Efficacy and Safety of Sitagliptin Versus Glipizide in Patients With Type 2 Diabetes and Moderate-to-Severe Chronic Renal Insufficiency

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OBJECTIVE—Patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease have an increased risk of micro- and macrovascular disease, but limited options for antihyperglycemic therapy. We compared the efficacy and safety of sitagliptin with glipizide in patients with T2DM and moderate-to-severe chronic renal insufficiency and inadequate glycemic control.

RESEARCH DESIGN AND METHODS—Patients (n = 426) were randomized 1:1 to sitagliptin (50 mg every day [q.d.] for moderate renal insufficiency and 25 mg q.d. for severe renal insufficiency) or glipizide (2.5 mg q.d., adjusted based on glycemic control to a 10-mg twice a day maximum dose). Randomization was stratified by: *1*) renal status (moderate or severe renal insufficiency); 2) history of cardiovascular disease; and 3) history of heart failure.

RESULTS—At week 54, treatment with sitagliptin was noninferior to treatment with glipizide in A1C change from baseline (−0.8 vs. −0.6%; between-group difference −0.11%; 95% CI −0.29 to 0.06) because the upper bound of the 95% CI was less than the prespecified noninferiority margin of 0.4%. There was a lower incidence of symptomatic hypoglycemia adverse events (AEs) with sitagliptin versus glipizide (6.2 and 17.0%, respectively; P = 0.001) and a decrease in body weight with sitagliptin (−0.6 kg) versus an increase (1.2 kg) with glipizide (difference, −1.8 kg; $P < 0.001$). The incidence of gastrointestinal AEs was low with both treatments.

CONCLUSIONS—In patients with T2DM and chronic renal insufficiency, sitagliptin and glipizide provided similar A1C-lowering efficacy. Sitagliptin was generally well-tolerated, with a lower risk of hypoglycemia and weight loss versus weight gain, relative to glipizide.

Diabetes Care 36:1067–1073, 2013

Approximately 40% of patients with type 2 diabetes mellitus (T2DM) have elevated urinary albumin excretion consistent with underlying renal disease, and >17% of patients with diabetes have chronic kidney disease (CKD) (1). These patients have an increased risk of cardiovascular-related disease and death relative to those with normal renal function (2). Improved glycemic control in patients with T2DM and CKD is associated with positive clinical outcomes (3); however, antihyperglycemic treatment options for such patients are limited due to safety and tolerability concerns (4). Metformin is contraindicated in patients with T2DM whose creatinine clearance is <60 mL/min (5). Although select sulfonylureas may be used, these agents are associated with an increased incidence of hypoglycemia and weight gain (4,6–8). Consequently, many patients with T2DM and CKD do not achieve or maintain adequate glycemic control (6), underscoring the need for a therapeutic agent with significant glycemic efficacy but with a safety and tolerability profile that supports its use in this patient population.

Sitagliptin, a dipeptidyl peptidase-4 inhibitor, is a medication for patients with T2DM that improves glycemic control through enhancement of the incretin axis (9–11). A randomized, double-blind study in patients with T2DM and normal to mildly impaired renal function who had inadequate glycemic control on metformin monotherapy showed that the addition of sitagliptin provided similar A1C-lowering efficacy over 52 weeks compared with the addition of the sulfonylurea glipizide (12); however, patients on glipizide reported >10 times as many hypoglycemia events as did patients on sitagliptin, and body weight decreased with sitagliptin and increased with glipizide, resulting in a significant between-group difference (13).

Sitagliptin is cleared primarily by the kidney, with ~80% of an oral dose excreted unchanged in the urine (13,14). Based on the pharmacokinetics of sitagliptin and its renal clearance, in order to achieve a plasma concentration of sitagliptin similar to that achieved with a 100-mg daily dose in patients with normal to mildly impaired renal function, patients with moderate renal insufficiency should receive one-half of the usual clinical dose (50 mg every day), and patients with severe renal insufficiency or end-stage renal disease should receive one-quarter of the usual clinical dose (25 mg every day) (15). In a placebo-controlled, phase III clinical trial, sitagliptin, at the appropriate doses for patients with T2DM and chronic renal insufficiency or end-stage renal disease, provided clinically relevant reductions in A1C and fasting plasma glucose (FPG) and was generally well-tolerated,

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Received 10 July 2012 and accepted 10 October 2012.
DOI: 10.2337/dc12-1365. Clinical trial reg. no. NCT00509262, clinicaltrials.gov.
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-1365/-/DC1.

with a rate of hypoglycemia similar to that of placebo and a neutral effect on body weight (15). The current study compared the efficacy and safety of sitagliptin with that of glipizide, a sulfonylurea agent recommended by the Kidney Disease Outcomes Quality Initiative guidelines for use in this patient population (6), in patients with T2DM and moderate (estimated glomerular filtration rate [eGFR] ≥30 to <50 mL/min/1.73 m^2) or severe (eGFR <30 mL/min/1.73 m^2) renal insufficiency who had inadequate glycemic control.

RESEARCH DESIGN AND METHODS

Study design

This was a multinational, randomized, double-blind, parallel-group, 54-week study. The study included a 1-week screening period, a diet/exercise and oral antihyperglycemic agent (AHA) wash-off period of up to 14 weeks, a 2-week, single-blind placebo run-in period, and a 54-week, double-blind treatment period. At screening, patients not taking AHAs for ≥12 weeks with an A1C of 7–9% directly entered the single-blind placebo run-in period and those with an A1C >9% entered a 6-week diet and exercise period. Patients taking oral AHAs with an A1C of 7–9% entered an 8-week drug wash-off and diet and exercise period (those taking thiazolidinediones underwent a 10-week wash-off period), and those with an A1C of 6.5 to <7% entered an 8–12-week drug wash-off and diet and exercise period (those on thiazolidinediones underwent a 10–14-week wash-off period). Patients received diet and exercise counseling throughout the study, consistent with American Diabetes Association recommendations and appropriate for their renal insufficiency status.

Following the placebo run-in, eligible patients were randomized (1:1) using a computer-generated randomization schedule to receive sitagliptin or glipizide. Randomization was stratified based on: *1*) renal insufficiency status (moderate or severe), 2) history of cardiovascular disease (yes or no), and 3) history of heart failure (yes or no). Sitagliptin and glipizide matching placebos were used to maintain blinding. Patients with moderate renal insufficiency received 50 mg/day of sitagliptin (two 25-mg tablets) or matching placebo. Patients with severe renal insufficiency received 25 mg/day of sitagliptin (one 25-mg tablet) or matching placebo. The dose of sitagliptin was reduced from 50 mg/day to 25 mg/day for patients whose renal status changed from moderate to severe during the study. Glipizide was administered at a starting dose of 2.5 mg/day, prior to the morning meal, and electively titrated to a maximum of 20 mg/day as considered appropriate by the investigator based on the patient's glycemic control; the dose of glipizide could also be reduced or interrupted to prevent hypoglycemia.

After maximally tolerated uptitration of glipizide or matching placebo, patients had insulin rescue therapy initiated, with the regimen and dose determined by investigator, if they met the following criteria: confirmed FPG >240 mg/dL any time from randomization to week 6; confirmed FPG >220 mg/dL from week 6 to 12; confirmed FPG >200 mg/dL from week 12 to 24; and confirmed A1C >8% after week 24. Once insulin rescue therapy was initiated, patients continued to take blinded sitagliptin or matching placebo, but discontinued blinded glipizide or matching placebo.

Patients

Patients with T2DM could participate if they had moderate to severe chronic renal insufficiency (eGFR <50 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease equation), were not on dialysis and unlikely to require dialysis for the duration of the study, had an A1C ≥7.0 and ≤9.0%, and were ≥30 years of age at the screening visit. Patients taking insulin within 12 weeks of the screening visit, patients with type 1 diabetes, history of ketoacidosis, acute renal disease, history of renal transplant, liver disease, a recent (within 3 months) cardiovascular event, hepatic transaminase levels two or more times the upper limit of normal, thyroid stimulating hormone outside the reference range, or triglycerides >600 mg/dL were excluded from participation. Patients were also excluded if they met one of the following prespecified glycemic criteria: visit 2, FPG >260 mg/dL, unlikely to improve with diet/exercise; visit 3, FPG >250 mg/dL consistently (i.e., measurement repeated and confirmed within 7 days); visit 4, FPG >240 mg/dL consistently; and visit 5, finger-stick glucose >240 or <120 mg/dL.

The study was performed in accordance with Good Clinical Practice standards and the ethical principles that have their origin in the Declaration of Helsinki. The study protocol was reviewed and approved by the appropriate committees and authorities. All patients provided written informed consent to participate.

Efficacy assessments

The primary efficacy end point was the change from baseline in A1C at week 54. Other efficacy assessments included FPG, fasting serum insulin and proinsulin, and plasma lipid profiles (total cholesterol, LDL cholesterol [LDL-C], HDL cholesterol [HDL-C], non–HDL-C, and triglycerides). Homeostasis model assessment–β-cell function (HOMA-β), HOMA-insulin resistance (HOMA-IR), and proinsulin/insulin ratio were calculated from fasting measurements of FPG, insulin, and proinsulin (16,17). The proportion of individuals whose A1C values met glycemic goals (<7.0% as primary; <6.5% as secondary) at week 54 was analyzed. A prespecified analysis evaluated the consistency of the A1C-lowering effects of sitagliptin versus glipizide across predefined subgroups based on baseline characteristics A1C (< and ≥8%), age (< and ≥65 years), severity of CKD (eGFR ≥ 30 to <50 [moderate] and <30 [severe] mL/min/1.73 m^2), BMI (< and ≥ median), duration of T2DM (< and ≥ median), ethnicity (Hispanic or Latino and non-Hispanic or non-Latino), sex, prior antihyperglycemic therapy status (yes or no), and race (Asian, black, white, or other). A post hoc analysis evaluated the effect of sitagliptin versus glipizide on a composite end point consisting of glycemic control (reduction in A1C >0.5%), no body weight gain, and no hypoglycemia.

Safety and tolerability assessments

Safety measurements included evaluation of adverse events (AEs), physical examination and vital signs, and electrocardiograms. Laboratory safety studies included serum chemistry, hematology, and urinalysis. All AEs were rated by the investigator for intensity and relationship to study drug. Serious AEs consistent with vascular events (cardiovascular, cerebrovascular, and peripheral vascular events) and heart failure, revascularization procedures, and all deaths, regardless of cause, were adjudicated by an expert committee external to Merck Sharp & Dohme Corp.

AEs of hypoglycemia were considered of special interest. Patients were instructed to monitor and record their glucose concentrations and counseled regarding the symptoms of hypoglycemia, as previously described (16). Investigators reviewed the hypoglycemia assessment logs to

assess each hypoglycemic episode. Events deemed by the investigator as hypoglycemia were reported as an AE of symptomatic hypoglycemia and did not require documentation of a glucose measurement. Events of hypoglycemia requiring (nonmedical) assistance of others, requiring medical intervention, or exhibiting markedly depressed level of consciousness, loss of consciousness, or seizure were considered severe. Other parameters of special interest included change in body weight and gastrointestinal AEs (nausea, vomiting, diarrhea, and abdominal pain).

Blood collection and assays

Patients were instructed to fast overnight for ~10 h prior to collection of blood for laboratory assessment. Blood was collected at baseline (predose) and at various time points throughout the treatment period of 54 weeks for efficacy and safety measurements. All laboratory measurements were performed by a central laboratory (PPD Global Central Laboratories, LLC, Highland Heights, KY, and Zaventem, Belgium).

Statistical analysis

The primary study end points were change from baseline in A1C, the incidence of hypoglycemia events, and overall safety and tolerability. Secondary end points were change from baseline in body weight and FPG. The primary time point was week 54.

The primary efficacy analysis population was the per-protocol (PP) population, which included all randomized patients who had measurements of the respective end point both at baseline and week 54 and did not have any major protocol violations. An ANCOVA model was used to compare the A1C change from baseline between groups. The ANCOVA model included terms for treatment, renal insufficiency stratum at visit 4/week −2 (moderate or severe), prior diabetes pharmacotherapy (on or not on AHA), and a covariate for baseline A1C. Sitagliptin was to be declared noninferior to glipizide in lowering A1C at week 54 if the upper bound of the 95% CI around the between-group difference was less than the noninferiority margin of 0.4%. The changes (or percent changes) from baseline in all other continuous efficacy end points at week 54, except for serum triglycerides and HOMA-β, were analyzed using the ANCOVA model described for A1C at week 54, substituting the relevant baseline efficacy measurement as a covariate. The analysis of triglycerides used a nonparametric approach based on ranks. Due to the presence of outliers, HOMA-β was analyzed using a robust M-estimation approach that minimized the influence of outliers (18). The proportion of individuals whose A1C values met predefined glycemic goals was based on the Miettinen and Nurminen (M&N) method (19). Subgroup analyses were performed using an ANCOVA model. For each subgroup factor, the ANCOVA model included the following terms: treatment, renal insufficiency stratum, prior diabetes pharmacotherapy, baseline value, subgroup, and treatment-by-subgroup interaction.

Due to enrollment challenges, the total sample size was revised from 500 (original design) to 430. Approximately 324 patients (162 patients per group) were expected to be available for the PP analysis. Using an SD of 1.1% for A1C change from baseline at week 54, the study had 90% power to declare noninferiority for a margin of 0.4% at an α level of 0.05, assuming the true mean difference was 0%.

A composite end point of A1C reduction from baseline of >0.5%, no body weight gain, and no hypoglycemia was evaluated post hoc. The 95% CI for proportion difference was calculated using the M&N method (19), stratified by renal insufficiency stratum, prior diabetes pharmacotherapy (on or not on oral AHAs), and baseline A1C (<8 or ≥8%). The odds ratio and 95% CI of achieving the composite end point for sitagliptin versus glipizide were provided using logistic regression, adjusting for treatment, renal insufficiency stratum, prior diabetes pharmacotherapy, and baseline A1C. All patients who had measurements at baseline and week 54 for both A1C and body weight were included in the analysis.

Safety analyses included all randomized patients who received at least one dose of study drug and included data through 28 days following the last day of study medication. Additional analyses of cardiovascular events included data through 28 days following week 54. In these additional analyses, events that occurred up to 54 weeks postrandomization in patients who discontinued prior to week 54 were included. For all AE end points, the proportions of patients with one or more events were analyzed using the M&N method (19). Analysis of continuous safety end points required measurements at baseline and at one or more postbaseline time points. Change from baseline in body weight at week 54 was analyzed using an ANCOVA model similar to that used for the efficacy analyses, based on all patients with measurements both at baseline and week 54. Between-group differences and 95% CIs for the exposure-adjusted incidence rates (i.e., number of patients with ≥1 event per 100 patient-years) were provided [using the M&N method (19), stratified as per the study randomization] for confirmed, adjudicated cardiovascular AEs. Except for end points related to confirmed, adjudicated heart failure and cardiovascular AEs, analyses of both efficacy and safety excluded data following initiation of insulin rescue therapy.

RESULTS

Patient characteristics and disposition

Overall, 426 patients were randomized into the study. Data from one study site (three patients) were considered potentially unreliable due to lack of compliance with Good Clinical Practice and excluded from all analyses. Of the remaining 423 randomized patients (sitagliptin, $n = 211$; glipizide, $n = 212$), 77.7% in the sitagliptin group and 80.2% in the glipizide group completed the 54-week study. The primary reasons for discontinuation in both treatment groups were AEs and withdrawal of informed consent (Supplementary Fig. 1). Demographic and anthropometric traits were generally similar for both treatment groups (Supplementary Table 1).

The mean dose of glipizide was 7.7 mg/day for the PP population. For the overall cohort of patients, the mean duration of exposure to study drug was 312 days in the sitagliptin group and 318 days in the glipizide group.

Efficacy

At week 54, similar reductions from baseline (mean of 7.8% in both groups) in A1C were observed in both treatment groups (Table 1). The difference in least squares (LS) mean change for sitagliptin versus glipizide (−0.11% [95% CI −0.29 to 0.06]) met the criterion for noninferiority because the upper bound of the 95% CI was less than the prespecified noninferiority margin (0.4%). Change from baseline in A1C over time is presented in Fig. 1*A*. At week 54, 47.4% of patients in the sitagliptin group versus 41.5% in the glipizide group met the

Table 1—*Change from baseline in efficacy end points in the PP population at week 54*

	Sitagliptin		Glipizide		Difference in LS mean change (95% CI)
	N	LS mean (95% CI)	*N*	LS mean (95% CI)	
A1C (%)	135	−0.8 (−0.9 to −0.6)	142	−0.6 (−0.8 to −0.5)	−0.1 (−0.3 to 0.1)
FPG (mg/dL)	136	−17.5 (−24.5 to −10.5)	142	−24.6 (−31.5 to −17.8)	7.1 (−1.9 to 16.1)
Fasting insulin (μIU/mL)	124	−1.4 (−2.0 to 4.8)	131	3.1 (−0.3 to 6.4)	−1.7 (−6.0 to 2.7)
Fasting proinsulin (pmol/L)	122	−5.0 (−10.6 to 0.6)	129	5.1 (−0.5 to 10.7)	−10.1 (−17.4 to −2.8)
Proinsulin/insulin ratio	121	−0.030 (−0.080 to 0.019)	129	0.002 (−0.047 to 0.050)	−0.032 (−0.096 to 0.033)
HOMA-β*	123	21.0 (9.4–32.6)	131	48.4 (37.0–59.8)	−27.4 (−42.3 to −12.4)
HOMA-IR	123	−0.2 (−1.9 to 1.5)	131	0.6 (−1.1 to 2.2)	−0.7 (−2.9 to 1.4)
TC (mg/dL)**	137	−1.4 (−5.4 to 2.5)	139	5.4 (1.4–9.4)	−6.8 (−12.0 to −1.7)
HDL-C (mg/dL)**	136	5.4 (1.9–8.9)	139	2.9 (−0.6 to 6.4)	2.5 (−2.0 to 7.0)
LDL-C (mg/dL)**	136	−0.5 (−7.2 to 6.2)	139	11.3 (4.7–18.0)	−11.8 (−20.5 to −3.1)
Non–HDL-C (mg/dL)**	136	−2.9 (−8.7 to 2.9)	139	8.2 (2.5–14.0)	−11.1 (−18.6 to −3.6)
TG (mg/dL)**†	137	−7.7 (−13.9 to −1.4)	139	−3.0 (−11.6 to 5.7)	−7.5 (−15.5 to 0.3)

Treatment group data are presented as LS mean change (95% CI), unless otherwise noted. TC, total cholesterol; TG, triglycerides. *Results from M-estimation approach. **Percentage change from baseline. †Median.

A1C goal of <7% (difference 5.6% [95% CI −5.9 to 16.9]) and 17.8% in the sitagliptin group versus 14.8% in the glipizide group met the A1C goal of <6.5% (difference 3.3% [95% CI −5.7 to 12.1]). The between-group differences in A1C were generally consistent across predefined subgroups. However, greater changes from baseline in A1C were observed in patients with higher A1C at baseline (baseline A1C ≥8%; LS mean change from baseline −1.25% [95% CI −1.48 to −1.02] in the sitagliptin group and −1.10% [−1.32 to −0.87] in the glipizide group) relative to those with lower A1C at baseline (baseline A1C <8%; LS mean change from baseline −0.46% [95% CI −0.63 to −0.28] in the sitagliptin group and −0.38% [−0.55 to −0.21] in the glipizide group) for both treatment groups. The post hoc composite end point (reduction in A1C >0.5%, no body weight gain, and no hypoglycemia) was achieved in a significantly greater proportion of patients with sitagliptin versus glipizide (35.7 vs. 14.2%, respectively). The odds ratio for achieving the composite end point with sitagliptin compared with glipizide was 3.4 (95% CI 1.9–6.2).

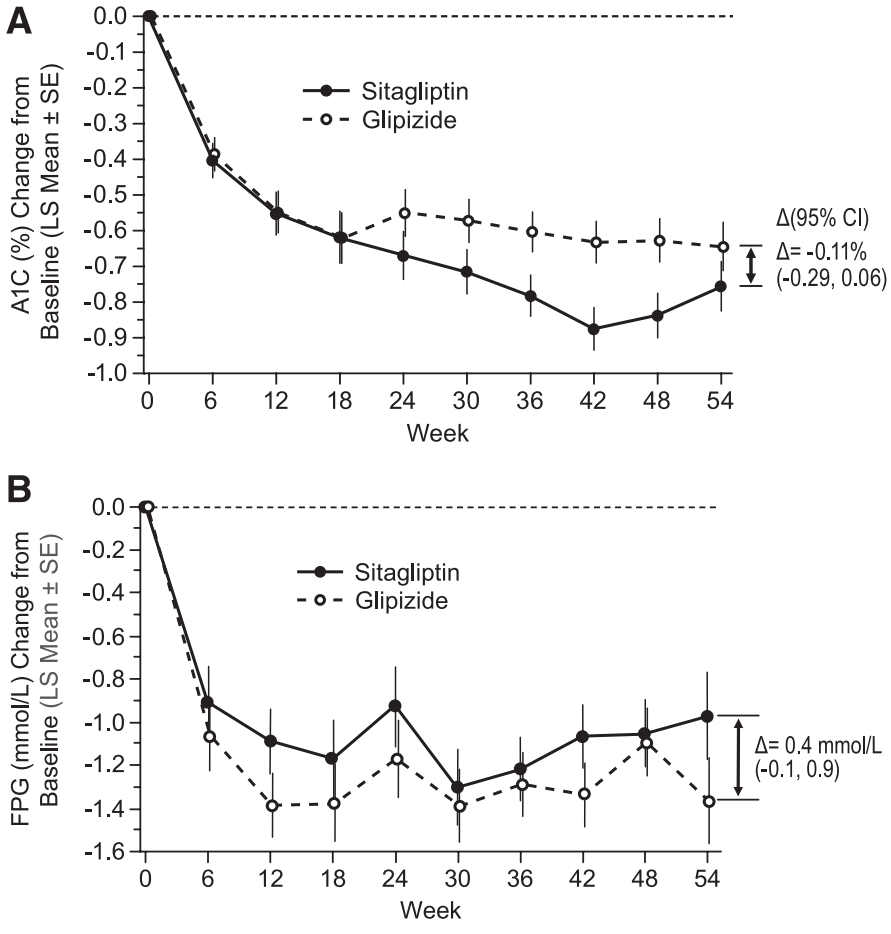

Figure 1—A: *Change in A1C over time in PP population.* B: *Change in FPG over time in PP population.*

Reductions from baseline in FPG at week 54 were observed in both treatment groups (Table 1). The profiles of mean change from baseline in FPG over time showed similar trends in both groups, beginning with a decrease in the first 12 weeks, followed by generally stable levels for the remainder of the study (Fig. 1*B*). Within-group changes from baseline in fasting insulin, proinsulin/insulin ratio, and HOMA-IR were similar for both treatment groups (Table 1). Significant increases from baseline in HOMA-β were observed in both treatment groups, with a greater increase in the glipizide group (Table 1).

Through the 54-week treatment period, 19 of 211 (9.0%) patients in the sitagliptin group and 23 of 212 (10.8%) in the glipizide group were started on glycemic rescue therapy with insulin.

In the sitagliptin group, decreases relative to baseline for total cholesterol, LDL-C, non–HDL-C, and triglycerides and an increase relative to baseline for HDL-C were observed (Table 1). In the glipizide group, increases relative to baseline were observed for total cholesterol, HDL-C, LDL-C, and non–HDL-C, and a decrease relative to baseline was observed for triglycerides (Table 1). Between-group comparisons showed significantly greater reductions in the sitagliptin group compared with the glipizide group for total cholesterol, LDL-C, and non–HDL-C (Table 1).

Safety

Sitagliptin and glipizide were generally well-tolerated over 54 weeks. The incidences of overall AEs and discontinuation due to AEs were similar between groups (Table 2). A total of 10 patient deaths were reported during the study: 3 in the sitagliptin group and 7 in the glipizide group (Supplementary Table 2). AEs occurring in ≥5% of patients in either group are summarized in Table 2. The incidences of AEs by system organ classes were generally similar between groups. AEs in the neoplasms, benign, malignant, and unspecified (including cysts and polyps) system organ class were reported for six patients (2.9%) in the sitagliptin group and none in the glipizide group (Supplementary Table 3). Of the six events reported in the sitagliptin group, three were confirmed malignant disease, and three were either nonmalignant or not histologically confirmed. Each event comprised a different type of lesion (breast cancer, chronic myeloid leukemia, lung cancer, pancreatic head mass, polycythemia vera, and thyroid nodule), all were first identified within 6 months of initiation of therapy, and all were considered as not related to the study drug by the investigator.

The proportion of patients reporting AEs of symptomatic hypoglycemia was significantly lower ($P = 0.001$) in the sitagliptin group (6.2%) compared with the glipizide group (17.0%). Overall, 1.4% of patients in the sitagliptin group were reported with a severe episode of hypoglycemia compared with 2.8% in the glipizide group (between-group difference −1.4 [95% CI −4.8 to 1.5]). For gastrointestinal AEs, there were no significant differences between groups in the incidences of abdominal pain, diarrhea, and vomiting and a significantly lower incidence of nausea ($P = 0.025$) with sitagliptin versus glipizide. Eight patients experienced vascular events in the sitagliptin group and 11 in the glipizide group. In the prespecified analysis adjusting for exposure to treatment, the incidence rate of vascular events was 3.5 incident events per 100 patient-years with sitagliptin compared with 4.8 incident events per 100 patient-years with glipizide. No patients in the sitagliptin group and four patients in the glipizide group experienced an AE of heart failure.

Table 2—*Summary of AEs*

	Sitagliptin ($N = 210$)	Glipizide ($N = 212$)
With one or more AEs	143 (68.1)	153 (72.2)
With drug-related AEs†	27 (12.9)	39 (18.4)
With serious AEs	34 (16.2)	37 (17.5)
With serious drug-related AEs†	2 (1.0)	1 (0.5)
Who died	3 (1.4)	7 (3.3)
Discontinued due to an AE	16 (7.6)	17 (8.0)
Discontinued due to a drug-related AE†	3 (1.4)	2 (0.9)
Discontinued due to a serious AE	10 (4.8)	15 (7.1)
Discontinued due to a serious drug-related AE†	2 (1.0)	1 (0.5)
AEs with an incidence ≥5% in either group		
Blood glucose decreased	15 (7.1)	32 (15.1)
Diarrhea	11 (5.2)	12 (5.7)
Dizziness	7 (3.3)	11 (5.2)
Hypertension	11 (5.2)	6 (2.8)
Hypoglycemia	13 (6.2)	36 (17.0)
Peripheral edema	15 (7.1)	10 (4.7)
Upper respiratory tract infection	10 (4.8)	15 (7.1)
Urinary tract infection	13 (6.2)	21 (9.9)

Data are *n* (%). †Assessed by the investigator as related to the study drug.

Over the study period, body weight decreased in the sitagliptin group (−0.6 kg) and increased in the glipizide group (1.2 kg), resulting in a statistically significant ($P < 0.001$) between-group difference of −1.8 kg (Fig. 2).

In both treatment groups, similar decreases from baseline in eGFR were observed at week 54 (sitagliptin, −3.9 mL/min/1.73 m^2; glipizide, −3.3 mL/min/1.73 m^2; Supplementary Fig. 2*A*). Of the randomized patients with moderate renal insufficiency at baseline, 28 of 149 (18.8%) in the sitagliptin group and 17 of 154 (11.0%) in the glipizide group transitioned to severe renal insufficiency status during the study. The change from baseline in urine albumin/creatinine ratio at week 54 is provided in Supplementary Fig. 2*B*; the 95% CI around the between-group difference for this analysis included 0.

No clinically meaningful between-group differences were noted in the proportions of patients with values meeting predefined limits of change criteria for any of the measured chemistry and hematology parameters or in blood pressure or other vital signs.

CONCLUSIONS—In patients with T2DM and chronic renal insufficiency, sitagliptin and glipizide provided similar A1C-lowering efficacy after 54 weeks of treatment, confirming noninferiority of sitagliptin relative to glipizide. In the sitagliptin group, the maximal A1C reduction occurred at week 42, with a subsequent small increase at week 54. In the glipizide group, the maximal A1C reduction occurred at week 18, which remained generally stable for the duration of the study. The stable response with glipizide was likely due to dose uptitration, which was permitted throughout the study to maintain adequate glycemic control. In contrast, the sitagliptin dose was to remain unchanged throughout the study, except for dose reduction as required if a patient's renal insufficiency status changed from moderate to severe. The effects on A1C were generally consistent across prespecified demographic and disease-related subgroups. In both treatment groups, greater A1C reductions were observed in patients with baseline A1C >8% relative to patients with A1C ≤8%.

Similar to the reductions from baseline in A1C, FPG decreased to a similar extent in the two treatment groups over 54 weeks. Results from assessment of additional efficacy end points were generally similar with sitagliptin and

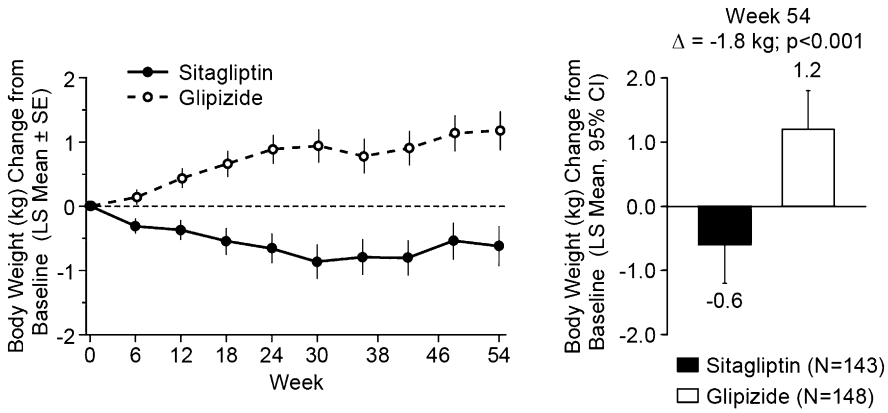

Figure 2—*Change in body weight over time.*

glipizide. No significant within-group changes from baseline in fasting insulin, proinsulin, or the proinsulin/insulin ratio were observed with either treatment. These results are consistent with the findings of a prior study (12).

Greater reductions from baseline in total cholesterol, LDL-C, and non–HDL-C and increased HDL-C were observed with sitagliptin compared with glipizide. Other studies have shown a generally neutral effect of sitagliptin on lipid parameters.

The results from this study support the favorable safety and tolerability profile of sitagliptin in patients with moderate or severe renal insufficiency. The incidences of AEs, including those considered drug-related by the investigator, serious AEs, as well as most other AE summary measures, tended to be lower for the sitagliptin group relative to the glipizide group. The incidences of specific AEs were generally similar between groups.

Use of sulfonylureas is associated with an increased risk of hypoglycemia (4,6–8). The percent of patients with events of symptomatic hypoglycemia in the glipizide group was almost three times higher and the number of events of hypoglycemia was more than four times higher with glipizide than with sitagliptin, despite the similar A1C reductions in both groups. In addition, a higher incidence of AEs of decreased blood glucose was reported for patients in the glipizide group compared with those in the sitagliptin group. These results are consistent with those from another study comparing sitagliptin and glipizide (12).

In this study, neoplasms were reported for six patients (2.9%) in the sitagliptin group and none in the glipizide group. None of the events was considered by the investigator as related to the study drug, the neoplasms reported comprised diverse types and are those generally observed in older patients, and all were first identified within 6 months of initiation of therapy. Neither the overall neoplasm incidence nor the characteristics of these events are suggestive of an underlying relationship between the events and treatment with sitagliptin.

Assessment of vascular events was of particular interest, given the high frequency of such events in patients with T2DM and chronic renal insufficiency. The incidences of confirmed adjudicated vascular events were generally similar in both treatment groups.

Overall, three (1.4%) patients in the sitagliptin group died, compared with seven (3.3%) patients in the glipizide group. The overall mortality observed was consistent with the expected rate for a patient population with long-standing diabetes (mean of ~10 years) and multiple comorbidities, including hypertension, that typically accompany chronic renal insufficiency.

A thorough assessment of the effects of study therapy on renal function showed no meaningful between-group differences in changes from baseline in eGFR, serum creatinine, urine albumin/creatinine ratio, or uric acid or in the number of patients with laboratory values meeting the predefined limits of change for serum creatinine or uric acid.

Change in body weight was notably different between groups. Over the 54-week treatment period, treatment with glipizide resulted in weight gain, whereas treatment with sitagliptin resulted in weight loss, resulting in a statistically significant and clinically meaningful between-group difference of 1.8 kg. These effects on body weight are consistent with previous reports (20,21). A significantly greater proportion of patients in the sitagliptin group achieved the composite end point of reduction in A1C >0.5%, no body weight gain, and no hypoglycemia compared with those in the glipizide group.

In summary, sitagliptin provided glycemic control that was noninferior to that observed with glipizide in patients with T2DM and chronic renal insufficiency who had inadequate glycemic control. Both agents provided clinically important improvements in A1C and FPG. The percentage of patients with reported hypoglycemia and the number of events of hypoglycemia were substantially and clinically meaningfully lower with sitagliptin compared with glipizide. Treatment with sitagliptin led to a small reduction in body weight, and treatment with glipizide led to weight gain. Other than the differences in hypoglycemia and body weight, both agents had similar safety profiles, with a low and similar rate of serious AEs and discontinuations due to AEs.

Acknowledgments—This study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, the manufacturer of sitagliptin.

J.C.A.F., H.G., G.T.G., C.M.S., K.D.K., and B.J.G. are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and may have stock or stock options in the company. N.B. has served on the National Diabetes Advisory Board. M.M. is a consultant for Association Diabete Risque Vasculaire, serves on the Merck global advisory board and the French subsidiary advisory board, and is a speaker for Merck, Sanofi, Novo Nordisk, Servier, and Abbott Diagnostics. No other potential conflicts of interest relevant to this article were reported.

J.C.A.F. assembled the data, interpreted the results, wrote sections of the initial draft, provided substantive suggestions for revision, critically reviewed subsequent iterations of the manuscript, and reviewed and approved the final version of the manuscript. M.M. provided patients, interpreted the results, provided substantive suggestions for revision, critically reviewed subsequent iterations of the manuscript, and reviewed and approved the final version of the manuscript. N.B. conceived and designed the study, interpreted the results, provided substantive suggestions for revision, critically reviewed subsequent iterations of the manuscript, and reviewed and approved the final version of the manuscript. H.G. performed analyses, interpreted the results, provided substantive suggestions for revision, critically reviewed subsequent iterations of the manuscript, and reviewed and approved the

final version of the manuscript. G.T.G. performed and supervised analyses, interpreted the results, provided substantive suggestions for revision, critically reviewed subsequent iterations of the manuscript, provided statistical expertise, and reviewed and approved the final version of the manuscript. C.M.S. interpreted the results, wrote sections of the initial draft, provided substantive suggestions for revision, critically reviewed subsequent iterations of the manuscript, and reviewed and approved the final version of the manuscript. K.D.K. conceived, designed and planned the study, interpreted the results, provided substantive suggestions for revision, critically reviewed subsequent iterations of the manuscript, and reviewed and approved the final version of the manuscript. B.J.G. supervised analyses, interpreted the results, provided substantive suggestions for revision, provided technical and logistical support, critically reviewed subsequent iterations of the manuscript, and reviewed and approved the final version of the manuscript. J.C.A.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

This study was presented as a poster at the 4th Annual Meeting of the Diabetes and Cardiovascular Disease EASD Study Group, Munich, Germany, 27–29 October 2011.

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