The Efficacy and Safety of Saxagliptin When Added to Metformin Therapy in Patients With Inadequately Controlled Type 2 Diabetes With Metformin Alone

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OBJECTIVE — This 24-week trial assessed the efficacy and safety of saxagliptin as add-on therapy in patients with type 2 diabetes with inadequate glycemic control with metformin alone.

RESEARCH DESIGN AND METHODS — This was a randomized, double-blind, placebo-controlled study of saxagliptin (2.5, 5, or 10 mg once daily) or placebo plus a stable dose of metformin (1,500–2,500 mg) in 743 patients (A1C ≥7.0 and ≤10.0%). Efficacy analyses were performed using an ANCOVA model using last observation carried forward methodology on primary (A1C) and secondary (fasting plasma glucose [FPG] and postprandial glucose [PPG] area under the curve [AUC]) end points.

RESULTS — Saxagliptin (2.5, 5, and 10 mg) plus metformin demonstrated statistically significant adjusted mean decreases from baseline to week 24 versus placebo in A1C (−0.59, −0.69, and −0.58 vs. +0.13%; all $P < 0.0001$), FPG (−14.31, −22.03, and −20.50 vs. +1.24 mg/dl; all $P < 0.0001$), and PPG AUC (−8,891, −9,586, and −8,137 vs. −3,291 mg · min/dl; all $P < 0.0001$). More than twice as many patients achieved A1C <7.0% with 2.5, 5, and 10 mg saxagliptin versus placebo (37, 44, and 44 vs. 17%; all $P < 0.0001$). β-Cell function and postprandial C-peptide, insulin, and glucagon AUCs improved in all saxagliptin treatment groups at week 24. Incidence of hypoglycemic adverse events and weight reductions were similar to those with placebo.

CONCLUSIONS — Saxagliptin once daily added to metformin therapy was generally well tolerated and led to statistically significant improvements in glycemic indexes versus placebo added to metformin in patients with type 2 diabetes inadequately controlled with metformin alone.

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Saxagliptin is a potent, selective dipeptidyl peptidase-4 (DPP-4) inhibitor, specifically designed for extended inhibition of the DPP-4 enzyme (1,2). DPP-4 rapidly cleaves and inactivates the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (1). GLP-1 and GIP regulate blood glucose homeostasis by stimulation of glucose-dependent insulin secretion (3). GLP-1 also delays gastric emptying and inhibits glucagon secretion (3,4). In rodents, GLP-1 has been shown to stimulate β-cell growth and differentiation and inhibit β-cell apoptosis (5). Such an approach is needed because the majority of patients with type 2 diabetes fail to achieve recommended glycemic targets with existing therapies, owing to safety and tolerability issues and loss of efficacy over time (6).

Metformin is the most widely prescribed first-line agent for the management of type 2 diabetes and is standard first-line pharmacotherapy, along with diet and exercise (7). Mechanistically, metformin reduces hepatic glucose production and improves insulin sensitivity (8); however, metformin alone is frequently insufficient to maintain glycemic goals in the face of progressive β-cell failure and increasing insulin resistance (9). Consequently, many patients require multiple oral antihyperglycemic agents (9,10). Metformin works through pathways complementary to saxagliptin, and the combination of saxagliptin with metformin may improve glycemic control (11,12). Studies of other DPP-4 inhibitors in combination with metformin over 24 weeks have demonstrated increased efficacy versus placebo (13–15). The safety and efficacy of saxagliptin monotherapy in treatment-naive patients were established previously in a 12-week study across a dose range of 2.5 to 40 mg/day. Significant A1C reductions were demonstrated in all active treatment groups with maximal A1C efficacy observed with 5 mg saxagliptin. A test for log-linear trend across the treatment groups did not demonstrate a statistically significant dose response after 12 weeks of treatment. The overall frequency of adverse events was comparable across all treatment groups and placebo and did not appear to be dose related (16). The current trial (CV181-014) examined the efficacy and safety of saxagliptin in combination with metformin administered for up to 24 weeks in patients with type 2 diabetes inadequately controlled with metformin alone.

RESEARCH DESIGN AND METHODS

— The study included men and women with type 2 diabetes and

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inadequate glycemic control (A1C ≥7.0 and ≤10.0%) taking a stable dose of metformin (≥1,500 but not >2,550 mg/day) for at least 8 weeks before screening, fasting C-peptide concentration ≥1.0 ng/ml, age 18–77 years, and BMI ≤40 kg/m^2. Patients were excluded if they had one or more of the following: symptoms of poorly controlled diabetes, a history of diabetic ketoacidosis or hyperosmolar nonketotic coma, use of any other antihyperglycemic medication (8 weeks before) or insulin (1 year before), a cardiovascular event within 6 months before study entry or New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction ≤40%, chronic or repeated intermittent corticosteroid treatment, a history of alcohol or drug abuse within the previous year, treatment with potent systemic cytochrome P450 3A4 inhibitors or inducers, active liver disease and/or clinically significant abnormalities on screening tests of hepatic, renal, endocrine, metabolic, or hematologic function, or assessment of an immunocompromised state. Women who were pregnant or breast-feeding were also excluded.

This was a 24-week randomized, four-arm, double-blind, placebo-controlled study of patients with type 2 diabetes and inadequate glycemic control with a stable dose of metformin monotherapy. Eligible patients enrolled in a 2-week, single-blind, dietary and exercise placebo lead-in period and received open-label metformin at their prestudy dose. After the lead-in period, eligible patients were randomly assigned 1:1:1:1 (permuted blocks stratified by site) by an interactive voice response system to 2.5, 5, or 10 mg saxagliptin or placebo for 24 weeks in addition to their lead-in dose of open-label metformin. Saxagliptin tablets were identical in appearance to the matched placebo. Patients completing the 24-week treatment period or those who met the rescue criteria (supplementary Fig. A1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc08-1984/DC1) could enter the 42-month long-term extension. Results will be presented separately.

The study protocol was approved by the institutional review board for each participating site and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided informed consent.

The primary efficacy outcome was change from baseline in A1C to week 24. Secondary end points included change from baseline to week 24 in fasting plasma glucose (FPG), the percentage of patients at the glycemic target (defined as A1C <7.0%), and postprandial glucose (PPG) 3-h area under the curve (AUC) during a 75-g oral glucose tolerance test (OGTT). Per protocol, the OGTT occurred 30 min after administration of study medication. Other efficacy outcomes included 2-h postprandial plasma glucose (as measured during the OGTT), percentage of patients at glycemic target based on predefined A1C and glucose values, and change from baseline to week 24 in fasting and postprandial plasma glucagon, insulin, and C-peptide concentrations; homeostasis model assessment (HOMA)-2–derived indexes of insulin resistance and β-cell function (HOMA-2β) (17); and indexes of insulin sensitivity and β-cell function derived from the OGTT (18,19). Safety monitoring included assessments of reported adverse events, data from physical examinations, vital signs, and electrocardiograms and standard laboratory measurements. Adverse event reporting included investigator assessments for severity and relationship to study medication. Hypoglycemia adverse events, including confirmed hypoglycemia (fingerstick glucose value of ≤50 mg/dl associated with symptoms), were recorded.

Efficacy analyses were performed on the randomly assigned patient population, consisting of randomly assigned patients who received at least one dose of study medication and had a baseline and at least one postbaseline measurement. Each saxagliptin group was compared with the placebo group for changes from baseline to week 24 in continuous end points using an ANCOVA with treatment group as an effect and baseline value as a covariate. Point estimates and 95% CIs for the least-squares mean change within each treatment group as well as the differences in least-squares mean changes between each saxagliptin group and the placebo group at week 24 were calculated. Sequential testing methodology was used for secondary efficacy end points. Other continuous efficacy variables were summarized using descriptive statistics. The percentage of patients achieving a therapeutic glycemic response at week 24 was compared between each saxagliptin group and the metformin plus placebo group using the Fisher's exact test. Last observation carried forward methodology was used to handle missing data. Safety analyses were performed on the treated patient population, consisting of randomly assigned patients who received at least one dose of study medication. Efficacy and safety measurements obtained after rescue were not included in analyses. With 153 patients per treatment group, there would be at least 90% power to detect a difference in A1C means of 0.5% between each saxagliptin plus metformin treatment group and the placebo plus metformin group, presuming a SD of 1.2%. Assuming a dropout rate of 15%, 720 patients (180 per treatment group) needed to be randomly assigned.

RESULTS — Patient disposition is shown in supplementary Fig. A1. Of the 1,462 patients screened, 743 were randomly assigned and received study treatment and 73% (543 of 743) completed 24 weeks of treatment. A higher incidence of discontinuations occurred in the placebo group (37.4%) versus the saxagliptin groups (22.9, 25.1, and 22.7% in the 25, 5, and 10 mg treatment groups, respectively). Demographic and baseline characteristics were generally similar across all treatment groups (supplementary Table A1, available in an online appendix). For the entire study population, mean age, duration of diabetes, baseline A1C, and baseline FPG were 54.6 years, 6.5 years, 8.0%, and 176 mg/dl, respectively. Daily metformin doses at study entry ranged from 500 to 2,550 mg. A history of being overweight (64.47%) and hypertension (59.08%) were the most commonly reported diabetes-related conditions.

At week 24, treatment with saxagliptin led to clinically and statistically significant reductions in A1C from baseline versus metformin plus placebo (Table 1). Differences in adjusted mean change from baseline versus placebo (95% CI) were −0.73% (−0.92 to −0.53), −0.83% (−1.02 to −0.63), and −0.72% (−0.91 to −0.52) for 2.5, 5, and 10 mg saxagliptin, respectively (all $P < 0.0001$). A1C reductions relative to metformin plus placebo occurred in all saxagliptin treatment groups at week 4, the earliest time point assessed. Maximal A1C reductions were reached at 12 weeks and were sustained through 24 weeks (Fig. 1*A*).

The percentage of patients achieving A1C <7.0% was comparable for 5 and 10 mg saxagliptin and higher than that for 2.5 mg saxagliptin (Table 1). A greater percentage of patients taking saxagliptin achieved A1C <7.0% versus those taking

Table 1—*Key glycemic efficacy end points: changes from baseline*

Efficacy end point (week 24)	PBO + MET	2.5 mg SAXA + MET	5 mg SAXA + MET	10 mg SAXA + MET
n	179	192	191	181
A1C (%)				
n	175	186	186	180
Adjusted change from baseline	0.13 ± 0.07	−0.59 ± 0.07*	−0.69 ± 0.07*	−0.58 ± 0.07*
Difference vs. PBO		−0.73 ± 0.10	−0.83 ± 0.10	−0.72 ± 0.10
FPG (mg/dl)				
n	176	188	187	181
Adjusted change from baseline	1.2 ± 2.56	−14.3 ± 2.48*	−22.0 ± 2.49*	−20.5 ± 2.53*
Difference vs. PBO		−15.6 ± 3.56	−23.3 ± 3.57	−21.7 ± 3.60
A1C <7.0% (%)				
n	175	186	186	180
n (%)	29 (16.6)	69 (37.1)*	81 (43.5)*	80 (44.4)*
Difference vs. PBO		20.5	27.0	27.9
PPG AUC (mg/dl)				
n	131	150	146	148
Adjusted change from baseline	−3,291 ± 853.2	−8,891 ± 798.0*	−9,586 ± 810.5*	−8,137 ± 807.9*
Difference vs. PBO		−5,599 ± 1,168.2	−6,294 ± 1,176.8	−4,845 ± 1,175.1
PPG at 120 min (mg/dl)				
n	135	155	155	152
Adjusted change from baseline	−18.0 ± 6.02	−61.5 ± 5.62*	−58.2 ± 5.62*	−49.8 ± 5.70*
Difference vs. PBO		−43.5 ± 8.23	−40.3 ± 8.23	−31.8 ± 8.31
PP glucagon AUC (pg · min/ml)				
n	123	140	138	142
Adjusted change from baseline	−4,315 ± 332.7	−5,511 ± 311.9†	−5,704 ± 314.0‡	−5,816 ± 309.6§
PP insulin AUC (μU · min/ml)				
n	118	137	133	136
Adjusted change from baseline	−7 ± 288.0	1,521 ± 267.3*	1,079 ± 271.4‖	1,635 ± 268.3*
PP C-peptide AUC (ng · min/ml)				
n	123	143	138	137
Adjusted change from baseline	66 ± 32.9	231 ± 30.5¶	278 ± 31.1*	249 ± 31.2*
OGIS (ml/min · m^2)				
n	117	135	135	136
Change from baseline	3.2 ± 7.60	27.7 ± 9.15	46.7 ± 8.14	30.4 ± 10.27
Insulinogenic index				
n	109	124	126	121
Change from baseline	0.04 ± 0.04	0.04 ± 0.09	0.16 ± 0.04	0.20 ± 0.09
HOMA-2β (%)				
n	166	175	180	173
Adjusted change from baseline	4.9 ± 2.25	16.5 ± 2.19	17.6 ± 2.16	18.1 ± 2.20

Data are means ± SE unless indicated otherwise. *$P \leq 0.0001$ vs. placebo; †$P = 0.0090$ vs. placebo; ‡$P = 0.0025$ vs. placebo; §$P = 0.0010$ vs. placebo; ‖$P = 0.0063$ vs. placebo; ¶$P = 0.0003$ vs. placebo. MET, metformin; PBO, placebo; PP, postprandial; SAXA, saxagliptin.

metformin plus placebo. The differences from metformin plus placebo (95% CI) were 20.5% (10.6–30.5), 27.0% (17.0–36.7), and 27.9% (17.7–37.7) for 2.5, 5, and 10 mg saxagliptin, respectively (all $P < 0.0001$).

As in the overall population, treatment with saxagliptin resulted in A1C reductions from baseline to week 24 in all A1C categories evaluated (baseline A1C <8.0, ≥8.0–<9.0, or ≥9.0%). An interaction of treatment with baseline A1C was observed ($P < 0.05$) with numerically greater A1C reductions in the higher baseline A1C categories for 2.5 and 5 mg saxagliptin, whereas 10 mg saxagliptin produced similar reductions in the two higher A1C categories. A1C-lowering effects were consistent across treatment groups in all other tested subgroups including duration of diabetes, geographic region, sex, age, ethnicity, and BMI.

Statistically significant FPG reductions at week 24 were observed in all saxagliptin treatment groups versus the metformin plus placebo group ($P < 0.0001$) (Table 1). Differences in adjusted mean change from baseline versus metformin plus placebo (95% CI) were −15.6 mg/dl (−22.5 to −8.5), −23.3 mg/dl (−30.3 to −16.3), and −21.7 mg/dl (−28.8 to −14.7) for 2.5, 5, and 10 mg saxagliptin, respectively. Differences between the effects of saxagliptin and metformin plus placebo on mean FPG were apparent and near maximal as early as week 2 in all saxagliptin treatment groups, with the effect maintained throughout 24 weeks (Fig. 1*B*).

Statistically significant reductions were seen in the PPG 3-h AUC during the OGTT from baseline to week 24 in all

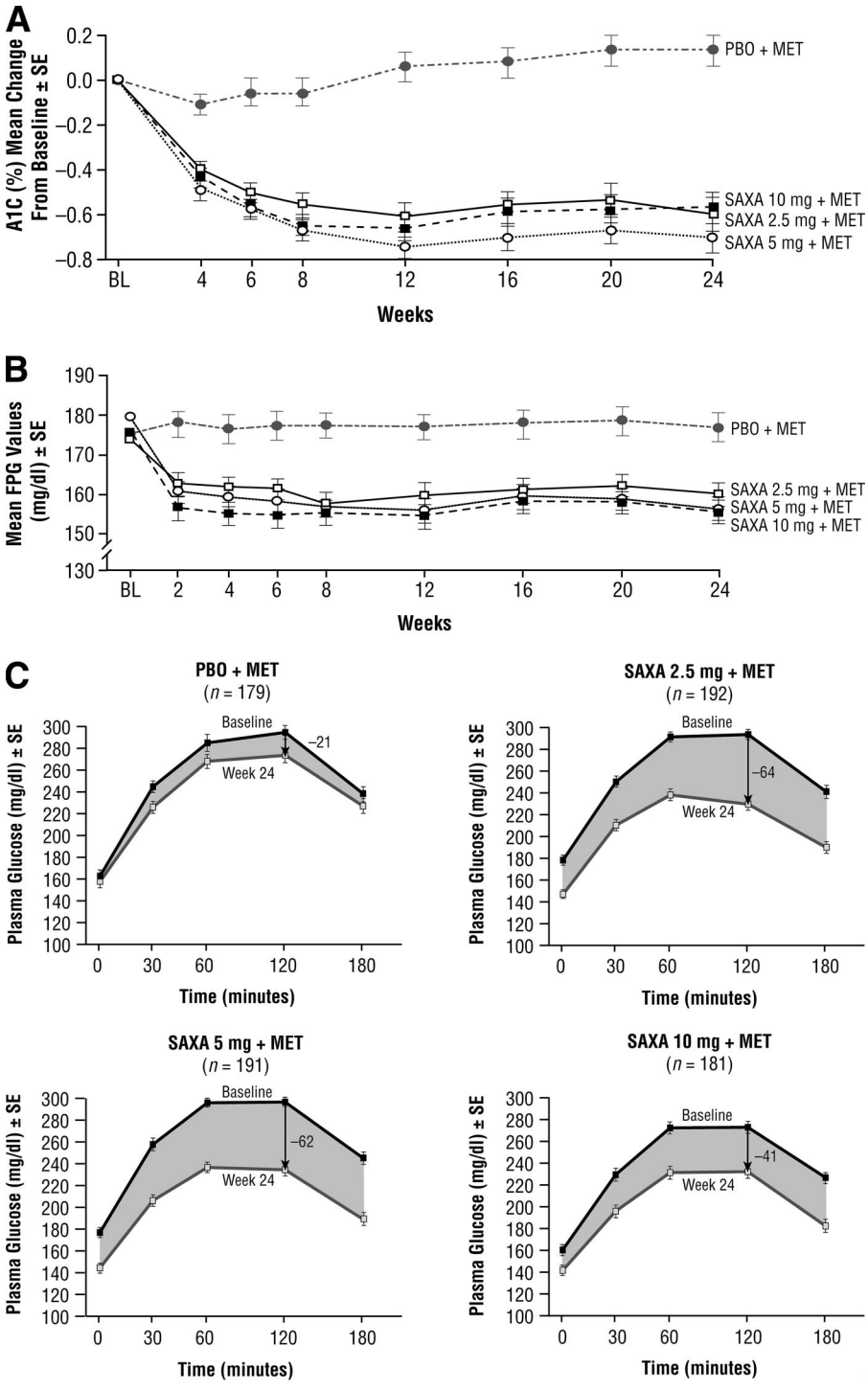

Figure 1—*Effect of saxagliptin added to metformin versus placebo added to metformin.* A*: A1C mean change from baseline values (last observation carried forward [LOCF]) during the 24-week treatment period.* B*: Mean fasting plasma glucose values (LOCF) during the 24-week treatment period.* C*: Postprandial glucose 3-h AUC during the OGTT (LOCF): baseline versus week 24.*

saxagliptin treatment groups versus the metformin plus placebo group ($P < 0.0001$) (Table 1). Differences in adjusted mean change from baseline versus metformin plus placebo (95% CI) were −5,599 mg·min/dl (−7,894 to −3,305), −6,294 mg·min/dl (−8,606 to −3,983), and −4,845 mg · min/dl (−7,153 to −2,537) for 2.5, 5, and 10 mg saxagliptin, respectively. Maximal A1C, FPG, and PPG reductions were observed at the 5 mg saxagliptin dose, without evidence of a dose-response relationship at greater than 5 mg.

There was an overall decrease from baseline in glucose concentration at all time points of the OGTT in the saxagliptin treatment groups at week 24 (Fig. 1*C*). At the 120-min time point of the OGTT, mean changes from baseline were greater for 2.5, 5, and 10 mg saxagliptin versus metformin plus placebo (−63.9, −62.1, and −40.7 mg/dl; all $P \leq 0.0001$ versus −21.0 mg/dl for placebo). The 95% CI for the mean change from baseline excluded zero in all treatment groups.

At all doses, saxagliptin demonstrated increases in mean postprandial insulin AUC and C-peptide AUC levels versus metformin plus placebo (supplementary Figure A2*a* and *b*, available in an online appendix). The change from baseline in postprandial glucagon AUC at week 24 revealed a greater decrease for all saxagliptin doses versus metformin plus placebo without any apparent dose dependency. The 95% CI for the placebo-subtracted adjusted mean change from baseline for postprandial insulin AUC, glucagon AUC, and C-peptide AUC excluded zero for all saxagliptin treatment groups (Table 1). β-Cell function, calculated using HOMA-2β (20), improved in all saxagliptin treatment groups at week 24 (Table 1). Differences in adjusted mean changes from baseline versus metformin plus placebo (95% CI) were 11.5% (5.4–17.7), 12.7% (6.6–18.8), and 13.1% (7.0–19.3) for the 2.5, 5, and 10 mg saxagliptin groups, respectively. Patients treated with saxagliptin had decreases in fasting glucagon measurements of greater magnitude than those observed for metformin plus placebo (data not shown, NS). No discernible effects on fasting C-peptide and insulin levels were observed for saxagliptin versus metformin plus placebo.

The early insulin response based on the insulinogenic index, calculated as $\Delta I_{0-30\ min}/\Delta G_{0-30\ min}$, and insulin sensitivity, calculated using the oral glucose insulin sensitivity (OGIS) index, increased in all saxagliptin treatment groups at week 24 (Table 1). No significant treatment effect was observed in the HOMA-2 insulin resistance index or the Matsuda index of insulin sensitivity at week 24. Mean changes from baseline in body weight at week 24 were −1.43, −0.87, and −0.53 kg for 2.5, 5, and 10 mg saxagliptin versus −0.92 kg for metformin plus placebo. Effects of saxagliptin on BMI, mean waist circumference, and mean fasting lipid levels were similar to those for metformin plus placebo.

Table 2—*Adverse events in double-blind treatment period: total, serious, deaths, discontinuations, most frequent (≥5%), reported hypoglycemia, confirmed hypoglycemia, and exposure to study medication*

	PBO + MET	2.5 mg SAXA + MET	5 mg SAXA + MET	10 mg SAXA + MET	Total SAXA + MET
n	179	192	191	181	564
Adverse event	116 (64.8)	153 (79.7)	134 (70.2)	132 (72.9)	419 (74.3)
Serious adverse event	5 (2.8)	5 (2.6)	8 (4.2)	5 (2.8)	18 (3.2)
Deaths*	1 (0.6)	0	0	0	0
Discontinuation due to adverse event	2 (1.1)	5 (2.6)	6 (3.1)	5 (2.8)	16 (2.8)
Adverse events ≥5%†					
Nasopharyngitis	14 (7.8)	18 (9.4)	13 (6.8)	18 (9.9)	49 (8.7)
Headache	13 (7.3)	18 (9.4)	11 (5.8)	16 (8.8)	45 (8.0)
Diarrhea	20 (11.2)	19 (9.9)	11 (5.8)	10 (5.5)	40 (7.1)
URI	9 (5.0)	13 (6.8)	9 (4.7)	15 (8.3)	37 (6.6)
Influenza	13 (7.3)	12 (6.3)	12 (6.3)	10 (5.5)	34 (6.0)
UTI	8 (4.5)	10 (5.2)	10 (5.2)	9 (5.0)	29 (5.1)
Arthralgia	5 (2.8)	8 (4.2)	8 (4.2)	9 (5.0)	25 (4.4)
Back pain	12 (6.7)	11 (5.7)	5 (2.6)	8 (4.4)	24 (4.3)
Hypertension	6 (3.4)	11 (5.7)	4 (2.1)	5 (2.8)	20 (3.5)
Cough	6 (3.4)	10 (5.2)	6 (3.1)	3 (1.7)	19 (3.4)
Dyspepsia	6 (3.4)	4 (2.1)	10 (5.2)	4 (2.2)	18 (3.2)
Pain in extremity	10 (5.6)	5 (2.6)	4 (2.1)	8 (4.4)	17 (3.0)
Reported hypoglycemia	9 (5.0)	15 (7.8)	10 (5.2)	7 (3.9)	32 (5.7)
Confirmed hypoglycemia	1 (0.6)	1 (0.5)	1 (0.5)	1 (0.6)	3 (0.5)
Exposure (days)	134 ± 54.4	152 ± 42.8	150 ± 44.3	151 ± 40.2	

Data are *n* (%) or means ± SD. Treated patients dataset. An adverse event was defined as any new or worsening illness, sign, symptom, or clinically significant laboratory test abnormality as noted by the investigator during the course of the study, regardless of the investigator's attribution of the event to study treatment. Confirmed hypoglycemia is defined by symptoms of hypoglycemia in the setting of a fingerstick blood glucose value ≤50 mg/dl. Extent of exposure is defined as the time from the first day to the last day, inclusive, that a patient took double-blind study medication during the 24-week short-term treatment period. *Death from cardiogenic shock. †Hypoglycemia events excluded. MET, metformin; PBO, placebo; SAXA, saxagliptin; URI, upper respiratory tract infection; UTI, urinary tract infection.

The percentage of patients who discontinued the study for lack of glycemic control or who were rescued for unacceptable glycemic control was approximately 2 times higher for metformin plus placebo (27.4%) versus saxagliptin (14.6, 12.6, and 14.9% for 2.5, 5, and 10 mg saxagliptin, respectively). Consequently, mean duration of exposure to double-blind study medication was similar across the saxagliptin treatment groups (mean range, 150–152 days) but shorter for the metformin plus placebo group (134 days), given that rescued patients were entered directly into the long-term extension.

Treatment with saxagliptin was generally well tolerated across all doses. The percentage of patients who had at least one adverse event was 74.3% (saxagliptin-treated patients) versus 64.8% (metformin plus placebo group), without evidence of a dose-response relationship. Generally, the frequency of the most common adverse events (≥5%) reported in saxagliptin-treated patients was similar to that in the metformin plus placebo group as was the percentage of patients with one or more serious adverse events (Table 2). No patients had a serious adverse event that was considered to be treatment related. The overall percentage of patients who had skin-related adverse events was similar for saxagliptin-treated patients (47 patients, 8.3%) and patients in the metformin plus placebo group (14 patients, 7.8%), with no apparent dose-related effects. The incidence of adverse events related to gastrointestinal disorders was similar in patients treated with saxagliptin (23.0%) versus placebo plus metformin (24.0%).

The overall frequency of confirmed hypoglycemia during the 24-week treatment period was similar for saxagliptin-treated patients (0.5%) and metformin plus placebo–treated patients (0.6%). No dose relationship was observed among the three saxagliptin groups. All events were of mild or moderate intensity and did not require treatment or medical intervention (Table 2).

The 2.5- and 5-mg doses of saxagliptin had no discernible effect on mean absolute lymphocyte count. There was a small numerical decrease from baseline in mean absolute lymphocyte count in the 10 mg saxagliptin group (-0.14×10^3 cells/μl) without evidence of clinical sequelae. Mean lymphocyte counts remained well within normal limits throughout the study. There is no known clinical significance to the findings observed in the 10 mg saxagliptin treatment group. Other safety laboratory parameters, including hematological, hepatic, renal, and musculoskeletal tests, showed no drug-related issues.

CONCLUSIONS — The current study demonstrated that saxagliptin once daily in combination with ongoing metformin for 24 weeks provided clinically relevant and statistically significant reductions in A1C versus placebo in patients with type 2 diabetes inadequately controlled with metformin alone. A1C reductions across all saxagliptin dose groups were seen as early as week 4, reached a maximum at approximately week 12, and were maintained throughout the remaining 12 weeks. Saxagliptin at all doses also led to clinically meaningful and statistically significant reductions in FPG and PPG AUC. Maximal A1C, FPG, and PPG AUC reductions were observed with the 5 mg saxagliptin dose, without evidence of a dose-response relationship above the threshold 5-mg dose. The lack of a dose-response relationship at doses above 5 mg was noted previously (16) and is likely to reflect similar inhibi-

tion of DPP-4 over a 24-h period in the dose range studied. Given that saxagliptin administered as monotherapy also produced greater A1C reductions versus placebo and in the same general range as the current study suggests that the actions of saxagliptin are direct and are not reflective of a restoration of the sensitizing ability of metformin.

Notably, the percentage of patients who achieved an A1C <7% was more than 2 times greater in patients who received saxagliptin than in patients who received metformin plus placebo. This finding is particularly important given the inadequate glycemic control observed in a high proportion of patients with type 2 diabetes in real-world settings. The incidence of microvascular complications from diabetes has been shown to be meaningfully reduced with each 1% reduction in A1C; thus, it is reasonable to suggest that saxagliptin added to metformin therapy would yield clinical benefits in terms of risk reduction (21).

As is frequently observed with antihyperglycemic agents, greater A1C reductions were seen in patients with higher baseline A1C values and were most evident for the 2.5 and 5 mg saxagliptin groups. Importantly, the effect of saxagliptin on A1C lowering was consistent across all three treatment groups for other prespecified subgroups, suggesting its appropriateness across a variety of patients with type 2 diabetes. FPG reductions and percentage of patients achieving a targeted A1C glycemic response in the 5 mg saxagliptin arm were within the range of similar DPP-4 inhibitor add-on to metformin studies with sitagliptin, vildagliptin, and alogliptin, although the absence of head-to-head comparisons precludes definitive conclusions. In general, DPP-4 inhibitors in combination with metformin demonstrate enhanced glycemic-lowering efficacy versus comparators without a significant increase in associated hypoglycemia or weight gain (13,15,22).

The incretin hormones GLP-1 and GIP are secreted in response to enteral nutrient stimulation. Saxagliptin is thought to exert its actions by slowing the inactivation of incretin hormones through inhibition of DPP-4, thereby enhancing and prolonging incretin function. This results in an improvement in glucose-mediated insulin release and a reduction in postprandial glucagon secretion (4). Consistent with this mechanism, treatment with saxagliptin also led to statistically significant decreases in PPG that were associated with greater increases in postprandial insulin and C-peptide AUC levels versus metformin plus placebo, suggesting that saxagliptin improved postprandial β-cell responsiveness to glucose. Saxagliptin added to metformin was also associated with β-cell function improvements as assessed by HOMA-2β. HOMA-2β improvements, based on fasting indexes of glucose and insulin levels, may represent enhancement of basal incretin action and/or amelioration of β-cell glucotoxicity. Further, treatment with saxagliptin produced a greater decrease from baseline in postprandial glucagon AUC versus placebo. This greater suppression of glucagon secretion also may have contributed to the reduction in postprandial hyperglycemia by decreasing hepatic glucose output. Although the OGIS index of insulin sensitivity improved, the Matsuda index did not change. More sensitive indicators of insulin action are required to draw definitive conclusions on the effect of saxagliptin on insulin sensitivity.

Generally, treatment with saxagliptin plus metformin was well tolerated over 24 weeks. Although the overall percentage of patients with adverse events was numerically higher in the saxagliptin treatment groups, the metformin plus placebo group had a shorter mean duration of exposure to the study medication and consequently a shorter mean time of risk for experiencing adverse events than the saxagliptin treatment groups. There was no evidence for a dose-response relationship for adverse events. The incidence of skin-related adverse events was similar for the metformin plus saxagliptin treatment groups relative to the metformin plus placebo group. This result is of particular importance given that certain dermal toxicities have been associated with the DPP-4 inhibitor class; however, in the absence of a direct comparison, specific conclusions cannot be drawn as longer observation periods in a greater number of patients may yield different results (23,24). In keeping with the mechanism of action of saxagliptin, the addition of saxagliptin to metformin did not increase the incidence of hypoglycemia versus that with metformin alone, which is relevant as use of DPP-4 inhibitors in combination regimens becomes more accepted (3,25).

Study limitations included differences in exposure time for the saxagliptin treatment groups versus the metformin plus placebo group, which may have influenced adverse event occurrence rates. Only data before rescue were used for efficacy and safety analyses, which may have also affected the results.

Saxagliptin added to metformin produced clinically and statistically significant improvements in A1C, FPG, and PPG. Statistically significant improvements in β-cell function as well as a reduction of glucagon were also demonstrated. Treatment across all saxagliptin groups was generally well tolerated with no increase in weight or hypoglycemia compared with metformin plus placebo. Taken together, these results suggest that saxagliptin represents a valuable therapeutic option for the management of patients with type 2 diabetes inadequately controlled with metformin monotherapy.

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