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# Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naive patients with type 2 diabetes*

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**Aim:** Enhancing the physiologic actions of the endogenous incretin hormones, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, by inhibiting dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for their degradation, is an emerging treatment for type 2 diabetes mellitus (T2DM). The aim of this study was to evaluate the safety and efficacy of dose ranges of the DPP-4 inhibitor saxagliptin (BMS-477118) in patients with T2DM.
**Methods:** In a 12-week, multicentre, randomized, parallel-group, double-blind, placebo-controlled trial conducted at 152 out-patient US study centres, 338 (low-dose cohort) and 85 (high-dose cohort) drug-naive patients with T2DM and inadequate glycaemic control (baseline HbA1c $\geq$6.8 and $\leq$9.7%) were randomized. Following a 2-week washout, patients received saxagliptin 2.5, 5, 10, 20 or 40 mg once daily, or placebo, for 12 weeks (low-dose cohort). In a second cohort, patients received saxagliptin 100 mg once daily, or placebo, for 6 weeks (high-dose cohort). The main outcome measure was saxagliptin dose response assessed as change from baseline in HbA1c following double-blind treatment.
**Results:** In all treatment arms, saxagliptin significantly reduced HbA1c by 0.7–0.9% from an average baseline of 7.9% vs. placebo (0.3% reduction) in the low-dose cohort. Placebo-subtracted HbA1c reductions were 0.45–0.63% (low-dose cohort). Saxagliptin had significant placebo-subtracted reductions in fasting serum glucose (14–25 mg/dl). Postprandial glucose levels at 60 min following a standard liquid meal test were reduced by 24–41 mg/dl vs. placebo. Saxagliptin was weight neutral. Adverse events were similar across treatment groups, including placebo, with a very low incidence of confirmed hypoglycaemia in saxagliptin treatment arms.
**Conclusions:** Saxagliptin effectively improved glycaemic control in drug-naive patients with T2DM and was generally safe, with a tolerability profile similar to placebo.

Keywords: DPP-4, GIP, GLP-1, HbA1c, incretin, saxagliptin (BMS-477118), type 2 diabetes
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**Disclosure summary:**
S. S., PhD was previously employed by Bristol-Myers Squibb. J. F. L., MD, PhD has nothing to declare. J. R., MD has served on advisory boards and received honorarium or consulting fees from Pfizer, Sanofi-Aventis, Novo Nordisk, Eli Lilly, GlaxoSmithKline, MannKind, Takeda, Centocor, Johnson & Johnson, Roche and Emisphere. J. R. has received grant support from Merck, Pfizer, Sanofi-Aventis, Novo Nordisk, Eli Lilly, GlaxoSmithKline, Takeda, Novartis, AstraZeneca, Amylin, Roche, Sankyo and MannKind.
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## Introduction

New strategies that promote glucose homeostasis are needed as a majority of patients with type 2 diabetes mellitus (T2DM) are not meeting glycaemic targets [1–3]. The long-term effectiveness of existing therapies has been largely unsatisfactory because of safety and tolerability issues, loss of efficacy over time and inability to affect declining β-cell function [4,5].

A new treatment option for patients with T2DM is to enhance the function of endogenous incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [6,7]. Endogenous incretin hormones are rapidly degraded by dipeptidyl peptidase-4 (DPP-4); however, oral agents that specifically inhibit this enzyme have been shown to effectively enhance the circulating levels of these peptides [8,9]. Incretin hormones, and more specifically subcutaneous GLP-1 receptor agonists and oral DPP-4 inhibitors, have been demonstrated to exert beneficial effects on glycaemic control and in indirect measurements of pancreatic β-cell function [4,9]. Most notably, β-cell mass has been preserved or increased by inhibiting apoptosis or promoting neogenesis in several preclinical studies in different rodent models [9,10]. Saxagliptin (formerly referred to as BMS-477118) is an oral, reversible, competitive DPP-4 inhibitor with a pharmacodynamic half-life suitable for once-daily administration [6,11]. The present study evaluated the safety and efficacy of a wide range of doses of saxagliptin in drug-naive patients with T2DM.

## Methods

### Patients

Drug-naive patients (defined as not ever having received more than 6 months' total antihyperglycaemic drug treatment since diagnosis; patients in the study could have received antihyperglycaemic medication on no more than 7 of the 56 days preceding enrolment and no more than 3 of these days could have been consecutive) were evaluated. The study population comprised men and non-breastfeeding, non-pregnant women aged $\geq$21 to $\leq$70 years, with T2DM and a baseline HbA1c $\geq$6.8 to $\leq$9.7%. Patients were required to have a body mass index (BMI) $\leq$37 kg/m$^2$ and a screening fasting or random C-peptide >0.5 ng/ml (0.17 nmol/l). Patients aged <35 years had to test negative for anti-glutamic acid decarboxylate antibodies.

Patients were excluded from the study if they had type 1 diabetes; symptoms of poorly controlled diabetes or a history of ketoacidosis or hyperosmolar coma; congestive heart failure; a history of significant gastrointestinal disease, recent cardiovascular illness, rapidly progressive renal disease, malignancy, immunodeficiency, asthma or atopic skin disorder; or clinically significant abnormalities on screening tests of hepatic, renal, endocrine, metabolic or haematological function or on chest x-ray or electrocardiogram. To be randomized, patients had to demonstrate adequate treatment compliance with placebo in the washout phase (defined as >80 and <120%). The use of systemic corticosteroids and cytochrome p450 3A4 inhibitors was prohibited.

### Study Protocol

This was a multicentre, randomized, parallel-group, double-blind, placebo-controlled trial exploring the antihyperglycaemic effects of six doses of saxagliptin in drug-naive patients with T2DM. Following a 2-week dietary and placebo washout phase, the initial cohort of patients (referred to as the low-dose cohort) were randomized 1 : 1 : 1 : 1 : 1 : 1 to saxagliptin 2.5, 5, 10, 20 or 40 mg once daily or placebo for 12 weeks. In order to explore the possible added efficacy of a higher 100-mg dose of saxagliptin, the initial study protocol was subsequently amended to include a second cohort (referred to as the high-dose cohort) in which patients were randomized 1 : 1 to saxagliptin 100 mg once daily or placebo for 6 weeks.

During the single-blind placebo washout phase, all patients received dietary counselling in accordance with American Diabetes Association guidelines. Eligible patients were randomized and instructed to take study medication once daily in the morning, 30–60 min prior to the morning meal. Patients returned at approximately 2-week intervals for follow-up and evaluation of safety and adverse events (AEs) and for assessment of glycaemic efficacy. Progressively strict glycaemic control criteria were defined for early termination from the study if fasting serum glucose (FSG) was >250, 240, 220 and 200 mg/dl (*conversion to SI units: mg/dl* $\times$ *0.0555* = *mmol/l*) for weeks 4, 6, 8 and 10, respectively. Patients meeting these criteria were discontinued from the double-blind study medication and entered directly into the follow-up period. Patients who discontinued prematurely were required to have all final visit procedures performed at the time of discontinuation.

Following double-blind treatment, all patients in both cohorts entered a 4-week follow-up period, in which they received single-blind placebo. Patients discontinued from the double-blind study phase for hyperglycaemia and patients meeting the prespecified hyperglycaemic rescue criterion in the follow-up phase (FSG > 250 mg/dl)

received open-label treatment with metformin in addition to single-blind placebo, and additional or alternative antihyperglycaemic agents were permitted during the follow-up period as clinically indicated. The study protocol was approved by the institutional review board for each participating site. All participants provided written consent. This study was performed in accordance with the Declaration of Helsinki.

### Study Measurements

The following efficacy outcomes were assessed: HbA1c, FSG, postprandial glucose at 60 min (PPG60) during a liquid meal tolerance test (MTT) and β-cell function and insulin resistance indices using the homeostatic model assessment (HOMA) [12]. All samples were analysed at a central laboratory, and all samples except those of the MTT were collected in the morning after the patient had fasted for at least 10 h.

For safety assessment, standard haematology, serum chemistry and urinalysis were collected at every scheduled visit of the double-blind and follow-up periods and performed at a central laboratory. Urine testing for pregnancy was performed at every visit locally at the investigative site for women of childbearing potential. All AEs were recorded at each study visit and assessed as to severity and possible relationship to study medication. Symptoms of hypoglycaemia and hypoglycaemic AEs were recorded and analysed separately from other AEs. Confirmed hypoglycaemia was defined as a finger-stick blood glucose value of $\leq$50 mg/dl associated with classical symptoms. AEs and hypoglycaemic events were coded using the Medical Dictionary for Regulatory Activities terminology. Laboratory safety evaluation included evaluation based on predefined marked abnormality criteria.

The prespecified primary end-point was to analyse for a dose-related trend in the lowering of HbA1c from baseline across the saxagliptin doses of the low-dose cohort. Assuming changes in HbA1c levels from baseline across the five saxagliptin dose levels (2.5, 5, 10, 20 and 40 mg) of 0.10, 0.25, 0.40, 0.55 and 0.70%, respectively, and a standard deviation of 1%, with 50 patients per group, a 90% power to detect a log-linear trend would be expected.

Analyses of each dose vs. placebo for lowering HbA1c, FSG and PPG60 from baseline were prespecified secondary end-points. For HbA1c, with 50 patients per treatment group, there was an 80% power to detect a difference of 0.7% between any saxagliptin treatment arm and placebo, assuming a standard deviation of 1%. Change from baseline in HbA1c was analysed using an analysis of covariance (ANCOVA) model with the randomization group as the effect and baseline as a covariate. Sites were not considered as a covariate because of the expected sparseness of patients at each site. Point estimates and 95% confidence intervals for the change within each treatment group as well as the differences between each of the saxagliptin treatment groups and placebo were constructed. Each comparison of saxagliptin dose vs. placebo was performed using F test at $\alpha = 0.012$ level. FSG and PPG60 were analysed using ANCOVA models similar to the one used to analyse HbA1c, with randomization group as the effect and baseline as a covariate. The last observation was carried forward (LOCF) where no data were available for week 12 (low-dose cohort) or week 6 (high-dose cohort).

Other analyses carried out at week 12 (low-dose cohort) or week 6 (high-dose cohort) included the proportion of subjects who achieved a therapeutic glycaemic goal (defined as HbA1c $<$7% for subjects with a baseline HbA1c $\geq$7%), and the change from baseline in β-cell function and insulin resistance indices using the HOMA. All analyses were performed with SAS version 8.2 or higher.

Two analysis sets were defined for the study. All efficacy analyses were based on a modified intent to treat population defined as the *Randomized Patients* data set, consisting of all randomized patients who received at least 6 weeks of active treatment and had a baseline and $\geq$1 postrandomization HbA1c measurement. Safety was assessed using a *Treated Patients* data set, consisting of all patients who were enrolled, randomized and received $\geq$1 dose of double-blind study medication during the double-blind period.

## Results

### Patient Disposition and Clinical Characteristics

Between May 2003 and May 2004, 363 patients were enrolled through the low-dose cohort. Of the 338 patients who were randomized to double-blind treatment, 282 (83.4%) completed the 12-week double-blind treatment period (figure 1a). Demographic and baseline characteristic profiles were generally similar between treatment arms, with differences seen in the ratio of females to males across study arms. There were no meaningful differences between treatment groups in baseline diabetes characteristics (table 1).

Ninety-four patients were enrolled in the high-dose cohort. Of the 85 patients randomized to double-blind treatment, 79 (93%) completed the treatment period. There were no discontinuations in the saxagliptin 100-mg treatment arm (figure 1b). There were no meaningful differences between the treatment groups in demographic or baseline diabetes characteristics in the high-dose

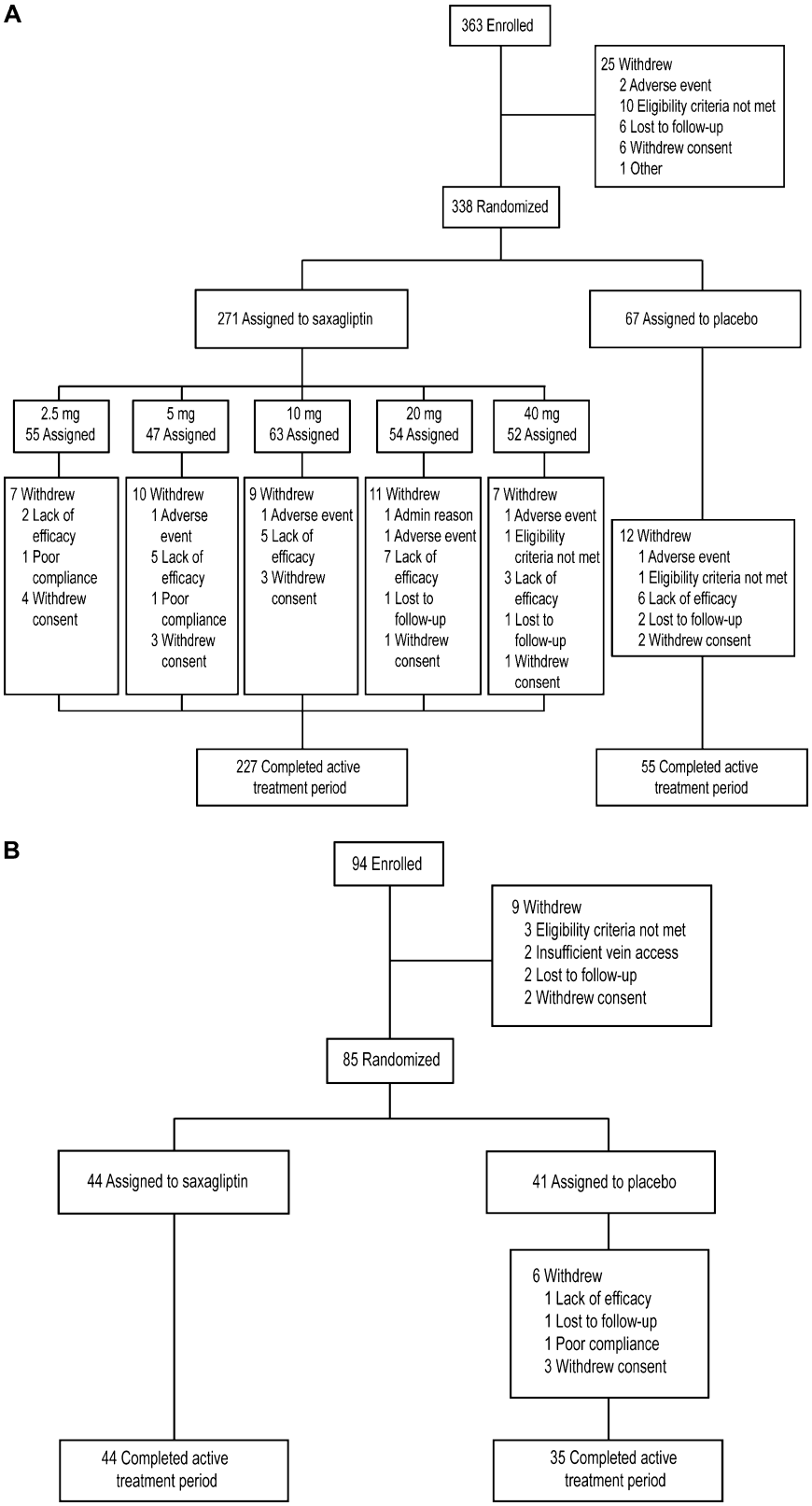


**Fig. 1** (A) Patient study flow: low-dose cohort. (B) Patient study flow: high-dose cohort.

**Table 1** Demographic and baseline characteristics of drug-naive patients with type 2 diabetes by randomized group: low-dose and high-dose cohorts

| | Low-dose cohort | | | | | | High-dose cohort | |
|---|---|---|---|---|---|---|---|---|
| | | Saxagliptin | | | | | | Saxagliptin |
| | Placebo | 2.5 mg | 5 mg | 10 mg | 20 mg | 40 mg | Placebo | 100 mg |
| Characteristics | n = 67 | n = 55 | n = 47 | n = 63 | n = 54 | n = 52 | n = 41 | n = 44 |
| Age in years, mean (s.d.) | 55.2 (9.80) | 52.5 (10.53) | 53.7 (10.14) | 54.5 (8.61) | 53.6 (8.59) | 54.1 (11.12) | 52.8 (10.18) | 51.4 (9.91) |
| <65 years, mean (%) | 55 (82) | 50 (91) | 39 (83) | 54 (86) | 50 (93) | 41 (79) | 35 (85) | 38 (86) |
| Sex, mean (%) | | | | | | | | |
| Male | 42 (63) | 22 (40) | 25 (53) | 40 (63) | 38 (70) | 30 (58) | 23 (56) | 27 (61) |
| Female | 25 (37) | 33 (60) | 22 (47) | 23 (37) | 16 (30) | 22 (42) | 18 (44) | 17 (39) |
| Race, mean (%) | | | | | | | | |
| Caucasian | 58 (87) | 47 (85) | 41 (87) | 53 (84) | 47 (87) | 48 (92) | 33 (80) | 34 (77) |
| African-American | 7 (10) | 6 (11) | 6 (13) | 5 (8) | 4 (7) | 2 (4) | 4 (10) | 7 (16) |
| Other | 2 (3) | 2 (4) | 0 (0) | 5 (8) | 3 (6) | 2 (4) | 4 (10) | 3 (7) |
| Body weight (kg), mean (s.d.) | 93.1 (19.21) | 86.6 (14.17) | 89.8 (15.92) | 92.4 (17.78) | 88.9 (14.63) | 86.8 (19.55) | 91.2 (16.39) | 92.2 (16.24) |
| BMI (kg/m$^2$), mean (s.d.) | 31.1 (4.46) | 30.8 (3.73) | 30.8 (4.21) | 31.0 (4.03) | 29.7 (3.63) | 29.8 (4.29) | 31.2 (4.06) | 31.3 (3.88) |
| Diabetes duration in years, median (range) | 1.8 (0.0–23.0) | 1.0 (0.0–14.0) | 0.8 (0.0–8.2) | 0.7 (0.0–12.9) | 1.7 (0.0–13.0) | 1.3 (0.0–19.0) | 0.3 (0.0–13.0) | 0.5 (0.0–26.0) |
| HbA1c %, mean (s.d.) | 8.0 (0.98) | 7.7 (0.97) | 7.9 (1.09) | 8.0 (1.14) | 7.9 (0.99) | 7.8 (1.00) | 7.5 (1.05) | 7.8 (1.01) |
| FSG (mg/dl), mean (s.d.)* | 164.8 (42.60) | 155.6 (40.23) | 168.9 (50.39) | 168.8 (44.44) | 172.1 (48.58) | 158.1 (43.40) | 144.8 (35.11) | 152.3 (36.42) |

BMI, body mass index; FSG, fasting serum glucose.

*SI conversion to mmol/l: mg/dl $\times$ 0.0555.

cohort (table 1). Treatment groups in both cohorts had similar baseline physical characteristics, vital signs and lipid characteristics.

### Efficacy Outcomes

Figure 2a shows the adjusted mean change from baseline in HbA1c at week 12 for the low-dose cohort. HbA1c was significantly reduced from baseline in all saxagliptin treatment arms compared with placebo following 12 weeks of double-blind treatment ($p < 0.007$). Similar and clinically meaningful reductions in HbA1c were achieved with all doses of saxagliptin, and the test for log-linear trend across the treatment groups (the primary end-point) did not demonstrate a statistically significant dose-response relationship after 12 weeks of treatment. Reductions were greatest among patients with a higher baseline HbA1c and were already evident by week 4 (figure 2b). Adjusted mean reductions from baseline exceeded 0.7% at each saxagliptin dose level vs. 0.27% for placebo (table 2). Placebo-subtracted adjusted mean changes from baseline to week 12 for saxagliptin ranged from −0.45 to −0.63%, with no apparent significant dose–response relationship ($p = 0.9888$). The proportion of patients with a baseline HbA1c ≥7% who achieved an HbA1c goal of <7% at week 12 ranged from 41 to 53% in the saxagliptin treatment arms vs. 20% for placebo (table 2).

HbA1c was also significantly reduced from baseline relative to placebo in the high-dose cohort, with an adjusted mean change following 6 weeks of double-blind treatment of −1.09 vs. −0.36% for placebo (figure 2c, d).

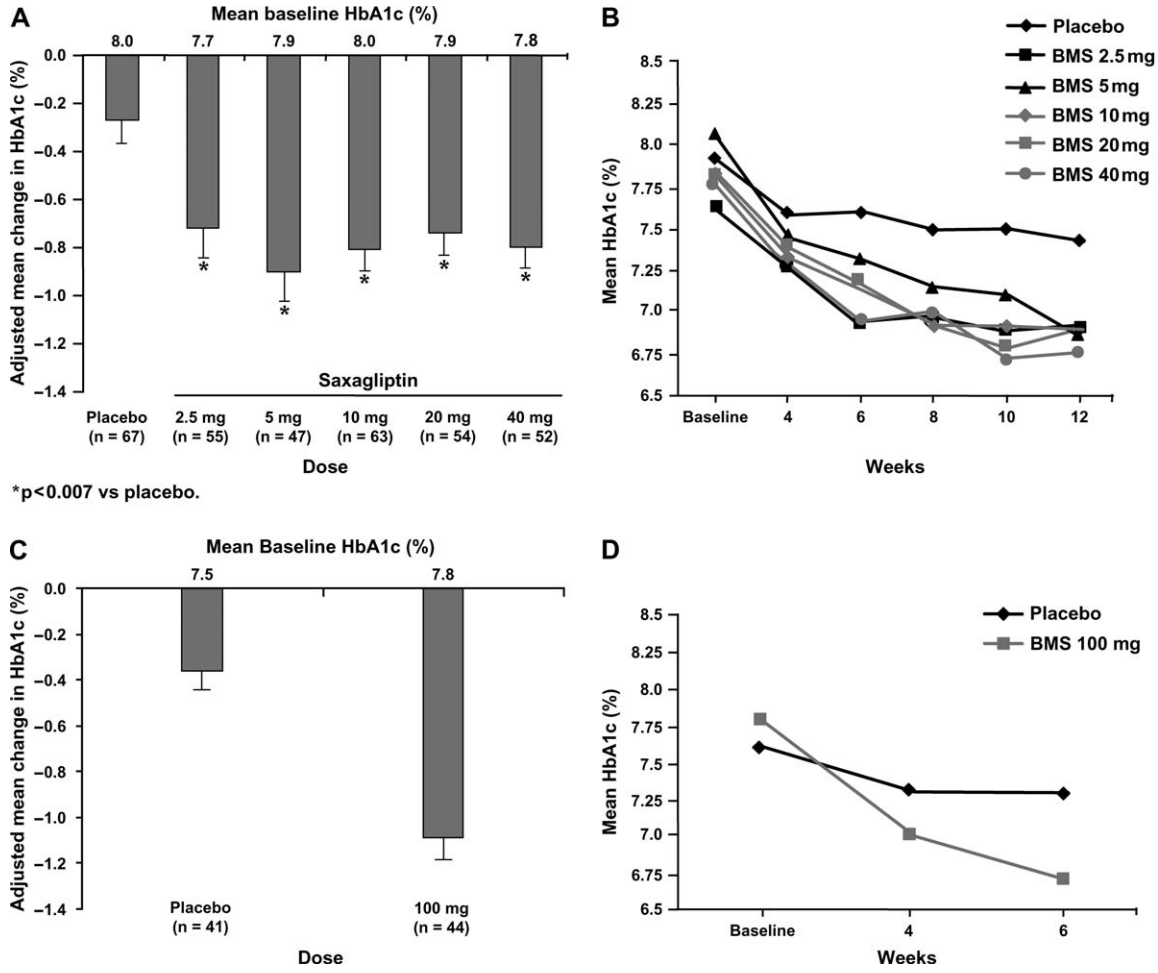


**Fig. 2** (A) Adjusted mean change (±s.e.) from baseline in HbA1c at week 12 (LOCF): low-dose cohort. (B) Mean HbA1c over time during double-blind treatment: low-dose cohort. (C) Adjusted mean change (±s.e.) from baseline in HbA1c at week 6 (LOCF): high-dose cohort. (D) Mean HbA1c over time during double-blind treatment: high-dose cohort. LOCF, last observation was carried forward.

**Table 2** Change in efficacy outcomes from baseline at week 12 (low-dose cohort), last observation was carried forward*

| | **Low-dose cohort** | | | | | |
|---|---|---|---|---|---|---|
| | | **Saxagliptin** | | | | |
| | **Placebo** | **2.5 mg** | **5 mg** | **10 mg** | **20 mg** | **40 mg** |
| HbA1c response | | | | | | |
| HbA1c <7% | 10/50 (20%) | 20/40 (50%) | 16/34 (47%) | 20/49 (41%) | 21/42 (50%) | 21/40 (53%) |
| HbA1c change from baseline, mean (s.e.) | | | | | | |
| N | 62 | 51 | 42 | 60 | 51 | 50 |
| Adjusted Δ from baseline | −0.27 (0.11) | −0.72 (0.12) | −0.90 (0.14) | −0.81 (0.11) | −0.74 (0.12) | −0.80 (0.12) |
| 95% CI | [−0.49, −0.05] | [−0.97, −0.48] | [−1.17, −0.63] | [−1.03, −0.58] | [−0.98, −0.50] | [−1.04, −0.56] |
| Difference vs. placebo | — | −0.45 (0.17) | −0.63 (0.18) | −0.54 (0.16) | −0.47 (0.17) | −0.53 (0.17) |
| 95% CI | | [−0.78, −0.13] | [−0.97, −0.29] | [−0.85, −0.23] | [−0.80, −0.14] | [−0.86, −0.20] |
| FSG (mg/dl), mean (s.e.)† | | | | | | |
| N | 63 | 50 | 46 | 61 | 53 | 50 |
| Adjusted Δ from baseline | 2.81 (4.10) | −10.85 (4.61) | −21.68 (4.80) | −15.91 (4.16) | −13.61 (4.48) | −16.36 (4.60) |
| 95% CI | [−5.25, 10.87] | [−19.92, −1.77] | [−31.11, −12.24] | [−24.10, −7.71] | [−22.42, −4.80] | [−25.42, −7.30] |
| Difference vs. placebo | — | −13.66 (6.17) | −24.49 (6.31) | −18.72 (5.84) | −16.42 (6.07) | −19.17 (6.16) |
| 95% CI | | [−25.80, −1.51] | [−36.90, −12.07] | [−30.21, −7.22] | [−28.36, −4.48] | [−31.30, −7.05] |
| PPG60 (mg/dl), mean (s.e.)† | | | | | | |
| N | 50 | 41 | 30 | 49 | 38 | 41 |
| Adjusted Δ from baseline | −1.41 (6.08) | −24.42 (6.73) | −35.30 (7.84) | −41.04 (6.14) | −27.54 (6.97) | −33.98 (6.71) |
| | [−13.39, 10.56] | [−37.67, −11.16] | [−50.75, −19.86] | [−53.13, −28.94] | [−41.27, −13.80] | [−47.20, −20.75] |
| Difference vs. placebo | — | −23.00 (9.05) | −33.39 (9.92) | −39.62 (8.65) | −26.12 (9.62) | −32.56 (9.07) |
| 95% CI | | [−40.84, −5.17] | [−53.43, −14.35] | [−56.65, −22.59] | [−44.36, −7.89] | [−50.42, −14.71] |
| HOMA-%β, mean (s.d.) | | | | | | |
| N | 48 | 41 | 29 | 47 | 37 | 41 |
| Δ from baseline | −0.73 (66.04) | 23.84 (73.38) | 16.89 (38.78) | 24.68 (58.38) | 20.76 (45.91) | 18.33 (57.83) |
| 95% CI | [−19.90, 18.45] | [0.68, 47.00] | [2.14, 31.64] | [7.54, 41.82] | [5.45, 36.06] | [0.08, 36.58] |
| Body weight (kg), mean (s.d.) | | | | | | |
| N | 54 | 47 | 31 | 52 | 42 | 44 |
| Δ from baseline | −1.03 (2.79) | −0.94 (2.40) | −0.23 (2.28) | −1.28 (2.91) | −0.11 (2.25) | 0.51 (3.01) |
| 95% CI | [−1.80, −0.27] | [−1.64, −0.23] | [−1.07, 0.60] | [−2.09, −0.47] | [−0.81, 0.59] | [−0.41, 1.42] |

FSG, fasting serum glucose; HOMA, homeostatic model assessment; PPG60, postprandial glucose at 60 min.
*Randomized patients' data set.
†SI conversion to mmol/l: mg/dl × 0.0555.

The placebo-subtracted adjusted mean change from baseline to week 6 was −0.73% for patients on saxagliptin. Additionally, of those patients with a baseline HbA1c ≥7% in the high-dose saxagliptin treatment arm, 66% achieved an HbA1c <7% at week 6 vs. 22% in the placebo arm (table 3).

FSG reductions from baseline were evident by week 2 in both treatment cohorts for all saxagliptin treatment arms (figure 3a, b). Adjusted mean FSG changes from baseline for the low-dose cohort at week 12 ranged from −11 to −22 mg/dl across active treatment arms vs. +3 mg/dl for placebo (figure 3c). Adjusted mean changes from baseline in FSG for the high-dose cohort at week 6 were −26.3 mg/dl for saxagliptin vs. −3.3 mg/dl for placebo (figure 3d). Analyses of efficacy by baseline subgroup of HbA1c (<7%, 7 to <8%, 8 to <9% and ≥9%) and FSG (<140 mg/dl, 140 to <180 mg/dl and ≥180 mg/dl) showed reductions in HbA1c and FSG, respectively, which were generally greater in groups with higher baseline concentrations (data not shown).

In both treatment cohorts, reductions in PPG60 during a liquid MTT were evident for all saxagliptin treatment arms. Adjusted mean changes from baseline in the low-dose cohort saxagliptin treatment arms ranged from −24 to −41 mg/dl vs. −1 mg/dl for placebo (table 2). Adjusted mean changes for the high-dose cohort at week 6 were −45 mg/dl for saxagliptin vs. −17 mg/dl for placebo (table 3).

No consistent treatment effect was observed for changes from baseline in fasting or postprandial insulin and C-peptide. The HOMA formula was employed to assess changes of β-cell function in the setting of differences in glycaemic control. β-cell function by HOMA increased from baseline in both cohorts across all saxagliptin treatment arms (tables 2 and 3). In the low-dose cohort, the week 12 mean change from baseline in HOMA-%β

**Table 3** Change in efficacy outcomes from baseline at week 6 (high-dose cohort), last observation was carried forward*

| | High-dose cohort | |
|---|---|---|
| | **Placebo** | **Saxagliptin (100 mg)** |
| HbA1c response | | |
| HbA1c <7% | 5/23 (22%) | 23/35 (66%) |
| HbA1c change from baseline, mean (s.e.) | | |
| N | 35 | 43 |
| Adjusted Δ from baseline 95% CI | −0.36 (0.09) [−0.55, −0.17] | −1.09 (0.09) [−1.26, −0.92] |
| Difference vs. placebo 95% CI | — | −0.73 (0.13) [−0.98, −0.48] |
| FSG (mg/dl), mean (s.e.)† | | |
| N | 41 | 44 |
| Adjusted Δ from baseline 95% CI | −3.29 (3.81) [−10.88, 4.29] | −26.33 (3.53) [−33.36, −19.30] |
| Difference vs. placebo 95% CI | — | −23.04 (5.20) [−33.39, −12.68] |
| PPG60 (mg/dl), mean (s.e.)† | | |
| N | 35 | 38 |
| Adjusted Δ from baseline | −17.22 [5.88] | −44.58 [5.65] |
| Difference vs. placebo 95% CI | — | −27.36 (8.15) [−43.62, −11.09] |
| HOMA-%β, mean (s.d.) | | |
| N | 36 | 39 |
| Δ from baseline 95% CI | 2.07 (29.32) [−7.85, 11.99] | 13.82 (49.25) [−2.15, 29.78] |
| Body weight (kg), mean (s.d.) | | |
| N | 33 | 40 |
| Δ from baseline | −0.85 (1.47) [−1.37, −0.33] | −0.20 (2.04) [−0.85, 0.45] |

FSG, fasting serum glucose; HOMA, homeostatic model assessment; PPG60, postprandial glucose at 60 min.
*Randomized patients data set.
†SI conversion to mmol/l: mg/dl × 0.0555.

ranged from +16.9 to +24.7% vs. −0.7% for placebo. In the high-dose cohort, the week 6 mean change from baseline in HOMA-%β was +13.8% for saxagliptin 100 mg vs. +2.1% for placebo. There was no clear treatment effect on insulin resistance by HOMA (HOMA-IR).

### Safety and Tolerability

AEs occurring during the double-blind treatment period in both cohorts are summarized in table 4. The overall frequency of AEs was comparable across all treatment groups and placebo and did not appear to be dose related. No deaths were reported during the double-blind treatment period in either cohort. There was a low incidence of serious adverse events (SAEs) and AE-related study discontinuations, with no SAEs or discontinuations occurring in the high-dose cohort. The most common AEs were headache, upper respiratory tract infection, urinary tract infection (UTI), nasopharyngitis, arthralgia, nausea and cough (low-dose cohort) and headache, UTI, constipation and fatigue (high-dose cohort). In both treatment cohorts, a weight-neutral effect was observed over time for the saxagliptin treatment groups compared with placebo (table 2). No meaningful differences in BMI or waist circumference were observed across the saxagliptin dose groups over time during double-blind treatment in either cohort. The proportion of subjects experiencing hypoglycaemia symptoms (such as confusion and dizziness) as an AE in the low-dose cohort was 6.3% for saxagliptin-treated subjects vs. 1.5% for placebo. The lowest incidence of hypoglycaemic AEs was 4.8% in the saxagliptin 10-mg treatment arm, and the highest incidence was 7.7% in the 40-mg treatment arm. In the high-dose cohort, 13.6% of subjects in the saxagliptin 100-mg treatment arm experienced hypoglycaemic symptoms vs. 0% in the placebo arm. Generally, hypoglycaemic symptoms were judged by the investigator to be of mild intensity. No hypoglycaemic AE in either cohort required treatment, dose reduction or discontinuation. In the low-dose cohort, there were no cases of confirmed hypoglycaemia, defined as a finger-stick blood glucose value ≤50 mg/dl. In the high-dose cohort, there were two cases of confirmed hypoglycaemia; both occurred in the saxagliptin 100-mg treatment arm, both were judged by the investigator to be of mild intensity and neither required third-party assistance or medical treatment.

In both cohorts, small dose-dependent reductions in absolute lymphocyte count were observed. Mean absolute lymphocyte counts remained within normal limits across

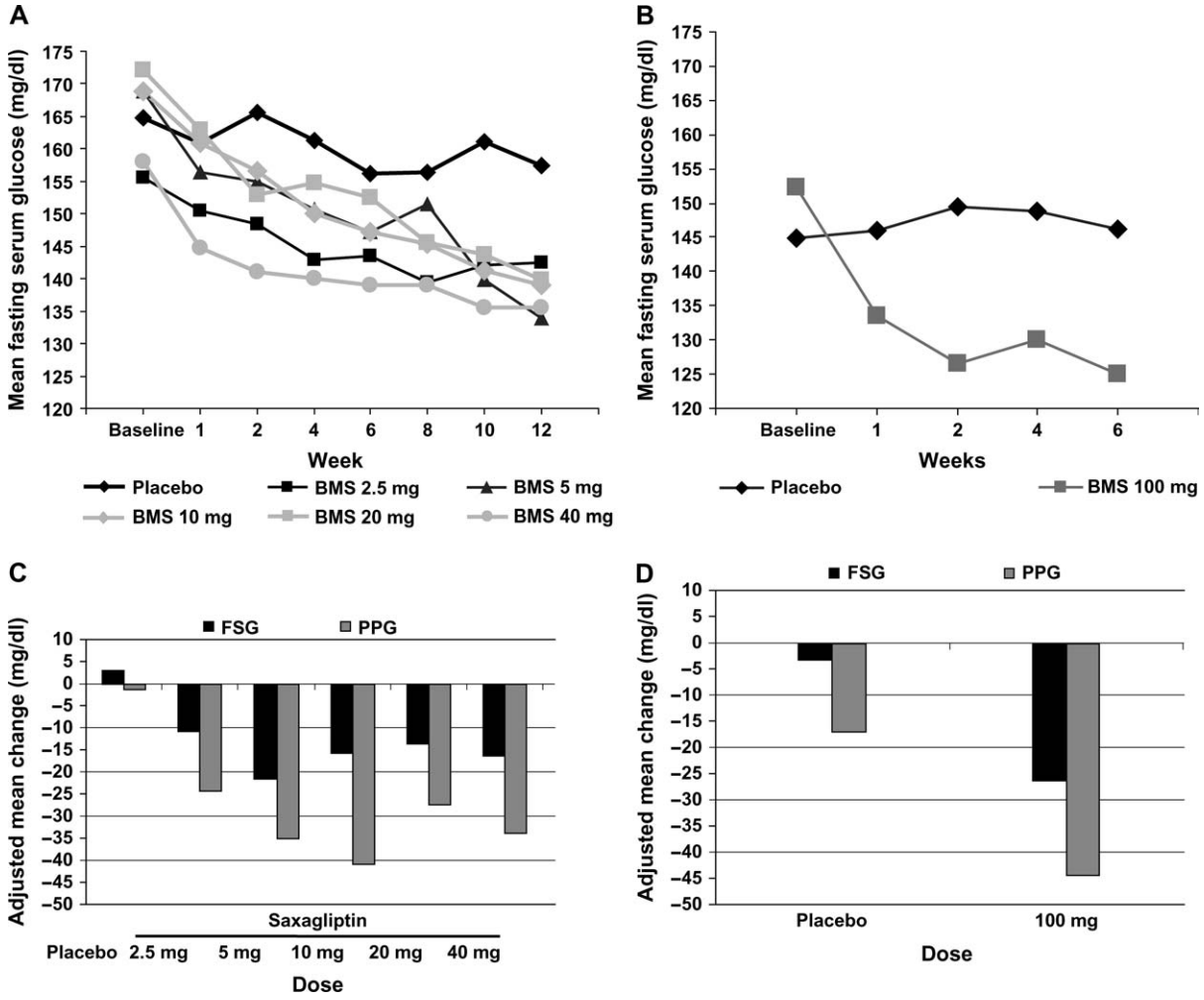


**Fig. 3** (A) Mean FSG over time during double-blind treatment: low-dose cohort. (B) Mean FSG over time during double-blind treatment: high-dose cohort. (C) Adjusted mean change (±s.e.) from baseline in FSG and PPG at week 12 (LOCF): low-dose cohort. (D) Adjusted mean change (±s.e.) from baseline in FSG and PPG at week 6 (LOCF): high-dose cohort. FSG, fasting serum glucose; LOCF, last observation was carried forward; PPG, postprandial glucose.

all treatment arms. The effect was more apparent at doses $\geq$20 mg in the saxagliptin treatment arms and was reversible on discontinuation of study drug. The mean change from baseline in absolute lymphocyte count at week 12 in the low-dose cohort ranged from no change in the 2.5-mg arm to $-0.38 \times 10^3$ cells/μl in the 40-mg arm, with no change in the placebo arm. The mean change from baseline in the saxagliptin 100-mg arm at week 6 was $-0.28 \times 10^3$ cells/μl, with a change of $-0.10 \times 10^3$ cells/μl in the placebo arm. No clear evidence for altered immune function, based on AE reporting, was seen. No effect on white blood cell count, neutrophil count or haemoglobin/haematocrit was noted. For both study cohorts, no clinically relevant signals were observed in liver function tests, renal laboratory tests or creatine kinase levels.

## Discussion

The current study demonstrated that saxagliptin, an inhibitor of the DPP-4 enzyme with a pronounced and prolonged pharmacodynamic effect, significantly improved glycaemic control over a 40-fold dose range when used as monotherapy in drug-naive patients with T2DM. Consistent and clinically significant reductions from baseline in HbA1c compared with placebo were demonstrated for all saxagliptin treatment arms in this dose range, with a large proportion of saxagliptin-treated

**Table 4** AEs* in double-blind treatment period in low-dose and high-dose cohorts: total, serious, discontinuations, most frequent (≥5%) and confirmed hypoglycaemia†‡

| | Low-dose cohort | | | | | | | High-dose cohort | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo | 2.5 mg | 5 mg | 10 mg | 20 mg | 40 mg | Total | | Placebo | 100 mg | Total |
| N | 67 | 55 | 47 | 63 | 54 | 52 | | | 41 | 44 | |
| AE§ | 53 (79.1) | 44 (80.0) | 36 (76.6) | 49 (77.8) | 47 (87.0) | 39 (75.0) | | | 24 (58.5) | 29 (65.9) | |
| Serious AE | 1 (1.5) | 1 (1.8) | 0 | 1 (1.6) | 1 (1.9) | 0 | | | 0 | 0 | |
| Discontinuation due to AE | 1 (1.5) | 0 | 1 (2.1) | 1 (1.6) | 1 (1.9) | 2 (3.8) | | | 0 | 0 | |
| Headache | 6 (9.0) | 8 (14.5) | 4 (8.5) | 10 (15.9) | 6 (11.1) | 5 (9.6) | 39 (11.5) | Headache | 2 (4.9) | 5 (11.4) | 7 (8.2) |
| URI | 4 (6.0) | 6 (10.9) | 3 (6.4) | 6 (9.5) | 6 (11.1) | 0 | 25 (7.4) | UTI | 2 (4.9) | 4 (9.1) | 6 (7.1) |
| UTI | 5 (7.5) | 6 (10.9) | 2 (4.3) | 4 (6.3) | 5 (9.3) | 2 (3.8) | 24 (7.1) | Constipation | 2 (4.9) | 3 (6.8) | 5 (5.9) |
| Nasopharyngitis | 5 (7.5) | 0 | 2 (4.3) | 5 (7.9) | 3 (5.6) | 6 (11.5) | 21 (6.2) | Fatigue | 2 (4.9) | 3 (6.8) | 5 (5.9) |
| Arthralgia | 2 (3.0) | 6 (10.9) | 3 (6.4) | 3 (4.8) | 5 (9.3) | 2 (3.8) | 21 (6.2) | | | | |
| Nausea | 5 (7.5) | 1 (1.8) | 2 (4.3) | 2 (3.2) | 2 (3.7) | 5 (9.6) | 17 (5.0) | | | | |
| Cough | 3 (4.5) | 4 (7.3) | 3 (6.4) | 1 (1.6) | 3 (5.6) | 3 (5.8) | 17 (5.0) | | | | |
| Confirmed hypoglycaemia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 2 (4.5) | 2 (4.5) |

AE, adverse events; URI, upper respiratory tract infection; UTI, urinary tract infection.
*AE was defined as any new or worsening illness, sign, symptom or clinically significant laboratory test abnormality as noted by the investigator during the course of the study, regardless of the investigator's attribution of the event to study treatment.
†Confirmed hypoglycaemia defined by symptoms of hypoglycaemia in the setting of a finger-stick blood glucose value ≤50 mg/dl.
‡Treated patients data set. Values expressed as n (%).
§Hypoglycaemia events excluded.

patients achieving a goal HbA1c of <7%. No dose–response for reduction in HbA1c was demonstrated for doses of saxagliptin from 2.5 to 40 mg. Given the relatively low mean baseline HbA1c of 7.9% in the low-dose cohort and 7.7% in the high-dose cohort, the HbA1c reductions with saxagliptin were particularly clinically meaningful.

GLP-1 and GIP are secreted in response to an enteral nutrient load. DPP-4 inhibitors, such as saxagliptin, are proposed to lower postprandial blood sugar by enhancing endogenous incretin function. This results in an enhancement of glucose-mediated insulin release and reduction of postprandial glucagon secretion [4,7]. Saxagliptin also improved fasting blood sugar, an effect that occurred within 2 weeks of starting therapy. FSG reductions suggest that saxagliptin may have an effect on hepatic glucose production, perhaps from enhanced islet-cell function and reduced glucagon secretion. HOMA analysis of β-cell function, which is based on fasting indices of glucose and insulin levels [12], shows that saxagliptin at all doses tested improved β-cell function compared with placebo. There was no clear effect of saxagliptin on HOMA-IR, suggesting that saxagliptin does not directly impact insulin resistance.

β-cell function deficiency and progressive decline are central to the pathophysiology of T2DM. Preclinical studies in rodents have shown that incretins can stimulate β-cell proliferation and inhibit β-cell apoptosis [9]. Although no clinical evidence is yet available in humans, it seems reasonable to speculate that DPP-4 inhibition, leading to increased concentrations of incretins, might have beneficial effects on islet mass and β-cell survival [10,13]. However, further studies are needed to demonstrate the intriguing hypothesis that DPP-4 inhibitors may alter the natural history of T2DM [4].

In this study, the AEs for all doses of saxagliptin was similar to placebo. Hypoglycaemia, a common complication of blood-glucose–lowering therapies, is a primary obstacle in achieving optimal glycaemic control. Because incretins enhance insulin secretion in a glucose-dependent manner, DPP-4 inhibitors would not be expected to cause hypoglycaemia [9]. Compatible with an incretin-based mechanism of action, there were no confirmed cases of hypoglycaemia at the 2.5-, 5-, 10-, 20- or 40-mg doses and only two confirmed cases of hypoglycaemia at the 100-mg dose. Obesity and weight control are also important considerations as nearly 90% of patients with T2DM are overweight [14]. Most antidiabetic therapies, with the exception of metformin and incretin-related agents, result in weight gain [4]. In both treatment cohorts, a weight-neutral effect was observed over time for the saxagliptin treatment groups compared with placebo. The low propensity for hypoglycaemia and the weight neutrality of DPP-4 inhibition therapy may offer clinically attractive advantages over non–incretin-mediated treatment modalities [15,16].

Treatment with high daily doses of saxagliptin was associated with small dose-dependent reductions from baseline in mean absolute lymphocyte count. The reductions were barely detectible or absent at the lower end of the effective dose range, and mean lymphocyte counts remained well within normal limits over the entire 40-fold dose range tested. Furthermore, there was no evidence for altered immune function, even at the highest doses tested. At the present time, there is no known clinical significance to these findings.

This dose-ranging, proof-of-concept study demonstrates that daily doses of saxagliptin 2.5, 5, 10, 20 and 40 mg for 12 weeks or saxagliptin 100 mg for 6 weeks consistently improved glycaemic control with meaningful reductions in HbA1c in a weight-neutral manner and with a low incidence of confirmed hypoglycaemia. The results of this study served as the basis to select the therapeutic doses that are being tested in a comprehensive phase 3 clinical research programme. The outcome of these ongoing studies will be critical to evaluating the long-term efficacy, safety and tolerability of saxagliptin as monotherapy or in combination with other antidiabetic agents in different clinical scenarios.

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## References

1 King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 1998; **21:** 1414–1431.
2 Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. Diabetes Care 2004; **27:** 17–20.
3 Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS. Racial and ethnic differences in glycemic control of adults with type 2 diabetes. Diabetes Care 1999; **22:** 403–408.
4 Rosenstock J, Zinman B. Dipeptidyl peptidase-4 inhibitors and the management of type 2 diabetes mellitus. Curr Opin Endocrinol Diabetes Obes 2007; **14:** 98–107.
5 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999; **281:** 2005–2012.
6 Augeri DJ, Robl JA, Betebenner DA *et al.* Discovery and preclinical profile of Saxagliptin (BMS-477118): a highly potent, long-acting, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. J Med Chem 2005; **48:** 5025–5037.
7 Drucker DJ. Enhancing incretin action for the treatment of type 2 diabetes. Diabetes Care 2003; **26:** 2929–2940.
8 Rotella CM, Pala L, Mannucci E. Glucagon-like peptide 1 (GLP-1) and metabolic diseases. J Endocrinol Invest 2005; **28:** 746–758.
9 Drucker DJ. The biology of incretin hormones. Cell Metab 2006; **3:** 153–165.
10 Pospisilik JA, Martin J, Doty T *et al.* Dipeptidyl peptidase IV inhibitor treatment stimulates beta-cell survival and islet neogenesis in streptozotocin-induced diabetic rats. Diabetes 2003; **52:** 741–750.
11 Kim YB, Kopcho LM, Kirby MS *et al.* Mechanism of Gly-Pro-pNA cleavage catalyzed by dipeptidyl peptidase-IV and its inhibition by saxagliptin (BMS-477118). Arch Biochem Biophys 2006; **445:** 9–18.
12 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; **28:** 412–419.
13 Prentki M, Nolan CJ. Islet beta cell failure in type 2 diabetes. J Clin Invest 2006; **116:** 1802–1812.
14 American Diabetes Association. Weight Loss Matters. 2007. http://www.diabetes.org/utils/printthispage.jsp?PageID=WEIGHTLOSS3_233377. Accessed October 30, 2007.
15 Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. Diabetologia 2006; **49:** 2564–2571.
16 Ristic S, Byiers S, Foley J, Holmes D. Improved glycaemic control with dipeptidyl peptidase-4 inhibition in patients with type 2 diabetes: vildagliptin (LAF237) dose response. Diabetes Obes Metab 2005; **7:** 692–698.