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Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study

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Disclosure
M. Nowicki has been a study investigator for AstraZeneca, Amgen, Roche, Otsuka, Mitsubishi Pharma, Astellas Pharma, Cerexa, and AMAG Pharmaceuticals. I. Rychlik has no conflicts of interest to disclose. H. Haller has been a consultant for Daiichi Sankyo, Novartis, Genzyme, Roche, Bayer-Schering, Sanofi-Aventis, Noxxon, MedWiss, Phenos, MSD, and has received honoraria for speaking from Amgen, Astra-Zeneca, Recordati, Menarini, Pfizer, Daiichi Sankyo Europe and Deutschland and Co. Ltd., Novartis, Genzyme, Roche, Otsuka, Bayer-Schering, Sanofi-Aventis, Noxxon, MedWiss, Phenos, MSD, Bristol-Myers Squibb, and CVRx. M. Warren has received clinical trial funding from Abbott, Boehringer Ingelheim, NPS Pharmaceuticals, Mannkind, Novo Nordisk, Novartis, Johnson & Johnson, Bristol-

SUMMARY

Objective: Therapeutic options are limited for diabetes patients with renal disease. This report presents 52-week results from a study assessing the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus (T2DM) and renal impairment. **Design:** Double-blind study in patients stratified by baseline renal impairment (moderate, severe or end-stage renal disease [ESRD] on haemodialysis) randomised to saxagliptin 2.5 mg once daily or placebo added to other antidiabetic drugs in use at baseline, including insulin. **Patients:** A total of 170 adults with glycated haemoglobin (HbA_{1c}) 7–11% and creatinine clearance < 50 ml/min or ESRD were randomised and treated. **Measurements:** Absolute changes in HbA_{1c} and fasting plasma glucose (FPG) from baseline to week 52 were evaluated using analysis of covariance (ANCOVA) with last observation carried forward. Repeated-measures analyses were also performed. **Results:** Adjusted mean decrease in HbA_{1c} was greater with saxagliptin than placebo (difference, −0.73%, $p < 0.001$ [ANCOVA]). Reductions in adjusted mean HbA_{1c} were numerically greater with saxagliptin than placebo in patients with renal impairment rated as moderate (−0.94% vs. 0.19% respectively) or severe (−0.81% vs. −0.49%), but similar to placebo for those with ESRD (−1.13% vs. −0.99%). Reductions in adjusted mean FPG were numerically greater with saxagliptin in patients with moderate or severe renal impairment. Saxagliptin was generally well tolerated; similar proportions of patients in the saxagliptin and placebo groups reported hypoglycaemic events (28% and 29% respectively). **Conclusions:** Saxagliptin 2.5 mg once daily offers sustained efficacy and good tolerability for patients with T2DM and renal impairment.

What's known
The presence of renal impairment makes diabetes treatment more complex and difficult, whether it occurs as an independent condition in diabetic patients or as a microvascular complication of diabetes. Concerns include risk of hypoglycaemia, metabolism of antihyperglycaemic agents and long-term effects on cardiovascular function. There is an unmet need for antihyperglycaemic treatments with demonstrated long-term safety and effectiveness in this population.

What's new
This article reports on the long-term safety and effectiveness of the DPP-4 inhibitor saxagliptin in patients with renal impairment and inadequately controlled type 2 diabetes as documented in a 40-week double-blind controlled extension of a previously published 12-week trial. The finding that saxagliptin 2.5 mg provided sustained reductions in HbA_{1c}, especially in patients with moderate or severe renal impairment, suggests that saxagliptin may be a useful option in this population.

Introduction

Diabetes is a leading cause of chronic kidney disease worldwide (1,2). Although several studies have found that improved glycaemic control has a protective effect on kidney function in patients with type 2 diabetes mellitus (T2DM) (3,4), glycaemic control in patients with renal impairment is challenging because some oral antidiabetic drugs (OADs) are not appropriate for use in this population. Sulfonylurea treatment and renal impairment both independently increase a patient's risk for hypoglycaemia, and accumulation of sulfonylurea in patients with renal impairment further contributes to this risk (5–7). Accumulation of metformin may increase the risk for lactic acidosis. Metformin is therefore contraindicated in patients with creatinine clearance (CrCl) < 60 ml/min (8) or with serum creatinine ≥ 1.5 mg/dl in males or ≥ 1.4 mg/dl in females (9).

Saxagliptin, a selective dipeptidyl peptidase-4 (DPP-4) inhibitor, is approved as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM (10–12). Saxagliptin has a favourable tolerability profile, and its glucose-dependent mechanism of action reduces the risk of hypoglycaemia (13). Clinical studies of saxagliptin administered as monotherapy (14) and as an add-on to other OADs (15–21) have demonstrated significant reductions in glycated haemoglobin (HbA_{1c}), fasting plasma glucose (FPG) and postprandial glucose levels in

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patients with T2DM and normal or mildly impaired renal function.

There is a clear unmet need for additional therapeutic options for T2DM in patients with renal disease, especially in view of the fact that metformin, the first-line agent in most patients with T2DM, is contraindicated in patients with renal disease marked by elevated serum creatinine or abnormal creatinine clearance (9). Nowicki et al. (22) reported that 12-week treatment with saxagliptin 2.5 mg once daily significantly reduced HbA_{1c} compared with placebo and was well tolerated in patients with inadequately controlled T2DM and renal impairment. This manuscript describes the efficacy and safety of saxagliptin 2.5 mg once daily vs. placebo observed in the same study over a 52-week period that combined the 12-week primary study with a 40-week double-blinded extension.

Patients and methods

Design

This 52-week, randomised, parallel-group, placebo-controlled, double-blind, international, multicenter, phase III trial (NCT00614939) assessed the efficacy and safety of saxagliptin in adults with T2DM, inadequate glycaemic control (HbA_{1c} 7–11%) and renal impairment. Details of study design, patient eligibility and end-points have been published previously (22).

Briefly, the study consisted of a 12-week double-blind treatment period followed by a 40-week double-blind controlled extension with continuation of treatment. Using CrCl estimated by the Cockcroft-Gault equation (23), patients were stratified by degree of renal impairment: moderate (CrCl ≥ 30 and < 50 ml/min), severe (CrCl < 30 ml/min and not receiving dialysis) or end-stage renal disease (ESRD) on haemodialysis at baseline. Patients were randomised 1 : 1 via an interactive voice response system in balanced blocks within each renal impairment category to once-daily double-blind treatment with saxagliptin 2.5 mg or placebo. Other antidiabetic drugs in use at enrolment were continued, subject to adjustment as needed to prevent hypoglycaemia throughout the 52-week study or to improve glycaemic control during the 40-week extension; addition of new drugs except thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonists, metformin and other DPP-4 inhibitors was allowed. The first week of randomised study medication was designated as week 1. Study-specific discontinuation criteria were FPG > 15.0 mmol/l at weeks 2 or 4, > 13.3 mmol/l at weeks 6 or 9, > 12.2 mmol/l at week 12 or > 11.1 mmol/l at week 20; and HbA_{1c} > 8% (> 7.5% at sites in Germany) at weeks 28, 36 or 44.

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 and amendments were approved by an independent ethics committee or institutional review board. All patients provided written informed consent.

Patients

Adults with a diagnosis of T2DM and CrCl < 50 ml/min within the past 3 months were eligible for enrolment. Enrolled patients were eligible for randomisation based on documentation of inadequate glycaemic control (HbA_{1c} 7–11%), C-peptide ≥ 0.33 nmol/l and CrCl < 50 ml/min (estimated by the Cockcroft-Gault equation). Exclusion criteria, described in detail previously (22), were current or anticipated need for peritoneal dialysis or expected kidney transplant within 3 months after enrolment; aspartate aminotransferase, alanine aminotransferase and/or total bilirubin > 1.5 times the upper limit of normal; creatine kinase ≥ 3 times the upper limit of normal; treatment with metformin within 4 weeks before enrolment and previous or current treatment with any DPP-4 inhibitor or GLP-1 agonist.

Efficacy and safety assessments

The primary efficacy end-point was absolute HbA_{1c} change (assessment by validated liquid chromatography/tandem mass spectrometry) from baseline to week 12; week 12 results were published previously (22). Secondary end-points included assessment of efficacy at 52 weeks using absolute change from baseline in HbA_{1c} and FPG and changes from baseline in the type and/or daily doses of background OAD therapy and insulin.

Safety and tolerability of saxagliptin over the 52-week study period were compared with placebo using adverse events (AEs), treatment-related AEs, AEs leading to discontinuation of study medication and serious AEs. Comparisons were also made on laboratory values, including estimated glomerular filtration rate using the Cockcroft-Gault and modification of diet in renal disease (MDRD) (24) equations and the urinary albumin:creatinine ratio. Electrocardiograms, measurement of body weight and vital signs and physical examinations were performed at predetermined intervals. Other safety assessments included the incidence of doubling of serum creatinine concentration and shifts in renal impairment category, including progression to ESRD.

Myers Squibb, and Esai, serves on advisory boards for Novo Nordisk, and is a member of the speaker bureaus for Novo Nordisk, Eli Lilly, Amylin, Novartis, Amgen, Sanofi-Aventis, Daiichi Sankyo, Merck, and Abbott. I. Gause-Nilsson, and K.-M. Schützer are employees of AstraZeneca and hold shares in AstraZeneca stock. L. Suchower is an employee of AstraZeneca.

Clinical Trial identifier: NCT00614939

Results posted on: http://www.clinicaltrials.gov

Statistical analysis

Sample size calculations were described by Nowicki et al. (22). Analysis of efficacy end-points was based on the full analysis set, which included randomised patients who received ≥ 1 dose of study medication and had a baseline and ≥ 1 post-baseline efficacy measurement. Efficacy values obtained after changes in insulin and/or OAD dosing were excluded from the efficacy evaluation at week 52. Change in insulin was defined as > 10 days of use at a dose > 20% different from the baseline daily dose; shorter periods of dose adjustment for insulin or OADs were not recorded as changes in concomitant medication.

Absolute changes in HbA_{1c} and FPG from baseline to week 52 were compared between treatment groups using adjusted means generated by an analysis of covariance (ANCOVA) model, with treatment group and baseline renal impairment group (moderate, severe or ESRD) as fixed effects and baseline value as covariate. Data were included up to completion, discontinuation or change in insulin or OAD dose; missing efficacy data were imputed using last observed data carried forward (LOCF; in this case, last observed data prior to any change in insulin or OAD usage). Point estimates and two-sided 95% confidence intervals (CI) for the mean changes from baseline within each treatment group and for the difference in mean change from baseline with saxagliptin vs. placebo were calculated using this ANCOVA model.

To assess the robustness of the ANCOVA, an analysis using a mixed model for repeated measures was also performed for HbA_{1c} and FPG results throughout the 52-week treatment period, including terms for treatment group, baseline measurement, baseline renal impairment, time (i.e. each relevant visit) and time-by-treatment group. Missing data (e.g. due to study discontinuation or exclusion due to a change in insulin and/or OAD use) were inferred using available values from these patients, assuming that the time course of values after exclusion or discontinuation was consistent with patients who were not excluded or discontinued. Point estimates and two-sided 95% CIs were determined for the mean changes from baseline within each treatment group and for the between-group difference in mean change from baseline to week 52. Finally, absolute changes in HbA_{1c} from baseline to week 52 were additionally assessed using observed data only.

Safety parameters were analysed using descriptive statistics for all treated patients (safety analysis set of patients who received ≥ 1 dose of randomised, double-blind study medication). 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 finger-stick glucose value ≤ 2.8 mmol/l with associated symptoms.

Results

A total of 170 patients were randomised and treated between January 2008 and March 2010. Of these, 129 (76%) completed the 12-week short-term treatment period and 92 (54%) completed the 52-week study (saxagliptin, 49%; placebo, 59%) (Figure 1). Baseline demographic and clinical characteristics of the randomised population have been published (22). Briefly, mean age was 67 years, all patients were white and most (75%) had T2DM for ≥ 10 years. Mean baseline HbA_{1c} and FPG were higher in the saxagliptin group (8.5% and 10.4 mmol/l respectively) than in the placebo group (8.1% and 9.4 mmol/l respectively). Nearly all patients (98%) were on background antihyperglycaemic medication. During the lead-in period, the proportions of patients receiving insulin and OADs were 84% and 27% respectively in the saxagliptin group, and 67% and 35% respectively in the placebo group. Among patients taking insulin (and possibly, also an OAD) during lead-in, study completion rates were comparable in the saxagliptin and placebo groups (47% and 49% respectively).

For the entire 52-week period, the most common primary reasons that patients discontinued from the study were withdrawn consent (saxagliptin, $n = 17$; placebo, $n = 10$) and development of protocol-defined discontinuation criteria, such as failure to achieve the increasingly stringent glycaemic targets throughout the study, as described in the Methods section (saxagliptin, $n = 16$; placebo, $n = 13$; shown in Figure 1 as 'No longer meets study criteria'). Combined, these two causes accounted for 77% and 66% of the patients who did not complete the 52-week treatment period in the saxagliptin and placebo groups respectively.

Efficacy

In the full analysis set, similar small proportions of patients in the saxagliptin (20 of 81; 24.7%) and placebo (19 of 83; 22.9%) groups had changes during the 52-week treatment period in the use of insulin and/or OADs vs. those in use at baseline, with efficacy data collected after such changes excluded from the efficacy analysis. There was no apparent association between medication change and baseline renal impairment category in either treatment group.

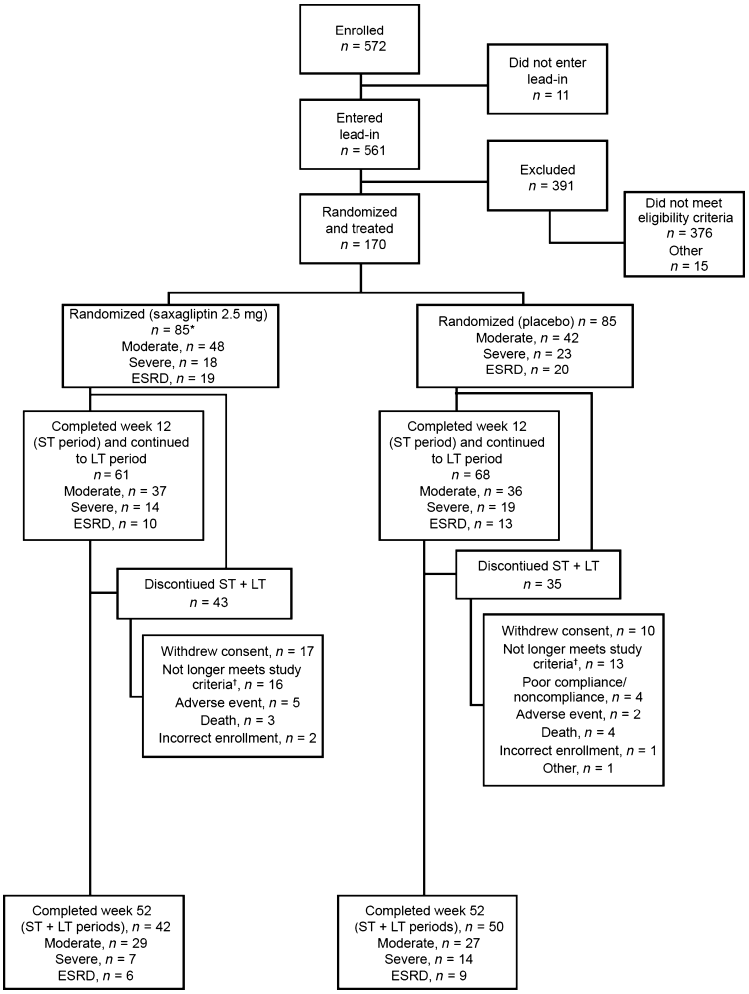

Figure 1 Patient disposition. *An additional patient was randomised to the saxagliptin group, but this patient did not take any randomised study medication. †'No longer meets study criteria' corresponds to discontinuation criterion 'development of study-specific discontinuation criteria' in the case report form. ESRD, end-stage renal disease; LT, long-term (40-week extension); SAXA, saxagliptin; ST, short-term (12 weeks)

Reductions in the adjusted mean change in HbA_{1c} from baseline to week 52 were greater in patients receiving saxagliptin 2.5 mg once daily (−1.08%; 95% CI, −1.37% to −0.80%) than in patients receiving placebo (−0.36%; 95% CI, −0.63% to −0.08%; ANCOVA; Table 1). The difference for saxagliptin vs. placebo was −0.73% (95% CI, −1.11% to −0.34%; $p < 0.001$).

Reductions from baseline in absolute mean HbA_{1c} were observed in both treatment groups at each visit up to week 12, although mean reductions were larger with saxagliptin than with placebo (Figure 2). During the ensuing 40-week period to week 52, absolute mean HbA_{1c} continued to decline gradually from baseline in the saxagliptin group but increased slightly in the placebo group.

Consistent with the ANCOVA using LOCF methodology, the repeated-measures analysis showed that the reduction in adjusted mean HbA_{1c} from baseline to week 52 was greater with saxagliptin than with placebo (−1.35% [95% CI, −1.69 to −1.00] vs. −0.53% [95% CI, −0.83 to −0.23] respectively; difference, −0.82% [95% CI, −1.27 to −0.37]; $p < 0.001$).

Although 92 patients completed 52 weeks of treatment (42 in the saxagliptin group and 50 in the placebo group), only 60 patients included in the efficacy full analysis set (26 saxagliptin and 34 placebo) had observed data at week 52 (Figure 2) (i.e. had efficacy results prior to changes in insulin and/or OADs). Therefore, the analysis was also performed using observed data only. In this analysis, the reduction in adjusted mean HbA_{1c} from baseline to week 52 was greater with saxagliptin than with placebo (−1.44% [95% CI, −1.90 to −0.98] vs. −0.81% [95% CI, −1.20 to −0.42] respectively; difference, −0.63% [95% CI, −1.18 to −0.08]; $P=.026$).

Table 1 Changes in HbA_{1c} (%) from baseline to week 52 (analysis of covariance, LOCF)

	Saxagliptin 2.5 mg (*n* = 81)	Placebo (*n* = 83)
All patients		
n (*n* with observed values at week 52)	78 (26)	82 (34)
Baseline mean (SE)	8.44 (0.13)	8.10 (0.12)
Mean adjusted change from baseline (SE)	−1.08 (0.15)	−0.36 (0.14)
Two-sided 95% CI	−1.37 to −0.80	−0.63 to −0.08
Difference vs. placebo*		
Mean (SE)†	−0.73 (0.20)	
Two-sided 95% CI	−1.11 to −0.34	
p-value	< 0.001	
Moderate baseline renal impairment		
n (*n* with observed values at week 52)	44 (18)	42 (18)
Baseline mean (SE)	8.50 (0.18)	8.23 (0.17)
Mean adjusted change from baseline (SE)	−0.94 (0.18)	0.19 (0.18)
Two-sided 95% CI	−1.30 to −0.59	−0.17 to 0.56
Severe baseline renal impairment		
n (*n* with observed values at week 52)	17 (5)	23 (11)
Baseline mean (SE)	8.04 (0.32)	7.77 (0.24)
Mean adjusted change from baseline (SE)	−0.81 (0.29)	−0.49 (0.25)
Two-sided 95% CI	−1.41 to −0.22	−1.00 to 0.02
End-stage renal disease at baseline		
n (*n* with observed values at week 52)	17 (3)	17 (5)
Baseline mean (SE)	8.65 (0.23)	8.25 (0.23)
Mean adjusted change from baseline (SE)	−1.13 (0.28)	−0.99 (0.28)
Two-sided 95% CI	−1.70 to −0.55	−1.57 to −0.42

*Difference in adjusted change from baseline for saxagliptin vs. placebo. †Estimate = adjusted mean change for saxagliptin − adjusted mean change for placebo. HbA_{1c}, haemoglobin A1c; LOCF, last observation carried forward.

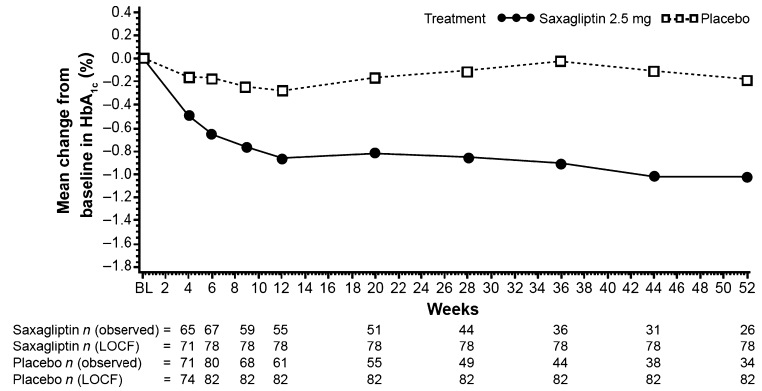

Figure 2 Mean change from baseline in HbA_{1c} (%) during the 52-week treatment period (full analysis set with last observation carried forward [LOCF] methodology). Numbers of patients with observed and LOCF values are listed at each time point. SAXA, saxagliptin

The ANCOVA in each stratum by baseline renal impairment status showed that reductions in adjusted mean HbA_{1c} from baseline to week 52 were numerically larger with saxagliptin vs. placebo in patients with moderate or severe renal impairment, but similar between treatment groups in patients with ESRD (Table 1).

With respect to treatment effects on FPG, the ANCOVA revealed a significant treatment-by-baseline renal impairment interaction at week 52 ($p = 0.045$), which was considered qualitative based on plots of treatment-specific regression lines; that is, the difference in the adjusted mean change from baseline to week 52 between saxagliptin and placebo

Table 2 Changes in fasting plasma glucose (mmol/l) from baseline to week 52 (analysis of covariance, LOCF)

	Saxagliptin 2.5 mg (*n* = 81)		Placebo (*n* = 83)
Moderate baseline renal impairment			
n (*n* with observed values at week 52)	44 (17)		40 (16)
Baseline mean (SE)	11.25 (0.55)		9.01 (0.50)
Mean adjusted change from baseline (SE)	−0.80 (0.48)		0.02 (0.51)
Two-sided 95% CI	−1.75 to 0.16		−0.99 to 1.02
Difference vs. placebo*			
Mean (SE)†		−0.81 (0.72)	
Two-sided 95% CI		−2.24 to 0.61	
Severe baseline renal impairment			
n (*n* with observed values at week 52)	18 (5)		23 (11)
Baseline mean (SE)	9.17 (1.11)		9.63 (0.65)
Mean adjusted change from baseline (SE)	−1.65 (0.62)		−1.06 (0.55)
Two-sided 95% CI	−2.90 to −0.40		−2.16 to 0.04
Difference vs. placebo*			
Mean (SE)†		−0.59 (0.82)	
Two-sided 95% CI		−2.26 to 1.07	
End-stage renal disease at baseline			
n (*n* with observed values at week 52)	15 (2)		18 (5)
Baseline mean (SE)	9.83 (0.59)		9.46 (0.81)
Mean adjusted change from baseline (SE)	2.17 (1.29)		−0.56 (1.18)
Two-sided 95% CI	−0.47 to 4.81		−2.97 to 1.85
Difference vs. placebo*			
Mean (SE)†		2.73 (1.75)	
Two-sided 95% CI		−0.85 to 6.30	

*Difference in adjusted change from baseline for saxagliptin vs. placebo. †Estimate = adjusted mean change for saxagliptin − adjusted mean change for placebo. LOCF, last observation carried forward.

was not consistent for the baseline renal impairment categories. Thus, FPG data were analysed only within each renal impairment subgroup and not for all patients combined. The study was not designed or powered to detect differences between treatment groups within the individual baseline renal impairment categories.

Among patients with moderate and severe renal impairment, the ANCOVA showed numerically larger reductions in adjusted mean FPG from baseline to week 52 with saxagliptin than with placebo; however, among patients with ESRD, adjusted mean FPG increased with saxagliptin (mainly in the first 12 weeks) but decreased with placebo (Table 2).

The results of the repeated-measures analysis for FPG were similar to those of the ANCOVA in patients with moderate or severe renal impairment at baseline. Adjusted mean FPG changes from baseline to week 52 for saxagliptin vs. placebo based on the repeated-measures analysis were −0.82 mmol/l (95% CI, −2.22 to 0.59) vs. 0.15 mmol/l (95% CI, −1.30 to 1.60) in patients with moderate renal impairment (difference, −0.97 [95% CI, −2.99 to 1.04]) and −2.25 mmol/l (95% CI, −4.53 to 0.02) vs. −1.37 mmol/l (95% CI, −2.96 to 0.22) in patients with severe renal impairment (difference, −0.89 [95% CI, −3.66 to 1.89]). However, among saxagliptin-treated patients with ESRD at baseline, in whom the ANCOVA showed an increase in adjusted mean FPG from baseline to week 52 (Table 2), the repeated-measures analysis showed a decrease (−2.25 mmol/l [95% CI, −7.23 to 2.73]), which was numerically larger than that seen with placebo (−0.11 mmol/l [95% CI, −3.31 to 3.10]; difference, −2.14 [95% CI, −8.04 to 3.76]). The number of patients with observed values at week 52 was low, especially in the ESRD group.

Safety and tolerability

Overall, saxagliptin was generally well tolerated in patients with moderate or severe renal disease or ESRD. The percentages of patients who experienced ≥ 1 AE (including hypoglycaemia) and ≥ 1 serious AE over the 52-week period were similar in patients receiving saxagliptin (75% and 27% respectively) and placebo (71% and 28%) (Table 3). There were some differences in percentages of patients with ≥ 1 AE (excluding hypoglycaemia) by baseline renal impair-

Table 3 Reported adverse events during 52 weeks of treatment

	Patients, *n* (%)	
	Saxagliptin 2.5 mg (*n* = 85)	**Placebo (*n* = 85)**
AEs*		
Patients reporting ≥ 1 AE	64 (75.3)	60 (70.6)
Patients reporting ≥ 1 serious AE	23 (27.1)	24 (28.2)
Discontinuation of study medication owing to AE	10 (11.8)	7 (8.2)
Discontinuation of study medication owing to serious AE	6 (7.1)	6 (7.1)
Death	3 (3.5)	4 (4.7)
Most common AEs (≥ 5% in either treatment group)†		
Urinary tract infection	6 (7.1)	3 (3.5)
Anaemia	5 (5.9)	7 (8.2)
Hypertension	5 (5.9)	5 (5.9)
Dyspnoea	5 (5.9)	0
Peripheral oedema	3 (3.5)	6 (7.1)
Reported hypoglycaemic event‡	24 (28.2)	25 (29.4)
Moderate baseline renal impairment	14/48 (29.2)	16/42 (38.1)
Severe baseline renal impairment	6/18 (33.3)	4/23 (17.4)
ESRD at baseline	4/19 (21.1)	5/20 (25.0)
Confirmed hypoglycaemic event‡	8 (9.4)	4 (4.7)
Moderate baseline renal impairment	5/48 (10.4)	3/42 (7.1)
Severe baseline renal impairment	1/18 (5.6)	0/23
ESRD at baseline	2/19 (10.5)	1/20 (5.0)

*Includes hypoglycaemic events. †Excludes hypoglycaemic events. ‡Reported hypoglycaemic event = characteristic signs and symptoms with or without documentation of glucose levels; confirmed hypoglycaemic event = finger-stick glucose ≤ 2.8 mmol/l in patients with associated signs and symptoms. For reported and confirmed hypoglycaemic event by renal impairment group, denominator is total number of patients per renal category. AE, adverse event; ESRD, end-stage renal disease.

ment category: for the saxagliptin and placebo groups, incidence rates were 58% vs. 60% respectively among patients with moderate renal impairment; 83% vs. 70% respectively among patients with severe renal impairment and 58% vs. 70% respectively among patients with ESRD. There was no clear pattern in the incidence of AEs leading to discontinuation of study medication across the baseline renal impairment categories; the incidence was low in each renal impairment category and treatment group.

Table 3 summarises safety and tolerability data in patients in the treated population (randomised patients who received ≥ 1 dose of study medication). Among patients with reported AEs, most rated the AEs as mild or moderate. The most frequent AEs in saxagliptin-treated patients included urinary tract infection, hypertension, dyspnoea and anaemia. Hypoglycaemic events were reported in similar percentages of patients receiving saxagliptin (132 events in 24 patients [28%]) and placebo (90 events in 25 patients [29%]). There were 16 confirmed hypoglycaemic events in 8 patients (9%) in the saxagliptin group and 9 confirmed events in 4 patients (5%) in the placebo group. The majority of hypoglycaemic events were mild, although two events in two patients receiving placebo were considered severe. No hypoglycaemic event required medical assistance. There were seven deaths (none considered treatment-related) during the 52-week treatment period: three among patients taking saxagliptin (sudden death, cardiac arrest, cerebrovascular accident) and four among patients taking placebo (sepsis, cardiac failure and two sudden deaths).

Among other safety outcomes, three patients taking saxagliptin and insulin had a doubling of serum creatinine concentration from baseline at some time during the 52-week treatment period. The LOCF analysis showed the following shifts from baseline to week 52 in renal impairment category: 8 patients shifted from severe to moderate renal impairment (4 of 18 patients on saxagliptin, 4 of 23 on placebo); 16 shifted from moderate to severe renal impairment (6 of 45 patients on saxagliptin, 10 of 42 on placebo); 2 of 23 patients on placebo shifted from severe renal impairment to ESRD. Among patients with moderate or severe renal impairment, mean glomerular filtration rates (estimated by the Cockcroft-Gault and MDRD equations) declined slightly from baseline to

week 52 in both treatment groups; in patients with ESRD on haemodialysis, these measures are not relevant because the results are strongly influenced by the timing of dialysis.

No clinically relevant drug effects on haematology or blood chemistry tests were observed. There was a trend toward reduction in mean systolic and diastolic blood pressure from baseline to week 52 with saxagliptin (−6.6 and −2.7 mmHg respectively) vs. placebo (2.1 and 0.7 mmHg respectively), but no other clinically relevant changes were observed for vital signs, electrocardiogram, body mass index or waist circumference. Slightly larger reductions from baseline in mean body weight were observed at week 52 (safety set with LOCF) with saxagliptin vs. placebo (−0.7 kg vs. −0.1 kg).

Discussion

A general treatment goal for patients with T2DM is to achieve glycaemic control without causing hypoglycaemia or weight gain. Intensive therapy with insulin or a sulfonylurea incurs risk of hypoglycaemia and/or weight gain (25). Adding an agent that is not associated with these risks is an alternate treatment strategy. In the current study, patients who received add-on saxagliptin showed a slight reduction in weight and had no higher rate of hypoglycaemia than did those who received add-on placebo. Treatment with saxagliptin for up to 52 weeks led to clinically relevant reductions in HbA_{1c} and was generally well tolerated in patients with renal impairment of varying severity. The adjusted mean change in HbA_{1c} was greater with saxagliptin than with placebo (ANCOVA). Even though mean HbA_{1c} and FPG at baseline were higher in the saxagliptin group than in the placebo group (see Tables 1 and 2) and these differences might contribute to larger improvements in these glycaemic measures with saxagliptin, each statistical comparison was made on the adjusted mean changes from baseline where baseline values were included in the statistical models.

Reductions in HbA_{1c} observed in this 52-week study are consistent with previously reported 52-week (18), 76-week (26), 102-week (16) and 104-week (27) data from studies of saxagliptin as an add-on to or as initial combination with metformin in adults with T2DM.

Among patients with moderate or severe renal impairment at baseline, the reductions in adjusted mean HbA_{1c} were numerically greater with saxagliptin than with placebo. Among ESRD patients on dialysis, however, the reduction was comparable in the two groups although there were relatively few patients with observed data at the 52-week time point (3 of 17 patients on saxagliptin, 5 of 17 on placebo). It should also be noted that ESRD patients may have carbamylated haemoglobin, which can interfere with laboratory analysis of HbA_{1c} levels, although the use of high-performance liquid chromatography standardised and aligned to The Diabetes Control and Complications Trial nearly eliminates this interference (28). In addition, standard laboratory assessments were performed at a centralised facility (Quintiles Laboratory Europe, Livingston, Scotland, UK; Quintiles Laboratory, Ltd., Marietta, GA, USA).

Similarly, as measured by changes in FPG, the antihyperglycaemic effects of saxagliptin appeared less robust among ESRD patients than among patients with moderate or severe renal impairment. Adjusted mean reductions from baseline FPG were numerically greater with saxagliptin than with placebo in patients with moderate or severe renal impairment. Among saxagliptin-treated ESRD patients, the ANCOVA showed an increase in adjusted mean FPG at week 52, whereas the repeated-measures analysis showed a decrease, which was numerically larger than the decrease seen with placebo.

Fluid retention and consequent haemodilution between dialysis sessions varies considerably for each intersession interval and may contribute to fluctuations in FPG in ESRD patients. Further, ensuring a fasting state before blood sampling in ESRD patients is challenging. Mirani et al. (29) reported increased glycaemic variability in insulin-treated T2DM patients on haemodialysis days vs. interdialytic days (possibly related to variability in glucose content of dialysates).

Similar to previous studies (14,15,17,18), saxagliptin was associated with small decreases in mean body weight. In addition, mean blood pressure decreased among patients taking saxagliptin, which is consistent with reports indicating that incretin-based therapies (DPP-4 inhibitors and GLP-1 agonists) cause modest reductions in blood pressure (30,31).

The percentage of patients with ≥ 1 episode of confirmed hypoglycaemia was higher with saxagliptin than with placebo (9% vs. 5% respectively), but the percentage of patients who reported any hypoglycaemic event was similar (28% vs. 29% respectively). Although these rates are higher than those typically reported in clinical trials of OADs, it should be kept in mind that 75% of study participants were receiving insulin at study entry and the proportion was higher with saxagliptin than with placebo (84% vs. 67% respectively); it should also be noted that patients with T2DM who have renal impairment are at increased risk of hypoglycaemia (5,32).

Incidence rates of death, serious AEs, marked laboratory abnormalities and acute cardiovascular events were not unexpected for this patient population, and were similar between treatment groups. The safety profile of saxagliptin in the long-term treatment period was consistent with that previously observed in clinical trial experience (16,18,26,27) and the short-term (12-week) treatment period of this study (22). There was no evidence of adverse effects on renal function in the saxagliptin group. Thus, saxagliptin was generally well tolerated in a population that included patients with severe chronic illness.

Protocol-defined glycaemic criteria that became increasingly stringent over the course of the study accounted for 37% of all discontinuations in each treatment group. Protocol-mandated study discontinuation for patients not achieving specific glycaemic targets allowed investigators to provide best care for the patient by allowing discretionary titration or addition of antidiabetic therapy (excluding disallowed and study medication) to improve glycaemic control. The other main reason for discontinuation was withdrawal of consent (40% and 29% of all discontinuations in the saxagliptin and placebo groups respectively); which are notably higher than the corresponding rates of 2.0–7.6% reported in other published studies of saxagliptin (15,20,21). Although those studies were of shorter duration, there is no clear explanation for why the proportion of patients who withdrew from the present study for this reason was so much larger.

It may be noted that the classification system developed by the National Kidney Foundation defines moderate renal impairment as CrCl 30–59 ml/min, which extends beyond the upper limit used in the present study (CrCl < 50 ml/min). However, the CrCl value of 50 ml/min was the classification boundary recommended by both the European Medicine Agency and the United States Food and Drug Administration at the time the study was designed (33,34). This boundary also has been used as a classification boundary in other reports (35–37). There has been discussion of revising the 2002 NKF Guidelines by Kidney Initiative: Improving Global Guidelines (KDIGO) to divide stage 3 of chronic kidney disease into two substages using a new CrCl boundary of 45 ml/min (38). The boundary used in this report reflects the need to define a patient population of adequate but manageable size, with appropriate distribution of patients across the spectrum of moderate to ESRD while excluding patients with mild or even borderline-mild renal impairment.

Study limitations include a significant interaction of treatment group by baseline renal impairment category for the FPG analysis, which led to the FPG results being summarised only by renal impairment subgroups. Interpretation of results must also take into account the limited numbers of patients still participating by end of the study as patients dropped out due to withdrawal of consent and to the progressively stringent protocol-defined discontinuation criteria for glycaemic control. Exclusion of efficacy results after changes in insulin and/or OAD medications from the efficacy analysis further reduced the availability of data later in the study. Thus, the robustness of the data is limited by the heavy reliance on LOCF methodology throughout the study. Finally, as this study was conducted in a specialised patient population composed of only white patients, specific findings may not be generalisable.

In conclusion, saxagliptin represents a valuable new treatment option for the improvement of glycaemic control in patients with T2DM and renal impairment. In this population, saxagliptin 2.5 mg once daily resulted in clinically relevant, sustained reductions in HbA_{1c} over 52 weeks, with glycaemic benefits most evident in patients with moderate or severe renal impairment. Treatment was generally well tolerated, with a similar percentage of patients experiencing AEs in both treatment groups.

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