

Long-term safety and tolerability of saxagliptin add-on therapy in older patients (aged ≥ 65 years) with type 2 diabetes

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Background: Treatment decisions for older patients with type 2 diabetes mellitus must balance glycemic control and adverse event risk. The objective of this study was to evaluate the long-term safety and tolerability of saxagliptin 5 mg as add-on therapy to common antihyperglycemic drugs in patients aged ≥ 65 years and < 65 years.

Methods: Pooled adverse event data from three placebo-controlled trials of 76–206 weeks' duration in older (≥ 65 years) and younger (< 65 years) patients receiving saxagliptin 5 mg or matching placebo added to metformin, glyburide, or a thiazolidinedione were analyzed. Measurements were calculated from day of first dose to specified event or last dose and included time at risk for adverse events, treatment-related adverse events, serious adverse events, adverse events leading to discontinuation, and events of special interest. Weighted incidence rates (number of events/total time) and incidence rate ratios (saxagliptin/placebo) with 95% confidence intervals were calculated (Mantel-Haenszel test).

Results: A total of 205 older (mean age 69 years; saxagliptin, n=99; placebo, n=106) and 1,055 younger (mean age 52 years; saxagliptin, n=531; placebo, n=524) patients were assessed. Regardless of age category, the adverse event incidence rates were generally similar between treatments, with confidence intervals for incidence rate ratios bridging 1. Treatment-related adverse events occurred in 36 older patients receiving saxagliptin versus 32 receiving placebo (incidence rate 34.1 versus 27.1 per 100 person-years) and in 150 younger patients in both treatment groups (incidence rate 24.0 versus 27.8 per 100 person-years). With saxagliptin versus placebo, serious adverse events occurred in eight versus 14 older (incidence rate 5.7 versus 9.9 per 100 person-years) and 49 versus 44 younger patients (incidence rate 6.5 versus 6.6 per 100 person-years). There were two deaths (one patient ≥ 65 years) with saxagliptin and six (none aged ≥ 65 years) with placebo. Older patients rarely experienced symptomatic confirmed hypoglycemia (fingerstick glucose ≤ 50 mg/dL; saxagliptin, n=1; placebo, n=2).

Conclusion: Saxagliptin add-on therapy was generally well tolerated in older patients aged ≥ 65 years with type 2 diabetes mellitus, with a long-term safety profile similar to that of placebo.

Keywords: older patients, glyburide, metformin, saxagliptin, thiazolidinedione

Introduction

It is important to identify effective and well tolerated therapies for older individuals with type 2 diabetes mellitus (T2DM), given that the prevalence of the disease is increasing in the older population. In 2012, it was estimated that 11.2 million or 26% of US residents aged 65 years or older would have diabetes.¹ Further, 400,000 adults in this age group were projected to be diagnosed with diabetes in 2012.

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The clinical and functional heterogeneity of older patients with T2DM requires special consideration by clinicians when making treatment decisions² and necessitates an individualized approach.³ Because of limited life expectancy, increased hypoglycemia risk, and longstanding or more complicated disease, less stringent glycemic targets may be appropriate in the older patient.^{3,4}

Treatment decisions for older patients with T2DM must balance glycemic control and the risk of adverse events (AEs).⁴ Several antihyperglycemic agents are associated with AEs that may limit their use in older patients. The most specific concern with antihyperglycemic agents in older patients is the risk of hypoglycemia.^{3,4} Metformin, which is recommended as first-line therapy in conjunction with diet and exercise for the general population of patients with T2DM,⁴ is appropriate in many older patients with diabetes³ but is contraindicated in those with renal impairment (serum creatinine ≥ 1.5 mg/dL for men and ≥ 1.4 mg/dL for women or abnormal creatinine clearance), may cause vitamin B12 malabsorption, and is associated with gastrointestinal disturbances that may be treatment-limiting in older individuals.^{4,5} A concern with other agents is weight gain, as treatments associated with weight gain may be undesirable in obese older patients because of the potential for additional cardiovascular risk.^{6,7} Sulfonylureas and insulin cause weight gain and hypoglycemia,⁴ whereas thiazolidinediones are associated with weight gain, congestive heart failure, edema, bladder cancer, and fracture risk.⁴ Thus, many of the therapies recommended for use in the general population of patients with T2DM may not be good choices for certain older patients.

The report from the Consensus Development Conference on Diabetes and Older Adults convened by the American Diabetes Association provides a framework for differentiating treatment goals in the older patient based on health status (presence and number of comorbidities or impairments of functional status).³ Patient background factors and functional status must be assessed before initiation of treatment, because older individuals with diabetes often have multiple comorbidities.^{4,8} These comorbidities may include cardiovascular conditions, nephropathy, depression, and cognitive impairment.^{2,8} In addition to the effect of these comorbidities on diabetes treatment, potential AEs related to polypharmacy for comorbidities must also be taken into account.^{3,8} Even in individuals with no comorbidities, age-related decreases in renal and hepatic function may influence the metabolism of certain antihyperglycemic drugs. In addition, frailty, common in the older patient, often influences the tolerability of antihyperglycemic therapies.^{2,4,5}

Dipeptidyl peptidase-4 inhibitors are a newer class of antihyperglycemic agents that have shown a low incidence of hypoglycemia and weight neutrality in clinical trials, suggesting that they may be well suited for use in older patients.⁷ Saxagliptin is an oral, once-daily, selective dipeptidyl peptidase-4 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM in multiple clinical settings.⁹ Saxagliptin has a glucose-dependent mechanism of action and a subsequent low risk of hypoglycemia, and is not associated with weight gain.¹⁰

In randomized, double-blind studies in patients with inadequately controlled T2DM, saxagliptin was effective and well tolerated as add-on therapy to metformin,¹¹ a thiazolidinedione,¹² or a sulfonylurea (glyburide),¹³ and also as add-on therapy to insulin, alone or combined with metformin.¹⁴ Long-term extensions of these studies (total study duration 76–206 weeks) also demonstrated sustained incremental efficacy with saxagliptin compared with placebo or a comparator.^{15–17} Previously published pooled analyses of data from five randomized controlled trials of saxagliptin, including the three trials analyzed in this report, provided evidence of its short-term efficacy and tolerability in older patients (aged ≥ 65 years).^{18,19} Saxagliptin 2.5 mg was also demonstrated to be effective, with a favorable tolerability profile in patients with T2DM and significant renal impairment.

The current paper presents the results of pooled tolerability and safety data with saxagliptin 5 mg versus placebo as add-on therapy to metformin, a thiazolidinedione, or glyburide in patients aged ≥ 65 years and patients aged < 65 years from three randomized controlled trials of up to 4 years. The objective of this analysis was to evaluate the long-term safety and tolerability of saxagliptin 5 mg as add-on therapy in patients aged ≥ 65 years and < 65 years.

Materials and methods

Study design

This analysis included data pooled from three previously reported randomized, double-blind, placebo-controlled studies of saxagliptin add-on therapy in patients with T2DM (Clinicaltrials.gov identifiers NCT00121667, NCT00295633, NCT00313313)^{12,13,20} that had a short-term phase (24 weeks) and long-term extensions (12–42 months). Add-on therapy regimens were saxagliptin as add-on to metformin (1,500–2,550 mg/day) for a total treatment period of 206 weeks,¹⁷ saxagliptin as add-on to thiazolidinedione (pioglitazone 30 or 45 mg/day or rosiglitazone 4 or 8 mg/day) for a total treatment period of 76 weeks,¹⁶ and saxagliptin as

add-on to glyburide (7.5 mg/day in the saxagliptin group, uptitrated to 10 mg/day in the placebo group and adjustable to 5 or 15 mg/day in the short-term phase and up to 20 mg/day in the placebo group in the long-term extension phase) for a total treatment period of 76 weeks.¹⁵ Rescue medication was provided during the studies to the end of the long-term extension phases based on predefined fasting plasma glucose and glycated hemoglobin (HbA_{1c}) criteria that became increasingly stringent over time.

Study protocols were approved by the institutional review board/independent ethics committee at each site and conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation. All patients provided written informed consent.

Patients

As described previously, patients were adults with T2DM inadequately controlled on metformin (HbA_{1c} $\geq 7\%$ and $\leq 10\%$),¹¹ a thiazolidinedione (HbA_{1c} $\geq 7\%$ and $\leq 10\%$),¹² or a submaximal dose of a sulfonylurea (HbA_{1c} $\geq 7.5\%$ and $\leq 10\%$),¹³ with a body mass index ≤ 40 kg/m² and fasting C-peptide ≥ 1.0 ng/mL (SI conversion to nmol/L: ng/mL $\times 0.333$). Common exclusion criteria were history or current symptoms of poorly controlled diabetes; a cardiovascular event in the past 6 months; New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction $\leq 40\%$; significant history of renal or hepatic disease; history of substance abuse in the previous year; immunocompromised; or use of potent cytochrome P450 3A4 inhibitors or inducers.

Outcomes

Safety and tolerability data were pooled from the three studies and analyzed by age subgroup (≥ 65 years and < 65 years). The analysis focused on saxagliptin 5 mg, the highest dose approved for this agent,⁹ but additional analyses were performed that included all doses of saxagliptin combined. AEs (any AE, treatment-related AE, serious AE, AE leading to discontinuation, and events of special interest [ie, acute cardiovascular AEs, infections, lymphopenia, hypersensitivity, dermatologic AEs, and hypoglycemia]) were counted for all patients who received at least one dose of study medication, starting from the day of first dose. AEs were coded and grouped into system-organ classes and preferred terms using the Medical Dictionary for Regulatory Activities. With the exception of infection, which was based on the system-organ class categorization of "Infections and Infestations," the events of special interest were based on

customized special search categories and are events that may potentially be associated with the mechanism of action of dipeptidyl peptidase-4 inhibitors or associated with T2DM. Total time at risk (in years) for these AEs was calculated from the day of the first dose to the day of the first AE or the day of the last dose, regardless of administration of rescue medication. AEs were collected until one day after the last dose; serious AEs were monitored until 30 days after the last dose.

Statistical analysis

Weighted incidence rates (IRs), IR ratios (IRRs), and 95% confidence intervals (CIs) for the IRRs comparing saxagliptin with placebo were calculated with the Mantel-Haenszel method stratified by study. The equations used to calculate IR and IRR were as follows: IR = number of events (n) divided by total time, reported as n per 100 person-years \pm standard error of the mean, and IRR = IR_{saxagliptin} divided by IR_{placebo}.

Results Patients

The analysis population included 205 older patients (mean age 69 years; saxagliptin, n=99; placebo, n=106) and 1,055 younger patients (mean age 52 years; saxagliptin, n=531; placebo, n=524). Baseline demographic and clinical characteristics are summarized in Table 1. Across the four groups, 49%–52% of patients were women and 64%–66% of the patients were white. Clinical characteristics were generally comparable between the saxagliptin and placebo groups, irrespective of age. Mean exposure times to saxagliptin 5 mg and placebo for all patients in the individual studies were 118 weeks and 130 weeks, respectively, in the add-on to metformin study, 58.2 and 56.2 weeks in the add-on to thiazolidinedione study, and 64.7 and 61.0 weeks in the add-on to glyburide study. Mean 120-minute postprandial glucose was somewhat higher for older patients receiving saxagliptin versus placebo. In older versus younger patients, disease duration was longer (8.6–8.9 years versus 5.7–5.8 years across treatment groups), baseline fasting plasma glucose was lower (163.0–166.0 mg/dL versus 172.5–173.1 mg/dL across treatment groups), and a higher proportion of patients had low creatinine clearance (≤ 80 mL/min: 54%–57% versus 15% across treatment groups).

As previously reported in the individual studies, the placebo-corrected change in HbA_{1c} from baseline with saxagliptin 5 mg/day for all patients was -0.83% for the add-on to metformin study,¹¹ -0.72% for the add-on to glyburide study,¹³ and -0.63% for the add-on to

Table 1 Demographic and clinical characteristics of the pooled population

| Characteristic ^a | Age ≥65 years | | Age <65 years | |
|---|---------------------|--------------------|----------------------|--------------------|
| | SAXA 5 mg (n=99) | Placebo (n=106) | SAXA 5 mg (n=531) | Placebo (n=524) |
| Age, years | 68.9 (3.3) | 69.0 (3.2) | 51.6 (8.4) | 51.8 (8.8) |
| Women, n (%) | 51 (52) | 52 (49) | 277 (52) | 274 (52) |
| Race, n (%) | | | | |
| White | 63 (64) | 70 (66) | 346 (65) | 333 (64) |
| Asian | 13 (13) | 14 (13) | 102 (19) | 104 (20) |
| Black | 4 (4) | 3 (3) | 24 (5) | 18 (3) |
| Other | 19 (19) | 19 (18) | 59 (11) | 69 (13) |
| BMI, kg/m ² | 29.1 (4.5) | 29.2 (4.7) | 30.1 (4.9) | 30.2 (5.3) |
| Duration of T2DM, years | 8.9 (7.1) | 8.6 (7.2) | 5.7 (4.9) | 5.8 (5.1) |
| Creatinine clearance, mL/ min, n (%) | | | | |
| ≤80 | 56 (57) | 57 (54) | 81 (15) | 79 (15) |
| >80 | 43 (43) | 49 (46) | 450 (85) | 445 (85) |
| HbA _{1c} , % | 8.3 (0.9) | 8.0 (0.8) | 8.3 (1.0) | 8.3 (1.0) |
| 120-min PPG, mg/dL | 318.0 (73.6) | 306.8 (77.8) | 302.5 (77.6) | 304.7 (80.0) |
| FPG, mg/dL | 166.0 (38.7) | 163.0 (41.8) | 173.1 (47.5) | 172.5 (44.5) |

Note: ^aMean (SD) unless specified as n (%).

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; PPG, postprandial glucose; SAXA, saxagliptin; SD, standard deviation; T2DM, type 2 diabetes mellitus.

thiazolidinedione study.¹² Long-term extensions of these studies reported placebo-corrected changes in HbA_{1c} of −0.5% at week 154 for the add-on to metformin study,¹⁷ and −0.66% and −0.89% at 76 weeks for the add-on to glyburide and add-on to thiazolidinedione studies, respectively.^{15,16}

Safety

IRs for most AE categories, including those for treatment-related AEs and death, were similar in patients receiving saxagliptin 5 mg versus placebo, with 95% CIs for IRRs bridging 1, regardless of age (Table 2 and Figure 1A). Results were consistent with those obtained in the analysis of all doses of saxagliptin when pooled (data not shown). With saxagliptin 5 mg versus placebo, respectively, at least one AE occurred in 84 (IR 260.6 per 100 person-years) versus 93 (IR 388.8 per 100 person-years) older patients and 447 (IR 227.6 per 100 person-years) versus 431 (IR 250.9 per 100 person-years) younger patients. Treatment-related AEs were experienced by 36 older patients (IR 34.1 per 100 person-years) receiving saxagliptin 5 mg and 32 older patients (IR 27.1 per 100 person-years) receiving placebo (total exposure 109 and 114 person-years, respectively) and 150 younger patients in each treatment group (IR 24.0 and 27.8 per 100 person-years; total exposure 637 and 536 person-years, respectively; Table 2).

With saxagliptin 5 mg versus placebo, respectively, serious AEs occurred in eight versus 14 older patients (IR 5.7 versus 9.9 per 100 person-years) and 49 versus 44

younger patients (IR 6.5 versus 6.6 per 100 person-years). AEs led to discontinuation in 13 (IR 9.3 per 100 person-years) older patients receiving saxagliptin 5 mg and six (IR 4.4 per 100 person-years) older patients receiving placebo (total exposure 152 and 146 person-years, respectively); in the younger group, AEs led to discontinuation in 37 (IR 4.7 per 100 person-years) and 24 (IR 3.4 per 100 person-years) patients, respectively (total exposure 797 and 689 person-years, respectively; Table 2). Serious AEs led to discontinuation in five (IR 3.5 per 100 person-years) older patients receiving saxagliptin 5 mg and one (IR 0.6 per 100 person-years) older patient receiving placebo (total exposure 152 and 146 person-years, respectively); in the younger group, serious AEs led to discontinuation in seven (IR 0.9 per 100 person-years) and six (IR 0.8 per 100 person-years) patients, respectively (total exposure, 800 and 690 person-years, respectively; Table 2). There were two deaths (including one older patient) in the saxagliptin 5 mg group and six (no older patients) in the placebo group (Table 2); all were deemed unrelated or unlikely to be related to treatment. AEs with an IR >5 per 100 person-years (excluding hypoglycemia) are summarized for saxagliptin 5 mg and placebo in older and younger patients in Table 3. The most common were nasopharyngitis and influenza.

With the exception of infection, few AEs of special interest were noted in older patients, regardless of treatment group (Table 4 and Figure 1B), resulting in wide CIs for the IRR. Results were consistent with those obtained in the

Table 2 AEs by category with saxagliptin versus placebo

| Adverse event | Age ≥ 65 years | | Age < 65 years | |
|---------------------------------------|---------------------|--------------------|----------------------|--------------------|
| | SAXA 5 mg (n=99) | Placebo (n=106) | SAXA 5 mg (n=531) | Placebo (n=524) |
| Any AE | | | | |
| Patients with event, n | 84 | 93 | 447 | 431 |
| Total exposure, person-years | 32 | 25 | 199 | 172 |
| IR per 100 person-years \pm SE | 260.6 \pm 29.3 | 388.8 \pm 40.9 | 227.6 \pm 10.8 | 250.9 \pm 12.1 |
| Serious AE | | | | |
| Patients with event, n | 8 | 14 | 49 | 44 |
| Total exposure, person-years | 147 | 134 | 750 | 667 |
| IR per 100 person-years \pm SE | 5.7 \pm 2.0 | 9.9 \pm 2.7 | 6.5 \pm 0.9 | 6.6 \pm 1.0 |
| Treatment-related AE | | | | |
| Patients with event, n | 36 | 32 | 150 | 150 |
| Total exposure, person-years | 109 | 114 | 637 | 536 |
| IR per 100 person-years \pm SE | 34.1 \pm 5.8 | 27.1 \pm 4.9 | 24.0 \pm 2.0 | 27.8 \pm 2.3 |
| Treatment-related serious AE | | | | |
| Patients with event, n | 1 | 0 | 4 | 3 |
| Total exposure, person-years | 152 | 146 | 799 | 689 |
| IR per 100 person-years \pm SE | 0.5 \pm 0.5 | – | 0.5 \pm 0.3 | 0.4 \pm 0.3 |
| AE leading to discontinuation | | | | |
| Patients with event, n | 13 | 6 | 37 | 24 |
| Total exposure, person-years | 152 | 146 | 797 | 689 |
| IR per 100 person-years \pm SE | 9.3 \pm 2.6 | 4.4 \pm 1.8 | 4.7 \pm 0.8 | 3.4 \pm 0.7 |
| Serious AE leading to discontinuation | | | | |
| Patients with event, n | 5 | 1 | 7 | 6 |
| Total exposure, person-years | 152 | 146 | 800 | 690 |
| IR per 100 person-years \pm SE | 3.5 \pm 1.6 | 0.6 \pm 0.6 | 0.9 \pm 0.3 | 0.8 \pm 0.3 |
| Death | | | | |
| Patients with event, n | 1 | 0 | 1 | 6 |
| Total exposure, person-years | 152 | 146 | 801 | 690 |
| IR per 100 person-years \pm SE | 0.8 \pm 0.8 | – | 0.1 \pm 0.1 | 0.9 \pm 0.4 |

Abbreviations: AE, adverse event; IR, incidence rate; SAXA, saxagliptin; SE, standard error.

analysis of all doses of saxagliptin when pooled (data not shown). Confirmed hypoglycemia, defined as symptoms of hypoglycemia with a concomitant fingerstick glucose value ≤ 50 mg/dL, was reported by one older patient (IR 0.8 per 100 person-years) receiving saxagliptin 5 mg and two older patients (IR 1.2 per 100 person-years) receiving placebo (total exposure 152 and 145 person-years, respectively). Among younger patients, nine in each group (IR 1.2 and 1.3 per 100 person-years, respectively) had confirmed hypoglycemia (total exposure 791 and 686 person-years, respectively). Lymphopenia was reported by five older patients (IR 3.2 per 100 person-years) receiving saxagliptin 5 mg and three older patients (IR 2.2 per 100 person-years) receiving placebo (total exposure 148 and 144 person-years, respectively). Among the younger patients, six (IR 0.8 per 100 person-years) receiving saxagliptin 5 mg and five (IR 0.7 per 100 person-years) receiving placebo experienced lymphopenia (total exposure 796 and 687 person-years, respectively). Hypersensitivity was reported by two older patients each (IR 1.4 and 1.3 per

100 person-years, respectively) in the saxagliptin 5 mg and placebo groups (total exposure 150 and 145 person-years, respectively). Among younger patients, 13 (IR 1.7 per 100 person-years) receiving saxagliptin 5 mg and two (IR 0.3 per 100 person-years) receiving placebo had hypersensitivity events (total exposure 790 and 688 person-years, respectively). Acute cardiovascular events were reported by three (IR 2.1 per 100 person-years) older patients receiving saxagliptin 5 mg and two (IR 1.5 per 100 person-years) older patients receiving placebo (total exposure 148 and 144 person-years, respectively). For younger patients, six (IR 0.8 per 100 person-years) in the saxagliptin 5 mg group and eleven (IR 1.6 per 100 person-years) in the placebo group had acute cardiovascular events (total exposure 794 and 688 person-years, respectively).

Regardless of age, the IRs for the AEs of special interest were generally low and similar between patients receiving saxagliptin 5 mg and placebo, with most IRRs bridging 1 (Table 4 and Figure 1B). An exception was infections in older

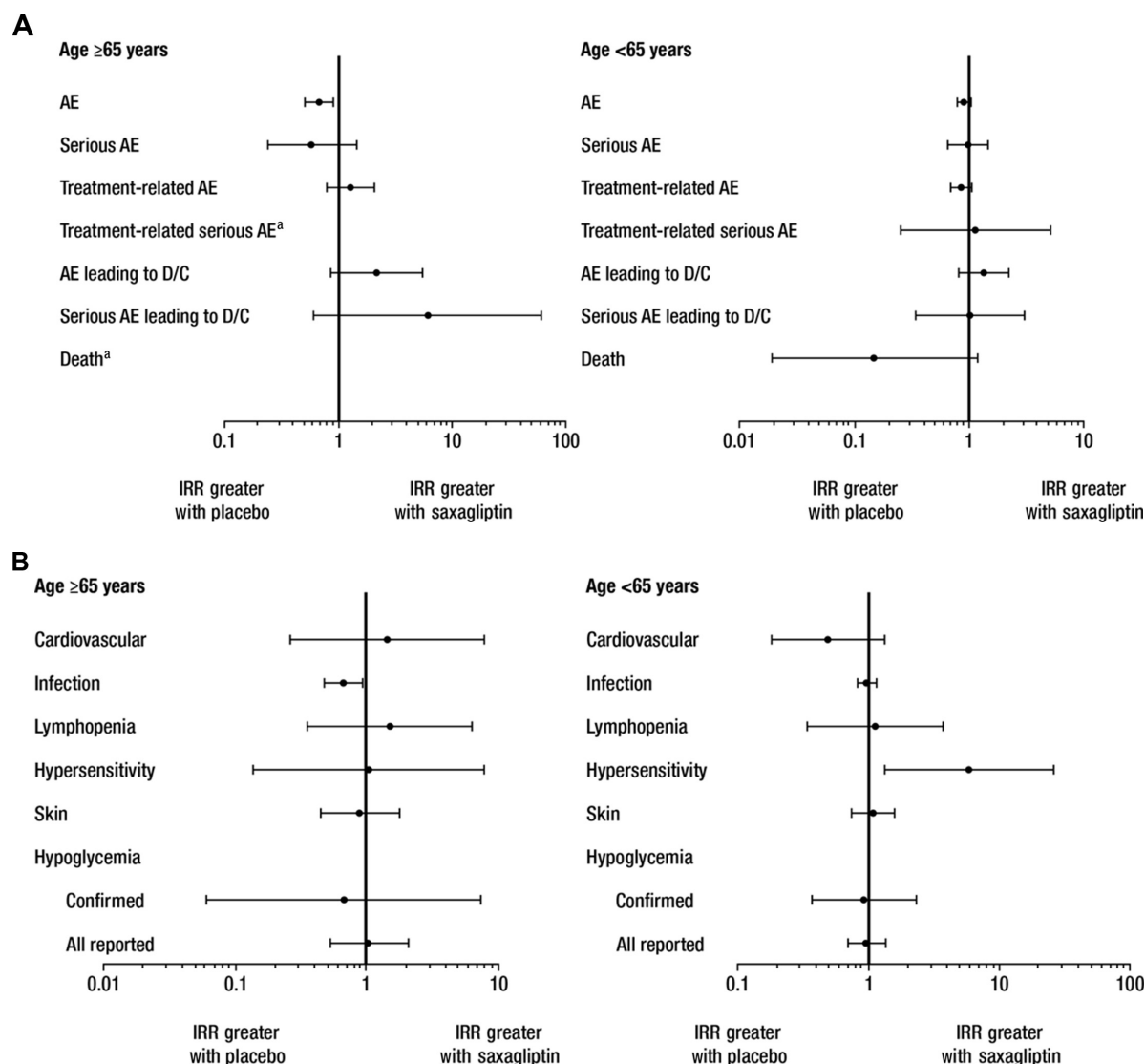


Figure 1 IRRs of AEs by (A) category and (B) type with saxagliptin 5 mg versus placebo.

Notes: Error bars are 95% CIs. ^aPoint estimate could not be computed, and CI for IRR was not provided. In the elderly patients in the saxagliptin 5 mg and placebo groups, treatment-related serious AEs were reported in 1 and 0 patients and death occurred in 1 and 0 patients, respectively.

Abbreviations: AE, adverse event; CI, confidence interval; D/C, discontinuation; IRR, incidence rate ratio.

patients (IR 67.7 per 100 person-years in the saxagliptin 5 mg group and 102.4 per 100 person-years in the placebo group). Results were consistent with those obtained in the pooled analysis for all doses of saxagliptin (data not shown).

Discussion

Treatment of T2DM in older patients is complicated by comorbidities, polypharmacy, and age-related decreases in physiological function.^{4,8} The 2012 position statement on the management of hyperglycemia in patients with T2DM issued by the American Diabetes Association and the European Association for the Study of Diabetes stresses the importance of a patient-centered approach to care that considers the preferences, needs, and values of the patient.⁴ In an effort to

determine the long-term tolerability of saxagliptin in older patients with T2DM, data from patients aged ≥ 65 years and < 65 years who participated in trials of saxagliptin 5 mg as add-on to metformin, a thiazolidinedione, or glyburide were analyzed. The results of this analysis indicated that saxagliptin had an overall safety profile similar to that of placebo. The IRs for most AE categories and types, including hypoglycemia, were similar for patients receiving saxagliptin 5 mg versus placebo, with 95% CIs for most IRRs bridging 1, regardless of age category. In addition, with the exception of infection, AEs of special interest were infrequent in older patients. These results for saxagliptin 5 mg were consistent with results in older patients obtained from pooled analyses of all doses of saxagliptin tested in clinical trials (data not shown).

Table 3 AEs with an IR ≥ 5 events per 100 person-years in any group^a

| IR ^b | Age ≥ 65 years | | Age <65 years | |
|-----------------------------------|---------------------|--------------------|----------------------|--------------------|
| | SAXA 5 mg (n=99) | Placebo (n=106) | SAXA 5 mg (n=531) | Placebo (n=524) |
| Nasopharyngitis | 13.1 | 12.3 | 7.1 | 8.4 |
| Influenza | 8.7 | 11.5 | 5.9 | 7.0 |
| Arthralgia | 8.2 | 5.9 | 5.3 | 5.6 |
| Hypertension | 8.1 | 5.0 | 4.9 | 5.0 |
| Back pain | 7.9 | 6.1 | 4.4 | 5.6 |
| Diarrhea | 6.7 | 9.2 | 4.7 | 8.2 |
| Upper respiratory tract infection | 6.3 | 6.5 | 7.9 | 8.2 |
| Urinary tract infection | 5.5 | 9.2 | 9.7 | 8.1 |
| Bronchitis | 4.1 | 7.6 | 4.1 | 3.0 |
| Peripheral edema | 4.1 | 7.3 | 5.5 | 4.8 |
| Headache | 3.5 | 6.9 | 7.2 | 7.5 |
| Extremity pain | 3.4 | 5.3 | 3.4 | 4.7 |
| Dizziness | 2.8 | 6.7 | 1.9 | 3.9 |
| Cough | 2.7 | 9.1 | 3.3 | 4.4 |

Notes: ^aExcluding hypoglycemia. ^bEvents are sorted in order of descending IR in the saxagliptin 5 mg group for patients ≥ 65 years.

Abbreviations: AE, adverse event; IR, incidence rate; SAXA, saxagliptin.

Table 4 AEs of special interest with saxagliptin 5 mg versus placebo

| Adverse event | Age ≥ 65 years | | Age <65 years | |
|----------------------------------|---------------------|--------------------|----------------------|--------------------|
| | SAXA 5 mg (n=99) | Placebo (n=106) | SAXA 5 mg (n=531) | Placebo (n=524) |
| Cardiovascular | | | | |
| Patients with event, n | 3 | 2 | 6 | 11 |
| Total exposure, person-years | 148 | 144 | 794 | 688 |
| IR per 100 person-years \pm SE | 2.1 \pm 1.3 | 1.5 \pm 1.1 | 0.8 \pm 0.3 | 1.6 \pm 0.5 |
| Infection^a | | | | |
| Patients with event, n | 54 | 62 | 283 | 269 |
| Total exposure, person-years | 87 | 66 | 425 | 382 |
| IR per 100 person-years \pm SE | 67.7 \pm 9.9 | 102.4 \pm 13.5 | 67.1 \pm 4.0 | 70.2 \pm 4.3 |
| Lymphopenia | | | | |
| Patients with event, n | 5 | 3 | 6 | 5 |
| Total exposure, person-years | 148 | 144 | 796 | 687 |
| IR per 100 person-years \pm SE | 3.2 \pm 1.5 | 2.2 \pm 1.3 | 0.8 \pm 0.3 | 0.7 \pm 0.3 |
| Hypersensitivity | | | | |
| Patients with event, n | 2 | 2 | 13 | 2 |
| Total exposure, person-years | 150 | 145 | 790 | 688 |
| IR per 100 person-years \pm SE | 1.4 \pm 1.0 | 1.3 \pm 0.9 | 1.7 \pm 0.5 | 0.3 \pm 0.2 |
| Skin-related | | | | |
| Patients with event, n | 15 | 15 | 61 | 50 |
| Total exposure, person-years | 140 | 126 | 737 | 640 |
| IR per 100 person-years \pm SE | 11.2 \pm 3.0 | 12.8 \pm 3.4 | 8.3 \pm 1.1 | 7.8 \pm 1.1 |
| Hypoglycemia | | | | |
| Confirmed ^b | | | | |
| Patients with event, n | 1 | 2 | 9 | 9 |
| Total exposure, person-years | 152 | 145 | 791 | 686 |
| IR per 100 person-years \pm SE | 0.8 \pm 0.8 | 1.2 \pm 0.8 | 1.2 \pm 0.4 | 1.3 \pm 0.4 |
| All reported | | | | |
| Patients with event, n | 16 | 18 | 71 | 68 |
| Total exposure, person-years | 138 | 130 | 724 | 623 |
| IR per 100 person-years \pm SE | 12.6 \pm 3.2 | 12.3 \pm 2.9 | 10.2 \pm 1.2 | 10.7 \pm 1.3 |

Notes: ^aBased on system-organ class categorization of infections and infestations. ^bDefined as episodes confirmed by fingerstick glucose ≤ 50 mg/dL and associated symptoms.

Abbreviations: IR, incidence rate; SAXA, saxagliptin; SE, standard error.

Available data on the safety of dipeptidyl peptidase-4 inhibitors in older individuals are limited largely to subgroup analyses.^{7,18,21} Previously published pooled analyses of five clinical trials, including those discussed in the present report, assessing the short-term (24 weeks) efficacy and safety of saxagliptin in patients ≥ 65 years and < 65 years clearly demonstrated that saxagliptin 5 mg/day reduced HbA_{1c}, fasting plasma glucose, and postprandial glucose in both age groups.^{18,19} The current study, while also a subgroup analysis, is unique in providing long-term safety data of up to 206 weeks and in assessing certain AE categories of special interest. In general, older patients are at greater risk for drug-related AEs. Specifically, severe or fatal hypoglycemia is more common in older patients than in younger patients,²² and any hypoglycemia is more dangerous in older patients than in younger patients, being associated with dizziness, falls, dysrhythmias, confusion, and infection.⁴ Additionally, infectious diseases, particularly influenza and pneumonia, are prominent sources of mortality and morbidity in older patients.²³ Accordingly, the American Diabetes Association/European Association for the Study of Diabetes position statement recommends that in older individuals, the choice of antihyperglycemic therapy should focus on drug safety, especially with regard to hypoglycemia, heart failure, renal dysfunction, bone fractures, and drug-drug interactions.⁴

The current findings should be confirmed by a prospective, randomized controlled trial in older patients. At present, there is a paucity of published prospective trial data assessing efficacy and safety of dipeptidyl peptidase-4 inhibitors in older patients with T2DM. A 24-week study of the efficacy and safety of sitagliptin versus placebo as monotherapy in older patients (aged ~ 72 years) with T2DM showed a safety and tolerability profile similar to that observed in younger patients.²⁴ The randomized, double-blind Phase IV SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) trial (ClinicalTrials.gov identifier NCT01107886) evaluated the cardiovascular efficacy and safety of saxagliptin over a median follow-up of 2.1 years in men and women aged ≥ 40 years with T2DM and a history of established cardiovascular disease (atherosclerosis involving the coronary, cerebrovascular, or peripheral vascular system) and in men aged ≥ 55 years and women aged ≥ 60 years with T2DM and one or more additional risk factors (ie, dyslipidemia, hypertension, or active smoking).²⁵ Saxagliptin was noninferior to placebo for the composite primary end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke, which occurred in 7.3% of patients receiving saxagliptin and

7.2% of patients receiving placebo (hazard ratio [95% CI] 1.00 [0.89–1.12]; $P < 0.001$ for noninferiority). However, more hospitalizations for heart failure occurred in patients in the saxagliptin group versus the placebo group (3.5% versus 2.8%; hazard ratio 1.27; 95% CI 1.07–1.51; $P = 0.007$). In a subgroup analysis according to age, hazard ratios (95% CI) for the primary end point were 1.01 (0.89–1.15) in patients < 75 years of age and 0.96 (0.75–1.22) in patients ≥ 75 years of age, with no significant interaction ($P = 0.67$). Thus, subgroup analyses from SAVOR support the cardiovascular efficacy and safety of saxagliptin in older patients. It should be noted that the mean age of patients participating in SAVOR was 65 years, with 52% ($n = 8,561$) ≥ 65 years and 14% ($n = 2,330$) ≥ 75 years.

This analysis is unique in that it focuses on the long-term (up to 206 weeks) safety of saxagliptin in older patients, but it has limitations. This was a retrospective analysis, and the small number of patients reporting an event in some categories of AEs made between-group comparisons less reliable. The population was pooled from three separate studies, and the specific inclusion and exclusion criteria may not have allowed for a population generally representative of older patients with T2DM. In addition, the number of older patients in this analysis was low and their mean age was 69 years, and based on their baseline creatinine clearance, they were relatively healthy and thus not representative of more frail elderly patients with T2DM. Despite these limitations, the results of this analysis suggest that the long-term use of saxagliptin 5 mg as add-on therapy to metformin, a thiazolidinedione, or glyburide is generally well tolerated in older, relatively healthy patients with T2DM.

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Author contributions

All authors contributed to the conception and design of the analyses, critically revised the manuscript, and approved the final manuscript draft for publication. The authors were responsible for final approval to submit for publication.

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NI is an employee and stockholder of Bristol-Myers Squibb. EA is a former employee of Bristol-Myers Squibb and a current employee of Novo Nordisk. PÖ is an employee and stockholder of AstraZeneca LP. The results of this analysis were presented at the American Diabetes Association 72nd Scientific Sessions, Philadelphia, PA, USA, June 8–12, 2012, and the 4th World Congress on Controversies to Consensus in Diabetes, Obesity, and Hypertension, Barcelona, Spain, November 8–11, 2012.

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