Drugs 2009; 69 (15): 2103-2114
0012-6667/09/0015-2103/$55.55/0

Saxagliptin

Sohita Dhillon and *Juliane Weber*

Adis, a Wolters Kluwer Business, Auckland, New Zealand

Contents

Abstract

▲ Saxagliptin and its active metabolite M2 are dipeptidyl peptidase-4 inhibitors that improve glycaemic control by preventing the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide. This increases GLP-1 levels, stimulates insulin secretion and reduces postprandial glucagon and glucose levels.

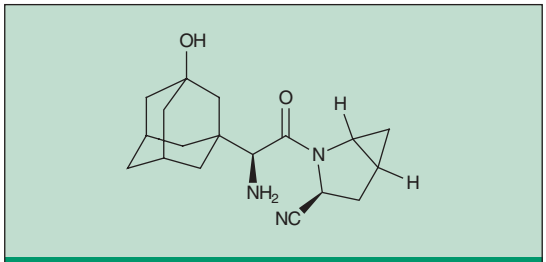
▲ In well designed, 24-week trials in treatment-naive patients with type 2 diabetes mellitus, monotherapy with oral saxagliptin 2.5 or 5 mg once daily significantly improved glycaemic control, as measured by mean glycosylated haemoglobin (HbA_{1c}) levels, relative to placebo.

▲ In large, well designed, 24-week trials, combination therapy with saxagliptin 5 mg once daily plus metformin significantly improved HbA_{1c} levels relative to single-agent saxagliptin or metformin in treatment-naive patients; in treatment-experienced patients with inadequate glycaemic control, the addition of saxagliptin 2.5 or 5 mg once daily to metformin, glyburide or a thiazolidinedione, significantly improved HbA_{1c} levels relative to continued use of existing monotherapy.

▲ Saxagliptin as monotherapy or in combination with other oral antihyperglycaemics was generally well tolerated, with most adverse events being of mild to moderate severity. In clinical trials, the incidence of hypoglycaemic events in patients receiving saxagliptin was generally similar to that in patients receiving placebo or other oral antihyperglycaemic agents.

▲ Saxagliptin therapy was not associated with an increased risk of cardiovascular events according to pooled data from eight clinical trials. Saxagliptin generally had a weight-neutral effect.

Features and properties of saxagliptin (SAXA) [Onglyza™]	
Indication	
An adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus	
Mechanism of action	
Inhibits dipeptidyl peptidase-4 enzyme from inactivating the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, thereby prolonging incretin activity in response to the ingestion of nutrients	
Dosage and administration	
Dose	2.5 or 5 mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile of single-dose SAXA 5 mg and its active metabolite M2 in healthy volunteers	
Mean peak plasma concentrations	SAXA: 24 ng/mL M2: 47 ng/mL
Mean area under the plasma concentration-time curve	SAXA: 78 ng • h/mL M2: 214 ng • h/mL
Median time to peak plasma concentration	SAXA: 2 h M2: 4 h
Mean plasma elimination half-life	SAXA: 2.5 h M2: 3.1 h
Most common adverse events (incidence ≥5%) with SAXA 5 mg (monotherapy or combination therapy)	
Upper respiratory tract infection, urinary tract infection, headache, nasopharyngitis	



Diabetes mellitus is a group of chronic metabolic diseases characterized by hyperglycaemia[1] and is estimated to affect more than 180 million people worldwide according to the WHO.[2] Approximately 90% of these cases are type 2 diabetes,[2] which is the result of underlying insulin resistance and a progressive insulin secretory defect.[1] Patients with type 2 diabetes are often obese, with obesity itself causing some degree of insulin resistance.[1]

According to the current consensus statement, the goal of therapy in these patients is to achieve and maintain glycaemic control (i.e. glycosylated haemoglobin [HbA_{1c}] levels of <7%), thereby reducing the long-term risk of microvascular, macrovascular and neuropathic complications.[3] To achieve this goal, lifestyle modifications and treatment with one or more antihyperglycaemic agents, such as metformin, insulin or a sulfonylurea, is recommended.[3] However, these therapies have several limitations, including less than optimal control of postprandial hyperglycaemia, increased risk of hypoglycaemia and weight gain.[4] Moreover, glycaemic control declines over time in most patients despite intensive treatment with several antihyperglycaemic agents,[5] which reflects ongoing deterioration of β-cell function and pancreatic islet health.[6]

Over the past few years, new antihyperglycaemic agents have been developed targeting the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) that stimulate insulin output from pancreatic β-cells in a glucose-dependent manner.[7,8] Dipeptidyl peptidase (DPP)-4 inhibitors are a class of drugs that prevent the inactivation of GLP-1 and GIP by inhibiting the enzyme DPP-4 (expressed in many tissues including liver, kidney, lung and small intestine), thereby enhancing and prolonging the activity of the incretin hormones and attenuating postprandial glucose excursions.[4,7,8]

Saxagliptin (Onglyza™) is one such DPP-4 inhibitor that has recently been approved for use in patients with type 2 diabetes.[9] This article reviews the pharmacological properties, clinical efficacy and tolerability of oral saxagliptin in adult patients with type 2 diabetes. Medical literature on the use of saxagliptin in type 2 diabetes was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference list of published articles.

1. Pharmacodynamic Profile

This section provides a summary of the pharmacodynamic properties of saxagliptin, which were evaluated in four randomized, double-blind, placebo-controlled studies in patients with type 2 diabetes (n = 40[10] or 36[11]) or healthy volunteers (n = 50[10] or 40[12]) [available only as abstracts and/or posters]. Patients (aged 18–70[10] or 43–69[11] years) had a disease duration of <10 years[10] or baseline HbA_{1c} levels of 6.5–9.5%[10] or 5.9–8.1%.[11] Also discussed are data presented in an abstract by Wang et al.[13] and from the US prescribing information.[9]

- Saxagliptin is a potent, selective, reversible inhibitor of the DPP-4 enzyme.[13] It is 10-fold more potent than vildagliptin or sitagliptin, with an inhibitory constant (K_i) of 1.3 nmol/L for DPP-4 at 37°C (K_i = 13 and 18 nmol/L for vildagliptin and sitagliptin).[13] The active metabolite of saxagliptin, M2 (BMS-510849), is 2-fold less potent than saxagliptin, with a K_i of 2.6 nmol/L.[13]
- Saxagliptin dosages of 2.5–400 mg once daily for 14 days inhibited DPP-4 enzymatic activity in a dose-dependant manner in patients with type 2 diabetes and in healthy volunteers, with the inhibition profile at these dosages being consistent with once-daily administration.[10] Plasma DPP-4 enzymatic activity 24 hours after the administration of a single dose of saxagliptin 2.5 or 400 mg was inhibited by 50% and

79% compared with predose values; maximal enzymatic inhibition was achieved with dosages ≥150 mg/day.

- Saxagliptin and M2 are more selective for the inhibition of DPP-4 than DPP-8 (400- and 950-fold) or DPP-9 (75- and 160-fold) enzymes or a large panel of other proteases (>4000-fold).[13] Both the parent drug and the active metabolite dissociate slowly from the DPP-4 enzyme (dissociation half-life of 50 and 23 minutes at 37°C), but not from other enzymes tested, including DPP-8 and DPP-9. It has been suggested that once bound, saxagliptin and its active metabolite would continue to inhibit DPP-4 during rapid increases of substrate *in vivo*, owing to their slow dissociation from the enzyme.[13]
- Saxagliptin 2.5–400 mg once daily increased postprandial plasma intact GLP-1 levels by 1.5- to 3-fold after breakfast, lunch and dinner on day 13 (in patients with type 2 diabetes) or day 14 (in healthy volunteers) compared with placebo, with no apparent dose-relationship being observed.[10]
- Saxagliptin therapy improved ($p < 0.05$) pancreatic β-cell function in fasting and postprandial states (as indicated by an increase from baseline in total insulin secretion), and decreased postprandial glucagon levels in patients with type 2 diabetes during 12 weeks of therapy,[11] thereby lowering fasting glucose concentrations and reducing glucose excursions after an oral glucose load or a meal.[9]
- Saxagliptin as monotherapy or in combination with other antihyperglycaemic agents improved glycaemic control and generally improved β-cell function in large clinical trials of up to 24 weeks' duration in patients with type 2 diabetes (section 3). However, saxagliptin therapy did not affect insulin resistance or sensitivity in these trials.
- Saxagliptin (2.5–400 mg/day for ≤14 days) or its active metabolite did not prolong the corrected QT interval in patients with type 2 diabetes or healthy volunteers.[10,12]

2. Pharmacokinetic Profile

This section focuses on the pharmacokinetic properties of oral saxagliptin, which have been evaluated in patients with type 2 diabetes[10] (see section 1 for patient characteristics) and in healthy volunteers.[14] Also discussed are studies that evaluated the pharmacokinetics of saxagliptin in patients with renal[15] or hepatic impairment,[16] and studies in healthy volunteers that assessed the effect of age,[17] gender[17] or coadministration of other drugs[18-25] on the pharmacokinetics of saxagliptin. These data are supplemented with data available from the US prescribing information.[9]

- The pharmacokinetics of saxagliptin (2.5–400 mg/day for 14 days) and its major metabolite M2 were generally similar in patients with type 2 diabetes and healthy volunteers.[10] Oral saxagliptin 2.5–50 mg is rapidly absorbed after single dose administration in healthy volunteers and has a predicted human oral bioavailability of 67%.[14]
- Dose proportional increases in the peak plasma concentrations (C_{max}) and the area under the plasma concentration-time curves (AUC) were observed with saxagliptin dosages of 2.5–400 mg.[9] After a single oral dose of saxagliptin 5 mg, the mean plasma C_{max} of saxagliptin was 24 ng/mL and of M2 was 47 ng/mL, which were reached in a median time of 2 and 4 hours (t_{max}); the mean plasma AUCs of saxagliptin and M2 were 78 and 214 ng • h/mL. The average variability for AUC and C_{max} of saxagliptin and M2 was <25%.[9]
- Saxagliptin t_{max} increased by ≈20 minutes and the AUC increased by 27% when the drug was administered with a high-fat meal compared with fasting conditions; however, saxagliptin may be administered without regard for food.[9]
- Systemic exposures to saxagliptin and M2 were dose-dependent and were generally similar on days 1 and 14, suggesting that the drug did not accumulate or inhibit its own metabolism after multiple dose administration.[10] Systemic exposure to M2 on a molar basis was 1.7- to 6.9-fold higher than, and independent of the dosage of, saxagliptin (2.5–400 mg/day for 14 days) in patients with type 2 diabetes or healthy volunteers.[10]
- Saxagliptin and M2 are extensively distributed in extravascular tissues according to studies in rodents, with the lowest concentrations of these agents being observed in the brain and the highest in the intestinal

tissues and the kidneys.[14] As the *in vitro* protein binding of saxagliptin in human serum is negligible, the pharmacokinetics of the drug are not expected to alter with changes in blood protein levels in disease states such as renal or hepatic impairment.[9]

- Saxagliptin is metabolized largely by cytochrome P450 (CYP) 3A4 and CYP3A5 isoenzymes[9] to its major metabolite M2 and other minor metabolites.[14] The major metabolic pathway is the hydroxylation of saxagliptin.[14]
- Saxagliptin is eliminated via both hepatic and renal routes.[9,14] After a single 50 mg dose of ^{14}C-labelled saxagliptin, 24%, 36% and 75% of the dose was excreted as saxagliptin, M2 and total radioactivity, respectively, in the urine; 22% of the dose was recovered in the faeces in bile and/or as unabsorbed drug (study population details not reported).[9] The renal clearance of saxagliptin (mean ≈230 mL/min) was greater than the estimated glomerular filtration rate (mean ≈120 mL/min), which suggests some active renal excretion of the drug.[9]
- The mean plasma terminal elimination half-lives of saxagliptin and M2 were 2.5 and 3.1 hours after a single dose of saxagliptin 5 mg in healthy volunteers;[9] the apparent oral clearance of saxagliptin 1 mg/kg was 17.4 mL/min/kg and the apparent oral renal clearance was 2.5 mL/min/kg.[14]

Special Populations

- In patients with mild renal impairment (creatinine clearance [CL_{CR}] 50–80 mL/min [3–4.8 L/h]), the AUC from time zero to infinity (AUC_∞) of saxagliptin and M2 were 1.2- and 1.7-fold higher than in patients with normal renal function (CL_{CR} >80 mL/min [>4.8 L/h]); however, this increase was not considered clinically relevant and no dosage adjustment is recommended (section 5).[9,15]
- In patients with moderate (CL_{CR} 30–50 mL/min [1.8–3.0 L/h]) or severe (CL_{CR} <30 mL/min [<1.8 L/h]) renal impairment, the AUC_∞ of saxagliptin and M2 were up to 2.1- and 4.5-fold higher than in patients with normal renal function; therefore, dosage reduction is recommended in these patients (section 5).[9,15] In eight patients with end-stage renal disease, 23% of the saxagliptin dose was eliminated during a 4-hour haemodialysis session.[9,15]
- No dosage adjustments are required in patients with hepatic impairment (Child-Pugh classes A, B or C), as, overall, the pharmacokinetics of saxagliptin differed by less than 2-fold between individuals with mild to severe hepatic impairment and healthy volunteers, and were not considered clinically relevant.[9,16]
- The pharmacokinetics of saxagliptin are generally not affected by sex or age in healthy volunteers and no dosage adjustments are considered necessary.[9,17] However, females had approximately 25% higher exposure to the active metabolite of saxagliptin than males, and in elderly (aged 65–80 years) individuals, the geometric mean C_{max} and AUC of saxagliptin were 23% and 59% higher, and the apparent volume of distribution and metabolic renal clearances of saxagliptin were lower than in young (aged 18–40 years) individuals.[9,17]

Drug Interactions

- As the metabolism of saxagliptin is mediated by CYP3A4 and CYP3A5 isoenzymes, strong inhibitors and inducers of these isoenzymes will alter the pharmacokinetics of saxagliptin.[9] Saxagliptin and M2 did not inhibit CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A4, or induce CYP1A2, 2B6, 2C9 or 3A4 isoenzymes *in vitro*. Consequently, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Saxagliptin is a P-glycoprotein (P-gp) substrate, but does not inhibit or induce P-gp to a significant extent *in vitro*.[9]
- Coadministration of saxagliptin with oral magnesium and aluminium hydroxide plus simethicone, famotidine (administered 3 hours prior to saxagliptin) or omeprazole generally did not alter the pharmacokinetics of saxagliptin or its active metabolite.[18] Similarly, coadministration of saxagliptin with glyburide (glibenclamide),[22] metformin,[23] pioglitazone,[24] digoxin[19] or simvastatin[25] generally did not alter the pharmacokinetics of these drugs.[9] Consequently, no dosage adjustments of

saxagliptin or the coadministered drugs are required.[18,19,22-25]

- Coadministration of a single dose of saxagliptin 10 mg with diltiazem (360 mg long-acting formulation at steady state; a moderate CYP3A4/5 inhibitor) increased the C_{max} and AUC of saxagliptin by 63% and 2.1-fold, and decreased the C_{max} and AUC of M2 by 44% and 36%.[9,20] Similar increases in plasma concentrations of saxagliptin are expected when coadministered with other moderate CYP3A4/5 inhibitors, such as amprenavir, fluconazole and erythromycin; however, dosage adjustment of saxagliptin is not recommended.[9]
- Coadministration of a single dose of saxagliptin 5 mg with rifampin (rifampicin) [600 mg once daily at steady state; a CYP3A4/5 inducer] significantly decreased the C_{max} and AUC of saxagliptin by 53% and 76%, and increased the C_{max} of M2 by 39%; there was no significant change in the AUC of M2.[9] However, dosage adjustment of saxagliptin is not recommended.[26]
- Coadministration of a single dose of saxagliptin 100 mg with ketoconazole (200 mg every 12 hours at steady state) [a strong inhibitor of CYP3A4/5 and P-gp] significantly increased the C_{max} and AUC of saxagliptin by 62% and 2.5-fold, and decreased the C_{max} and AUC of M2 by 95% and 91%.[9,21] Similar significant increases in plasma concentrations of saxagliptin are expected with other strong CYP3A4/5 inhibitors, such as atazanavir, ritonavir and clarithromycin; therefore, dosage adjustment of saxagliptin is recommended (section 5).[9]

3. Therapeutic Efficacy

The therapeutic efficacy of saxagliptin as monotherapy[9,26,27] or in combination with other oral antihyperglycaemics[28-31] has been evaluated in several trials of up to 24 weeks' duration and in a long-term (102 weeks' therapy) extension trial[32] in treatment-naive[26-28] or -experienced[29-31] patients with type 2 diabetes. Two of these studies are available only as abstract presentations,[31,32] whereas data for a third study (038) are available from the US prescribing information.[9]

Apart from the dose-ranging study that assessed saxagliptin dosages of 2.5–100 mg once daily,[27] patients participating in these trials received saxagliptin 2.5,[26,29-31] 5[26,28-31] or 10[26,28,29] mg once daily. Discussion in this section will focus on data pertaining to the approved dosages of saxagliptin 2.5 and 5 mg/day; the 10 mg dosage of saxagliptin did not provide greater efficacy than the 5 mg dosage[9] and these data are not discussed further.

Where reported, eligible patients in these studies were aged 21–70[27] or 18–77 years,[26,28-31] had HbA_{1c} levels of 7–12%,[26-31] a body mass index ≤37[27] or ≤40[26,28-30] kg/m^2 and a screening fasting or random C-peptide >0.5[27] or ≥1.0 ng/mL.[26,28-30] The mean duration of disease, where reported, was 1.4–2.0,[28] 2.3–3.1,[26] 5.2,[31] 6.5[29] or 6.8–7.1[30] years. In one study, patients with a median disease duration of 0.7–1.8 years received lower dosages of saxagliptin, whereas those with a disease duration of 0.3–0.5 years received a higher dosage of saxagliptin.[27]

The exclusion criteria, where reported, included a diagnosis of type 1 diabetes,[27] symptoms of poorly controlled diabetes or a history of ketoacidosis or hyperosmolar coma,[26-30] use of any other antihyperglycaemic medication 8 weeks prior to,[29] or insulin 1 year prior to, study entry,[28-30] occurrence of congestive heart failure (New York Heart association stage III/IV),[26-30] and/or known left ventricular ejection fraction ≤40%,[26,28-30] or recent (within 6 months[26,28-30]) cardiovascular illness.[26-30]

In most trials, the primary efficacy outcome was the change from baseline in HbA_{1c} levels.[26-30] Other efficacy endpoints included the proportion of patients achieving target HbA_{1c} goals, and changes from baseline in other measures of glycaemic control or β-cell function.

Where reported, demographic and disease activity/health status of patients at baseline was generally similar within each individual trial.[26-31] Where specified, analyses were based on data from all randomized patients who recieved at least one dose of medication[26,28-30] or the modified intent-to-treat (mITT) [all patients who received ≥6 weeks' active treatment and at least one HbA_{1c} assessment after

randomization] populations[27] with the last observation carried forward (LOCF),[26-31] and data were evaluated using analysis of co-variance.[26-31]

Monotherapy

The efficacy of saxagliptin monotherapy was assessed in treatment-naive patients with type 2 diabetes in three randomized, double-blind, placebo-controlled trials.[9,26,27] Treatment-naive patients were defined as those who had never received antihyperglycaemic treatment or had received treatment for a total of no more than 6 months since diagnosis and for no more than 3 consecutive days or for a total of 7 non-consecutive days 8 weeks prior to enrolment.[26,27]

One study was a dose-ranging study in which patients received saxagliptin 2.5, 5, 10, 20 or 40 mg once daily or placebo for 12 weeks (mITT LOCF, n = 338) or saxagliptin 100 mg once daily or placebo for 6 weeks (mITT LOCF, n = 85).[27] In the second trial (011), patients with HbA_{1c} levels of 7–10% (n = 401) received double-blind saxagliptin 2.5, 5 or 10 mg once daily or placebo, while those with HbA_{1c} levels of >10 to ≤12% (n = 66) received open-label saxagliptin 10 mg once daily, for 24 weeks.[26] In a third study (038) [n = 365], which was undertaken to assess various dosing regimens of saxagliptin, patients received saxagliptin 2.5 or 5 mg every morning, 2.5 mg every morning (which may be titrated to 5 mg) or 5 mg every evening or placebo for 24 weeks.[9] All three studies had a 2-week diet, exercise and placebo lead-in period prior to randomization.[9,26,27] Patients who did not achieve specific glycaemic goals during the study were eligible for the addition of metformin as rescue therapy.[9,26,27]

- Saxagliptin was shown to be effective in terms of improving glycaemic control in a 12-week, dose-ranging study in treatment-naive patients with type 2 diabetes.[27] HbA_{1c} levels were reduced from baseline (mean 7.9%) with saxagliptin 2.5–40 mg/day after 12 weeks (mean change of –0.72% to –0.90% vs –0.27%; $p < 0.007$) or with saxagliptin 100 mg/day after 6 weeks (–1.09% vs –0.36%) of treatment compared with placebo, with no significant dose-response relationship being observed.[27]
- Improvements in HbA_{1c} levels were also observed in the two 24-week trials.[9,27] Significant ($p < 0.0001$) reductions from baseline (mean 7.8–7.9%) in HbA_{1c} levels were observed with saxagliptin 2.5 or 5 mg/day relative to placebo at 24 weeks in study 011 (adjusted mean change of –0.43% and –0.46% vs +0.19%).[26] Significant reductions from baseline in HbA_{1c} levels were also seen with saxagliptin 2.5 mg/day (every morning) or 5 mg/day (every morning or evening) in study 038 (mean placebo-corrected reductions of 0.4%, 0.4% and 0.3%; p-value not reported).[9]
- Reductions from baseline in HbA_{1c} levels were evident as early as week 4, with numerically greater reductions in HbA_{1c} levels being observed in patients with higher baseline levels.[26,27]
- In patients receiving saxagliptin 2.5 or 5 mg or placebo, target HbA_{1c} levels of <7% were achieved by 35% and 38% versus 24% of patients ($p = 0.044$ for saxagliptin 5 mg vs placebo).[26]
- Fasting plasma glucose (FPG) and 2-hour postprandial glucose (PPG; assessed during an oral glucose tolerance test [OGTT]) levels also reduced ($p < 0.005$) from baseline after treatment with saxagliptin, with decreases in FPG being apparent as early as week 2.[26] The adjusted mean changes from baseline in FPG levels were –15 and –9 versus +6 mg/dL (baseline values 172–178 mg/dL), and in PPG levels were –45 and –43 versus –6 mg/dL, with saxagliptin 2.5 or 5 mg/day or placebo.[26]
- Postprandial insulin AUCs increased from baseline by 26% and 24% (vs 3% with placebo), and postprandial C-peptide AUCs increased from baseline by 25% and 43% (vs 7%) with saxagliptin 2.5 or 5 mg/day after 24 weeks of treatment.[26]
- In addition, β-cell function as assessed by homeostatic model assessment (HOMA)-2β improved from baseline with saxagliptin 2.5 and 5 mg/day (adjusted mean change of 15% and 13% vs 8% with placebo).[26] However, saxagliptin therapy had no clear effect on insulin resistance (as assessed by the HOMA-IR) or insulin sensitivity (as assessed by the Matsuda index).[26]

Combination Therapy

In patients with type 2 diabetes, the efficacy of saxagliptin in combination with metformin as initial therapy in treatment-naive patients[28] and as add-on therapy to metformin,[29] a sulfonylurea (glyburide)[30] or a thiazolidinedione (pioglitazone or rosiglitazone)[31] in patients who had inadequate glycaemic control despite existing antihyperglycaemic therapy[29-31] was evaluated in four 24-week, randomized, double-blind, placebo-[29-31] or active-comparotor-[28] controlled, multicentre trials[28-31] and a double-blind, extension (102 weeks' therapy)[32] of one study.[29] Some data are also available from the US prescribing information.[9]

Treatment-naive patients (n = 1306) were defined as those who had never received antihyperglycaemic treatment or had received treatment for a total of <1 month since diagnosis and for no more than 3 consecutive days or for a total of 7 nonconsecutive days 8 weeks prior to screening.[28] After a 1-week diet, exercise and placebo lead-in period, patients received saxagliptin 5 or 10 mg once daily in combination with immediate-release (IR) metformin 500–2000 mg/day, saxagliptin 10 mg once daily or metformin 500–2000 mg/day for 24 weeks. Metformin IR was initiated at 500 mg/day and was uptitrated based on FPG levels (>110 mg/dL) in 500 mg/day increments to a maximum of 2000 mg/day during weeks 1–5 of therapy.[28]

Treatment-experienced patients (n = 565,[31] 743[29] or 768[30]) had inadequate glycaemic control with stable dosages of metformin for ≥8 weeks,[29] a submaximal dosage of glyburide for ≥2 months,[30] or stable pioglitazone or rosiglitazone for ≥12 weeks prior to screening.[31] In two studies,[29,31] following a 2-week diet, exercise and placebo lead-in period (during which patients continued to receive ongoing antihyperglycaemic therapy), patients received 24 weeks' treatment with saxagliptin 2.5,[29,31] 5[29,31] or 10[29] mg once daily in combination with ongoing metformin 1500–2500 mg/day,[29] or pioglitazone 30 or 45 mg/day or rosiglitazone 4 or 8 mg/day,[31] or received the ongoing antihyperglycaemic therapy alone. In the third study,[30] patients received a submaximal dosage of glyburide 7.5 mg/day during a 4-week diet, exercise and placebo lead-in period, followed by 24 weeks' treatment with saxagliptin 2.5 or 5 mg once daily in combination with ongoing glyburide 7.5 mg/day, or an initial total daily dose of glyburide 10 mg once daily (2.5 mg/day in combination with ongoing 7.5 mg/day; the uptitrated glyburide group). Glyburide dosage could be reduced once during the study in the event of hypoglycaemia. In the uptitrated group, further increase in glyburide dosage to a maximum of 15 mg/day was permitted, provided the dosage had not been reduced previously because of hypoglycaemia (≈92% of patients in this group had the dosage uptitrated to 15 mg/day by study end).[30] In the long-term extension study, patients continued to receive double-blind saxagliptin 2.5, 5 or 10 mg/day in combination with ongoing metformin 1500–2500 mg/day therapy.[32]

In all trials, rescue therapy with pioglitazone[28,29] or metformin,[9,30] in addition to ongoing study medication, was permitted if specific glycaemic goals were not met.

In Treatment-Naive Patients

- In treatment-naive patients with type 2 diabetes and inadequate glycaemic control, saxagliptin in combination with metformin IR as initial therapy significantly improved glycaemic control relative to saxagliptin or metformin monotherapy.[28] After 24 weeks, HbA_{1c} levels were significantly ($p < 0.0001$ vs both comparators) reduced from baseline (9.4–9.6%) with saxagliptin 5 mg/day plus metformin IR combination therapy compared with saxagliptin 10 mg/day or metformin IR monotherapy (adjusted mean change from baseline −2.5% vs −1.7% and −2.0%).

- Furthermore, more ($p < 0.0001$ vs both comparators) patients receiving saxagliptin 5 mg/day plus metformin IR combination therapy than saxagliptin 10 mg/day or metformin IR monotherapy achieved target HbA_{1c} levels of <7% at week 24 (60% vs 32% and 41% of patients).[28]

- In addition, significant ($p < 0.001$ vs both comparators) reductions from baseline to week 24 in FPG (adjusted mean changes of −60 vs −31 and −47 mg/dL; baseline values 198–201 mg/dL) and 2-hour

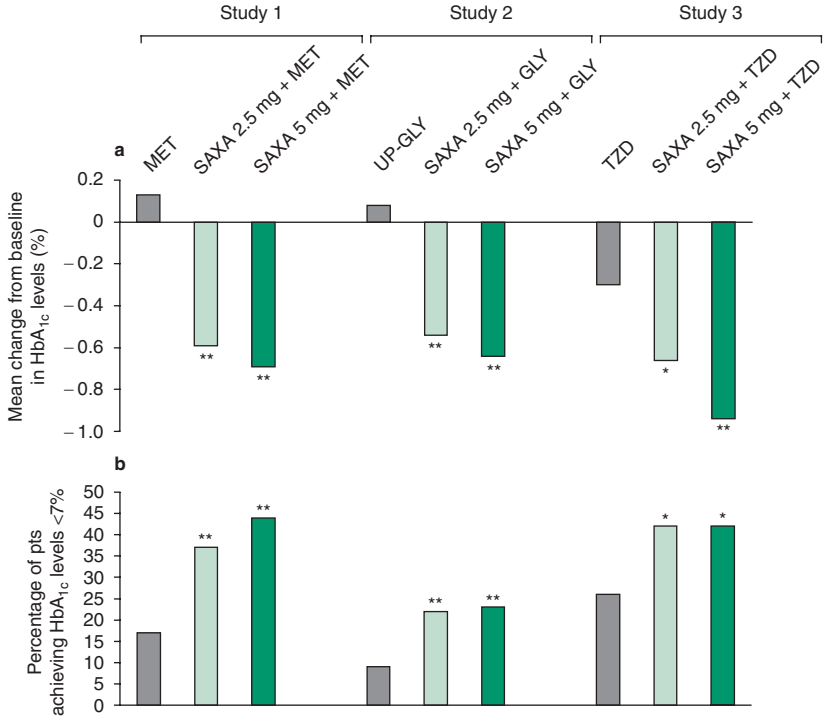


Fig. 1. Efficacy of oral saxagliptin (SAXA) 2.5 or 5 mg in combination with metformin (MET), glyburide (GLY) or a thiazolidinedione (TZD; rosiglitazone or pioglitazone) in patients (pts) with type 2 diabetes who had inadequate glycaemic control with existing therapy with these agents. (**a**) Adjusted mean change from baseline in glycosylated haemoglobin (HbA_{1c}) levels and (**b**) the percentage of pts achieving HbA_{1c} levels <7%. Pts received SAXA 2.5 or 5 mg/day plus MET or MET (study 1; n = 192, 191 and 179),[29] SAXA 2.5 or 5 mg/day plus GLY or uptitrated GLY (UP-GLY) [study 2; n = 246, 250 and 264][9,30] or SAXA 2.5 or 5 mg/day plus TZD or TZD (study 3; n = 192, 183 and 180)[9,31] in three 24-week, randomized, double-blind, placebo-controlled, multicentre trials (see section 3 for study design details). Baseline HbA_{1c} levels in studies 1, 2 and 3 were mean 8%,[29] 8.2–8.4%[9] or 8.4–8.5%.[30] * $p < 0.005$, ** $p \leq 0.0001$ vs monotherapy.

PPG (−138 vs −106 and −97 mg/dL; assessed during an OGTT) levels and in the exposure to glucose (as assessed by the change from baseline in the PPG-AUC from 0 to 3 hours) were observed with saxagliptin 5 mg plus metformin IR combination therapy compared with saxagliptin 10 mg/day or metformin IR monotherapy.[28]

- A significant ($p < 0.001$ vs both comparators) improvement in β-cell function (as assessed by HOMA-2β) was also observed with saxagliptin 5 mg plus metformin IR combination therapy compared with saxagliptin 10 mg/day or metformin IR monotherapy.[28]

In Treatment-Experienced Patients

- The addition of saxagliptin therapy to ongoing metformin,[29] glyburide[30] or thiazolidinedione[31] therapy improved glycaemic control in patients with type 2 diabetes who had inadequate glycaemic control with existing therapy.
- In these patients, 24 weeks of add-on treatment with saxagliptin 2.5 or 5 mg/day significantly ($p < 0.001$) reduced HbA_{1c} levels from baseline relative to ongoing metformin,[29] glyburide[30] or thiazolidinedione[31] therapy alone (figure 1). The reductions in HbA_{1c} levels were evident from week 4 and were sustained until week 24 of therapy.[29,30] A significant ($p < 0.05$) correlation between treatment-effect and baseline HbA_{1c} levels was observed in one study,[29] but not in another study.[30]
- In addition, after 24 weeks, more ($p < 0.005$) patients receiving saxagliptin add-on treatment achieved target HbA_{1c} levels of <7% than those receiving ongoing metformin,[29] glyburide[30] or

thiazolidinedione[31] therapy alone (figure 1). At 24 weeks, significant ($p < 0.05$) reductions from baseline in FPG levels were also observed with saxagliptin add-on therapy relative to metformin,[29] glyburide[30] or thiazolidinedione[31] therapy alone.

- Furthermore, the addition of saxagliptin to ongoing metformin,[29] glyburide[30] or thiazolidinedione[31] therapy reduced ($p \leq 0.0001$ vs comparators) PPG levels from baseline, as assessed by 2-hour PPG levels (during an OGTT) and 3-hour PPG AUCs.[29-31] In addition, postprandial glucagon levels (as assessed by AUC) decreased from baseline, and postprandial insulin release (as assessed by insulin and C-peptide AUCs) increased from baseline, following the addition of saxagliptin to ongoing metformin or glyburide treatment ($p < 0.05$ vs metformin for all comparisons; statistical data not available for comparisons with glyburide).[29,30]
- In two studies, the change from baseline to week 24 in β-cell function (as assessed by HOMA-2β) did not differ significantly between patients receiving saxagliptin as add-on treatment relative to those receiving metformin or glyburide alone;[29,30] insulin resistance (as assessed by the HOMA-IR) and sensitivity (as assessed by the Matsuda index) were not significantly affected by saxagliptin plus metformin or glyburide therapy.[29,30] However, a significant ($p < 0.05$) improvement in β-cell function (as assessed by HOMA-2β) from baseline to week 24 was observed when saxagliptin was added to ongoing thiazolidinedione therapy relative to thiazolidinedione monotherapy at 24 weeks.[31]
- The improvement in glycaemic control observed during 24 weeks of treatment with saxagliptin as add-on therapy to metformin[29] was sustained in the long-term.[32] After 102 weeks of treatment, the placebo-subtracted changes from baseline in HbA_{1c} levels in patients receiving saxagliptin 2.5 or 5 mg/day add-on therapy versus metformin therapy alone were –0.62% (95% CI –0.84, –0.40) and –0.72% (95% CI –0.94, –0.50).[32] During this period, 58% and 52% of saxagliptin 2.5 or 5 mg/day plus metformin combination therapy recipients compared with 72% of metformin monotherapy recipients discontinued treatment or received rescue therapy for lack of glycaemic control.[32]

4. Tolerability

This section focuses on tolerability data from the clinical trials discussed in section 3, with the focus being on data pertaining to the approved dosages of saxagliptin.[26-32] Also discussed are pooled tolerability data (available from the US prescribing information)[9] from five 24-week (monotherapy [011[26] and 038[9]] or add-on therapy[29-31]) trials, and pooled incidences of hypoglycaemic events (symptoms suggestive of low blood glucose levels, e.g. sweating and shakiness),[33] confirmed hypoglycaemic events (fingerstick blood glucose ≤50 mg/dL),[33] major adverse cardiovascular events (stroke, myocardial infarction or cardiovascular death)[34] and acute cardiovascular events (acute clinically significant events, including cardiac revascularization procedures)[34] from six ($n = 4148$)[33] or eight ($n = 4607$)[34] randomized, double-blind clinical trials [available as abstract presentations].

- Saxagliptin was generally well tolerated as monotherapy[9,26,27] or in combination[28-31] with other antihyperglycaemic agents in treatment-naive[9,26-28] or -experienced[29-31] patients with type 2 diabetes in clinical trials of up to 24 weeks and in a long-term extension trial (102 weeks' therapy).[32]

General Profile

- Most adverse events in patients receiving saxagliptin therapy were of mild or moderate intensity,[26-30] and the incidence of adverse events generally did not appear to be dependent on the dose of saxagliptin.[26,27,29,30]
- The incidence of treatment-emergent adverse events in saxagliptin 2.5 or 5 mg/day (monotherapy or add-on therapy) recipients was generally similar to that in patients receiving other oral antihyperglycaemic agents or placebo in a pooled analysis of five, 24-week trials (72% and 72% vs 71%).[9] Treatment-emergent adverse events occurred in 55% of treatment-naive patients receiving saxagliptin plus metformin as initial therapy for 24 weeks (vs 59% of metformin recipients).[28] Less than 4% of

saxagliptin recipients discontinued therapy because of these adverse events.[9,28]

- Treatment-related adverse events occurred in 10–21% of saxagliptin 2.5 or 5 mg/day monotherapy[26] or combination (initial[28] or add-on[30]) therapy recipients compared with 11–18% of patients receiving other oral antihyperglycaemic agents or placebo.
- Treatment-emergent (<6%)[26-30] and treatment-related (<1%; two patients)[26,28,30] serious adverse events occurred in few patients receiving saxagliptin 2.5 or 5 mg/day as monotherapy[26,27] or as combination therapy (initial[28] or add-on therapy to metformin[29] or glyburide[30]). There were no deaths in saxagliptin recipients.[26-30]
- The most common (incidence ≥5%) treatment-emergent adverse events that occurred more frequently in saxagliptin 2.5 or 5 mg/day (monotherapy or add-on therapy) recipients than in patients receiving other oral antihyperglycaemic agents or placebo in the pooled analysis were upper respiratory tract infection (0% and 8% vs 8%), urinary tract infection (0% and 7% vs 6%) and headache (7% and 7% vs 6%).
- In patients receiving initial saxagliptin combination therapy, the most frequent (incidence ≥5%) treatment-emergent adverse events that occurred more frequently in patients receiving saxagliptin 5 mg/day plus metformin than in those receiving metformin alone were headache (8% vs 5%) and nasophyaryngitis (7% vs 4%).[28]
- Lymphopenia (0.1% and 0.5% with saxagliptin 2.5 or 5 mg/day vs 0% with comparators or placebo), rash (0.2% and 0.3% vs 0.3%), increase in blood creatinine (0.3% and 0% vs 0%) or blood creatine phosphokinase (0.1% and 0.2% vs 0%) levels were the most common (occurring in at least two patients receiving saxagliptin treatment) adverse events associated with discontinuation of therapy in the pooled analysis.[9]
- The incidence of hypersensitivity-related adverse events (e.g. urticaria and facial oedema) during 24 weeks of treatment with saxagliptin 2.5 or 5 mg/day was 1.5% and 1.5% (vs 0.4% in patients receiving comparators or placebo) in the pooled analysis.[9] None of the adverse events in saxagliptin recipients required hospitalization or were reported as life-threatening; however, one patient discontinued therapy due to generalized urticaria and facial oedema.[9]
- The incidence of peripheral oedema with saxagliptin 2.5 or 5 mg/day as monotherapy was 3.6% and 2% (vs 3% in placebo recipients), as add-on therapy to metformin was 2.1% and 2.1% (vs 2.2% in metformin recipients), as add-on therapy to glyburide was 2.4% and 1.2% (vs 2.2% in glyburide recipients) and as add-on therapy to a thiazolidinedione was 3.1% and 8.1% (vs 4.3% in thiazolidinedione recipients) during 24 weeks of treatment.[9]
- Saxagliptin monotherapy[26,27] or combination therapy with metformin generally did not alter body weight[28,29] during 24 weeks' therapy. However, a significant ($p < 0.05$) increase in body weight was observed in patients receiving saxagliptin 2.5 or 5 mg/day plus glyburide relative to those receiving glyburide therapy alone (0.7 and 0.8 vs 0.3 kg).[30]
- No clinically significant changes in vital signs or platelet counts have been observed in saxagliptin recipients.[9] Although dose-related decreases in lymphocyte counts have been observed with saxagliptin treatment, these were not associated with clinically relevant adverse events, and their clinical significance is unknown.[9]

Hypoglycaemia

- During 24 weeks of treatment, the incidence of hypoglycaemia in saxagliptin recipients was generally similar to that in patients receiving placebo or other oral antihyperglycaemic therapy.[33]
- Hypoglycaemic events were reported in 4% and 6% of patients receiving saxagliptin 2.5 or 5 mg/day as monotherapy (vs 4% of placebo recipients), and in 9% and 8% of patients receiving these dosages as add-on treatment to other oral antihyperglycaemics (vs 7% of patients receiving metformin, glyburide or a thiazolidinedione) in pooled data[33] from two monotherapy[9,26] and three[29-31] add-on therapy trials. In treatment-naive patients, the incidence of hypoglycaemia was 3% in patients receiving initial

therapy with saxagliptin plus metformin compared with 4% in those receiving metformin alone.[28]

Cardiovascular Events

- Saxagliptin as monotherapy or in combination with other oral antihyperglycaemic agents was not associated with an increased risk of cardiovascular events, according to pooled data from eight clinical trials.[34] In these trials, the overall exposure to saxagliptin was 3758 patient-years and to the comparators (placebo, metformin or glyburide) was 1293 patient-years; 81% of patients had at least one cardiovascular risk factor in addition to diabetes (including hypertension [52%], dyslipidaemia [44%] or history of smoking [39%]) and 12% had prior history of cardiovascular disease.[34]
- In this analysis, acute cardiovascular events occurred in 1.1% of patients in the saxagliptin group compared with 1.8% of patients in the comparator group (hazard ratio [HR] 0.59 [95% CI 0.35, 1.0]; n = 3356 and 1251); few patients receiving saxagliptin had major adverse cardiovascular events (0.7% vs 1.4% in the comparator group; HR 0.44 [95% CI 0.24, 0.82]).[34] The incidences of all-cause death (0.3% vs 1.0% comparators) and cardiovascular death (0.2% vs 0.8%) were also low in patients receiving saxagliptin therapy.[34]

5. Dosage and Administration

In patients with type 2 diabetes, the recommended dosage of saxagliptin is 2.5 or 5 mg once daily administered orally without regard for food.[9]

In patients with moderate or severe renal impairment (CL_{CR} ≤50 mL/min [≤3 L/h]), and in patients with end-stage renal disease requiring haemodialysis, the dosage of saxagliptin should be adjusted to 2.5 mg/day to achieve plasma exposures of saxagliptin and M2 that are similar to those in patients with normal renal function; no dosage adjustment is required in patients with mild renal impairment.[9] Saxagliptin dosage should also be adjusted to 2.5 mg/day when the drug is coadministered with strong CYP3A4/5 inhibitors (e.g. ketoconazole, atazanavir or clarithromycin) [see also section 2]. Saxagliptin should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis and the drug has not been studied in combination with insulin.[9]

Local prescribing information should be consulted for comprehensive dosage and administration guidelines, contraindications, precautions and drug interactions.

6. Saxagliptin: Current Status

In the US, saxagliptin is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes. Oral saxagliptin as monotherapy or in combination with other antihyperglycaemic agents improved glycaemic control and was generally well tolerated in several large, well designed trials of up to 24 weeks' duration and in a long-term extension study in adult patients with type 2 diabetes.

Acknowledgements and Disclosures

The manuscript was reviewed by: ***R.K. Campbell***, College of Pharmacy, Washington State University, Pullman, Washington, USA; ***J. Eriksson***, Department of General Practice and Primary Health Care, University of Helsinki, and Unit of General Practice, Helsinki University Central Hospital, Helsinki, Finland.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2009 Jan; 32 Suppl. 1: S62-7
2. World Health Organization. Diabetes: fact sheet (no. 312) [online]. Available from URL: http://www.who.int/mediacentre/factsheets/fs312/en/ [Accessed 2009 Jun 24]
3. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009 Jan; 32 (1): 193-203
4. Rosenstock J, Zinman B. Dipeptidyl peptidase-4 inhibitors and the management of type 2 diabetes mellitus. Curr Opin Endocrinol Diabetes Obes 2007 Apr; 14 (2): 98-107
5. Turner RC, Cull CA, Frighi V, et al. 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 Jun 2; 281 (21): 2005-12

6. Campbell RK. Rationale for dipeptidyl peptidase 4 inhibitors: a new class of oral agents for the treatment of type 2 diabetes mellitus. Ann Pharmacother 2007 Jan; 41 (1): 51-60
7. Ahren B. Dipeptidyl peptidase-4 inhibitors: clinical data and clinical implications. Diabetes Care 2007 Jun; 30 (6): 1344-50
8. Inzucchi SE, McGuire DK. New drugs for the treatment of diabetes. Part II: incretin-based therapy and beyond. Circulation 2008 Jan 29; 117 (4): 574-84
9. Bristol-Myers Squibb. Onglyza (saxagliptin) tablets: US prescribing information [online]. Available from URL: http://packageinserts.bms.com/pi/pi_onglyza.pdf [Accessed 2009 Aug 6]
10. Boulton DW, Geraldes M. Safety, tolerabilty, pharmacokinetics and pharmacodynamics of once-daily oral doses of saxagliptin for 2 weeks in type 2 diabetic and healthy subjects [abstract no. 606-P plus poster]. 67th Scientific Sessions of the American Diabetes Association; 2007 Jun 22-26; Chicago (IL)
11. Henry R, Smith S, Schwartz S, et al. β-cell stimulation by saxagliptin in patients with T2D [abstract no. 447-P plus poster]. 69th Annual Scientific Sessions of the American Diabetes Association; 2009 Jun 5-9; New Orleans (LA)
12. Patel CG, Li L, Komoroski BJ, et al. No effect of saxagliptin on QTc interval in healthy subjects [abstract no. 2072-PO]. 69th Annual Scientific Sessions of the American Diabetes Association; 2009 Jun 5-9; New Orleans (LA)
13. Wang A, Dorso C, Kopcho L, et al. Implications of the prolonged dissociation rate of saxagliptin, a highly potent and selective DPP4 inhibitor, on plasma DPP measurements [abstract no. 2088-PO]. Diabetes 2008 Jun; 57 Suppl. 1: A576-7
14. Fura A, Khanna A, Vyas V, et al. Pharmacokinetics of the dipeptidyl peptidase 4 inhibitor saxagliptin in rats, dogs, and monkeys and clinical projections. Drug Metab Dispos 2009 Jun; 37 (6): 1164-71
15. Boulton D, Tang A, Patel C, et al. Pharmacokinetics of dipeptidyl pepetidase-4 inhibitor saxagliptin in subjects with renal impairment [abstract no. P357]. 11th European Congress of Endocrinology; 2009 Apr 25-29; Istanbul
16. Patel C, Castaneda L, Frevert U, et al. Single-dose pharmacokinetics and safety of saxagliptin in subjects with hepatic impairment compared with healthy subjects [abstract no. 537-P]. Diabetes 2008 Jun; 57 Suppl. 1: A160
17. Boulton DW, Goyal A, Li L, et al. The effects of age and gender on the single-dose pharmacokinetics and safety of saxagliptin in healthy subjects [abstract no. 551-P]. Diabetes 2008 Jun; 57 Suppl. 1: A164
18. Boulton DW, Adams D, Li L, et al. Magnesium and aluminum hydroxides plus simethicone, famotidine, or omeprazole do not meaningfully affect the pharmacokinetics of saxagliptin in healthy subjects [abstract no. PIII-68]. Clin Pharmacol Ther 2008 Mar; 83 Suppl. 1: S92-3
19. Boulton DW, Li L, Patel CG, et al. No pharmacokinetic interaction between saxagliptin and digoxin in healthy subjects [abstract no. PIII-69]. Clin Pharmacol Ther 2008 Mar; 83 Suppl. 1: S93
20. Girgis S, Patel CG, Li L, et al. The effect of diltiazem on the pharmacokinetics of saxagliptin in healthy volunteers [abstract no. 72]. J Clin Pharmacol 2007; 47 (9): 1199
21. Boulton DW, Brenner E, Royzman K, et al. Effect of ketoconazole on the pharmacokinetics of saxagliptin in healthy sunjects [abstract no. 89]. J Clin Pharmacol 2007; 47 (9): 1203
22. Patel C, Li L, Komoroscki B, et al. No meaningful drug-drug interaction between saxagliptin and glyburide in healthy subjects [abstract no. 212]. 36th Annual Meeting of the American College of Clinical Pharmacology; 2007 Sep 9-11; San Fransisco (CA)
23. Patel C, Li L, Komoroscki B, et al. No meaningful drug-drug interaction between saxagliptin and metformin in healthy subjects [abstract no. 213]. 36th Annual Meeting of the American College of Clinical Pharmacology; 2007 Sep 9-11; San Fransisco (CA)
24. Patel C, Li L, Komoroscki B, et al. No meaningful drug-drug interaction between saxagliptin and pioglitazone subjects [abstract no. 226]. 36th Annual Meeting of the American College of Clinical Pharmacology; 2007 Sep 9-11; San Fransisco (CA)
25. Girgis S, You X, Maurer C, et al. The effect of simvastatin on the pharmacokinetics of saxagliptin in healthy volunteers [abstract no. 28]. J Clin Pharmacol 2007; 47 (9): 1188
26. Rosenstock J, Aguilar-Salinas C, Klein E, et al. Effect of saxagliptin monotherapy in treatment-naive patients with type 2 diabetes. Curr Med Res Opin 2009; 25 (10): 2401-11
27. Rosenstock J, Sankoh S, List JF. Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naive patients with type 2 diabetes. Diabetes Obes Metab 2008 May; 10 (5): 376-86
28. Jadzinsky M, Pfutzner A, Paz-Pacheco E, et al. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. Diabetes Obes Metab 2009 Jun; 11 (6): 611-22
29. DeFronzo RA, Hissa MN, Garber AJ, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes on metformin alone. Diabetes Care 2009; 32 (9): 1649-55
30. Chacra AR, Tan GH, Apanovitch A, et al. Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: a randomised controlled trial. Int J Clin Pract 2009 Jul 15; 63 (9): 1395-406
31. Allen E, Hollander P, Li J, et al. Saxagliptin added to a thiazolidinedione improves glycaemic control in patients with inadequately controlled type 2 diabetes [abstract no. 859]. Diabetologia 2008; 51 Suppl. 1: S342-3
32. Defronzo RA, Hissa MN, Garber AJ, et al. Once-daily saxagliptin added to metformin provides sustained glycemic control and is well tolerated over 102 weeks in patients with T2D [abstract no. 547-P]. 69th Annual Scientific Sessions of the American Diabetes Association; 2009 Jun 5-9; New Orleans (LA)
33. Chen R, Donovan M, Rusnak JM, et al. Saxagliptin used as monotherapy or in combination with other anti-hyperglycaemic agents does not significantly increase risk of hypoglycaemia [abstract no. 2082-PO]. 69th Annual Scientific Sessions of the American Diabetes Association; 2009 Jun 5-9; New Orleans (LA)
34. Wolf R, Frederich R, Fiedorek F, et al. Evaluation of CV risk in saxagliptin clinical trials [abstract no. 8-LB plus poster]. 69th Annual Scientific Sessions of the American Diabetes Association; 2009 Jun 5-9; New Orleans (LA)

Correspondence: *Sohita Dhillon*, Adis, a Wolters Kluwer Business, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand.
E-mail: demail@adis.co.nz