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REVIEW

Saxagliptin: a New DPP-4 Inhibitor for the Treatment of Type 2 Diabetes Mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a global epidemic with increasing impact on individuals and healthcare providers. Available treatments (such as metformin, sulfonylureas, glitazones, and insulin) have proven unsatisfactory in producing a long-lasting impact on glycemic control. In addition, most of these treatments have undesirable side effects such as weight gain and hypoglycemia. As a result, exploring new treatment targets and new therapies is mandatory in order to treat this condition. The incretin pathway, in particular glucagon-like peptide (GLP-1), plays an important pathological role in the development of T2DM, and treatments targeting the incretin system have recently become available. These can mainly be divided into two broad categories; GLP-1 agonists/analogs (exenatide, liraglutide), and dipeptidyl peptidase-4 (DPP-4; the enzyme responsible for rapid inactivation of incretins) inhibitors (sitagliptin, vildagliptin). Saxagliptin is a novel DPP-4 inhibitor that has recently completed phase 3 studies. Saxagliptin is a potent and specific inhibitor of DPP-4 (in comparison with other dipeptidyl peptidase enzymes) that is given once daily. Current data suggest that saxagliptin as monotherapy or in combination with metformin, glyburide, or a glitazone results in significant reductions in fasting and postprandial plasma glucose and hemoglobin A_{1c} (HbA_{1c}). Saxagliptin is well tolerated and does not increase hypoglycemia compared with the placebo, and is probably weight neutral. Saxagliptin will be a new effective drug in the currently available variety of antidiabetic medications for patients with T2DM.

Keywords: DPP-4; GLP-1; hypoglycemia; incretin; saxagliptin; sitagliptin; type 2 diabetes mellitus; vildagliptin

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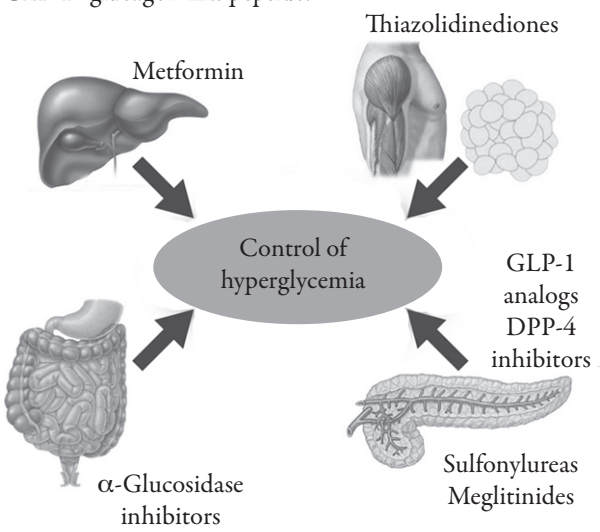
INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a global epidemic with an estimated prevalence of 6% (246 million people) worldwide in 2007, which is forecast to rise to 7.3% (380 million people) by 2025.[1] The health, social, and economic burden of T2DM is significant;[2-4] consequently, T2DM presents a major challenge to healthcare systems around the world.

T2DM is a complex disorder in which the interaction between environmental and genetic factors results in the development of insulin resistance (IR) and β-cell dysfunction.[5,6] Although IR is an important predisposing factor, β-cell dysfunction is the critical step in T2DM development.[5,6] Obesity is the single most important contributor to IR; however, most obese insulin-resistant individuals do not develop T2DM[6-8] because their β-cells are capable of producing significantly elevated levels of insulin to maintain glycemic control.[8-11] Hence, the failure of β-cells to secrete sufficient insulin to overcome IR (ie, β-cell dysfunction) is the crucial step in the development and progression of T2DM.[8,12] In addition to β-cell dysfunction, patients with T2DM have α-cell dysfunction, which manifests as elevated glucagon secretion in the presence of hyperglycemia.[13]

Based on the current understanding of the pathophysiology of T2DM, multiple pharmacological and nonpharmacological interventions have been developed over the past five decades to improve glycemic control and slow disease progression (Figure 1). However, these agents have largely been disappointing in the sense that most of the observed initial improvements in glycemic control are not sustained because of the progressive nature of β-cell dysfunction.[14,15] Furthermore, most of these treatments have undesired side effects:

Figure 1. Currently available pharmacotherapy in patients with type 2 diabetes mellitus. DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide.



sulfonylureas (SUs) increase insulin secretion, but are associated with hypoglycemia and weight gain;[14] metformin reduces hepatic glucose output, is weight neutral, and is not associated with hypoglycemia, but has a relatively high frequency of gastrointestinal side effects;[14] thiazolidinediones (TZDs) improve β-cell function and reduce IR, but are associated with weight gain and can cause peripheral edema;[14] meglitinides improve insulin secretion from β-cells, but increases the incidence of hypoglycemia and weight gain compared with metformin;[16] finally, insulin therapy produces sustainable glycosylated hemoglobin A_{1c} (HbA_{1c}) reductions and might improve β-cell function, but causes hypoglycemia and weight gain.[14] Hence, interventions that can slow and/or reverse β-cell decline, which result in weight loss and do not result in hypoglycemia, might be expected to have a significant sustained impact in patients with T2DM. Incretin-based therapies are a new class of antidiabetic medication that may address some of the abovementioned shortfalls of current treatments.

The Incretin System and T2DM

The possibility that intestinal factors are secreted in response to nutrients and can lower blood glucose levels was first described in the early twentieth century.[17,18] These factors were named "incretins" in the 1930s.[17] The incretin effect was first described by Elrick et al.,[19] following the observation that the insulin response to oral glucose exceeded that measured after intravenous administration of equivalent amounts of glucose. The incretins are secreted from the gastrointestinal tract during food intake and bind to receptors on β-cells, resulting in insulin secretion.[20] Both glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) bind to specific G-protein-coupled receptors located in the pancreas, stomach, skeletal muscle, heart, lung, and brain.[21] In healthy individuals, the incretin effect is responsible for 50%-70% of the insulin response to a meal.[22] GIP is secreted from the K-cells in the duodenum and jejunum in response to the ingestion of carbohydrates and/or lipids,[17,23,24] and results in glucose-dependent insulin secretion in humans.[17,24,25] In addition, GIP is associated with lipid metabolism in adipocytes and has a proliferative effect on β-cells.[24,26,27] GLP-1 is secreted from the L-cells in the distal ileum and colon.[17,24] GLP-1 has a number of functions, including stimulation of glucose-dependent insulin secretion, glucose-dependent suppression of glucagon secretion, slowing of gastric emptying, reduction of food intake, and possibly improved insulin sensitivity.[20,22,28] In addition, GLP-1 increases insulin gene transcription and all steps of insulin biosynthesis.[29,30] Animal studies have shown that GLP-1 increases β-cell mass, maintains β-cell efficiency, and reduces β-cell apoptosis.[28,31] GLP-1 and GIP contribute to and potentiate glucose-dependent insulin secretion in an additive manner, but GLP-1 appears to be responsible for most of the incretin effect on the β-cell.[17,20] Although GLP-1 levels are reduced in patients with T2DM, their response to exogenous GLP-1 remains intact.

Dipeptidyl Peptidase-4 (DPP-4) and DPP-4 Inhibitors

Incretins are rapidly degraded by the enzyme DPP-4.[17] DPP-4 cleaves the active peptide at the position 2 alanine (N-terminal) resulting in inactive peptide.[24] DPP-4 is widely expressed in human tissues including the brain, lungs, kidneys, adrenals, pancreas, intestine, and lymphocytes.[24] DPP-4 has effects beyond its proteolytic action, including T-cell proliferation.[32] In addition, many neuropeptides, growth factors, cytokines, and chemokines have been identified as potential DPP-4 substrates.[32]

DPP-4 is found in the endothelial cells of the blood vessels that drain the intestinal mucosa where the L-cells are situated.[24,33] This suggests that most GLP-1 is inactivated almost immediately following secretion. This rapid inactivation of GLP-1 and GIP contributes to a half-life ($t_{½}$) of less than 2 minutes and 5-7 minutes, respectively.[17,24,34,35] Thus, the short half-life of incretins limits their therapeutic potential. DPP-4 belongs to a whole enzyme family of endopeptidases;[32,36] therefore, to inhibit DPP-4 exclusively, DPP-4 inhibitors need to be highly specific. Inhibition of DPP-4 leads to elevated levels of endogenous uncleaved, biologically-active incretins and prolongs their action.[37] However, endogenous GLP-1 levels obtained with DPP-4 inhibitors are lower than those provided by pharmacological administration of injectable GLP-1 analogs.[30,38]

Preclinical studies for DPP-4 inhibitors showed enhancement of the biological actions of GLP-1 receptor agonists, including an improvement in insulin secretion, and promotion of β-cell proliferation, β-cell regeneration, neogenesis, islet-cell function and survival, and insulin biosynthesis.[30,39-42] DPP-4 inhibitors, unlike GLP-1 analogs, do not cause significant decreases in body weight and are generally regarded as weight neutral.[30] A range of DPP-4 inhibitors are approved or are in development: sitagliptin is approved in the USA and Europe; vildagliptin is approved in Europe; saxagliptin and alogliptin are currently undergoing phase 3 studies; and several others are currently in phase 1 and 2 studies. Sitagliptin and vildagliptin, when administered as monotherapy or in combination with other hypoglycemic agents (including metformin, SUs, and pioglitazone), lowered HbA_{1c}, fasting glucose levels, and postprandial glucose levels.[30,43] Further details on the clinical efficacy and safety of sitagliptin and vildagliptin, including interactions with other drugs, are discussed in the paper by Richter et al.[44]

SAXAGLIPTIN

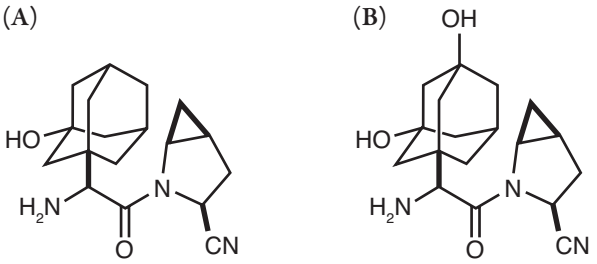
Development

Saxagliptin is a novel DPP-4 inhibitor developed by Bristol-Myers Squibb and AstraZeneca for the treatment of T2DM. Saxagliptin has recently completed its phase 3 clinical program. Details on the development and preclinical profile of saxagliptin can be found in the paper by Augeri et al.[45]

Pharmacokinetics and Pharmacodynamics

Saxagliptin is a selective, durable, but reversible inhibitor of DPP-4 (Figure 2). At 37°C, saxagliptin has an inhibition constant

Figure 2. (**A**) Saxagliptin (dipeptidyl peptidase-4 Ki=1.3 nM). (**B**) BMS-510849 (active metabolite of saxagliptin; dipeptidyl peptidase-4 Ki=2.6 nM).



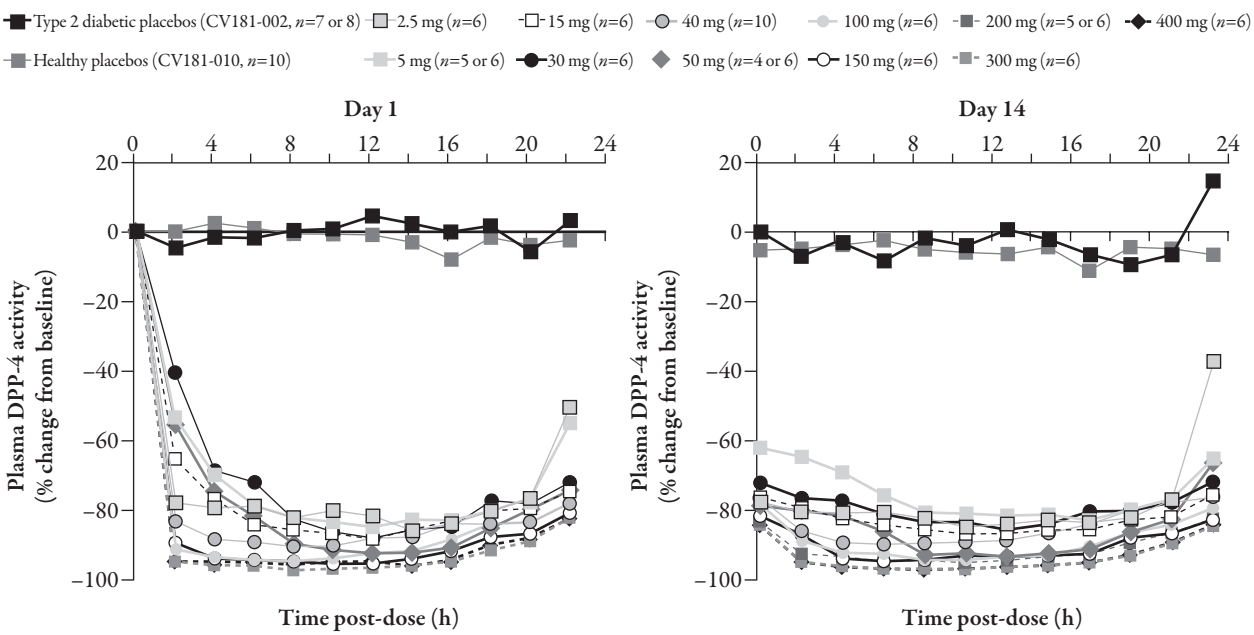
(Ki) of 1.3±0.3 nM (n=12) for DPP-4 inhibition, which is 10-fold more potent than either vildagliptin (13±3 nM) or sitagliptin (18±2 nM).[46] Saxagliptin demonstrates greater specificity for DPP-4 than for either the DPP-8 or DPP-9 enzymes (400- and 75-fold, respectively).[46] The active metabolite of saxagliptin (BMS-510849) is two-fold less potent than the parent. Both saxagliptin and its metabolite are highly selective (>4000-fold) for the inhibition of DPP-4 compared with a range of other proteases (selectivity of sitagliptin and vildagliptin for DPP-4 is >2600 and 32-250-fold, respectively, compared with DPP-8/9).[44] Dissociation of saxagliptin and its metabolite from DPP-4 is slow, with a $t_{½}$ of 50 and 23 minutes, respectively (sitagliptin and vildagliptin have a $t_{½}$ of 1 and 1.7 hours, respectively).[44] Slow dissociation of saxagliptin from DPP-4 has not been observed with any other enzymes tested, including DPP-8 and DPP-9.[46,47] Preclinical studies suggest that saxagliptin shows a high sensitivity for DPP-4 (the half maximal inhibitory concentration [IC_{50}]=3.5, 18, and 26 nM for vildagliptin, sitagliptin, and saxagliptin, respectively).[32] Conversely, saxagliptin demonstrates a low affinity for DPP-8 and DPP-9 (IC_{50} for DPP-8=9 and >50 nM for vildagliptin and sitagliptin, respectively; IC_{50} for DPP-9= >50 nM for sitagliptin).[32]

The pharmacokinetic and pharmacodynamic properties of saxagliptin were investigated in two double-blind, randomized, 2-week studies. In the first study, 40 patients with T2DM received once-daily doses of saxagliptin 2.5-50 mg, or a placebo; in the second study, 50 healthy individuals received once-daily doses of saxagliptin 40-400 mg, or a placebo. Systemic exposure to saxagliptin was shown to be dose proportional, and pharmacokinetic parameters were similar in patients with T2DM and in healthy individuals. Saxagliptin inhibited DPP-4 at all doses studied, with doses greater than 150 mg providing the same maximal inhibition (Figure 3).[48]

The impact of age and/or gender was assessed in a study of 56 healthy participants.[13] It was shown that saxagliptin exposure was slightly increased (less than twofold) in elderly individuals (aged ≥65 years) following a single oral 10 mg dose, compared with younger individuals (aged 18-40 years). In the same study, only small differences in saxagliptin pharmacokinetics were observed between healthy male and female participants. The authors of the study concluded that no dosage adjustment for saxagliptin was necessary on the basis of age or gender.[49] Similarly, the pharmacokinetics of sitagliptin and vildagliptin do not seem to be affected by age or gender.[44]

The impact of hepatic impairment on the pharmacokinetics of saxagliptin (10 mg) was assessed in one study,[46] comparing 18 patients with hepatic impairment (based on Child-Pugh scores, class A-C)[50] with 18 matched healthy individuals. A less than twofold difference was observed for the pharmacokinetics of saxagliptin, or its active metabolite, in patients with any category of hepatic impairment compared with healthy individuals. Thus, the authors stated that no dosage adjustment for saxagliptin would be required when treating patients with hepatic impair-

Figure 3. Plasma dipeptidyl peptidase-4 activity in multiple ascending-dose studies. CV181-002 and CV181-010 data are means. DPP-4=dipeptidyl peptidase 4.[48]



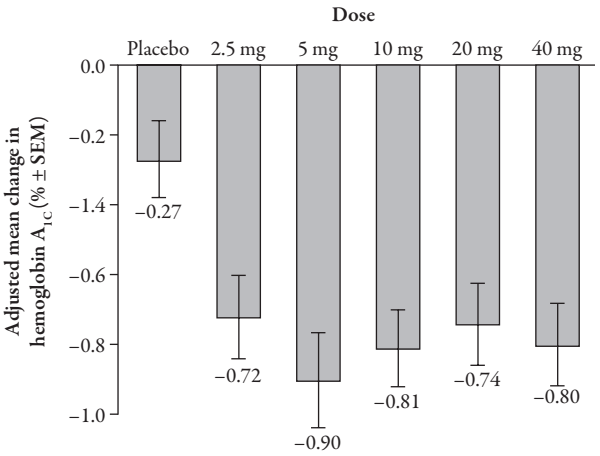
ment.[51] Hepatic insufficiency does not seem to alter the pharmacokinetics of sitagliptin or vildagliptin.[44]

Patients with T2DM usually require a combination of two or more antidiabetic drugs, such as metformin, a TZD, or a SU, to maintain effective glycemic control (HbA_{1c}, <7%).[52] When two or more drugs are coadministered in patients there is a possibility that the pharmacokinetics of one drug can be affected by an interaction with the second drug. Thus, new antidiabetic agents need to be tested alongside existing treatments to evaluate whether their pharmacokinetics are affected. The pharmacokinetics of saxagliptin in combination with metformin, pioglitazone (a TZD) or glyburide (an SU) were investigated in healthy male participants in three separate studies. In one study, the effect of coadministering metformin 1000 mg and saxagliptin 100 mg on the single-dose pharmacokinetics of each individual drug was investigated in 16 healthy males.[49] Metformin coadministration lowered saxagliptin C_{max} (the maximum plasma concentration of the drug; geometric mean 0.79; 90% CI 0.71, 0.87) although the authors of the study concluded that this was unlikely to be of clinical consequence. Metformin did not affect the overall exposure of saxagliptin or its metabolite, and saxagliptin did not alter the overall exposure of metformin.[53] In a second study, the effect of coadministering pioglitazone 45 mg (a CYP2C8 and CYP3A substrate), and saxagliptin 10 mg for 5 days on the steady-state pharmacokinetics of each individual drug was analyzed in 30 healthy male participants.[50] Coadministration of pioglitazone did not alter the pharmacokinetics of saxagliptin or its metabolite. Although saxagliptin increased pioglitazone C_{max} by 14%, the authors did not consider this to be clinically relevant.[53] In a third study, the effect of coadministering glyburide 5 mg with saxagliptin 10 mg on the single-dose pharmacokinetics of each individual drug was investigated in 30 healthy male participants.[48] Glyburide did not alter the pharmacokinetics of saxagliptin or its metabolite. Saxagliptin increased glyburide C_{max} by 16%, although the authors did not consider this to be of clinical relevance.[53] Based on their findings, the authors of these three studies concluded that saxagliptin can be coadministered with metformin, pioglitazone, or glyburide without any requirement for dosage adjustment of either drug.[53]

Phase 2 Trials

The efficacy and safety of saxagliptin monotherapy was investigated in a randomized, double-blind, placebo-controlled, phase 2 study in drug-naïve patients with inadequately-controlled T2DM (HbA_{1c}, 6.8%-9.7%).[54,55] Drug-naïve patients received either a low (2.5-40 mg; n=338) or high (100 mg; n=85) dose of saxagliptin once daily for 12 or 6 weeks, respectively. At week 12 in the low-dose cohort (mean baseline HbA_{1c}, 7.9%), all saxagliptin doses provided significant (P<0.007) reductions in adjusted-mean HbA_{1c} change from baseline (range –0.72% to –0.90%) compared with the placebo (–0.27%; Figure 4).[54,55] A higher proportion of patients achieved glycemic control (HbA_{1c}, <7%) with saxagliptin treatment (41%-53%) compared with the placebo (20%).[54,55] Saxagliptin also provided greater reductions in fasting plasma glucose (FPG; 11-22 mg/dL) and postprandial glucose (PPG; 24-41 mg/dL) compared with the placebo (an increase of 3 mg/dL and a reduction of 1 mg/dL, respectively).[54,55] At week 6 in the high-dose cohort (mean baseline HbA_{1c}, 7.7%), saxagliptin 100 mg treatment demonstrated similar results to the low-dose

Figure 4. Adjusted-mean HbA_{1c} changes from baseline at week 12 in the saxagliptin monotherapy low-dose cohort.[55] SEM=standard error of the mean.

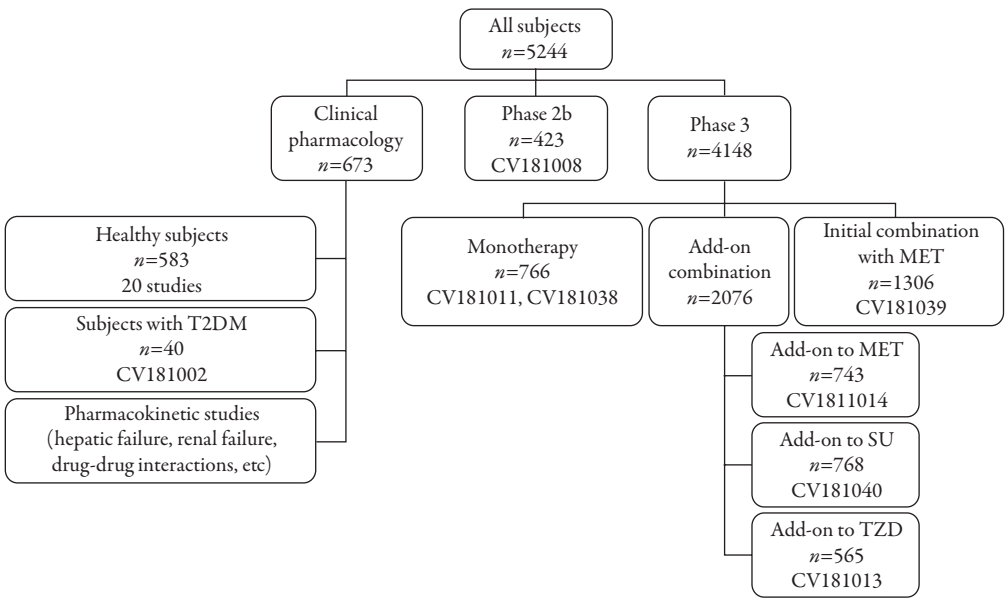


cohort with an adjusted-mean HbA_{1c} change from baseline of –1.09%, compared with the placebo (–0.36%).[54,55] In both cohorts, improvements in β-cell function (measured by homeostatic model assessment; HOMA-β) were observed in all saxagliptin-treatment arms.[54,55]

Phase 3 Trials

There have been several phase 3 trials assessing saxagliptin-based therapy in groups of patients with T2DM (Figure 5). The efficacy and safety of saxagliptin in drug-naïve patients with T2DM was investigated in two patient cohorts in a multicenter, randomized, double-blind, placebo-controlled trial: a main treatment cohort (HbA_{1c}, 7%-10%; *n*=401) treated once daily with saxagliptin (2.5, 5, or 10 mg), and an open-label cohort (HbA_{1c}, >10% and ≤12%; *n*=66) treated once daily with saxagliptin 10 mg, for 24 weeks.[56] At week 24, saxagliptin at all doses provided significant (*P*<0.0001) reductions in HbA_{1c} from baseline (–0.62% to –0.73%) compared with the placebo, with reductions observed relative to the placebo as early as week 4. Significant (*P*<0.0075) reductions in FPG compared with the placebo were observed in all saxagliptin treatment arms (15-23 mg/dL), with reductions observed as early as week 2. Saxagliptin reduced PPG area under the curve (AUC; placebo-

Figure 5. Saxagliptin clinical program indicating number of treated patients. MET=metformin; SU=sulfonylurea; TZD=thiazolidinedione; T2DM=type 2 diabetes mellitus.



subtracted differences, –6221 to –7437 mg·min/dL), and patients achieving target HbA_{1c} levels (<7%) was higher with saxagliptin (35%-41%) than with the placebo (24%).[56]

The efficacy and safety of saxagliptin as add-on therapy was investigated in three trials in patients with T2DM inadequately controlled by treatment with metformin, a TZD, or an SU alone.[57-59] The efficacy of saxagliptin as add-on therapy was investigated in 743 patients with T2DM inadequately controlled (HbA_{1c}, 7%-10%) with metformin (1500-2550 mg/day) alone. At week 24, once-daily saxagliptin (2.5-10 mg) add-on treatment to stable metformin provided significant (P<0.0001) reductions in HbA_{1c} (0.71%-0.83%) over the placebo. Saxagliptin treatment significantly (P<0.0001) reduced FPG (adjusted-mean differences of 16-24 mg/dL) and PPG compared with the placebo, following a standard oral glucose tolerance test (OGTT).[57] In the TZD study, 565 patients with inadequate glycemic control (HbA_{1c}, 7%-10.5%) were randomized to receive add-on therapy with saxagliptin (2.5 or 5 mg) or a placebo once daily, in addition to either pioglitazone (30 or 45 mg) or rosiglitazone (4 mg or 8 mg) for 24 weeks.[59] At week 24, saxagliptin (2.5 and 5 mg) add-on treatment provided significant adjusted-mean reductions in HbA_{1c} from baseline (–0.66% and –0.94%, respectively) compared with the placebo (–0.30%; both P<0.001). Significant reductions were also observed with saxagliptin (2.5 and 5 mg) for FPG (–14.3 and –17.3 mg/dL, respectively) compared with the placebo (2.8 mg/dL; both P<0.01), and for PPG AUC (–7849 and –9269 mg·min/dL, respectively) compared with the placebo (–2690 mg·min/dL; both P<0.0001). Finally, a significantly (P<0.01) greater proportion of patients reached target HbA_{1c} levels (<7%) in the saxagliptin groups (both 42%) compared with the placebo group (26%).[59] In the SU study, 768 patients with T2DM inadequately controlled (HbA_{1c}, 7.5%-10%) with glyburide 7.5 mg alone, were randomized to receive saxagliptin 2.5 or 5 mg, or glyburide 2.5 mg in addition to open-label glyburide for 24 weeks.[58] Blinded uptitration of glyburide to a maximum of 15 mg daily was permitted in the glyburide treatment arm only.[58] At week 24, saxagliptin 2.5 and 5 mg add-on treatment provided significant (P<0.0001) adjusted mean reductions in HbA_{1c} (–0.54% and –0.64%, respectively) compared with an increase for uptitrated glyburide (0.08%). Significant reductions were also observed with saxagliptin 2.5 and 5 mg add-on treatment for FPG (–7.1 and –9.7 mg/dL, respectively) compared with the placebo (0.7 mg/dL; both P<0.05), and for PPG at 120 minutes during OGTT (–30.9 and –34.2 mg/dL, respectively) compared with the placebo (7.6 mg/dL; both P<0.0001).[58]

Initial combination therapy with saxagliptin plus metformin was investigated in drug-naïve patients with inadequately controlled T2DM (HbA_{1c}, 8%-12%; n=1306). Patients were treated with saxagliptin (5 or 10 mg) plus metformin 500 mg, or the placebo, in addition to either saxagliptin 10 mg alone or metformin 500 mg alone, for 24 weeks.[60] Saxagliptin (5 and 10 mg) initial combination therapy with metformin (500 mg) provided significant (P<0.001) reductions in HbA_{1c} (–2.53% and –2.49%, respectively), FPG (–59.8 and –62.2 mg/dL, respectively), PPG at 120 minutes during an OGTT (–137.9 and –137.3 mg/dL, respectively), and improved β-cell function (HOMA-2β; 33% and 38%, respectively), compared with saxagliptin 10 mg alone (HbA_{1c}, –1.69%; FPG, –30.9 mg/dL; PPG, –106.3 mg/dL; HOMA-2β,18.2%) or metformin 500 mg alone (HbA_{1c}, –1.99%; FPG, –47.3 mg/dL; PPG, –96.8 mg/dL; HOMA-2β, 22.6%).[60]

Tolerability and Side Effects

Saxagliptin as monotherapy and in combination with other antidiabetic drugs has demonstrated a good safety and tolerability profile in multiple randomized trials in patients with T2DM. In drug-naïve patients with T2DM, saxagliptin 2.5-100 mg monotherapy once daily showed a similar tolerability profile to the placebo, with a very low incidence of confirmed hypoglycemia (≤50 mg/dL) in the saxagliptin treatment arms.[55,56] The most commonly reported adverse events with saxagliptin monotherapy include headache, upper respiratory tract infections, and urinary tract infections.[54-56]

When given as add-on treatment in patients with inadequate glycemic control, despite monotherapy with metformin, a TZD, or an SU, saxagliptin 2.5-10 mg was well tolerated, showed similar rates of adverse events to the placebo, and did not increase the risk of hypoglycemia.[57-59] Initial combination therapy with saxagliptin (5 and 10 mg) and metformin (in drug-naïve patients) was also well tolerated, with few occurrences of hypoglycemic events (saxagliptin 5 mg + metformin: 3.4%; saxagliptin 10 mg + metformin: 5%; saxagliptin 10 mg alone: 1.5%; and metformin alone: 4%).[60] When added to glyburide, the most common adverse events with occurrence rates ≥5% included (all comparisons are saxagliptin + glyburide vs. glyburide): urinary tract infection (8% vs. 8.2%), headache (7.6% vs. 5.6%), nasopharyngitis (5.8% vs. 6.7%), upper respiratory tract infection (5.4% vs. 6.7%), back pain (5.4% vs. 4.5%), hypertension (5% vs. 2.2%), diarrhea (4.8% vs. 5.2%), influenza (4.6% vs. 6%), and pain in the extremities (4% vs. 5.6%).[58] Reported hypoglycemia did not differ between groups (saxagliptin + glyburide 13.3%-14.6%, vs. glyburide 10.1%, *P*=nonsignificant).[58] The addition of saxagliptin to pioglitazone or rosiglitazone resulted in similar rates of adverse events to the placebo.[59] Similarly, all reported hypoglycemic events were similar to the placebo (saxagliptin 2.5 mg, 4.1%; saxagliptin 5 mg, 2.7%; placebo, 3.8%).[59] Saxagliptin treatment was weight neutral relative to the placebo when added to metformin (change from baseline to week 24 of –1.5, –0.9, –0.5, and –1 kg for saxagliptin 2.5, 5, 10 mg, and the placebo, respectively).[57]

Drug Interactions

A series of studies in healthy individuals investigated whether any pharmacokinetic interactions occurred between saxagliptin and a range of commonly-prescribed therapeutic agents.[61-65] Saxagliptin is metabolized to its active metabolite by cytochrome P450 CYP3A4/5, but does not inhibit or induce CYP3A4.[62] Simvastatin is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor prescribed to control hypercholesterolemia and prevent cardiovascular disease, which shares the CYP3A4 metabolic pathway with saxagliptin.[62] Therefore, the effect of the coadministration of saxagliptin 10 mg and simvastatin 40 mg once daily on the multiple-dose pharmacokinetics of each individual drug was investigated in 24 healthy individuals.[62] Coadministration of simvastatin increased saxagliptin C_{max} (by 21%), and AUC_{tau} (by 12%; AUC_{tau}: measurement of total exposure by area under the curve over the dosing interval at steady state). Saxagliptin administration did not meaningfully alter the pharmacokinetics of simvastatin. The authors concluded that the increase in C_{max} had no clinical significance, and that no dosage adjustment is necessary for either

drug when saxagliptin and simvastatin are coadministered.[62]

Ketoconazole is a broad-spectrum antifungal agent and a potent inhibitor of CYP3A4/5, which might be expected to alter the pharmacokinetics of saxagliptin.[65] The effect of coadministering saxagliptin 100 mg and ketoconazole 200 mg once daily on the single-dose pharmacokinetics of saxagliptin and the multiple-dose pharmacokinetics of ketoconazole were investigated in 16 healthy individuals.[65] Coadministration of ketoconazole increased saxagliptin C_{max} and AUC_{∞} values by 62% and 145%, respectively, and decreased metabolite C_{max} and AUC_{∞} values by 95% and 88%, respectively. Saxagliptin did not meaningfully affect ketoconazole steady-state pharmacokinetics.[65] Therefore, dosage adjustment of saxagliptin may be required when coadministered with ketoconazole.

Diltiazem is a calcium-channel blocker used in the treatment of hypertension; it is a moderate inhibitor of CYP3A4/5 and would be expected to alter the pharmacokinetics of saxagliptin.[61] The effect of the coadministration of saxagliptin 10 mg and diltiazem 360 mg on the single-dose pharmacokinetics of saxagliptin and multiple-dose pharmacokinetics of diltiazem was investigated in 14 healthy individuals.[61] Coadministration of diltiazem increased saxagliptin C_{max} by 63% and AUC_{∞} by 109%, and decreased its metabolite C_{max} by 43% and AUC_{∞} by 34%. Saxagliptin did not meaningfully affect diltiazem multiple-dose pharmacokinetics.[61] Therefore, dosage adjustment of saxagliptin may be required when coadministered with diltiazem.

Maalox Max® (MM; Novartis, East Hanover, NJ, USA; comprised of aluminum hydroxide + magnesium hydroxide + simethicone), famotidine (FAM), and omeprazole (OMZ) are agents that alter gastric pH and could potentially be coadministered with saxagliptin in patients with T2DM. In an open-label, randomized, three-way crossover study, on separate occasions single doses of saxagliptin 10 mg were coadministered with an oral dose of MM 30 mL, FAM 40 mg (dosed 3 hours earlier), or OMZ 40 mg (dosed to steady-state) in 14 healthy individuals.[63] Coadministration of MM or FAM altered saxagliptin C_{max} (point estimates [95% CI] of 0.74 [0.65, 0.84] and 1.14 [1, 1.30], respectively) but changes were not considered to be clinically relevant. OMZ showed no effect on saxagliptin pharmacokinetics. The pharmacokinetics of saxagliptin's metabolite generally paralleled those of the parent. The authors concluded that no separation of dosing or dosage adjustment is needed when saxagliptin is used with these medications.[63]

Digoxin is a cardiac glycoside widely used in the treatment of various cardiac conditions and is a P-glycoprotein substrate. The effect of coadministering saxagliptin 10 mg and digoxin 0.25 mg on the steady-state pharmacokinetics of each drug was investigated in 14 healthy individuals.[64] Coadministration of digoxin did not alter the steady-state pharmacokinetics of saxagliptin, and coadministration of saxagliptin did not alter the steady-state pharmacokinetics of digoxin. Boulton et al.[64] concluded that no dosage adjustment would be required when these two drugs are coadministered.

Therapeutic Applications

All available data suggest that saxagliptin can be used as monotherapy or in combination with other antidiabetic agents. Once-daily administration might also increase patient compliance. The lack of an increased risk of hypoglycemia and the possible neutral effect on weight makes saxagliptin an attractive therapy option.

However, as with other DPP-4 inhibitors, the lack of long-term safety data, and data in regard to cardiovascular outcomes, make it more likely that saxagliptin will be used as add-on rather than monotherapy when it becomes available.

CONCLUSION

Saxagliptin is a novel and highly selective DPP-4 inhibitor that has recently completed phase 3 clinical trials. It is an oral antidiabetic agent that is administered once daily, and produces significant reductions in HbA_{1c}, FPG, and PPG levels, when used as monotherapy or in combination with metformin, SUs, or TZDs. Treatment with saxagliptin is well tolerated and does not result in a significant increase in hypoglycemia. The impact of saxagliptin on weight has not been widely assessed, but the limited data available suggest that it might be weight neutral.

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