Effect of Initial Combination Therapy With Sitagliptin, a Dipeptidyl Peptidase-4 Inhibitor, and Metformin on Glycemic Control in Patients With Type 2 Diabetes

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OBJECTIVE — To assess the efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes and inadequate glycemic control on diet and exercise.

RESEARCH DESIGN AND METHODS — In a 24-week, randomized, double-blind, placebo-controlled, parallel-group study, 1,091 patients with type 2 diabetes and A1C 7.5–11% were randomized to one of six daily treatments: sitagliptin 100 mg/metformin 1,000 mg (S100/M1000 group), sitagliptin 100 mg/metformin 2,000 mg (S100/M2000 group), metformin 1,000 mg (M1000 group), metformin 2,000 mg (M2000 group) (all as divided doses administered twice daily [b.i.d.]), sitagliptin 100 mg q.d. (S100 group), or placebo. Patients who had an A1C >11% or a fasting glucose value >280 mg/dl after the run-in period were not eligible to be randomized; these patients could participate in an open-label substudy and were treated with S100/M2000 for 24 weeks.

RESULTS — The mean baseline A1C was 8.8% in the randomized patients. The placebo-subtracted A1C change from baseline was −2.07% (S100/M2000), −1.57% (S100/M1000), −1.30% (M2000), −0.99% (M1000), and −0.83% (S100) ($P < 0.001$ for comparisons versus placebo and for coadministration versus respective monotherapies). The proportion of patients achieving an A1C <7% and <6.5% was 66 and 44%, respectively, in the S100/M2000 group ($P < 0.001$ vs. S100 or M2000). For the open-label cohort ($n = 117$; baseline A1C 11.2%) treated with S100/M2000, the within-group mean A1C change from baseline was −2.9%. The incidence of hypoglycemia was low (0.5–2.2%) across active treatment groups and not significantly different from that in the placebo group (0.6%). The incidence of gastrointestinal adverse experiences was similar for coadministration therapies compared with their respective metformin monotherapy.

CONCLUSIONS — The initial combination of sitagliptin and metformin provided substantial and additive glycemic improvement and was generally well tolerated in patients with type 2 diabetes.

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Abbreviations: APT, all patients treated; AUC, area under the curve; FPG, fasting plasma glucose; GLP, glucagon-like peptide; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, HOMA of insulin resistance; OHA, oral antihyperglycemic agent; PPG, postprandial plasma glucose.

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

Initial antihyperglycemic monotherapy is often unsuccessful at getting patients with type 2 diabetes to glycemic goals, and as the glycemic targets recommended by standard guidelines are lowered, even fewer patients will achieve the goal with single-agent treatment (1,2). Due to the progressive nature of the disease, even patients getting to goal may require additional agents to maintain glycemic control over time (3). Initial combination therapy has emerged as an alternative approach, getting more patients to goal initially and avoiding or delaying the need for subsequent treatment regimen changes to maintain glycemic goals. Several current initial combination therapies are approved for use in the U.S., and at least one national guideline suggests the use of such initial combination therapy when patients have more marked hyperglycemia (4).

Sitagliptin, an oral and highly selective dipeptidyl peptidase-4 inhibitor, represents a novel therapeutic approach for the treatment of patients with type 2 diabetes (5). Dipeptidyl peptidase-4 inhibitors prevent the enzymatic degradation and inactivation of glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic peptide, the major incretins involved in glucose homeostasis (6). Following an oral glucose tolerance test, sitagliptin produced twofold increases in intact (active) GLP-1 and glucose-dependent insulinotropic peptide concentrations and, in a glucose-dependent manner, enhanced insulin release and reduced glucagon secretion relative to placebo in patients with type 2 diabetes (7). These changes contributed to the significant reduction in postprandial glucose concentration in these patients (7). Furthermore, in larger clinical trials, sitagliptin provided clinically meaningful reductions in A1C and in fasting and postprandial glucose concentrations and was well tolerated either as monotherapy or as an add-on therapy to metformin or pioglitazone (8–12).

Of the available therapies, metformin is the most commonly used oral antihyperglycemic agent (OHA), both as mono-

therapy and in combination with other agents such as sulfonylureas or thiazolidinediones (13–16). Metformin reduces elevated blood glucose levels by reducing hepatic glucose output and also by improving insulin resistance (17). Additionally, metformin has been reported to increase active GLP-1 concentrations by 1.5- to 2-fold following an oral glucose load in obese, nondiabetic subjects (18). This effect on GLP-1 was not the result of inhibiting dipeptidyl peptidase-4 activity (19,20).

Since sitagliptin and metformin lower glucose concentrations through different, but potentially complementary, mechanisms the initial combination of sitagliptin and metformin should provide effective, potentially additive, glycemic control. Beyond the complementary effects on the pathogenetic defects in patients with type 2 diabetes, the effects of these therapies on GLP-1 could provide another basis for complementary glucose lowering. The present study examined the efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patients with type 2 diabetes, 18–78 years of age, who were either on or not on an OHA at the screening visit were eligible to participate. Those with type 1 diabetes, unstable cardiac disease, significant renal impairment (estimated creatinine clearance <60 ml/min), or elevated (more than twofold the upper limit of normal) alanine aminotransferase or aspartate aminotransferase were excluded. Patients received counseling on diet and exercise consistent with American Diabetes Association recommendations throughout the study. Written informed consent was obtained from all patients. 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 (Sitagliptin Protocol 036). At screening, patients with an A1C of 7.5–11% 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 >11% and not on an OHA entered a diet and exercise run-in period of up to 6 weeks; and patients on an OHA with an A1C of 7–10.5% had the agent(s) discontinued and entered a wash-off period of 6–10 weeks (8–12 weeks for those on thiazolidinediones). After the wash-off/run-in period, patients with an A1C of 7.5–11% entered a 2-week, single-blind, placebo run-in period. All patients with adequate compliance (≥75% as assessed by tablet counts) during the placebo run-in period had baseline assessments and were randomized to one of six treatment regimens for 24 weeks: sitagliptin 50 mg/metformin 500 mg b.i.d. (S100/M1000 group), sitagliptin 50 mg/metformin 1,000 mg b.i.d. (S100/M2000 group), metformin 500 mg b.i.d. (M1000 group), metformin 1,000 mg b.i.d. (M2000 group), sitagliptin 100 mg q.d. (S100 group), or placebo. Patients who met nonglycemic eligibility criteria but who had an A1C >11% or a fasting glucose value >280 mg/dl after the run-in period were not eligible for randomization; these patients could participate in an open-label substudy and were treated with S100/M2000 for 24 weeks.

To reduce gastrointestinal intolerance associated with metformin, a brief period of uptitration was implemented. For patients randomized to receive metformin monotherapy (500 or 1,000 mg b.i.d.) or coadministration of sitagliptin (50 mg b.i.d.) and metformin, therapy was started at metformin 500 mg q.d. and increased in a blinded manner by increments of 500 mg per week to achieve a stable dose of either metformin 500 or 1,000 mg b.i.d. Since this study was designed to examine the potential benefit of a fixed-dose combination tablet of these two agents, sitagliptin was uptitrated as it would be with the use of a fixed-dose combination tablet (50 mg q.d. increased after 1 week to the stable study dose of 50 mg b.i.d.). Doses of study medication were administered before the morning and evening meals. Patients randomized to the sitagliptin 100 mg q.d. treatment group were administered two 50-mg tablets once daily before the morning meal.

During the active treatment period, patients not meeting progressively stricter glycemic goals were provided glycemic rescue therapy (glyburide [glibenclamide]) until study completion. The glycemic rescue criteria were fasting plasma glucose (FPG) >270 mg/dl between randomization (day 1) and week 6, FPG >240 mg/dl after weeks 6–12, and FPG >200 mg/dl after weeks 12–24. Study investigators were responsible for titration of the sulfonylurea rescue medication.

Study evaluations

Efficacy assessments. Change from baseline at week 24 was assessed for A1C (primary end point), FPG, fasting serum insulin, fasting serum proinsulin, and fasting lipids. Change from baseline in the proinsulin-to-insulin ratio and homeostasis model assessment of β-cell function (HOMA-β), which are estimates of β-cell function (21,22), and change from baseline in HOMA of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index, which are estimates of insulin resistance (21,23), were also evaluated. A standard meal tolerance test was administered at baseline (before the first dose of study medication) and week 24, with the end points analyzed as previously described (9).

Safety assessments. Data were collected regarding adverse experiences, physical examinations, vital signs, electrocardiograms, and body weight throughout the study. 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 electrocardiograms were analyzed at central laboratories (PPD Global Central Labs, Highland Heights, KY; and Zaventem, Belgium, and Covance Central Diagnostics, Reno, NV, respectively) by personnel blinded to treatment group as previously described (12).

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. The primary analyses focused on the efficacy response to the coadministration of sitagliptin and metformin compared with placebo and the respective monotherapies. An ANCOVA model compared 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 percent change) from baseline at week 24. Missing data were handled using the last-observation-carried-forward method. To avoid the confounding influence of glycemic rescue therapy on efficacy comparisons, efficacy data col-

lected after initiation of rescue therapy were treated as missing.

The proportion of patients achieving A1C <7 or <6.5% 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 A1C change from baseline were performed to explore whether treatment effects were consistent within subgroups, which included OHA status at screening (on or not on an OHA), baseline A1C, sex, age (< or ≥65 years), race, baseline BMI, known duration of diabetes, baseline HOMA-IR, and baseline HOMA-β.

Safety and tolerability were assessed in patients who received at least one dose of study medication by review of safety parameters. For body weight 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 hypoglycemia and gastrointestinal adverse experiences excluded data obtained after initiation of glycemic rescue therapy.

RESULTS

Randomized cohort

The disposition of screened patients is shown in Fig. 1 of the online appendix (available at http://dx.doi.org/10.2337/dc07-0627). Of 2,336 patients excluded from the study, the major reasons for exclusion were not meeting study entry criteria (84%), including 53% who did not meet A1C entry criteria, and consent withdrawal (10%) before randomization. For 1,091 patients who were randomized, the treatment groups were generally well balanced for baseline demographics and efficacy characteristics (online appendix Table 1). Overall, patients had a mean baseline A1C of 8.8% (range 6.3–11.9; 59% of patients had a baseline A1C <9%) and an FPG of 200 mg/dl. Since the A1C inclusion criterion was assessed at entry into the 2-week, single-blind, placebo run-in period, the baseline (i.e., randomization day) A1C could have differed from the week 2 value. Mean known duration of diabetes was 4.5 years, and 50% of patients were not taking an OHA for at least 8 weeks before screening visit. After randomization, 906 (83.0%) completed 24 weeks of treatment and 1,056 patients (96.8%) were included in the APT analysis. Of 35 patients excluded from the APT analysis, 1 had no baseline data and 34 had no on-treatment data.

Efficacy

All active treatments produced statistically significant ($P < 0.001$) changes in A1C from baseline at week 24 relative to placebo (Table 1). The least-squares mean differences for A1C were also statistically significant ($P < 0.001$) between the coadministration treatment groups and the sitagliptin and respective metformin monotherapy groups (Table 1). The magnitude of the placebo-adjusted reduction in A1C in the coadministration groups relative to that of the individual monotherapies demonstrated an additive response when the two agents were administered together (Table 1). The change in A1C profiles showed that the response was consistent over time with stable values, once the full effect was achieved, over the 24-week treatment period (Fig. 1*A*).

The proportion of patients achieving an A1C <7% at week 24 was significantly ($P < 0.001$) greater with all active treatments (*n*/*N* [%]: S100/M2000, 118/178 [66]; S100/M1000, 79/183 [43]; M2000, 68/177 [38]; M1000, 41/178 [23]; and S100, 35/175 [20] compared with placebo, 15/165 [9]). The proportion of patients achieving an A1C <6.5% at week 24 was also significantly ($P \leq 0.005$) greater with all active treatments (S100/M2000, 78/178 [44]; S100/M1000, 40/183 [22]; M2000, 36/177 [20]; M1000, 16/178 [9]; and S100, 18/175 [10] compared with placebo, 4/165 [2]). The differences in proportions achieving an A1C <7 or <6.5% were also statistically significant ($P < 0.01$) between the coadministration treatment groups and the respective monotherapy groups. The time to the initiation of protocol-specified glycemic rescue therapy was significantly longer with all active treatments relative to placebo ($P < 0.01$ for all groups vs. placebo). More patients in the placebo group (*n* [%] = 57 [32]) required glycemic rescue therapy than in the S100/M2000 (4 [2]), S100/M1000 (15 [8]), M2000 (21 [12]), M1000 (31 [17]), and S100 (38 [21]) groups.

Treatment effects were generally consistent in subgroups defined by demographic (e.g., sex, age, ethnic group/race), anthropometric (e.g., BMI), and disease (e.g., known disease duration, HOMA-β, HOMA-IR, proinsulin-to-insulin ratio) characteristics. However, a significant baseline A1C by treatment interaction ($P < 0.001$) was observed with greater placebo-subtracted A1C reductions in patients with baseline A1C ≥9% (−2.01% in the S100/M1000 and −2.57% in the S100/M2000 groups) compared with those with baseline A1C ≥8 to <9% (−1.49 and −1.96%) or baseline A1C <8% (−1.07 and −1.45%).

All active treatments produced statistically significant ($P < 0.001$) changes in FPG from baseline at week 24 relative to placebo (Table 1). Changes in FPG were statistically significant ($P < 0.001$) between the coadministration treatment groups and the sitagliptin and respective metformin monotherapy groups (Table 1). Similar to the A1C results, the magnitude of the FPG reduction in the coadministration groups was additive relative to the individual monotherapy effects. Across all active treatment groups, FPG response over time was generally stable after the nadir was achieved by week 6 (Fig. 1*B*).

The proinsulin-to-insulin ratio was significantly ($P < 0.05$) improved with all active treatments versus placebo after 24 weeks, and the differences between the coadministration treatment groups and the sitagliptin and respective metformin monotherapy groups were also significantly different (Table 1). HOMA-β was significantly ($P < 0.05$) improved in the coadministration and the high-dose metformin groups relative to the placebo group, and coadministration also significantly increased HOMA-β relative to sitagliptin and the respective metformin monotherapy groups (Table 1). HOMA-IR was significantly ($P < 0.05$) reduced in the coadministration and metformin groups relative to the placebo group, and coadministration with high-dose metformin produced significant changes in HOMA-IR relative to the monotherapy components (Table 1). Improvements similar to those observed for HOMA-IR were also observed for quantitative insulin sensitivity check index (data not shown).

Following ingestion of a standard meal, 2-h postprandial plasma glucose (PPG), total glucose area under the curve (AUC), and the ratio of insulin AUC to glucose AUC were significantly ($P \leq 0.05$) improved with all active treatments relative to placebo (Table 2).

Table 1—*Fasting efficacy end points*

Parameter	Placebo	Sitagliptin 100 mg q.d.	Metformin 500 mg b.i.d.	Metformin 1,000 mg b.i.d.	Sitagliptin 50 mg + metformin 500 mg b.i.d.	Sitagliptin 50 mg + metformin 1,000 mg b.i.d.
A1C (%)						
n	165	175	178	177	183	178
Baseline	8.68 ± 1.00	8.87 ± 0.99	8.90 ± 1.00	8.68 ± 0.91	8.79 ± 1.00	8.76 ± 0.95
Week 24	8.88 ± 1.47	8.18 ± 1.45	8.04 ± 1.36	7.58 ± 1.27	7.37 ± 1.20	6.87 ± 1.09
Change from baseline	0.17 (0.00–0.33)	−0.66 (−0.83 to −0.50)	−0.82 (−0.98 to −0.66)	−1.13 (−1.29 to −0.97)	−1.40 (−1.56 to −1.24)	−1.90 (−2.06 to −1.74)
Change from placebo	—	−0.83 (−1.06 to −0.60)*	−0.99 (−1.22 to −0.75)*	−1.30 (−1.53 to −1.06)*	−1.57 (−1.80 to −1.34)*†	−2.07 (−2.30 to −1.84)*†
FPG (mg/dl)						
n	169	178	179	179	183	180
Baseline	196.3 ± 47.4	201.4 ± 49.4	205.2 ± 50.6	197.0 ± 46.8	203.9 ± 51.7	196.7 ± 48.2
Week 24	203.6 ± 61.0	183.4 ± 54.8	175.8 ± 56.0	169.0 ± 64.9	155.1 ± 47.6	134.2 ± 36.1
Change from baseline	5.8 (−1.0 to 12.7)	−17.5 (−24.1 to −10.8)	−27.3 (−34.0 to −20.7)	−29.3 (−35.9 to −22.6)	−47.1 (−53.7 to −40.6)	−63.9 (−70.5 to −57.3)
Change from placebo	—	−23.3 (−32.8 to −13.8)*	−33.1 (−42.7 to −23.6)*	−35.1 (−44.6 to −25.6)*	−52.9 (−62.4 to −43.5)*†	−69.7 (−79.2 to −60.2)*†
Fasting proinsulin (pmol/l)						
n	91	114	130	138	153	161
Baseline	33.3 ± 32.8	30.6 ± 25.5	36.1 ± 30.3	38.5 ± 31.3	36.9 ± 34.7	36.2 ± 30.6
Week 24	33.7 ± 30.7	31.5 ± 30.2	30.4 ± 25.8	27.7 ± 29.1	30.2 ± 35.0	20.4 ± 19.1
Change from baseline	−0.5 (−4.7 to 3.7)	−1.0 (−4.8 to 2.8)	−5.5 (−9.1 to −2.0)	−9.7 (−13.1 to −6.3)	−6.2 (−9.5 to −3.0)	−15.5 (−18.6 to −12.3)
Change from placebo	—	−0.5 (−6.1 to 5.1)	−5.0 (−10.5 to 0.4)	−9.2 (−14.6 to −3.8)*	−5.7 (−11.0 to −0.4)‡§	−14.9 (−20.2 to −9.7)*‖
Proinsulin-to-insulin ratio						
n	91	114	129	137	152	157
Baseline	0.42 ± 0.22	0.44 ± 0.21	0.48 ± 0.30	0.48 ± 0.25	0.51 ± 0.31	0.49 ± 0.35
Week 24	0.45 ± 0.39	0.38 ± 0.20	0.39 ± 0.26	0.35 ± 0.18	0.35 ± 0.24	0.28 ± 0.17
Change from baseline	−0.01 (−0.05 to 0.04)	−0.08 (−0.12 to −0.04)	−0.09 (−0.12 to −0.05)	−0.12 (−0.16 to −0.09)	−0.14 (−0.17 to −0.11)	−0.20 (−0.23 to −0.17)
Change from placebo	—	−0.08 (−0.13 to −0.01)‡	−0.08 (−0.14 to −0.03)‡	−0.12 (−0.17 to −0.06)*	−0.14 (−0.19 to −0.08)*‖	−0.20 (−0.25 to −0.15)*†
HOMA-β						
n	139	147	159	154	166	160
Baseline	40.9 ± 34.1	37.9 ± 32.2	43.1 ± 38.3	44.8 ± 37.7	41.8 ± 37.6	41.4 ± 33.4
Week 24	44.7 ± 49.8	48.7 ± 43.5	54.2 ± 45.1	59.1 ± 50.6	72.8 ± 61.1	74.4 ± 56.8
Change from baseline	3.7 (−2.5 to 9.9)	10.8 (4.8 to 16.9)	11.1 (5.3 to 16.9)	14.3 (8.4 to 20.3)	31.0 (25.3 to 36.7)	33.0 (27.2 to 38.8)
Change from placebo	—	7.1 (−1.6 to 15.8)	7.3 (−1.2 to 15.9)	10.6 (2.0 to 19.2)‡	27.3 (18.9 to 35.7)*†	29.3 (20.8 to 37.8)*†
HOMA-IR						
n	139	147	159	154	166	160
Baseline	6.0 ± 4.0	6.0 ± 4.5	6.6 ± 5.0	6.9 ± 4.8	7.0 ± 6.6	6.6 ± 5.6
Week 24	6.6 ± 4.7	6.1 ± 5.0	5.9 ± 4.7	5.4 ± 4.3	6.0 ± 5.6	4.2 ± 3.3
Change from baseline	0.3 (−0.3 to 1.0)	−0.2 (−0.8 to 0.4)	−0.7 (−1.3 to −0.1)	−1.3 (−1.9 to −0.7)	−0.8 (−1.4 to −0.2)	−2.4 (−2.9 to −1.8)
Change from placebo	—	−0.5 (−1.4 to 0.4)	−1.1 (−1.9 to −0.2)‡	−1.6 (−2.5 to −0.8)*	−1.1 (−2.0 to −0.3)‡	−2.7 (−3.5 to −1.8)*

Data are means ± SD for baseline and week 24 data and least-squares mean change (95% CI) for change from baseline or placebo. *$P \leq 0.001$ for the between-group difference relative to placebo. †$P \leq 0.001$ for the between-group difference comparing coadministration and both of its respective components. ‡$P \leq 0.05$ for the between-group difference relative to placebo. §$P < 0.05$ for the between-group difference comparing coadministration and sitagliptin 100 mg q.d. ‖$P \leq 0.05$ for the between-group difference comparing coadministration and both of its respective components.

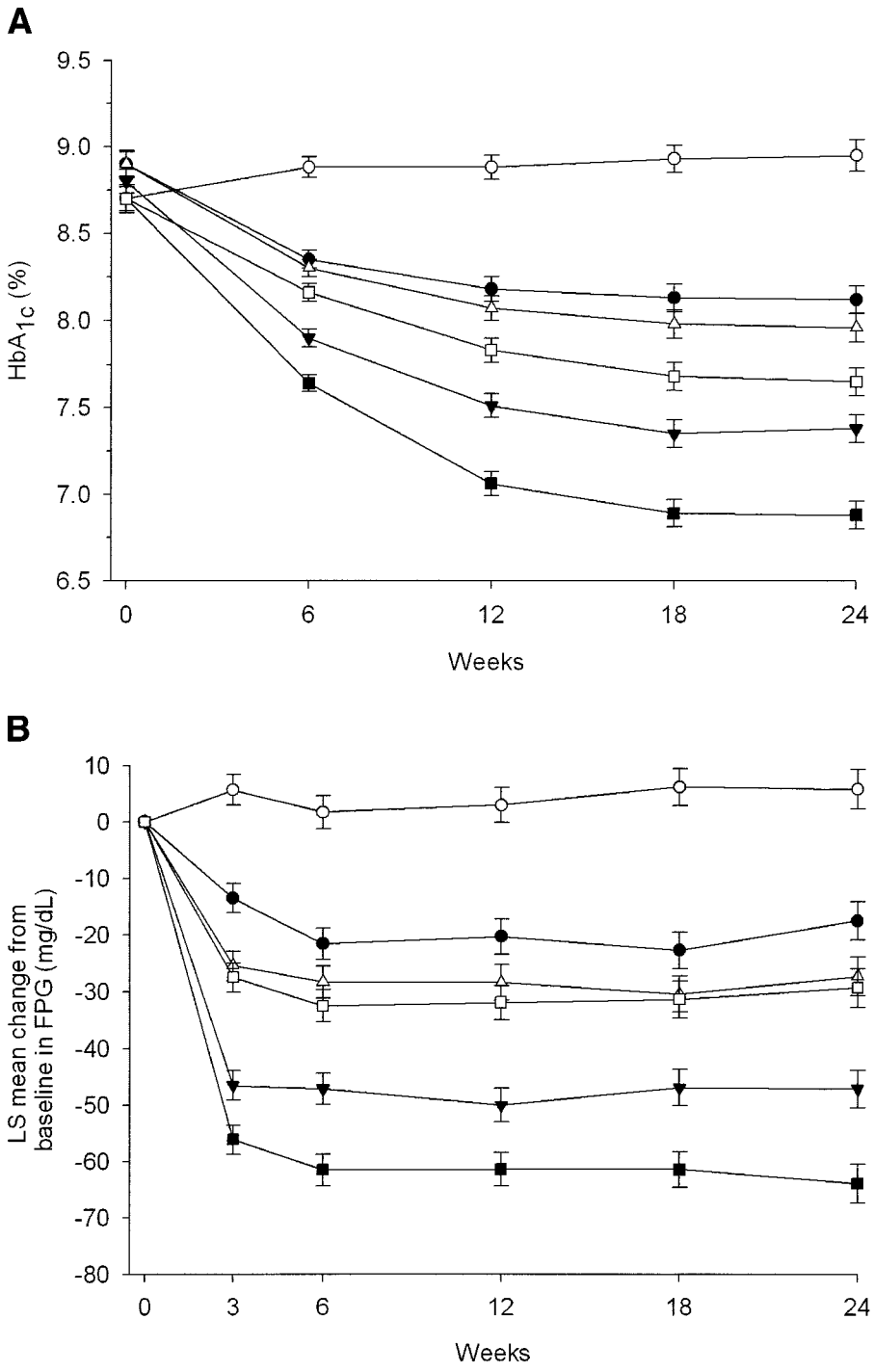

Figure 1—*Least-squares (LS) mean (±SE) A1C over time* (A) *and least-squares mean change in FPG from baseline (±SE)* (B) *over time for randomized patients treated with sitagliptin 50 mg + metformin 1,000 mg b.i.d. (■), sitagliptin 50 mg + metformin 500 mg b.i.d. (▼), metformin 1,000 mg b.i.d. (□), metformin 500 mg b.i.d. (△), sitagliptin 100 mg q.d. (●), or placebo (○).*

Moreover, the changes in these parameters with coadministration were all significant ($P \leq 0.05$) when compared with the sitagliptin and respective metformin monotherapy groups. Results from additional end points of the meal tolerance test are provided in Table 2.

Safety and tolerability

The incidence of adverse experiences varied only modestly across the treatment groups, with the highest incidence in the high-dose metformin monotherapy group and the lowest incidence in the placebo group (Table 3). The sitagliptin monotherapy group had the lowest incidence of drug-related adverse experiences relative to all other groups including the placebo group. The incidence of drug-related adverse experiences was similar between the coadministration groups and their respective metformin monotherapy groups. The incidence of serious adverse experiences was generally similar across treatment groups, with slightly higher incidences in the placebo and sitagliptin monotherapy groups (that were similar). One drug-related serious adverse experience was reported (a patient in the placebo group with ketoacidosis). One patient in the placebo treatment group died during the study (due to sudden cardiac death). There were no meaningful between-group differences observed for adverse experiences (including serious and/or drug related) leading to discontinuation.

The incidence of hypoglycemia was low (0.6–2.2%) and similar among all groups (Table 3). No episode of hypoglycemia exhibited marked severity (i.e., loss of consciousness or requirement for medical assistance). Relative to the placebo group, the proportion of patients reporting gastrointestinal adverse experiences was slightly increased in the sitagliptin and low-dose metformin groups (monotherapy and coadministration) and modestly increased in the high-dose metformin groups (monotherapy and coadministration) (Table 3). For the prespecified specific gastrointestinal adverse experiences, the incidences tended to be higher in the high-dose metformin groups (monotherapy and coadministration) relative to the other treatment groups (Table 3). Incidences of gastrointestinal adverse experiences for a given metformin dose were similar for the coadministration groups compared with the metformin monotherapy groups.

After 24 weeks, significant reductions in body weight relative to baseline (−0.6 to −1.3 kg; $P < 0.05$) were observed in all groups, except in the sitagliptin group in which no change from baseline (0.0 kg) was observed. The change from baseline in body weight with placebo (−0.9 kg) was significantly ($P < 0.01$) different from that observed with sitagliptin.

Open-label cohort

A total of 117 patients were enrolled in the open-label cohort, of whom 79 patients completed 24 weeks of treatment and 38 discontinued for various reasons (online appendix Fig. 1). Of the discontinuations, 19 patients were discontinued

Table 2—*Efficacy end points following a meal tolerance test*

Parameter	Placebo	Sitagliptin 100 mg q.d.	Metformin 500 mg b.i.d.	Metformin 1,000 mg b.i.d.	Sitagliptin 50 mg + metformin 500 mg b.i.d.	Sitagliptin 50 mg + metformin 1,000 mg b.i.d.
2-h PPG (mg/dl)						
n	129	136	141	138	147	152
Baseline	276.8 ± 66.7	285.4 ± 82.8	292.7 ± 74.6	283.4 ± 81.8	291.8 ± 84.6	286.9 ± 76.2
Week 24	281.3 ± 88.2	233.8 ± 89.5	236.3 ± 70.8	207.0 ± 69.4	196.3 ± 72.5	170.3 ± 58.6
Change from baseline	0.3 (−10.4 to 11.0)	−51.9 (−62.3 to −41.5)	−53.4 (−63.6 to −43.2)	−78.0 (−88.3 to −67.6)	−92.5 (−102.6 to −82.5)	−116.6 (−126.4 to −106.7)
Change from placebo	—	−52.2 (−67.1 to −37.3)*	−53.7 (−68.5 to −38.9)*	−78.3 (−93.1 to −63.4)	−92.8 (−107.5 to −78.1)*†	−116.9 (−131.4 to −102.3)*†
Glucose AUC ($mg \cdot h^{-1} \cdot dl^{-1}$)						
n	127	133	144	137	149	146
Baseline	523.0 ± 109.4	530.2 ± 123.9	538.4 ± 116.0	532.1 ± 125.6	539.9 ± 136.7	530.0 ± 120.7
Week 24	533.3 ± 146.9	453.2 ± 135.3	451.3 ± 118.4	401.7 ± 120.4	383.9 ± 114.0	339.0 ± 100.4
Change from baseline	6.1 (−11.7 to 23.9)	−78.0 (−95.4 to −60.6)	−84.4 (−101.1 to −67.7)	−130.8 (−147.9 to −113.6)	−152.4 (−168.9 to −136.0)	−192.3 (−209.0 to −175.7)
Change from placebo	—	−84.2 (−109.1 to −59.3)*	−90.5 (−115.5 to −66.1)*	−136.9 (−161.6 to −112.2)*	−158.6 (−182.8 to −134.3)*†	−198.5 (−222.8 to −174.1)*†
Insulin AUC ($\mu IU \cdot h^{-1} \cdot ml^{-1}$)						
n	119	117	130	125	126	133
Baseline	76.5 ± 52.9	71.2 ± 50.2	80.1 ± 56.4	84.3 ± 53.6	79.0 ± 57.2	74.9 ± 47.2
Week 24	75.0 ± 50.3	78.1 ± 49.3	83.1 ± 54.6	82.2 ± 51.4	86.3 ± 55.7	74.5 ± 40.6
Change from baseline	−1.8 (−7.5 to 3.9)	5.2 (−0.6 to 11.0)	3.6 (−1.9 to 9.1)	−0.4 (−6.0 to 5.2)	7.5 (2.0 to 13.1)	−1.1 (−6.5 to 4.4)
Change from placebo	—	7.0 (−1.2 to 15.1)	5.4 (−2.5 to 13.3)	1.4 (−6.6 to 9.4)	9.4 (1.4 to 17.3) ‡	0.7 (−7.1 to 8.6)
C-peptide AUC ($ng \cdot h^{-1} \cdot ml^{-1}$)	125	135	143	138	146	145
n						
Baseline	9.8 ± 4.3	9.8 ± 4.3	10.3 ± 4.1	10.9 ± 4.3	9.9 ± 4.3	10.1 ± 4.1
Week 24	9.8 ± 4.2	10.5 ± 4.0	10.2 ± 4.1	10.6 ± 4.1	10.6 ± 4.1	10.4 ± 4.1
Change from baseline	−0.1 (−0.5 to 0.3)	0.6 (0.2 to 1.0)	0.0 (−0.4 to 0.4)	−0.1 (−0.5 to 0.3)	0.6 (0.2 to 1.0)	0.3 (−0.1 to 0.7)
Change from placebo	—	0.7 (0.1 to 1.3)‡	0.1 (−0.5 to 0.7)	0.0 (−0.6 to 0.6)	0.7 (0.1 to 1.3)‡§	0.4 (−0.2 to 1.0)
Insulin AUC/glucose AUC	117	115	128	121	125	130
n						
Baseline	0.16 ± 0.14	0.15 ± 0.12	0.16 ± 0.12	0.18 ± 0.15	0.16 ± 0.14	0.16 ± 0.12
Week 24	0.16 ± 0.14	0.19 ± 0.13	0.20 ± 0.15	0.23 ± 0.17	0.24 ± 0.17	0.23 ± 0.14
Change from baseline	0.00 (−0.02 to 0.02)	0.04 (0.02 to 0.05)	0.04 (0.02 to 0.06)	0.05 (0.03 to 0.07)	0.08 (0.06 to 0.10)	0.08 (0.06 to 0.09)
Change from placebo	—	0.03 (0.01 to 0.06)‡	0.04 (0.01 to 0.06)‡	0.05 (0.02 to 0.07)*	0.08 (0.05 to 0.10)*†	0.07 (0.05 to 0.10)*‖

Data are means ± SD for baseline and week 24 and least-squares mean change (95% CI) for change from baseline or placebo. *$P \leq 0.001$ for the between-group difference relative to placebo. †$P \leq 0.001$ for the between-group difference comparing coadministration and its respective components. ‡$P \leq 0.05$ for the between-group difference relative to placebo. §$P < 0.05$ for the between-group difference comparing coadministration and metformin 500 mg b.i.d. ‖$P \leq 0.05$ for the between-group difference comparing coadministration and its respective components.

Table 3—*Clinical adverse experience summary*

Patients*	Placebo	Sitagliptin 100 mg q.d.	Metformin 500 mg b.i.d.	Metformin 1,000 mg b.i.d.	Sitagliptin 50 mg + metformin 500 mg b.i.d.	Sitagliptin 50 mg + metformin 1,000 mg b.i.d.	Open-label cohort†
n	176	179	182	182	190	182	117
One or more adverse experiences	89 (50.6)	96 (53.6)	101 (55.5)	113 (62.1)	110 (57.9)	105 (57.7)	69 (59.0)
Drug-related adverse experiences‡	17 (9.7)	12 (6.7)	21 (11.5)	30 (16.5)	24 (12.6)	28 (15.4)	23 (19.7)
Serious adverse experiences	10 (5.7)	9 (5.0)	4 (2.2)	2 (1.1)	6 (3.2)	1 (0.5)	3 (2.6)
Drug-related serious adverse experiences‡	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Who died	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to adverse experiences	7 (4.0)	5 (2.8)	4 (2.2)	5 (2.7)	5 (2.6)	2 (1.1)	3 (2.6)
Discontinued due to drug-related adverse experiences	2 (1.1)	0 (0.0)	2 (1.1)	5 (2.7)	2 (1.1)	1 (0.5)	2 (1.7)
Discontinued due to serious adverse experiences	5 (2.8)	4 (2.2)	2 (1.1)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Discontinued due to drug-related serious adverse experiences	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Special adverse experiences of interest							
Hypoglycemia	1 (0.6)	1 (0.6)	1 (0.5)	2 (1.1)	2 (1.1)	4 (2.2)	2 (1.7)
All gastrointestinal adverse experiences	19 (10.8)	27 (15.1)	29 (15.9)	46 (25.3)	34 (17.9)	45 (24.7)	32 (27.4)
Selected gastrointestinal adverse experiences							
Diarrhea	7 (4.0)	5 (2.8)	9 (4.9)	19 (10.4)	12 (6.3)	16 (8.8)	10 (8.5)
Nausea	2 (1.1)	2 (1.1)	5 (2.7)	15 (8.2)	8 (4.2)	10 (5.5)	7 (6.0)
Abdominal pain	4 (2.3)	6 (3.4)	5 (2.7)	9 (4.9)	5 (2.6)	6 (3.3)	6 (5.1)
Vomiting	1 (0.6)	0 (0.0)	0 (0.0)	2 (1.1)	2 (1.1)	6 (3.3)	4 (3.4)

Data are *n* (%). *Excludes data after initiation of glycemic (glyburide/glibenclamide) rescue therapy. †Open-label cohort treated with sitagliptin 50 mg + metformin 1,000 mg b.i.d. ‡Considered by the investigator to be drug related.

due to insufficient glycemic control. The baseline characteristics of the patients in the open-label cohort were a mean age of 53 years, 57% male, 46% Hispanic and 38% white, a mean BMI of 31 kg/m^2, a mean A1C of 11.2% (range 8.0–15.5; with 86% ≥10.0%), a mean FPG of 314 mg/dl (184–490), and a mean known duration of type 2 diabetes of 6.1 years (0.1–36). After 24 weeks of treatment with sitagliptin 50 mg and metformin 1,000 mg coadministered twice daily, the within-group mean A1C change from baseline was −2.9% in the APT population. The proportion of patients achieving an A1C <7 or <6.5% was 22% (*n*/*N* = 24/111) and 8% (9/111), respectively. For the completers' population (mean baseline A1C 11.2%), the change from baseline for A1C was −3.5%. FPG change from baseline was −127 mg/dl in the APT population and −137 mg/dl in the completers' population (mean baseline FPG 311 mg/dl). Following a meal tolerance test, 2-h PPG was reduced by −208 mg/dl from a baseline of 441 mg/dl at week 24. HOMA-β was increased from a baseline value of 17 to 56 at week 24. In this open-label cohort, treatment was generally well tolerated, with a profile similar to that observed in patients in the randomized cohort receiving the same treatment regimen (Table 3). There was an increase in body weight of 1.3 kg relative to baseline.

CONCLUSIONS — Therapy with the initial combination of sitagliptin and metformin was assessed for efficacy and tolerability in patients with type 2 diabetes who had inadequate glycemic control with diet and exercise. In this study, all active treatments produced clinically meaningful reductions in A1C, FPG, and 2-h PPG compared with placebo, and the coadministration groups provided greater reductions relative to the individual monotherapies (compared at the same metformin dose). After reaching the nadir, the changes in A1C and FPG were relatively stable over 24 weeks in all active treatment groups. Greater proportions of patients achieved A1C targets with all active treatments relative to placebo, with the coadministration of sitagliptin and high-dose metformin getting about two-thirds of patients to the A1C goal of <7%.

As with other antihyperglycemic agents (24), including sitagliptin (9,11), patients with more severe baseline hyperglycemia (i.e., A1C ≥9%) had the largest reductions with coadministration of sitagliptin and metformin. This observation

in the randomized cohort was reinforced by the large reduction of 2.9% from baseline observed in the open-label cohort. The marked reductions observed in A1C with coadministration corresponded with the substantial improvements in both FPG and PPG.

Sitagliptin and metformin have different mechanisms, thus predicting a potential complementary effect on lowering glucose levels. In addition, a recently completed study demonstrated that sitagliptin and metformin each increased fasting and postmeal active GLP-1 levels in healthy subjects and, in combination, increased active GLP-1 levels in an additive fashion (E.M. Migoya, G.A. Herman, J.A. Wagner, personal communication). Consistent with the overall complementary mechanisms of action, essentially additive efficacy of sitagliptin and metformin was observed for A1C, FPG, and 2-h PPG. Additivity of glycemic improvement is an unusual observation not generally demonstrated in other studies of initial combination therapies (14,15,25–27), although such differences could be explained by differences in study design or patient populations studied. Since the extent of glucose lowering is generally closely related to the pretreatment glucose levels, the lack of additivity for most other initial combination treatments is likely explained by the effect of one agent attenuating the extent of response to the other agent. Thus, the full additivity on A1C lowering observed in this study suggests the presence of complementary glucose lowering for initial treatment with the combination of sitagliptin and metformin.

Evidence from the present study suggests that the combination of sitagliptin and metformin improves the pathologic defects associated with type 2 diabetes: diminished β-cell function with reduced insulin release, increased insulin resistance, and increased hepatic glucose output (28–30). Coadministration improved markers of β-cell function (including HOMA-β, proinsulin-to-insulin ratio, insulin AUC–to–glucose AUC ratio), improved markers of insulin resistance (HOMA-IR, quantitative insulin sensitivity check index), and substantially lowered fasting glucose, which tightly correlates with hepatic glucose production (28).

In the randomized cohort, all metformin-based groups and the placebo group experienced small but significant reductions in body weight, while there was no change in the sitagliptin group in the present study. These results are consistent with previous findings for both treatments (8–10). Since weight gain has been observed with intensive glycemic control (31), the substantially greater glycemic improvement with coadministration therapy might have been expected to lead to an attenuation of the weight loss typically seen with metformin. Of interest, the weight loss in the coadministration groups relative to the monotherapy metformin groups was similar. The modest increase in body weight observed in the open-label cohort is not surprising given the marked improvement in glycemic control observed, which, as noted above, would be expected to be associated with weight gain.

All active treatments were generally well tolerated in this study. There was a slightly higher incidence of drug-related adverse experiences (related to higher incidence of gastrointestinal adverse experiences) in both high-dose metformin groups (i.e., monotherapy and coadministration therapy), with more discontinuations due to these drug-related adverse experiences in the higher-dose metformin monotherapy group. The gastrointestinal adverse experience profile of the combination was similar to that of metformin monotherapy, when compared at the same dose. Despite marked improvements in glycemic control, there was a low incidence of hypoglycemia across the treatment groups. Prior studies (8–10,12) with sitagliptin have reported a low incidence of hypoglycemia that was similar to placebo. This is consistent with the glucose-dependent effects of incretins (11). Similarly, metformin has been associated with a low incidence of hypoglycemia (32).

In summary, initial combination therapy with sitagliptin and metformin provided substantial and additive glycemic improvement in these patients with type 2 diabetes, suggesting that the marked benefit of this combination is the product of the complementary actions of these two agents. This combination was also generally well tolerated, with a tolerability profile similar to metformin alone.

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