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REVIEW

Saxagliptin: a New Dipeptidyl Peptidase-4 Inhibitor for the Treatment of Type 2 Diabetes

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ABSTRACT

Saxagliptin is a potent and selective reversible inhibitor of dipeptidyl peptidase-4, which is being developed for the treatment of type 2 diabetes. It is absorbed rapidly after oral administration and has a pharmacokinetic profile compatible with once daily dosing. Saxagliptin is metabolized in vivo to form an active metabolite, and both parent drug and metabolite are excreted primarily via the kidneys. Saxagliptin reduces the degradation of the incretin hormone glucagon-like peptide-1, thereby enhancing its actions, and is associated with improved β-cell function and suppression of glucagon secretion. Clinical trials of up to 24 weeks duration have shown that saxagliptin improves glycemic control in monotherapy and provides additional efficacy when used in combination with other oral antidiabetic agents (metformin, sulfonylurea, thiazolidinedione). Both fasting and postprandial glucose concentrations are reduced, leading to clinically meaningful reductions in glycated hemoglobin, and due to the glucose-dependency of its mechanism of action, there is a low risk of hypoglycemia. Saxagliptin is reported to be well tolerated with a side-effect profile similar to placebo. It has a neutral effect on body weight and dose adjustment because of age, gender, or hepatic impairment is not necessary. Saxagliptin is being co-developed by Bristol-Myers-Squibb (New York, NY, USA) and AstraZeneca (Cheshire, UK), and is currently undergoing regulatory review.

Keywords: dipeptidyl peptidase-4; DPP-4; GLP-1; glucagon-like peptide-1; glycemic control; incretin enhancer; saxagliptin; type 2 diabetes

INTRODUCTION

Saxagliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4), which is the enzyme responsible for the initial rapid degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[1] These peptides are incretin hormones that enhance meal stimulated insulin secretion and have also attracted much interest because of their antidiabetic actions.[1-4] In addition to stimulating

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insulin secretion, they upregulate all steps in insulin biosynthesis and are associated with improvements in β-cell function. Preclinical studies have indicated that they are β-cell protective, increasing differentiation and proliferation and reducing apoptosis; in animal models this has been associated with increases in β-cell mass. GLP-1 potently reduces glucagon secretion, thereby suppressing endogenous glucose production, and delays gastric emptying to reduce postprandial glucose (PPG) excursions.[1-4] Additionally, appetite is reduced leading to lower food intake and body weight loss, and there may be beneficial cardiovascular effects.[1-4] While the β-cell effects are shared by both incretins, GIP does not inhibit glucagon secretion, and gastric emptying and food intake are not altered.[2] However, GIP may play a part in the control of lipid metabolism.[2]

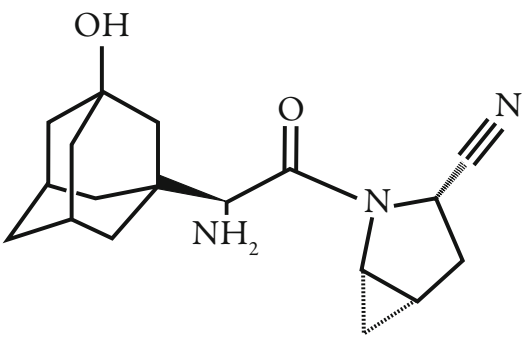
In type 2 diabetes mellitus (T2DM), incretin actions are impaired,[5] but exogenously infused GLP-1 can normalize both fasting and PPG concentrations.[6,7] When given by continuous subcutaneous infusion over 6 weeks, GLP-1 improved β-cell function, resulting in lowered glucose profiles and reduced glycated hemoglobin (HbA_{1c}) levels and was associated with weight loss.[8] However, because of its rapid degradation, native GLP-1 cannot be used therapeutically and, therefore, there has been much interest in using DPP-4 inhibitors to reduce the degradation of endogenous GLP-1 as a therapeutic strategy in T2DM.[9] Early preclinical studies with prototype DPP-4 inhibitors proved that this approach was feasible, with enhancement of intact incretin hormone concentrations being accompanied by improvements in glucose tolerance in animal models of insulin resistance, glucose intolerance, and T2DM.[10] Subsequently, a number of DPP-4 inhibitors have entered clinical development. Of these, sitagliptin and vildagliptin have been approved and are now available for the treatment of T2DM. Alogliptin is awaiting regulatory approval, and others (eg, BI1356) are in phase 3 clinical trials.

The focus of this article is saxagliptin, a potent inhibitor of DPP-4 that is being co-developed for the treatment of T2DM by Bristol-Myers-Squibb and AstraZeneca. Saxagliptin is currently undergoing regulatory review by the Food and Drug Administration in the USA and the European Medicines Agency in Europe.

SAXAGLIPTIN

Saxagliptin (BMS-477118; (*S*)-3 hydroxyadamantylglycine-L-*cis*-4,5 methanoprolinenitrile) is a nitrile-containing DPP-4 inhibitor (Figure 1), with the molecular formula $C_{18}H_{27}N_3O_3$ and a molecular weight of 333.4 Da.[11] It is a potent inhibitor of DPP-4 (inhibition constant, K_i=0.6-1.3 nM) that displays slow-binding properties.[11-13] Thus, kinetic studies have suggested that inhibition of DPP-4 by saxagliptin is a two-step process that involves formation of a reversible covalent enzyme-inhibitor complex, in which there is a slow onset of inhibition and a slow rate of inhibitor dissociation, resulting in the enzyme slowly equilibrating between the active and inactive forms.[13]

Figure 1. Chemical structure of saxagliptin.



Saxagliptin is metabolized in vivo to form an active metabolite (BMS-510849), which is twofold less potent than the parent molecule.[12] It appears that this metabolism is largely mediated via the cytochrome CYP3A in the liver; in subjects with liver failure, plasma concentrations of the metabolite are reduced (7%-33% lower) with increasing severity of hepatic impairment, while at the same time exposure to the parent drug increases (10%-77% higher).[14] Both saxagliptin and its primary metabolite are potent inhibitors of DPP-4 activity in mouse, rat, dog, cynomolgus and rhesus monkey, and human plasma in vitro.[12] Both are selective for DPP-4 versus DPP-8 (400-fold and 950-fold, respectively) and DPP-9 enzymes (75-fold and 160-fold, respectively) and do not inhibit any other members of the DPP-4 family (>4000-fold selectivity).[12]

Preclinical Studies

Saxagliptin dose-dependently inhibits plasma DPP-4 activity in Han-Wistar rats, by ~70% at 7 hours postdose with 1 mg/kg and by ~90% at 7 hours postdose with 10 mg/kg. At 24 hours postdose, ~20% and 70% inhibition, respectively, remained.[15] In C57BL/6J mice, saxagliptin at a dose of 1 mg/kg, suppressed the glucose excursion by ~50% compared with the control when given 45 minutes before the glucose challenge, but the effect was lost when the glucose challenge was given 16 hours postdose. However, consistent with the effect on plasma DPP-4 activity, when the dose was increased to 10 mg/kg, the glucose-lowering effect was evident 16 hours postdose.[15]

In Zucker fatty rats, maximal reductions in the glucose excursion following oral glucose (2 g/kg) were attained when plasma DPP-4 activity was inhibited by ~60%, with no further increase in efficacy with greater inhibition.[11] Single doses of saxagliptin (0.3, 1, and 3 μmol/kg) given 4 hours prior to an oral glucose tolerance test dose-dependently reduced the glucose excursion by ~30 up to ~60% in this model. When given 1 hour before a glucose load in *ob/ob* mice, saxagliptin (1, 3, and 10 μmol/kg) significantly lowered glucose concentrations at the 60-minute postglucose time point at the two highest doses, and this was associated with raised insulin levels at the 15-minute time point with the highest dose.[11]

Clinical Studies

Early studies investigated the safety and tolerability of saxagliptin and its primary metabolite (BMS-510849) as well as their pharmacokinetic (PK) and pharmacodynamic profiles in healthy subjects and in patients with T2DM.[16] In these two 2-week studies, healthy subjects (*n*=50) were randomized to receive saxagliptin (40, 100, 150, 200, 300, or 400 mg once daily) or placebo, and subjects with T2DM (*n*=40) received saxagliptin (2.5, 5, 15, 30, or 50 mg once daily) or placebo. Drug exposure to saxagliptin was dose proportional and similar on day 1 and day 14, with PK being similar in the healthy subjects and in patients with T2DM. Exposure to the primary metabolite increased in proportion to the dose of saxagliptin, ranging from 1.7-fold up to 6.9-fold higher than the parent molecule. The time to maximum plasma concentration (T_{max}) for saxagliptin was ≤2 hours, and the half-life ranged from 2.2 to 3.8 hours; the corresponding values for BMS-510849 were T_{max} ≤4 hours and half-life 3-7.4 hours. Saxagliptin was well absorbed following oral administration, and was excreted primarily via the kidneys, with 12%-29% of the dose being recovered in the urine as the parent drug and 21%-52% as the metabolite. Plasma DPP-4 activity was dose-dependently inhibited (by ~80% to >95%), with maximum inhibition

being attained with doses of 150 mg and above; 24 hours postdose, plasma DPP-4 activity was inhibited by 50% with the 2.5 mg dose and by 79% with the 400 mg dose. All saxagliptin doses increased postprandial intact GLP-1 concentrations up to threefold, although no clear dose-response was evident and there were no clear saxagliptin-related changes in glycemic or lipid parameters over the 2-week dosing period. In this study, saxagliptin was well tolerated and no dose-related adverse events, including hypoglycemia, were observed.[16]

Subsequently, a single-dose study investigated the effect of age and gender on saxagliptin (10 mg) PK in healthy subjects.[17] Metabolic and renal clearances of saxagliptin were reduced in elderly subjects (≥65 years), with the apparent volume of distribution being lower, leading to a higher drug exposure (maximum concentration [C_{max}] 1.2-fold higher, area under the curve [AUC] 1.6-fold higher) compared with younger (age 18-40 years) subjects; about half of this difference was accounted for by an age-related decline in renal function. There were no gender differences in saxagliptin PK parameters, and the PK of the active metabolite tended to follow those of the parent drug, although females had a slightly higher exposure (~25%) than males. Saxagliptin was well tolerated and there were no saxagliptin-related adverse events or laboratory abnormalities, leading to the conclusion that dose adjustment for age or sex was unnecessary.[17]

In a larger placebo-controlled, double-blind study, the safety and efficacy of saxagliptin was examined over a range of doses. Drug-naïve subjects with T2DM (baseline HbA_{1c} ≥6.8% to HbA_{1c} ≤9.7%) were randomized to receive saxagliptin (2.5-40 mg once daily for 12 weeks; low-dose cohort; *n*=338) or 100 mg once daily for 6 weeks (high-dose cohort; *n*=85).[18] At the end of the 12- or 6-week study periods, patients entered a 4-week follow-up period with single-blinded placebo treatment. Eighty-three percent (low dose) and 93% (high dose) of subjects that were randomized completed the double-blind treatment period. In the low-dose cohort, there were reductions from baseline HbA_{1c} (~7.9%) with all doses of saxagliptin (of –0.7% up to –0.9% vs. –0.3% with placebo) at week 12; reductions were apparent by week 4 and generally greater in subjects with higher HbA_{1c} levels at baseline. Maximal efficacy appeared to be reached with the 5 mg dose, and no dose-response relationship was apparent; 41%-53% of saxagliptin-treated subjects reached the target HbA_{1c} of <7% (compared with 20% of those on placebo). In the high-dose cohort, 6 weeks of treatment with saxagliptin reduced HbA_{1c} by 1.1% from baseline (7.7%) compared with –0.4% for placebo, with 66% of subjects reaching an HbA_{1c} of <7%. In both cohorts, reductions in fasting glucose (FPG) levels were evident by week 2. Levels decreased by 11-22 mg/dL with saxagliptin, but increased with placebo (+3 mg/dL) in the low-dose cohort, and decreased by 26.3 mg/dL in the high-dose cohort (placebo –3.3 mg/dL). Similarly, PPG levels were reduced to a greater extent with saxagliptin (by 24-41 mg/dL in the low-dose group and by 45 mg/dL for the high-dose group) than with placebo (low dose, –1 mg/dL; high dose, –17 mg/dL). There were no consistent treatment effects on either fasting or postprandial insulin or C-peptide levels, but in both studies, β-cell function, as assessed by pancreatic β-cell function (HOMA-B), was improved (by 17%-25%) with saxagliptin. Saxagliptin was body weight neutral, and was well tolerated, with the incidence of adverse events being similar across all doses, and not different to placebo.[18]

In a 24-week, placebo-controlled, randomized trial, the efficacy of saxagliptin (2.5-10 mg once daily) as monotherapy was investigated in drug-naïve subjects with T2DM (baseline HbA_{1c} ≥7 to ≤10%; *n*=401); an open-label cohort with

more poorly controlled diabetes (baseline HbA_{1c} >10 to ≤12%; *n*=66) received 10 mg saxagliptin.[19] Saxagliptin lowered HbA_{1c} (by 0.6% to 0.7%; placebo-subtracted reduction from baseline) with differences from placebo being apparent by week 4 (the earliest assessment point). Placebo-subtracted reductions in FPG of up to 23 mg/dL were obtained, with changes being apparent at week 2. Saxagliptin treatment was associated with increased postprandial insulin and C-peptide concentrations and reduced postprandial glucagon concentrations, leading to reductions in PPG. At week 24, 35%-41% of subjects taking saxagliptin reached target HbA_{1c} of <7% compared with 24% of subjects randomized to placebo. In the open-label cohort, HbA_{1c} and FPG were reduced from baseline by 1.9% and 33 mg/dL, respectively. Saxagliptin was weight neutral.[19]

Adjuvant Clinical Studies

Initial combination treatment with saxagliptin and metformin was investigated in a 24-week study in 1306 drug-naïve patients with poorly controlled T2DM (baseline HbA_{1c}, 9.5%).[20] Subjects were randomized to metformin monotherapy, saxagliptin monotherapy (10 mg), or combination treatment with saxagliptin (5 or 10 mg) plus metformin. The metformin treatment was initiated at a dose of 500 mg/day and up-titrated to a maximum of 2000 mg/day. In this study, both combination doses gave similar results, and were more efficacious than either monotherapy, reducing HbA_{1c} levels by 2.5% from baseline, compared with reductions of 1.7% (saxagliptin monotherapy) and 2.0% (metformin monotherapy). In those subjects with more poorly controlled hyperglycemia (baseline HbA_{1c} ≥10%), reductions of ~3.3% were obtained with the saxagliptin/metformin combinations. At week 24, ~60% of subjects reached target HbA_{1c} levels of <7% with the combination (compared with 31% and 41% of subjects on saxagliptin or metformin alone). FPG and PPG were also reduced to a greater extent (by ~60 and ~138 mg/dL, respectively) with the combination treatment than with either monotherapy. Again, saxagliptin was well tolerated, with the incidence of adverse events being similar across all groups and the occurrence of hypoglycemic events being low.[20]

The efficacy of saxagliptin as add-on treatment in patients inadequately controlled with a single oral antidiabetic agent has been investigated in three separate studies. In a placebo-controlled trial in patients with inadequate glycemic control with metformin monotherapy (≥1500 mg/day; *n*=743; baseline HbA_{1c}, 8%), subjects were randomized to receive the addition of saxagliptin (2.5, 5, or 10 mg) or placebo once daily for 24 weeks.[21] All doses of saxagliptin reduced HbA_{1c}, by up to 0.8% (placebo-subtracted), although no clear dose-response relationship was apparent. FPG was reduced by up to 24 mg/dL relative to placebo, and the glucose excursion following an oral glucose load was significantly lowered. Saxagliptin was associated with reductions in postprandial glucagon and increases in postprandial insulin and C-peptide levels. In this study, saxagliptin was body weight neutral (–1.5 to –0.5 kg change from baseline compared with –1.0 kg for placebo).[21]

In another 24-week study, the effect of adding saxagliptin to a sulfonylurea was compared with up-titration of the sulfonylurea;[22] this was a study of 768 patients with T2DM (baseline HbA_{1c}, 8.4%), inadequately controlled with a submaximal dose of glyburide. Patients on previous submaximal sulfonylurea monotherapy were given glyburide (7.5 mg; open label) during a 4-week run-in period, after which they were randomized to receive, in addition, saxagliptin (2.5 or 5 mg once daily) or glyburide (2.5 mg),

with up-titration of the glyburide dose allowed (to a maximum dose of 15 mg/day); 92% of the patients in this arm had reached the maximum permitted dose by week 24. Both doses of saxagliptin resulted in additional efficacy compared with up-titration of the sulfonylurea. HbA_{1c} was reduced by 0.5% and 0.6% from baseline with the two saxagliptin doses, compared with an increase of 0.1% with glyburide up-titration, with ~22% of saxagliptin-treated subjects reaching target HbA_{1c} levels of <7% compared with only 9% of those in the glyburide arm. FPG (–7 and –10 mg/dL) and PPG (–31 and –34 mg/dL) were similarly improved with saxagliptin (2.5 and 5 mg, respectively) compared with a deterioration seen in the sulfonylurea up-titration arm (FPG, +1 mg/dL; PPG, +8 mg/dL). Compared with baseline, the addition of saxagliptin improved islet cell responses to glucose (increased insulin and decreased glucagon levels) to a greater extent than glyburide. In this study, body weight and body mass index increased in all three arms—the increase in body weight with saxagliptin (+0.7 kg and +0.8 kg for the 2.5 mg and 5 mg doses, respectively) was significantly greater than the 0.3 kg increase seen in the glyburide arm.[22]

In the third study, saxagliptin was added to a thiazolidinedione (TZD) in 565 patients with T2DM (baseline HbA_{1c}, 8.3%), who had inadequately controlled hyperglycemia on stable TZD monotherapy (pioglitazone 30 or 45 mg; or rosiglitazone 4 or 8 mg for ≥12 weeks).[23] Patients were randomized to receive saxagliptin (2.5 or 5 mg) or placebo in addition to their stable TZD dose for 24 weeks. At the end of the study, subjects receiving saxagliptin experienced greater reductions in HbA_{1c} (–0.7% and –0.9% from baseline for 2.5 mg and 5 mg dose, respectively) than those receiving placebo (–0.3%), resulting in more patients reaching the HbA_{1c} target of <7% (~42%) with saxagliptin than with placebo (26%). FPG was largely unchanged on placebo (–3 mg/dL from baseline), but was reduced with both saxagliptin doses (–14 and –17 mg/dL, respectively) while, similarly, placebo treatment had only a minor effect on the PPG excursion (–15 mg/dL from baseline), whereas it was significantly reduced with both saxagliptin doses (–55 and –65 mg/dL, respectively). Compared with placebo treatment, saxagliptin was associated with increased postprandial insulin and decreased postprandial glucagon responses, and β-cell function (assessed using HOMA-2) was improved to a greater extent. Body weight increased slightly over the 24-week study period in all three arms (+1.3, +1.4, and +0.9 kg; saxagliptin 2.5 and 5 mg, and placebo respectively).[23]

SAFETY AND TOLERABILITY

Generally, saxagliptin has been reported to be well tolerated in clinical studies; no dose-related or laboratory adverse events were noted after administration over 2 weeks with doses up to 400 mg, and there was no effect on QTc interval.[16] Similarly, in the dose-ranging study, there were no apparent dose-related adverse events, and the frequency of adverse events was comparable between saxagliptin and placebo.[18] The most common adverse events reported have been headache, upper respiratory tract infection, urinary tract infection, and nasopharyngitis, seen during the 12-week study with doses up to 40 mg[18] and the 24-week study with doses up to 10 mg.[19] Small, reversible, dose-dependent reductions in absolute lymphocyte count were observed that were more apparent at doses ≥20 mg, which, however, remained within normal limits.[18] There was no effect on white blood cell or neutrophil count, and no evidence of altered immune function based on adverse event reporting.[18] Other laboratory

tests, including liver function tests, showed no abnormalities.[18]

Similarly, saxagliptin has been well tolerated when used in combination treatment. There was no difference in the occurrence of adverse events when used in combination with metformin, compared with metformin alone,[20] and saxagliptin was well tolerated when added to a sulfonylurea, with the adverse event profile being similar to that of up-titrated glyburide alone.[22] The combination of saxagliptin with TZD was also well tolerated with no clinically meaningful differences in adverse events between the treatment groups.[23]

The PK of a single dose of saxagliptin (10 mg) has been examined in subjects with liver failure (Child-Pugh class A, B, or C), and although there were small (less than twofold) differences in PK of both the parent drug (increased exposure) and its primary metabolite (decreased exposure), there were no saxagliptin-related adverse events or laboratory abnormalities.[14] It was concluded that no dose adjustment on the basis of hepatic impairment is necessary.[14]

Hypoglycemia

In monotherapy, hypoglycemic symptoms were experienced by 6.3% of saxagliptin-exposed subjects in the low-dose (2.5-40 mg) cohort (vs. 1.5% on placebo) and by 13.6% of subjects in the high-dose (100 mg) cohort (vs. 0% with placebo).[18] However, at doses up to 10 mg, it has not been associated with any increased incidence of hypoglycemia relative to placebo.[18,19]

When added to a sulfonylurea, hypoglycemic events were reported by 14% of patients receiving combination therapy with saxagliptin (2.5 or 5 mg), which was similar to that reported by the glyburide arm (10%), with the occurrence of confirmed hypoglycemia (finger stick glucose ≤50 mg/dL) being similar in all three arms (2.4%, 0.8%, and 0.7% for saxagliptin 2.5 and 5 mg, and glyburide up-titration, respectively).[22]

A low incidence of hypoglycemia was reported by those patients taking saxagliptin together with a TZD (4.1% and 2.7% for the 2.5 and 5 mg doses), compared with 3.8% for TZD monotherapy, and only a single case of confirmed hypoglycemia (finger stick glucose ≤50 mg/dL) occurred (2.5 mg saxagliptin arm).[23]

DISCUSSION

Saxagliptin belongs to one of two new classes of antidiabetic drugs, the DPP-4 inhibitors, whose effects are based upon the actions of the incretin hormone, GLP-1 (the other class being the injectable GLP-1 analogs). Presently, clinical experience with the DPP-4 inhibitors is limited, with only two members of the class so far being approved for treatment of T2DM; sitagliptin received US Food and Drug Administration approval in October 2006 and received European Medicines Agency in Europe approval in March 2007, and vildagliptin was approved by the European Medicines Agency in Europe in July 2007.

Although the DPP-4 inhibitors comprise a group of chemically diverse and structurally unrelated compounds,[11,24-27] their mechanism of action is thought to be the same (enhancement of endogenous incretins), and at present, there seems little to distinguish between them in terms of efficacy, although as yet, no direct head-to-head comparisons have been made. However, saxagliptin appears to be more potent, with maximal glycemic efficacy being attained in the range 2.5-10 mg (anticipated therapeutic dose, 5 mg), compared with the therapeutic dose of 100 mg/day with sitagliptin and vildagliptin.

DPP-4 inhibitors, including saxagliptin, are effective in monotherapy, and although superiority to metformin was narrowly missed in one

study with vildagliptin,[28] as a class, they appear comparable with monotherapy with glitazones.[29] However, current treatment algorithms advocate lifestyle interventions (dietary modification, increased exercise, weight loss) together with starting metformin treatment at the time that the T2DM is diagnosed;[30] therefore, it is likely that until their long-term efficacy and safety are established in clinical practice, the DPP-4 inhibitors will most probably be used as add-on therapy, once metformin fails to maintain glycemic control. In this setting, saxagliptin gives additional reductions in HbA_{1c},[21] in common with observations made with alogliptin, sitagliptin, and vildagliptin.[31-33] Moreover, experience with these other compounds suggests that the addition of the DPP-4 inhibitor to metformin has comparable effects on HbA_{1c} to the addition of a sulfonylurea[34,35] or glitazone,[36,37] but with neither the weight gain seen with the sulfonylurea and glitazone, nor the increased risk of hypoglycemia posed by the sulfonylurea.

The DPP-4 inhibitors may also have a place as second-line treatment in patients where monotherapy with sulfonylureas or glitazones no longer gives inadequate control. Not only has DPP-4 inhibition with alogliptin, sitagliptin, or vildagliptin been shown to give additional efficacy when added to ongoing sulfonyl-urea therapy,[38-40] but the addition of saxagliptin to submaximal glyburide actually resulted in superior glycemic efficacy than up-titration of the sulfonylurea.[22] This was achieved without increasing the incidence of hypoglycemia, although rather surprisingly, it was associated with an increase in body weight that was greater than that seen with up-titration of the sulfonylurea alone.[22] Furthermore, and in line with sitagliptin and vildagliptin,[41,42] saxagliptin also provides additional reductions in HbA_{1c} levels when added to a glitazone.[23] As β-cell function continues to decline with time it leads to progressive loss of glycemic control,[43-45] whereas the mechanism of action of DPP-4 inhibitors includes enhancement of endogenous stimulation of insulin secretion; therefore, it follows that their early use, before β-cell function declines too far, may be associated with greater efficacy. How the glycemic efficacy of the DPP-4 inhibitors will compare with the other class of incretin-based therapies, the GLP-1 analogs, remains to be determined; apart from a single mechanistic study over 2 weeks,[46] no direct comparisons have yet been made.

At the time of writing, most of the clinical data available on saxagliptin have been published only in abstract form, and because of this, not much is known about its safety profile. In the clinical trials, saxagliptin has been reported as generally being well tolerated with an adverse event profile resembling placebo;[18,19,23] the most common adverse events reported were headache, upper respiratory tract infection, urinary tract infection, and nasopharyngitis. A meta-analysis of clinical trials with sitagliptin and vildagliptin published before the end of May 2007, carried out by Amori et al.,[47] also identified nasopharyngitis, urinary tract infection, and headache as adverse events that occurred more often with sitagliptin and vildagliptin than with placebo or comparator agent. However, the majority of the trials included in the analysis were of 12-24 weeks duration; only two were longer than 24 weeks.

Since then, an updated safety analysis of sitagliptin has been published, including over 3400 patients who had been exposed to sitagliptin during various clinical trials of 18 up to 104 weeks duration.[48] The incidence rate of all adverse events, including headache, upper respiratory tract infection, urinary tract infection, and nasopharyngitis was similar in the sitagliptin-exposed group compared with non-

exposed individuals; however, hypoglycemia was higher in the non-exposed group because of the inclusion of sulfonylurea as an active comparator in some of the trials.[48] Small reductions in absolute lymphocyte count, which still, however, remained within normal limits, have been observed with saxagliptin[18] and have not been reported with other DPP-4 inhibitors. The clinical significance, if any, of this is unknown, and it is noteworthy that no evidence for disturbances in immune function has been reported with saxagliptin or any of the other DPP-4 inhibitors in clinical development.

Additionally, selectivity for DPP-4 over other related members of the DPP family may be relevant, as inhibition of DPP-8 and/or DPP-9 has been shown to be associated with toxicity and mortality in some,[49] but not all[50] preclinical studies. All the inhibitors in clinical development provide effective inhibition of DPP-4, but there are some differences between them regarding selectivity for DPP-8 and DPP-9. Saxagliptin[12] resembles vildagliptin[51] in this respect, with in vitro assays revealing them to be an order of magnitude less selective than either alogliptin[24] or sitagliptin.[25] However, whether this is of any significance in vivo is unknown. It should also be emphasized that many thousands of patients have now been exposed to DPP-4 inhibitors during the clinical development programs and in general practice, showing them all to be well tolerated and apparently not to be causally associated with adverse side effects in humans.[1,48]

CONCLUSIONS

In conclusion, the relatively limited data so far available on saxagliptin indicate that it is efficacious in improving glycemic control, both as monotherapy and in combination with other oral antidiabetic agents, without posing undue risk of hypoglycemia. It is apparently well tolerated, with a side-effect profile similar to that of placebo, and in particular, it is not associated with nausea or other gastrointestinal side effects, and it generally does not increase body weight. Further studies are now required to reveal the long-term efficacy and tolerability of this drug.

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Disclosure

Prior to peer review the manufacturers of saxagliptin were offered the opportunity to review the article to ensure accuracy of the data. No changes were made to the content as a result. No writing assistance was utilized in the production of this manuscript.

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