The Efficacy and Safety of Saxagliptin When Added to Metformin Therapy in Patients With Inadequately Controlled Type 2 Diabetes on 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 on metformin alone.

Research design and methods: Randomized, double-blind, placebo-controlled study of saxagliptin (2.5, 5, 10 mg once daily) or placebo plus stable dose of metformin (1500–2500 mg) in 743 patients (A1C ≥7.0% and ≤10.0%). Efficacy analyses were performed using an ANCOVA model utilizing last-observation-carried-forward methodology on primary (A1C) and secondary (FPG, PPG-AUC) endpoints.

Results: Saxagliptin 2.5, 5, and 10 mg plus metformin demonstrated statistically significant adjusted mean decreases from baseline to week 24 vs. placebo in A1C (–0.59%, –0.69%, –0.58% vs. + 0.13%, all \(P< 0.0001\) ) FPG (–14.31, –22.03, –20.50 mg/dl vs. +1.24 mg/dl, all \(P< 0.0001\) ) and PPG-AUC (–8891, –9586, –8137 mg•min/dl vs. –3291 mg•min/dl, all \(P< 0.0001\) ). More than twice as many patients achieved A1C <7.0% with saxagliptin 2.5, 5, and 10 mg vs. placebo (37%, 44%, 44% vs. 17%, all \(P< 0.0001\) ). \(\beta\)-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 placebo.

Conclusions: Saxagliptin once daily added to metformin therapy was generally well tolerated and led to statistically significant improvements in glycemic indices vs. placebo added to metformin in patients with type 2 diabetes inadequately controlled on metformin alone.
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 since 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 vs. placebo (13-15). The safety and efficacy of saxagliptin monotherapy in treatment-naïve patients was previously established in a 12-week study across a dose range of 2.5–40 mg/day. Significant A1C reductions were demonstrated in all active treatment groups with maximal A1C efficacy observed with saxagliptin 5 mg. 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 (AEs) 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 on metformin alone.

**RESEARCH DESIGN AND METHODS**

The study included men and women with type 2 diabetes and inadequate glycemic control (A1C ≥7.0% and ≤10.0%) on a stable dose of metformin (≥1,500 mg/day, but not >2,550 mg/day) for at least 8 weeks prior to screening, fasting C-peptide concentration ≥1.0 ng/ml, age 18–77 years, and BMI ≤40 kg/m². Patients were excluded if they had one or more of the following: symptoms of poorly controlled diabetes; history of diabetic ketoacidosis or hyperosmolar nonketotic coma; use of any other antihyperglycemic medication (8 weeks prior) or insulin (1 year prior); 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; history of alcohol or drug abuse within the previous year; treatment with potent systemic cytochrome P450 3A4 (CYP 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 on 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 pre-study dose. Following the lead-in period, eligible patients were randomized 1:1:1:1 (permuted blocks stratified by site) by IVRS to saxagliptin 2.5, 5, or 10 mg, or placebo for 24 weeks in addition to their lead-in dose of open-label metformin. Saxagliptin tablets were identical in appearance with matched placebo. Patients completing the 24-week treatment period or who met rescue criteria (Figure A1, online appendix, http://care.diabetesjournals.org) could enter the 42-month long-term extension (LTE). 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 endpoints included change from baseline to week 24 in fasting plasma glucose (FPG), the percentage of patients at glycemic target (defined as A1C <7.0%), and postprandial glucose (PPG) 3-hour area-under-the-curve (AUC) during a 75-g oral glucose tolerance test (OGTT). Per protocol, the OGTT occurred 30 minutes after administration of study medication. Other efficacy outcomes included 2-hour 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 indices of insulin resistance and β-cell function (17); and indices of insulin sensitivity and β-cell function derived from the OGTT (18,19). Safety monitoring included assessments of reported AEs, data from physical examinations, vital signs and electrocardiograms and standard laboratory measurements. AE reporting included investigator assessments for severity and relationship to study medication. Hypoglycemia AEs, including confirmed hypoglycemia (finger-stick glucose value of ≤50 mg/dl associated with symptoms), were recorded.

Efficacy analyses were performed on the randomized patient population, consisting of randomized patients who received at least one dose of study medication and had a baseline and at least one post-baseline measurement. Each saxagliptin group was compared with placebo for changes from baseline to week 24 in continuous endpoints utilizing an ANCOVA with treatment group as an effect and baseline value as a covariate. Point estimates and 95% confidence intervals (CIs) for the least square mean change within each treatment group, as well as the differences in least square mean changes between each saxagliptin group and placebo at week 24, were calculated. Sequential testing methodology was utilized for secondary efficacy endpoints. 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 placebo using the Fisher exact test. Last-observation-carried-forward methodology was utilized to handle missing data. Safety analyses were performed on the treated patient population, consisting of randomized 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
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In each 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 placebo plus metformin, presuming a standard deviation of 1.2%. Assuming a dropout rate of 15%, 720 patients (180 per treatment group) needed to be randomized.

RESULTS

The patient disposition is shown in Figure A1 of the online appendix. Of the 1,462 patients screened, 743 were randomized and received study treatment, and 73% (543/743) completed 24 weeks of treatment. A higher incidence of discontinuations occurred in the placebo group (37.4%) vs saxagliptin (22.9%, 25.1%, and 22.7% in the 2.5-, 5-, and 10-mg treatment groups, respectively). Demographic and baseline characteristics were generally similar across all treatment groups (Table A1, 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 500–2550 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 vs. metformin plus placebo (Table 1). Differences in adjusted mean change from baseline vs. 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 saxagliptin 2.5-, 5-, and 10-mg, 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 sustained through 24-weeks (Figure 1A).

The percentage of patients achieving A1C <7.0% was comparable for saxagliptin 5- and 10-mg and higher than saxagliptin 2.5-mg (Table 1). A greater percentage of saxagliptin patients achieved an A1C <7.0% vs metformin plus placebo. The difference from metformin plus placebo (95% CI) was 20.5% (10.6–30.5), 27.0% (17.0–36.7), and 27.9% (17.7–37.7) for saxagliptin 2.5-, 5-, and 10-mg, respectively (all P < 0.0001).

As in the overall population, treatment with saxagliptin resulted in A1C reductions from baseline to week 24 in all evaluated A1C categories (baseline A1C <8.0%; ≥8.0% to <9.0%; ≥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 saxagliptin 2.5- and 5-mg whereas saxagliptin 10-mg had 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, gender, age, ethnicity, and BMI.

Statistically significant FPG reductions at week 24 were observed in all saxagliptin treatment groups vs metformin plus placebo (P < 0.0001) (Table 1). Differences in adjusted mean change from baseline vs. metformin plus placebo (95% CI) was −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 saxagliptin 2.5-, 5-, and 10-mg, 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 effect maintained throughout 24 weeks (Figure 1B).

There were statistically significant reductions in PPG 3-hour AUC during the OGGT from baseline to week 24 in all saxagliptin treatment groups vs. metformin plus placebo (P < 0.0001) (Table 1). Differences in adjusted mean change from
baseline vs. 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 saxagliptin 2.5-, 5-, and 10-mg, respectively. Maximal A1C, FPG, and PPG reductions were observed at the saxagliptin 5-mg dose, without evidence of a dose-response relationship above 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 (Figure 1C). At the 120-min time point of the OGTT, mean changes from baseline were greater for saxagliptin 2.5-, 5-, and 10-mg vs metformin plus placebo (–63.9, –62.1, –40.7 mg/dl, all \( P \leq 0.0001 \) vs. –21.0 mg/dl for placebo) (Table 1). 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 vs metformin plus placebo (Figures A2a and 2b, online appendix). The change from baseline in postprandial glucagon AUC at week 24 revealed a greater decrease for all saxagliptin doses vs. 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). \( \beta \)-Cell function, calculated using HOMA-2 \( \beta \) (20), improved in all saxagliptin treatment groups at week 24 (Table 1). Differences in adjusted mean changes from baseline vs. 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 saxagliptin 2.5-, 5-, and 10-mg groups, respectively. Patients treated with saxagliptin had decreases in fasting glucagon measurements of greater magnitude than observed for metformin plus placebo (data not shown, \( P=\text{NS} \)). No discernible effect on fasting C-peptide and insulin levels were observed for saxagliptin vs. 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 –0.53kg for saxagliptin 2.5-, 5-, and 10-mg vs –0.92kg for metformin plus placebo. Effects of saxagliptin on BMI, mean waist circumference, and mean fasting lipid levels were similar to metformin plus placebo.

The percentage of patients who discontinued for lack of glycemic control or were rescued for unacceptable glycemic control was approximately two times higher for metformin plus placebo (27.4%) vs. saxagliptin (14.6, 12.6, and 14.9% for saxagliptin 2.5-, 5-, and 10-mg, 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 metformin plus placebo (134 days) given that rescued patients entered directly into the LTE.

Treatment with saxagliptin was generally well tolerated across all doses. The percentage of patients who had at least one AE was 74.3% (saxagliptin-treated patients) vs 64.8% (metformin plus placebo group), without evidence of a dose-response relationship. Generally, frequency of the most common AEs (\( \geq 5\% \)) reported in saxagliptin-treated patients was similar to metformin plus placebo, as was the percentage of patients with one or more serious AEs (Table 2). No patients had a serious AE that was considered treatment related. The overall percentage of patients who had skin-related AEs was similar.
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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. Incidence of AEs related to gastrointestinal disorders was similar in patients treated with saxagliptin (23.0%) vs. 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 (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 saxagliptin 2.5- and 5-mg doses had no discernible effect on mean absolute lymphocyte count. There was a small numerical decrease from baseline in mean absolute lymphocyte count in the saxagliptin 10-mg group (–0.14 x 10^3 c/ìL) 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 saxagliptin 10-mg treatment group. Other safety laboratory parameters, including hematologic, hepatic, renal, and musculoskeletal tests, showed no drug-related safety 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 vs 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 saxagliptin 5-mg 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 inhibition of DPP-4 over a 24-hour period in the dose range studied. Given that saxagliptin administered as monotherapy also produced greater A1C reductions vs placebo and in the same general range as the current study suggests that saxagliptin’s actions are direct and not reflective of a restoration of metformin’s sensitizing ability.

Notably, the percentage of patients who achieved an A1C<7% was more than 2 times greater in patients who received saxagliptin than 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 was most evident for the saxagliptin 2.5- and 5-mg groups. Importantly, saxagliptin’s effect 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 saxagliptin 5-mg arm were within the range of similar DPP-4 inhibitor add-on to metformin studies with sitagliptin, vildagliptin and alogliptin, although the
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absence of head-to-head comparisons precludes definitive conclusions. In general, DPP-4 inhibitors in combination with metformin demonstrate enhanced glycemic-lowering efficacy vs comparator 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 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 vs. 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 indices 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 vs. 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. While the overall percentage of patients with AEs was numerically higher in the saxagliptin treatment groups, the metformin plus placebo group had a shorter mean duration of exposure to study medication and consequently a shorter mean time of risk for experiencing AEs than the saxagliptin treatment groups. There was no evidence for a dose-response relationship for AEs. The incidence of skin-related AEs was similar for the metformin plus saxagliptin treatment groups relative to metformin plus placebo. 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 saxagliptin’s mechanism of action, the addition of saxagliptin to metformin did not increase the incidence of hypoglycemia vs 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 vs. metformin plus placebo, which may have influenced AE occurrence rates and rescue and discontinuation rates in the metformin plus placebo group. Only data before rescue were used for efficacy and safety analyses, which may have also impacted 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 reduction of glucagon were also demonstrated. Treatment across all saxagliptin groups was generally well tolerated with no increase in weight or hypoglycemia compared to 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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Table 1—Key glycemic efficacy endpoints: changes from baseline

| Efficacy Endpoint (Week 24) | PBO + MET | SAXA 2.5 mg + MET | SAXA 5 mg + MET | SAXA 10 mg + MET |
|----------------------------|-----------|-------------------|----------------|-----------------|
| **N**                      | 179       | 192               | 191            | 181             |
| **A1C (%)**                |           |                   |                |                 |
| n                          | 175       | 186               | 186            | 180             |
| Adjusted mean change from baseline (SE) | 0.13 (0.07) | -0.59 (0.07)     | -0.69 (0.07)  | -0.58 (0.07)  |
| Difference vs PBO (SE)     | -0.73 (0.10) | -0.83 (0.10)     | -0.72 (0.10)  |                 |
| **FPG (mg/dl)**            |           |                   |                |                 |
| n                          | 176       | 188               | 187            | 181             |
| Adjusted mean change from baseline (SE) | 1.2 (2.56)  | -14.3 (2.48)     | -22.0 (2.49)  | -20.5 (2.53)  |
| Difference vs PBO (SE)     | -15.6 (3.56) | -23.3 (3.57)     | -21.7 (3.60)  |                 |
| **A1C <7.0% (%)**          |           |                   |                |                 |
| n                          | 175       | 186               | 186            | 180             |
| Week 24 mean (SE)          | 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 mean change from baseline (SE) | -3291 (853.2) | -8891 (798.0)     | -9586 (810.5) | -8137 (807.9) |
| Difference vs PBO (SE)     | -5599 (1168.2) | -6294 (1176.8)   | -4845 (1175.1)|                 |
| **PPG at 120 min (mg/dl)**|           |                   |                |                 |
| n                          | 135       | 155               | 155            | 152             |
| Adjusted mean change from baseline (SE) | -18.0 (6.02) | -61.5 (5.62)     | -58.2 (5.62)  | -48.9 (5.70)  |
| Difference vs PBO (SE)     | -43.5 (8.23) | -40.3 (8.23)     | -31.8 (8.31)  |                 |
| **PP Glucagon AUC (pg•min/ml)**|         |                   |                |                 |
| n                          | 123       | 140               | 138            | 142             |
| Adjusted mean change from baseline (SE) | -4315 (332.7) | -5511 (311.9)    | -5704 (314.0) | -5816 (309.6) |
| **PP Insulin AUC (uU•min/ml)**|         |                   |                |                 |
| n                          | 118       | 137               | 133            | 136             |
| Adjusted mean change from baseline (SE) | -7 (288.0)  | 1521 (267.3)     | 1079 (271.4) | 1635 (268.3)  |
| **PP C-Peptide AUC (ng•min/ml)**|         |                   |                |                 |
| n                          | 123       | 143               | 138            | 137             |
| Adjusted mean change from baseline (SE) | 66 (32.9)   | 231 (30.5)       | 278 (31.1)   | 249 (31.2)    |
| **OGIS (ml/min•m²)**       |           |                   |                |                 |
| n                          | 117       | 135               | 135            | 136             |
| Mean change from baseline (SE) | 3.2 (7.60)   | 27.7 (9.15)      | 46.7 (8.14)  | 30.4 (10.27)  |
| **Insulinogenic Index**    |           |                   |                |                 |
| n  | Mean change from baseline (SE) | HOMA-2β (%)       |
|----|-------------------------------|------------------|
|    |                               | n                |
|    | 0.04 (0.04)                   | 166              |
| 109|                               | 175              |
| 124| 0.04 (0.09)                   | 180              |
| 126| 0.16 (0.04)                   | 173              |
| 121| 0.20 (0.09)                   |                  |

| Adjusted mean change from baseline (SE) | 4.9 (2.25) | 16.5 (2.19) | 17.6 (2.16) | 18.1 (2.20) |

FPG: fasting plasma glucose; HOMA-2β: Homeostasis Model Assessment-2β; MET: metformin; PBO: placebo; PPG: postprandial glucose; PP glucagon AUC: postprandial glucagon AUC; PP insulin AUC: postprandial insulin AUC; PP C-peptide: postprandial C-peptide; OGIS: oral glucose insulin sensitivity; SAXA: saxagliptin.

* $P \leq 0.0001$ 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.
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 | SAXA 2.5 mg + MET | SAXA 5 mg + MET | SAXA 10 mg + MET | Total SAXA + MET |
|----------------------|-----------|-------------------|-----------------|------------------|------------------|
|                      | N = 179   | N = 192           | N = 191         | N = 181          | N = 564          |
| AE (n[%])            | 116 (64.8)| 153 (79.7)        | 134 (70.2)      | 132 (72.9)       | 419 (74.3)       |
| Serious AE (n[%])    | 5 (2.8)   | 5 (2.6)           | 8 (4.2)         | 5 (2.8)          | 18 (3.2)         |
| Deaths† (n[%])       | 1 (0.6)   | 0                 | 0               | 0                | 0                |
| Discontinuation due to AE (n[%]) | 2 (1.1) | 5 (2.6) | 6 (3.1) | 5 (2.8) | 16 (2.8) |
| AEs ≥5%‡ (n[%])      |           |                   |                 |                  |                  |
| 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 (n[%]) | 9 (5.0) | 15 (7.8) | 10 (5.2) | 7 (3.9) | 32 (5.7) |
| Confirmed hypoglycemia (n[%]) | 1 (0.6) | 1 (0.5) | 1 (0.5) | 1 (0.6) | 3 (0.5) |
| Exposure (days)      | Mean (SD) | 134 (54.4) | 152 (42.8) | 150 (44.3) | 151 (40.2) |

*AE 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 defined by symptoms of hypoglycemia in the setting of a finger-stick blood glucose value ≤50 mg/dl.
‡Treated patients data set. Values expressed as n (%).
§Extent of exposure defined as time from first day to 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.
AE: adverse event; MET: metformin; PBO: placebo; SAXA: saxagliptin; URI: upper respiratory tract infection; UTI: urinary tract infection
Figure 1—Effect of saxagliptin added to metformin vs. placebo added to metformin
A. A1C mean change from baseline values (LOCF) during 24-week treatment period
B. Mean fasting plasma glucose values (LOCF) during 24-week treatment period
C. Postprandial glucose 3-hour AUC during the OGTT (LOCF): baseline vs. week 24

LOCF: last-observation-carried-forward.
Saxagliptin added to metformin therapy

**PBO + MET**

(n = 179)

**SAXA 2.5 mg + MET**

(n = 192)

**SAXA 5 mg + MET**

(n = 191)

**SAXA 10 mg + MET**

(n = 181)

Plasma Glucose (mg/dl) ± SE

Time (minutes)