Effect of the Dipeptidyl Peptidase-4 Inhibitor Sitagliptin as Monotherapy on Glycemic Control in Patients With Type 2 Diabetes

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OBJECTIVE — To examine the efficacy and safety of once-daily oral sitagliptin as monotherapy in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — In a randomized, double-blind, placebo-controlled study, 741 patients (baseline HbA_{1c} [A1C] 8.0%) were randomized to sitagliptin 100 or 200 mg or placebo for 24 weeks.

RESULTS — Sitagliptin 100 and 200 mg produced significant ($P < 0.001$) placebo-subtracted reductions in A1C (−0.79 and −0.94%, respectively) and fasting plasma glucose (−1.0 mmol/l [−17.1 mg/dl] and −1.2 mmol/l [−21.3 mg/dl], respectively). Patients with baseline A1C ≥9% had greater reductions in placebo-subtracted A1C with sitagliptin 100 and 200 mg (−1.52 and −1.50%, respectively) than those with baseline A1C <8% (−0.57 and −0.65%) or ≥8 to <9.0% (−0.80 and −1.13%, respectively). In a meal tolerance test, sitagliptin 100 and 200 mg significantly decreased 2-h postprandial glucose (PPG) (placebo-subtracted PPG −2.6 mmol/l [−46.7 mg/dl] and −3.0 mmol/l [−54.1 mg/dl], respectively). Results for the above key efficacy parameters were not significantly different between sitagliptin doses. Homeostasis model assessment of β-cell function and proinsulin-to-insulin ratio improved with sitagliptin. The incidence of hypoglycemia was similar, and overall gastrointestinal adverse experiences were slightly higher with sitagliptin. No meaningful body weight changes from baseline were observed with sitagliptin 100 (−0.2 kg) or 200 mg (−0.1 kg). The body weight change with placebo (−1.1 kg) was significantly ($P < 0.01$) different from that observed with sitagliptin.

CONCLUSIONS — In this 24-week study, once-daily sitagliptin monotherapy improved glycemic control in the fasting and postprandial states, improved measures of β-cell function, and was well tolerated in patients with type 2 diabetes.

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Abbreviations: ANC, absolute neutrophil count; APT, all-patients-treated; AUC, area under the glucose concentration–time curve; DPP-4, dipeptidyl peptidase-4; ECG, electrocardiogram; FPG, fasting plasma glucose; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, HOMA of insulin resistance; OHA, oral antihyperglycemic agent; PPG, postprandial glucose; QUICKI, quantitative insulin sensitivity check index; WBC, white blood cell.

A table elsewhere in this issue shows conventional and Système Intenational (SI) units and conversion factors for many substances.

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Treatments that mimic or enhance the incretin axis are therapeutic approaches for managing type 2 diabetes (1). In response to a meal, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are released and, in turn, stimulate insulin and suppress glucagon release (both in a glucose-dependent manner), delay gastric emptying, and increase satiety (2–5). These incretins are rapidly degraded by dipeptidyl peptidase-4 (DPP-4) (6). DPP-4 inhibitors are a novel class of oral antihyperglycemic agents (OHAs) (7). By slowing incretin degradation, DPP-4 inhibitors enhance meal-stimulated active GLP-1 and GIP levels by two- to threefold (8–10). Studies in animal models of, and in patients with, type 2 diabetes demonstrated that treatment with DPP-4 inhibitors improves measures of β-cell function (8,11–13). In rodent models of type 2 diabetes, both GLP-1 and DPP-4 inhibitors led to β-cell neogenesis and survival (14,15). Long-term studies are required to determine whether these β-cell effects occur in patients with type 2 diabetes.

Sitagliptin, a once-daily, oral, potent, and highly selective DPP-4 inhibitor, inhibits plasma DPP-4 activity ≥80% over 24 h with single doses of ≥100 mg (10). In patients with type 2 diabetes, ≥80% inhibition of plasma DPP-4 activity with single doses of sitagliptin produced two- to threefold increases in active GLP-1 and GIP levels, increased insulin and C-peptide levels, reduced plasma glucagon levels, and reduced glycemic excursion following an oral glucose tolerance test (9). Two 12-week studies in patients with type 2 diabetes demonstrated that sitagliptin dose-dependently reduced HbA_{1c} (A1C) and fasting plasma glucose (FPG), with a neutral effect on body weight and incidences of hypoglycemia and gastrointestinal adverse experiences similar to placebo (16,17).

Sitagliptin 100 mg q.d. was the most effective dose and was selected for continued development. In the present study, we tested once-daily sitagliptin 100 and

200 mg as monotherapy to explore tolerability and potential dose-dependent efficacy in patients with inadequately controlled type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Patients, 18–75 years of age, on and not on an OHA were eligible. Patients with type 1 diabetes, unstable cardiac disease, significant renal impairment (creatinine clearance <50 ml/min), or elevated (more than twofold the upper limit of normal) alanine aminotransferase, aspartate aminotransferase, or creatine phosphokinase were excluded. Patients received counseling on exercise and a weight-maintenance diet consistent with American Diabetes Association recommendations throughout the study.

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.

This was a multinational, randomized, double-blind, placebo-controlled study. At screening, patients with an A1C of 7–10% and not on an OHA for ≥8 weeks were eligible to directly enter a 2-week single-blind placebo run-in period; patients with A1C >10% and not on an OHA entered a run-in period of up to 6 weeks; patients with an A1C of 6–10% and on an OHA discontinued the agent and entered a wash-out period of 6–10 weeks (8–12 weeks for those on thiazolidinediones). If A1C was 7–10% after the wash-out period, patients were eligible to enter the placebo run-in period. Patients with adequate compliance (≥75%) during the placebo run-in period underwent baseline evaluation and were randomized to sitagliptin 100 or 200 mg q.d. or placebo (1:1:1) for 24 weeks.

During the study, patients not meeting progressively stricter glycemic goals were provided rescue therapy (metformin) until study completion. Glycemic rescue criteria were FPG >15.0 mmol/l (270 mg/dl) between randomization (day 1) and week 6, FPG >13.3 mmol/l (240 mg/dl) after week 6 through week 12, or FPG >11.1 mmol/l (200 mg/dl) after week 12 through week 24. The study includes a long-term treatment period beyond week 24, the results of which will be the subject of a subsequent report.

Study evaluations

Efficacy assessments. After an overnight fast, A1C, FPG, insulin, proinsulin, and fasting lipids were measured at baseline (randomization visit) and during the study. Proinsulin-to-insulin ratio and homeostasis model assessment of β-cell function (HOMA-β) assessed β-cell function (18,19); HOMA of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) assessed insulin resistance (18,20).

A standard meal tolerance test was administered at baseline (before the first dose of study medication) and at weeks 12 and 24. Patients took study medication 30 min before the standard meal, which was ingested within 15 min and consisted of two nutrition bars and one nutrition drink (~680 kcal; 111 g carbohydrate, 14 g fat, 26 g protein). Plasma glucose, insulin, and C-peptide concentrations were measured at 0, 60, and 120 min from the meal start for the determination of 2-h postprandial glucose (PPG), area under the glucose concentration–time curve (AUC), insulin AUC, C-peptide AUC, and the insulin AUC–to–glucose AUC ratio.

Safety assessments. Data on adverse experiences, physical examinations, vital signs, electrocardiograms (ECGs), and body weight were collected. All adverse experiences were rated by investigators for intensity and relationship to study drug. Laboratory evaluations included complete blood chemistry, hematology, and urinalysis.

Laboratory measurements and ECGs were performed at central laboratories (PPD Global Central Labs, Highland Heights, KY, and Zaventem, Belgium and Covance Central Diagnostics, Reno, NV, respectively) by technicians blinded to treatment group.

Statistical analysis

Efficacy analyses were based on the all-patients-treated (APT) population, consisting of all randomized patients who received at least one dose of study treatment and who had both a baseline and at least one postbaseline measurement. ANCOVA was used to compare treatment groups for continuous efficacy parameters, focusing on change from baseline at week 24, with baseline values and prior OHA status as covariates. The between-group differences for efficacy end points were assessed by testing the difference in the least-squares mean change (or percentage of change) from baseline at week 24. Missing data were handled using the last observation carried forward method. To avoid the confounding influence of rescue therapy on efficacy comparisons, data collected after initiation of rescue therapy were treated as missing.

The proportion of patients achieving A1C <7% was compared among groups using a logistic regression analysis. Time-to-rescue analysis was performed using the Kaplan-Meier estimate and the log-rank test, and the proportion of patients rescued in each group was summarized. Prespecified subgroup analyses for the primary efficacy end point (A1C) were performed to explore whether treatment effects were consistent among subgroups, which included OHA status at screening (on or not on an OHA), baseline A1C (<8, 8 to <9, or ≥9%), sex, age (< or ≥65 years), race, baseline BMI (less than or equal to or more than the median), duration of diabetes (less than or equal to or more than the median), baseline HOMA-IR (less than or equal to or more than the median), and baseline HOMA-β (less than or equal to or more than the median).

Safety and tolerability were assessed in patients who received at least one dose of study medication by review of safety parameters. For body weight change and the prespecified clinical adverse experiences of hypoglycemia and specific gastrointestinal adverse experiences (abdominal pain, nausea, vomiting, and diarrhea), inferential testing was performed for between-group comparisons. Data for body weight change and the incidence of gastrointestinal adverse experiences excluded data obtained after initiation of rescue therapy.

RESULTS

— The disposition of screened and randomized patients is shown in online appendix Fig. 1 (available at http://care.diabetesjournals.org). For the 741 patients randomized to treatments, groups were generally well-balanced for baseline demographics and efficacy variables. Patients had mild to moderate hyperglycemia with an average baseline A1C of 8.0% (range 6.3–10.9; ~54% of patients <8.0%) and FPG of 9.6 mmol/l (173.7 mg/dl). The average duration of known diabetes was 4.4 years; 51% were not on an OHA at screening. After randomization, 639 (86.2%) completed 24 weeks of treatment, and 711 patients (96.0%) were included in the APT analysis. Of 30 patients excluded from the APT analysis, 2 had no baseline data, and 28 had no on-treatment data. More patients in the placebo group (52 [20.6%]) required rescue therapy than in

Table 1—*Baseline and week 24 mean A1C, FPG, proinsulin-to-insulin ratio, and HOMA-β and least-squares mean change from baseline to study end point with sitagliptin or placebo treatment*

	n	Week 0 (baseline) mean ± SD	Week 24 mean ± SD	Least-squares mean change from baseline (95% CI)
A1C (%)				
Placebo	244	8.03 ± 0.82	8.20 ± 1.37	0.18 (0.06 to 0.30)
Sitagliptin 100 mg q.d.	229	8.01 ± 0.88	7.39 ± 1.15	−0.61 (−0.74 to −0.49)*
Sitagliptin 200 mg q.d.	238	8.08 ± 0.94	7.31 ± 1.14	−0.76 (−0.88 to −0.64)*
FPG (mmol/l)				
Placebo	247	9.8 ± 2.3	10.0 ± 3.1	0.3 (−0.0 to 0.5)
Sitagliptin 100 mg q.d.	234	9.5 ± 2.4	8.8 ± 2.5	−0.7 (−1.0 to −0.4)*
Sitagliptin 200 mg q.d.	244	9.7 ± 2.5	8.7 ± 2.6	−0.9 (−1.2 to −0.7)*
Proinsulin-to-insulin ratio				
Placebo	220	0.44 ± 0.30	0.44 ± 0.28	−0.01 (−0.04 to 0.02)
Sitagliptin 100 mg q.d.	210	0.47 ± 0.82	0.37 ± 0.25	−0.08 (−0.11 to −0.05)†
Sitagliptin 200 mg q.d.	217	0.44 ± 0.48	0.34 ± 0.22	−0.11 (−0.14 to −0.07)*
HOMA-β				
Placebo	235	55.8 ± 52.1	56.3 ± 61.5	0.3 (−6.0 to 6.5)
Sitagliptin 100 mg q.d.	218	57.6 ± 71.7	70.9 ± 91.8	13.2 (6.7 to 19.7)†
Sitagliptin 200 mg q.d.	228	55.2 ± 53.4	68.4 ± 66.3	13.1 (6.8 to 19.5)†

*$P \leq 0.001$ for least-squares mean difference for sitagliptin 100 or 200 mg vs. placebo; †$P \leq 0.01$ for least-squares mean difference for sitagliptin 100 or 200 mg vs. placebo. P = NS for sitagliptin at 200- vs. 100-mg comparisons. (To convert glucose values from mmol/l to mg/dl, divide by 0.05551.)

the sitagliptin 100-mg (21 [8.8%]) or 200-mg (12 [4.8%]) groups ($P < 0.001$ for sitagliptin vs. placebo). Time to rescue was significantly longer with sitagliptin versus placebo.

At week 24, sitagliptin 100 and 200 mg significantly ($P < 0.001$) reduced A1C compared with placebo (between-group differences −0.79% [95% CI −0.96 to −0.62] and −0.94% [−1.11 to −0.77], respectively) (Table 1) without deterioration in the sitagliptin effect throughout 24 weeks (Fig. 1*A*). The percentage of patients achieving A1C <7% was 41% with 100 mg and 45% with 200 mg versus 17% for placebo ($P < 0.001$ for sitagliptin vs. placebo). The effect of sitagliptin on A1C was consistent across subgroups defined by demographic, anthropometric, and disease characteristics. A significant interaction between baseline A1C and treatment effect was observed ($P < 0.001$), which was consistent with the finding of greater efficacy in patients with higher baseline A1C. In patients with baseline A1C ≥9%, placebo-subtracted reductions of −1.52 and −1.50% were observed for the 100- and 200-mg treatment groups, respectively (Fig. 1*B*).

At week 24, sitagliptin treatment led to significant ($P < 0.001$) between-treatment differences versus placebo in FPG change from baseline of −1.0 mmol/l (−17.1 mg/dl) and −1.2 mmol/l (−21.3 mg/dl) for the 100- and 200-mg

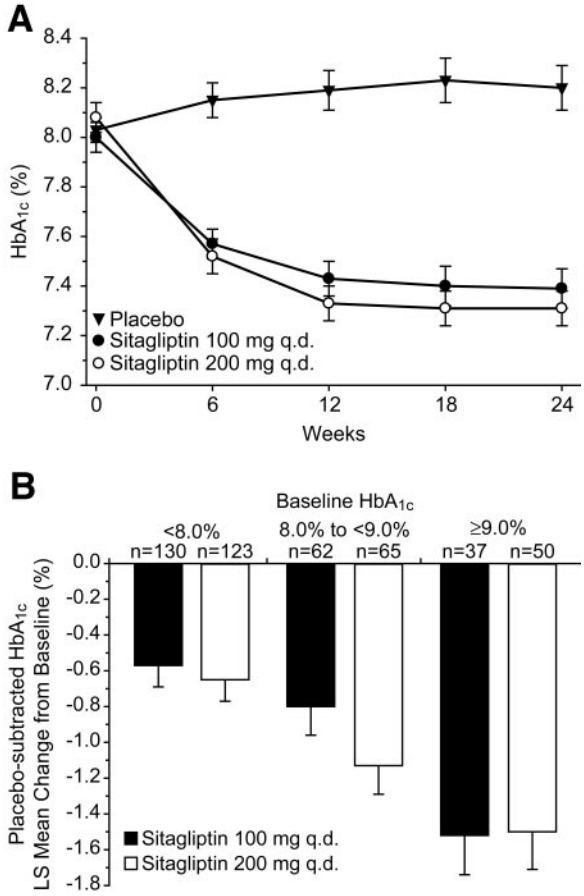

Figure 1—A*: A1C (means ± SE) over time during the 24-week treatment period for patients treated with sitagliptin 100 or 200 mg q.d. or with placebo.* B*: Placebo-subtracted least-squares (LS) mean change in A1C from baseline (±SE) by baseline A1C at study end point.*

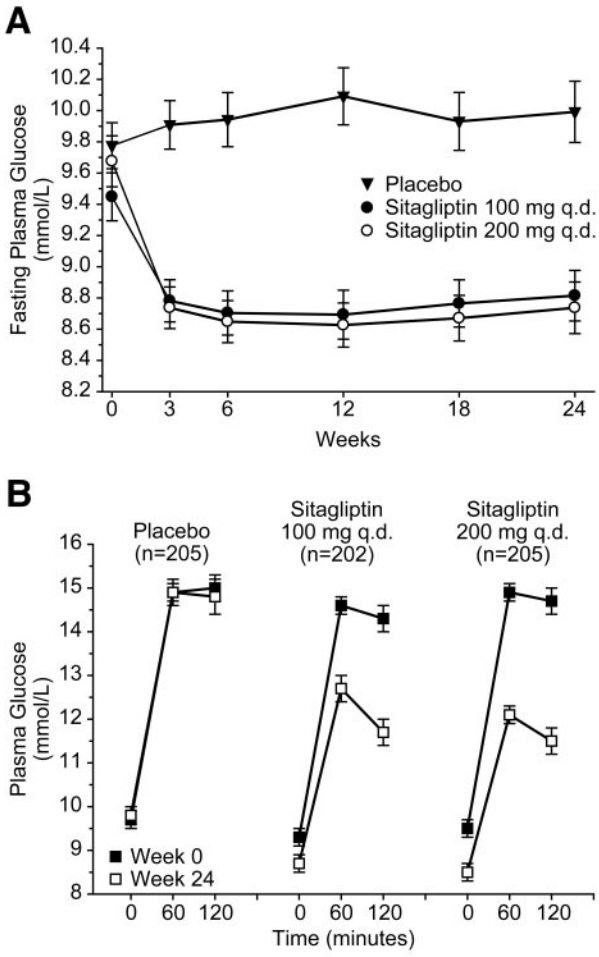

Figure 2—*Change in plasma glucose with treatments. A: Fasting plasma glucose (means ± SE) over time during the 24-week treatment period for patients treated with sitagliptin 100 or 200 mg q.d. or placebo. B: Plasma glucose response during a meal tolerance test at baseline and week 24 by treatment group (means ± SE).*

groups, respectively (Table 1). The effects on FPG were maintained over 24 weeks with a slight upward trend starting at week 12 (Fig. 2*A*).

Both proinsulin-to-insulin ratio and HOMA-β were significantly improved with sitagliptin versus placebo after 24 weeks (Table 1). There were no statistically significant effects on fasting C-peptide, insulin, proinsulin, HOMA-IR, or QUICKI. Sitagliptin had no significant effects on fasting lipids.

At week 24, the reduction in 2-h PPG from baseline was significantly ($P < 0.001$) greater with sitagliptin 100 mg (−2.7 mmol/l [−48.9 mg/dl]) and 200 mg (−3.1 mmol/l [−56.3 mg/dl]) than with placebo (−0.1 mmol/l [−2.2 mg/dl]) (online appendix Table 1 and Fig. 2*B*). Additionally, glucose total AUC was significantly ($P < 0.001$) decreased with sitagliptin versus placebo. Sitagliptin treatment significantly ($P < 0.05$) increased insulin total AUC, C-peptide total AUC, and ratio of insulin AUC to glucose AUC versus placebo (online appendix Table 1).

Safety and tolerability

There were no meaningful differences between groups in incidences of overall clinical adverse experiences or of those assessed as serious, drug-related, or leading to discontinuation (Table 2). Three patients had a serious drug-related adverse experience (one on placebo [discontinued for cholecystitis] and two on sitagliptin 100 mg, including one with

Table 2—*Safety summary of adverse experiences*

	Placebo	Sitagliptin 100 mg q.d.	Sitagliptin 200 mg q.d.
n	253	238	250
One or more clinical AE	167 (66.0)	157 (66.0)	160 (64.0)
Drug-related clinical AE*	19 (7.5)	23 (9.7)	27 (10.8)
Clinical SAE	9 (3.6)	12 (5.0)	12 (4.8)
Drug-related clinical SAE*	1 (0.4)	2 (0.8)	0 (0)
Discontinuation due to AE	4 (1.6)	5 (2.1)	4 (1.6)
Discontinuation due to drug-related AE	2 (0.8)	1 (0.4)	0 (0)
Discontinuation due to SAE	3 (1.2)	3 (1.3)	3 (1.2)
Discontinuation due to drug-related SAE	1 (0.4)	0 (0)	0 (0)
Hypoglycemia	2 (0.8)	3 (1.3)†	2 (0.8)
Overall gastrointestinal AE‡	29 (11.5)	39 (16.4)	41 (16.4)
Prespecified selected gastrointestinal AE‡			
Abdominal pain§	4 (1.6)	5 (2.1)	3 (1.2)
Nausea§	3 (1.2)	5 (2.1)	10 (4.0)
Vomiting§	3 (1.2)	3 (1.3)	2 (0.8)
Diarrhea§	6 (2.4)	11 (4.6)	10 (4.0)

Data are *n* (%). *Considered by investigator as possibly, probably, or definitely related to study drug; †includes one hypoglycemia episode occurring after initiation of glycemic rescue therapy (metformin); ‡excludes adverse experiences after initiating glycemic rescue therapy (metformin). §$P > 0.05$ for sitagliptin (100 or 200 mg) vs. placebo. AE, adverse experience; SAE, serious adverse experience.

mild nonalcoholic steatohepatitis with increased hepatic enzymes noted at discontinuation and one with mild diarrhea meeting criteria for a serious event due to temporal association with an overdose of two 100-mg tablets). Two other patients were discontinued for drug-related adverse experiences (one on placebo [tachycardia] and one on sitagliptin 100 mg [depression]).

The incidence of specific adverse experiences was generally similar across treatment groups. For specific adverse experiences with an incidence ≥2% in any treatment group, relatively few (constipation, nasopharyngitis, pharyngitis, pharyngolaryngeal pain, urinary tract infection, myalgia, arthralgia, hypertension, and dizziness) had a slightly higher incidence in one or both sitagliptin groups versus placebo (online appendix Table 2). None of the above adverse experiences resulted in study drug discontinuation.

The incidence of hypoglycemia was similar among groups (Table 2). No episode of hypoglycemia exhibited marked severity (i.e., loss of consciousness or requirement for medical assistance). The proportion of patients reporting gastrointestinal adverse experiences was slightly higher with sitagliptin versus placebo, but for the prespecified specific gastrointestinal adverse experiences, the incidences were not statistically significant between groups (Table 2).

For laboratory adverse experiences, there were no statistically or clinically meaningful differences among groups, and only a few specific laboratory adverse experiences had an incidence ≥2% in any treatment group (online appendix Table 2). At 24 weeks, mean percentages of change in white blood cells (WBCs) were 4.7, 4.2, and 0.6% in the 100-mg treatment, 200-mg treatment, and placebo groups, respectively. These small, nonprogressive increases in WBCs were mainly accounted for by small increases in absolute neutrophil counts (ANCs) (mean change ± SD) of 330 ± 91, 255 ± 89, and 36 ± 85 cells/μl in the 100-mg treatment, 200-mg treatment, and placebo groups, respectively. The incidence of patients with laboratory values meeting predefined limits of change for increases in ANC (last measured value on treatment with increase ≥20% above the upper limit of normal) was similar in the 100- and 200-mg treatment groups versus placebo (0.9, 0.8, and 0.4%, respectively). A small mean decrease in alkaline phosphatase was found with sitagliptin treatment (−3.8 and −3.3 IU/ml with 100 and 200 mg, respectively) versus placebo. A small mean increase from baseline of ~0.2 mg/dl in uric acid was observed with sitagliptin versus placebo. No meaningful differences among groups were observed in mean changes or occurrences of prespecified elevations in alanine aminotransferase, aspartate aminotransferase, or creatine phosphokinase. No meaningful differences were observed in vital signs or in mean changes in ECG data.

After 24 weeks, sitagliptin 100 and 200 mg had a neutral effect on body weight relative to baseline (change from baseline ± SE −0.2 ± 0.2 and −0.1 ± 0.2 kg, respectively). The change (−1.1 ± 0.2 kg) in the placebo group was significantly ($P < 0.01$) different from that observed with sitagliptin.

CONCLUSIONS — This study was performed to provide an assessment of the efficacy and tolerability of sitagliptin at doses of 100 and 200 mg once daily as monotherapy in patients with type 2 diabetes with inadequate glycemic control on diet and exercise. Treatment with sitagliptin provided clinically meaningful reductions in A1C, FPG, and 2-h PPG compared with placebo. Results for these key efficacy parameters were not significantly different between sitagliptin doses. A general persistence of response for both A1C and FPG reduction over 24 weeks was observed in both sitagliptin groups. The improvements in 2-h PPG and glucose AUC after a standard meal, combined with the improvement in FPG, show that sitagliptin provides clinically important glucose lowering in both the fasting and postprandial states.

Sitagliptin treatment increased the proportion of patients achieving the glycemic goal of A1C <7% (21), led to fewer patients requiring glycemic rescue therapy, and extended the time to rescue versus placebo. Sitagliptin lowered A1C consistently across subgroups defined by demographic, anthropometric, and disease characteristics. As with other antihyperglycemic agents, sitagliptin lowered A1C more in patients with higher baseline A1C, with a 1.5% reduction in patients with a baseline A1C ≥9%.

The increases in HOMA-β and in the amount of insulin secreted relative to glucose levels during a meal tolerance test and the reduction in the proinsulin-to-insulin ratio support the conclusion that sitagliptin improved β-cell function. Poorly functioning β-cells in patients with type 2 diabetes secrete greater amounts of proinsulin relative to insulin, and a decline in this ratio has been suggested to be a marker of improved β-cell function (22). Other DPP-4 inhibitors have also been reported to improve β-cell function in patients with type 2 diabetes (8,11) and in animal models (12–14).

Sitagliptin had no effect on indexes of insulin resistance and sensitivity (HOMA-IR and QUICKI), consistent with incretin studies demonstrating small, inconsistent effects on insulin sensitivity (23). Studies using more sensitive, direct measures are needed to further evaluate these findings.

Increased body weight observed with OHAs (24) is generally an undesired effect. After 24 weeks, treatment with sitagliptin had a neutral effect on body weight relative to baseline, consistent with results from earlier studies (16,17). The small, significant weight loss observed with placebo likely reflected less adequate glycemic control.

Overall assessment of safety demonstrated that both sitagliptin doses were well tolerated in this study. No meaningful differences were found in the adverse experience profiles between sitagliptin and placebo treatments. There was a very low incidence of hypoglycemia with sitagliptin that was similar to placebo and consistent with the glucose-dependent effects of incretins (2). Slightly higher, but not statistically significant, incidences of nausea, constipation, diarrhea, and nasopharyngitis/pharyngitis were reported with sitagliptin, but these events were generally mild or moderate, self-limited, and not temporally related to initiation of study medication.

Sitagliptin did not lead to changes in hepatic or muscle enzymes. A small decrease in alkaline phosphatase was observed, which is unlikely to be clinically meaningful. Very small increases in WBCs and ANCs were observed. These changes were nonprogressive, not associated with increased reports of laboratory adverse experiences, and were thus unlikely to be clinically meaningful. Sitagliptin had no effect on fasting lipids.

Lastly, while efficacy end points in this study generally showed trends toward greater improvement in the 200- compared with the 100-mg group, treatment with 200 mg tended to be less effective than with 100 mg in a similarly designed 18-week monotherapy study (25). Collectively, these data suggest the 100- and 200-mg doses are similarly effi-

cacious. This conclusion is supported by modeling of pharmacokinetic and pharmacodynamic data in patients with type 2 diabetes predicting that sitagliptin 100 mg would provide optimal 24-h inhibition of DPP-4 activity (i.e., ≥80%) in order to increase active incretin levels greater than twofold and produce significant glucose lowering following an oral glucose tolerance test (9).

In conclusion, in this 24-week study, once-daily sitagliptin monotherapy provided effective glycemic control in both the fasting and postprandial states in patients with type 2 diabetes. Sitagliptin produced significant improvements in indexes of insulin release and β-cell function. Sitagliptin was generally well tolerated, with a rate of hypoglycemia similar to placebo and a neutral effect on body weight relative to baseline.

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