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ARTICLE

Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus

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Abstract
Aims/hypothesis The aim of this study was to assess the efficacy and safety of sitagliptin (MK-0431) as monotherapy in patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA_{1c} ≥7% and ≤10%) on exercise and diet.
Methods A total of 521 patients aged 27–76 years with a mean baseline HbA_{1c} of 8.1% were randomised in a 1:2:2 ratio to treatment with placebo, sitagliptin 100 mg once daily, or sitagliptin 200 mg once daily, for 18 weeks. The efficacy analysis was based on an all-patients-treated population using an analysis of covariance, excluding data obtained after glycaemic rescue.
Results After 18 weeks, HbA_{1c} was significantly reduced with sitagliptin 100 mg and 200 mg compared with placebo (placebo-subtracted HbA_{1c} reduction: −0.60% and −0.48%, respectively). Sitagliptin also significantly decreased fasting plasma glucose relative to placebo. Patients with higher baseline HbA_{1c} (≥9%) experienced greater placebo-subtracted HbA_{1c} reductions with sitagliptin (−1.20% for 100 mg and −1.04% for 200 mg) than those with HbA_{1c} <8% (−0.44% and −0.33%, respectively) or ≥8% to 8.9% (−0.61% and −0.39%, respectively). Homeostasis model assessment beta cell function index and fasting proinsulin: insulin ratio, markers of insulin secretion and beta cell function, were significantly improved with sitagliptin. The incidence of hypoglycaemia and gastrointestinal adverse experiences was not significantly different between sitagliptin and placebo. Sitagliptin had a neutral effect on body weight.
Conclusions/interpretation Sitagliptin significantly improved glycaemic control and was well tolerated in patients with type 2 diabetes mellitus who had inadequate glycaemic control on exercise and diet.

Keywords Diabetes · Dipeptidyl peptidase-4 · DPP-4 · Glucagon-like peptides · Incretins · MK-0431 · Sitagliptin

Abbreviations

APT	all patients treated
CK	creatine phosphokinase
DPP-4	dipeptidyl peptidase-4
FPG	fasting plasma glucose
GIP	glucose-dependent insulinotrophic polypeptide
GLP-1	glucagon-like peptide-1
HOMA-β	homeostasis model assessment beta cell function index
HOMA-IR	homeostasis model assessment insulin resistance index
LS	least-squares
OHA	oral antihyperglycaemic agent

Electronic supplementary material Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s00125-006-0416-z and is accessible to authorised users.

For the Sitagliptin Study 023 Group see electronic supplementary material for list of study investigators.

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Introduction

Sitagliptin (MK-0431) is an orally active, potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor in development for the treatment of patients with type 2 diabetes mellitus [1]. Sitagliptin acts through increasing active incretin hormone concentrations. Following ingestion of a meal, incretins, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotrophic polypeptide (GIP), attenuate the post-meal rise in glucose concentration and reduce fasting glucose concentrations [2]. Both GLP-1 and GIP are rapidly inactivated by the enzyme DPP-4 [3, 4]. In patients with type 2 diabetes, treatment with single doses of sitagliptin provided sustained 24-h inhibition of DPP-4 enzyme activity and increased active GLP-1 and GIP concentrations, leading to increases in insulin and C-peptide, reductions in glucagons and improvements in oral glucose tolerance [5]. Administration of the GLP-1 analogue, exenatide, and the DPP-4 inhibitors, NVP DPP728, P32/98, vildagliptin, and des-fluoro sitagliptin, in diabetic animal models has been shown to lead to improvements in beta cell function and/or neogenesis [6–10]. Improvements in beta cell function have also been observed with exenatide and vildagliptin in patients with type 2 diabetes [11–14]. In 12-week dose-range-finding studies (25–100 mg daily) in patients with type 2 diabetes mellitus, sitagliptin 100 mg was the most effective dose across various glycaemic parameters [15, 16]. The current study assessed the safety and efficacy of once-daily sitagliptin 100 mg and 200 mg in patients with type 2 diabetes mellitus with inadequate glycaemic control on diet and exercise.

Subjects and methods

Subjects

Men and women with type 2 diabetes mellitus, 18–75 years of age, were recruited. Patients not currently on oral antihyperglycaemic agent (OHA) therapy and patients on OHA monotherapy (or dual oral combination therapy in low doses) who could be taken off their OHA(s) during the run-in period, were eligible. Key exclusion criteria included type 1 diabetes, insulin therapy, significant hepatic or renal disease, hepatic transaminase or creatine phosphokinase (CK) levels ≥2 times the upper limit of normal, fasting plasma glucose (FPG) >15 mmol/l (270 mg/dl) and BMI <20 kg/m^2 or >43 kg/m^2. Patients received counselling on a diet consistent with American Diabetes Association recommendations at study entry.

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

Study design

This was a multinational, randomised, double-blind, placebo-controlled, parallel-group study. The current report presents the initial 18-week, placebo-controlled study period; patients completing this period were eligible to enter an active-controlled, double-blind period, which was ongoing at the time of this report and which will be the subject of a later publication. Patients who entered the study on OHA therapy had the agent(s) discontinued and underwent a wash-off and diet and exercise run-in period of up to 12 weeks, based upon their prior therapy and HbA_{1c} at study entry. Patients not on an OHA (for ≥8 weeks prior to screening visit) at study entry who met randomisation HbA_{1c} criteria directly entered the 2-week, single-blind placebo run-in period. Patients whose HbA_{1c} was ≥7% and ≤10% and who had adequate compliance (≥75%) during the single-blind run-in period were eligible to be randomised in a 1:2:2 ratio to receive placebo, sitagliptin 100 mg or sitagliptin 200 mg once daily for 18 weeks. During the double-blind treatment period, patients not meeting specific glycaemic limits were provided rescue therapy (metformin). The glycaemic rescue criteria were as follows: FPG >15.0 mmol/l (270 mg/dl) between randomisation (day 1) and the post-randomisation visit at week 6; FPG >13.3 mmol/l (240 mg/dl) after week 6 through to week 12; or FPG >11.1 mmol/l (200 mg/dl) after week 12 through to week 18. Patients on rescue therapy remained in the study to provide additional safety experience with sitagliptin treatment, but only data collected prior to rescue were included in the efficacy analyses (see Statistical analyses section below).

Study endpoints

Efficacy assessments The primary endpoint was HbA_{1c}; key secondary endpoints included FPG, insulin and proinsulin and lipids. Insulin was assayed using the Elecsys Insulin system (reportable range: 1.2–6,000 pmol/l; average CV of controls: 5.5%) [17]. Proinsulin was assayed using the Mercodia Pro-insulin EIA assay (reportable range: 1–132 pmol/l; average CV of controls: 5.7%) [18]. A subset of patients underwent a meal tolerance test at baseline (day 1/randomisation) and at week 18. The meal for this test consisted of a nutrition bar and drink (approximately 460 kcal; 75 g of carbohydrate, 9 g of fat and 18 g of protein). Key postprandial endpoints included 2-h post-meal glucose, insulin and C-peptide, and 3-h post-meal glucose, insulin, C-peptide, and insulin and glucose AUCs.

Safety assessments Data for adverse experiences, physical examinations, vital signs, ECGs, and body weight were collected throughout the study. All adverse experiences were rated by the investigators for relationship to study treatment according to the following categories: definitely not, probably not, possibly, probably or definitely. Adverse experiences assessed as possibly, probably or definitely related were grouped as drug-related. Laboratory safety was collected during the study and included blood chemistry (including alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, CK and creatinine), haematology and urinalysis.

Statistical analyses

All efficacy analyses were based on the all-patients-treated (APT) cohort that consisted of randomised patients who had at least one dose of study treatment and both a baseline and at least one post-baseline measurement. Only efficacy data collected prior to rescue were included in the efficacy analysis. An analysis of covariance model was used to compare the treatment groups for the continuous efficacy parameters, focusing on change from baseline (day 1/randomisation) at week 18. The model included terms for baseline values and the presence/absence of prior OHA therapy. Missing data were handled using the last observation carried forward method. The primary hypothesis regarding a significant benefit of sitagliptin compared with placebo in decreasing HbA_{1c} was assessed using a closed testing procedure. First, the statistical significance of the difference in the least-squares (LS) means of sitagliptin 100 mg vs placebo was determined, and, if significant ($p<0.05$, two-sided), the same comparison was made between sitagliptin 200 mg and placebo. Subgroup analyses of HbA_{1c} effect by pre-specified baseline factors were also performed. The proportion of patients requiring metformin rescue therapy was determined for each treatment group.

Safety and tolerability were assessed by reviewing adverse experiences, laboratory parameters, body weight, vital signs and ECGs. Continuous safety endpoints were analysed via analysis of covariance as described for the efficacy parameters. The analysis of safety parameters used a multi-tiered, all-patients-as-treated approach. For the clinical adverse experiences of hypoglycaemia, and pre-specified, selected gastrointestinal adverse experiences of nausea, vomiting, diarrhoea and abdominal pain, and for change from baseline in body weight, between-group differences were tested for statistical significance. For other adverse experiences and predefined limits of change in laboratory variables, the between-group differences and associated 95% CIs were provided. The analyses of body weight and gastrointestinal adverse experiences excluded data obtained after patients received rescue therapy.

Results

Disposition, baseline demographics and disease characteristics The overall disposition of patients during the placebo-controlled period is shown in Electronic supplementary material (ESM) Fig. 1. Of the 1,387 patients screened, 866 did not meet inclusion or met exclusion criteria. Of the 521 randomised patients, the treatment groups were generally well balanced for baseline demographics and glycaemic efficacy variables (ESM Table 1). For the entire study population, the average duration of diabetes was 4.5 years, average baseline HbA_{1c} was 8.1% (range: 6.2–10.5%, with 51% of patients having baseline HbA_{1c} <8%), and the average baseline FPG was 10.1 mmol/l (182.2 mg/dl). A total of 463 (88.9%) patients completed 18 weeks of treatment, and 495 (95.0%) patients were included in the APT analysis. Of the 26 randomised patients excluded from the APT analysis, five had no baseline data and 21 had no on-treatment data. There were no clinically meaningful differences among treatment groups in the percentage of patients who completed or discontinued from the study. The proportions of patients requiring metformin rescue therapy during the 18-week study were 8.8% (n=18), 11.7% (n=24) and 17.3% (n=19) for the sitagliptin 100 mg, sitagliptin 200 mg and placebo groups, respectively.

Efficacy At week 18, treatment with sitagliptin at both the 100 mg and 200 mg doses led to a significant ($p<0.001$) reduction from baseline in HbA_{1c} compared with placebo (Table 1). Relative to placebo, HbA_{1c} was reduced by −0.60% (95% CI −0.82 to −0.39) with sitagliptin 100 mg and by −0.48% (−0.70 to −0.26) with 200 mg. After the nadir was reached at week 12, the mean change from baseline over time in HbA_{1c} rose slightly in the sitagliptin 200 mg and placebo groups, while the mean change from baseline in HbA_{1c} appeared stable after week 12 in the sitagliptin 100 mg group (Fig. 1).

Sitagliptin, at both doses studied, led to a significantly ($p\leq0.001$) higher proportion (35.8% with 100 mg and 28.6% with 200 mg) of patients achieving an HbA_{1c} <7% at week 18 compared with placebo (15.5%).

In general, the HbA_{1c}-lowering effects of sitagliptin 100 mg and 200 mg at week 18 were consistent among subgroups defined by sex, age, race, baseline BMI, baseline homeostasis model assessment insulin resistance index (HOMA-IR), baseline homeostasis model assessment beta cell function index (HOMA-β), prior use of OHAs, and baseline metabolic syndrome status. Patients with a baseline duration of diabetes at or below the median

(≤3.0 years) had a greater HbA_{1c} reduction with sitagliptin (placebo-subtracted LS mean [95% CI] HbA_{1c} reductions at week 18 for 100 mg and 200 mg were −0.90% [−1.21 to −0.60] and −0.70% [−1.00 to −0.39], respectively) than those with a baseline duration of diabetes >3.0 years (−0.28% [−0.59 to 0.20] and −0.28% [−0.58 to 0.03] for the sitagliptin 100 mg and 200 mg groups, respectively; p=0.019 for treatment-by-subgroup interaction).

Patients with higher baseline HbA_{1c} (≥9%) experienced numerically greater mean placebo-subtracted reductions in HbA_{1c} at week 18 with sitagliptin (−1.20% for 100 mg, −1.04% for 200 mg) than those with baseline HbA_{1c} <8% (−0.44% for 100 mg, −0.33% for 200 mg) or those with baseline HbA_{1c} 8–8.9% (−0.61% for 100 mg, −0.39% for 200 mg); however, the treatment-by-subgroup interaction was not significant (p=0.087).

Sitagliptin treatment also led to significant (p<0.001) reductions at week 18 in FPG compared with placebo, with the FPG-lowering effect showing persistence over the 18 weeks of treatment (Table 1; Fig. 1).

The proinsulin:insulin ratio was significantly reduced with sitagliptin 100 mg, and HOMA-β was significantly improved with both sitagliptin doses, compared with placebo (Table 1). There were no significant treatment effects of sitagliptin on fasting insulin or proinsulin (Table 1), or on HOMA-IR, quantitative insulin sensitivity check index or lipid parameters examined (data not shown).

In the subset of patients (n=150) who underwent a meal tolerance test, treatment with sitagliptin at both doses at week 18 led to a significant decrease relative to placebo in 2-h post-meal glucose and 3-h post-meal glucose AUC, and significant increases in 2-h post-meal C-peptide, 3-h post-

Table 1 HbA_{1c} and fasting and postprandial glycaemic parameters

	n	Week 0, mean (SD)	Week 18, mean (SD)	LS change from week 0 at week 18, mean (95% CI)	Placebo-subtracted LS change from week 0 at week 18, mean (95% CI)
HbA_{1c} (%)					
Placebo	103	8.05 (0.90)	8.21 (1.35)	0.12 (−0.05 to 0.30)	
Sitagliptin 100 mg q.d.	193	8.04 (0.82)	7.58 (1.15)	−0.48 (−0.61 to −0.35)	−0.60 (−0.82 to −0.39)***
Sitagliptin 200 mg q.d.	199	8.14 (0.91)	7.81 (1.31)	−0.36 (−0.48 to −0.23)	−0.48 (−0.70 to −0.26)***
Fasting glycaemic parameters					
FPG (mmol/l)					
Placebo	107	10.2 (2.7)	10.6 (3.3)	0.4 (−0.1 to 0.9)	
Sitagliptin 100 mg q.d.	201	10.0 (2.4)	9.3 (3.0)	−0.7 (−1.1 to −0.4)	−1.1 (−1.7 to −0.5)***
Sitagliptin 200 mg q.d.	202	10.2 (2.5)	9.6 (3.2)	−0.6 (−0.9 to −0.2)	−0.9 (−1.5 to −0.3)**
Fasting insulin (pmol/l)					
Placebo	81	101.4 (72.0)	108.0 (103.2)	7.2 (−7.2 to 21.0)	
Sitagliptin 100 mg q.d.	168	86.4 (50.4)	90.6 (58.8)	4.2 (−5.4 to 13.8)	−2.4 (−19.8 to 14.4)
Sitagliptin 200 mg q.d.	173	94.8 (73.8)	97.8 (105.6)	3.6 (−6.0 to 13.2)	−3.6 (−20.4 to 13.2)
Fasting proinsulin (pmol/l)					
Placebo	77	42.3 (35.7)	44.2 (45.8)	2.9 (−2.5 to 8.2)	
Sitagliptin 100 mg q.d.	167	34.6 (28.1)	32.1 (31.6)	−2.9 (−6.5 to 0.8)	−5.7 (−12.2 to 0.8)
Sitagliptin 200 mg q.d.	168	36.6 (32.6)	34.5 (34.2)	2.0 (−5.7 to 1.6)	−4.9 (−11.4 to 1.6)
Proinsulin:insulin ratio					
Placebo	76	0.43 (0.23)	0.50 (0.69)	0.07 (−0.02 to 0.16)	
Sitagliptin 100 mg q.d.	162	0.42 (0.21)	0.37 (0.30)	−0.05 (−0.11 to 0.01)	−0.12 (−0.23 to −0.01)*
Sitagliptin 200 mg q.d.	166	0.42 (0.22)	0.40 (0.32)	−0.02 (−0.08 to 0.04)	−0.09 (−0.20 to 0.12)
HOMA-β					
Placebo	80	67.9 (56.6)	69.0 (63.9)	1.0 (−8.0 to 10.0)	
Sitagliptin 100 mg q.d.	168	53.3 (40.5)	65.4 (45.5)	12.1 (6.0 to 18.3)	11.2 (0.3 to 22.0)*
Sitagliptin 200 mg q.d.	171	56.4 (58.8)	69.5 (82.2)	13.0 (6.9 to 19.2)	12.0 (1.2 to 22.9)*
Postprandial glycaemic parameters[a]					
2-h post-meal glucose (mmol/l)					
Placebo	27	14.7 (3.7)	15.1 (4.9)	0.3 (−1.1 to 1.6)	
Sitagliptin 100 mg q.d.	62	14.6 (4.3)	12.5 (4.4)	−2.3 (−3.2 to −1.4)	−2.6 (−4.2 to −1.0)**
Sitagliptin 200 mg q.d.	61	15.5 (4.2)	12.7 (4.4)	−2.7 (−3.6 to −1.8)	−2.9 (−4.6 to −1.3)***
2-h post-meal insulin (pmol/l)					
Placebo	26	442.8 (484.2)	368.4 (426.6)	−43.8 (−118.2 to 30.6)	
Sitagliptin 100 mg q.d.	57	342.0 (263.4)	364.2 (298.2)	27 (−22.8 to 76.8)	70.8 (−16.2 to 158.4)
Sitagliptin 200 mg q.d.	59	306.0 (176.4)	312.0 (193.2)	−0.6 (−48.0 to 47.4)	43.8 (−44.4 to 131.4)

Table 1 (continued)

	n	Week 0, mean (SD)	Week 18, mean (SD)	LS change from week 0 at week 18, mean (95% CI)	Placebo-subtracted LS change from week 0 at week 18, mean (95% CI)
2-h post-meal C-peptide (nmol/l)					
Placebo	27	2.5 (0.9)	2.3 (1.2)	−0.2 (−0.4 to 0.1)	
Sitagliptin 100 mg q.d.	60	2.4 (0.9)	2.6 (1.0)	0.2 (−0.0 to 0.3)	0.3 (0.0 to 0.6)*
Sitagliptin 200 mg q.d.	61	2.3 (0.8)	2.5 (0.9)	0.2 (0.0 to 0.4)	0.4 (0.1 to 0.7)**
3-h post-meal glucose AUC (mmol·h·l^{-1})					
Placebo	27	42.0 (9.4)	43.4 (12.9)	1.1 (−2.4 to 4.5)	
Sitagliptin 100 mg q.d.	63	41.3 (10.7)	36.2 (11.3)	−5.7 (−7.9 to −3.4)	−6.7 (−10.7 to −2.7)***
Sitagliptin 200 mg q.d.	61	43.8 (10.6)	36.9 (10.6)	−6.6 (−8.9 to −4.3)	−7.6 (−11.7 to −3.6)***
3-h post-meal insulin AUC (pmol·h·l^{-1})					
Placebo	27	1,213.8 (1345.2)	1,000.2 (1123.2)	−141.6 (−289.8 to 6.0)	
Sitagliptin 100 mg q.d.	54	844.8 (506.4)	925.8 (604.2)	72.6 (−31.8 to 177.0)	214.2 (38.4 to 390.6)*
Sitagliptin 200 mg q.d.	55	828.0 (386.4)	826.8 (394.8)	−15.6 (−116.4 to 84.6)	126.0 (−51.0 to 303.0)
3-h post-meal C-peptide AUC (nmol·h·l^{-1})					
Placebo	27	6.5 (3.2)	6.1 (3.0)	−0.4 (−0.9, 0.2)	
Sitagliptin 100 mg q.d.	60	5.9 (2.0)	6.5 (2.4)	0.8 (0.1 to 0.9)	0.9 (0.2 to 1.5)*
Sitagliptin 200 mg q.d.	62	5.8 (2.0)	6.4 (2.2)	0.8 (0.1 to 0.9)	0.9 (0.2 to 1.5)*
3-h post-meal insulin:glucose AUC ratio					
Placebo	27	0.30 (0.37)	0.26 (0.37)	−0.03 (−0.08, 0.01)	
Sitagliptin 100 mg q.d.	54	0.21 (0.16)	0.27 (0.21)	0.06 (0.03 to 0.09)	0.09 (0.04 to 0.15)***
Sitagliptin 200 mg q.d.	54	0.19 (0.11)	0.23 (0.15)	0.05 (0.02 to 0.08)	0.08 (0.03 to 0.13)**

***$p \leq 0.001$; **$p \leq 0.01$; *$p < 0.05$; [a] Meal tolerance test was performed in a subset of patients (n=150); To convert glucose from mmol/l to mg/dl, divide by 0.05551; *q.d.* once daily

meal C-peptide AUC and 3-h post-meal glucose:insulin AUC ratio (Table 1). Treatment with sitagliptin also led to an increase from baseline in 3-h post-meal insulin AUC, although this was only significant for the 100 mg dose (Table 1).

Safety and tolerability There were no meaningful differences among the three treatment groups in the incidence of overall, serious or drug-related clinical adverse experiences, including those that led to discontinuation (Table 2). There was no statistically significant difference in the incidence of hypoglycaemia between the placebo and sitagliptin groups (Table 2). The overall incidence of gastrointestinal adverse experiences was similar across all treatment groups (Table 2). There were no statistically significant differences in the incidences of the prespecified, selected gastrointestinal adverse experiences of abdominal pain, diarrhoea, nausea and vomiting between the placebo and sitagliptin groups (Table 2). Few specific adverse experiences occurred at more than a minimally higher incidence with sitagliptin compared with placebo—these included nasopharyngitis, back pain, osteoarthritis and pain in extremities (ESM Table 2).

No laboratory adverse experiences had a notably greater incidence among the treatment groups (ESM Table 2). No clinically meaningful differences were observed in mean changes from baseline or in the frequency of elevations in alanine aminotransferase, aspartate aminotransferase or CK among the treatment groups. A small mean increase was observed in white blood cell count, primarily due to a small increase (5–10%) in absolute neutrophil count for both sitagliptin doses relative to placebo. A small mean increase (~12 μmol/l) from baseline (~330 μmol/l) in uric acid, and a small decrease (5–10%) in alkaline phosphatase were also observed in both sitagliptin groups relative to placebo. No adverse experiences of hyperuricaemia or gout were reported. There were no meaningful differences for other laboratory assessments.

Similarly, no meaningful differences were observed between treatment groups in mean changes in vital signs or ECG data, including QTc intervals. After 18 weeks, only small differences in change in body weight were observed in the sitagliptin groups relative to placebo (LS mean changes [95% CI] from baseline for placebo, 100 mg and 200 mg were −0.7 kg [−1.3 to −0.1], −0.6 kg [−1.0 to −0.2] and −0.2 [−0.7 to 0.2], respectively).

Discussion

This study demonstrated that once-daily sitagliptin at doses of 100 mg and 200 mg provided clinically meaningful and statistically significant reductions in HbA_{1c} over 18 weeks compared with placebo in patients with type 2 diabetes mellitus with mild to moderate hyperglycaemia (baseline HbA_{1c} ~8%). Treatment with sitagliptin also provided

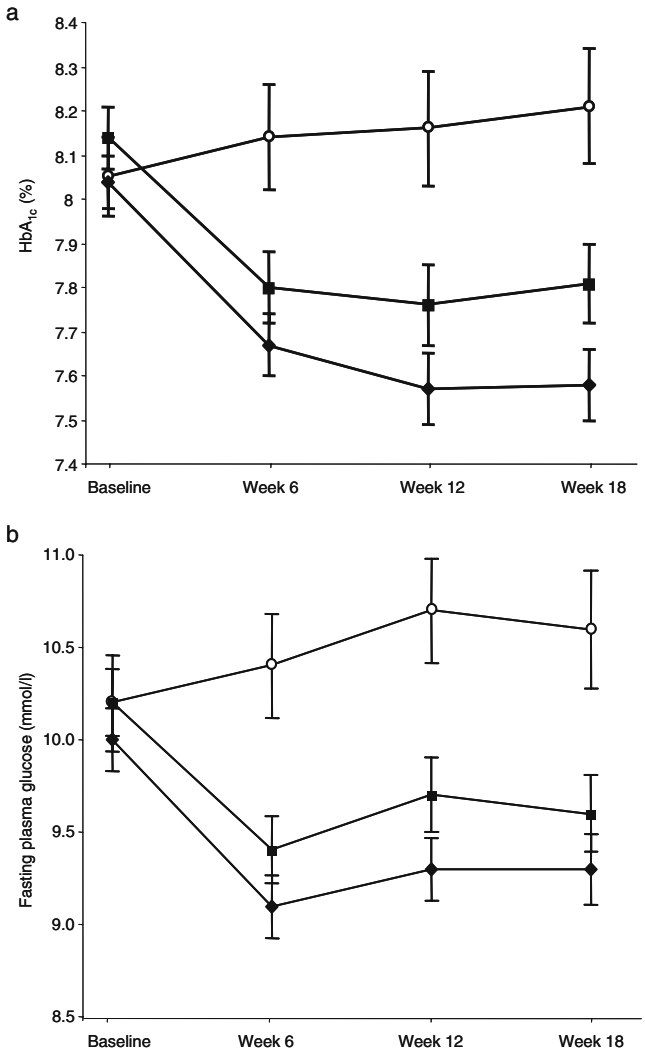

Fig. 1 Mean (±SEM) HbA_{1c} (**a**) and fasting plasma glucose (**b**) over time for placebo (*open circles*), once-daily sitagliptin 100 mg (*filled diamonds*) and once-daily sitagliptin 200 mg (*filled squares*) groups

significant improvements in the secondary glycaemic endpoints compared with placebo, including FPG, 2-h post-meal glucose and C-peptide, 3-h post-meal AUCs for glucose, C-peptide and insulin, and the 3-h post-meal insulin:glucose AUC ratio. Across all efficacy endpoints, only small differences in response between the 100 mg and 200 mg groups were observed—generally favouring the 100 mg group—indicating no advantage obtained in the efficacy of 200 mg over that of 100 mg. The reduction in post-meal glucose observed with sitagliptin treatment is consistent with enhancement of incretin levels post-meal. The reduction in FPG with sitagliptin is of interest and suggests that enhancement of active incretin concentrations in the fasting state also leads to glucose lowering. The rise in HOMA-β suggests improved fasting insulin secretion, which probably contributed to the observed reduction in FPG. Since hepatic glucose production is an important determinant of FPG, and since higher active GLP-1 levels lower glucagon concentrations, the likely mechanism of the lowered FPG with sitagliptin is that higher insulin secretion coupled with reduced glucagon levels leads to reduced overnight hepatic glucose production.

Sitagliptin led to a significantly higher proportion of patients achieving the glycaemic goal of HbA_{1c} <7% [19] compared with placebo. The HbA_{1c}-lowering response to sitagliptin was generally consistent across the subgroups examined. In this study, patients with a shorter duration of diabetes at baseline (≤3.0 years) had a significantly greater HbA_{1c}-lowering response to sitagliptin compared with those with a longer duration of diabetes, suggesting that earlier initiation of DPP-4 inhibitor therapy may provide a greater response. However, in a 24-week monotherapy trial of once-daily sitagliptin [20], this effect was not observed. In this study, severity of hyperglycaemia at baseline impacted the HbA_{1c}-lowering response; patients with higher baseline HbA_{1c} had numerically greater reductions in HbA_{1c} compared with those with lower baseline HbA_{1c}. The same finding was observed in the 24-week monotherapy trial with once-daily sitagliptin [20] and is a phenomenon observed with other antihyperglycaemic agents.

Loss of insulin secretion due to impaired beta cell function and mass occurs in patients with type 2 diabetes mellitus, suggesting that earlier initiation of DPP-4 inhibitor therapy may provide a greater response [21]. The improvements in HOMA-β, fasting proinsulin:insulin ratio, and 3-h post-meal insulin:glucose AUC ratio observed with sitagliptin in the present study suggests that sitagliptin improved certain parameters of beta cell function, consistent with preclinical findings as well as clinical studies with other DPP-4 inhibitors [6–8, 13, 14]. There was no significant effect of sitagliptin treatment compared with placebo on HOMA-IR, suggesting that sitagliptin may not affect peripheral insulin sensitivity.

Treatment with sitagliptin was well tolerated in this study. The incidence of hypoglycaemia in the sitagliptin groups was low and not significantly different from that seen in the placebo group. This is expected since it has been demonstrated that incretin stimulation of insulin secretion is glucose-dependent, i.e. it is not observed when glucose levels are low. Pharmacological therapy with GLP-1 has been associated with gastrointestinal adverse experiences, including nausea, vomiting and diarrhoea. Since sitagliptin increases the concentrations of active incretins, the potential for increased gastrointestinal adverse experiences with sitagliptin treatment was specifically assessed in this study. In the present study, the incidence of gastrointestinal adverse experiences was low and not significantly different from placebo. Treatment with sitagliptin had a neutral effect on body weight.

A limitation of this study was use of glycaemic rescue therapy when patients met progressively stricter glucose criteria, implemented to avoid exposure of patients to

Table 2 Safety summary

	Placebo (*N*=110), *n* (%)	Sitagliptin 100 mg q.d. (*N*=205), *n* (%)	Sitagliptin 200 mg q.d. (*N*=206), *n* (%)
All clinical adverse experiences	57 (51.8)	102 (49.8)	92 (44.7)
Drug-related clinical adverse experiences[a]	19 (17.3)	21 (10.2)	17 (8.3)
Serious adverse experiences	3 (2.7)	8 (3.9)	4 (1.9)
Drug-related serious adverse experiences	0	0	0
Discontinuations due to adverse experiences	4 (3.6)	5 (2.4)[b]	0
Discontinuations due to drug-related adverse experiences	3 (2.7)	1 (0.5)	0
Discontinuations due to serious adverse experiences	0	3 (1.5)	0
Discontinuations due to drug-related serious adverse experiences	0	0	0
Hypoglycaemia	0	3 (1.5)	2 (1.0)
Overall gastrointestinal adverse experiences[c]	16 (14.5)	25 (12.2)	19 (9.2)
Prespecified selected gastrointestinal adverse experiences[c]			
Abdominal pain	3 (2.7)	4 (2.0)	3 (1.5)
Diarrhoea	4 (3.6)	8 (3.9)	2 (1.0)
Nausea	0	2 (1.0)	3 (1.5)
Vomiting	1 (0.9)	0	1 (0.5)

[a] Determined by the investigator to be possibly, probably or definitely drug-related
[b] Includes one patient who discontinued during the initial placebo-controlled phase, and four patients who discontinued after completing this phase because of adverse experiences that had an onset during the placebo-controlled phase
[c] Excludes events that occurred after initiation of glycaemic rescue therapy with metformin
q.d. once daily

prolonged hyperglycaemia. Only efficacy data prior to rescue were used in the analysis; however, the use of rescue therapy could impact the estimation of glycaemic efficacy, especially as more patients in the placebo group were rescued. Nonetheless, since <20% of placebo patients required rescue, this is unlikely to be a source of substantial bias in estimation of efficacy.

In this study, there was a slight numerical benefit of sitagliptin 100 mg compared with 200 mg. In another monotherapy trial of once-daily sitagliptin that was similarly designed (except for a 24-week double-blind period) [20], there was a slight numerical benefit of 200 mg compared with 100 mg. Taken together, these data do not demonstrate a consistent benefit of sitagliptin 200 mg over 100 mg.

In conclusion, this 18-week study in patients with type 2 diabetes mellitus and inadequate glycaemic control on diet and exercise demonstrated that once-daily sitagliptin, at doses of 100 mg and 200 mg, provided statistically significant and clinically important reductions in HbA_{1c}, FPG and 2-h post-meal glucose, as well as significant improvements in indices of insulin secretion and beta cell function, including HOMA-β and fasting proinsulin:insulin ratio. Treatment with sitagliptin was well tolerated and was associated with a low rate of hypoglycaemia, which was not significantly different from placebo, as well as a neutral effect on body weight.

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