Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor Sitagliptin Added to Ongoing Metformin Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Alone

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OBJECTIVE — The efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, added to ongoing metformin therapy, were assessed in patients with type 2 diabetes who had inadequate glycemic control (HbA_{1c} [A1C] ≥7 and ≤10%) with metformin alone.

RESEARCH DESIGN AND METHODS — After a screening diet/exercise run-in period, a metformin dose titration/stabilization period, and a 2-week, single-blind, placebo run-in period, 701 patients, aged 19–78 years, with mild to moderate hyperglycemia (mean A1C 8.0%) receiving ongoing metformin (≥1,500 mg/day) were randomly assigned to receive the addition of placebo or sitagliptin 100 mg once-daily in a 1:2 ratio for 24 weeks. Patients exceeding specific glycemic limits were provided rescue therapy (pioglitazone) until the end of the study. The efficacy analyses were based on an all-patients-treated population using an ANCOVA and excluded data obtained after glycemic rescue.

RESULTS — At week 24, sitagliptin treatment led to significant reductions compared with placebo in A1C (−0.65%), fasting plasma glucose, and 2-h postmeal glucose. Fasting insulin, fasting C-peptide, fasting proinsulin-to-insulin ratio, postmeal insulin and C-peptide areas under the curve (AUCs), postmeal insulin AUC–to–glucose AUC ratio, homeostasis model assessment of β-cell function, and quantitative insulin sensitivity check index were significantly improved with sitagliptin relative to placebo. A significantly greater proportion of patients achieved an A1C <7% with sitagliptin (47.0%) than with placebo (18.3%). There was no increased risk of hypoglycemia or gastrointestinal adverse experiences with sitagliptin compared with placebo. Body weight decreased similarly with sitagliptin and placebo.

CONCLUSIONS — Sitagliptin 100 mg once-daily added to ongoing metformin therapy was efficacious and well tolerated in patients with type 2 diabetes who had inadequate glycemic control with metformin alone.

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Abbreviations: AUC, area under the 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, homeostasis model assessment of insulin resistance; OHA, oral antihyperglycemic agent; QUICKI, quantitative insulin sensitivity check index.

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

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Sitagliptin is an oral, once-daily, potent, and highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes (1–5). DPP-4 inhibitors enhance levels of active incretin hormones, gut-derived peptides that are released into the circulation after ingestion of a meal (6–8). Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) account for the majority of incretin action (9). In the presence of elevated glucose concentrations, GLP-1 and GIP increase insulin release and GLP-1 lowers glucagon secretion, thereby decreasing the postmeal rise in glucose concentration and reducing fasting glucose concentrations (9). Both GLP-1 and GIP are rapidly inactivated by the enzyme DPP-4 (10,11). By blocking this inactivation, DPP-4 inhibitors increase active incretin levels, enhancing incretin effects, and thereby offer a new therapeutic approach for the management of patients with type 2 diabetes.

Treatment with a single antihyperglycemic agent is often unsuccessful in achieving and/or maintaining glycemic control in patients with type 2 diabetes, and many patients require combinations of antihyperglycemic agents (12). Metformin, a biguanide, is one of the most commonly used first-line antihyperglycemic agents in the treatment of type 2 diabetes, which acts primarily by lowering hepatic glucose production and may also improve insulin resistance (12). Because sitagliptin and metformin target potentially complementary pathways, the addition of sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin monotherapy may provide improved glycemic control. In an earlier, short-term study (13) of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes with inadequate glycemic control with metformin alone, a sustained 24-h reduction in glucose compared with placebo was observed after 28 days of treat-

ment. In light of these findings, the present placebo-controlled study assessed the efficacy and safety of sitagliptin 100 mg once-daily added to ongoing metformin therapy in patients with type 2 diabetes who were inadequately controlled on metformin alone. The 100 mg once-daily dose of sitagliptin was selected based on the results of two previous, 12-week, dose-range-finding studies in patients with type 2 diabetes in which treatment at this dose produced the greatest improvement in glycemic control (4,5).

RESEARCH DESIGN AND METHODS

— Men and women (aged 18–78 years) with type 2 diabetes and inadequate glycemic control (defined by an HbA_{1c} [A1C] level ≥7 and ≤10%) while taking metformin monotherapy at a stable dose of at least 1,500 mg/day, either at entry into the study or after a metformin dose-stable run-in period, were eligible to be randomized. Patients who were not currently taking an oral antihyperglycemic agent (OHA), were taking any OHA in monotherapy, or were taking metformin in combination with another OHA were potentially eligible to participate in the study if their A1C level met the screening criteria. Patients were excluded if they had a history of type 1 diabetes, insulin use within 8 weeks of screening, renal function impairment inconsistent with the use of metformin, or a fasting plasma glucose (FPG) (or a fasting fingerstick glucose) at, or just before, randomization >14.4 mmol/l (260 mg/dl). A history of hypoglycemia was not an exclusion criterion. Other OHAs were prohibited during the study. Concurrent lipid-lowering and antihypertensive medications, thyroid medications, hormone replacement therapy, and birth control medications were allowed but were expected to remain at stable doses.

This was a multinational, randomized, parallel-group study with a placebo-controlled, double-blind treatment period. The screening/eligibility run-in period was designed to allow patients with type 2 diabetes being treated with a variety of different regimens, as described in the prior section, to participate. Patients who were already taking metformin at a dose of at least 1,500 mg/day whose A1C level was ≥7 and ≤10% directly entered a 2-week placebo run-in period and were eligible to be randomized. Patients not currently taking an OHA, patients taking any OHA in monotherapy (other than metformin ≥1,500 mg/day), or patients taking metformin in combination with another OHA entered a metformin monotherapy treatment titration and dose-stable period of up to 19 weeks (the duration was variable, on the basis of prior therapy, to ensure sufficient time to respond to metformin monotherapy). After the dose-stable run-in period of metformin monotherapy, patients with A1C ≥7 and ≤10% entered a 2-week placebo run-in period and were eligible to be randomized. Patients were randomly assigned to receive the addition of placebo or sitagliptin 100 mg once-daily in a 1:2 ratio. The double-blind treatment period was 24 weeks. Patients exceeding specific glycemic limits during the 24-week treatment period were provided rescue therapy (pioglitazone, administered in accordance with the product label) until the completion of the placebo-controlled study period. Rescue therapy was initiated if FPG was >15.0 mmol/l (270 mg/dl) from baseline through week 6, >13.3 mmol/l (240 mg/dl) after week 6 through week 12, and >11.1 mmol/l (200 mg/dl) after week 12. An ongoing active-comparator treatment phase for patients who completed the placebo-controlled period will be the subject of a subsequent report.

Study end points

The primary efficacy end point was change from baseline at week 24 in A1C. Secondary efficacy end points included change from baseline at week 24 in FPG as well as in glucose, insulin, and C-peptide concentrations, measured immediately before and at 60 and 120 min after a standard meal, and a lipid panel (total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and triglyceride-to-HDL cholesterol ratio). Exploratory end points included mean glucose, insulin, and C-peptide concentrations, as well as area under the curve (AUC) for glucose, insulin, and C-peptide, and insulin AUC–to–glucose AUC ratio, after a standardized morning meal. All assays were performed by technicians blinded to the treatment sequence at PPD Global Central Labs (Lexington, KY).

Safety and tolerability were assessed throughout the study. Monitoring for adverse experiences, physical examinations, vital signs, body weight, 12-lead electrocardiograms (ECGs) (read at a central reading laboratory), and safety laboratory measurements comprising routine hematology, serum chemistry, and urinalysis were performed. Investigators evaluated each clinical adverse experience for intensity (mild, moderate, or severe), duration, outcome, and relationship to study drug. Adverse experiences of special interest included hypoglycemia and gastrointestinal adverse experiences.

Statistical analysis

Efficacy analyses were based on the all-patients-treated population, which consisted of randomly assigned patients who had received at least one dose of study treatment and had both a baseline and at least one postbaseline measurement. An ANCOVA model was used to analyze the treatment groups for the continuous efficacy parameters, comparing change from baseline (day 1/randomization) at week 24. Analyses were adjusted for baseline values and the presence/absence of prior antihyperglycemic therapy. Missing data were handled using the last observation carried forward method. To avoid the confounding influence of rescue therapy on efficacy comparisons, in efficacy analyses we treated data obtained after initiation of rescue therapy as missing data. The primary efficacy hypothesis for this study was that the addition of sitagliptin 100 mg compared with placebo would lead to a greater reduction in A1C at week 24 and was assessed by testing the statistical significance of the difference in the least-squares mean change from baseline at week 24 in A1C for the sitagliptin group versus the placebo group. The testing procedures for the secondary efficacy end points proceeded in a conditional manner and were prioritized in the order of FPG and then 2-h postmeal glucose, provided the primary efficacy hypothesis for A1C was met. The proportion of patients in each group achieving an A1C goal <7% at week 24 was also assessed. A time-to-glycemic-rescue analysis was performed using the Kaplan-Meier estimator and the log-rank test. The proportion of patients in each treatment group who had received glycemic rescue therapy during the study was also determined.

Safety analyses were performed using the all-patients-as-treated population, which included all randomly assigned patients who received at least one dose of double-blind study therapy. For hypoglycemia as well as prespecified selected gastrointestinal adverse experiences (abdominal pain, diarrhea, nausea, and vomiting) and change in body weight, inferential testing was done to determine

Table 1—*Glycemic efficacy end points*

Parameter	*n*	Baseline	Week 24	Least-squares change from baseline
A1C (%)				
Placebo	224	8.03 ± 0.82	7.95 ± 1.10	−0.02 (−0.15 to 0.10)
Sitagliptin 100 mg q.d.	453	7.96 ± 0.81	7.26 ± 0.97	−0.67 (−0.77 to −0.57)*
FPG (mmol/l)				
Placebo	226	9.6 ± 2.3	9.9 ± 2.8	0.5 (0.2 to 0.8)
Sitagliptin 100 mg q.d.	454	9.4 ± 2.3	8.4 ± 2.2	−0.9 (−1.2 to −0.7)*
Insulin (pmol/l)				
Placebo	197	72.0 ± 45.6	72.0 ± 40.8	−1.2 (−10.2 to 8.4)
Sitagliptin 100 mg q.d.	419	72.6 ± 58.2	81.6 ± 76.2	7.8 (0.6–15.0)†
Proinsulin-to-insulin ratio				
Placebo	169	0.37 ± 0.20	0.37 ± 0.21	0.02 (−0.02 to 0.05)
Sitagliptin 100 mg q.d.	397	0.36 ± 0.21	0.33 ± 0.21	−0.03 (−0.05 to 0.00)‡
C-peptide (nmol/l)				
Placebo	186	0.83 ± 0.40	0.87 ± 0.40	0.03 (−0.03 to 0.01)
Sitagliptin 100 mg q.d.	390	0.83 ± 0.43	0.93 ± 0.43	0.10 (0.03–0.13)‡
HOMA-β				
Placebo	196	45.1 ± 34.2	47.6 ± 37.5	3.5 (−4.9 to 11.8)
Sitagliptin 100 mg q.d.	418	46.4 ± 38.9	65.2 ± 68.9	19.5 (12.9–26.2)*
QUICKI				
Placebo	196	0.314 ± 0.031	0.312 ± 0.028	−0.002 (−0.007 to 0.003)
Sitagliptin 100 mg q.d.	418	0.315 ± 0.032	0.318 ± 0.036	0.003 (−0.000 to 0.007)†

Data are means ± SD or mean (95% CI). To convert glucose from millimoles per liter to milligrams per deciliter, divide by 0.05551.*$P < 0.001$ vs. placebo; †$P < 0.050$ vs. placebo; ‡$P < 0.010$ vs. placebo.

statistical significance levels for between-group comparisons.

RESULTS

Demographics and baseline characteristics

The overall disposition of patients who were screened and randomly assigned in the placebo-controlled period of the study is shown in Fig. 1 of the online appendix (available at http://care.diabetesjournals.org). Of the 1,464 patients who were screened, 701 were randomly assigned to study treatment. The demographic and baseline anthropometric and disease characteristics of the randomly assigned patients were similar between the treatment groups (see Fig. 1 of the online appendix). For the entire study population, the average duration of diabetes was 6.2 years, average baseline A1C was 8% (range 6.4–11.0%; 55% of patients had a baseline A1C <8%), and the average baseline FPG was 9.5 mmol/l (171.5 mg/dl). A greater percentage of patients in the placebo group discontinued the study compared with patients in the sitagliptin group (19 vs. 10%) (see Fig. 1 of the online appendix). The most common reasons for discontinuation were lack of efficacy (placebo 5.5 vs. sitagliptin 1.5%), withdrawal of consent (placebo 4.2 vs. sitagliptin 2.2%), clinical adverse experiences (placebo 2.1 vs. sitagliptin 2.4%), and lost to follow-up (placebo 2.1 vs. sitagliptin 0.9%).

Efficacy

At week 24, treatment with sitagliptin 100 mg once-daily led to a significant ($P < 0.001$) reduction from baseline in A1C compared with placebo (Table 1). The placebo-subtracted least-squares mean (95% CI) reduction from baseline in A1C for the sitagliptin 100 mg group was −0.65% (−0.77 to −0.53). A1C decreased in the sitagliptin group relative to the placebo group during the first 12 weeks of treatment and then remained generally stable, with a slight trend toward further reduction, over the subsequent double-blind treatment period (Fig. 1*A*). No significant treatment-by-baseline A1C or treatment-by-prior diabetes pharmacotherapy interaction was observed. Treatment with sitagliptin led to a significant increase in the proportion of patients achieving an A1C <7% compared with placebo (213 of 453 patients [47.0%] in the sitagliptin group versus 41 of 224 patients [18.3%] in the placebo group; $P < 0.001$ for between-group comparison).

Treatment with sitagliptin 100 mg also led to a significant ($P < 0.001$) reduction from baseline at week 24 in FPG compared with placebo (Table 1). The placebo-subtracted least-squares mean (95% CI) reduction from baseline in FPG for the sitagliptin 100 mg group was −1.4 mmol/l (−1.7 to −1.1) (−25.4 mg/dl [−31.0 to −19.8]). The mean reduction from baseline in FPG in the sitagliptin group was near maximal for the study by week 6, with a trend toward a progressive further decrease in FPG through the remainder of the double-blind treatment period (Fig. 1*B*). In contrast, there was a generally sustained mean increase from baseline in FPG levels in the placebo group from weeks 6 through 24 (Fig. 1*B*).

In addition to the significant decreases in A1C and FPG, treatment with sitagliptin 100 mg also led to significant increases relative to placebo in fasting insulin ($P < 0.050$), fasting C-peptide ($P < 0.010$), homeostasis model assessment of β-cell function (HOMA-β) ($P < 0.001$), and quantitative insulin sensitivity check index (QUICKI) ($P < 0.050$) and a significant decrease in fasting proinsulin-to-insulin ratio ($P < 0.010$) at week 24 (Table 1). Sitagliptin 100 mg had no significant effect on fasting proinsulin levels or homeostasis model assessment of insulin resistance (HOMA-IR) (see Table 1 of the online appendix).

Treatment with sitagliptin 100 mg led

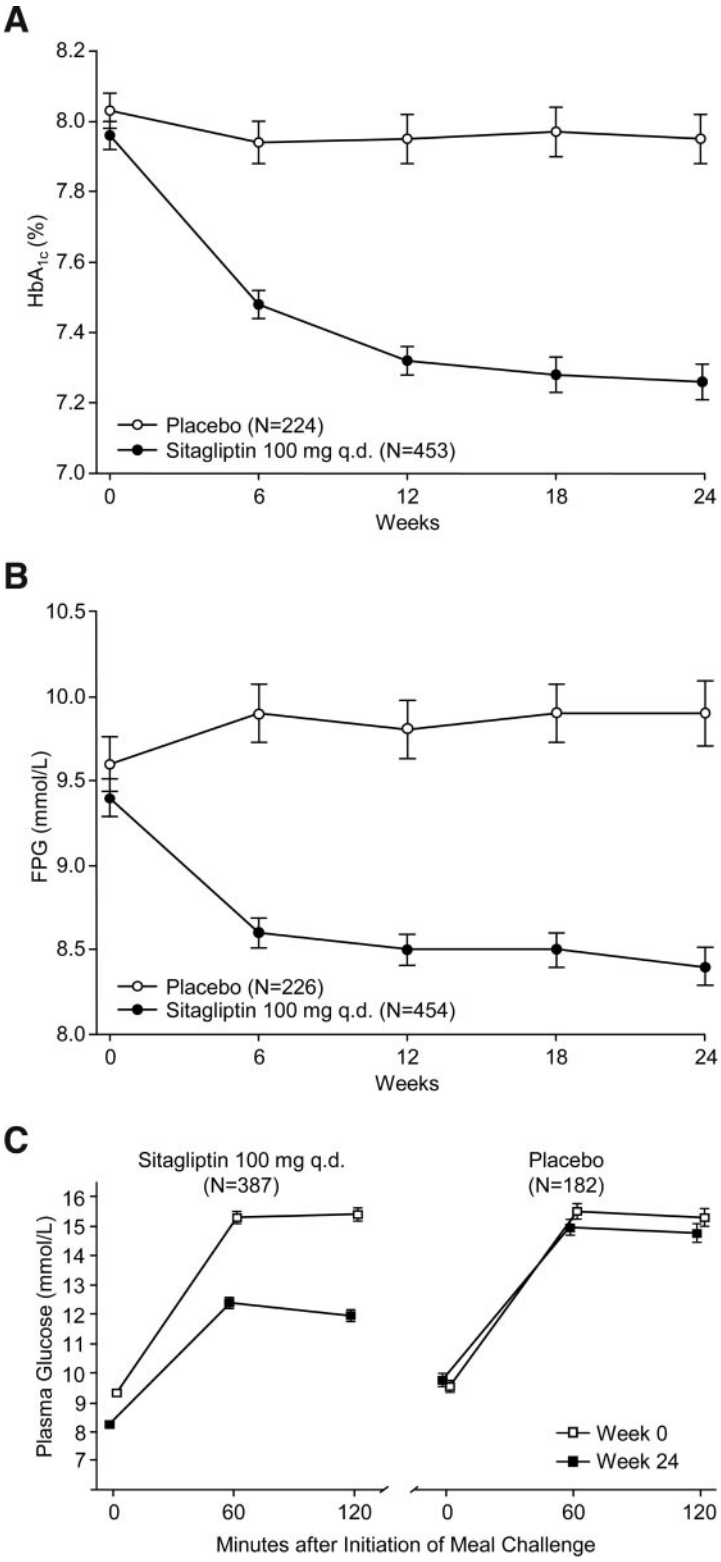

Figure 1—*Key glycemic efficacy end points:* A*: Mean (SE) A1C (percentage) over time for sitagliptin 100 mg once-daily (q.d.) versus placebo added to ongoing metformin therapy in patients with type 2 diabetes who had inadequate glycemic control with metformin alone.* B*: Mean (SE) FPG (millimoles per liter) over time for sitagliptin 100 mg once-daily versus placebo added to ongoing metformin therapy in patients with type 2 diabetes who had inadequate glycemic control with metformin alone.* C*: Mean (SE) plasma glucose concentrations (millimoles per liter) over 2 h after a standard meal at baseline (week 0) and week 24 for sitagliptin 100 mg once-daily or placebo added to ongoing metformin therapy in patients with type 2 diabetes who had inadequate glycemic control with metformin alone.*

to a significant decrease in 2-h postmeal glucose ($P < 0.001$) (see Table 1 of the online appendix and Fig. 1*C*) and significant increases in 2-h postmeal insulin ($P < 0.050$) (see Table 1 of the online appendix) and 2-h postmeal C-peptide ($P < 0.001$) relative to placebo at week 24 (see Table 1 of the online appendix). Treatment with sitagliptin also led to a significant decrease in 2-h postmeal glucose total AUC ($P < 0.001$) and significant increases in 2-h postmeal insulin total AUC ($P < 0.010$), 2-h postmeal C-peptide AUC ($P < 0.001$), and 2-h postmeal insulin-to-glucose AUC ratio ($P < 0.001$) relative to placebo at week 24 (see Table 1 of the online appendix).

A significantly smaller proportion of patients in the sitagliptin group required glycemic rescue therapy during the 24-week study compared with the placebo group (21 of 464 patients [4.5%] receiving sitagliptin required rescue therapy during the study compared with 32 of 237 patients [13.5%] in the placebo group; $P < 0.001$). Additionally, the time to initiation of rescue therapy was significantly ($P < 0.001$) later in the sitagliptin group than in the placebo group.

Treatment with sitagliptin 100 mg led to statistically significant, albeit generally small, decreases in total cholesterol, triglycerides, non-HDL cholesterol, and triglyceride-to-HDL cholesterol ratio, as well as a small, statistically significant, increase in HDL cholesterol relative to placebo at week 24. However, no significant between-group difference in LDL cholesterol was observed (placebo-subtracted least-squares mean [95% CI] percent changes from baseline at week 24: total cholesterol −2.8% [−5.3 to −0.4]; triglycerides −16.9% [−24.3 to −9.4]; HDL cholesterol 2.0% [0.0–4.0]; non-HDL cholesterol −4.8% [−8.3 to −1.3]; triglyceride-to-HDL cholesterol ratio −19.4% [−27.9 to −10.8]; LDL cholesterol −0.8% [−5.4 to 3.8]) (see Table 1 of the online appendix).

Safety

Treatment with sitagliptin 100 mg once-daily added to ongoing metformin therapy was generally well tolerated. The overall incidence of clinical adverse experiences, drug-related clinical adverse experiences, serious clinical adverse experiences, and drug-related serious clinical adverse experiences was similar in the two treatment groups (Table 2). The incidence of discontinuation due to adverse experiences was also similar between

Table 2—*Safety summary*

Safety parameter	Placebo	Sitagliptin 100 mg q.d.
n	237	464
Patients with one or more clinical adverse experience	128 (54.0)	262 (56.5)
Patients with drug-related clinical adverse experiences*	25 (10.5)	45 (9.7)
Patients with serious clinical adverse experiences	7 (3.0)	13 (2.8)
Patients with drug-related serious clinical adverse experiences	0	0
Patients who discontinued due to clinical adverse experiences	7 (3.0)†	11 (2.4)
Patients who discontinued due to drug-related clinical adverse experiences	0	4 (0.9)
Patients who discontinued due to serious clinical adverse experiences	1 (0.4)	6 (1.3)
Patients who discontinued due to serious drug-related clinical adverse experiences	0	0
Hypoglycemia	5 (2.1)	6 (1.3)
Overall gastrointestinal adverse experiences	25 (10.5)	55 (11.9)
Selected gastrointestinal adverse experiences		
Abdominal pain	9 (3.8)	10 (2.2)
Diarrhea	6 (2.5)	12 (2.6)
Nausea	2 (0.8)	6 (1.3)
Vomiting	2 (0.8)	5 (1.1)

Data are *n* (%). *Determined by the investigator to be possibly, probably, or definitely drug related. †Includes five patients who discontinued during the initial placebo-controlled phase and two patients who discontinued after completing this phase because of adverse experiences that had an onset during the placebo-controlled phase.

the two treatment groups (Table 2). There were no statistically significant differences in the incidence of either hypoglycemia or predefined gastrointestinal adverse experiences between the sitagliptin and placebo groups (Table 2).

For most specific clinical adverse experiences, the incidences were generally similar in the sitagliptin and placebo groups. Only a few adverse experiences occurred at a higher incidence with sitagliptin compared with placebo, and for these, which included nasopharyngitis, urinary tract infection, arthralgia, back pain, and cough, the differences were generally small (see Table 2 of the online appendix). The incidence of other adverse experiences classified by body system, including the incidence of cardiac-related adverse experiences, infections, and musculoskeletal adverse experiences, was generally comparable between the two treatment groups.

There were no laboratory adverse experiences that had a notably greater incidence in the sitagliptin group compared with the placebo group (see Table 2 of the online appendix). No meaningful differences between treatment groups were observed in mean changes from baseline or in the occurrence of elevations in alanine aminotransferase or aspartate aminotransferase. A small mean increase (≤10%) was observed in white blood cell count related to an increase in absolute neutrophil count in the sitagliptin 100 mg group compared with placebo. These changes appeared to remain stable over the course of the treatment period. A small mean increase (~10 μmol/l) from baseline in uric acid was observed in the sitagliptin group relative to the placebo group at week 24 (baseline uric acid levels: 330.7 μmol/l for sitagliptin 100 mg once-daily vs. 335.5 μmol/l for placebo); no laboratory adverse experiences of hyperuricemia or clinical adverse experiences of gout were reported. A small mean decrease (~4%) from baseline in alkaline phosphatase was also detected in the sitagliptin group compared with placebo at week 24. There was a slightly greater, albeit not statistically significant, incidence of hemoglobin values that met the predefined limit of change criteria for at least one decrease of ≥1.5 g/l in the sitagliptin 100 mg group (5.7%) compared with the placebo group (3.5%). There was no meaningful difference between the two treatment groups in mean change from baseline for hemoglobin. No meaningful differences were observed between treatment groups in the mean changes from baseline or in changes meeting predefined limits of change criteria for other laboratory assessments.

There were no clinically meaningful changes in ECGs or vital signs with sitagliptin treatment. Small (0.6–0.7 kg), but statistically significant ($P < 0.05$), mean decreases from baseline in body weight were observed in both treatment groups; however, the mean between-group difference was not significant ($P = 0.835$ for between-group comparison for change from baseline at Week 24).

CONCLUSIONS — In this study, sitagliptin 100 mg once-daily provided statistically significant and clinically meaningful reductions in A1C compared with placebo when added to ongoing metformin therapy in patients with type 2 diabetes and mild to moderate hyperglycemia who had inadequate glycemic control with metformin monotherapy. Secondary glycemic end points including FPG and 2-h postmeal glucose also showed clinically important and statistically significant improvements with sitagliptin 100 mg compared with placebo. The A1C- and FPG-lowering responses to sitagliptin treatment were sustained during the 24-week treatment period, with a trend of continuing reductions in both end points throughout the treatment period. Nearly half of the patients receiving sitagliptin 100 mg once-daily achieved the current American Diabetes Association glycemic goal of A1C <7% (14) compared with less than one-fifth of placebo-treated patients.

Consistent with its mechanism of action, treatment with sitagliptin 100 mg led to a statistically significant increase compared with placebo in HOMA-β, a surrogate end point that has been used to assess the ability of pancreatic β-cells to secrete insulin under fasting conditions. In addition, improvement in the fasting proinsulin-to-insulin ratio, consistent with improved β-cell function, was also observed with sitagliptin treatment. Preclinical studies have shown that GLP-1 can stimulate β-cell differentiation and

proliferation; additionally, GLP-1 has been shown to inhibit apoptosis of β-cells, including that of human β-cells in vitro (8,9). Moreover, DPP-4 inhibitors have been shown to stimulate β-cell neogenesis and survival in streptozotocin-treated rats (15). The implications of such effects of DPP-4 inhibition on β-cell mass and function in humans still need to be determined with additional clinical studies. End points reflecting changes in insulin sensitivity (QUICKI and HOMA-IR) showed a mixed response with a small, but statistically significant, increase in QUICKI and no significant change in HOMA-IR.

During this study, patients underwent a standard 2-h meal tolerance test, enabling an assessment of the effect of treatment on postmeal glucose, insulin, and C-peptide concentrations and the ratio of insulin to glucose. Treatment with sitagliptin led to clinically important and statistically significant improvements in all of these end points compared with placebo.

Sitagliptin 100 mg was well tolerated in this clinical trial. No clinically meaningful differences in the overall incidence of clinical adverse experiences, clinical adverse experiences leading to discontinuation, serious clinical adverse experiences, or laboratory adverse experiences were observed in the sitagliptin group compared with the placebo group. The addition of sitagliptin to ongoing metformin therapy did not lead to an increase in the incidence of gastrointestinal side effects, which are typically associated with metformin treatment alone. Sitagliptin treatment was associated with a very low incidence of hypoglycemia adverse experiences, with a rate similar to that seen in the placebo group. Furthermore, none of the hypoglycemia episodes exhibited marked severity. Treatment with sitagliptin led to a small, but statistically significant, mean decrease from baseline in body weight, with no significant difference in weight change compared with placebo. Sitagliptin treatment also led to slight, statistically significant improvements in lipid parameters. No clinically meaningful differences were observed in the sitagliptin group compared with placebo with respect to mean changes in serum chemistry and hematology analytes, and there were no clinically meaningful changes in vital signs or ECGs with sitagliptin treatment.

In summary, in patients with type 2 diabetes who had inadequate glycemic control with metformin alone, the addition of sitagliptin 100 mg once-daily was well tolerated and provided effective and sustained improvement in A1C, FPG, and 2-h postmeal glucose, as well as significant improvements in indexes of insulin secretion and β-cell function, including HOMA-β and the fasting proinsulin-to-insulin ratio. Treatment with sitagliptin was associated with a low rate of hypoglycemia that was similar to that seen with placebo, as well as a neutral effect on body weight.

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A list of author contributions regarding the work performed in this study can be found in the online appendix.

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