SUBJECT REVIEW

Tolerability of Saxagliptin in Patients with Inadequately Controlled Type 2 Diabetes: Results from 6 Phase III Studies

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ABSTRACT

BACKGROUND: Oral antihyperglycemic drugs used to treat type 2 diabetes mellitus (T2DM) vary in safety and tolerability. Treatment-related hypoglycemia and weight gain can exacerbate underlying disease.

OBJECTIVE: To evaluate the tolerability of saxagliptin using data from phase III clinical trials.

METHODS: Six 24-week randomized studies in 4,214 patients with T2DM were assessed. Saxagliptin 2.5 mg or 5 mg was compared with placebo in 2 trials of monotherapy in treatment-naïve patients and in 3 trials of add-on therapy to metformin, glyburide, or a thiazolidinedione; initial combination therapy with saxagliptin 5 mg plus metformin was compared with metformin monotherapy in treatment-naïve patients. Data from the monotherapy and add-on studies were pooled; data from the initial combination study were analyzed separately. No statistical analyses of between-group comparisons across studies were conducted for these safety analyses because of multiplicity of end points and relative lack of statistical power and because small differences not reaching statistical significance have the potential to be clinically relevant.

RESULTS: In the pooled analysis, incidence rates for adverse events (AEs) with saxagliptin 2.5 mg, 5 mg, and placebo were 72.0% (635/882), 72.2% (637/882), and 70.6% (564/799), respectively; rates for serious AEs (SAEs) were 3.5% (31/882), 3.4% (30/882), and 3.4% (27/799); rates of discontinuation due to AEs were 2.2% (19/882), 3.3% (29/882), and 1.8% (14/799). AEs reported in ≥2% of patients receiving saxagliptin and occurring ≥1% more frequently with saxagliptin than with placebo were sinusitis, gastroenteritis, abdominal pain, and vomiting. In the initial combination study, AE incidence rates with saxagliptin 5 mg plus metformin and metformin monotherapy were 55.3% (177/320) and 58.5% (192/328), respectively; incidence rates for SAEs were 2.5% (8/320) and 2.4% (8/328); and rates of discontinuation due to AEs were 2.5% (8/320) and 3.4% (11/328).

CONCLUSION: Saxagliptin 2.5 mg or 5 mg was generally well tolerated as monotherapy, add-on combination therapy with other oral antihyperglycemic drugs, and initial combination with metformin.

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What is already known about this subject

- Oral antidiabetic drugs (OADs) differ in their safety and tolerability profiles. For example, the sulfonylureas are associated with weight gain and risk of hypoglycemia, whereas metformin is associated with gastrointestinal intolerance, and its use is limited by renal impairment. Thiazolidinediones (TZDs) are associated with increased risk of bone fracture (mainly in women), edema, weight gain, congestive heart failure, and possibly myocardial infarction (rosiglitazone).
- Dipeptidyl peptidase-4 (DPP-4) inhibitors are a newer class of OADs. The DPP-4 inhibitor saxagliptin is approved as an adjunct to diet and exercise for improving glycemic control in patients with type 2 diabetes mellitus (T2DM) and has also been shown to be efficacious as add-on therapy to metformin, a sulfonylurea (glyburide), and a TZD, as well as in initial combination therapy with metformin. The current evaluation of saxagliptin tolerability is based on an analysis of the phase III clinical trial program, consisting of 6 phase III studies, all of which were 24-week randomized, double-blind, placebo- or active-controlled studies.

What this study adds

- The purpose of the pooled analysis of placebo-controlled monotherapy and add-on therapy trials was to identify any safety signals for saxagliptin that might not have been identified in the smaller populations of the individual trials. The initial combination study was reported separately because patients in that study had new-onset T2DM, and the comparison was of initial add-on rather than sequential add-on therapies.
- Across 6 double-blind phase III clinical trials, saxagliptin was generally well tolerated as monotherapy; as add-on combination therapy with metformin, glyburide, or a TZD; and as initial combination therapy with metformin in patients with T2DM. Incidence rates of adverse events were comparable with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo (pooled analysis) and with saxagliptin 5 mg plus metformin and metformin monotherapy (initial combination study).

Despite many available therapies, only 57% of patients with type 2 diabetes mellitus (T2DM) in the United States reach the American Diabetes Association (ADA) recommended glycated hemoglobin (HbA1c) goal of <7%,[1] according to the 2003-2004 interval of the National Health and Nutrition Examination Survey. Even fewer patients with T2DM reach the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) recommended goal of <6.5%.[2]

In their recent position statement, the ADA and European Association for the Study of Diabetes recommend initial drug therapy with metformin or, if metformin cannot be used, another oral antidiabetic drug (OAD) such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase-4 (DPP-4)

inhibitor for patients with T2DM.[3] OADs differ in their safety and tolerability profiles. For example, the sulfonylureas are associated with weight gain and risk of hypoglycemia, whereas metformin is associated with gastrointestinal (GI) intolerance, and its use is limited by renal impairment.[4-7] Thiazolidinediones (TZDs) are associated with increased risk of bone fracture (mainly in women), edema, weight gain, congestive heart failure, and possibly myocardial infarction (rosiglitazone).[4,8-10] The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial confirmed that rosiglitazone doubled the risk of heart failure and showed a nonsignificant trend for increasing the risk of myocardial infarction but found no increase in overall cardiovascular (CV) morbidity or mortality.[11,12]

DPP-4 inhibitors represent a useful therapeutic approach for the management of T2DM.[13] DPP-4 inhibitors prolong the activity of incretin hormones (glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide), thereby promoting insulin production and suppressing glucagon secretion, which results in reduced blood glucose.[14] A formal meta-analysis of 41 clinical trials has demonstrated that DPP-4 inhibitors are, as a class, weight neutral and carry essentially no risk of hypoglycemia.[15] The DPP-4 inhibitors currently approved in the United States are sitagliptin, saxagliptin, linagliptin, and alogliptin; vildagliptin is available in Europe.

The DPP-4 inhibitor saxagliptin is approved as an adjunct to diet and exercise for improving glycemic control in patients with T2DM.[16-18] Saxagliptin monotherapy has been shown to improve glycemic control in patients with T2DM in both 12-week[19] and 24-week[20] studies. Saxagliptin has also been shown to be efficacious as add-on therapy to metformin,[17] a sulfonylurea (glyburide),[21] and a TZD,[22] as well as in initial combination therapy with metformin.[23] In phase III studies, adverse events (AEs) occurring in ≥5% of patients and more commonly with saxagliptin versus placebo were upper respiratory tract infection, urinary tract infection, and headache.[24]

The current evaluation of saxagliptin tolerability is based on an analysis of the phase III clinical trial program, consisting of 6 phase III studies, all of which were 24-week, randomized, double-blind, placebo-, or active-controlled studies. The 6 phase III studies included 2 monotherapy studies; 3 add-on combination studies with metformin, glyburide, or a TZD; and an initial combination study of saxagliptin plus metformin.[17,20-23,25] The evaluation includes a pooled analysis of the 5 placebo-controlled monotherapy and add-on therapy trials and separate presentation of the initial combination study. The purpose of the pooled analysis was to identify any safety signals for saxagliptin that might not have been identified in the smaller populations of the individual trials. Based on the mechanism of action and clinical profile of the DPP-4 inhibitors and risks associated with T2DM, certain types of AEs were of special interest, including hypoglycemia, skin and subcutaneous tissue disorders, hypersensitivity events, infections and infestations, lymphopenia, thrombocytopenia, localized edema, and CV AEs.[24,26,27]

Methods

Table 1 presents an overview of the 6 phase III saxagliptin studies. Briefly, each study included a 1- to 4-week dietary and placebo lead-in period followed by a 24-week double-blind treatment period.[17,20-23,25] Patients with T2DM, aged 18 to 77 years, were eligible if they had inadequate glycemic control (HbA1c: 7%-10%, 7.5%-10%, 7%-10.5%, or 8%-12%; study dependent [Table 1], fasting C-peptide ≥1.0 nanograms per milliliter [ng/mL], and body mass index [BMI] ≤40 kilograms per square meter [kg/m^2]; in the add-on to the TZD study, the BMI inclusion range was revised to ≤45 kg/m^2).

Patients in the monotherapy and initial combination with metformin studies were treatment-naïve, defined as not receiving medical treatment for diabetes for ≥6 months since original diagnosis (in the monotherapy studies), or as never having received medical treatment for diabetes or having received medical treatment for diabetes for a total period of <1 month since original diagnosis (initial combination with metformin study).[20,23,25] In each of these studies, patients were also not to have received antihyperglycemic therapy for >3 consecutive days or for a total of 7 nonconsecutive days during the 8 weeks before screening.[20,23,25] Patients in the add-on combination therapy studies did not achieve glycemic control despite a stable dose of metformin, glyburide (2 months before screening), or a TZD (3 months before screening).[17,21,22] In these studies, comparisons were made between add-on saxagliptin versus placebo;[17,21,22] however, the add-on to glyburide trial allowed glyburide up-titration in the control arm.[21]

Exclusion criteria were symptoms of poorly controlled diabetes; history of diabetic ketoacidosis or hyperosmolar nonketotic coma; insulin therapy within 1 year of screening; significant CV event within 6 months of study entry or New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction ≤40%; significant history of renal or liver disease; psychiatric disorder; history of alcohol or drug abuse within the previous year; treatment with potent cytochrome (CYP) 3A4 inhibitors or inducers; immunocompromised individuals; and active liver disease or clinically significantly abnormal hepatic, renal, endocrine, metabolic, or hematologic screening tests.[17,20-23,25] For all 6 studies used in this analysis, study protocols were approved by the institutional review board or independent ethics committee for each participating site and carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study End Points

Safety and tolerability analyses included assessment of overall AEs, serious AEs (SAEs), discontinuations for AEs, most common AEs, subgroup analyses of AEs, and AEs of special

TABLE 1 Overview of Phase III Clinical Trials of Saxagliptin

Study	Target Population	Treatment Groups	HbA1c Inclusion Criteria
Monotherapy studies (N = 832)			
NCT00121641[20] N = 401 (+66 OL)	Treatment-naïve patients	• SAXA (2.5 mg, 5 mg, or 10 mg) • PBO	≥ 7% to ≤ 10%
NCT00316082[25] N = 365	Treatment-naïve patients	• SAXA (2.5 mg or 5 mg AM, 2.5/5 mg[a] AM, 5 mg PM) • PBO	≥ 7% to ≤ 10%
Add-on combination therapy studies (N = 2,076)			
Add-on to MET NCT00121667[17] N = 743	MET failure patients (MET 1,500 mg-2,550 mg TDD[b])	• MET + SAXA (2.5 mg, 5 mg, or 10 mg) • MET + PBO	≥ 7% to ≤ 10%
Add-on to SU NCT00313313[21] N = 768	SU failure patients (4-week lead-in with GLY 7.5 mg)	• OL GLY 7.5 mg + SAXA (2.5 mg or 5 mg) • OL GLY 7.5 mg + DB uptitratable GLY 2.5 mg to 7.5 mg + PBO (TDD of GLY 10 mg to 15 mg)	≥ 7.5% to ≤ 10%
Add-on to TZD NCT00295633[22] N = 565	TZD failure patients (ROSI 4 mg or 8 mg, or PIO 30 mg or 45 mg)	• TZD + SAXA (2.5 mg or 5 mg) • TZD + PBO	≥ 7% to ≤ 10.5%
Initial combination study (N = 1,306)			
NCT00327015[23] N = 1,306	Treatment-naïve patients	• MET + PBO • SAXA 10 mg + PBO • SAXA 5 mg + MET • SAXA 10 mg + MET	≥ 8% to ≤ 12%

[a]2.5/5 mg = titration from 2.5 mg to 5 mg.
[b]In NCT00121667, patients with pretreatment maximum metformin daily dose of 2,550 mg were treated during the trial with metformin 2,500 mg.
AM = every morning; DB = double-blind; GLY = glyburide; HbA1c = glycated hemoglobin; MET = metformin; mg = milligram; OL = open-label; PBO = placebo; PIO = pioglitazone; PM = every evening; ROSI = rosiglitazone; SAXA = saxagliptin; SU = sulfonylureas; TDD = total daily dose: TZD = thiazolidinedione.

interest. As previously described, AEs of special interest were a predefined subset of AEs, which were selected based on their general importance for antihyperglycemic agents (e.g., hypoglycemia and CV AEs); findings observed in the saxagliptin nonclinical and clinical trial programs (e.g., lymphopenia and thrombocytopenia); safety-related concerns reported for other DPP-4 inhibitors (e.g., abnormal liver function tests, skin disorders, localized edema, and hypersensitivity reactions); or theoretical considerations related to the mechanism of action of saxagliptin (e.g., infections and infestations, localized edema, and skin disorders). AE intensity was defined as mild (awareness of event but easily tolerated), moderate (discomfort enough to cause some interference with usual activity), severe (inability to carry out usual activity), and very severe (debilitating, significantly incapacitates patient despite symptomatic therapy). AE reporting included investigator assessments for severity and relationship to study medication. Classification of AEs was based on the Medical Dictionary for Regulatory Activities (MedDRA) version 10.1 (MedDRA MSSO, McLean, VA). Safety was also assessed using data from physical examinations, vital signs, electrocardiograms (ECGs), and standard laboratory measurements (e.g., hematology, serum chemistry, urinalysis).[17,20-23,25]

Data Analysis

Two populations were assessed for the safety of saxagliptin. The first was the pooled safety population that participated in the placebo-controlled trials of saxagliptin as monotherapy[20,25] and as add-on therapy to metformin,[17] glyburide,[21] or a TZD.[22] Data for saxagliptin 2.5 milligrams (mg), saxagliptin 5 mg, and placebo were separately pooled across the 5 studies for analysis. The second population participated in the trial of saxagliptin 5 mg as initial combination therapy with metformin versus metformin monotherapy.[23] In the analyses of these 2 populations, only doses of saxagliptin common to all studies (approved doses of 2.5 mg and 5 mg) were included; safety findings for saxagliptin 10 mg can be found in the publications for the primary study in which it was assessed.[17,20,23]

All safety data are presented for treated patients, defined as patients who received at least 1 dose of the study drug. The extent of exposure was defined as the time from the first day that a patient received the study drug to 1 day after the last day that a patient received the study drug. A pooled analysis was conducted of the placebo-controlled phase III studies with a duration of up to 24 weeks (including rescue therapy to avoid potential imbalances in exposure to study treatment) to

TABLE 2 Baseline Demographic and Clinical Characteristics

	Placebo-Controlled Pooled[a] Analysis[17,20-22,25]						Initial Combination Study[23]			
	SAXA 2.5 mg (n = 882)		SAXA 5 mg (n = 882)		Placebo (n = 799)		SAXA 5 mg + MET (n = 320)		MET (n = 328)	
Age, years[b]	54.8	(10.0)	54.4	(10.2)	54.7	(10.6)	52.0	(10.4)	51.8	(10.7)
Age ≥ 65 years[c]	149	(17)	142	(16)	137	(17)	33	(10)	36	(11)
Gender[c]										
Men	422	(48)	427	(48)	386	(48)	165	(52)	163	(50)
Women	460	(52)	455	(52)	413	(52)	155	(48)	165	(50)
Race (self-reported)[c]										
White	603	(68)	599	(68)	535	(67)	246	(77)	251	(77)
Asian	154	(18)	155	(18)	138	(17)	51	(16)	52	(16)
Black	30	(3)	46	(5)	31	(4)	7	(2)	4	(1)
Other	95	(11)	82	(9)	95	(12)	16	(5)	21	(6)
Weight, kg[b]	82.6	(18.6)	82.7	(19.0)	81.6	(18.8)	82.1	(16.2)	82.8	(17.5)
BMI, kg/m^2[b]	30.4	(5.1)	30.3	(5.0)	30.2	(5.1)	29.9	(4.5)	30.2	(4.9)
Duration of diabetes, years[b]	5.2	(5.3)	5.0	(5.3)	5.4	(5.4)	2.0	(3.7)	1.7	(3.1)
HbA1c, %[b]	8.2	(1.0)	8.2	(1.0)	8.2	(1.0)	9.4	(1.2)	9.4	(1.3)
< 8[c]	408	(46)	382	(43)	375	(47)	31	(10)	37	(11)
≥ 8 to < 9[c]	288	(33)	305	(35)	251	(31)	92	(29)	98	(30)
≥ 9[c]	185	(21)	193	(22)	173	(22)	195	(61)	192	(59)
Not reported[c]	1	(0.1)	2	(0.2)	0	(0)	2	(0.6)	1	(0.3)
FPG, mg/dL[b]	169	(44.6)	170	(45.0)	170	(44.6)	199	(56.6)	198	(58.7)

[a]*Included 2 saxagliptin monotherapy trials and 1 trial each of saxagliptin as add-on to metformin, thiazolidinedione, and glyburide.*
[b]*Values are expressed as mean (SD).*
[c]*Values are expressed as n (%).*
BMI = body mass index; FPG = fasting plasma glucose; HbA1c = glycated hemoglobin; kg/m^2 = kilogram per square meter; MET = metformin 500-2,000 mg/d; mg/dL = milligram per deciliter; SAXA = saxagliptin; SD = standard deviation.

identify any safety signals that might not have been apparent in the context of the smaller populations of the 5 individual trials. However, due to multiplicity of end points and a lack of statistical power, formal statistical analyses of between-group differences across studies were not performed. Data collected after rescue therapy were excluded in the initial combination with metformin analysis; however, no formal statistical comparison of between-group differences in safety was performed. Rescue therapy (metformin or pioglitazone) was initiated in accordance with study protocols and was given in addition to blinded study medication if patients failed to meet prespecified glycemic goals.[17,20-23,25] The analyses of AEs of special interest were performed on datasets obtained up to week 24, including safety data acquired after rescue. Data on hypoglycemia, an AE of special interest, are classified as "reported hypoglycemia" (signs or symptoms consistent with hypoglycemia with or without documented glucose levels) and "confirmed hypoglycemia" (fingerstick glucose ≤ 50 milligrams per deciliter [mg/dL] with associated symptoms). AEs were tabulated; other safety-related variables were summarized using descriptive statistics. Clinical AEs were coded and grouped into System Organ Class (SOC), preferred term, and treatment using MedDRA version 10.1.

Results

Study Population Characteristics and Patient Disposition

Baseline demographics and clinical characteristics in the pooled placebo-controlled and phase III initial combination study analysis populations are summarized in Table 2. In the placebo-controlled pooled safety analysis, mean age ranged from 54.4 to 54.8 years across groups, with 16% to 17% of patients aged ≥ 65 years. In the initial combination with metformin study, patients were younger, with a mean age of 51.8 to 52.0 years across groups and 10% to 11% of patients aged ≥ 65 years. Mean baseline HbA1c and fasting plasma glucose (FPG) were 8.2% and 169 to 170 mg/dL across groups, respectively, in the placebo-controlled pooled safety analysis, and 9.4% and 198 to 199 mg/dL across groups, respectively, in the initial combination with metformin study, consistent with the higher HbA1c entry criteria for the latter study. Mean duration of T2DM was 5.2 to 5.4 years across groups in the placebo-controlled pooled safety analysis and 1.7 to 2.0 years in the initial combination with metformin study, reflecting the expected longer T2DM duration for patients receiving add-on therapy compared with initial therapy.

TABLE 3 *Adverse Events During Double-Blind Treatment to Week 24*

	Placebo-Controlled Pooled Analysis[a] (Including Rescue)[17,20-22,25]						Initial Combination Study (Excluding Rescue)[23]			
	SAXA 2.5 mg (n = 882)		SAXA 5 mg (n = 882)		Placebo (n = 799)		SAXA 5 mg + MET (n = 320)		MET (n = 328)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total patients with ≥ 1 adverse event	635	(72.0)	637	(72.2)	564	(70.6)	177	(55.3)	192	(58.5)
Total patients with ≥ 1 serious adverse event	31	(3.5)	30	(3.4)	27	(3.4)	8	(2.5)	8	(2.4)
Discontinuations due to adverse events	19	(2.2)	29	(3.3)	14	(1.8)	8	(2.5)	11	(3.4)
Adverse events (excluding hypoglycemia) by SOC[b]										
Infections and infestations	321	(36.4)	317	(35.9)	278	(34.8)	73	(22.8)	77	(23.5)
Gastrointestinal disorders	195	(22.1)	162	(18.4)	153	(19.1)	62	(19.4)	66	(20.1)
Musculoskeletal/connective tissue disorders	161	(18.3)	158	(17.9)	155	(19.4)	30	(9.4)	30	(9.1)
Nervous system disorders	118	(13.4)	113	(12.8)	116	(14.5)	37	(11.6)	36	(11.0)
General disorders/administration site conditions	78	(8.8)	85	(9.6)	73	(9.1)	18	(5.6)	15	(4.6)
Injury, poisoning, procedural complications	82	(9.3)	71	(8.0)	63	(7.9)	15	(4.7)	14	(4.3)
Respiratory, thoracic, mediastinal disorders	73	(8.3)	67	(7.6)	84	(10.5)	13	(4.1)	13	(4.0)
Skin/subcutaneous tissue disorders	82	(9.3)	63	(7.1)	58	(7.3)	11	(3.4)	9	(2.7)
Investigations	58	(6.6)	57	(6.5)	49	(6.1)	16	(5.0)	22	(6.7)
Vascular disorders	49	(5.6)	51	(5.8)	43	(5.4)	21	(6.6)	15	(4.6)
Metabolism and nutrition disorders	36	(4.1)	46	(5.2)	33	(4.1)	11	(3.4)	10	(3.0)
Common adverse events[c]										
Sinusitis	26	(2.9)	23	(2.6)	13	(1.6)	—		—	
Gastroenteritis	17	(1.9)	20	(2.3)	7	(0.9)	—		—	
Abdominal pain	21	(2.4)	15	(1.7)	4	(0.5)	—		—	
Vomiting	19	(2.2)	20	(2.3)	10	(1.3)	—		—	
Nasopharyngitis	—		—		—		22	(6.9)	13	(4.0)
Headache	—		—		—		24	(7.5)	17	(5.2)
Bronchitis	—		—		—		9	(2.8)	0	(0)
Upper respiratory tract infection	—		—		—		11	(3.4)	6	(1.8)
Arthralgia	—		—		—		7	(2.2)	2	(0.6)
Dyspepsia	—		—		—		8	(2.5)	4	(1.2)
Hypertension	—		—		—		15	(4.7)	11	(3.4)

[a]*Included 2 saxagliptin monotherapy trials and 1 trial each of saxagliptin as add-on to metformin, thiazolidinedione, and glyburide.*

[b]*SOCs occurring in ≥ 5% of patients in any group were sorted by decreasing frequency in the SAXA 5 mg column.*

[c]*Adverse events occurring in ≥2% of patients with SAXA and at ≥ 1% higher frequency with SAXA versus placebo in the placebo-controlled pooled analysis or with SAXA + metformin versus metformin monotherapy in the initial combination study (excludes hypoglycemia).*

MET = metformin; mg = milligram; SAXA = saxagliptin; SOC = system organ class.

Placebo-Controlled Pooled Analysis

As shown in Table 3, the overall frequency of AEs for saxagliptin 2.5 mg, 5 mg, and placebo was 72.0%, 72.2%, and 70.6%, respectively. AE frequency for saxagliptin 2.5 mg or 5 mg was comparable with placebo for each individual SOC, with the exception of GI disorders, which were more common with saxagliptin 2.5 mg (22.1%) than with saxagliptin 5 mg or placebo (18.4% and 19.1%, respectively). No other AEs by SOC occurred at a rate > 2% higher with saxagliptin 2.5 mg or 5 mg compared with placebo. Respiratory, thoracic, and mediastinal disorders were more common with placebo than saxagliptin.

Few AEs occurred at a frequency ≥ 5%; these included upper respiratory tract infection (7.0%, 7.7%, 7.6%), urinary tract infection (5.1%, 6.8%, 6.1%), nasopharyngitis (5.7%, 5.6%, 6.8%), headache (6.5%, 6.5%, 5.9%), diarrhea (6.0%, 4.1%, 6.1%), and back pain (3.7%, 4.3%, 5.1%) for saxagliptin 2.5 mg, 5 mg, or placebo, respectively. The majority of AEs were mild to moderate in intensity and were considered unrelated to the study medication by the investigator. The AEs that occurred at a frequency of ≥ 2% with saxagliptin 2.5 mg or 5 mg and also occurred at a ≥ 1% higher frequency with saxagliptin compared with placebo were sinusitis, gastroenteritis, abdominal pain, and vomiting.

The frequency of SAEs for saxagliptin 2.5 mg, 5 mg, and placebo was 3.5%, 3.4%, and 3.4%, respectively. AEs leading to discontinuation occurred in 2.2%, 3.3%, and 1.8% of patients receiving saxagliptin 2.5 mg, 5 mg, or placebo, respectively. AEs leading to discontinuation included lymphopenia (1, 4, and 0 patients receiving saxagliptin 2.5 mg, 5 mg, and placebo, respectively); rash (2, 3, and 2); increased blood creatinine (3, 0, and 0); and increased blood creatine phosphokinase (1, 2, and 0).

TABLE 4 *Adverse Events of Special Interest*

	Placebo-Controlled Pooled Analysis[a] (Including Rescue)[17,20-22,25]						Initial Combination Study (Excluding Rescue)[23]			
	SAXA 2.5 mg (n = 882)		SAXA 5 mg (n = 882)		Placebo (n = 799)		SAXA 5 mg + MET (n = 320)		MET (n = 328)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
All reported hypoglycemia	67	(7.6)	69	(7.8)	54	(6.8)	11	(3.4)	13	(4.0)
Confirmed hypoglycemia	7	(0.8)	4	(0.5)	3	(0.4)	0	(0)	1	(0.3)
Skin and subcutaneous tissue disorders	82	(9.3)	63	(7.1)	58	(7.3)	11	(3.4)	9	(2.7)
Hypersensitivity events	13	(1.5)	13	(1.5)	3	(0.4)	2	(0.6)	2	(0.6)
Infections and infestations	321	(36.4)	317	(35.9)	278	(34.8)	73	(22.8)	77	(23.5)
Lymphopenia	4	(0.5)	13	(1.5)	8	(1.0)	0	(0)	1	(0.3)
Thrombocytopenia	4	(0.5)	2	(0.2)	1	(0.1)	0	(0)	1	(0.3)
Localized edema	8	(0.9)	20	(2.3)	9	(1.1)	2	(0.6)	0	(0)
Cardiovascular AEs	5	(0.6)	2	(0.2)	8	(1.0)	0	(0)	3	(0.9)

[a]*Included 2 saxagliptin monotherapy trials and 1 trial each of saxagliptin as add-on to metformin, thiazolidinedione, and glyburide.*
AE = adverse event; MET = metformin; mg = milligram; SAXA = saxagliptin.

Initial Combination Study

The safety profile of saxagliptin in the initial combination with metformin study was generally consistent with observations in the placebo-controlled pooled safety analysis. The frequency of AEs was 55.3% for saxagliptin 5 mg plus metformin and 58.5% for metformin monotherapy (Table 3). No AEs by SOC had a >2% higher incidence in the saxagliptin 5 mg plus metformin group compared with the metformin monotherapy group, although vascular disorders approached this threshold (6.6% vs. 4.6%). AEs in the SOC of cardiac disorders were less frequent for saxagliptin 5 mg plus metformin than for metformin monotherapy (2.2% vs. 4.9%).

Few AEs occurred at a frequency ≥5%; these included nasopharyngitis (6.9% and 4.0%), headache (7.5% and 5.2%), and diarrhea (6.9% and 7.3%) for saxagliptin 5 mg plus metformin or metformin monotherapy, respectively. The majority of events were mild to moderate in intensity; most were considered unrelated to study medication by the investigator. The AEs that occurred at a frequency of ≥2% with saxagliptin 5 mg plus metformin and also occurred at a ≥1% higher frequency with saxagliptin compared with metformin monotherapy were nasopharyngitis, bronchitis, headache, upper respiratory tract infection, arthralgia, dyspepsia, and hypertension. The frequency of SAEs for saxagliptin 5 mg plus metformin and metformin monotherapy was 2.5% and 2.4%, respectively, and the frequency of AEs leading to discontinuation of study drug was 2.5% and 3.4%, respectively).

Additional Safety Considerations

Data on the occurrence of AEs of special interest in patients treated with saxagliptin or comparators are summarized in Table 4.

Hypoglycemia. In the placebo-controlled pooled safety analysis, the frequency of all reported hypoglycemic events, up to week 24 regardless of rescue status, was 7.6%, 7.8%, and 6.8% for saxagliptin 2.5 mg, 5 mg, and placebo, respectively; the frequency of confirmed hypoglycemic events was 0.8%, 0.5%, and 0.4%, respectively, and there was no evidence of a dose relationship for hypoglycemic risk. In the initial combination with metformin study, the frequency of reported hypoglycemic events up to week 24 was 3.4% with saxagliptin 5 mg plus metformin and 4.0% with metformin monotherapy; the frequency of confirmed hypoglycemia was 0% and 0.3%, respectively.

Skin and Subcutaneous Tissue Disorders. In the placebo-controlled pooled safety analysis, the frequency of skin-related AEs, up to week 24 regardless of rescue status, was 9.3%, 7.1%, and 7.3% for saxagliptin 2.5 mg, 5 mg, and placebo groups. A dose relationship was not evident for saxagliptin 2.5 mg or 5 mg in this analysis. In the initial combination with metformin study, the frequency of skin-related AEs up to week 24 excluding rescued patients was 3.4% and 2.7% in the saxagliptin 5 mg plus metformin and metformin monotherapy groups.

Hypersensitivity Events. In the placebo-controlled pooled safety analysis, the frequency of hypersensitivity AEs was 1.5%, 1.5%, and 0.4% for the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. All hypersensitivity AEs in the saxagliptin groups were characterized by the investigator as mild or moderate in intensity, and none were SAEs. In the initial combination with metformin study, the frequency of hypersensitivity AEs was 0.6% in both of the saxagliptin 5 mg plus metformin and metformin monotherapy groups.

Infections and Infestations. Infections were the most common types of AEs across the phase III clinical trial program. In the placebo-controlled pooled safety analysis, the frequency of infection-related AEs was comparable across treatment groups up to week 24 regardless of rescue status (saxagliptin 2.5 mg,

TABLE 5 Changes from Baseline in Lymphocyte Counts in the Placebo-Controlled Pooled Analysis[a] at Week 24, Including Rescue

	SAXA 2.5 mg (n = 434)		SAXA 5 mg (n = 445)		Placebo (n = 394)	
	Mean ± SE (95% CI)	Median	Mean ± SE (95% CI)	Median	Mean ± SE (95% CI)	Median
Change from baseline (x 10^3 cells/μL)	0.00 ± 0.026 (–0.05, 0.05)	–0.04	–0.11 ± 0.025 (–0.16, –0.06)	–0.11	–0.01 ± 0.028 (–0.06, 0.05)	–0.02
Percentage of change from baseline	3.06 ± 1.450 (0.21, 5.91)	–1.64	–2.23 ± 1.160 (–4.51, 0.05)	–5.10	2.90 ± 1.375 (0.19, 5.60)	–0.88

[a]*Included 2 saxagliptin monotherapy trials and 1 trial each of saxagliptin as add-on to metformin, thiazolidinedione, and glyburide.*

CI = confidence interval; mg = milligram; SAXA = saxagliptin; SE = standard error; μL = microliter.

36.4%; saxagliptin 5 mg, 35.9%; placebo, 34.8%). The most frequent infection-related AEs across the placebo-controlled pooled safety analysis studies (≥ 2% in the saxagliptin 2.5 mg or 5 mg groups compared with placebo) were upper respiratory tract infection (7.0%, 7.7%, 7.6%), urinary tract infection (5.1%, 6.8%, 6.1%), nasopharyngitis (5.7%, 5.6%, 6.8%), influenza (3.9%, 3.4%, 4.4%), sinusitis (2.9%, 2.6%, 1.6%), gastroenteritis (1.9%, 2.3%, 0.9%), pharyngitis (2.5%, 2.3%, 2.3%), and bronchitis (2.7%, 2.2%, 1.8%). The only infection-related AEs with > 1% difference in the saxagliptin 2.5 mg or 5 mg groups when compared with the placebo group were sinusitis and gastroenteritis. In the initial combination with metformin study, the frequency of infection-related AEs up to week 24, excluding events occurring after rescue, was 22.8% and 23.5% for saxagliptin 5 mg plus metformin versus metformin monotherapy.

Lymphopenia. In the placebo-controlled pooled safety analysis, the frequency of AEs of lymphopenia up to week 24, regardless of rescue status, was 0.5%, 1.5%, and 1.0% for saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. In the initial combination with metformin study, the frequency of lymphopenia up to week 24, excluding events occurring after rescue, was 0% and 0.3% for saxagliptin 5 mg plus metformin versus metformin monotherapy.

Absolute Lymphocyte Count. A reduction of lymphocyte count was observed in patients receiving saxagliptin 5 mg but not those receiving the 2.5 mg dose; however, the clinical relevance of this decline was not evident. The decline from baseline to week 24 was approximately 100 cells per microliter (μL; 5%) with saxagliptin 5 mg relative to placebo (mean baseline absolute lymphocyte count approximately 2,200 cells/μL; Table 5). No increase in the magnitude of this effect was discernable over time. Similar effects were observed when saxagliptin 5 mg was given in initial combination with metformin compared with metformin alone.

Thrombocytopenia. In the placebo-controlled pooled safety analysis, the frequency of AEs of thrombocytopenia was 0.5%, 0.2%, and 0.1% for the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. No clinically meaningful or consistent effects on platelet counts were seen with saxagliptin 2.5 mg or 5 mg across the phase III clinical trial program. In the initial combination with metformin study, thrombocytopenia was not observed in the saxagliptin 5 mg plus metformin group; 1 event (0.3%) occurred in the metformin monotherapy group.

Localized Edema. The frequency of localized edema AEs in the placebo-controlled pooled safety analysis was 0.9%, 2.3%, and 1.1% in the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. The frequency of localized edema AEs was 0.6% in the saxagliptin 5 mg plus metformin and metformin monotherapy group; no cases of edema were reported in the initial combination with metformin study.

Cardiovascular Adverse Events. In the placebo-controlled pooled safety analysis, the frequency of cardiovascular AEs up to week 24 regardless of rescue status was 0.6%, 0.2%, and 1.0% for the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. In the initial combination with metformin study, the frequency of CV-related AEs was 0.9% in the metformin monotherapy group and 0% in the saxagliptin 5 mg plus metformin group.

Overall, there were no safety signals or trends identified for saxagliptin from vital signs, physical findings, or ECGs. Blood pressure minimally declined in all saxagliptin phase III studies; this was similar to the blood pressure reductions seen with placebo or comparator. Clinical laboratory values (e.g., liver function tests, creatine kinase levels, hematology, serum chemistries, hypoglycemia, and renal function) did not show any imbalances between saxagliptin and placebo or comparator.

Discussion

This safety analysis of the saxagliptin phase III clinical trial program demonstrated that saxagliptin was generally well tolerated as monotherapy; add-on combination with metformin, glyburide, or a TZD; or initial combination with metformin.[17,20-23,25] Specifically, the placebo-controlled pooled safety analysis demonstrated that the overall frequency of AEs was comparable for patients who received saxagliptin 2.5 mg, 5 mg, or placebo. In addition, the overall safety of the initial combination of saxagliptin 5 mg plus metformin was comparable to that with metformin monotherapy.[23] Analyses of AEs in

long-term extension trials of the phase III studies for which data are available have not revealed any differences in the AE profile when compared with analyses performed for the 24-week trials.[28,29]

The safety profile of saxagliptin reflects general observations within the class of DPP-4 inhibitors.[4] The overall incidence of AEs with sitagliptin and vildagliptin was comparable to that reported with placebo in monotherapy trials.[14,27,30-32] In a pooled analysis, AEs were similar between sitagliptin (100 mg/day) and placebo, and there was a low incidence of hypoglycemia and a small increase in the incidence of nasopharyngitis.[27] A meta-analysis by Amori et al. (2007)[13] suggested that DPP-4 inhibitors are associated with increased risk for nasopharyngitis, urinary tract infections, and headache. In the current placebo-controlled pooled safety analysis, these AEs occurred at a frequency ≥ 5% in the saxagliptin 2.5 mg or 5 mg treatment groups, but none occurred at rates ≥ 1% higher than the rate in the placebo group. AEs that occurred at a frequency of ≥ 2% with saxagliptin 2.5 mg or 5 mg and also occurred at a ≥ 1% higher frequency with saxagliptin compared with placebo were sinusitis, gastroenteritis, abdominal pain, and vomiting. A 5% decrease from baseline to week 24 in absolute lymphocyte counts occurred in the pooled-study patients receiving saxagliptin 5 mg but not in patients receiving saxagliptin 2.5 mg or placebo. The decrease in lymphocytes was not statistically significant and did not appear to be clinically relevant. In the initial combination with metformin study, the only AEs that occurred at a frequency ≥ 5% in the saxagliptin plus metformin group when compared with the metformin monotherapy group were nasopharyngitis and headache.

The incidence of AEs of special interest was generally comparable among the treatment arms of saxagliptin 2.5 mg, 5 mg, and placebo in the placebo-controlled pooled safety analysis and between the treatment arms of saxagliptin 5 mg plus metformin and metformin alone in the initial combination study. However, there was a higher incidence of hypersensitivity-related events in saxagliptin-treated patients compared with placebo-treated patients in the placebo-controlled pooled safety analysis (1.5% vs. 0.4%). None of these AEs in saxagliptin-treated patients required hospitalization or were reported as life threatening by the investigator.

While there was a modest decrease in absolute lymphocyte count in patients receiving saxagliptin 5 mg, it was not associated with an increased frequency of infection-related AEs. The overall frequency of lymphopenia was low in each study and similar among all treatment groups in the placebo-controlled pooled safety analysis. Therefore, the observed decrease in lymphocyte count with saxagliptin 5 mg does not appear to be associated with adverse clinical consequences.

Treatment with glyburide has been associated with an increased frequency of hypoglycemia, both in monotherapy and in combination with other oral antidiabetic agents.[6] The incidence of reported hypoglycemic events was not significantly increased when saxagliptin 2.5 mg or 5 mg was added to glyburide compared with up-titrated glyburide (13.3%, 14.6%, and 10.1%, respectively). Nevertheless, the frequency of reported hypoglycemic events was higher in the add-on glyburide study than in the other placebo-controlled trials. Therefore, an additional pooled analysis was conducted that excluded the add-on glyburide trial; it demonstrated no differences in hypoglycemic events between the saxagliptin and placebo groups. Similar results were obtained in the initial combination with metformin study. These findings suggest that saxagliptin does not increase the risk of hypoglycemia when used in nonsulfonylurea OAD combination regimens. Notably, the combination of saxagliptin and metformin may offer particular advantages over other combination regimens, such as complementary mechanisms of action that result in enhanced efficacy without increasing the risk of hypoglycemia. This reflects the glucose-dependent mechanism of action of DPP-4 inhibitors, in contrast with antihyperglycemic agents, such as glyburide, which induce insulin secretion irrespective of circulating glucose concentrations.[14,33,34]

Assessment of hypoglycemia with the DPP-4 inhibitors sitagliptin and vildagliptin has demonstrated similar results in add-on and combination studies. For example, sitagliptin was well tolerated with no increased risk of hypoglycemia as an add-on to pioglitazone versus pioglitazone monotherapy (incidence rate: 1.1% vs. 0%),[35] as add-on to metformin versus metformin monotherapy (1.3% vs 2.1%),[36] as add-on to metformin versus sitagliptin monotherapy (no hypoglycemia events in either group),[37] and as add-on to metformin versus glipizide plus metformin (4.9% vs. 32.0%).[38] Similarly, there was a low incidence of hypoglycemia with vildagliptin plus metformin compared with pioglitazone plus metformin (0.3% vs. 0%)[39] and compared with metformin monotherapy (0% vs 0.7%).[40] The current analysis supports these findings, demonstrating that the DPP-4 inhibitors are well tolerated with a low risk of hypoglycemia when used as monotherapy or add-on to OAD therapy.

Limitations

Certain limitations should be considered when evaluating the data presented in this article. The purpose of the pooled analysis of placebo-controlled monotherapy and add-on therapy trials was to identify any safety signals that might not have been identified in the smaller populations of the individual trials; the initial combination study was reported separately because patients in that study had new-onset T2DM and the comparison was of initial add-on rather than sequential add-on therapies. However, because of a multiplicity of end points and a lack of statistical power, no formal statistical analysis of between-group differences across the studies (saxagliptin 2.5 mg vs. 5 mg, saxagliptin 2.5 mg vs. placebo, saxagliptin

5 mg vs. placebo) was performed. Similarly, there was no formal analysis of differences between saxagliptin plus metformin versus metformin monotherapy in the initial combination study. These findings are nonetheless informative, as even differences not large enough to achieve statistical significance have the potential to be clinically relevant. In addition, the studies included in this analysis were of relatively short duration (i.e., 24 weeks) and, therefore, may not have revealed AEs that may occur with longer exposure to the study drug. A recent long-term analysis, however, demonstrated that there is no increase in AEs associated with administration of saxagliptin versus placebo for up to 102 weeks.[28]

Conclusion

Across 6 double-blind phase III clinical trials, saxagliptin was generally well tolerated as monotherapy; as add-on combination therapy with metformin, glyburide, or a TZD; and as initial combination therapy with metformin in patients with T2DM.

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DISCLOSURES

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Davidson is president of WorldWIDE Diabetes, a nonprofit organization with a mission to educate health care providers globally on the state of the art in diabetes. He has served as a consultant and/or member of an advisory board or speakers bureau for Animas, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Generex, GlaxoSmithKline, Johnson & Johnson (LifeScan), Merck Serono, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, sanofi-aventis, and Takeda. Davidson contributed to the acquisition and analysis/interpretation of the study data and drafted, critically revised, and approved the final manuscript.

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