original article

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ORIGINAL ARTICLE

Initial combination therapy with saxagliptin and metformin provides sustained glycaemic control and is well tolerated for up to 76 weeks

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Aim: To assess the efficacy and safety of saxagliptin + metformin initial combination therapy compared with saxagliptin or metformin alone over 76 weeks (24-week short-term + 52-week long-term extension) in treatment-naïve type 2 diabetes mellitus patients with inadequate glycaemic control.

Methods: In this phase 3, parallel-group, double-blind, active-controlled study, 1306 patients 18–77 years of age (HbA1c 8.0–12.0%) were randomized to saxagliptin 5 mg + 500 mg metformin, saxagliptin 10 mg + 500 mg metformin, saxagliptin 10 mg + placebo or 500 mg metformin + placebo. Blinded metformin was titrated during weeks 1–5 of the short-term treatment period in 500 mg/day increments to 2000 mg/day maximum in the metformin-based treatment groups. No titration of metformin was permitted during the long-term treatment period. A total of 888 patients completed the study (76 weeks), 613 without being rescued. Changes in HbA1c, fasting plasma glucose, 120-min postprandial glucose (PPG) and PPG-area under the curve (AUC) from baseline to week 76 were analysed using a repeated-measures model.

Results: At 76 weeks, adjusted mean changes from baseline HbA1c (95% CI) for saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg and metformin were −2.31 (−2.44, −2.18), −2.33 (−2.46, −2.20), −1.55 (−1.70, −1.40) and −1.79% (−1.93, −1.65), respectively (*post hoc* and nominal $p < 0.0001$ vs. metformin and saxagliptin monotherapies for saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin). The proportions of patients requiring rescue or discontinuation for insufficient glycaemic control were lower for saxagliptin + metformin than for either monotherapy. Little or no attenuation in PPG-AUC or 120-min PPG was observed between weeks 24 and 76 for saxagliptin + metformin, indicating persistent efficacy. Adverse event rates were similar across groups; hypoglycaemic events occurred at a low frequency.

Conclusion: Saxagliptin + metformin initial combination therapy was well tolerated and produced sustained glycaemic control for up to 76 weeks, with greater improvements in glycaemic parameters compared with either drug alone.

Keywords: combination therapy, DPP-4 inhibitor, metformin, saxagliptin, type 2 diabetes mellitus

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Introduction

Long-term glycaemic control slows the progression of type 2 diabetes mellitus (T2DM)-related complications [1–4]. Monotherapy with oral antidiabetic drugs (OADs) may be effective in improving glycaemic control in the short term, but dose adjustments or combination therapy are often required for long-term control because of the progressive loss of β-cell function and increase in insulin resistance [5]. Patients presenting with higher glycosylated haemoglobin (HbA1c) are usually unable to achieve glycaemic control with a single OAD and therefore patients receiving initial combination therapy may be more likely to achieve glycaemic control [6]. Current guidelines from the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommend early initiation of combination therapy with OADs in patients with HbA1c >8.5% and 7.6–9.0%, respectively [4,6].

Oral antidiabetic drugs used in combination therapy should have complementary mechanisms of action and favourable safety and tolerability profiles to treat T2DM over the long term [4,6]. The combination of a dipeptidyl peptidase-4 (DPP-4) inhibitor with metformin meets these criteria [6]. DPP-4 inhibitors inhibit degradation of the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) to enhance glucose-dependent insulin secretion [7]. Inhibition of the proteolytic DPP-4 enzyme results in a two- to threefold increase in circulating levels of GLP-1 and GIP, suppresses glucagon secretion in the postprandial state, stimulates glucose-dependent insulin secretion from pancreatic β-cells [8–11]

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and decreases hepatic glucose production in the fasting state, thereby reducing both fasting plasma glucose (FPG) and postprandial glucose (PPG) [6,12]. Metformin improves insulin sensitivity and suppresses hepatic glucose production in the fasting and postprandial states, which also leads to the reduction of FPG and PPG [6]. DPP-4 inhibitors and metformin are well tolerated, weight neutral and associated with low risk for hypoglycaemia, although metformin use may sometimes be limited by gastrointestinal intolerance [4].

Saxagliptin is a potent, selective DPP-4 inhibitor indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM [9]. In this study, saxagliptin given in combination with metformin as initial therapy was compared with each agent alone in a multicentre, international, phase 3 trial involving treatment-naïve T2DM patients with inadequate glycaemic control. In the 24-week short-term period of this study of 1306 patients with T2DM, saxagliptin was effective in initial combination with metformin and demonstrated a tolerability profile similar to the monotherapy components [13]. Patients were treated with saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg or metformin. Saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin provided statistically significant adjusted mean HbA1c decreases from baseline to week 24 vs. saxagliptin 10 mg and metformin monotherapies (−2.5 and −2.5 vs. −1.7 and −2.0%, all $p < 0.0001$ vs. monotherapy). The combination therapies were well tolerated, as was each agent alone [13]. The present study assessed the long-term efficacy and safety up to week 76 (including the 24-week short-term period and a 52-week extension) of saxagliptin, given in combination with metformin as initial therapy compared with saxagliptin or metformin alone for the treatment of hyperglycaemia in treatment-naïve patients.

Methods

Patients

Full inclusion and exclusion criteria have been previously published [13]. In brief, treatment-naïve T2DM patients 18–77 years of age with inadequate glycaemic control (HbA1c at screening 8.0–12.0%), body mass index ≤40 kg/m^2 and fasting C-peptide concentration ≥1.0 ng/ml were eligible. Treatment naïve was defined as patients who had never received treatment for diabetes or who had received medical treatment for diabetes for less than 1 month since original diagnosis, and who had not received antihyperglycaemic therapy for more than three consecutive days or seven non-consecutive days during the 8 weeks before screening [13].

Exclusion criteria included symptoms of poorly controlled diabetes; history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; insulin therapy within 1 year of screening; cardiovascular event within the prior 6 months or New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction ≤40%; significant history of renal or hepatic disease, or a psychiatric disorder; alcohol or drug abuse within the previous year; treatment with potent CYP3A4 inhibitors or inducers; immunocompromised individuals; active liver disease or clinically significant abnormal hepatic, renal, endocrine, metabolic or haematological screening tests [13].

Study Design

The design for the initial 24-week period is described in detail in a previous publication [13]. Briefly, following a 1-week placebo lead-in period, eligible patients were randomly assigned 1 : 1 : 1 : 1 to saxagliptin 5 mg + metformin immediate release (IR) 500 mg; saxagliptin 10 mg + metformin IR 500 mg; saxagliptin 10 mg + placebo or metformin IR 500 mg + placebo. For the metformin-based treatment groups, the initial dose of metformin IR was titrated to 1000 mg/day at week 1; if FPG was >110 mg/dl, metformin IR was titrated, as tolerated, in 500 mg/day increments during weeks 2–5 to a maximum of 2000 mg/day [13]. Saxagliptin was taken once daily before the morning meal; metformin was taken in divided doses with the morning and evening meals [13].

Patients who completed all visits during the 24-week, short-term period or who met progressively strict glycaemic rescue criteria (FPG >240 mg/dl at week 6, >220 mg/dl at week 8 or >200 mg/dl at week 12 and thereafter) entered the long-term period, continuing their assigned treatment [13]. Patients who were rescued in the 24-week initial phase were advanced directly to the 52-week extension period and received open-label pioglitazone 15 mg once daily (titratable to 45 mg once daily) added to their blinded study medication. No changes in metformin dose were permitted during the long-term treatment period.

Patients with HbA1c >8.0% at week 30, 37 or 50, or >7.5% at week 63 were similarly rescued with pioglitazone 15 mg once daily, titrated to a maximum of 45 mg once daily according to local or regional policy, in addition to their blinded study medication. Patients who did not have a reduction in FPG ≥30 mg/dl within 8 weeks of starting rescue therapy were discontinued from the study and referred for additional antihyperglycaemic intervention.

The study protocol, amendments and patient informed consent were approved by the Institutional Review Board or Independent Ethics Committee for each participating site. The study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines as defined by the International Conference on Harmonisation. All patients were informed of the study purpose and potential risks; they then provided written informed consent before being allowed to participate in the study.

Assessments

Study visits during the 52-week extension period at weeks 30, 37, 50, 63 and 76 included assessments of HbA1c, FPG, vital signs, body weight, adverse events (AEs) and a focused physical examination (complete examination at week 76). An oral glucose tolerance test (OGTT) was conducted at weeks 0, 24 and 76.

Specified efficacy assessments included change from baseline in HbA1c, FPG, 120-min PPG and PPG-area under the curve (PPG-AUC); proportion of patients achieving therapeutic

glycaemic responses defined as HbA1c <7.0%; time to rescue therapy for failing to achieve prespecified glycaemic targets or discontinuation because of insufficient efficacy; and proportion of patients requiring rescue therapy for failing to achieve prespecified glycaemic targets or discontinuing for insufficient efficacy at weeks 4, 6, 8, 12, 16, 20, 24, 30, 37, 50 and 63. Other end-points were examined, but are not presented in this manuscript.

A total of 315 patients (24% of the randomized patients) had OGTT samples that were rendered invalid when incorrect quantities of glucose were administered. Patients were to begin administration of 75 g of oral glucose solution at time 0 min during the OGTT. However, bottles containing more than 75 g of oral glucose solution were administered at certain study sites in Europe. At those sites, patients who were dispensed an amount >10% in excess of the prespecified 75 g of oral glucose solution were not included in any analysis of OGTT parameters. The percentage of patients who received the excess oral glucose solution was evenly distributed across the four treatment groups (23, 22, 24 and 24% for saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg and metformin, respectively).

Safety assessments included the incidence of AEs, serious adverse events (SAEs), and discontinuations because of AEs, and changes from baseline laboratory parameters and vital signs. Hypoglycaemia was evaluated separately from other AEs; confirmed hypoglycaemia was defined by a fingerstick glucose value ≤50 mg/dl in the presence of associated symptoms.

Statistical Analyses

Efficacy parameters were evaluated in randomized patients who received at least one dose of double-blind treatment and had baseline and postbaseline efficacy measurements taken before any rescue medication (if used). For HbA1c, FPG, PPG-AUC and 120-min PPG, a repeated measures analysis was used to analyse the change from baseline to each time point. The model used in this analysis contained terms for treatment group, time and time × treatment group, and changes from baseline were adjusted for baseline value. Estimated differences in the adjusted mean changes from baseline between treatments and 95% confidence limits are presented; for HbA1c, mean differences at week 76 were assessed with a *post hoc* and nominal p-value. The Toeplitz covariance structure was used to model the covariance over time. Continuous efficacy end-points were also analysed with an analysis of covariance model using a last-observation-carried-forward (LOCF) approach with treatment group as an effect and the baseline value as a covariate. The proportion of patients achieving therapeutic glycaemic response (LOCF) was summarized descriptively and the exact 95% confidence intervals (CIs) were determined from the standardized statistic and inverting the two-sided test. Time to discontinuation for inadequate glycaemic control or rescue intervention was summarized using Kaplan–Meier estimates and displayed by treatment group. The 95% CIs were calculated using Greenwood's method. All efficacy analyses used data collected prior to initiation of any rescue therapy or discontinuation. The primary efficacy end-point of the short-term period analysis was HbA1c change from baseline to week 24; end-points in the long-term extension were exploratory. System International (SI) conversion from mg/dl to mmol/l of glucose can be calculated with the following equation: mg/dl × 0.0555.

Safety parameters were evaluated in all patients who received at least one dose of double-blind treatment, regardless of rescue therapy. Clinical AEs were coded and grouped into system organ classes, preferred terms and treatment group using MedDRA version 11.1.

Results

Patient Disposition and Demographics

A total of 1306 patients were randomized and treated with double-blind therapy (figure 1). Of these, 1103 patients (84.5%) entered the long-term extension, including 991 (75.9%) who completed the short-term period without rescue. In total, 888 patients (68%) completed the study, including 613 (47%) who completed without rescue. Discontinuations occurred at higher rates in the saxagliptin 10 mg (37.6%) and metformin (33.2%) groups than in the saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin combination therapy groups (28.4 and 28.5%, respectively). In the long-term extension, insufficient efficacy was the most common reason for discontinuation in all four treatment groups and accounted for much of the difference in discontinuation between groups:

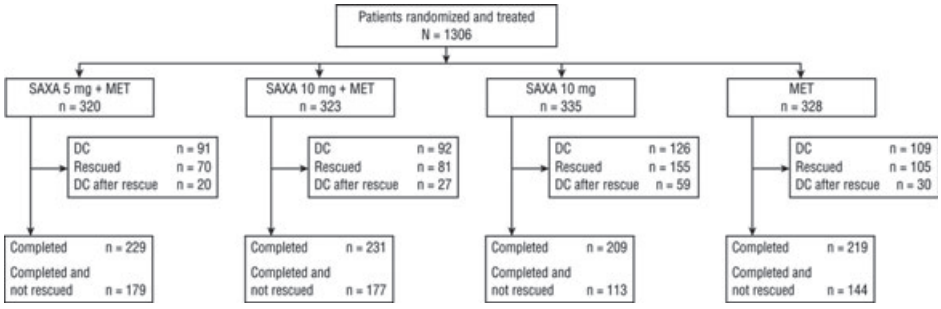

Figure 1. Patient disposition. Rescued patients include all patients who were rescued in short-term or long-term extension period. Rescued patients may later have discontinued from the study. DC, total number of patients who discontinued from the study; MET, metformin; PBO, placebo; SAXA, saxagliptin.

Table 1. Baseline demographic and clinical characteristics.

Characteristics	SAXA 5 mg + MET n = 320	SAXA 10 mg + MET n = 323	SAXA 10 mg n = 335	MET n = 328
Age (years)*	52.0 (10.4)	52.1 (11.6)	52.1 (10.2)	51.8 (10.7)
Age ≥65 years†	33 (10.3)	54 (16.7)	43 (12.8)	36 (11.0)
Sex†				
Men	165 (51.6)	146 (45.2)	169 (50.4)	163 (49.7)
Women	155 (48.4)	177 (54.8)	166 (49.6)	165 (50.3)
Race†				
White	246 (76.9)	243 (75.2)	255 (76.1)	251 (76.5)
Asian	51 (15.9)	54 (16.7)	56 (16.7)	52 (15.9)
Black/African American	7 (2.2)	7 (2.2)	6 (1.8)	4 (1.2)
Other	16 (5.0)	19 (5.9)	18 (5.4)	21 (6.4)
BMI (kg/m^2)*	29.9 (4.5)	30.4 (4.9)	30.2 (4.9)	30.2 (4.9)
Diabetes duration (years)*	2.0 (3.6)	1.4 (2.5)	1.7 (2.8)	1.7 (3.1)
HbA1c (%)*	9.4 (1.2)	9.5 (1.2)	9.6 (1.3)	9.4 (1.3)
FPG (mg/dl)*‡	199 (56.6)	204 (59.7)	201 (54.8)	198 (58.7)

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin; MET, metformin; SAXA, saxagliptin.
*Values expressed as mean (s.d.).
†Values expressed as n (%).
‡System International conversion to mmol/l: mg/dl × 0.0555.

11.5% for saxagliptin 10 mg and 8.6% for metformin vs. 6.2% and 6.5% for saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin, respectively.

Demographic and clinical characteristics are summarized in Table 1. Overall, the initial study cohort had a mean age of 52 years and included 166 patients (12.7%) ≥65 years of age. Patients had T2DM for a median of 0.4 years (range 0–29.4 years). Baseline HbA1c averaged 9.5%, with 475 patients (36.4%) having HbA1c values ≥10.0%. The mean duration of exposure to saxagliptin prior to rescue was longer in the combination therapy groups than in the monotherapy group (56.5, 56.6 and 44.6 weeks for saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin and saxagliptin 10 mg, respectively); 54.4, 53.6 and 32.8% of saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin and saxagliptin 10 mg patients, respectively, received ≥74 weeks of saxagliptin therapy. Mean duration of exposure to metformin prior to rescue was also longer in the combination therapy groups (56.5, 56.7 and 50.3 weeks for saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin and metformin, respectively), with 54.7, 54.2 and 43.6%, respectively, exposed for ≥74 weeks.

Efficacy

Glycaemic Indices. Among the 1240 patients in the analysis, including 612 patients with observed values at week 76, adjusted mean changes (95% CI) from baseline HbA1c (repeated measures analysis) for saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg and metformin were −2.31% (−2.44, −2.18), −2.33% (−2.46, −2.20), −1.55% (−1.70, −1.40) and −1.79% (−1.93, −1.65), respectively, at week 76 (Table 2), and were similar to adjusted mean changes from baseline HbA1c (repeated measures analysis) at week 24 (figure 2). Results from the week 24 and week 76 LOCF analyses (not shown) were similar. Compared with saxagliptin 10 mg, the differences (95% CI) in the adjusted mean change from baseline HbA1c at week 76 were −0.76% (−0.96, −0.56) for saxagliptin 5 mg + metformin and −0.78% (−0.98, −0.58) for saxagliptin 10 mg + metformin (*post hoc* and nominal $p < 0.0001$ for both saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin vs. saxagliptin 10 mg). Compared with metformin monotherapy, the respective differences (95% CI) at week 76 were −0.52% (−0.71, −0.33) and −0.54% (−0.73, −0.35) for saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin (*post hoc* and nominal $p < 0.0001$ for both saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin vs. metformin monotherapy). The results over time are graphically illustrated in figure 2. A small attenuation of effect was observed in all groups between weeks 24 and 76.

The adjusted mean changes (s.e.) from baseline FPG (repeated measures analysis) for each group at week 76 are reported in Table 2. At week 76, the saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin groups had similar results [−54 (2.6) and −55 (2.6) mg/dl, respectively]. At week 76, the adjusted mean changes (s.e.) from baseline FPG for the monotherapy groups were smaller [−24 (3.0) mg/dl for saxagliptin 10 mg and −40 (2.8) mg/dl for metformin]. At week 24, the adjusted mean changes (s.e.) from baseline FPG for these treatment groups were −59 (2.3), −61 (2.3), −35 (2.4), and −47 (2.3) mg/dl, respectively. A small attenuation of effect was observed in all groups between weeks 24 and 76.

A higher proportion of patients achieved an HbA1c <7% at week 76 (LOCF analysis) with saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin than with either agent alone (Table 2). Similarly, a higher proportion of patients achieved an HbA1c <6.5% at week 76 (LOCF analysis) with saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin than with either agent alone (not shown).

Post-absorptive glycaemia assessed by adjusted mean change (s.e.) from baseline PPG-AUC (repeated measures analysis) at week 76 is reported in Table 2. At week 76, the saxagliptin

Table 2. Changes in efficacy measures at 76 weeks.

	SAXA 5 mg + MET n = 320	SAXA 10 mg + MET n = 323	SAXA 10 mg n = 335	MET n = 328
HbA1c (%)*				
n included in analysis	303	313	316	308
n with observed data at 76 weeks	177	178	110	147
BL mean (s.e.)	9.41 (0.07)	9.53 (0.07)	9.61 (0.08)	9.43 (0.07)
Adjusted mean change from BL (s.e.)	−2.31 (0.07)‡	−2.33 (0.07)‡	−1.55 (0.08)	−1.79 (0.07)
Mean difference vs. SAXA 10 mg (s.e.)	−0.76 (0.10)	−0.78 (0.10)		
95% CI	(−0.96, −0.56)	(−0.98, −0.58)		
Mean difference vs. MET (s.e.)	−0.52 (0.10)	−0.54 (0.10)		
95% CI	(−0.71, −0.33)	(−0.73, −0.35)		
FPG (mg/dl)*				
n included in analysis	315	317	327	320
n with observed data at 76 weeks	154	151	98	125
BL mean (s.e.)	199 (3.2)	204 (3.4)	201 (3.0)	199 (3.3)
Adjusted mean change from BL (s.e.)	−54 (2.6)	−55 (2.6)	−24 (3.0)	−40 (2.8)
Mean difference vs. SAXA 10 mg (s.e.)	−30 (4.0)	−32 (4.0)		
95% CI	(−38.0, −22.3)	(−39.4, −23.7)		
Mean difference vs. MET (s.e.)	−14 (3.8)	−15 (3.8)		
95% CI	(−21.0, −6.1)	(−22.4, −7.5)		
Patients achieving HbA1c <7.0%†				
N	307	315	320	314
n (%)	157 (51.1)	160 (50.8)	80 (25)	109 (34.7)
Difference in proportion vs. SAXA 10 mg (%)	26.1	25.8		
95% CI	(18.6, 33.4)	(18.4, 33.0)		
Difference in proportion vs. MET (%)	16.4	16.1		
95% CI	(8.6, 24.1)	(8.3, 23.7)		
PPG-AUC (mg • min/dl)*				
n included in analysis	145	138	123	130
n with observed data at 76 weeks	119	106	85	104
BL mean (s.e.)	54 585 (1048.1)	56 181 (1061.1)	55 355 (1235.5)	55 811 (1210.2)
Adjusted mean change from BL (s.e.)	−21 174 (781.4)	−20 308 (821.5)	−13 913 (907.4)	−13 601 (833.4)
Mean difference vs. SAXA 10 mg (s.e.)	−7261 (1197.4)	−6395 (1224.1)		
95% CI	(−9615, −4907)	(−8801, −3988)		
Mean difference vs. MET (s.e.)	−7573 (1142.8)	−6707 (1170.1)		
95% CI	(−9820, −5327)	(−9007, −4407)		
120-min PPG (mg/dl)*				
n included in analysis	150	143	124	135
n with observed data at 76 weeks	124	109	88	110
BL mean (s.e.)	334 (7.1)	345 (7.2)	343 (8.4)	344 (8.0)
Adjusted mean change from BL (s.e.)	−137 (5.6)	−129 (5.9)	−94 (6.6)	−86 (5.9)
Mean difference vs. SAXA 10 mg (s.e.)	−43 (8.6)	−35 (8.8)		
95% CI	(−60.3, −26.4)	(−52.4, −17.7)		
Mean difference vs. MET (s.e.)	−51 (8.2)	−43 (8.4)		
95% CI	(−67.3, −35.2)	(−59.4, −26.5)		

BL, baseline; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin; MET, metformin; 120-min PPG, 120-min postprandial glucose; SAXA, saxagliptin.

System International conversion to mmol/l: mg/dl × 0.0555. System International conversion to mmol • min/l: mg • min/dl × 0.0555.

*Values expressed as adjusted mean change from baseline (95% CI) in repeated measures analysis.

†LOCF analysis.

‡*Post hoc* and nominal $p < 0.0001$ vs. both SAXA 10 mg and MET alone.

5 mg + metformin and saxagliptin 10 mg + metformin groups had similar results [−21 174 (781.4) and −20 308 (821.5) mg • min/dl, respectively]. The week 76 mean change (s.e.) from baseline PPG-AUC values for the monotherapy groups were smaller [−13 913 (907.4) mg • min/dl for saxagliptin 10 mg and −13 601 (833.4) mg • min/dl for metformin]. At week 24, the adjusted mean changes (s.e.) from baseline PPG-AUC for these treatment groups were −21 168 (727.4), −21 243 (743.7), −17 930 (792.2) and −15 969 (772.6) mg • min/dl, respectively. A small attenuation of effect was observed in the monotherapy groups between weeks 24 and 76. Little or no attenuation of effect was observed in the saxagliptin + metformin treatment groups. At the 120-min time point of the OGTT, adjusted mean decreases from baseline PPG were greater in the saxagliptin + metformin groups than in either monotherapy group at week 76 (Table 2).

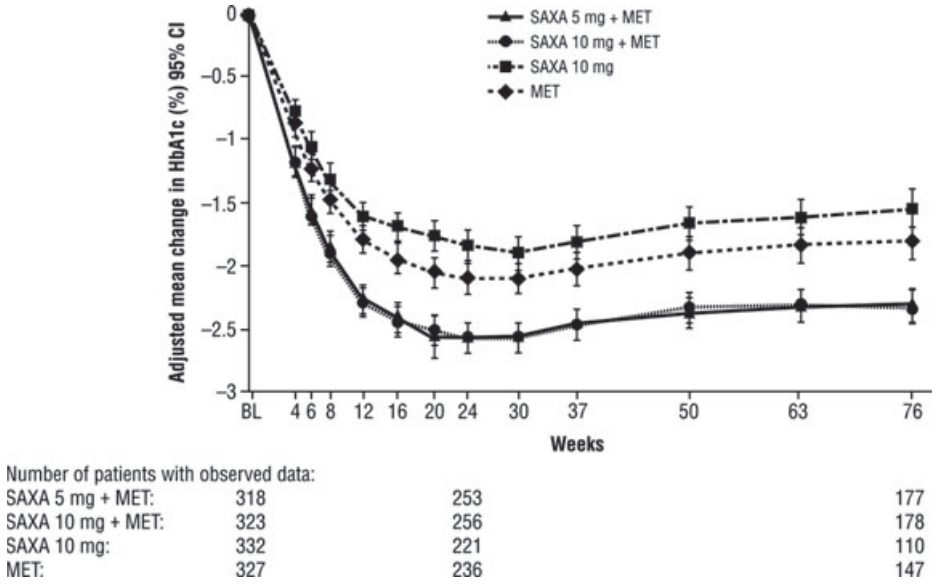

Figure 2. Adjusted mean change from baseline HbA1c (repeated measures analysis). BL, baseline; HbA1c, glycosylated haemoglobin; MET, metformin; PBO, placebo; SAXA, saxagliptin.

Body Weight. Small decreases in mean body weight were observed in all treatment groups. In the LOCF analysis, the mean change from baseline to week 76 in body weight was −1.2 kg with saxagliptin 5 mg + metformin, −0.7 kg with saxagliptin 10 mg + metformin, −0.3 kg with saxagliptin 10 mg and −1.0 kg with metformin.

Rescue and Discontinuation. The proportion of patients requiring rescue therapy for failing to achieve prespecified glycaemic targets or discontinuing because of insufficient glycaemic control was higher in the monotherapy groups than in the combination therapy groups at all time points after week 6. This proportion became progressively greater over time (figure 3), especially as more stringent criteria for rescue were applied. On Kaplan–Meier analysis, 56.1% of patients treated with saxagliptin 10 mg and 41.9% of patients treated with metformin had been rescued or discontinued for insufficient glycaemic control by week 76 compared with 27.8 and 30.9% of those treated with saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin, respectively (figure 3).

Safety and Tolerability

Overall, as reported at week 24 [13], the safety profile was similar across treatment groups. The proportions of patients reporting AEs and SAEs were generally similar across treatment groups, as were discontinuation rates because of AEs (Table 3). Ten deaths occurred, including one in the saxagliptin 5 mg + metformin group (tetanus in a non-immunized patient with a puncture wound), two in the saxagliptin 10 mg + metformin group (sudden death, cardiac arrest), two in the saxagliptin 10 mg group (coronary artery arteriosclerosis, ischaemic stroke) and five in the metformin monotherapy group (cardiac failure, acute myocardial infarction, cerebrovascular accident, pancreatic neoplasm/sepsis and sudden death).

The majority of AEs were mild or moderate in intensity in all treatment groups. AEs reported by ≥5% of patients in any treatment group are summarized in Table 4. In the subset of patients age ≥65 years, the proportion reporting AEs was lower in the saxagliptin 10 mg [58.1% (25/43)] and metformin [58.3% (21/36)] groups compared with the saxagliptin 5 mg + metformin [75.8% (25/33)] and saxagliptin 10 mg + metformin [63.0% (34/54)] groups. However, these results must be interpreted with caution because of the small number of patients in this age group.

The proportions of patients with gastrointestinal-related AEs were 21.3, 27.9 and 16.7% in the saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin and saxagliptin 10 mg treatment groups, respectively, compared with 23.2% in the metformin monotherapy treatment group.

The proportions of patients with skin-related AEs were 7.2, 7.7 and 6.9% in the saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin and saxagliptin 10 mg treatment groups, respectively, compared with 4.9% in the metformin monotherapy treatment group. No events of angio-oedema or Stevens–Johnson syndrome were reported, and only one skin-related event led to discontinuation (allergic dermatitis in a patient treated with metformin). Acute cardiovascular AEs occurred at low rates, ranging from 0.3% in the saxagliptin 5 mg + metformin group to 2.1% in the metformin monotherapy group.

The overall frequency of hypoglycaemic events was low (4.7% with saxagliptin 5 mg + metformin, 6.8% with saxagliptin 10 mg + metformin, 2.1% with saxagliptin 10 mg and 6.1% with metformin alone) (Table 4). Five patients had confirmed hypoglycaemia, including three patients in the saxagliptin 10 mg + metformin group with a total of four events and two patients in the metformin group with a total of three events. None of the confirmed hypoglycaemic events needed management or treatment by the physician. One of the

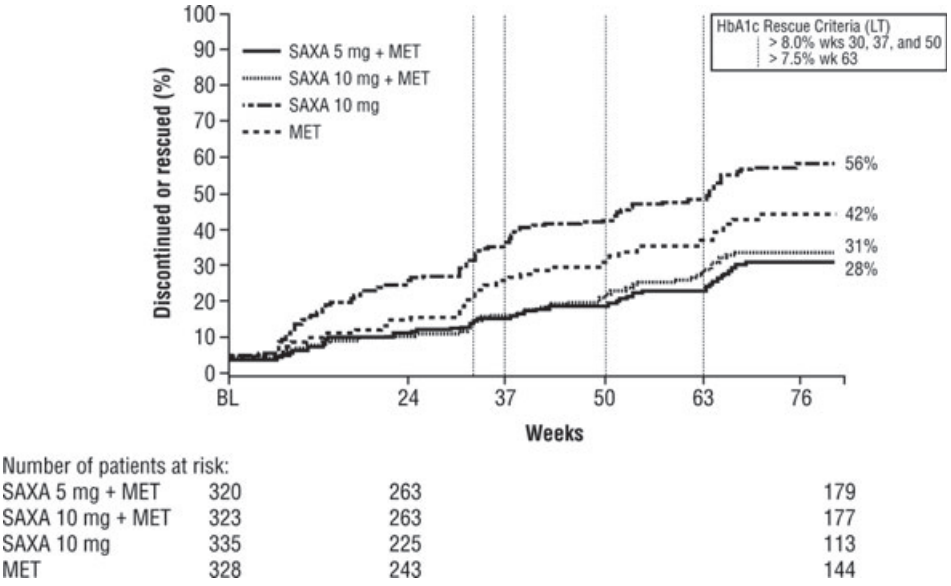

Figure 3. Time to study discontinuation for insufficient glycaemic control or rescue: Kaplan–Meier analysis. BL, baseline; MET, metformin; PBO, placebo; SAXA, saxagliptin.

five patients with confirmed hypoglycaemic events in the study was age ≥65 years. No hypoglycaemic event was judged to be serious by the investigator and no report of a hypoglycaemic event led to discontinuation from the study.

Mean absolute lymphocyte counts remained within the normal range in all treatment groups throughout the study. AE reports of lymphopaenia or decreased lymphocyte count occurred in seven patients (2.1%) treated with saxagliptin 10 mg alone and three patients (0.9%) treated with saxagliptin 10 mg + metformin (compared with zero patients with saxagliptin 5 mg + metformin and one patient with metformin). There were no clinically meaningful drug effects on any laboratory safety parameter, including haematological, renal, hepatic and musculoskeletal parameters.

Discussion

Initial combination therapy with saxagliptin + metformin was more effective than metformin or saxagliptin 10 mg in improving glycaemic control for up to 76 weeks, as reflected by reductions in HbA1c, FPG, PPG-AUC and 120-min PPG, and in the percentage of patients achieving HbA1c <7%. The highest study completion rates, especially completion without glycaemic rescue, were observed in the combination therapy groups. Efficacy was generally similar in the saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin groups. Discontinuations because of AEs were infrequent and similar across treatment groups, and other measures of safety and tolerability suggested a generally comparable safety profile in all treatment groups. A higher percentage of patients who started on saxagliptin or metformin monotherapy required rescue (46 and 32%, respectively) compared with those who received saxagliptin 5 mg + metformin or saxagliptin 10 mg + metformin (22 and 25%, respectively). The proportions of patients reporting AEs and SAEs were generally similar across treatment groups, as were discontinuation rates because of AEs. Thus, the increased efficacy of initial combination therapy was achieved without affecting tolerability or safety.

Table 3. Adverse event summary.

	SAXA 5 mg + MET n = 320	SAXA 10 mg + MET n = 323	SAXA 10 mg n = 335	MET n = 328
Adverse events (AEs), n (%)*				
≥1 AE	211 (65.9)	221 (68.4)	222 (66.3)	224 (68.3)
≥1 related AE	45 (14.1)	72 (22.3)	59 (17.6)	67 (20.4)
Deaths	1 (0.3)	2 (0.6)	2 (0.6)	5 (1.5)
≥1 SAE	16 (5.0)	22 (6.8)	16 (4.8)	15 (4.6)
≥1 related SAE	1 (0.3)	4 (1.2)	0 (0)	1 (0.3)
Discontinuations because of SAEs	2 (0.6)	4 (1.2)	0 (0)	2 (0.6)
Discontinuations because of AEs	14 (4.4)	10 (3.1)	14 (4.2)	14 (4.3)

MET, metformin; SAEs, serious adverse events; SAXA, saxagliptin.
*Includes hypoglycaemia.

Table 4. Adverse events reported by ≥5%* of patients in any treatment group.

	SAXA 5 mg + MET n = 320	SAXA 10 mg + MET n = 323	SAXA 10 mg n = 335	MET n = 328
Most common AEs [≥5%, n (%)]				
Nasopharyngitis	29 (9.1)	19 (5.9)	24 (7.2)	19 (5.8)
Urinary tract infection	13 (4.1)	22 (6.8)	23 (6.9)	25 (7.6)
Influenza	20 (6.3)	13 (4.0)	17 (5.1)	19 (5.8)
Upper respiratory tract infection	15 (4.7)	19 (5.9)	14 (4.2)	10 (3.0)
Diarrhoea	26 (8.1)	41 (12.7)	12 (3.6)	30 (9.1)
Headache	31 (9.7)	36 (11.1)	31 (9.3)	18 (5.5)
Back pain	13 (4.1)	16 (5.0)	12 (3.6)	11 (3.4)
Hypertension	27 (8.4)	21 (6.5)	19 (5.7)	17 (5.2)
Reported hypoglycaemia†	15 (4.7)	22 (6.8)	7 (2.1)	20 (6.1)
Confirmed hypoglycaemia‡	0 (0)	3 (0.9)	0 (0)	2 (0.6)

AEs, adverse events; MET, metformin; SAXA, saxagliptin.
*Excludes hypoglycaemia.
†Reported hypoglycaemia includes events consistent with signs and symptoms of hypoglycaemia with or without documented blood glucose levels.
‡Confirmed hypoglycaemia defined by a fingerstick glucose value ≤50 mg/dl with associated symptoms.

It is now widely recognized that diabetes is a progressive disease [14,15]. The United Kingdom Prospective Diabetes Study (UKPDS) data identified the predominant component of this loss of efficacy as failure of sulphonylurea or metformin to halt the decline in β-cell function seen with diet only [16], rather than loss in insulin sensitivity [17] assessed in the fasting state by homeostatic model assessment. Analyses of a 5-year study using glucose challenge confirmed that declining β-cell function is the primary mechanism of progression [18,19]. Improvements in glycaemic parameters with initial combination therapy relative to monotherapy observed at the end of the short-term period of this study were largely sustained during the 52-week long-term extension, with only a modest attenuation in change from baseline HbA1c between weeks 24 and 76 observed in the treatment groups.

The 52-week extension after the initial 24-week short-term period provided an opportunity to make a preliminary assessment regarding the effect of combined treatment over time for fasting and postprandial glucose. For the fasting state, assessed by FPG, there appeared to be a modest and comparable loss of glycaemic control across all treatment groups. For the postprandial state, assessed by PPG, partial attenuation was documented with the two monotherapy treatments. In contrast, for the combined saxagliptin + metformin treatment groups, no loss of glycaemic efficacy could be detected by PPG. The effects seen in the combination groups may reflect the complementary benefits in insulin secretion and sensitivity provided by the components, saxagliptin and metformin, respectively. It should be noted that the combination of a DPP-4 inhibitor and metformin has been reported to lead to complementary increases in intact GLP-1, which may have contributed to the findings observed in this study [20]. These postprandial results appear to be detected in overall glycaemic efficacy (assessed by HbA1c), as the combination therapy groups had less attenuation compared with the monotherapy groups.

These findings are noteworthy given the importance of PPG in various diabetes-related complications. For example, the Whitehall study of British males demonstrated that plasma glucose levels ≥96 mg/dl measured 2 h after a meal were associated with an approximate twofold increase in mortality from coronary heart disease (CHD) [21]. Similarly, the Islington Diabetes Survey found that the incidence of major CHD was 17% in patients with 2-h PPG levels between 120 and 180 mg/dl, compared with 9% in patients whose levels were <120 mg/dl [22].

Initial saxagliptin + metformin combination therapy was associated with a safety and tolerability profile similar to those of each drug alone. Adverse event rates, as well as discontinuations because of AEs, were comparable across treatment groups. Hypoglycaemic events occurred at a low frequency and did not occur more often with saxagliptin + metformin compared with metformin alone. The sustained glycaemic control achieved with saxagliptin + metformin, combined with the similar or lower risk of hypoglycaemia relative to metformin, may provide a substantial long-term benefit for T2DM patients. There was no evidence for an adverse impact that might be introduced by the complementary actions of metformin and saxagliptin (e.g. on intact GLP-1 levels). This study suggests that a treatment strategy based on initial combination therapy with saxagliptin + metformin offers increasing benefit without added risk. The promise of earlier benefit is particularly important given recent evidence of the glycaemic 'legacy effect' demonstrated by the UKPDS and the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications [23,24].

After adjusting for other risk factors, each 1% increase in HbA1c is associated with an 18% increased risk of cardiovascular disease [25] and a 12–14% increased risk of death in T2DM patients [26,27]. The sustained HbA1c control observed in this trial may, therefore, translate into a potentially reduced cardiovascular risk for patients treated with the saxagliptin + metformin combination.

Although firm conclusions cannot be drawn from comparisons between studies performed in different patient populations with different designs, the results of this study are generally similar to an initial combination study performed

with sitagliptin and metformin [28,29]. At 1 year, the least squares reduction from baseline results of HbA1c were greater for sitagliptin + metformin 2000 mg (−1.9%) than for metformin 2000 mg alone (−1.6%) [28]. At 2 years, the initial combination reduction (−1.7%) remained greater than that for metformin alone (−1.3%). Other glycaemic measures were consistent with the HbA1c results. There was a low occurrence of hypoglycaemia and AE frequency was generally similar across treatment groups, with highest rates in the high-dose metformin combination therapy group and lowest in the sitagliptin monotherapy and metformin monotherapy groups [29]. These sitagliptin + metformin results, in addition to those demonstrated in the current study, support the utility of initial combination therapy of a DPP-4 inhibitor and metformin.

As with any long-term clinical trial, this study has limitations with respect to patient retention over longer periods of follow-up. Completion rates were higher in the saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin groups (71.6 and 71.5%, respectively) than in the saxagliptin 10 mg (62.4%) or metformin (66.8%) monotherapy groups. This pattern is expected for a more effective treatment regimen, and indeed, discontinuations for insufficient efficacy were more common in the monotherapy groups, whereas discontinuations for other reasons were generally comparable across treatment groups.

For ethical reasons, this study included provisions to add pioglitazone to the regimens of patients with insufficient glycaemic control while receiving study medication. Combining patients with rescue treatment and patients missing HbA1c values for reasons other than rescue, 55% of patients in the combination therapy groups, 33% of patients in the saxagliptin 10 mg group and 45% of patients in the metformin group remained without rescue and had available HbA1c measurements at week 76. Statistical analytical methods used to compare mean changes between treatment groups assumed that missing values for glycaemic variables in previously rescued or discontinued patients could be inferred using available pre-rescue/discontinuation values of these patients, along with observed values in the remaining patients. With 47% of patients with available measurements at week 76, the estimates and p-values are strongly dependent on this assumption. In addition, p-values associated with these comparisons were not prospectively specified and are not adjusted for multiplicity. For these reasons, the results of the long-term glycaemic parameter analyses should be interpreted with a level of caution.

Another limitation of this study is that not detecting an anticipated decline in postprandial glycaemic function for more than a year for the combined saxagliptin + metformin treatment, while noting a small attenuation in the monotherapy components, may reflect the length of time available for follow-up. Seventy-six weeks may not be a long enough period of time to detect slow decline in function. A certain number of OGTT samples were rendered invalid because of the administration of a non-standard amount of glucose during oral challenge. However, this affected comparable numbers of patients across the treatment groups and we do not believe that it strongly impacts the interpretation of the comparison between treatment groups.

In conclusion, initial therapy with saxagliptin + metformin produced sustained reductions in glycaemic parameters compared with each drug alone over 76 weeks. No attenuation of the effect on PPG-AUC was evident. Saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin were well tolerated, without increasing the risk of hypoglycaemic events. Taken together, these results support saxagliptin + metformin as an effective and well-tolerated option in the initial treatment of T2DM.

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Conflict of Interest

A. P. reports that he has received research grants, consultancy fees and travel support from AstraZeneca and Bristol-Myers Squibb, has served as a consultant for Biodel Inc., and has received research support from Boehringer Ingelheim, Eli Lilly, Grünthal, Novo Nordisk, Roche Diagnostics, Roche Pharmaceuticals, sanofi-aventis and Takeda Pharmaceutical Company. E. P. reports that she has served on advisory boards and received honoraria from AstraZeneca, Eli Lilly, sanofi-aventis and MSD, has served on speakers bureaus for GlaxoSmithKline and United Laboratories, and has received research support from Boehringer Ingelheim, Bristol-Myers Squibb and sanofi-aventis. E. A., R. F. and R. C. are employees of Bristol-Myers Squibb.

A. P., E. P., E. A., R. F. and R. C. assisted in the study design and conduct, data collection and analysis, and drafted and approved the final manuscript.

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