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ORIGINAL ARTICLE

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

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ABSTRACT

Objective: The purpose of this study was to evaluate the efficacy and safety of sitagliptin as an add-on to metformin therapy in patients with moderately severe (hemoglobin A_{1c} ≥ 8.0% and ≤ 11.0%) type 2 diabetes mellitus (T2DM).

Research design and methods: This was a multinational, randomized, placebo-controlled, parallel-group, double-blind study conducted in 190 patients with T2DM. After ≥ 6 weeks of stable metformin monotherapy (≥ 1500 mg/day), patients were randomized to either the addition of sitagliptin 100 mg once daily or placebo to ongoing metformin for 30 weeks.

Main outcome measures: The primary efficacy endpoint was reduction in hemoglobin A_{1c} (HbA_{1c}) measured after 18 weeks of sitagliptin treatment. Key secondary endpoints included reduction in fasting plasma glucose (FPG) and 2-hour (2-h) postprandial plasma glucose (PPG) at 18 weeks, and HbA_{1c} at 30 weeks. The proportion of patients meeting the goal of HbA_{1c} < 7.0% was also analyzed.

Results: Sitagliptin significantly reduced HbA_{1c}, FPG, and 2-h PPG, compared with placebo (all $p <$ 0.001). The net improvement in HbA_{1c} was –1.0% at both 18 and 30 weeks, and a significantly greater proportion of patients treated with sitagliptin achieved HbA_{1c} < 7.0% by the end of the study (22.1% vs. 3.3%, $p < 0.001$). Sitagliptin was well-tolerated. Compared with placebo, sitagliptin had a neutral effect on body weight and did not significantly increase the risk of hypoglycemia or gastrointestinal adverse events.

Conclusions: Addition of sitagliptin 100 mg once daily to ongoing metformin therapy was well-tolerated and resulted in significant glycemic improvement in patients with moderately severe T2DM who were treated for 30 weeks. (Registered on ClinicalTrials.gov as NCT00337610).

Introduction

Type 2 diabetes mellitus (T2DM) is a disease characterized by progressive loss of glycemic control over time[1]. Often, initial treatment with a single oral antihyperglycemic agent (OHA) is not sufficient to maintain good glucose control[2]; for this reason, combinations of OHA are usually required to manage patients with T2DM. Key underlying defects that contribute to hyperglycemia in patients with T2DM include insulin resistance in muscle and other tissues, inadequate insulin secretion by pancreatic β-cells, and hepatic

glucose overproduction[3]. In treating patients with T2DM, combinations of OHAs that target different pathophysiological defects may be particularly useful.

The biguanide metformin is currently the most commonly used initial OHA, and also the most frequently used agent in combination therapy[4]. It is recommended by treatment guidelines worldwide and widely considered to be the standard of care for initial OHA therapy in patients with T2DM[5,6]. Its primary mechanism of action is the suppression of hepatic glucose production, although it may also act peripherally to reduce insulin resistance[7,8]. Sitagliptin is a once-daily OHA with a novel mechanism of action that targets the incretin axis. Incretin hormones, including glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released by gut endocrine cells in response to a meal and contribute to glucoregulation by enhancing glucose-dependent insulin secretion[9,10]. In addition, GLP-1 suppresses glucagon release[9–12]. These hormones are rapidly inactivated by the enzyme dipeptidyl peptidase IV (DPP-4)[13,14]. By inhibiting DPP-4, sitagliptin increases levels of active incretin hormones, prolonging and increasing incretin activity, enhancing the effects on insulin stimulation and glucagon suppression, and thereby improving control of blood glucose[15,16]. This novel approach to treatment of patients with T2DM has led to new possibilities for effective monotherapy and combination therapy.

Previous studies of sitagliptin in add-on combination with metformin have demonstrated good efficacy and tolerability in patients with mild-to-moderate baseline hyperglycemia (HbA_{1c} 7.0–10.0%)[17,18]. Given the key role that metformin plays in the treatment of T2DM, broad experience of new OHAs in combination with metformin is important. Hence, the purpose of the present 30-week study was to provide additional experience with the combination therapy of sitagliptin and metformin, including experience in patients with a different range of baseline HbA_{1c} (8.0–11.0%) than was examined in these prior studies of sitagliptin as an add-on to metformin therapy. This study was designed with the primary goal of assessing efficacy after 18 weeks, when the full effect on glycemic parameters with sitagliptin treatment would be expected. An additional goal was to examine efficacy and safety over a longer duration of treatment, 30 weeks in total.

Methods

This was a multinational, randomized, placebo-controlled, parallel-group, double-blind study in which 190 patients were randomized into a 30-week double-blind treatment period (Merck protocol 053). The study was performed in accordance with the guidelines of good clinical practice and with ethical standards for human experimentation established by the Declaration of Helsinki. Each participating study site received approval by the local ethics review committee/institutional review board and all patients gave their written informed consent before participating.

Patients

Patients with T2DM, 18–78 years of age, who were currently on metformin monotherapy or any other single OHA, or being treated with metformin in combination with another OHA, were eligible to enter the study if their HbA_{1c} value met screening criteria (see below). Patients were excluded who had received treatment with insulin within 8 weeks prior to screening, treatment with a PPARγ agent (e.g., pioglitazone or rosiglitazone) or incretin mimetics (e.g., exenatide) within 12 weeks, had type 1 diabetes, a body mass index (BMI) $< 20\ kg/m^2$ or $> 43\ kg/m^2$, or a fasting plasma glucose (FPG) during run-in that was consistently < 7.2 mmol/L or > 15.6 mmol/L. Use of other OHAs besides metformin was not permitted during the study. However, patients were allowed to receive stable doses of lipid lowering medications, antihypertensive drugs, thyroid hormone medications, and hormonal contraceptives. Patients who were pregnant or breast-feeding were excluded.

Study design

Upon entry into the run-in period, patients on other OHAs were switched to monotherapy with metformin, which was then titrated upward to a dose of at least 1500 mg per day (maximum, 2550 mg per day). These patients then entered a metformin dose-stable diet and exercise period of at least 6 weeks (Figure 1). Patients who were already on metformin monotherapy at a stable dose of at least 1500 mg per day directly entered into the 6-week metformin dose-stable diet and exercise period. At the end of the run-in period, patients who had an HbA_{1c} of 8.0–11.0% were eligible to continue into a 2-week single-blind placebo run-in period. Upon completing this, patients who had shown adequate treatment compliance (had taken ≥ 85% of the tablets provided) and who had a fasting fingerstick glucose ≥ 7.2 mmol/L and ≤ 15.6 mmol/L were randomized in a 1 : 1 ratio following a computer-generated schedule to receive either placebo or sitagliptin 100 mg once daily for 30 weeks, in addition to their ongoing stable metformin dose. Throughout the 30-week period of double-blind study, treatment compliance was assessed at each patient visit by tablet counts. Patients who failed to achieve or maintain pre-specified FPG levels after randomization received rescue therapy with

glipizide (administered according to the product label) until completion of the study. (Details regarding these FPG levels are provided in Figure 1.) To avoid the confounding influence of rescue therapy on efficacy comparison, the last results prior to initiation of rescue therapy were carried forward for efficacy analyses. Patients were discontinued from the study if they were on rescue medication for at least 2 weeks and had an FPG consistently > 11.1 mmol/L.

Laboratory assays were performed at Quintiles Laboratories Limited (Smyrna, GA, USA) and Quintiles Laboratories Europe (Livingston, Scotland, UK). Blood HbA_{1c} was determined by high-performance liquid chromatography, insulin by solid-phase radioimmunoassay, and proinsulin by two-site enzyme immunoassay.

Study endpoints

Efficacy

The primary efficacy endpoint was change from baseline in HbA_{1c} after 18 weeks of treatment. Baseline measurements were made before initiating double-blind treatment on the day of randomization. It was expected (and observed) that some baseline HbA_{1c} levels would fall outside of the targeted eligibility range of 8.0–11.0% because the measurement of HbA_{1c} that determined eligibility was done 2 weeks prior to the measurement of HbA_{1c} that determined baseline for use in the analysis of efficacy.

Key secondary endpoints included change from baseline in FPG and 2-h postprandial plasma glucose (2-h PPG, measured after a standard meal) after 18 weeks of treatment, and change from baseline in HbA_{1c} after 30 weeks of treatment. Additional endpoints included fasting and postprandial blood levels of insulin, C-peptide, proinsulin, and the proinsulin-to-insulin ratio at week 18, total area under the curve (AUC) for glucose, insulin, C-peptide, and the insulin-to-glucose AUC ratio. From these, the homeostasis model assessment of β-cell function (HOMA-β) and proinsulin-to-insulin AUC ratio were calculated to evaluate β-cell function, and a homeostasis model assessment of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were calculated to assess insulin sensitivity. Additionally, the numbers of patients requiring rescue therapy and times at which rescued occurred were assessed, as well as the percentage of patients reaching the therapeutic goal of $HbA_{1c} < 7.0\%$.

Safety and tolerability

Safety and tolerability were evaluated by physical examination, vital signs, and safety laboratory measurements that included routine serum chemistry, hematology, urinalysis, and pregnancy testing in women of childbearing age. Adverse events (AEs) were monitored throughout the study and evaluated by the investigators for intensity, duration, outcome, relationship to study drug, and level of severity. Identification of serious AEs was based upon pre-specified criteria.

Statistical analysis

Efficacy

Efficacy outcomes were analyzed using full-analysis-set (FAS) populations composed of all randomized patients who had received at least one dose of sitagliptin or placebo and had a baseline plus at least one postrandom-

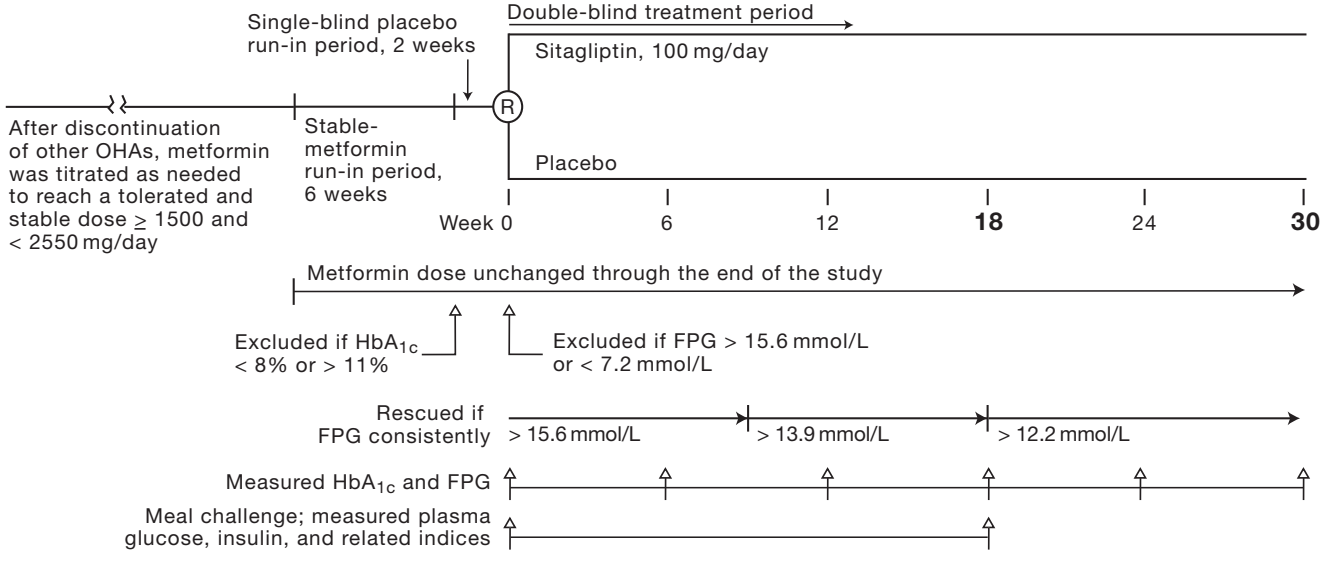

Figure 1. *The study design. FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin; OHA, oral antihyperglycemic agent; R, randomization*

ization measurement. The earliest postrandomization measurement of HbA_{1c} was made in week 6; hence all patients included in the FAS population had received at least 6 weeks of double-blind treatment. The analysis of covariance (ANCOVA) model was used to compare treatment groups for continuous efficacy parameters, focusing on change from baseline values at week 18 and week 30, with treatment allocation, baseline values, and prior OHA status as covariates. The between-group differences for efficacy endpoints were assessed by testing the difference in least-squares mean (LS-mean) change at week 18 and week 30. Missing data were handled using the last-observation-carried-forward (LOCF) method.

The primary hypothesis was that addition of sitagliptin to ongoing metformin therapy would result in significant reduction in HbA_{1c}, compared with placebo after 18 weeks of treatment. Endpoints associated with secondary hypotheses (superiority for FPG and 2h-PPG-lowering at week 18 and for HbA_{1c}-lowering at week 30) were conditionally tested using a step-down procedure that adjusted for multiplicity[19] and were prioritized in order of 2h-PPG at week 18, FPG at week 18, and then HbA_{1c} at week 30, provided the primary efficacy endpoint for HbA_{1c} at week 18 was met. The proportion of individuals meeting the primary HbA_{1c} goal of < 7.0% at week 18 and week 30 was compared among groups using a logistic regression model. The between-group difference in the proportions of patients requiring glycemic rescue therapy was evaluated using Kaplan–Meier estimates and the log-rank test. Results are presented as mean ± SD except when otherwise indicated.

Safety and tolerability

Safety and tolerability were analyzed using the all-patients-as-treated population composed of all randomized patients who had received at least one dose of double-blind study medication. Included in the safety analysis were all clinical or laboratory AEs, laboratory safety measurements, weight, and vital signs. Inferential testing was performed to evaluate the statistical significance of between-group differences in the incidence of hypoglycemia and pre-specified selected gastrointestinal AEs (nausea vomiting, diarrhea, and abdominal pain). The method of evaluation was Fisher's exact test, with estimation of confidence intervals by Wilson's method[20].

Subgroup analyses

Prespecified subgroups were analyzed for changes from baseline in HbA_{1c} at week 18 and week 30 to evaluate preexisting factors that could potentially influence treatment outcome. These subgroups were defined by differences in age, gender, race, duration of diabetes, prior OHA therapy, and baseline BMI, HbA_{1c}, HOMA-β, HOMA-IR, and proinsulin/insulin ratio.

Sample size and statistical power

Assuming a within-group standard deviation of 1% for measurements of HbA_{1c}[17], and that significance is evaluated at $\alpha = 0.05$ using a two-tailed test, approximately 86 patients per treatment group would provide 90% power to detect a true between-group difference of 0.5% in the mean change in HbA_{1c} from baseline.

Results

Demographics, baseline measures, and patient disposition

The overall patient disposition is described in Figure 2: of the 544 patients screened, a total of 190 were randomized to either sitagliptin (n = 96) or placebo (n = 94). The demographic, anthropometric, and disease characteristics of the randomized patients were similarly distributed between the two treatment groups (Table 1). Patients had a mean baseline HbA_{1c} of 9.2% (range, 7.5–11.1%; 42% of patients had a baseline HbA_{1c} < 9.0%) and the average baseline FPG was 11.1 mmol/L. The average duration of diabetes was 7.9 years; 52.1% were on metformin monotherapy and 44.7% of patients were on OHA combination therapy at screening. After randomization, 159 patients (83.7%) completed the 30-week study. One hundred eighty-seven patients (98.4%) were included in the FAS-analysis (three randomized patients were excluded because of missing on-treatment data). The proportions of patients who discontinued from the study were similar in the two treatment groups. Rates of treatment compliance were similar in the two groups with an overall mean of 98.5% over the 30 weeks of study.

Efficacy

At week 18, addition of sitagliptin 100 mg once-daily to ongoing metformin therapy significantly ($p < 0.001$) reduced HbA_{1c} from baseline compared with placebo (Table 2). The between-group difference in LS-mean change from baseline was –1.0% at both week 18 (the prespecified primary endpoint), and week 30 ($p <$ 0.001, both timepoints). The time course of HbA_{1c} reduction is shown in Figure 3A, and was generally stable from week 18 through week 30. Treatment effects on HbA_{1c} were consistent across subgroups

Table 1. *Baseline demographic, anthropometric, and disease severity characteristics of the randomized patient populations (total* n = *190)*

Characteristic	Number of patients (%) or mean ± SD	
	Placebo (*n* = 94)	Sitagliptin (*n* = 96)
Age (range), years	56.1 ± 9.5 (36–77)	53.6 ± 9.5 (29–73)
Sex, female	55 (58.5%)	47 (49.0%)
Race		
White	44 (47%)	40 (42%)
Hispanic	24 (25%)	31 (32%)
Black	1 (1%)	3 (3%)
Multiracial	23 (25%)	21 (22%)
Other	2 (2%)	1 (1%)
Weight (range), kg	81.2 ± 19.4 (40.0–137.5)	81.5 ± 16.8 (54.1–129.2)
Body mass index, kg/m^2	30.4 ± 5.3 (20.1–43.3)	30.1 ± 4.4 (22.4–40.9)*
Duration of type 2 diabetes mellitus, years	7.3 ± 5.3 (0.3–22)	8.4 ± 6.5 (0.2–40.0)
HbA_{1c}, %	9.1 ± 0.8	9.3 ± 0.9
HbA_{1c} distribution		
< 9%	45 (48%)	35 (36%)
≥ 9% and < 10%	36 (38%)†	41 (43%)
≥ 10%	13 (14%)	20 (21%)‡
FPG, mmol/L	11.0 ± 2.4	11.2 ± 2.6
Use of OHA at screening		
Metformin monotherapy	45 (47.9%)	54 (56.3%)
Other monotherapy	2 (2.1%)	4 (4.2%)
Combination therapy	47 (50.0%)	39 (40.6%)
None	0 (0%)	0 (0%)

*n = 95 because of a missing value for height
†This subgroup contributed 34 patients to the HbA_{1c} FAS population (37% of the total)
‡This subgroup contributed 19 patients to the HbA_{1c} FAS population (20% of the total)
FPG = fasting plasma glucose; SD = standard deviation; OHA = oral antihyperglycemic agent

defined by age, baseline BMI, gender, race, duration of diabetes, HOMA-β, HOMA-IR, prior OHA therapy, and proinsulin/insulin ratio (Table 3). Numerically greater HbA_{1c} reductions from baseline were observed in sitagliptin-treated patients with higher baseline HbA_{1c} values (Figure 4). In the subgroup with the highest HbA_{1c} baseline values (≥ 10.0%), the net reduction in HbA_{1c} with sitagliptin treatment, relative to placebo, was –1.8% at week 18 and –1.4% at week 30. The smaller decrease relative to placebo at week 30 was related to a drop in HbA_{1c} in the placebo group, with stable HbA_{1c} in the sitagliptin group from week 18 to week 30.

Compared with placebo, sitagliptin significantly increased the probability of achieving the HbA_{1c} goal of < 7.0% at both week 18 and week 30 (p= 0.012 and p < 0.001, respectively). The proportion of patients in the sitagliptin group achieving this goal was numerically greater at week 30 than at week 18 (22.1% vs. 13.7%). In the placebo group, this goal was reached by 3.3% of patients at both time points.

Treatment with sitagliptin resulted in significant reductions from baseline in FPG compared with placebo at week 18 and week 30 (p < 0.001 at both time-points; Table 2). The LS-mean net change from baseline in FPG was –1.4 mmol/L (95% CI –2.1 to –0.7) at both time-points. The nadir in FPG-lowering by sitagliptin occurred at week 18 (Figure 3B) followed by a slight rise in FPG in both treatment groups, with generally stable placebo-subtracted treatment effect. Sitagliptin treatment significantly (p < 0.001, compared with placebo) improved 2h-PPG after a standard meal challenge at week 18 (Table 2; Figure 3C), as well as the total glucose AUC (Table 4). The LS-mean net change from baseline in 2h-PPG at week 18 was –3.0 mmol/L (95% CI –4.2 to –1.9).

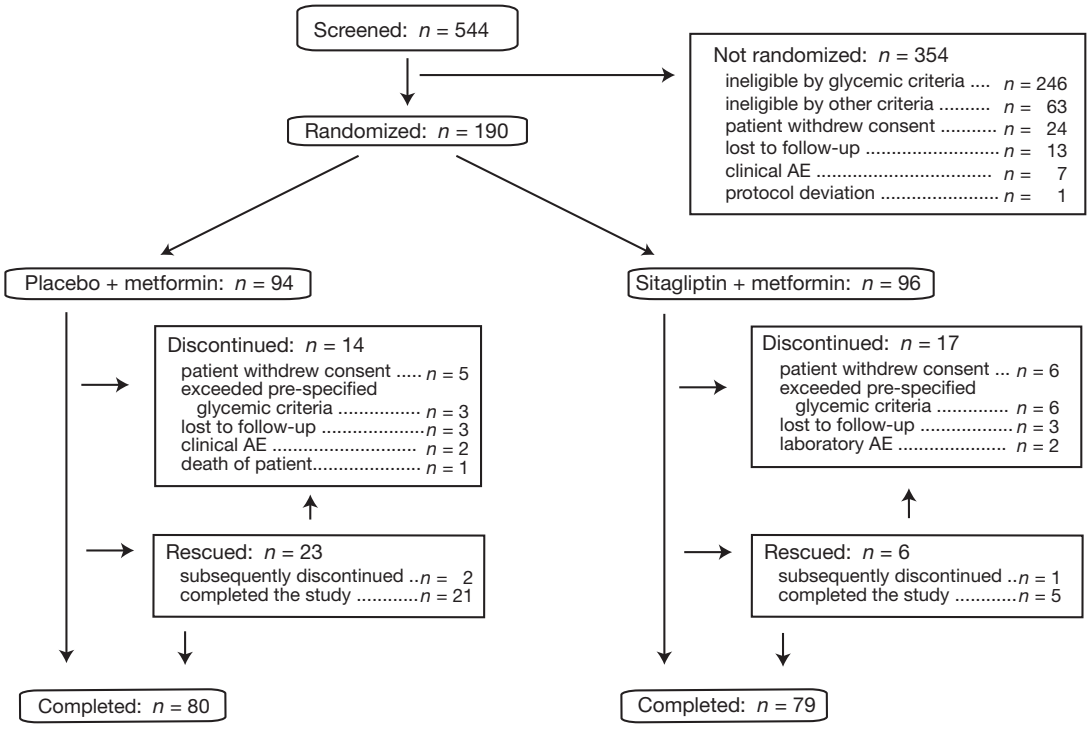

Figure 2. *Patient disposition. Following randomization, two patients in the placebo group and one in the sitagliptin group discontinued before contributing any posttreatment HbA_{1c} data; the respective FAS cohorts for the primary endpoint were thus composed of 92 and 95 patients. AE, adverse event*

Table 2. *Change in HbA_{1c} and key secondary endpoints in patients treated with sitagliptin or placebo plus ongoing metformin*

Endpoint	*n*	Change from baseline, LS-mean (95% CI)		Between-group difference in LS-means (95% CI)	
		Week 18	Week 30	Week 18	Week 30
HbA_{1c}, %					
Placebo (+ metformin)	92	0.0 (–0.2, 0.3)	0.0 (–0.2, 0.3)	–1.0 (–1.4, –0.7)*	–1.0 (–1.4, –0.6)*
Sitagliptin (+ metformin)	95	–1.0 (–1.2, –0.8)*	–1.0 (–1.3, –0.7)*		
FPG, mmol/L					
Placebo (+ metformin)	92	–0.4 (–0.8, 0.1)	–0.2 (–0.7, 0.3)	–1.4 (–2.1, –0.7)*	–1.4 (–2.1, –0.7)*
Sitagliptin (+ metformin)	96	–1.8 (–2.3, –1.3)*	–1.6 (–2.1, –1.1)*		
2-h PPG, mmol/L					
Placebo (+ metformin)	74	–0.8 (–1.6, 0.1)	nd	–3.0 (–4.2, –1.9)*	nd
Sitagliptin (+ metformin)	79	–3.8 (–4.6, –3.0)*	nd		

*$p < 0.001$
Negative between-group differences favor sitagliptin over placebo
FPG = fasting plasma glucose; LS = least-squares; nd = not determined; 2-h PPG = 2-h postprandial plasma glucose

Other meal-related measurements and parameters of β-cell function

Several indices related to glycemic control and β-cell function were found to be significantly improved in the sitagliptin group, relative to placebo, at week 18. These included HOMA-β ($p < 0.001$), a measure of fasting insulin secretion, and the fasting proinsulin-to-insulin ratio ($p < 0.001$). Indices of insulin sensitivity (QUICKI and HOMA-IR) showed no meaningful or statistically significant differences. Table 4 provides results of measures from the meal tolerance test.

Use of glycemic rescue therapy

Consistent with the significantly greater improvement in glycemic control, patients on sitagliptin treatment had a significantly ($p < 0.001$) lower rate of requiring

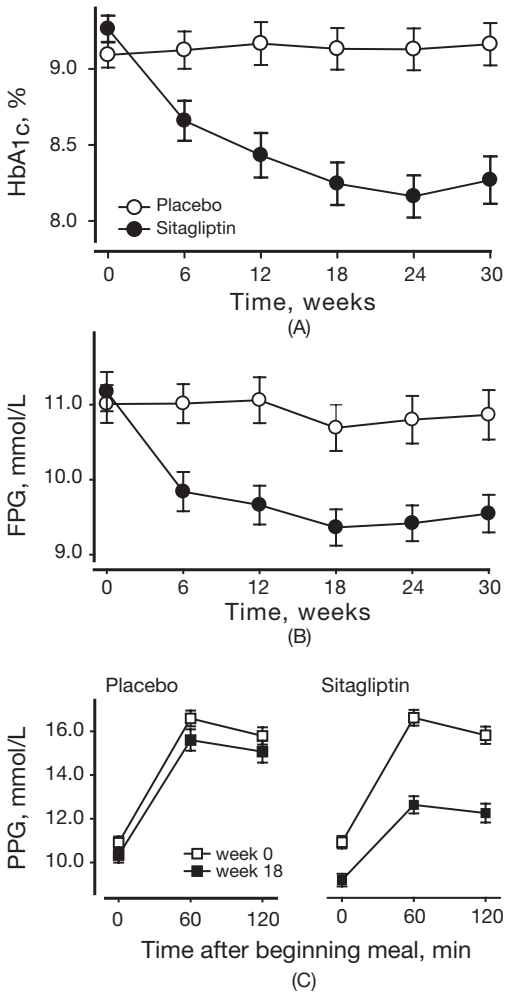

Figure 3. *The timecourse of change in key glycemic indices: (A) HbA_{1c}, (B) FPG, and (C) PPG. All values are mean ± SE*

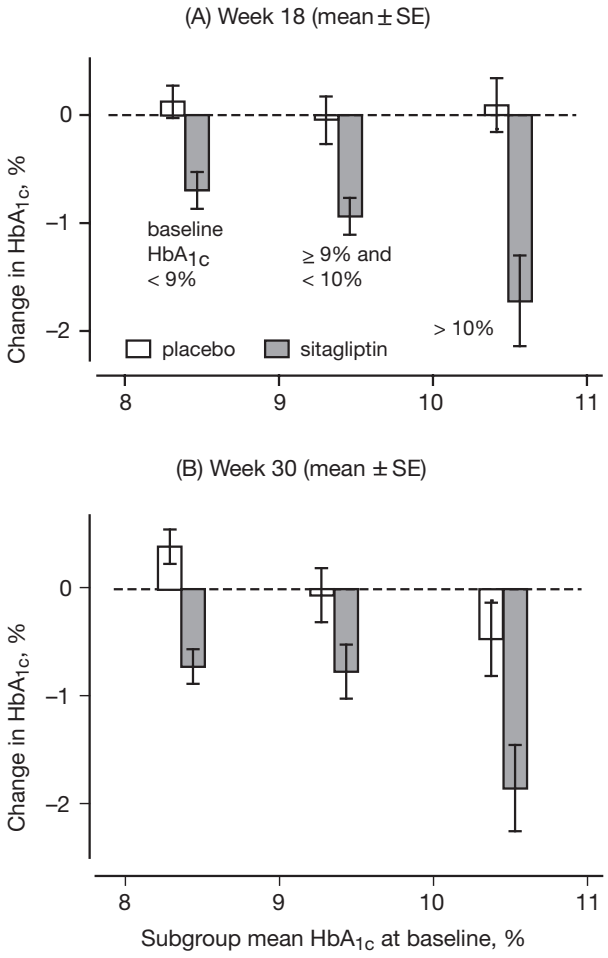

Figure 4. *The results of a subgroup analysis in which mean HbA_{1c} outcomes (± SE) were analyzed separately for three patient groups, assigned according to baseline HbA_{1c} value. In the low-baseline group (baseline HbA_{1c} < 9.0%), the mean HbA_{1c} at baseline was 8.4% for both treatment groups (left-most bars). In the intermediate-baseline group (baseline HbA_{1c} ≥ 9.0% and < 10.0%), the mean HbA_{1c} at baseline was 9.4% for both treatment groups (center-most bars), and in the high-baseline group (baseline HbA_{1c} ≥ 10.0%), the mean HbA_{1c} at baseline was 10.5% for both treatment groups (right-most bars). The data were obtained after (A) 18 and (B) 30 weeks of treatment. The subgroup sample sizes are provided in Table 1 under the heading 'HbA_{1c} distribution'*

rescue therapy compared with placebo. Six patients in the sitagliptin group required rescue, compared with 23 in the placebo group (Figure 2). In Kaplan–Meier plots, initiation of rescue therapy tended to occur much later in the sitagliptin group than in the placebo group (Figure 5). The Kaplan–Meier estimates of cumulative rate of rescue in these groups were 6.8 and 26.9%, respectively.

Lipids

There were no significant between-group differences in the fasting blood lipids measured. These included total cholesterol, LDL-, HDL-, and non-HDL-cholesterol, triglycerides, and the triglyceride-to-cholesterol ratio (data not shown).

Safety and tolerability

The addition of sitagliptin 100 mg to ongoing therapy with metformin was generally well-tolerated. Over the 30-week treatment period, the incidence of clinical AEs was similar in the two treatment groups (Table 5), as was the incidence of AEs considered by investigators to be drug-related. No serious AEs or discontinuations due to clinical AEs were reported in the sitagliptin group. In the placebo group, six serious clinical AEs were reported in five patients (including a fatal myocardial infarction, three neoplasms, a limb fracture, and an upper gastrointestinal hemorrhage) and were responsible for one death and two discontinuations. These were all regarded by investigators as not drug related. There were no statistically significant differences between the two treatment groups in the incidence of hypoglycemia

Table 3. *Subgroup analyses of changes in HbA_{1c} observed after 30 weeks of treatment with sitagliptin or placebo as an add-on to metformin therapy*

Demographic or disease characteristic at study entry	*n*	HbA_{1c} at baseline (mean ± SD)	Change from baseline (mean ± SE)
Age ≤ median (55.0 years)			
Placebo (+ metformin)	46	9.2 ± 0.8	–0.1 ± 0.2
Sitagliptin (+ metformin)	55	9.4 ± 1.0	–1.0 ± 0.2
Age > median			
Placebo (+ metformin)	46	9.0 ± 0.8	0.2 ± 0.2
Sitagliptin (+ metformin)	40	9.1 ± 0.6	–1.1 ± 0.2
BMI ≤ median (30.1 kg/m^2)			
Placebo (+ metformin)	46	9.0 ± 0.7	0.0 ± 0.2
Sitagliptin (+ metformin)	47	9.3 ± 1.0	–1.1 ± 0.2
BMI > median			
Placebo (+ metformin)	46	9.2 ± 0.9	0.2 ± 0.2
Sitagliptin (+ metformin)	47	9.2 ± 0.7	–0.9 ± 0.2
Female			
Placebo (+ metformin)	54	9.1 ± 0.9	0.1 ± 0.2
Sitagliptin (+ metformin)	47	9.4 ± 0.9	–1.1 ± 0.2
Male			
Placebo (+ metformin)	38	9.1 ± 0.7	0.0 ± 0.2
Sitagliptin (+ metformin)	48	9.2 ± 0.9	–0.9 ± 0.2
Duration of diabetes ≤ median (6.0 years)			
Placebo (+ metformin)	50	9.1 ± 0.9	0.0 ± 0.2
Sitagliptin (+ metformin)	47	9.3 ± 0.9	–0.9 ± 0.2
Duration of diabetes > median			
Placebo (+ metformin)	42	9.1 ± 0.7	0.2 ± 0.2
Sitagliptin (+ metformin)	48	9.2 ± 0.9	–1.1 ± 0.2
Previously on metformin monotherapy			
Placebo (+ metformin)	47	9.1 ± 0.8	0.0 ± 0.2
Sitagliptin (+ metformin)	58	9.4 ± 0.8	–0.9 ± 0.2
Previously on metformin-based combination therapy			
Placebo (+ metformin)	45	9.0 ± 0.8	0.2 ± 0.2
Sitagliptin (+ metformin)	37	9.1 ± 0.9	–1.2 ± 0.2
HOMA-β ≤ median (23.7)			
Placebo (+ metformin)	38	9.2 ± 0.8	0.3 ± 0.2
Sitagliptin (+ metformin)	42	9.3 ± 1.0	–1.0 ± 0.2
HOMA-β > median			
Placebo (+ metformin)	38	8.8 ± 0.7	0.1 ± 0.2
Sitagliptin (+ metformin)	40	9.2 ± 0.8	–0.9 ± 0.2
HOMA-IR ≤ median (4.0)			
Placebo (+ metformin)	42	9.0 ± 0.9	0.1 ± 0.2
Sitagliptin (+ metformin)	37	9.1 ± 1.0	–1.0 ± 0.2
HOMA-IR < median			
Placebo (+ metformin)	34	9.0 ± 0.8	0.3 ± 0.2
Sitagliptin (+ metformin)	45	9.3 ± 0.8	–0.9 ± 0.2

Negative between-group differences favor sitagliptin over placebo

BMI = body mass index; HOMA-β = homeostasis model assessment of β-cell function; HOMA-IR = homeostasis model assessment of insulin resistance; LS, least-squares

Table 4. *Additional glycemic endpoints measured at week 18*

Endpoint	*n*	Absolute value, mean ± SD		Change from baseline, LS-mean (95%CI)	Between-group difference in LS-means (95 %CI)
		Baseline	Week 18		
Fasting insulin, µIU/mL					
Placebo (+ metformin)	65	9.5 ± 6.7	9.5 ± 6.5	–0.3 (–1.8, 1.2)	1.6 (–0.5, 3.6)
Sitagliptin (+ metformin)	74	10.6 ± 11.3	11.7 ± 8.3	1.2 (–0.2, 2.6)	
Fasting proinsulin, pmol/L					
Placebo (+ metformin)	63	28.3 ± 22.8	27.5 ± 26.5	–1.9 (–6.7, 2.9)	–0.3 (–6.9, 6.2)
Sitagliptin (+ metformin)	74	32.1 ± 25.1	29.8 ± 20.9	–2.2 (–6.7, 2.2)	
Fasting proinsulin-to-insulin ratio					
Placebo (+ metformin)	60	0.51 ± 0.26	0.51 ± 0.29	–0.03 (–0.08, 0.03)	–0.09 (–0.17, –0.02)*
Sitagliptin (+ metformin)	72	0.61 ± 0.32	0.48 ± 0.24	–0.12 (–0.17, –0.07)*	
Fasting C-peptide, ng/mL					
Placebo (+ metformin)	65	2.9 ± 1.4	2.9 ± 1.1	–0.1 (–0.4, 0.1)	0.5 (0.2, 0.9)*
Sitagliptin (+ metformin)	73	3.2 ± 1.5	3.6 ± 1.4	0.4 (0.2, 0.6)*	
PPG total AUC, mmol · h/L					
Placebo (+ metformin)	73	30.0 ± 5.6	28.3 ± 7.7	–1.7 (–3.1, –0.2)‡	–5.0 (–7.0, –3.0)*
Sitagliptin (+ metformin)	78	29.6 ± 6.7	23.3 ± 6.3	–6.7 (–8.1, –5.3)*	
Postprandial insulin total AUC, µIU · h/mL					
Placebo (+ metformin)	63	48.6 ± 26.2	50.8 ± 28.5	1.7 (–4.8, 8.2)	7.5 (–1.4, 16.5)
Sitagliptin (+ metformin)	70	50.2 ± 38.7	60.0 ± 41.2	9.3 (3.0, 15.5)†	
Postprandial total AUC insulin-to-glucose ratio					
Placebo (+ metformin)	60	1.67 ± 0.94	1.91 ± 1.17	0.20 (–0.14, 0.56)	0.77 (0.29, 1.24)†
Sitagliptin (+ metformin)	68	1.93 ± 1.78	2.90 ± 2.27	0.97 (0.63, 1.30)*	
Postprandial C-peptide total AUC, ng · h/mL					
Placebo (+ metformin)	63	9.3 ± 3.8	9.4 ± 2.9	0.0 (–0.7, 0.7)	1.6 (0.7, 2.6)*
Sitagliptin (+ metformin)	69	9.9 ± 4.0	11.4 ± 4.5	1.6 (1.0, 2.3)*	
HOMA-β					
Placebo (+ metformin)	65	29.1 ± 21.9	31.6 ± 23.3	2.5 (–3.4, 8.4)	14.5 (6.3, 22.6)*
Sitagliptin (+ metformin)	74	28.9 ± 28.1	46.0 ± 35.8	17.0 (11.3, 22.6)*	
HOMA-IR					
Placebo (+ metformin)	65	4.5 ± 3.3	4.3 ± 3.1	–0.6 (–1.3, 0.2)	0.2 (–0.8, 1.3)
Sitagliptin (+ metformin)	74	5.5 ± 6.4	5.0 ± 4.0	–0.3 (–1.0, 0.4)	
QUICKI					
Placebo (+ metformin)	65	0.32 ± 0.03	0.32 ± 0.03	0.00 (–0.01, 0.01)	0.00 (–0.01, 0.01)
Sitagliptin (+ metformin)	74	0.32 ± 0.04	0.32 ± 0.04	0.00 (–0.004, 0.01)	

*$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$

AUC = area under the curve; FPG = fasting plasma glucose; HOMA-β = homeostasis model assessment of β-cell function; HOMA-IR = homeostasis model assessment of insulin resistance; LS = least-squares; nd = not determined; PPG = postprandial plasma glucose; SD = standard deviation

or in the incidence of prespecified gastrointestinal AEs (abdominal pain, diarrhea, nausea, vomiting) (Table 6).

The number of patients who had at least one laboratory AE was higher in the sitagliptin group (15.6%) than in the placebo group (4.3%) (Table 5). There was no discernible pattern of particular AEs with a higher rate, with the exception of decreased hemoglobin, which was reported in four (4.2%) patients in the sitagliptin group and none in the placebo group. Three of the four patients with decreased hemoglobin had illnesses that predisposed to blood loss (uterine myoma, intestinal parasitosis, and active gastric ulcer), and in the fourth patient, the hemoglobin level returned to values near baseline in subsequent measurements, continuing on sitagliptin treatment. None of the laboratory AEs was considered serious or drug-related by the investigators. There was also a higher incidence of hemoglobin values that met the predefined limit of change (PDLC) criterion for a decrease of ≥ 1.5 g/dL in the last value in the sitagliptin group (seven patients [7.4%] compared to placebo (one patient [1.1%]). Of these seven patients, two were reported to have a laboratory AE of decreased hemoglobin (see above), and two other patients had high baseline hemoglobin values, with subsequent normal values, but meeting the PDLC criterion. For the other three patients, the decrease occurred gradually and was modest, ranging from –1.5 to –1.9 g/dL. No meaningful decrease in mean hemoglobin was seen in either treatment group (at week 30, –0.07 ± 0.01 g/dL vs. –0.14 ± 0.07 g/dL in the sitagliptin and placebo groups, respectively). No notable changes in other serum chemistry or hematology analyses were observed during the study.

In the sitagliptin group, two patients were discontinued for laboratory AEs due to values meeting pre-specified discontinuation criteria: one patient experienced a slight increase in serum creatinine above the pre-specified discontinuation criterion of ≥ 1.5 mg/dL (with a return to values < 1.5 mg/dL immediately after discontinuation), and one other patient, in whom alanine aminotransferase (ALT) values were progressively increasing during the run-in period, discontinued due to ALT values > 3 times the upper limit of normal. Neither of these laboratory

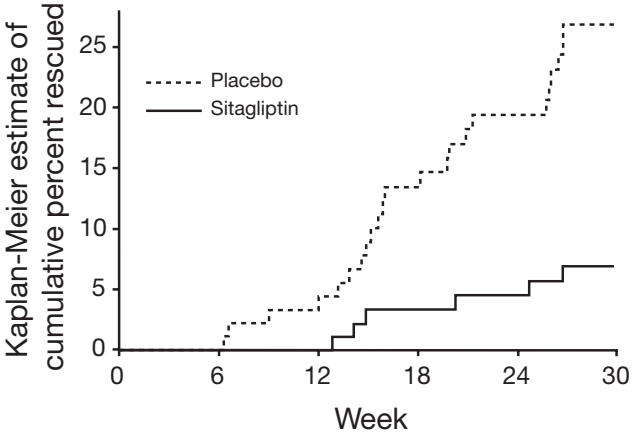

Figure 5. *Kaplan–Meier plots illustrating the incidence and timing of the 23 and 6 glycemic rescues initiated during double-blind treatment of patients in the placebo and sitagliptin groups, respectively. As prespecified, the FPG threshold for initiating rescue was lowered from 15.6 to 13.9 mmol/L at week 9, and from 13.9 to 12.2 mmol/L at week 18 (Figure 1)*

Table 5. *Summary of the incidence of adverse events (AEs) observed during the 30-week period of study*

Safety category	Placebo + metformin (*n* = 94)	Sitagliptin + metformin (*n* = 96)
Had one or more clinical AE	56 (59.6)	55 (57.3)
Had one or more drug-related* clinical AE	4 (4.3)	5 (5.2)
Had one or more serious clinical AE	5 (5.3)	0
Had one or more serious, drug-related* clinical AE	0	0
Had one or more laboratory AE	4 (4.3)	15 (15.6)
Had one or more drug-related* laboratory AE	0	0
Had one or more serious laboratory AE	0	0
Had one or more serious, drug-related* laboratory AE	0	0
Discontinued due to clinical AE	2 (2.1)	0
Discontinued due to laboratory AE	0	2 (2.1)
Died	1 (1.1)	0

*Considered by the investigator to be possibly or probably drug related
Data are number of patients (percent of total)
AE = adverse event/events

Table 6. *Numbers of patients having specific adverse events (AEs) that were either of prespecified interest or were reported with incidence ≥ 3% during the 30-week period of study*

Specific AE	Placebo (n = 94)	Sitagliptin (n = 96)
Hypoglycemia	0*	1 (1.0)
Prespecified gastrointestinal clinical AEs	7 (7.4)	10 (10.4)
Abdominal pain	0	2 (2.1)
Nausea	2 (2.1)	2 (2.1)
Vomiting	1 (1.1)	0
Diarrhea	5 (5.3)	6 (6.3)
Other clinical AEs		
Angina pectoris	0	3 (3.1)
Gastritis	3 (3.2)	2 (2.1)
Influenza	3 (3.2)	1 (1.0)
Nasopharyngitis	7 (7.4)	7 (7.3)
Pharyngitis	6 (6.4)	4 (4.2)
Pharyngotonsillitis	1 (1.1)	3 (3.1)
Respiratory tract infection	3 (3.2)	0
Tinea pedis	2 (2.1)	4 (4.2)
Urinary tract infection	3 (3.2)	4 (4.2)
Blood glucose increased†	15 (16.0)	6 (6.3)
Hyperglycemia‡	3 (3.2)	0
Pain in extremity	2 (2.1)	3 (3.1)
Diabetic neuropathy	2 (2.1)	4 (4.2)
Headache	4 (4.3)	4 (4.2)
Hypertension	4 (4.3)	2 (2.1)
Laboratory AEs		
Hemoglobin decreased	0/91	4/95 (4.2)
Urine bacteria increased	0/17	1/22 (4.5)
Creatinine renal clearance decreased	1/4 (25.0)	0/1

Data are number of patients (percent of total). The format 'n/m' is used for laboratory AEs, where 'm' indicates the number of patients for whom a post-baseline measurement was recorded. Multiple occurrences in the same patient are counted once within any specific AE category, but the same patient may be counted more than once in different specific categories.
*Excludes one patient in whom hypoglycemia occurred while on glipizide rescue therapy
†Asymptomatic increase in blood glucose observed by fingerstick test
‡Presence of symptoms of hyperglycemia (with or without confirmation by blood test)
AE = adverse event

measurements that led to discontinuation was considered drug-related.

Over the 30-week treatment period, a small decrease in mean body weight of 0.5 kg was seen in both groups, reflected also as a minimal decrease in BMI. Little or no change was observed in other vital signs.

Discussion

This study was designed to provide an assessment of the efficacy and safety of sitagliptin 100 mg once-daily when added to the treatment regimen of patients with T2DM and moderately severe hyperglycemia on metformin monotherapy. Results demonstrated that sitagliptin provided statistically significant ($p < 0.001$) and clinically meaningful improvement from baseline in HbA_{1c}, with a placebo-subtracted reduction of –1.0% observed after 18 and 30 weeks of treatment. The larger improvement in HbA_{1c} observed in the present study in patients with moderately severe baseline hyperglycemia, relative to that seen in a prior report of add-on to metformin treatment with sitagliptin (–0.65% in patients with a mean baseline HbA_{1c} of 8%[17]), is consistent with the impact of baseline severity of hyperglycemia on

absolute extent of reduction in HbA_{1c}, as discussed in a recent meta-analysis[21]. Within the present study, patients with higher baseline HbA_{1c} also trended towards larger reductions in HbA_{1c} – with patients in whom HbA_{1c} was > 10.0% at baseline reaching a reduction relative to placebo of –1.8% at week 18. A recent study[22] suggests an additional basis for the good efficacy of sitagliptin added to ongoing metformin therapy. In that study, metformin was shown to increase total GLP-1 and active GLP-1 levels, likely by increased release of this peptide, and sitagliptin increased active but not total GLP-1 levels, consistent with the expected effect of DPP-4 inhibition to prolong and increase active incretin levels by reducing metabolism of this peptide. When treatment with sitagliptin and metformin was combined, active GLP-1 was increased to a greater extent than with either agent alone. These complementary effects on the incretin axis, with further augmentation of active GLP-1 concentrations, could also explain the good efficacy observed when these agents are combined.

As has previously been described, this study confirmed substantial improvements in FPG and PPG with sitagliptin treatment. The decrease in FPG likely is reflective of a decrease in overnight hepatic glucose production, as excess hepatic glucose production tightly correlates with FPG in patients with T2DM[23]. The improvement in fasting and postprandial glucose likely reflects both basal and post-meal augmentation of incretin activity, with an improvement in the ratio of insulin to glucagon leading to enhanced glucose disposal and diminished hepatic glucose release. However, glucagon was not measured in this trial to confirm its potential role in post-meal glucose lowering. Significant improvements in indices of insulin secretion and β-cell function were observed in this study, including increases in HOMA-β ($p < 0.001$), measures of C-peptide (fasting and postprandial total AUC, both $p < 0.001$), the postprandial insulin-to-glucose ratio total AUC ($p < 0.01$), and the fasting proinsulin-to-insulin ratio ($p < 0.001$). The latter is a marker that is believed to rise when there is less efficient insulin processing by β-cells that are under stress[24,25]. It is elevated in patients with prediabetes, and increases with increasing severity of diabetes. In contrast, markers of insulin resistance were not significantly improved in this study, consistent with the observation that incretins target insulin secretion and do not alter insulin resistance[26].

Sitagliptin was generally well-tolerated in this study. There were few events of hypoglycemia with sitagliptin treatment. This low incidence, despite the marked improvement in glycemic control, is consistent with the observation that the glucose-lowering effects of GLP-1 and GIP are glucose-dependent[27]. In addition, there was no evident exacerbation of gastrointestinal AEs either overall or of a type typically associated with metformin therapy. Since GLP-1 therapy, such as with a GLP-1 analogue, is associated with gastrointestinal complaints such as nausea or diarrhea[28], the lack of an increase in such complaints with sitagliptin likely reflects the high physiological rather than pharmacological concentrations of this incretin that are reached with DPP-4 inhibition. With sitagliptin, there was a higher incidence of laboratory AEs of decreased hemoglobin and a higher number of patients with a decrease in hemoglobin meeting PDLC criteria. However, there was no meaningful difference in mean change in hemoglobin between groups. Moreover, the events of decreased hemoglobin observed were generally modest and tended to occur in patients with concomitant illnesses that could lower hemoglobin levels. In prior larger studies of sitagliptin treatment, including use as add-on to metformin, no notable differences were observed in the incidence of AEs of decreased hemoglobin or anemia, or in decreased hemoglobin that exceeded PLDC criteria[17,18].

Consistent with previous studies, in which sitagliptin has generally demonstrated a neutral effect on body weight[29], no meaningful between-group difference in body weight change was observed at the end of the 30-week treatment period, despite substantial improvement in glycemic control. Since glycemic control usually results in weight gain, the lack of an increase in weight may suggest that sitagliptin has a modest tendency to reduce weight counterbalanced in this study by the tendency of improved glycemic control to lead to weight gain[30].

The present study had some limitations. This was an evaluation of sitagliptin in patients with disease severity that fell within a specifically targeted range, and conclusions must be limited to the patient population studied. Previous studies have shown that sitagliptin is effective and well-tolerated as an add-on to metformin in patients with T2DM that is less severe[17] (with there being considerable overlap in T2DM severity between the prior and present studies). There are presently no data characterizing the effects of sitagliptin as an add-on therapy in patients who have a baseline HbA_{1c} > 11%, although there is published information on this population treated with the initial combination of sitagliptin plus metformin[31]. Another limitation of this study was that the period of treatment was relatively brief, compared with the natural history of T2DM, and conclusions

about the longer term efficacy and safety of sitagliptin plus metformin must await the results of long-term trials that are currently ongoing.

Conclusions

In patients with T2DM who had moderately severe hyperglycemia inadequately controlled by metformin alone, the addition of sitagliptin 100 mg once-daily provided significant and sustained improvements in HbA_{1c} and other glycemic endpoints, including FPG and 2-h PPG. In addition, sitagliptin provided statistically significant improvements in markers of β-cell function. Overall, the addition of sitagliptin to ongoing metformin therapy was well-tolerated with neutral effects on body weight relative to placebo, low incidence of hypoglycemia, and no worsening of gastrointestinal adverse events.

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