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REVIEW

Saxagliptin: the evidence for its place in the treatment of type 2 diabetes mellitus

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Introduction: The worldwide prevalence of type 2 diabetes mellitus (T2DM) is high, and the chronically poor metabolic control that can result from T2DM is associated with a high risk for microvascular and macrovascular complications. Because of the progressive pathophysiology of T2DM, oral antidiabetic agents often fail to provide sustained glycemic control, indicating the need for new therapies. Saxagliptin (Onglyza™; Bristol-Myers Squibb Company, Princeton, NJ, USA; AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA) is an oral dipeptidyl peptidase-4 inhibitor, recently approved for the treatment of T2DM.

Evidence review: Saxagliptin significantly improves glycemic control vs placebo, as demonstrated by decreasing glycated hemoglobin, fasting plasma glucose, and postprandial plasma glucose levels when used as monotherapy; in initial combination with metformin; and as add-on therapy with metformin, sulfonylurea (SU), or thiazolidinedione (TZD). Saxagliptin also significantly improves β-cell function, is weight neutral, has a low risk for hypoglycemia, and has been shown to have cardiovascular safety.

Place in therapy: The clinical profile for saxagliptin indicates that it is useful as an adjunct to diet and exercise as first-line monotherapy and in combination with metformin; or as add-on treatment for patients who cannot achieve glycemic control with a combination of diet and lifestyle changes and metformin, SU, or TZD.

Keywords: dipeptidyl peptidase-4 (DPP-4) inhibitor, GLP-1, HbA_{1c}, incretin, saxagliptin

Core evidence place in therapy summary for saxagliptin 5 mg once-daily in adults with T2DM

Outcome measure	Evidence	Implications
Disease-oriented evidence		
Reduction in HbA_{1c}	Clear	Significantly improves glycemic control compared with placebo by decreasing HbA_{1c}, as monotherapy; in initial combination with metformin; and as add-on therapy with metformin, SU, or TZD
Reduction in FPG and PPG-AUC	Clear	Significantly decreases FPG and PPG-AUC compared with placebo as monotherapy; in initial combination with metformin; and as add-on therapy to metformin, SU, or TZD
Glycemic control[a]		
Monotherapy	Clear	Significantly more patients achieve HbA_{1c} goal of $< 7\%$ compared with placebo
Combination therapy	Clear	Significantly more patients achieve HbA_{1c} goal of $< 7\%$ in initial combination with metformin; and as add-on therapy to metformin, SU, or TZD compared with placebo

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Outcome measure	Evidence	Implications
Effects on postprandial insulin	Substantial	Significantly increases postprandial insulin compared with placebo
Effects on postprandial glucagon	Substantial	Significantly decreases postprandial glucagon compared with placebo
Improvement in β-cell function	Substantial	Saxagliptin monotherapy significantly improves β-cell function as assessed by HOMA-2β, and increases β-cell responsiveness as measured by hyperglycemic clamp compared with placebo
Patient-oriented evidence		
Hypoglycemia	Clear	In multicenter, randomized, double-blind, 24-week trials in which saxagliptin was administered as monotherapy; as initial combination with metformin; or as add-on treatment in patients receiving metformin, SU, or TZD; the frequency of hypoglycemia was generally low
Weight effects	Clear	Saxagliptin is generally weight neutral
Tolerability	Clear	Saxagliptin is generally well tolerated, with adverse event frequencies similar to those observed with comparator when administered as monotherapy; as initial combination with metformin; or as add-on treatment in patients receiving metformin, SU, or TZD
CV effects	Substantial	*Post hoc* analysis provided no evidence of increased CV risk with saxagliptin as monotherapy or in combination with other oral antidiabetic agents. Results raise the possibility that saxagliptin may be cardioprotective
Patient adherence	No evidence	Studies required to assess effects of saxagliptin on adherence to treatment

Note: [a]Percentage of patients achieving $HbA_{1c} < 7\%$.
Abbreviations: CV, cardiovascular; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HOMA-2β, homeostatic model assessment-2 beta; PPG-AUC, postprandial glucose-area under the concentration–time curve; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione.

Scope, aims, and objectives

Dipeptidyl peptidase-4 (DPP-4) inhibitors have been added to the armamentarium of traditional antidiabetic medications and are currently recommended by the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) guidelines as an option for initial monotherapy in patients with glycated hemoglobin A_{1c} (HbA_{1c}) 6.5%–7.5%, and as part of combination treatment with metformin for patients with type 2 diabetes mellitus (T2DM) and an $HbA_{1c} \geq 7.6\%$.[1]

Saxagliptin (Onglyza™; Bristol-Myers Squibb Company, Princeton, NJ, USA; AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA) is a once-daily, oral DPP-4 inhibitor that has been submitted for regulatory review in more than 50 countries and is approved in 38 countries, including the United States and member states of the European Union, for patients with T2DM who are unable to maintain glycemic control with diet and exercise alone or on metformin, a sulfonylurea (SU), or a thiazolidinedione (TZD).[2] In addition to being well tolerated without increasing the risk of hypoglycemia, saxagliptin produces significant reductions in HbA_{1c}, fasting plasma glucose (FPG), and postprandial glucose (PPG) levels when used as monotherapy and in combination with metformin, SUs (eg, glyburide), and TZDs (eg, pioglitazone or rosiglitazone).[2–7]

The purpose of this article is to review the mechanism of action and current clinical evidence on saxagliptin as they relate to the management of patients with T2DM.

Methods

English language literature searches were conducted. Databases were searched between 1 January 2004 and 9 November 2009, using the search terms "saxagliptin" OR

"BMS-477118" and "type 2 diabetes". Databases searched included the following:

- PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fgci)
- EMBASE
- BIOSIS
- Derwent Database
- Cochrane DSR (Database of Systematic Review)
- www.clinicaltrials.gov
- www.clinicalstudyresults.org

A total of 86 records were identified via the searches described above and manually reviewed. Thirty-eight of these records were duplicates and were not considered further. Twenty-seven were excluded for reasons including nonsystematic reviews, letters, editorials, news items, notes, comments, corrections, articles pertaining to other drugs or treatments, and articles on pharmacokinetics and drug interactions. This review is based on the 21 records that comprised the evidence base (Figure 1).

Disease overview

Prevalence/economics

Diabetes has an estimated prevalence of 220 million people worldwide and is expected to affect approximately 440 million by 2030.[8] It is estimated that between 90% and 95% of adults with diabetes have T2DM.[9] The most recent estimate for the United States indicates that 23.7 million people have diabetes (both diagnosed and undiagnosed).[10] The prevalence of T2DM varies considerably, depending on race, ethnicity, age, and gender. In the United States, diabetes is more common among Native Americans, Alaska natives, Hispanics and Latinos, and non-Hispanic blacks.[9,11] The prevalence of diabetes also increases with advancing age, reaching approximately 21% among those aged $\geq$ 60 years.[11]

Diabetes-related spending in the United States was estimated to be $113 billion in 2009.[10] The individual, societal, and economic burdens resulting from diabetes are mainly due to the long-term microvascular (eg, retinopathy, nephropathy) and macrovascular (eg, cardiovascular [CV]) complications of the disease.[12,13]

It is estimated that the number of people in the United States with diabetes will rise to 44.1 million by 2034 and that spending on this disease will subsequently increase to $336 billion.[10] Various factors are expected to contribute to the rise in the United States prevalence of diabetes over the next 20 years, including the advancing age of the population

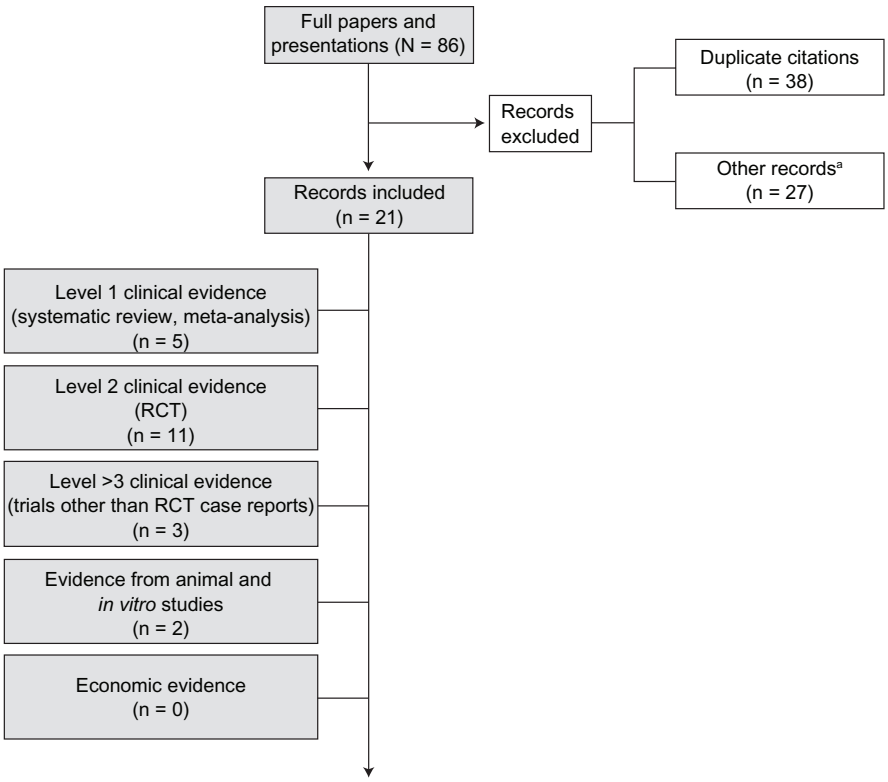

Figure 1 Evidence base included in the saxagliptin review.
Notes: [a]Includes nonsystematic reviews, letters, editorials, news items, notes, comments, corrections, articles pertaining to other drugs or treatments, and articles on pharmacokinetics and drug interactions.
Abbreviation: RCT, randomized-controlled trial.

(diabetes prevalence increases with age); reduced mortality rates and longer patient life spans due to improved screening, detection, and better health care; and the increase in diabetes risk factors, most notably physical inactivity and obesity.[11]

T2DM risk factors and pathophysiology

Both genetic and environmental factors contribute to the development of T2DM.[9,11] It is well known that multiple factors, including age, lack of physical activity, diet, and obesity strongly influence diabetes risk.[14] Characteristics of the disease for most patients with T2DM are progressively impaired insulin secretion that reflects pancreatic β-cell dysfunction; increased hepatic glucose production; insulin resistance; increased free fatty acid levels, which contribute to insulin resistance; increased α-cell secretion of glucagon; increased glucose reabsorption by the kidneys; alterations in brain pathways involved in the regulation of appetite and satiety; and possibly decreased activity of incretin hormones (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulin-releasing polypeptide [GIP]).[11,15]

Role of incretin therapy in treating the pathophysiology of T2DM

Incretins, intestinal hormones released in response to the ingestion of food, potentiate the glucose-induced insulin response. In humans, the incretin effect is mainly caused by 2 peptide hormones, GIP and GLP-1. GIP is secreted by K cells from the upper small intestine and GLP-1 is mainly produced in the enteroendocrine L cells located in the distal intestine. Circulating levels of GIP and GLP-1 are very low in the fasting state, and rapidly increase following food ingestion. The actions of the 2 peptides are similar. Both stimulate insulin secretion and promote β-cell proliferation. GLP-1 also binds to pancreatic β-cells to inhibit glucagon secretion along with other receptors in multiple tissues to slow gastric emptying, and increase satiety to decrease food ingestion (Figure 2A).[16–20]

Endogenous GLP-1 and GIP have half-lives of <2 minutes and 5–7 minutes, respectively, before they are rapidly degraded by the ubiquitous enzyme, DPP-4.[16] DPP-4 is widely expressed in multiple tissues, including the central nervous system, kidney, lung, adrenal gland, liver, intestine, spleen, testis, and pancreas, as well as on the surfaces of lymphocytes and macrophages.[16,17] As a result of DPP-4 degradative activity, intact and biologically active GLP-1 represents only 10%–20% of total plasma GLP-1.[20] By inhibiting the enzymatic activity of DPP-4, circulating plasma levels of active GIP and GLP-1 can be increased 2-fold to 3-fold.[2,21–23]

The utility of DPP-4 inhibitors in the treatment of T2DM arises from their ability to prevent catabolism and prolong the actions of endogenous GIP and GLP-1 (Figure 2B).[16–19] Administration of a DPP-4 inhibitor doubles the circulating levels of GLP-1 and increases the ratio of active/total GLP-1.[24] DPP-4 inhibitors enhance the actions ascribed to GLP-1 receptor agonists, including the stimulation of insulin and inhibition of glucagon secretion in a glucose-dependent manner, but are generally not associated with a deceleration of gastric emptying, satiety, or weight loss. This may explain the low incidence of gastrointestinal (GI) side effects with DPP-4 inhibitors.[2,24,25]

Saxagliptin is a potent, reversible, competitive DPP-4 inhibitor that selectively inhibits DPP-4.[16] This is in contrast to its effects on other DPP enzymes, including DPP-8 and DPP-9.[16] Based on calculated binding affinities to DPP-4, saxagliptin is 10-fold more potent than either sitagliptin or vildagliptin, although this does not translate clinically.[16,21,26] Saxagliptin exhibits prolonged binding to the DPP-4 active site, which results in an extended inhibition of this enzyme.[16,26]

In summary, inhibition of DPP-4 by saxagliptin slows the inactivation of incretin hormones, including GLP-1 and GIP, in T2DM patients.[2] This inhibition results in increased

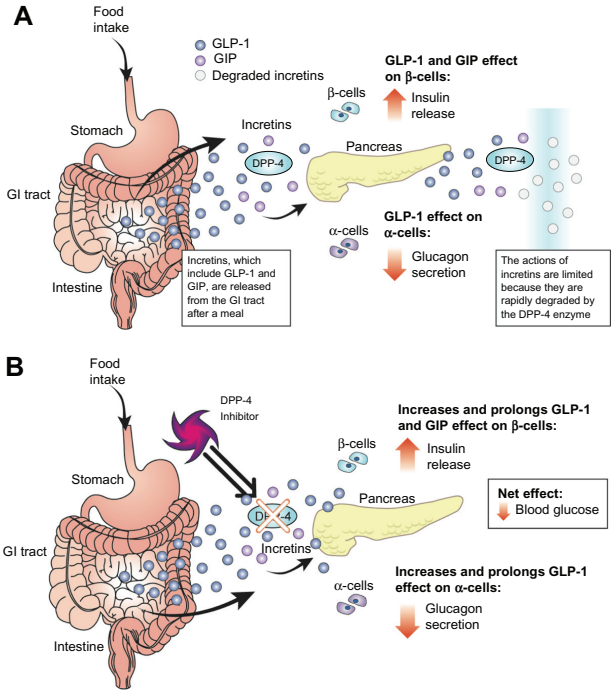

Figure 2 Mechanism of action of DPP-4 inhibitors. A) action of incretins.[16–19] B) action of DPP-4 inhibitors.[16–19] Reprinted from *Cell Metabolism*, Volume 3, Daniel J. Drucker, The biology of incretin hormones, 153–165, March 2006, with permission from Elsevier.[18]

Abbreviations: DPP-4, dipeptidyl peptidase-4; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

concentrations of active, intact, endogenous incretin hormones, and greater duration and magnitude of their actions in increasing glucose-dependent insulin secretion and in suppressing glucagon secretion and hepatic glucose production.[2,27]

Current therapy options

Summary of glucose-lowering therapies

There are many treatment options that can be combined with lifestyle interventions to achieve glycemic control in patients with T2DM. Agents that can be used as monotherapy or in combination to lower blood glucose and HbA_{1c} include biguanides (metformin), insulin, SUs (glyburide, glipizide, glibenclamide), TZDs (rosiglitazone, pioglitazone), GLP-1 receptor agonists (exenatide, liraglutide), α-glucosidase inhibitors (acarbose), glinides (repaglinide, nateglinide), amylin agonists (pramlintide), DPP-4 inhibitors (eg, saxagliptin, sitagliptin), bile acid sequestrants (colesevelam), and dopamine agonists (bromocriptine).[1,12,28]

In addition to lifestyle modification, which can lower HbA_{1c} by 1%–2%, current treatment guidelines all recommend metformin, unless contraindicated, as the first agent to be added to diet and lifestyle changes for the majority of patients.[1,12] Metformin monotherapy typically lowers HbA_{1c} by 1%–1.5%, is generally well tolerated with low risk for hypoglycemia, and is weight neutral.[12] It is contraindicated, however, in patients with renal insufficiency and its use is often associated with adverse GI effects.[12] SUs also decrease HbA_{1c} by about 1.5%, but their use is associated with hypoglycemia and weight gain.[12] There is also evidence, primarily from *in vitro* and animal data, that exposure to SUs may be toxic to β-cells.[15,29,30] Data from the A Diabetes Outcome Progression Trial (ADOPT) also show that SUs have a higher secondary failure rate.[31]

TZDs lower HbA_{1c} by 0.5%–1.5%, but their use has been associated with weight gain, edema, congestive heart failure, elevated risk for bone fractures, and possibly macular edema.[12,32,33] Glinides lower HbA_{1c} by 0.5%–1.5%, and their safety profile is similar to that of SUs, with hypoglycemia and weight gain as common adverse events (AEs).[12] Acarbose lowers HbA_{1c} by 0.5%–1.0% and the most common AEs are associated with GI disturbances.[34] Pramlintide lowers HbA_{1c} by 0.5%–1.0%, and GI events are the most common side effects associated with its use.[12] GLP-1 receptor agonists have been shown to lower HbA_{1c} levels by 0.5%–1.5%[35] without increasing the risk of hypoglycemia, and are associated with weight loss. However, they are injectable medications, and the most common AEs include mild to moderate nausea.[12] Due to the progressive nature of diabetes, insulin therapy is ultimately required for many patients.[11] AEs associated with insulin therapy include weight gain and hypoglycemia,[12] though the risks for both of these effects are reduced with the use of newer insulin analogs.[36]

Current treatment guidelines for patients with T2DM recommend an individualized treatment approach to balance glycemic efficacy with tolerability and long-term safety. Guidelines also consider that T2DM is a progressive disease characterized by worsening glycemic control, which requires treatment intensification with dose titration and the addition of medications over time to achieve and maintain treatment goals.[12] Maintenance of glycemic control requires frequent (every 2–3 months) evaluation of treatment efficacy and prompt adjustment of the therapeutic regimen when patients are not achieving HbA_{1c} goals.[1]

Clinical evidence with saxagliptin

Patient group/population

Patients included in well-controlled trial populations were treatment-naïve,[3,4] or unable to maintain glycemic control with metformin,[7] an SU,[5] or a TZD in conjunction with diet and exercise.[6] Pregnant women and pediatric patients aged <18 years were excluded from the study population.[2]

Clinical efficacy

Saxagliptin has been studied as monotherapy and in combination with metformin, glyburide, and the TZDs (pioglitazone and rosiglitazone) and has demonstrated glycemic efficacy regardless of age, gender, race/ethnicity, or body mass index (BMI). Although the text reports on saxagliptin effects on glycemic parameters at doses ranging from 2.5 to 100 mg, efficacy results in Table 1 and Figure 3 are presented for saxagliptin 5 mg, the usual clinical dose for patients with T2DM.[3–7,37–40]

Monotherapy

12-week study

A randomized, parallel-group, double-blind, placebo-controlled trial included 338 treatment-naïve patients with T2DM and mean HbA_{1c} 7.8% who received saxagliptin 2.5, 5, 10, 20, and 40 mg once-daily, or placebo, for 12 weeks (low-dose cohort). In addition, 85 patients received saxagliptin 100 mg once-daily (high-dose cohort), or placebo, for 6 weeks. Saxagliptin significantly reduced HbA_{1c} by 0.7%–0.9% vs placebo (−0.3%) from a mean baseline of 7.9%. Placebo-adjusted reductions in HbA_{1c} ranged from 0.45% to 0.63% (all doses $P < 0.007$ vs placebo). Percentages

Table 1 Saxagliptin 5 mg effects on glycemic parameters[3–7,37,39,40]

Design	N	Treatment and dose	Study duration (weeks)	Baseline HbA_{1c}	Outcome				Reference
					Adjusted mean change from baseline HbA_{1c} (%)	Patients (%) reaching $HbA_{1c} < 7.0\%$	Adjusted mean change from baseline FPG (mmol·min/L)	Adjusted mean change from baseline PPG-AUC (mmol·min/L)	
Monotherapy	106	SAXA 5 mg	24	8.0	–0.5[a]	38[a]	–0.50[a]	–383[a]	Rosenstock 2009[3]
	95	PBO		7.9	0.2	24	0.33	–36	
Monotherapy	74	SAXA 5 mg QAM	24	7.9	–0.7[a]	45	–0.61	–456	CV181038[39]
	72	SAXA 5 mg QPM		7.9	–0.6[a]	39	–0.44	–336	
	74	PBO		7.8	–0.3	35	0.17	–171	
With MET	191	SAXA 5 mg + MET	24	8.1	–0.7[a]	44[a]	–1.22	–532[a]	DeFronzo 2009[7]
	179	PBO + MET		8.1	0.1	17	0.07	–183	
With SU	253	SAXA 5 mg + GLY	24	8.5	–0.6[a]	23[a]	–0.56[a]	–278[a]	Chacra 2009[5]
	267	PBO + UP-GLY		8.4	0.08	9	0.06	66	
With TZD	186	SAXA 5 mg + TZD	24	8.4	–0.9[a]	42	–1.00	–514[a]	Hollander 2009[6]
	184	PBO + TZD		8.2	–0.3	26	–0.20	–149	
Initial combination with MET	320	SAXA 5 mg + MET	24	9.4	–2.5[a]	60[a]	–3.33[a]	–1,170[a]	Jadzinsky 2009[4]
	328	PBO + MET		9.4	–2.0	41	–2.61	–823	
Long-term with MET[b]	191	SAXA 5 mg + MET	102	8.1	–0.40	30	–0.63	–323[a]	DeFronzo 2009[37]
	179	PBO + MET		8.1	–0.32	12	0.38	–64	
Long-term with SU[b]	253	SAXA 5 mg + GLY	76	8.5	0.03	10	0.44	–122	Clinical study results.org, 2009[40]
	267	PBO + UP-GLY		8.4	0.69	5	0.23	181	

Notes: [a]Statistical significance. [b]Repeated measures analysis.

Abbreviations: FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; MET, metformin; PBO, placebo; PPG, postprandial plasma glucose; QAM, daily before noon; QPM, daily after noon; SAXA, saxagliptin; SU, sulfonylurea; TZD, thiazolidinedione; UP-GLY, uptitrated glyburide.

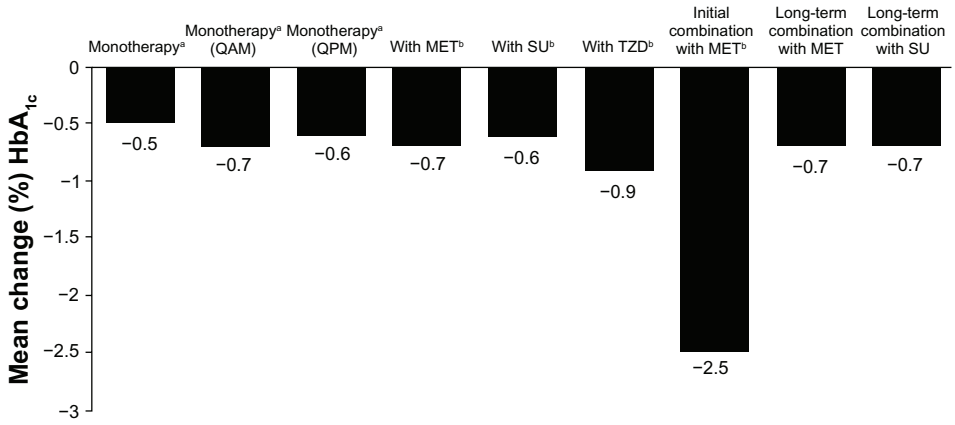

Figure 3 Saxagliptin 5 mg effects on HbA_{1c} in placebo-controlled and active-controlled comparative studies.[3–7,37,39,40]
Notes: [a]Statistical significance vs placebo. [b]Statistical significance vs comparator.
Abbreviations: HbA_{1c}, glycated hemoglobin; MET, metformin; QAM, daily before noon; QPM, daily after noon; SU, sulfonylurea; TZD, thiazolidinedione.

of patients with $HbA_{1c} < 7\%$ at 12 weeks for the 2.5, 5, 10, 20, or 40 mg doses were 50, 47, 41, 50, and 53%, respectively, vs 20% for placebo.[38] Thus, clinically significant reductions from baseline HbA_{1c} compared with placebo were demonstrated for 2.5–40 mg saxagliptin, with about 50% of patients in each treatment arm achieving the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) recommended glycemic target of $HbA_{1c} < 7\%$.[12,38] In addition, HbA_{1c} was significantly reduced from baseline in the 100 mg cohort (–1.09%) compared with placebo (–0.36; $P < 0.007$).[38] HbA_{1c} reductions with saxagliptin monotherapy were particularly meaningful, given the relatively low mean baseline HbA_{1c} (7.9%) of this study population.[38]

24-week study

A randomized, double-blind, placebo-controlled trial of 401 patients with T2DM not controlled with diet and exercise alone (mean baseline HbA_{1c} 7.9%) was conducted. Patients received oral saxagliptin 2.5, 5, or 10 mg once-daily or placebo for 24 weeks. Saxagliptin monotherapy produced clinically meaningful improvements in HbA_{1c} and FPG in treatment-naïve patients at all doses (2.5, 5, and 10 mg) compared with placebo. Saxagliptin (5 and 10 mg) also statistically significantly improved PPG-area under the concentration–time curve (AUC) compared with placebo ($P < 0.0002$, $P < 0.0001$, respectively). A separate open-label cohort of 66 patients with HbA_{1c} 10%–12% received saxagliptin 10 mg once-daily for 24 weeks.[3] Not surprisingly, clinically meaningful reductions in HbA_{1c} (–1.9%), FPG (–1.83 mmol/L), and PPG-AUC (–615 mmol·min/L) were also observed in the patients with high baseline HbA_{1c} (10%–12%; Figure 4).[3] Saxagliptin was more effective than placebo in achieving $HbA_{1c} < 7\%$ at week 24.

Monotherapy titration study

A 24-week monotherapy study compared saxagliptin with placebo, as a fixed-dose and with titration, 2.5 mg daily before noon (QAM), 5 mg QAM, 5 mg daily after noon (QPM), and 2.5 mg titrated to 5 mg QAM (2.5/5 mg QAM) in 365 treatment-naïve subjects with T2DM and inadequate glycemic control (mean baseline HbA_{1c} 7.9%) on diet and exercise.[39] Statistically significant mean changes from baseline HbA_{1c} were observed for 2.5 mg QAM (–0.71%; $P = 0.0023$), 5 mg QAM (–0.66%; $P = 0.0059$), 2.5/5 mg QAM (–0.63%; $P = 0.0119$), and 5 mg QPM (–0.61%; $P = 0.0157$) vs placebo (–0.26%). Respective reductions in FPG were –0.63 ($P = 0.0204$), –0.59 ($P = 0.0271$), –0.69 ($P = 0.0130$), –0.44 (P = NS), vs 0.18 mmol·min/L. A decrease in PPG-AUC was observed in all treatment groups, with the greatest decreases in the saxagliptin 2.5 mg QAM, 5 mg QAM, and 2.5/5 mg QAM, and a modest decrease in the 5 mg QPM vs placebo (–445, –456, –432, and –336 vs –171 mmol·min/L, respectively). The percentages of patients achieving $HbA_{1c} < 7\%$ with 2.5 mg QAM, 5 mg QAM, 2.5/5 mg QAM, and 5 mg QPM, vs placebo were 35.8, 44.9, 43.5, and 38.6%, vs 35.3%, respectively.[39]

Combination therapy

With metformin

Two clinical trials investigated the use of saxagliptin as an add-on to metformin or in combination as initial therapy. Both trials are described below.[4,7,41]

Add-on therapy

The efficacy of saxagliptin (2.5, 5, or 10 mg once-daily) or placebo when added to metformin (1,500–2,500 mg per day) was evaluated in a 24-week, randomized, double-blind, placebo-controlled study that included 743 patients

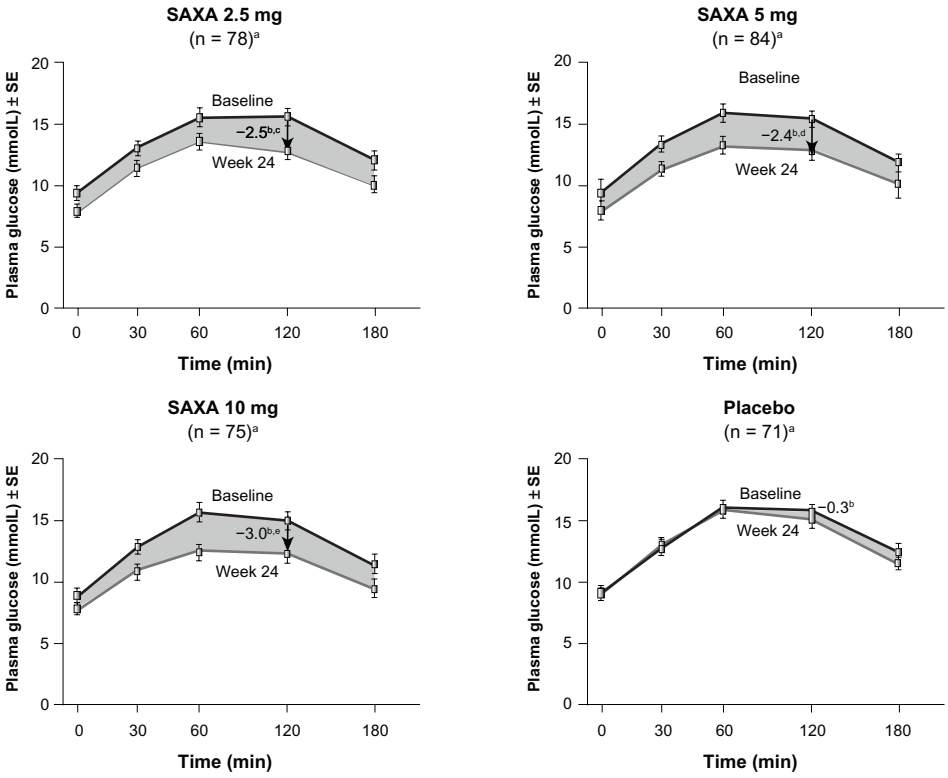

Figure 4 Postprandial concentrations during the 3-hour oral glucose tolerance test. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. Volume 25 by Rosenstock, et al. © 2009 by *Current Medical Research and Opinion*.[3]
Notes: [a]Sample size at 120-minute time point. [b]Adjusted mean change in 120 minute (PPG). [c]$P = 0.007$ vs PBO. [d]$P = 0.0009$ vs PBO. [e]$P < 0.0001$ vs PBO.
Abbreviations: PBO, placebo; PPG, postprandial glucose; SAXA, saxagliptin.

inadequately controlled on metformin alone (mean baseline HbA_{1c}, 8.0%).[7] Changes from baseline in HbA_{1c} for metformin plus saxagliptin 2.5, 5, or 10 mg were –0.59, –0.69, –0.58%, respectively, vs a 0.13% increase for placebo ($P < 0.0001$ for all saxagliptin doses vs placebo). The respective values for FPG were –0.79, –1.22, and –1.14, vs 0.07 mmol·min/L (all $P < 0.0001$); and for PPG-AUC were –493, –532, and –452, vs –183 mmol·min/L (all $P < 0.0001$). Saxagliptin added to metformin was also significantly more effective than metformin plus placebo in achieving $HbA_{1c} < 7.0\%$. Percentages of patients receiving saxagliptin 2.5, 5, and 10 mg vs placebo added to metformin achieving this goal were 37, 44, and 44%, vs 17%, respectively (all $P < 0.0001$).[7] Maximal HbA_{1c}, FPG, and PPG-AUC reductions were observed with the saxagliptin 5-mg dose. Furthermore, add-on saxagliptin did not affect body weight compared with metformin plus placebo.[7]

In a subset of patients, β-cell assessment was conducted via homeostatic model assessment-2 beta (HOMA-2β) and demonstrated that saxagliptin 2.5, 5, and 10 mg plus metformin improved β-cell function. In addition, saxagliptin added to metformin significantly increased postprandial insulin ($P \leq 0.0001$, $P = 0.0063$, $P \leq 0.0001$, respectively), C-peptide ($P = 0.0003$, $P \leq 0.0001$, $P \leq 0.0001$, respectively), and decreased postprandial glucagon ($P = 0.0090$, $P = 0.0025$, $P = 0.0010$, respectively) vs metformin alone.[7]

Patients who completed all visits during the initial 24-week study period without need for hyperglycemia rescue therapy were eligible to enter a 78-week controlled long-term study extension. Patients who received saxagliptin in the initial 24-week study period maintained their current dosage in the long-term extension. At 102 weeks, treatment with saxagliptin 5 mg plus metformin was associated with a greater reduction in HbA_{1c} than placebo plus metformin. At this time point, the placebo-corrected changes from baseline HbA_{1c} for saxagliptin 2.5, 5, and 10 mg added to metformin were –0.62, –0.72, and –0.52%, respectively.[37]

Initial combination therapy

Use of an initial combination of saxagliptin plus metformin was compared with the use of either agent alone in a randomized, double-blind, active-controlled trial that included 1,306 treatment-naïve patients with T2DM and baseline mean HbA_{1c} of 9.4%, fasting C-peptide concentration ≥ 1.0 ng/mL, and BMI ≤ 40 kg/m^2. Patients were randomized to 1 of 4 treatment arms: saxagliptin 5 mg plus

metformin 500 mg, saxagliptin 10 mg plus metformin 500 mg, saxagliptin 10 mg plus placebo, or metformin 500 mg plus placebo for 24 weeks.[4] At 24 weeks, saxagliptin 5 mg plus metformin, saxagliptin 10 mg plus metformin, saxagliptin 10 mg, and metformin 500 mg reduced HbA_{1c} by –2.5, –2.5, –1.7, and –2.0%, respectively (all $P < 0.0001$ for combination vs either agent alone). The respective values for FPG were –3.33, –3.44, –1.72, and –2.61 mmol·min/L (each combination $P < 0.0001$ vs saxagliptin 10 mg; and $P \leq 0.0002$ vs metformin 500 mg). Percentages of patients achieving $HbA_{1c} < 7\%$ were 60.3, 59.7, 32.2, and 41.1%, respectively, for saxagliptin 5 mg plus metformin, saxagliptin 10 mg plus metformin, saxagliptin 10 mg, and metformin 500 mg ($P < 0.0001$ for each combination vs monotherapy). The respective values for achievement of $HbA_{1c} \leq 6.5\%$ were 45.3, 40.6, 20.3, and 29.0% ($P < 0.0001$ for each combination vs monotherapy). All treatments reduced PPG-AUC; the respective declines were –1,170, –1,184, –891, and –833 mmol·min/L (all $P < 0.0001$ for combination treatment vs monotherapy).[4] Saxagliptin plus metformin initial combination therapy also provided significant improvements in β-cell function (HOMA-2β assessment) vs either agent alone, and numerically greater increases in postprandial insulin and early insulin responses were observed vs metformin, but not vs saxagliptin 10 mg. Similar to saxagliptin added to metformin, saxagliptin did not affect body weight compared with metformin alone.[4] In summary, saxagliptin given in combination with metformin as initial therapy significantly improved HbA_{1c}, FPG, and PPG-AUC, compared with either agent alone, with a tolerability profile comparable to either of the monotherapy agents.[4]

With sulfonylurea

The efficacy of adding saxagliptin (2.5 or 5 mg once-daily) to glyburide (7.5 mg once-daily) vs uptitration of glyburide to a maximum of 15 mg once-daily was assessed in 768 patients with mean baseline HbA_{1c} 8.4% receiving a submaximal dose of SU.[5] Patients enrolled in the trial started treatment on saxagliptin 2.5 or 5 mg or placebo plus glyburide 7.5 mg, or glyburide 10 mg. Uptitration of glyburide to a maximum of 15 mg was permitted at weeks 2 and 4, based on FPG and fasting whole blood glucose levels for patients receiving this drug as monotherapy. At the end of the 24-week treatment period, 92% of patients receiving glyburide only were uptitrated to a daily dose of 15 mg. The saxagliptin 2.5 and 5 mg plus glyburide 7.5 mg treatment groups showed statistically significant adjusted mean decreases from baseline HbA_{1c} and FPG vs the uptitrated glyburide group. Changes from baseline HbA_{1c} with saxagliptin 2.5 and 5 mg plus glyburide vs uptitrated glyburide were −0.54% and −0.64%, vs 0.08%, respectively ($P < 0.0001$ for both combinations vs uptitrated glyburide); and the respective values for FPG were −0.39 mmol/L, −0.56 mmol/L, vs 0.06 mmol/L ($P = 0.0218$ for 2.5 mg and $P = 0.002$ for 5 mg saxagliptin plus glyburide vs uptitrated glyburide). The proportion of patients achieving $HbA_{1c} < 7\%$ were 22.4% and 22.8%, vs 9.1%, respectively (both $P < 0.0001$), and the values for PPG-AUC were −238 and −278, vs 66 mmol·min/L, respectively (both $P < 0.0001$). In addition, 10.4% of patients treated with saxagliptin 5 mg plus glyburide achieved the $HbA_{1c} \leq 6.5\%$ treatment goal, vs 4.5% for uptitrated glyburide ($P = 0.0117$).[5] Mean body weight increases in the saxagliptin treatment group (2.5 and 5 mg) vs uptitrated glyburide were 1.5 lbs (0.7 kg; $P = 0.0381$) and 1.8 lbs (0.8 kg; $P = 0.0120$), vs 0.7 lbs (0.3 kg), respectively. In summary, the saxagliptin 2.5 and 5 mg plus glyburide 7.5 mg treatment groups showed statistically significant adjusted mean decreases from baseline in HbA_{1c} and FPG vs the uptitrated glyburide group.[5]

Patients who met glycemic rescue criteria or completed all of their visits during the initial 24 week, short-term period were eligible to enter the 52-week study extension. As with the metformin long-term extension study, patients who received saxagliptin in the initial 24-week study period maintained their current dosage in the long-term extension. Treatment with saxagliptin 5 mg plus glyburide was associated with a greater reduction in HbA_{1c} than placebo plus uptitrated glyburide sustained up to 76 weeks.[40]

With thiazolidinedione

The efficacy of saxagliptin plus TZD in patients with T2DM and inadequate glycemic control on TZD monotherapy was evaluated in a randomized, double-blind, placebo-controlled trial that included 565 patients with baseline mean HbA_{1c} 8.3% on stable monotherapy with pioglitazone 30 or 45 mg or rosiglitazone 4 or 8 mg for at least 12 weeks.[6] Patients were randomized to 1 of 3 treatment arms: saxagliptin (2.5 or 5 mg) or placebo and assessed for 24 weeks.[6] At 24 weeks, the reductions in HbA_{1c} for saxagliptin 2.5 and 5 mg plus TZD vs TZD alone were −0.66% ($P = 0.0007$) and −0.94% ($P < 0.0001$), vs −0.30%, respectively. The respective values for FPG vs TZD were −0.80 mmol/L ($P = 0.0053$) and −1.00 mmol·min/L ($P = 0.0005$), vs 0.20 mmol·min/L. The proportion of patients achieving $HbA_{1c} < 7.0\%$ was 42.2% ($P = 0.001$) and 41.8% ($P = 0.0013$), vs 25.6%, respectively, for 2.5 and 5 mg saxagliptin plus TZD vs TZD alone. The respective values for achievement of $HbA_{1c} \leq 6.5\%$ were

19.3% and 20.7%, vs 9.4%. Saxagliptin plus TZD was also significantly more effective than TZD alone in decreasing PPG-AUC. Reductions from baseline for saxagliptin 2.5 and 5 mg plus TZD vs TZD alone were −436 and −514, vs −149 mmol·min/L, respectively ($P < 0.0001$ for each comparison between saxagliptin plus TZD vs TZD alone).[6] Saxagliptin plus TZD also demonstrated significant improvements in β-cell function (HOMA-2β assessment), increases in postprandial insulin and C-peptide, and decreases in postprandial glucagon vs TZD monotherapy.[6] In conclusion, saxagliptin plus TZD demonstrated statistically significant reductions in HbA_{1c}, FPG, and PPG compared with TZD alone in patients inadequately controlled on TZD monotherapy.[6]

β-cell function

In addition to the improvements in β-cell function (HOMA-2β assessment) reported above, a significant improvement in β-cell responsiveness was demonstrated with use of saxagliptin, utilizing the hyperglycemic clamp in treatment-naïve patients. This randomized, parallel-group, placebo-controlled study assessed the effect of saxagliptin 5 mg on β-cell function by intravenous hyperglycemic clamp (IV HC) in the fasting state (0–180 min IV HC) and after stimulating incretin secretion by orally ingesting 75 g glucose (180–480 min IV oral HC) at baseline and after 12 weeks of saxagliptin treatment. Results showed that treatment with saxagliptin improved pancreatic β-cell responsiveness to glucose in the fasting and postprandial states and decreased postprandial glucagon concentration.[22]

Efficacy in elderly patients

The effects of saxagliptin treatment in elderly patients have been reported in a pooled subanalysis of elderly patients (aged ≥ 65 years) vs adults (aged < 65 years). Data from five 24-week studies in which saxagliptin 5 mg or placebo was administered as monotherapy or added to treatment with metformin, glibenclamide, or a TZD were included. Results indicated that saxagliptin lowered HbA_{1c} by −0.73% vs −0.17% for placebo, and that the efficacy of saxagliptin was similar in adult (aged < 65 years) and elderly (aged ≥ 65 years) patients with T2DM.[42]

Safety and tolerability

As determined in 8 clinical trials, saxagliptin was generally well tolerated when administered as monotherapy or combined with metformin, glyburide, or a TZD (Figure 3).[3–7,37,39,40] AEs observed in ≥ 5% of patients in any treatment group in the pivotal trials for saxagliptin are summarized in Tables 2 and 3. The most common AEs observed with saxagliptin are similar to those of other DPP-4 inhibitors, and include headache, upper respiratory tract infections, urinary tract infections, and nasopharyngitis.[3–7,37,43,44] Addition of saxagliptin to metformin was generally well tolerated, with no increase in hypoglycemia or weight over 102 weeks.[37] Combination of saxagliptin 5 mg plus TZD resulted in increased peripheral edema vs TZD alone (8.1% vs 4.3%, Table 2). However, peripheral edema was less common with saxagliptin 2.5 mg plus TZD vs TZD monotherapy (3.1% vs 4.3%). When pedal edema was excluded from the analysis, the frequencies for edema were 0.5% each for all saxagliptin-treated patients and those who received TZD alone.[6] Although the long-term clinical safety, tolerability, and efficacy of DPP-4 inhibitors have been demonstrated for up to 2 years, it is unclear if there are long-term neurological or immunological consequences of inhibiting DPP-4.[45–48]

Hypoglycemia

In the 8 multicenter, randomized, double-blind, 24-week, phase 3 trials in which saxagliptin was administered as monotherapy; as initial combination with metformin; or as add-on treatment in patients receiving metformin, glyburide, or TZD, the frequency of hypoglycemia was generally similar to that for placebo or to treatment arms not containing saxagliptin for up to 76 weeks (Table 3).[3–7,37,39,40,49] Note that significance values were not determined. The results from the pooled analysis of the monotherapy study, as well as the initial combination and add-on studies, concluded that saxagliptin had a low risk of hypoglycemia when used as monotherapy or in combination with metformin, SUs, or TZDs. Specifically, hypoglycemia was confirmed in <2.5% of patients treated with saxagliptin 2.5, 5, or 10 mg plus metformin or metformin monotherapy.[49]

Cardiovascular data

In December 2008, the US Food and Drug Administration (FDA) published guidance for the evaluation of CV safety of agents being developed for the treatment of T2DM. This guideline included a recommendation that sponsors perform a meta-analysis of the important CV events across phase 2 and phase 3 controlled clinical trials, and explore similarities and/or differences in subgroups (eg, age, sex, race), if possible. In addition, sponsors should compare the incidence of important CV events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the 2-sided 95% confidence interval (CI) for the estimated risk ratio was < 1.8.[50]

Table 2 Saxagliptin 5 mg adverse event reported more commonly in patients treated with placebo or control (incidence ≥ 5%)[a,b,3–7,37]

	Monotherapy		With MET		With SU		With TZD		Initial combination with MET		Long-term combination with MET	
	SAXA 5 mg	PBO	SAXA 5 mg + MET	PBO + MET	SAXA 5 mg + GLY	PBO + UP-GLY	SAXA 5 mg + TZD	PBO + TZD	SAXA 5 mg + MET	PBO + MET	SAXA 5 mg + MET	PBO + MET
N	106	95	191	179	253	267	186	184	320	328	191	179
Headache	10 (9.4)	7 (7.4)	11 (5.8)	13 (7.3)	19 (7.5)	15 (5.6)	10 (5.4)	7 (3.8)	24 (7.5)	17 (5.2)	17 (8.9)	20 (11.2)
Peripheral edema	–	–	–	–	–	–	15 (8.1)	8 (4.3)	–	–	–	–
URTI	9 (8.5)	11 (11.6)	9 (4.7)	9 (5.0)	16 (6.3)	18 (6.7)	17 (9.1)	13 (7.1)	–	–	17 (8.9)	14 (7.8)
Urinary tract infection	9 (8.5)	4 (4.2)	10 (5.2)	8 (4.5)	27 (10.7)	22 (8.2)	12 (6.5)	12 (6.5)	–	–	15 (7.9)	12 (6.7)
Reported hypoglycemia (%)[c]	5 (4.7)	6 (6.3)	10 (5.2)	9 (5.0)	37 (14.6)	27 (10.1)	5 (2.7)	7 (3.8)	11 (3.4)	13 (4.0)	17 (8.9)	18 (10.1)
Confirmed hypoglycemia (%)[d]	0 (0)	0 (0)	1 (0.5)	1 (0.6)	2 (0.8)	2 (0.7)	0 (0)	0 (0)	0 (0)	1 (0.3)	2 (1.1)	1 (0.6)

Notes: [a]Frequency was < 5% in saxagliptin group and respective comparator treatment group for each study. [b]Data from the saxagliptin monotherapy QAM and QPM study, as well as the saxagliptin + SU extension study were not available. [c]Reported hypoglycemia was defined as events consistent with symptoms of hypoglycemia with or without documented blood glucose levels. [d]Confirmed hypoglycemia was defined by a fingerstick glucose value of < 50 mg/dL with associated symptoms.

Abbreviations: GLY, glyburide; MET, metformin; PBO, placebo; SAXA, saxagliptin; TZD, thiazolidinedione, UP-GLY, uptitrated glyburide; URTI, upper respiratory tract infection.

Although the application for saxagliptin approval was filed before this guidance was issued by the FDA, the sponsors conducted a *post hoc* meta-analysis using the phase 2b/3 data from 8 randomized, double-blind trials for saxagliptin.[3–7,37,39,40,51] For this analysis, the primary end point was major adverse cardiovascular events ([MACE] stroke, myocardial infarction, or CV death) and acute cardiovascular events ([ACE] clinically significant events, including cardiac revascularization procedures). The analysis included 4,607 patients (3,206 randomized to saxagliptin 2.5, 5, or 10 mg; 150 randomized to saxagliptin 20, 40, or 100 mg; and 1,251 randomized to placebo, metformin, or uptitrated glyburide). Within the saxagliptin population, 81% of patients had at least 1 CV risk factor in addition to diabetes; hypertension (52%); hypercholesterolemia, including mixed dyslipidemia (44%); or a history of smoking (39%). The Cox proportional hazard ratio was 0.44 (95% CI, 0.24–0.82) for MACE and 0.59 (95% CI, 0.35–1.00) for ACE for saxagliptin vs other treatment arms (Table 4). These results support the conclusion that there was no evidence of increased CV risk with saxagliptin as monotherapy or in combination with other oral antidiabetic agents when used for up to 2.5 years.[51] To fulfill the FDA's requirement to demonstrate the exclusion of CV risk, a prospective outcomes study to evaluate potential cardioprotective effects in saxagliptin-treated patients is currently underway. The anticipated study completion date is 2015 and results are expected thereafter.[52]

Drug interactions

Data from *in vitro* studies revealed that saxagliptin and 5-hydroxy saxagliptin did not inhibit cytochrome P450 (CYP)1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, or 3A4. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes.[2] Saxagliptin metabolism is primarily mediated by CYP3A4/5 and 5-hydroxy saxagliptin, a major metabolite of saxagliptin, also a DPP-4 inhibitor. Saxagliptin does not meaningfully alter the pharmacokinetics of CYP3A4/5 inducers (eg, rifampin), metformin, glyburide, pioglitazone, or digoxin, nor does it alter simvastatin, diltiazem, or ketoconazole, which have CYP3A4/5-mediated metabolism.[2] Significant increases in plasma concentrations of saxagliptin are anticipated with strong CYP3A4/5 inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, nefazadone, nelfinavir, ritonavir, saquinavir, and telithromycin). Therefore, the dose of saxagliptin should be limited to 2.5 mg when coadministering it with a strong CYP3A4/5 inhibitor.[2]

Table 3 Hypoglycemia in pooled analysis of saxagliptin monotherapy and combination studies[a,3–7,37]

Trial	Drug/dose[a]	Reported hypoglycemia[b] (%)	Confirmed hypoglycemia[c] (%)
Monotherapy			
	SAXA 2.5 mg	2.9	None
	SAXA 5 mg	4.7	None
	SAXA 10 mg	8.2	None
	PBO	6.3	None
Add-on combination			
with MET	SAXA 2.5 mg + MET	7.8	0.5
	SAXA 5 mg + MET	5.2	0.5
	SAXA 10 mg + MET	3.9	0.6
	PBO + MET	5.0	0.6
with SU			
	SAXA 2.5 mg + GLY	13.3	2.4
	SAXA 5 mg + GLY	14.6	0.8
	PBO + UP-GLY	10.1	0.7
with TZD			
	SAXA 2.5 mg + TZD	4.1	0.5
	SAXA 5 mg + TZD	2.7	0
	PBO + TZD	3.8	0
Initial combination			
with MET (24 wks)	SAXA 5 mg + MET	3.4	0
	SAXA 10 mg + MET	5.0	0.6
	SAXA 10 mg	1.5	0
	PBO + MET	4.0	0.3
with MET (102 wks)			
	SAXA 2.5 mg + MET	10.4	1.0
	SAXA 5 mg + MET	8.9	1.0
	SAXA 10 mg	11.0	1.1
	PBO + MET	10.1	0.6

Notes: [a]Data from the saxagliptin monotherapy QAM and QPM study, as well as the saxagliptin + SU extension study were not available. [b]Reported hypoglycemia was defined as events consistent with symptoms of hypoglycemia with or without documented blood glucose levels. [c]Confirmed hypoglycemia was defined by a fingerstick glucose value of < 50 mg/dL with associated symptoms.
Abbreviations: GLY, glyburide; MET, metformin; PBO, placebo; SAXA, saxagliptin; TZD, thiazolidinedione; UP-GLY, uptitrated glyburide.

Although saxagliptin is a P-glycoprotein (P-gp) substrate, it is not a significant inhibitor or inducer of P-gp. The *in vitro* protein binding of saxagliptin and 5-hydroxy saxagliptin in human serum is minimal. Thus, protein binding is not expected to have a meaningful impact on the pharmacokinetics of saxagliptin or other drugs.[2]

Dosage, administration, and formulations

The recommended dose of saxagliptin is 2.5 or 5 mg once-daily, taken regardless of meals. No dosage adjustment is required for patients with hepatic impairment or for those with mild renal insufficiency (creatinine clearance [CrCl] > 50 mL/min). However, 2.5 mg daily is recommended for patients with moderate-to-severe renal impairment or end-stage renal disease (CrCl ≤ 50 mL/min). Renal function should be assessed prior to initiation of treatment with saxagliptin and periodically thereafter. Saxagliptin appears to be an effective treatment in adults of any age; however, care should be taken in dose selection in the elderly.[2] A saxagliptin dose of 2.5 mg daily is also recommended for patients taking strong CYP3A4/5 inhibitors, such as ketoconazole.[2]

Alternative to other oral antidiabetic drug classes

Newer antidiabetic medications may offer less complex regimens with fewer side effects than traditional oral

Table 4 Cardiovascular events in the phase 2b/3 clinical trial program for saxagliptin[51]

Event type, n (%)	Saxagliptin (n = 3,356)	Control (n = 1,251)
ACE	38 (1.1)	23 (1.8)
MACE	23 (0.7)	18 (1.4)
All death	10 (0.3)	12 (1.0)
CV death	7 (0.2)	10 (0.8)

Abbreviations: ACE, acute cardiovascular event; MACE, major adverse cardiovascular event; CV, cardiovascular.

antidiabetic drugs. As a consequence, adherence to therapy and improved HbA_{1c} control would be anticipated.[53]

Guidelines set forth by the AACE/ACE recognize the value of DPP-4 inhibitors, noting that they reduce both FPG and PPG and may be used in combination with metformin. The guidelines specifically recommend DPP-4 inhibitors as monotherapy for patients with HbA_{1c} levels between 6.5% and 7.5%, as part of 2-drug combination therapy with metformin in patients with HbA_{1c} levels between 7.6% and 9.0%, and as part of triple combination therapy (eg, with metformin and a TZD) for patients with $HbA_{1c} > 9.0\%$.[1] The guidelines also note that these agents have low risk for hypoglycemia and no long-term toxicities to date.[1]

ADA/EASD 2009 guidelines do not consider DPP-4 inhibitors as preferred (ie, tier 1 or tier 2) interventions because at the time of publication, DPP-4 inhibitors were considered too new and their long-term safety was still undetermined.[12] However, these guidelines take note of the fact that DPP-4 inhibitors lower HbA_{1c} levels by 0.6%–0.9%, are weight neutral, and are not associated with hypoglycemia when used as monotherapy.[12]

Emerging role of combination therapy

In addition to the emerging role of DPP-4 inhibitors as initial therapy, combination therapy is recommended by AACE/ACE for patients with $HbA_{1c} \geq 7.6\%$.[1] When patients are unsuccessful in achieving or sustaining their HbA_{1c} goals with lifestyle intervention and appropriately titrated monotherapy, advancement to dual therapy should be considered.[1] The ADA/EASD recommendations also indicate that if lifestyle intervention and the maximum tolerated dose of metformin fail to achieve or sustain glycemic goals, another medication should be added within 2–3 months of treatment initiation or at any time the target HbA_{1c} is not achieved.[12] The treatment algorithm put forward as part of the Banting Lecture by Dr Ralph DeFronzo in 2009 also favored combination therapy for the treatment of T2DM, noting that combination treatment based on the reversal of known pathophysiological defects provides greater potential for the achievement of sustained glycemic control.[15]

Place in therapy

Although metformin continues to be the recommended first-line agent for patients with T2DM, the value of DPP-4 inhibitors is becoming increasingly recognized in current treatment algorithms as first-line treatment and second-line treatment options due to their efficacy (including HbA_{1c} control and preferential targeting of PPG) and well-tolerated profile. Saxagliptin is a DPP-4 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.[2] Saxagliptin has been studied as monotherapy and in combination with metformin, glyburide, and TZD (pioglitazone and rosiglitazone) therapy.[3–7] When given as monotherapy, in initial combination with metformin, or in combination as add-on therapy for patients inadequately controlled with an SU or TZD in studies up to 24 weeks, and metformin up to 102 weeks, saxagliptin has documented efficacy in improving glycemic control (measured by HbA_{1c}, FPG, PPG, and proportions of patients achieving $HbA_{1c} < 7\%$) compared with placebo. Saxagliptin is generally well tolerated, and is weight neutral with a low risk of hypoglycemia.[3–7,37,39,47] The current evidence base supports use of saxagliptin in adult patients with diabetes in a broad range of patient types, as demonstrated by similar efficacy and tolerability regardless of age, gender, race/ethnicity, or BMI. In addition to its efficacy and safety profile, saxagliptin has also shown no risk of cardiac AEs.[51] An outcome study is currently being conducted to further evaluate CV risk and to assess a potential cardioprotective effect of saxagliptin.[52]

Unmet needs

Efficacy

The long-term efficacy of traditional oral antihyperglycemic medications is variable, and approximately half of patients do not achieve durable glycemic control.[16,54] Since as many as 90%–95% of patients with T2DM are also overweight or obese, it is imperative to implement lifestyle modifications to target not only the glycemic control in these patients, but also the hypertension, hyperlipidemia, and other CV risk factors often associated with obesity. However, in the majority of patients with T2DM, lifestyle modifications fail to achieve or maintain glycemic goals due to a combination of factors, including the failure to lose weight, weight regain, or progressive disease.[12] Long-term glycemic control is difficult to sustain with oral antidiabetic drugs because progressive β-cell dysfunction is characteristic of T2DM, especially if the diagnosis is delayed.[16] Results from 1 analysis demonstrated that the 5-year failure rates (defined as FPG > 10 mmol/L for 2 clinic visits in a row) for the TZD (rosiglitazone), metformin, and the SU (glyburide), were 15, 21, and 34%, respectively.[31] The limited long-term efficacy of these therapies underscores the significant need for new medications with novel mechanisms of action, as well as the need for combinations of agents targeting the multiple pathologies underlying T2DM.[12,15]

Summary

In summary, saxagliptin provides significant and clinically meaningful benefit with respect to glucose control, significantly reducing HbA_{1c} by 0.5%–2.5%, as monotherapy and in combination therapy without compromising tolerability. Notably, the drop in HbA_{1c} is highly correlated with results from the saxagliptin clinical trial program, which, taken together with current treatment guideline recommendations (AACE/ACE), supports a place for saxagliptin as a possible alternative to first-line treatment and second-line treatment options, including use as monotherapy in patients with HbA_{1c} 6.5%–7.5%, and in combination with other agents when $HbA_{1c} > 6.5\%$. In addition, AACE/ACE recommends the use of DPP-4 inhibitors vs other oral agents in patients when HbA_{1c} is in the range of 6.5%–7.5% and FPG and PPG levels are elevated.[1]

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