with rosiglitazone treatment compared with treatment with placebo or sitagliptin in the present study. Furthermore, rosiglitazone treatment was associated with a decrease in haemoglobin levels and the haematocrit relative to baseline in the present study. These effects with rosiglitazone were also shown in a previously reported add-on to metformin trial [17] and may be related to the fluid retention and haemodilution associated with TZDs [23].

In conclusion, in this study, the addition of sitagliptin was effective and well tolerated in patients with type 2 diabetes who had inadequate glycaemic control on metformin monotherapy. Sitagliptin treatment produced similar reductions in HbA_{1c} with beneficial lipid effects and without weight gain or decreases in haemoglobin compared with the addition of rosiglitazone.

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Appendix

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