original article

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ORIGINAL ARTICLE

Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment

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Aim: To evaluate the efficacy and safety of saxagliptin vs. placebo in patients with type 2 diabetes mellitus (T2DM) and renal impairment.
Methods: In this multicentre, randomized, parallel-group, double-blind, placebo-controlled study, patients with glycated haemoglobin (HbA1c) 7–11% and creatinine clearance <50 ml/min were stratified by baseline renal impairment (moderate, severe or end-stage on haemodialysis), and randomized (1 : 1) to saxagliptin 2.5 mg once daily or placebo for 12 weeks. Oral antihyperglycaemic drugs and insulin therapy present at enrolment were continued throughout the study. The absolute change in HbA1c from baseline to week 12 (primary efficacy end-point) was analysed using an analysis of covariance model with last observation carried forward methodology.
Results: A total of 170 patients were randomized and treated. The adjusted mean decrease from baseline to week 12 in HbA1c was statistically significantly greater in the saxagliptin group than in the placebo group; the difference between treatments was −0.42% (95% confidence interval: −0.71 to −0.12%, p = 0.007). Adjusted mean HbA1c decreases from baseline to week 12 were numerically greater with saxagliptin than with placebo in the subgroups of patients with moderate (−0.64 vs. −0.05%) and severe (−0.95 vs. −0.50%) renal impairment. HbA1c reductions were similar between saxagliptin and placebo in the subgroup with end-stage renal disease on haemodialysis (−0.84 vs. −0.87%). Saxagliptin was generally well tolerated; incidences of adverse events and hypoglycaemic events were similar to placebo.
Conclusions: Saxagliptin 2.5 mg once daily is a well-tolerated treatment option for patients with inadequately controlled T2DM and renal impairment.
Keywords: dipeptidyl peptidase-4 inhibitor, end-stage renal disease, glycaemic control, renal impairment, saxagliptin, type 2 diabetes mellitus

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Introduction

Kidney disease is common among patients with type 2 diabetes mellitus (T2DM) [1]. Approximately 20–30% of patients with diabetes will develop evidence of renal damage, ranging from microalbuminuria to overt nephropathy, and ultimately progress to end-stage renal disease (ESRD) [2]. The rapid increase in T2DM prevalence over the last several decades has been accompanied by higher rates of kidney disease, particularly among African Americans, and both are expected to continue to increase in most countries [1,3–5]. For patients with T2DM and impaired renal function, certain oral antihyperglycaemic agents should not be used because of safety and tolerability issues [6]. These include metformin, which is contraindicated in patients with creatinine clearance (CrCl) <60 ml/min, and glyburide, which should be avoided if CrCl is <50 ml/min [7].

Saxagliptin is a selective dipeptidyl peptidase-4 (DPP-4) inhibitor specifically designed for extended inhibition of the DPP-4 enzyme that is approved as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM [8–10]. Saxagliptin is primarily metabolized by cytochrome P450 (CYP) 3A4/5 to form an active metabolite, 5-hydroxy saxagliptin, which is cleared by the kidney. The parent drug is eliminated by both renal and hepatic routes [10]. In clinical trials, saxagliptin as monotherapy or in combination with metformin, a sulphonylurea (glyburide) or thiazolidinedione (pioglitazone or rosiglitazone) significantly lowered glycated haemoglobin (HbA1c), fasting plasma glucose (FPG) and postprandial plasma glucose, was well tolerated and did not increase hypoglycaemic events or cause weight gain vs. comparator [11–15].

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This study evaluated the efficacy and safety of saxagliptin vs. placebo in patients with T2DM and renal impairment (moderate, severe or ESRD).

Methods

Study Design

This was a 12-week, international, multicentre, randomized, parallel-group, double-blind, placebo-controlled, phase III study designed to assess the efficacy and safety of saxagliptin in adult patients with T2DM, inadequate glycaemic control (HbA1c 7–11%) and moderate or severe renal impairment, or ESRD. This study included an additional 40-week observational period, which will be reported separately after completion. The degree of renal impairment was categorized based on the estimated CrCl determined by the Cockcroft–Gault equation as moderate (CrCl ≥30 to <50 ml/min), severe (CrCl <30 ml/min, and not receiving dialysis) or ESRD (receiving haemodialysis) [16]. Enrolment was stratified to ensure inclusion of ≥40 patients with moderate renal impairment, ≥40 patients with severe renal impairment and 20–40 patients with ESRD.

After a 2-week, single-blind, placebo lead-in period, eligible patients were stratified based on degree of renal impairment (moderate, severe or ESRD), and randomized (1 : 1) via an interactive voice response system in balanced blocks within each renal impairment category to double-blind treatment with saxagliptin 2.5 mg or placebo once daily. Blinding was ensured using a single-dummy technique. Saxagliptin or placebo was taken orally, immediately before or with a meal. The first week of treatment with randomized study medication was designated as week 1. For patients with ESRD receiving haemodialysis, study medication was taken after completion of the haemodialysis treatment on the days that scheduled haemodialysis treatment occurred, with the exception of week 12 when patients took one dose for pharmacokinetic (PK) sampling and a second dose after haemodialysis treatment.

Patients were provided with a glucometer and diary, and instructed to monitor their plasma glucose at least every other day throughout the study, and record plasma glucose values and information about any hypoglycaemic events in their diaries. Counselling on dietary and lifestyle modifications was provided according to usual clinical practice during the lead-in period, and reinforced at all subsequent visits. Oral antihyperglycaemic drugs and/or insulin therapy present at enrolment were continued throughout the study; discontinuation or down titration of these medications was allowed only if needed to prevent hypoglycaemia.

Patients were to be discontinued from the study if they did not meet progressively stringent glycaemic control criteria. These prespecified glycaemic goals included confirmed FPG >15.0 mmol/l at weeks 2 or 4; >13.3 mmol/l at weeks 6 or 9 and >12.2 mmol/l at week 12. Study discontinuation criteria also included confirmed lymphopenia (≤400 cells/μl), thrombocytopenia (<75 000 cells/μl) or clinical symptoms of poorly controlled diabetes. Glycaemic parameters were assessed at each visit to determine if criteria for discontinuation were met.

This study was performed in accordance with ethical principles originating in the Declaration of Helsinki and in compliance with International Conference on Harmonisation/Good Clinical Practice guidelines and all applicable regulatory requirements. The study protocol, including subsequent amendments, was approved by an independent ethics committee or institutional review board. All patients provided written informed consent.

Patients

Men and women aged ≥18 years with a diagnosis of T2DM and documented history of CrCl <50 ml/min within the previous 3 months were eligible for enrolment. Patients were eligible for randomization if they had inadequate glycaemic control (HbA1c 7–11%), C-peptide ≥0.33 nmol/l and estimated CrCl <50 ml/min.

Patients were excluded if they had received metformin within 4 weeks of enrolment or if they were taking an allowed oral antihyperglycaemic drug that had not been stable for the previous 4 weeks (12 weeks for a thiazolidinedione) or were taking unstable doses of insulin for the previous 4 weeks. Other exclusion criteria were previous or current treatment with any DPP-4 inhibitor and/or glucagon-like peptide-1 mimetic; treatment with a CYP 3A4 inducer, human immunodeficiency virus antiviral drug or systemic glucocorticoid (equivalent to oral prednisolone >10 mg/day); current or anticipated need for peritoneal dialysis or expected kidney transplant within 3 months of enrolment; active liver disease and/or abnormal liver function tests [aspartate aminotransferase (AST), alanine aminotransferase (ALT) and/or total bilirubin >1.5 times upper limit of normal (ULN)]; creatine kinase ≥3 times ULN; anaemia (haemoglobin ≤90 g/l, or anticipated need for blood transfusion); significant cardiovascular disease history, New York Heart Association class III/IV congestive heart failure and/or left ventricular ejection fraction ≤40%; ≥2 major hypoglycaemic events (i.e. symptomatic and requiring external assistance) within 3 months before enrolment or any clinically significant abnormality on physical examination or ECG.

Efficacy and Safety Assessments

Efficacy was assessed by absolute changes from baseline to week 12 HbA1c (primary end-point) and FPG (secondary end-point). The percentage of patients achieving a therapeutic glycaemic response (defined as ≥0.5% decrease in HbA1c) in each treatment group was also determined. Results are presented in Systeme Internationale (SI) units. Conversion of mmol/l to mg/dl for FPG is determined by dividing FPG mmol/l results by 0.0555.

Safety and tolerability assessments included adverse events (AEs), serious AEs (SAEs), treatment-related AEs, discontinuations of randomized study medication because of AEs, deaths, AEs of special interest and hypoglycaemic events. Laboratory tests, vital signs, body weight, physical examinations and ECGs were also assessed. Renal function assessments consisted of estimated CrCl, estimated glomerular filtration rate (eGFR) determined by the Modification of Diet in Renal Disease (MDRD) study equation [17] and urinary albumin to

creatinine ratio. The proportion of patients with a doubling of serum creatinine or progression to ESRD was also determined to assess renal safety.

PK Assessment

At week 12, blood samples were collected before dosing and at 1, 2 and 4 h postdose for measurement of steady-state plasma concentrations of saxagliptin and its major metabolite, 5-hydroxy saxagliptin, by a validated liquid chromatography–tandem mass spectrometry method. Samples for PK analysis in patients receiving dialysis were collected on a scheduled dialysis day, before initiation of dialysis treatment.

Statistical Analysis

Sample size calculations determined that with 168 randomized patients (84 per treatment group), there would be 80% power to detect a 0.45% difference in HbA1c between the two randomized treatment groups in absolute mean change from baseline to week 12 at the 5% significance level, assuming the standard deviation (s.d.) for the change from baseline HbA1c was 1.0%, and assuming that 5% of randomized patients would not have postbaseline HbA1c values for the primary efficacy analysis.

The primary efficacy analysis was conducted in the full analysis set (FAS), which included all patients who received at least one dose of study treatment and had baseline and postbaseline efficacy measurements. Absolute change from baseline to week 12 HbA1c was compared between treatment groups using an analysis of covariance (ANCOVA) model, with treatment group and baseline renal impairment group (moderate, severe or ESRD) as fixed effects and baseline HbA1c value as a covariate. Missing week 12 efficacy data were imputed using a last observation carried forward (LOCF) method. Point estimates and 95% confidence intervals (CIs) for the absolute change from baseline HbA1c were calculated for each treatment group, as well as for the difference in absolute change from baseline HbA1c between groups. To assess robustness of the primary efficacy analysis, two sensitivity analyses were conducted that included (i) patients in the FAS with baseline and week 12 HbA1c assessments (i.e. observed values without LOCF methodology) and (ii) patients in the per-protocol (PP) analysis set (i.e. those without significant protocol deviations) using LOCF methodology. Point estimates and 95% CIs for the absolute HbA1c change in each treatment group were also determined for each baseline renal impairment group using two methods: (i) separately for each renal impairment group using the primary ANCOVA model but without the baseline renal impairment group term and (ii) using the ANCOVA model prespecified for the assessment of treatment by renal impairment category interaction, which included terms for baseline HbA1c, baseline renal impairment group, treatment group, and treatment by renal impairment group interaction. Comparisons between treatment groups for the absolute change in FPG from baseline to week 12 were made using a similar ANCOVA model; however, because of a statistically significant treatment by baseline renal impairment interaction, the analysis was performed for each baseline renal impairment category separately. A nominal p value for exploratory analysis was calculated using a two-sided Fisher exact test to compare the proportion of patients achieving a therapeutic glycaemic response from baseline to week 12 in each treatment group.

Safety parameters were analysed using descriptive statistics for all patients who received at least one dose of randomized, double-blind medication (safety analysis set). AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRAs) at the preferred term (PT) level and grouped by system organ class (SOC). Reported hypoglycaemia was defined as events consistent with signs or symptoms of hypoglycaemia with or without documented glucose levels. Confirmed hypoglycaemia was defined by a fingerstick glucose value $\leq$2.8 mmol/l with associated symptoms. Summary statistics for plasma concentrations of saxagliptin and 5-hydroxy saxagliptin were calculated and summarized per patient, treatment group, baseline renal impairment status and nominal time since last dose.

Results

Patient Disposition and Baseline Characteristics

A total of 170 patients were randomized and received study treatment (figure 1). Of these, 129 patients (75.9%) completed the 12-week, short-term treatment period. The most common reasons for discontinuation were withdrawn consent (11.8%) and development of study-specific discontinuation criteria (5.9%).

Although some differences were seen, baseline demographic and clinical characteristics were generally well balanced between treatment groups (Table 1). The study population had a mean age of 67 years and included 31 patients (18.2%) $\geq$75 years; all patients were White and most (75.3%) had T2DM for $\geq$10 years. There were more women in the study overall, with a higher proportion in the saxagliptin group than in the placebo group (62.4 vs. 51.8%). Almost all patients (98.2%) were on background antihyperglycaemic medication during the lead-in period, insulin therapy was more common in the saxagliptin treatment group (83.5 vs. 67.1% of patients) and oral antihyperglycaemic therapy was more common in the placebo group (27.1 vs. 35.3% of patients for saxagliptin vs. placebo, respectively). The most commonly used oral antihyperglycaemic medication in both groups was sulphonylurea. No patient was taking metformin. Few patients, but more patients in the saxagliptin treatment group than in the placebo group (12.9 vs. 3.5%, respectively), were treated with both an oral antihyperglycaemic medication and insulin. Mean [standard error (s.e.)] insulin dose at baseline was 50.7 IU (3.98 IU) in the saxagliptin group and 41.7 IU (3.25 IU) in the placebo group. Mean baseline HbA1c (8.5 vs. 8.1%) and FPG (10.4 vs. 9.4 mmol/l) were higher in the saxagliptin group than in the placebo group; the distribution of patients by baseline renal impairment was similar between treatment groups. Mean exposure to study treatment was 75 and 80 days in the saxagliptin and placebo groups, respectively; median exposure was 84 days in both groups.

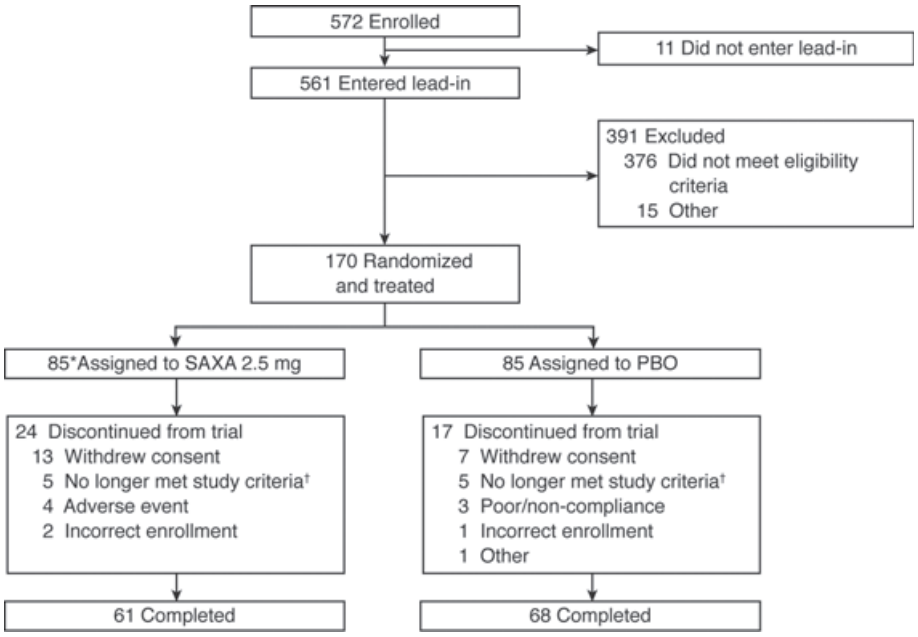

Figure 1. Patient disposition. PBO, placebo; SAXA, saxagliptin. *An additional patient was randomized to SAXA 2.5 mg but this patient did not take any randomized study medication. †'No longer met study criteria' corresponds to discontinuation criterion 'development of study-specific discontinuation criteria'.

Efficacy

At 12 weeks, patients randomized to saxagliptin 2.5 mg once daily achieved statistically significantly greater reductions from baseline HbA1c vs. placebo. In the primary efficacy analysis (FAS with LOCF methodology), the adjusted mean HbA1c change from baseline was −0.86% (95% CI: −1.08 to −0.64%) for saxagliptin vs. −0.44% (95% CI: −0.66 to −0.23%) for placebo (figure 2). The difference in adjusted mean change from baseline HbA1c for saxagliptin vs. placebo was −0.42% (95% CI: −0.71 to −0.12%; p = 0.007) (Table 2). Sensitivity analyses yielded comparable results; the adjusted mean HbA1c reduction from baseline to week 12 was greater for saxagliptin vs. placebo using observed values in the FAS [−0.92% (95% CI: −1.17 to −0.66%) vs. −0.53% (95% CI: −0.78 to −0.29%), p = 0.023] and using LOCF methodology in the PP set [−0.92% (95% CI: −1.16 to −0.69%) vs. −0.50% (95% CI: −0.73 to −0.27%), p = 0.010].

Adjusted mean changes in HbA1c from baseline to week 12 by baseline renal impairment subgroup are shown in figure 3. Both treatment groups had reductions in mean HbA1c in all three baseline renal impairment categories. Saxagliptin showed numerically greater reductions in HbA1c vs. placebo in the subgroups with moderate and severe renal impairment [adjusted mean change −0.64% (95% CI: −0.90 to −0.37%) vs. −0.05% (95% CI: −0.33 to 0.22%) and −0.95% (95% CI: −1.41 to −0.49%) vs. −0.50% (95% CI: −0.90 to −0.09%), respectively] (Table 2). In patients with end-stage renal impairment at baseline, adjusted mean HbA1c reductions were similar for saxagliptin and placebo [−0.84% (95% CI: −1.34 to −0.35%) vs. −0.87% (95% CI: −1.36 to −0.37%), respectively]. Similar results were obtained from the ANCOVA analysis, which included a treatment by renal impairment group interaction term. In this analysis, adjusted mean HbA1c changes for saxagliptin vs. placebo in the subgroups with moderate and severe renal impairment were −0.57% (95% CI: −0.86 to −0.29%) vs. −0.03% (95% CI: −0.32 to 0.26%) and −1.14% (95% CI: −1.59 to −0.70%) vs. −0.64% (95% CI: −1.04 to −0.24%), respectively. In patients with end-stage renal impairment at baseline, adjusted mean HbA1c reductions were similar for saxagliptin and placebo [−0.77% (95% CI: −1.22 to −0.32%) vs. −0.76% (95% CI: −1.21 to −0.32%), respectively].

On the basis of the results of the ANCOVA model for the FPG analysis, there was a significant treatment by baseline renal impairment interaction (p = 0.078) that was considered qualitative based on plots of treatment-specific regression lines; therefore, data were analysed only for each renal impairment subgroup (moderate, severe or ESRD) and not for all patients combined (Table 3). Numerically larger reductions in adjusted mean FPG from baseline to week 12 were observed for saxagliptin vs. placebo in patients with moderate or severe baseline renal impairment based on FAS and LOCF methodology (adjusted mean change −0.8 vs. −0.2 mmol/l; p = 0.339 and −1.9 vs. −1.7 mmol/l; p = 0.798, respectively) (figure 4). For patients with ESRD, the adjusted mean FPG increased from baseline to week 12 for the saxagliptin group, but decreased for the placebo group [adjusted mean change from baseline +1.8 vs. −0.6 mmol/l for saxagliptin vs. placebo, respectively (p = 0.164)]. Although these differences were not statistically significant, the study was not designed or powered to detect differences between treatment groups for each renal impairment category separately.

The proportion of patients achieving a ≥0.5% decrease in HbA1c from baseline to week 12 was greater in the saxagliptin

Table 1. Patient demographics and baseline characteristics.*

Parameters	SAXA 2.5 mg (n = 85)	PBO (n = 85)
Age (years), mean (s.d.)	66.8 (8.3)	66.2 (9.1)
Age category (years), n (%)		
<65	28 (32.9)	35 (41.2)
≥65	57 (67.1)	50 (58.8)
≥75	16 (18.8)	15 (17.6)
Gender, n (%)		
Men	32 (37.6)	41 (48.2)
Women	53 (62.4)	44 (51.8)
Race, n (%)		
White	85 (100)	85 (100)
Weight (kg), mean (s.d.)	83.6 (15.7)	82.2 (14.4)
Body mass index (kg/m^2), mean (s.d.)	31.2 (6.1)	30.2 (6.8)
Renal impairment, n (%)		
Moderate	48 (56.5)	42 (49.4)
Severe	18 (21.2)	23 (27.1)
ESRD	19 (22.4)	20 (23.5)
Duration of T2DM (years)		
Mean (s.d.)	15.1 (7.5)	18.2 (8.5)
≥5, n (%)	80 (94.1)	81 (95.3)
≥10, n (%)	61 (71.8)	67 (78.8)
HbA1c (%)	n = 85	n = 84
Mean (s.d.)	8.5 (1.2)	8.1 (1.1)
HbA1c category, n (%)		
<8.0%	34 (40.0)	42 (49.4)
≥8.0 to <9.0%	28 (32.9)	25 (29.4)
≥9.0%	23 (27.1)	17 (20.0)
FPG (mmol/l)	n = 83	n = 84
Mean (s.d.)	10.4 (3.9)	9.4 (3.3)
CrCl† (ml/min), mean (s.e.)	31.5 (1.5)	30.4 (1.4)
Diabetes therapy, n (%)	83 (97.6)	84 (98.8)
Insulin	71 (83.5)	57 (67.1)
Oral blood glucose-lowering drug	23 (27.1)	30 (35.3)
α-Glucosidase inhibitor	2 (2.4)	2 (2.4)
Sulphonylurea	17 (20.0)	26 (30.6)
Glinide	5 (5.9)	3 (3.5)
Thiazolidinedione	0 (0)	1 (1.2)
Oral blood glucose-lowering drug and insulin‡	11 (12.9)	3 (3.5)

CrCl, creatinine clearance; ESRD, end-stage renal disease; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; PBO, placebo; SAXA, saxagliptin; s.d., standard deviation; s.e., standard error; T2DM, type 2 diabetes mellitus.
*Randomized analysis set.
†Safety analysis set.
‡This includes patients who were taking both an oral blood glucose-lowering drug and insulin prior to randomization. These patients are also counted under the insulin category and under the oral blood glucose-lowering drug category.

group vs. the placebo group (85.2 vs. 62.7%, respectively, nominal p = 0.001).

Pharmacokinetics

The mean saxagliptin plasma concentrations at the nominal collection times of predose, and 1, 2 and 4 h postdose were generally similar across all of the baseline renal impairment categories studied (Table 4). On the basis of the mean predose plasma concentrations of saxagliptin, a small amount of accumulation was observed in all the categories of baseline renal impairment studied, but there was no clear pattern to the extent of accumulation associated with baseline renal impairment

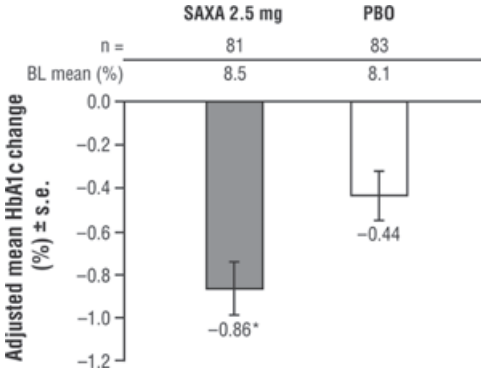

Figure 2. Adjusted mean change from BL to week 12 HbA1c (LOCF). BL, baseline; HbA1c, glycated haemoglobin; LOCF, last observation carried forward; PBO, placebo; SAXA, saxagliptin; s.e., standard error. *p = 0.007.

Table 2. HbA1c changes from baseline to week 12 (LOCF).*

Measures (%)	SAXA 2.5 mg	PBO
	n = 81	n = 83
Baseline HbA1c, mean (s.e.)	8.45 (0.135)	8.09 (0.119)
Week 12 HbA1c, mean (s.e.)	7.63 (0.132)	7.80 (0.137)
Adjusted change from baseline		
Mean (s.e.)	−0.86 (0.112)	−0.44 (0.109)
95% CI	−1.08 to −0.64	−0.66 to −0.23
Difference vs. PBO†		
Mean (s.e.)‡	−0.42 (0.151)	
95% CI	−0.71 to −0.12	
p value	0.007	
Moderate renal impairment	n = 45	n = 42
Baseline HbA1c, mean (s.e.)	8.50 (0.176)	8.23 (0.168)
Week 12 HbA1c, mean (s.e.)	7.84 (0.151)	8.21 (0.222)
Adjusted change from baseline		
Mean (s.e.)	−0.64 (0.134)	−0.05 (0.139)
95% CI	−0.90 to −0.37	−0.33 to 0.22
Severe renal impairment	n = 18	n = 23
Baseline HbA1c, mean (s.e.)	7.97 (0.308)	7.77 (0.244)
Week 12 HbA1c, mean (s.e.)	6.94 (0.290)	7.33 (0.181)
Adjusted change from baseline		
Mean (s.e.)	−0.95 (0.228)	−0.50 (0.201)
95% CI	−1.41 to −0.49	−0.90 to −0.09
ESRD	n = 18	n = 18
Baseline HbA1c, mean (s.e.)	8.79 (0.259)	8.19 (0.223)
Week 12 HbA1c, mean (s.e.)	7.82 (0.320)	7.46 (0.206)
Adjusted change from baseline		
Mean (s.e.)	−0.84 (0.243)	−0.87 (0.243)
95% CI	−1.34 to −0.35	−1.36 to −0.37

CI, confidence interval; ESRD, end-stage renal disease; FAS, full analysis set; HbA1c, glycated haemoglobin; LOCF, last observation carried forward; PBO, placebo; SAXA, saxagliptin; s.e., standard error.
*FAS.
†Difference in adjusted change from baseline for SAXA vs. PBO.
‡Estimated by the adjusted mean change for SAXA minus adjusted mean change for PBO.

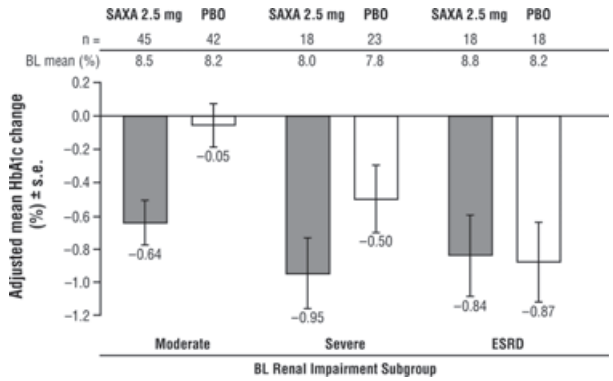

Figure 3. Adjusted mean change from BL to week 12 HbA1c (LOCF) by BL renal impairment subgroup. BL, baseline; ESRD, end-stage renal disease; HbA1c, glycated haemoglobin; LOCF, last observation carried forward; PBO, placebo; SAXA, saxagliptin; s.e., standard error.

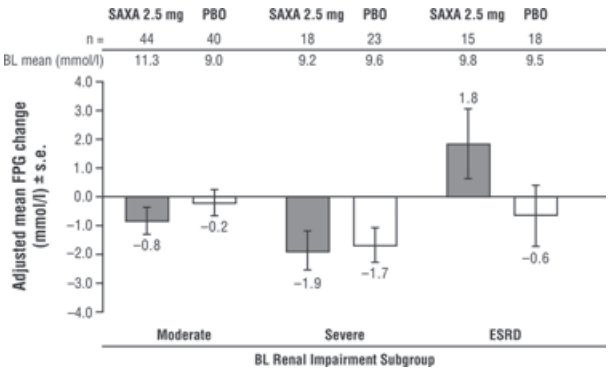

Figure 4. Adjusted mean change from BL to week 12 FPG (LOCF) by BL renal impairment subgroup. BL, baseline; ESRD, end-stage renal disease; FPG, fasting plasma glucose; LOCF, last observation carried forward; PBO, placebo; SAXA, saxagliptin, s.e., standard error.

category. Peak mean plasma concentrations of saxagliptin were observed at the first postdose nominal sampling time point of 1 h in all groups. Mean plasma concentrations of 5-hydroxy saxagliptin at the nominal collection times were generally higher with increasing severity of baseline renal impairment. On the basis of the mean predose plasma concentrations of 5-hydroxy saxagliptin, accumulation was observed in all the categories of baseline renal impairment. The extent of accumulation of 5-hydroxy saxagliptin was generally higher with increasing severity of renal impairment. It should be noted that among patients with ESRD, blood samples for PK analysis were taken in the morning before scheduled dialysis. Peak mean plasma concentrations of 5-hydroxy saxagliptin were observed at the last nominal sampling time point of 4 h postdose in all groups.

Safety and Tolerability

Overall, saxagliptin was generally well tolerated (Table 5). The proportion of patients reporting any AE (including hypoglycaemia) was similar between saxagliptin and placebo groups (57.6 vs. 54.1%). The majority of AEs were mild or moderate in intensity in both the saxagliptin and placebo groups. By PT, no AE occurred at an incidence ≥5% in either group. Table 5 presents AEs that occurred at an incidence ≥3%.

The percentage of patients experiencing AEs (excluding hypoglycaemic AEs) differed by baseline renal impairment group, with higher rates reported among patients with severe renal impairment or ESRD than among those with moderate renal impairment. When evaluated by treatment, AEs were more common in the saxagliptin group than in the placebo group for patients with moderate renal impairment (41.7 vs. 33.3%) and severe renal impairment (61.1 vs. 52.2%), whereas similar AE rates were seen in patients with ESRD (52.6 vs. 50.0%). In both the saxagliptin group and the placebo group, AEs were more common in patients who received background insulin therapy compared with patients who did not. Among patients who received background insulin, the AE

Table 3. FPG changes from baseline to week 12 (LOCF) by renal impairment subgroup.*

	Moderate renal impairment		Severe renal impairment		ESRD	
	SAXA 2.5 mg (n = 44)	PBO (n = 40)	SAXA 2.5 mg (n = 18)	PBO (n = 23)	SAXA 2.5 mg (n = 15)	PBO (n = 18)
Measures (mmol/l)						
Baseline FPG, mean (s.e.)	11.3 (0.6)	9.0 (0.5)	9.2 (1.1)	9.6 (0.6)	9.8 (0.6)	9.5 (0.8)
Week 12 FPG, mean (s.e.)	9.7 (0.4)	9.7 (0.6)	7.4 (0.6)	7.9 (0.8)	11.5 (1.7)	8.9 (0.7)
Adjusted change from baseline						
Mean (s.e.)	−0.8 (0.5)	−0.2 (0.5)	−1.9 (0.7)	−1.7 (0.6)	1.8 (1.3)	−0.6 (1.2)
95% CI	−1.8 to 0.1	−1.2 to 0.8	−3.3 to −0.5	−2.9 to −0.4	−0.8 to 4.4	−3.0 to 1.7
Difference vs. PBO†						
Mean (s.e.)‡	−0.7 (0.7)	—	−0.2 (0.9)	—	2.4 (1.7)	—
95% CI	−2.1 to 0.7		−2.1 to 1.7		−1.1 to 5.9	
p value	0.339		0.798		0.164	

CI, confidence interval; ESRD, end-stage renal disease; FAS, full analysis set; FPG, fasting plasma glucose; LOCF, last observation carried forward; PBO, placebo; SAXA, saxagliptin; s.e., standard error.

*FAS.

†Difference in adjusted change from baseline for SAXA vs. PBO.

‡Estimated by the adjusted mean change for SAXA minus adjusted mean change for PBO.

Table 4. Mean steady-state plasma concentrations (ng/ml)* of SAXA and 5-hydroxy saxagliptin at week 12.

Analytes	Baseline renal impairment	Predose		1 h postdose		2 h postdose		4 h postdose	
		n	mean (s.d.)	n	mean (s.d.)	n	mean (s.d.)	n	mean (s.d.)
SAXA	Moderate	41	5.4 (8.0)	41	18.0 (11.2)	41	17.3 (8.7)	41	14.3 (7.9)
	Severe	13	2.1 (4.7)	14	17.8 (9.0)	14	13.8 (8.5)	14	12.6 (7.5)
	ESRD	11	1.3 (1.0)	12	19.3 (12.8)	12	18.1 (9.6)	12	12.8 (7.3)
5-Hydroxy saxagliptin	Moderate	39	9.8 (8.2)	39	24.2 (12.4)	39	30.7 (11.4)	40	31.2 (11.3)
	Severe	14	16.5 (16.4)	14	35.3 (17.9)	14	42.2 (21.0)	14	43.0 (15.8)
	ESRD	11	38.0 (24.3)	11	49.2 (27.4)	12	54.4 (33.6)	12	58.0 (36.9)

The molecular weights for saxagliptin and 5-hydroxy saxagliptin are 315.42 and 331.42, respectively. ESRD, end-stage renal disease; SAXA, saxagliptin; s.d., standard deviation, SI, Systeme Internationale.

*Conversion factor for conventional to SI units: Concentration in nmol/l $= \frac{\text{concentration (in ng/ml)} \times 1000}{\text{molecular weight}}$.

Table 5. AE summary during 12-week treatment period.*

	SAXA 2.5 mg (n = 85)	PBO (n = 85)
AEs, n (%)†		
≥1 AE	49 (57.6)	46 (54.1)
≥1 treatment-related AE	9 (10.6)	6 (7.1)
Discontinuation because of AEs	5 (5.9)	1 (1.2)
≥1 SAE	12 (14.1)	7 (8.2)
≥1 treatment-related SAE	1 (1.2)	1 (1.2)
Discontinuation because of SAE	3 (3.5)	1 (1.2)
Deaths	0 (0)	0 (0)
Most common AEs (≥3%), n (%)‡		
Urinary tract infection	4 (4.7)	2 (2.4)
Hypertension	3 (3.5)	4 (4.7)
Diarrhoea	3 (3.5)	0 (0)
Hyperglycaemia	3 (3.5)	0 (0)
Anaemia	1 (1.2)	4 (4.7)
Dyspepsia	0 (0)	3 (3.5)
Reported hypoglycaemia, n (%)§	17 (20.0)	19 (22.4)
Moderate renal impairment	10/48 (20.8)	12/42 (28.6)
Severe renal impairment	5/18 (27.8)	3/23 (13.0)
ESRD	2/19 (10.5)	4/20 (20.0)
Confirmed hypoglycaemia, n (%)‖	4 (4.7)	3 (3.5)
Moderate renal impairment	2/48 (4.2)	3/42 (7.1)
Severe renal impairment	1/18 (5.6)	0/23 (0)
ESRD	1/19 (5.3)	0/20 (0)

Table represents counts of patients with events. For reported and confirmed hypoglycaemia by renal impairment group, denominator is total number of patients per renal category. AE, adverse event; ESRD, end-stage renal disease; PBO, placebo; SAE, serious AE; SAXA, saxagliptin.

*Safety analysis set.

†Includes hypoglycaemic events.

‡Excludes hypoglycaemia events.

§Reported hypoglycaemia was defined as events consistent with signs or symptoms of hypoglycaemia with or without documented glucose levels.

‖Confirmed hypoglycaemia was defined by a fingerstick glucose value ≤2.8 mmol/l with associated symptoms.

incidence was 50.0 and 47.3% in the saxagliptin and placebo groups, respectively; among those patients who did not receive background insulin, the AE incidence was 40.0 and 33.3%, respectively.

The incidence of hypoglycaemia was similar in the two treatment groups (20.0 vs. 22.4% for saxagliptin vs. placebo, respectively). The majority of events were mild in intensity, although two patients—both in the placebo group—had severe hypoglycaemic events. A total of four (4.7%) patients experienced six confirmed hypoglycaemic events (fingerstick glucose ≤2.8 mmol/l) with associated symptoms in the saxagliptin group and three (3.5%) patients reported six events in the placebo group; each of these events was self-managed by the patient. Hypoglycaemia by renal impairment subgroup is noted in Table 5. The percentage of patients experiencing hypoglycaemia during the 12-week treatment period in patients with moderate baseline renal impairment, severe baseline renal impairment or ESRD treated with saxagliptin vs. placebo was 21% (10/48) vs. 29% (12/42); 28% (5/18) vs. 13% (3/23) or 11% (2/19) vs. 20% (4/20), respectively.

No persistent or clinically meaningful changes in mean renal function parameters were seen from baseline to week 12 in either treatment group. Four patients, two in each treatment group, with moderate renal impairment at baseline shifted to severe renal impairment at week 12 based on CrCl values (LOCF analysis). Conversely, 10 patients, 4 in the saxagliptin group and 6 in the placebo group, with severe renal impairment at baseline shifted to moderate renal impairment (LOCF analysis). No patients shifted into the ESRD category and no patients had a doubling from baseline in serum creatinine.

There were no clinically relevant drug effects on haematologic, renal or clinical chemistry parameters. The frequency of marked laboratory abnormalities was generally low, with the exception of serum creatinine, alkaline phosphatase and potassium; the frequencies of these were similar in the two treatment groups. No clinically relevant changes from baseline were observed in vital signs or ECG measurements in either treatment group. Mean body weight decreased from baseline to week 12 by 0.5 kg in the saxagliptin group, whereas body weight was unchanged in the placebo group.

Discussion

In this study, there was a greater reduction in adjusted mean change in HbA1c from baseline to week 12 in patients treated with saxagliptin 2.5 mg vs. those receiving placebo. Analyses by baseline renal impairment category showed that numerically greater adjusted mean decreases in HbA1c were achieved with

saxagliptin than with placebo in patients with moderate or severe renal impairment. In the ESRD subgroup, the adjusted mean decrease in HbA1c with saxagliptin was comparable to improvements seen in the other renal impairment subgroups, but also similar to improvements noted with placebo. Analyses of outlier data and changes in use of concomitant antihyperglycaemic medications did not explain the observed HbA1c reductions with placebo in the ESRD subgroup. Although HbA1c levels can be falsely low in patients with ESRD because of uraemia-induced changes in haemoglobin structure (e.g. carbamylation), the new assays have nearly eliminated such an interference and are subsequently standardized to the Diabetes Control and Complications Trial (DCCT) [18].

Although FPG was improved in patients with moderate and severe renal impairment, numerically greater adjusted mean reductions from baseline to week 12 in the saxagliptin group, compared with placebo, were particularly evident in the moderate renal impairment subgroup. In contrast, an increase in FPG adjusted mean change was seen with saxagliptin in the ESRD subgroup—an observation that is not consistent with the adjusted mean decrease in HbA1c of −0.84% measured in ESRD patients taking saxagliptin. A reason for this discrepancy was not readily apparent, but may reflect the small sample size of the ESRD subgroup, or that glucose concentration reflects a momentary situation, whereas HbA1c is a measure of longer term glycaemic control. Alternatively, because variability of FPG in ESRD patients is very high and is influenced by a variety of factors, this glycaemic measure is less reliable as an instrument to assess glycaemic control in these patients compared with patients with moderate or severe renal impairment [19,20]. Additionally, there were four patients in the saxagliptin ESRD subgroup with unusually large increases from baseline FPG, which may have contributed to the high mean increase and the significant treatment by baseline renal impairment interaction. Many ESRD patients are poorly compliant and have unrestrained thirst; they often drink sweetened beverages before haemodialysis sessions thinking that the ultrafiltration during dialysis will free them of excess fluid. Haemodilution arising from fluid retention between dialysis sessions, which varies considerably for each intersession interval, may contribute to fluctuations in measured plasma parameters, including FPG.

Saxagliptin did not affect renal function in a clinically meaningful way as compared with placebo. In patients with moderate or severe renal impairment at baseline, no patient in either treatment group shifted to the end-stage category. In patients with severe renal impairment at baseline, the number of patients who shifted to the moderate category at week 12 was comparable for saxagliptin vs. placebo [4 (22.2%) vs. 6 (26.1%), respectively] as was the number of patients with moderate renal impairment at baseline who shifted to the severe category [2 (4.4%) vs. 2 (4.8%), respectively].

Overall, saxagliptin 2.5 mg once daily allowed patients with significant renal impairment to maintain systemic exposures of saxagliptin and 5-hydroxy saxagliptin and, therefore, optimal saxagliptin efficacy benefit. Minimal accumulation of saxagliptin was seen at trough, and mean plasma concentrations over the first 4 h after dosing were comparable across baseline renal impairment categories. In contrast, mean plasma concentrations of 5-hydroxy saxagliptin at trough and after saxagliptin administration increased with increasing severity of baseline renal impairment. This is not surprising because 5-hydroxy saxagliptin is a more polar compound that is excreted primarily via the kidneys.

Saxagliptin was generally well tolerated. When evaluated by treatment, AEs were more common in the saxagliptin group than in the placebo group for patients with moderate renal impairment and severe renal impairment, whereas similar AE rates were seen in patients with ESRD. However, when evaluated by treatment and background insulin use, overall AE incidence was similar between the two treatment groups. Because insulin use was more common in the saxagliptin group, there may be a perception that saxagliptin treatment is associated with more frequent AEs, when the imbalance may be attributable to insulin use. Notably, all discontinuations of study medication because of AEs were in patients receiving background insulin therapy.

Overall, the percentage of patients experiencing hypoglycaemia during the 12-week treatment period was similar for the saxagliptin group compared with the placebo group; most cases were mild in intensity and no patients required medical assistance. These findings are particularly relevant given that this population has more advanced disease, includes patients with multiple concomitant diseases who are on multiple concomitant medications and includes many patients on insulin. The frequency of hypoglycaemia was greater in this study than the overall saxagliptin phase III programme patient population (normal or mild renal impairment); however, this may be attributable to the use of insulin by patients in this study vs. other saxagliptin studies.

Almost all of the patients in the study were already receiving insulin or oral antihyperglycaemic therapy prior to receiving randomized treatment in the study; consequently, saxagliptin was used as add-on therapy. Previous studies have evaluated saxagliptin as add-on therapy to metformin, a sulphonylurea, and a thiazolidinedione, but none evaluated add-on therapy to insulin [13–15]. A study designed to explore the safety and efficacy of saxagliptin in insulin-treated T2DM patients without significant renal impairment is underway [21]. In this study, saxagliptin had a small effect on insulin requirements; at week 12, the mean insulin dose decreased slightly from baseline in the saxagliptin group and stayed constant in the placebo group.

This study had some limitations. First, study medication was administered for only 12 weeks, although this duration is sufficient for showing the glycaemic efficacy of saxagliptin as shown in previous clinical trials [11,13–15]. Second, there was a significant treatment group by baseline renal impairment category interaction for the FPG analysis; the FPG results were therefore summarized by renal impairment subgroups. However, the study was not designed or powered to detect differences between treatment groups for each renal impairment category separately. Finally, as in all clinical studies conducted in a specialized patient population, specific findings may not be generalizable.

In conclusion, the glycaemic benefits and favourable tolerability profile demonstrated in this study support the use of the DPP-4 inhibitor saxagliptin 2.5 mg once daily in patients with T2DM and significant renal impairment.

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Conflict of Interest

M. N. has received funding from AstraZeneca and Phenomix for investigator-sponsored studies. I. R. and H. H. have nothing to disclose. M. L. W. has participated in speakers bureaus for Merck, Novo Nordisk, Eli Lilly, Novartis and Abbott, has served on an advisory panel for Novo Nordisk and has received research support from Novo Nordisk, Eli Lilly, Novartis, Fibrogen, Mannkind, NPS Pharmaceuticals, Gilead, Abbott and Esai. L. S. and I. G.-N. are the employees of AstraZeneca.

M. N., I. R., H. H., M. L. W., L. S. and I. G.-N. conducted the study, collected the data, analysed and wrote the manuscript.

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Appendix

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