



Common Drug Review

Clinical Review Report

November 2013

Drug	saxagliptin (Onglyza)
Indication	Indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea when dual therapy with these two agents, with diet and exercise, does not provide adequate glycemic control.
Listing request	In combination with metformin and a sulfonylurea when dual therapy with these two agents, with diet and exercise, does not provide adequate glycemic control in patients for whom insulin is not an option.
Manufacturers	Bristol-Myers Squibb Canada and AstraZeneca Canada

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ABBREVIATIONS

A1C	glycated hemoglobin
AE	adverse event
ANCOVA	analysis of covariance
CDR	Common Drug Review
CI	confidence interval
CrCl	creatinine clearance
DPP-4	dipeptidyl peptidase-4
FAS	full analysis set
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
NMA	network meta-analysis
NPH	neutral protamine Hagedorn
PL	placebo
PP	per-protocol
PPG	post-prandial glucose
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
TZDs	thiazolidinediones
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Saxagliptin (Onglyza) is an oral antihyperglycemic agent belonging to the dipeptidyl peptidase-4 (DPP-4) inhibitor class. Saxagliptin is indicated for patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, a sulfonylurea, metformin and a sulfonylurea, or long- or intermediate-acting insulin (with or without metformin), when these drugs do not provide adequate glycemic control. The recommended dose of saxagliptin is 5 mg once daily for most patients and 2.5 mg once daily for patients with moderate or severe renal impairment (creatinine clearance [CrCl] $\leq$ 50 mL/min).

The current Common Drug Review (CDR) submission for saxagliptin is for the manufacturer's requested listed criterion of use in combination with metformin and a sulfonylurea for patients with inadequate glycemic control and for whom insulin is not an option.

Results and Interpretation

Included Studies

One trial was included in the systematic review. Study 06 investigated the use of saxagliptin in patients who were inadequately controlled with metformin and sulfonylurea combination therapy. Study 06 was a 24-week, multicentre, placebo-controlled, double-blind randomized controlled trial (RCT) that enrolled 257 patients. The primary efficacy end point was the difference in glycated hemoglobin (A1C) levels from baseline to week 24 between saxagliptin (5 mg once daily) versus placebo, both in combination with metformin and a sulfonylurea. Adults with type 2 diabetes were eligible if they had poor glycemic control (i.e., A1C $\geq$ 7% and $\leq$ 10%) despite using the maximum tolerated dose of metformin ($\geq$ 1,500 mg/day) and a sulfonylurea ($\geq$ half of the maximum recommended dose).

Efficacy

Study 06 did not evaluate outcomes related to the macrovascular or microvascular complications of type 2 diabetes. There were no deaths during the trial. There was a statistically significant difference favouring saxagliptin over placebo for a change from baseline in A1C (adjusted mean difference 95% confidence interval [CI] = -0.66% , -0.86 to -0.47); $P < 0.0001$. Subgroup analyses for age, race, and gender demonstrated findings that were similar to the overall assessment. The proportion of patients achieving A1C $< 7.0\%$ was higher in the saxagliptin group than in the placebo group (30.7% versus 9.4%; adjusted odds ratio = 9.01 [95% CI, 3.85 to 21.05]). There was no statistically significant difference between saxagliptin and placebo in the change from baseline fasting plasma glucose (FPG) (Table 1).

TABLE 1: SUMMARY OF RESULTS

Outcome	SAX + MET + SU		PL + MET + SU		SAX Group Versus PL ^a Group	
	BL	Δ from BL	BL	Δ from BL	MD (95% CI)	P Value
A1C (%)	8.37	-0.74 (-0.89 to -0.60)	8.17	-0.08 (-0.23 to 0.07)	-0.66 (-0.86 to -0.47)	< 0.0001
FPG (mmol/L)	8.99	-0.29 (-0.70 to 0.12)	8.63	0.15 (-0.25 to 0.54)	-0.44 (-0.94 to 0.06)	0.0868
Weight (kg)	82.0	0.2 (-0.2 to 0.6)	80.3	-0.6 (-1.0 to -0.2)	0.8 (0.24 to 1.36)	NR

Δ = change; A1C = glycated hemoglobin; BL = baseline; CI = confidence interval; FPG = fasting plasma glucose; MD = mean difference; MET = metformin; NR = not reported; PL = placebo; PPG = post-prandial glucose; SAX = saxagliptin; SU = sulfonylurea.

^aAdjusted results presented for A1C and FPG.

Health-related quality of life (QoL) was assessed with the EQ-5D questionnaire and the EQ-VAS scale. Overall, changes in patient-reported, health-related QoL from baseline were similar in the saxagliptin and placebo groups.

Harms

The proportion of patients who experienced at least one adverse event (AE) during the 24-week treatment period was lower in the saxagliptin group compared with the placebo group (63% versus 72%). Most AEs in both treatment groups were mild or moderate in intensity; four patients in each group had AEs that were classified as severe. The most common AEs in the saxagliptin group were nasopharyngitis (6.2%), diarrhea (5.4%), and hypertension (5.4%). Serious adverse events (SAEs) were reported for three patients (2.3%) in the saxagliptin group and for seven patients (5.5%) in the placebo group. One patient (0.8%) in the saxagliptin group and three patients (2.3%) in the placebo group discontinued treatment due to AEs.

Mean changes from baseline in body weight at 24 weeks were 0.2 and -0.6 kg in the saxagliptin and placebo groups, respectively (CDR-calculated mean difference = 0.8 kg [95% CI, 0.3 to 1.3]).

Thirteen patients (10.1%) in the saxagliptin group experienced a total of 19 hypoglycemic events, and eight patients (6.3%) in the placebo group experienced a total 16 hypoglycemic events. The relative risk for overall hypoglycemia was 1.61 (CDR-calculated 95% CI, 0.69 to 3.76). The majority of reported hypoglycemic events were asymptomatic (i.e., they were based on low blood glucose values alone). No patient experienced a major hypoglycemic event (Table 2).

TABLE 2: SUMMARY OF HARMS OUTCOMES

Adverse Events	Treatment + MET + SU	
	SAX (N=129) n (%)	PL (N=128) n (%)
At least 1 AE	81 (62.8)	91 (71.7)
At least 1 serious AE	3 (2.3)	7 (5.5)
Withdrawal due to AE	1 (0.8)	3 (2.3)
Hypoglycemia	13 (10.1)	8 (6.3)
Severe hypoglycemia	0	0
Gastrointestinal-related AE	24 (18.6)	23 (18.0)

AE = adverse event; MET = metformin; n = number of patients with an adverse event; N = total number of patients in analysis; PL = placebo; SU = sulfonylurea.

Pharmacoeconomic Summary

Saxagliptin (Onglyza) is available as a 5 mg tablet to be taken once daily. It is indicated in combination with metformin and a sulfonylurea when dual therapy with these two drugs, with diet and exercise, does not provide adequate glycemic control. At a confidential price of \$██████ per tablet (\$██████ daily), the daily cost of saxagliptin is less than that of sitagliptin (\$2.95; 100 mg) but is higher than or equal to that of linagliptin (\$2.25 to \$2.55; 5 mg). Saxagliptin is more expensive than all other oral antidiabetic drugs, including sulfonylureas, thiazolidinediones (TZDs), and alpha-glucosidase inhibitors.

Conclusions

One double-blind, 24-week, RCT demonstrated that the addition of saxagliptin to ongoing treatment with metformin and a sulfonylurea was statistically superior to placebo for reducing A1C in patients who were inadequately controlled on combination therapy with metformin and a sulfonylurea. The effect of saxagliptin on A1C (−0.66%) was in the range considered clinically significant, and was aligned with the effects of other DPP-4 inhibitors in the third-line setting. Saxagliptin was not associated with clinically important changes in body composition compared with placebo. AEs, SAEs, and withdrawal due to adverse events (WDAEs) were more commonly reported with placebo than with saxagliptin. The proportion of patients with hypoglycemia was numerically greater in patients treated with saxagliptin compared with those treated with placebo (10% versus 6%), but most events were asymptomatic and there were no events of severe hypoglycemia. Hence, the likelihood of clinically significant hypoglycemia events with saxagliptin appears to be low. There was no evidence regarding the effects of saxagliptin added to metformin and sulfonylurea on the macrovascular and microvascular complications of diabetes, specifically in patients unable to use insulin.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Diabetes is a chronic, metabolic disease with significant health impacts on individuals and societies. The incidence of diabetes is increasing at a dramatic rate around the world. The International Diabetes Federation estimated that 371 million people had diabetes in 2012, and it projected an increase to 552 million by 2030.¹ The prevalence of diabetes in Canada was 6.8% (2.4 million Canadians) in 2009 and is expected to rise to 3.7 million people by 2019.² People with diabetes are more likely to be hospitalized and to experience complications requiring specialist care. By 2020, the diabetes-associated costs to the Canadian health care system will be an estimated \$16.9 billion per year.³

Ninety per cent of people with diabetes have type 2 diabetes (type 2 diabetes).⁴ Type 2 diabetes is characterized by increased hepatic glucose output, reduced insulin secretion, and insulin resistance. It is generally diagnosed in adults older than 40 years, although increasingly it is being detected in adolescents and children. Diagnosis is based on an FPG level of ≥ 7.0 mmol/L, a 2-hour plasma glucose level with a 75 g oral glucose tolerance test of ≥ 11.1 mmol/L, or a glycated hemoglobin (A1C) of $\geq 6.5\%$. A diagnosis of type 2 diabetes based on A1C is restricted to adults without factors that can affect the accuracy of the A1C test results.¹

The thresholds for diagnosis have been established because they predict the development of retinopathy, which is one of the common microvascular complications of diabetes.¹ Other microvascular complications are nephropathy (which may progress to end-stage renal disease) and neuropathy (which may cause pain, tingling, gastroparesis, erectile dysfunction, or lower extremity peripheral vascular disease, often resulting in the need for amputation). The primary cause of blindness, end-stage renal disease, and non-traumatic amputation in Canadian adults is diabetes.¹ Cardiovascular disease (i.e., heart disease, stroke, and peripheral vascular disease) is a major macrovascular complication and is the leading cause of death in people with type 2 diabetes.²

1.2 Standards of Therapy

There are currently 10 classes of antihyperglycemic drugs approved for use in Canada: biguanides, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, TZDs, DPP-4 inhibitors, glucagon-like peptide-1 (GLP-1) analogues, basal insulins, bolus insulins, and biphasic insulins. Metformin is recommended as the first-line oral antidiabetes drug in most patients with type 2 diabetes when glycemic control cannot be achieved by lifestyle interventions alone.¹ In 2013, the Canadian Agency for Drugs and Technologies in Health (CADTH) published updated network meta-analyses (NMA) and pharmacoeconomic analyses assessing the comparative safety, efficacy, and cost-effectiveness of all available classes of antihyperglycemic therapies in the following clinical situations: (1) patients with type 2 diabetes with inadequate glycemic control on metformin monotherapy;⁵ and (2) patients with type 2 diabetes with inadequate glycemic control on metformin and a sulfonylurea.⁶

Based on this evidence, the Canadian Drug Expert Committee (CDEC) recommended the following:

- A sulfonylurea should be added to metformin for most adults with type 2 diabetes who are inadequately controlled on metformin alone.
- Insulin neutral protamine Hagedorn (NPH) should be added for most adults with type 2 diabetes inadequately controlled on metformin and a sulfonylurea.
- A DPP-4 inhibitor may be added to metformin and sulfonylurea therapy in circumstances where patients with type 2 diabetes are unable to use insulin as a third-line option.

1.3 Drug

Saxagliptin (Onglyza) is an oral antihyperglycemic drug belonging to the dipeptidyl peptidase-4 (DPP-4) inhibitor class. Saxagliptin is indicated for patients with type 2 diabetes to improve glycemic control in combination with metformin, a sulfonylurea, metformin and a sulfonylurea, or long or intermediate-acting insulin (with or without metformin), when these drugs do not provide adequate glycemic control. The recommended dose of saxagliptin is 5 mg once daily for most patients and 2.5 mg once daily for patients with moderate or severe renal impairment ($\text{CrCl} \leq 50 \text{ mL/min}$).

Indication under review
Patients with type 2 diabetes mellitus, to improve glycemic control in combination with metformin and a sulfonylurea when dual therapy with these two agents, with diet and exercise, does not provide adequate glycemic control type 2 diabetes.
Listing criteria requested by sponsor
List with criteria as a third-line agent added to metformin and a sulfonylurea for patients with inadequate glycemic control and for whom insulin is not an option.

TABLE 3: KEY CHARACTERISTICS OF DPP-4 INHIBITORS

	Saxagliptin	Linagliptin	Sitagliptin
Mechanism of Action	Inhibition of DPP-4	Inhibition of DPP-4	Inhibition of DPP-4
Indications^a	In combination with the following: MET, an SU, premixed or long- or intermediate-acting insulin (with or without MET), or MET and an SU	- As monotherapy - In combination with the following: MET, an SU, MET and an SU	- As monotherapy - In combination with the following: MET, an SU, MET and an SU, premixed or long/ intermediate acting insulin (with or without MET), PIO, or MET and PIO
Route of Administration	Oral	Oral	Oral
Recommended Dose	5 mg once daily 2.5 mg once daily (moderate or severe renal impairment)	5 mg once daily - No dose adjustment is required for patients with renal impairment	100 mg once daily 50 mg once daily (moderate renal impairment) 25 mg once daily (severe renal impairment or end-stage renal disease)
Warnings and Precautions^a	- Reports of acute pancreatitis - Not recommended for patients with CHF	- Reports of acute pancreatitis - Not recommended for patients with CHF	- Reports of acute pancreatitis - Not recommended for patients with CHF

CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; MET = metformin; PIO = pioglitazone; SU = sulfonylurea.

^aAbbreviated indications and selected Warnings and Precautions from the Product Monographs (please consult the Product Monographs for complete details).

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of saxagliptin 5 mg once daily for the treatment of adults with type 2 diabetes who have experienced inadequate glycemic control on combination therapy with metformin and a sulfonylurea.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with type 2 diabetes who have experienced inadequate glycemic control on combination therapy with metformin and a sulfonylurea
Intervention	Saxagliptin (2.5 mg once daily or 5 mg once daily) in combination with metformin and a sulfonylurea
Comparators	Other DPP-4 inhibitors, basal insulin, or placebo in combination with metformin and a sulfonylurea
Outcomes	Key efficacy outcomes • mortality • diabetes-related morbidity (macrovascular, microvascular) • glycemic control (A1C, FBG) • QoL (measured by any validated scale) Harms outcomes • hypoglycemia • total AEs • SAEs • WDAEs • changes in body weight Other outcomes • health care resource utilization
Study design	Published and unpublished RCTs ≥ 12 weeks duration

A1C = glycated hemoglobin; AEs = adverse events; DPP-4 = dipeptidyl peptidase-four; FBG = fasting blood glucose; QoL = quality of life; RCT = randomized controlled trial; SAEs = serious adverse events; T2DM = type 2 diabetes mellitus; WDAEs = withdrawals due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid, Embase (1974-) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were saxagliptin and Onglyza.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. As this search was conducted to support a resubmission, retrieval was limited by the following publication years: 2012 to the present. Conference abstracts were excluded from the search results.

The initial search was completed on June 25, 2013. Regular alerts were established to update the search until the meeting of the CDEC on October 16, 2013. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH “Grey Matters” checklist (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>): Regulatory Approvals, Advisories and Warnings, HTA Agency Standard, Databases, and Health Economics. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and by contacting appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. The reviewers independently made the final selection of studies to be included in the review; any differences were resolved through discussion. The included study is presented in Table 5.

3. RESULTS

3.1 Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The literature search was conducted as an update from previous CDR reviews of saxagliptin; therefore, the search was limited to the period from 2012 to the present.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

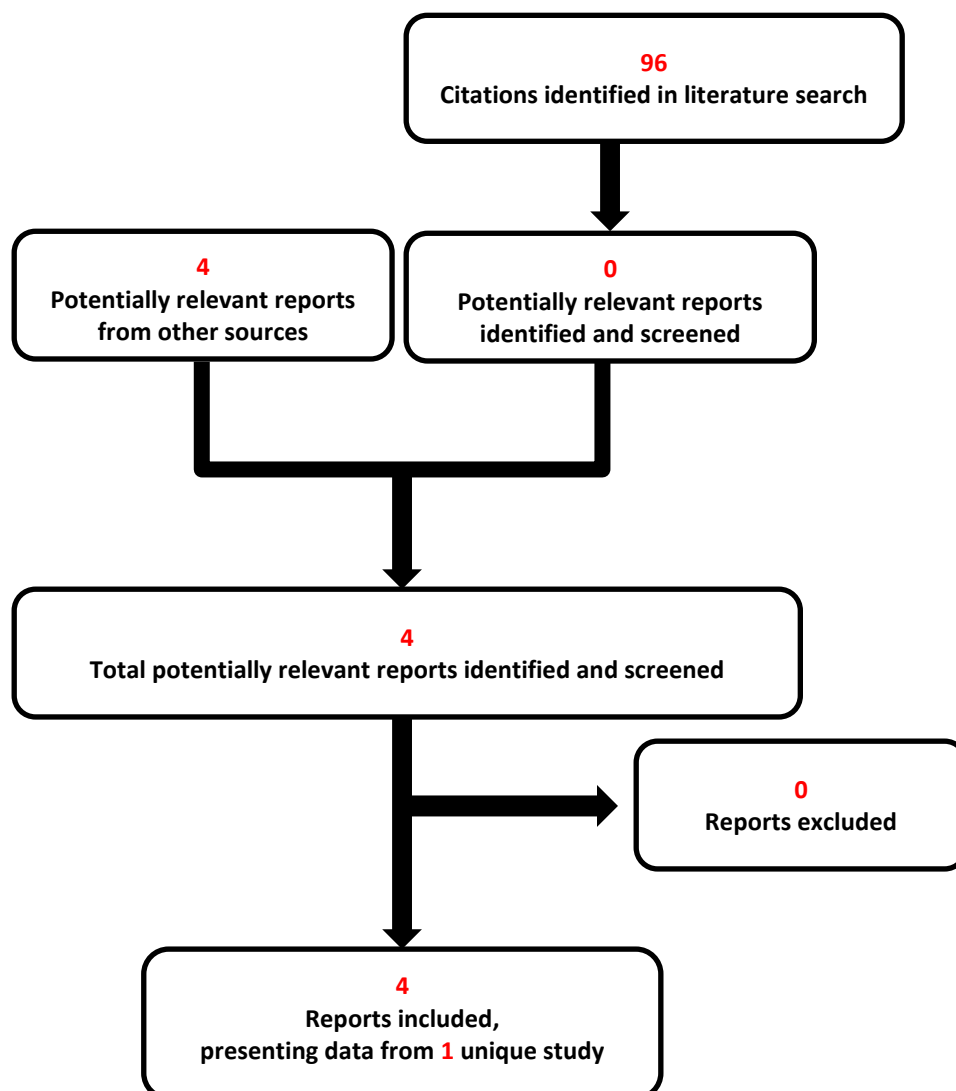


TABLE 5: DETAILS OF INCLUDED STUDY

DESIGNS AND POPULATIONS	Study Design	24-Week, Multicentre, Placebo-Controlled, Phase 3b, double-blind RCT
	Locations	Canada, Australia, India, Republic of Korea, Thailand, United Kingdom
	Randomized (N)	257
	Inclusion criteria	≥ 18 years; type 2 diabetes mellitus with uncontrolled glycemia (A1C ≥ 7% and ≤ 10%) despite metformin (≥ 1,500 mg) and a sulfonylurea (≥ 50% maximum recommended dose) daily for ≥ 8 weeks; BMI ≤ 40 kg/m ²
	Exclusion criteria	Current or prior use of insulin, DPP-4 inhibitor, GLP-1 analogues, and/or other oral antidiabetes drugs (other than metformin and SU); estimated CrCl < 60 mL/min
INTERVENTIONS	Intervention	Saxagliptin (5 mg once daily) + pretrial doses of metformin and a sulfonylurea (i.e., glyburide, gliclazide, glimepiride, or glipizide)
	Comparator(s)	Placebo (5 mg once daily) + pre-trial doses of metformin and a sulfonylurea (i.e., glyburide, gliclazide, glimepiride, or glipizide)
DURATION	Run-in	2 weeks
	Double-blind	24 weeks
	Follow-up	Not applicable
OUTCOMES	Primary end point	Change in A1C from baseline
	Secondary efficacy end point	• FPG • body weight • proportion of patients with A1C < 7% • EQ-5D • post-prandial glucose • lipids (TC, LDL-C, HDL-C, TG) • insulin, C-peptide, glucagon
	Safety assessments	• AEs, SAEs, WDAEs • hypoglycemia • vital signs, laboratory tests
NOTES	Data sources	• Study 06 Clinical Study Report⁷ • Saxagliptin CDR Submission⁸ • Saxagliptin Triple Oral Therapy (results posted on clinicaltrials.gov)⁹ • Moses et al., 2012 (conference abstract)¹⁰

A1C = glycated hemoglobin; AEs = adverse events; BMI = body mass index; CDR = Common Drug Review; CrCl = creatinine clearance; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; RCT = randomized control trial; SAEs = serious adverse events; TC = total cholesterol; TG = triglycerides; WDAEs = withdrawals due to adverse event.

3.2 Included Studies

3.2.1 Description of Studies

The literature search identified five RCTs published since the initial CDR review of saxagliptin in 2009 that investigated patient populations consistent with the Health Canada's indications for saxagliptin (Table 6). One of the trials (Study 06), which investigated the use of saxagliptin in patients who were inadequately controlled with metformin and sulfonylurea combination therapy, was included in this systematic review.

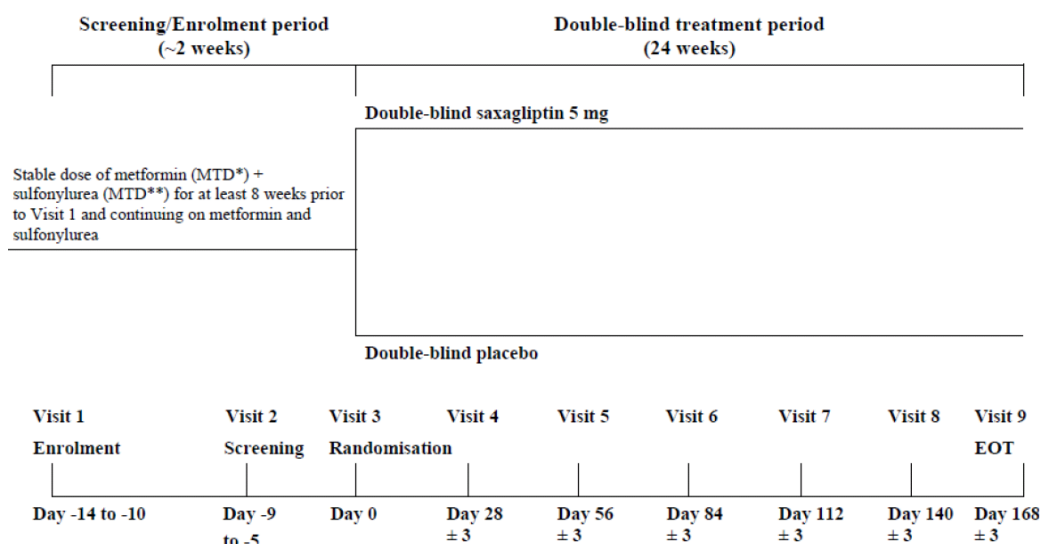
Study 06 was a 24-week, placebo-controlled, double-blind RCT involving 257 patients who were inadequately controlled with metformin and a sulfonylurea (Figure 2). The primary efficacy objective was to compare the difference in A1C levels from baseline to week 24 between saxagliptin 5 mg once daily versus placebo, both in combination with metformin and a sulfonylurea. This study was conducted at 35 study centres in six countries.

TABLE 6: LIST OF RCTs INCLUDED IN THE CDR REVIEWS OF SAXAGLIPTIN

Study ID	Comparators	N	Duration (weeks)	Primary End Point
Included in the Current CDR Review				
Study 06	SAX (5 mg) + MET + SU PL + MET + SU	257	24	Δ A1C
Additional Studies Identified in Updated Literature Search That did not Meet Inclusion Criteria for Review				
Study 07	SAX (2.5 mg) ± insulin ± OADs PL ± insulin ± OADs	170	52	Δ A1C
Study 57	SAX (5 mg) + insulin ± MET PL + insulin ± MET	455	52	Δ A1C
Study 54	SAX (5 mg) + MET Glipizide + MET	838	52	Δ A1C
Yang (2011)	SAX (5 mg) + MET PL + MET	570	24	Δ A1C
Included in the 2009 CDR Review				
Study 14	SAX (2.5 mg) + MET SAX (5 mg) + MET SAX (10 mg) + MET PL + MET	745	24	Δ A1C
Study 56	SAX (5 mg) + MET Sitagliptin (100 mg) + MET	801	18	Δ A1C
Study 40	SAX (5 mg) + Glyburide PL + Glyburide (Up-titrated)	768	24	Δ A1C

Δ = change; ID = identification; MET = metformin; N = total number of patients in analysis; OAD = oral antidiabetes drug; PL = placebo; SAX = saxagliptin; SU = sulfonylurea.

FIGURE 2: TRIAL DESIGN OF STUDY 06



EOT = end of double-blind trial; MTD = maximum-tolerated dose.

Source: Figure from Clinical Study Report.⁷

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Adults with type 2 diabetes were eligible for Study 06 if they had poor glycemic control (defined as A1C $\geq 7\%$ and $\leq 10\%$) despite using the maximum tolerated dose of metformin and a sulfonylurea for at least 8 weeks. The dosage of metformin was required to be at least 1,500 mg/day and the dosage of sulfonylurea was required to be at least half of the maximum recommended daily dose. Patients were required to have a body mass index of $\leq 40 \text{ kg/m}^2$ to be randomized. Patients were excluded if they had current or prior use of insulin, DPP-4 inhibitors, GLP-1 analogues, and/or any other oral antidiabetes drugs other than metformin and a sulfonylurea.

b) Baseline Characteristics

The demographic and baseline characteristics of patients in Study 06 are summarized in Table 7. Patients ranged in age from 25 to 83 years with a mean age of 57.0 years. A total of 196 patients (76.3%) were less than 65 years of age. The majority of patients in each treatment group were male (62.0% and 57.8% in the saxagliptin and placebo groups, respectively). Body weight ranged from 40 kg to 155 kg, with a mean of 82.4 kg and 80.3 kg for the saxagliptin and placebo groups, respectively. Baseline A1C, post-prandial glucose (PPG), and FPG were slightly higher in the saxagliptin group compared with the placebo group. Differences in these baseline disease characteristics were accounted for in the efficacy analysis by using the baseline value as a covariate in the analysis of covariance (ANCOVA).

TABLE 7: SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS FROM STUDY 06

Characteristics ^a	SAX + MET + SU (N = 129)	PL + MET + SU (N = 128)	Total (N = 257)
Mean age, years	57.2 (9.6)	56.8 (11.5)	57.0 (10.5)
≥ 65 years, n (%)	28 (21.7)	33 (25.8)	61 (23.7)
Female, n (%)	49 (38.0)	54 (42.2)	103 (40.1)
Race			
White, n (%)	59 (45.7)	57 (44.5)	116 (45.1)
Asian, n (%)	70 (54.3)	71 (55.5)	141 (54.9)
Mean weight, kg	82.4 (19.9)	80.3 (18.5)	81.4 (19.2)
Mean BMI, kg/m ²	29.4 (5.3)	29.1 (4.9)	29.2 (5.1)
Mean A1C, %	8.38 (0.86)	8.19 (0.83)	8.28 (0.85)
Mean PPG, mmol/L	14.9 (4.3)	14.7 (3.9)	14.8 (4.1)
Mean FPG, mmol/L	9.0 (2.6)	8.6 (2.1)	8.8 (2.4)
Mean dose of OADs (mg/day)			
metformin	1957.0 mg	1957.0 mg	1957.0 mg
glyburide	14.5 mg	16.5 mg	15.5 mg
glimepiride	5.2 mg	4.9 mg	5.0 mg
glipizide	20.0 mg	15.0 mg	17.8 mg
gliclazide	157.9 mg	161.5 mg	159.6 mg

BMI = body mass index; FPG = fasting plasma glucose; MET = metformin; OADs = oral antidiabetes drugs; PL = placebo; PPG = post-prandial glucose; SAX = saxagliptin; SU = sulfonylurea.

^aData are presented as mean (standard deviation) unless otherwise noted.

3.2.3 Interventions

Saxagliptin was taken orally at a dose of 5 mg once daily throughout the trial. Both saxagliptin and the matching placebo were administered in the morning with breakfast. On study visit days, study medications were taken after the relevant laboratory specimens had been collected. Throughout the 24-week double-blind treatment period, patients continued their (open-label) metformin and sulfonylurea therapy at the doses ascertained during enrolment. The dose of sulfonylurea could be reduced once if the patient experienced a major hypoglycemic event or recurring minor hypoglycemic events. Titration (up or down) of study medication during the double-blind treatment period was prohibited.

3.2.4 Outcomes

a) Glycemic Control

The primary efficacy outcome was the difference in change in A1C levels from baseline to week 24 between saxagliptin 5 mg versus placebo. Differences in the changes in PPG and FPG from baseline to week 24 were secondary end points. The proportion of patients in each group with a glycemic response of A1C < 7% at week 24 was also specified as a secondary end point. Patients were instructed to self-monitor their fasting blood glucose levels (at least every other day) and to record in their participant diary their fasting glucose values, any symptoms suggestive of hypoglycemia, and their self-monitored glucose values obtained at the time of a symptomatic event.

b) Hypoglycemia

Confirmed hypoglycemic events were defined as symptomatic hypoglycemia with a self-monitored glucose value of ≤ 2.8 mmol/L. Hypoglycemic adverse events (AEs) were classified as either major, minor, or suggestive, according to the following criteria:¹¹

- Major event — symptomatic episode requiring external assistance due to severe impairment in consciousness or behaviour, with a plasma glucose level < 3.0 mmol/L that resulted in prompt recovery after glucose or glucagon administration.
- Minor event — symptomatic episode associated with a blood glucose level < 3.0 mmol/L and no need for assistance, or an asymptomatic plasma glucose measurement < 3.0 mmol/L.
- Event suggestive of hypoglycemia — symptoms that the subject experiences as hypoglycemia, where plasma glucose measurements were not available.

c) Patient-Reported Outcomes

Health-related QoL was assessed using both sections of the EQ-5D survey of health status (i.e., the EQ-5D questionnaire and the EQ-VAS). The self-reported questionnaire covers the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels of response: no problems, some problems, or extreme problems. The EQ-VAS provides a self-assessment of overall health status using a visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). Patients in Study 06 completed the EQ-5D at baseline and at week 24.

3.2.5 Statistical Analysis

The change in A1C from baseline to week 24 was analyzed using an ANCOVA model, with treatment group and country as fixed effects and the baseline A1C as a covariate. The model was used to derive a least-squares estimate of the treatment difference in the mean change from baseline, with a corresponding two-sided 95% confidence interval and a 2-sided *P* value. The statistical analysis plan stated that a total of 240 patients (120 per treatment group) would be needed to provide approximately 80% power at a 2-sided significance level of 0.05, assuming a true difference of 0.40% in A1C and a standard deviation of 1.1%.

The changes in PPG and FPG from baseline to week 24 were also analyzed using an ANCOVA model, with treatment group and country as fixed effects and the baseline value as a covariate.

The proportion of patients with a glycemic response of A1C $< 7\%$ at week 24 were summarized per treatment group using counts and proportions. Comparisons of proportions between the treatment groups were performed using a logistic regression model, with treatment group and country as fixed effects and the baseline A1C as a covariate.

Missing values at week 24 were imputed with the last post-baseline value using the last observation carried forward (LOCF) method. A post-hoc sensitivity analysis was conducted using a mixed model repeated measures (MMRM) analysis for A1C and FPG.

Subgroup analyses were performed for A1C, PPG, and FPG, as well as for the proportions of patients achieving A1C $< 7.0\%$ based on age (< 65 years and ≥ 65 years), race, and gender.

a) Population Analysis Sets

The data analysis sets used in Study 06 included the following:

- The full analysis set (FAS) included all randomized patients who received at least one dose of investigational product during the 24-week double-blind treatment period and who had a non-missing baseline value and at least one post-baseline value for at least one efficacy parameter.
- The per-protocol (PP) analysis set included patients with no reasons for exclusion, i.e., exclusion from the FAS, non-compliance (< 80% or > 120% of the dosage), absence of baseline value and at least one post-baseline A1C value, or significant protocol violations.
- The safety analysis set included all randomized patients who received at least one dose of investigational product.

3.3 Patient Disposition

A total of 383 patients were screened for eligibility and 257 patients were enrolled in the trial. All 257 randomized patients received at least one dose of an investigational treatment. One hundred and twenty-nine patients were treated with saxagliptin and 128 with the matching placebo. Approximately 88% of patients in each group completed the 24-week trial. The most common reason for discontinuation in both treatment groups was worsening of type 2 diabetes (6.2% in the saxagliptin group and 5.5% in the placebo group). WDAEs were reported for one patient (0.8%) in the saxagliptin group and for three patients in the placebo group (2.3%) (Table 8).

TABLE 8: SUMMARY OF PATIENT DISPOSITION FROM STUDY 06

Disposition of Randomized and Treated Patients	SAX + MET + SU (N = 129) n (%)	PL + MET + SU (N = 128) n (%)
Completed	113 (87.6)	113 (88.3)
Discontinued	16 (12.4)	15 (11.7)
T2DM worsened	8 (6.2)	7 (5.5)
Patient's decision	2 (1.6)	3 (2.3)
Adverse events	1 (0.8)	3 (2.3)
Incorrect enrolment ^a	2 (1.6)	1 (0.8)
Severe non-compliance to protocol	2 (1.6)	0 (0.0)

MET = metformin; PL= placebo; SAX = saxagliptin; SU = sulfonylurea; T2DM = type 2 diabetes.

^aPatients did not meet inclusion and/exclusion criteria.

3.4 Exposure to Study Treatments**3.4.1 Investigation Products**

A summary of exposure to study treatment (saxagliptin 5 mg or placebo, as add-on to metformin plus sulfonylurea) during the double-blind treatment period is presented in Table 9.

TABLE 9: DURATION OF EXPOSURE TO INVESTIGATIONAL PRODUCT

Exposure (days)	SAX + MET + SU (N = 129)	PL + MET + SU (N = 128)
Mean (SD)	158.9 (31.41)	160.1 (29.73)
Median	168.0	168.0
Range	11 to 180	22 to 181

MET = metformin; N = total number of patients in analysis; PL = placebo; SAX = saxagliptin; SD = standard deviation; SU = sulfonylurea.

3.4.2 Concomitant Medications

Patients were required to be on a stable combined dose of metformin plus sulfonylurea for at least eight weeks prior to enrolment. The metformin and sulfonylurea doses were to remain constant during the 24-week double-blind treatment period at the doses ascertained during enrolment. Glimepiride (n = 119; 46%) and gliclazide (n = 109; 42%) were the most commonly used sulfonylureas in the trial population. Only a minority of patients used glyburide (n = 20; 8%) or glipizide (n = 9; 4%). The baseline doses of metformin and the sulfonylureas are summarized in Table 10. Three patients (one in the saxagliptin group and two in the placebo group) had their sulfonylurea dose down-titrated during the double-blind treatment period due to hypoglycemic events.

TABLE 10: DOSAGES OF METFORMIN AND SULFONYLUREAS AT BASELINE IN STUDY 06

Concomitant Medication	SAX + MET + SU		PL + MET + SU		Recommended Range in Canada ^a
	Mean	Range	Mean	Range	
Metformin	1,957 mg	1,500 mg to 3,000 mg	1,957 mg	1,500 mg to 3,000 mg	850 mg to 2,550 mg 1,000 mg to 2,000 mg (ER)
Glyburide	14.5 mg	5 mg to 20 mg	16.5 mg	10 mg to 25 mg	5 mg to 20 mg/day
Glimepiride	5.2 mg	2 mg to 8 mg	4.9 mg	2 mg to 8 mg	1 mg to 8 mg
Glipizide	20.0 mg	10 mg to 40 mg	15.0 mg	10 mg to 20 mg	5 mg to 40 mg/day
Gliclazide ^b	157.9 mg	60 mg to 480 mg	161.5 mg	60 mg to 320 mg	80 mg to 320 mg 30 mg to 120 mg (MR)

ER = extended release; MET = metformin; MR = modified release; PL = placebo; SAX = saxagliptin; SU = sulfonylurea.

^a Dosage ranges are from eCPS product monographs for metformin¹² and sulfonylureas.¹³

^b It is unclear what proportion of patients may have been using modified-release gliclazide.

3.5 Critical Appraisal

3.5.1 Internal Validity

Study 06 demonstrated a number of strengths with respect to internal validity. Randomization was performed via an interactive voice/Web response system, which would have provided adequate allocation concealment. The trial was double-blind and the treatment and placebo tablets were identical in appearance. Measurements of A1C were confirmed by a central laboratory. The dosages of metformin and sulfonylurea were to remain constant during the double-blind treatment.

A sample size calculation was provided and the number of patients randomized was in accordance with the statistical analysis plan. The proportion of patients who withdrew from the study was relatively low in both treatment groups; approximately 88% of patients in both groups completed the 24-week,

double-blind treatment period. Patient compliance was assessed at each visit by counting returned pills, and compliance was reported to be very high in both the saxagliptin (99.4%) and placebo (98.4%) treatment groups.

There were slight differences in baseline A1C, PPG, and FPG between the saxagliptin and placebo groups; however, these differences were accounted for in the efficacy analysis by using the baseline value as a covariate in the ANCOVA analysis. The results from the FAS were supported by a PP analysis. Sensitivity analyses were conducted for each efficacy variable using observed values as well as an MMRM analysis for A1C and FPG.

3.5.2 External Validity

The efficacy of saxagliptin was assessed using surrogate end points (e.g., A1C). Study 06 was of inadequate size or duration to assess the effect of saxagliptin on macrovascular or microvascular complications of diabetes, or on mortality. The relationship between glycemic control as measured by A1C and diabetes-related complications remains controversial, particularly for macrovascular events (Appendix 3). Study 06 was 24 weeks in duration, which is sufficient to detect differences in A1C; however, the findings may not be indicative of long-term efficacy and safety. Nonetheless, the duration of Study 06 is identical to similar published trials for other members of the DPP-4 inhibitor class.^{14,15}

The doses of the sulfonylureas used in Study 06 were consistent with the inclusion criteria of the trial (i.e., maximum tolerated dose or at least half of the maximum recommended daily dose). The only exception appears to be the mean dose of glipizide in the placebo group (15 mg/day) which is below 50% of the maximum recommended dose of 40 mg/day.¹³ It is also unclear if the mean dosage of gliclazide included the modified-release version of this agent, which has a much lower maximum recommended dosage (i.e., 120 mg versus 320 mg).

CADTH's recommendation for sequential therapy of diabetes is that a basal insulin agent (such as NPH) be used as third-line therapy for patients whose hyperglycemia is inadequately controlled with metformin and a sulfonylurea.¹⁶ There is no evidence regarding the efficacy of saxagliptin versus a basal insulin for patients who are inadequately controlled using metformin and a sulfonylurea. However, the design of Study 06 is consistent with studies of other DPP-4 inhibitors,^{14,15} and the lack of direct comparisons against basal insulin is of limited concern given the manufacturer's requested listing criterion for patients with type 2 diabetes who are unable to use insulin as a third-line option (consistent with the Canadian Expert Drug Advisory Committee [CEDAC] and CDEC recommendations for sitagliptin and linagliptin).^{17,18}

Study 06 involved extensive patient contact with health care professionals (i.e., nine visits during the study period). This is unlikely to be reflective of routine clinical practice in Canada; therefore, this factor may reduce generalizability of results to the general population with the type 2 diabetes.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. Please see APPENDIX 3: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Diabetes-Related Complications and Mortality

Study 06 did not evaluate outcomes related to macrovascular or microvascular complications of type 2 diabetes. There were no deaths in the study.

3.6.2 Glycemic Control

a) Glycated Hemoglobin (A1C)

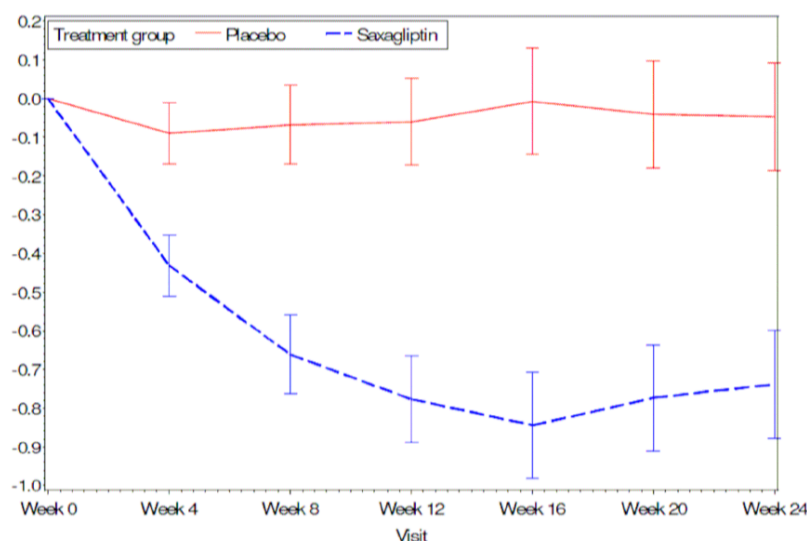
Mean baseline A1C values were slightly higher in the saxagliptin group compared with the placebo group (8.37% versus 8.17%). The adjusted mean change from baseline to week 24 was -0.74% for the saxagliptin group and -0.08% for the placebo group [mean difference = -0.66% [95% CI, -0.86 to -0.47]; $P < 0.0001$]. Results for A1C were similar when the analysis was performed using a PP population, without LOCF, and using MMRM (Table 11). Figure 3 shows the change in A1C during the 24-week study period for both the saxagliptin and placebo groups. Subgroup analyses for age (< 65 years, ≥ 65 years), race, and gender demonstrated findings that were similar to the overall assessment (see Figure on page 25).

The proportion of patients achieving A1C $< 7.0\%$ at week 24 was higher in the saxagliptin group than in the placebo group (30.7% versus 9.4%) (adjusted odds ratio = 9.01 [95% CI, 3.85 to 21.05]; $P < 0.0001$).

TABLE 11: CHANGES IN A1C FROM STUDY 06

Analysis	SAX + MET + SU		PL + MET + SU		SAX Group Versus PL Group	
	BL	Mean Δ from BL (95% CI)	BL	Mean Δ from BL (95% CI)	MD (95% CI)	P Value
A1C-FAS	8.37	-0.74 (-0.89 to -0.60)	8.17	-0.05 (-0.23 to 0.07)	-0.66 (-0.86 to -0.47)	< 0.0001
A1C-PP	8.35	-0.70 (-0.87 to -0.54)	8.20	-0.09 (-0.25 to 0.07)	-0.61 (-0.82 to -0.40)	< 0.0001

A1C = glycated hemoglobin; BL = baseline; CI = confidence interval; FAS = full analysis set; MD = mean difference; PL = placebo; PP = per-protocol (analysis set); SAX = saxagliptin.

FIGURE 3: CHANGES IN A1C FROM STUDY 06

A1C = glycated hemoglobin.

Figure from Study 06 Clinical Study Report.⁷

b) Fasting Plasma Glucose

Similar to A1C, the mean baseline FPG values were lower in the placebo group compared with the saxagliptin group (8.63 mmol/L versus 8.99 mmol/L). The adjusted mean change in FPG from baseline to week 24 was -0.29 mmol/L in the saxagliptin group and 0.15 mmol/L in the placebo group, with no statistically significant difference between treatments (mean difference = -0.44 mmol/L [95% CI, -0.94 to 0.06]; $P = 0.0868$).

3.6.3 Patient-Reported Outcomes

Health-related QoL was assessed using the EQ-5D questionnaire and the EQ-VAS. The manufacturer reported that for each EQ-5D dimension, a lower proportion of saxagliptin-treated patients compared with placebo-treated patients reported a worsening at week 24 relative to baseline. The mean (SD) change from baseline to week 24 on the EQ-VAS was 4.7 (20.2) in the saxagliptin group and 3.3 (17.7) in the placebo group.

3.7 Harms

Only those harms identified in the review protocol are reported below. See APPENDIX 3: DETAILED OUTCOME DATA for detailed harms data. A summary of harms data from Study 06 is shown in Table 12. A detailed listing of common AEs occurring in at least 2% of patients, SAEs, and WDAEs is provided in Table 1 on page 25.

TABLE 12: SUMMARY OF HARMS FROM STUDY 06

Summary of Adverse Events	SAX + MET + SU (N = 129) n (%)	PL + MET + SU (N = 128) n (%)
AEs	81 (62.8)	91 (71.7)
Deaths	0 (0.0)	0 (0.0)
SAEs	3 (2.3)	7 (5.5)
AE leading to discontinuation of IP	1 (0.8)	3 (2.3)
SAE leading to discontinuation of IP	0 (0.0)	1 (0.8)

AE = adverse event; IP = investigational product; MET = metformin; n = patients with ≥ 1 adverse event; N = total number of patients in analysis; PL = placebo; SAE = serious adverse event; SAX = saxagliptin; SU = sulfonylurea.

3.7.1 Adverse Events

The proportion of patients who experienced at least one AE during the 24-week treatment period was lower in the saxagliptin group compared with the placebo group (62.8% versus 71.7%). Most AEs in both treatment groups were mild or moderate in intensity. Four subjects (3.1%) in each group had AEs that were severe in intensity. The most common AEs in the saxagliptin group were nasopharyngitis (6.2%), diarrhea (5.4%), and hypertension (5.4%); the most common AEs in the placebo group were nasopharyngitis (9.4%), urinary tract infection (6.3%), and dyslipidemia (5.5%). AEs with an incidence of $\geq 2\%$ in the saxagliptin group and at least 1% greater than in the placebo group were diarrhea (5.4% versus 3.9% in the placebo group), hypertension (5.4% versus 1.6%), cough (3.1% versus 0.8%), flatulence (3.1% versus 0%), and peripheral neuropathy (2.3% versus 0%). Pancreatitis was reported for one patient (0.8%) in the saxagliptin group; no pancreatitis occurred in the placebo group.

3.7.2 Serious Adverse Events

There were no deaths during the study. Serious adverse events (SAEs) were reported for three patients (2.3%) in the saxagliptin group and for seven patients (5.5%) in the placebo group. In the saxagliptin group, the SAEs included lower respiratory tract infection, laryngeal cancer, and hepatitis in one patient each. In the placebo group, SAEs included influenza, osteomyelitis, squamous cell carcinoma, cartilage injury, renal colic, asthma, arthritis, and musculoskeletal stiffness in one patient each.

3.7.3 Withdrawals Due to Adverse Events

One patient (0.8%) in the saxagliptin group and three patients (2.3%) in the placebo group discontinued treatment due to AEs. One of the patients in the placebo withdrew as a result of an SAE.

3.7.4 Hypoglycemia

Thirteen patients (10.1%) in the saxagliptin group experienced a total of 19 hypoglycemic events and eight patients (6.3%) in the placebo group experienced a total 16 hypoglycemic events (Table 13). The CDR-calculated relative risk for overall hypoglycemia was 1.61 (95% CI, 0.69 to 3.76). No patients experienced a major hypoglycemic event. Of the 19 events in the saxagliptin group, 4 were minor events and 15 were suggestive events. Of the 16 hypoglycemic events in the placebo group, 5 were minor events and 11 were suggestive events.

TABLE 13: SUMMARY OF HYPOGLYCEMIA FROM STUDY 06

Parameter	Description	SAX + MET + SU (N = 129)	PL + MET + SU (N = 128)
Patients with hypoglycemia [n (%)]			
Had event		13 (10.1)	8 (6.3)
No event		116 (89.9)	120 (93.8)
Events of hypoglycemia^a			
Major event		0	0
Minor event		4	5
Suggestive event		15	11

MET = metformin; n = number of patients with event; N = total number of patients in analysis; PL = placebo;

SAX = saxagliptin; SU = sulfonylurea.

^aSome patients experienced multiple events of hypoglycemia.

3.7.5 Changes in Body Weight

Mean changes from baseline in body weight were minimal for both the placebo and the saxagliptin treatment groups. At week 24, mean changes (SD) from baseline in weight were 0.2 kg and -0.6 kg in the saxagliptin and placebo groups, respectively [CDR-calculated mean difference = 0.8 kg [95% CI, 0.3 to 1.3]].

TABLE 14: CHANGES IN BODY WEIGHT FROM STUDY 06

Outcome	SAX + MET + SU		PL + MET + SU		SAX Group Versus PL Group MD ^a (95% CI)
	BL	Mean Δ from BL	BL	Mean Δ from BL	
Body weight (kg)	82.0	0.2 (-0.2 to 0.6)	80.3	-0.6 (-1.0 to -0.2)	0.8 (0.3 to 1.3)

Δ = change; BL = baseline; CI = confidence interval; MD = mean difference; PL = placebo; SAX = saxagliptin.

^aCDR-calculated mean difference.

4. DISCUSSION

4.1 Summary of Available Evidence

The manufacturer has requested a “list with criteria” recommendation for the use of saxagliptin after failure of metformin and a sulfonylurea, when insulin is not an option. There was one placebo-controlled RCT identified in this review that investigated the use of saxagliptin in patients with type 2 diabetes with inadequate glycemic control despite combination therapy with metformin and a sulfonylurea. The population for Study 06 was not in accordance with the manufacturer’s listing criteria of “patients for whom insulin is not an option,” since enrolled patients were not required to present with any barriers to the use of insulin. However, the population and trial design were consistent with trials of other DPP-4 inhibitors in patients inadequately controlled with metformin and a sulfonylurea.^{14,15} Furthermore, this criterion is analogous to the listing criteria specified in the CEDAC and CDEC recommendations for linagliptin and sitagliptin.^{17,18}

4.2 Interpretation of Results

4.2.1 Efficacy

There was no evidence related to macrovascular or microvascular complications of type 2 diabetes for saxagliptin used in combination with metformin and a sulfonylurea. This is consistent with the paucity of evidence found in CADTH’s review of third-line diabetes pharmacotherapy⁶ and with other systematic reviews of oral antihyperglycemics.^{19,20} Similar to RCTs of most other antihyperglycemic drugs, the primary end point in the saxagliptin study was the change in A1C from baseline. Turnbull et al. (2009)²¹ and Boussageon et al. (2011)²² conducted two separate meta-analyses of major trials investigating the effects of reducing A1C on macrovascular and microvascular outcomes in patients with type 2 diabetes. Results from the meta-analyses suggest that a lower A1C is associated with a reduced risk of major cardiac events and myocardial infarction, but not of stroke, cardiovascular death, or all-cause mortality.²¹ Exploratory subgroup analysis suggested that the effects of lowering A1C may be more favourable for patients without coexisting macrovascular disease.²¹ Although the extent of glucose control may not be fully responsible for differences in clinical outcomes, A1C is considered an appropriate primary outcome in clinical trials of antihyperglycemic drugs.²³

Although there was no specific evidence regarding macrovascular end points in the third-line setting, the results of a large placebo-controlled RCT assessing long-term cardiovascular end points with saxagliptin (Saxagliptin Assessment of Vascular Outcomes Reported in Patients with Diabetes Mellitus — Thrombolysis in Myocardial Infarction [SAVOR-TIMI]) have recently been published.^{24,25} The study enrolled 16,942 patients with type 2 diabetes and a history of cardiovascular disease or risk factors for vascular disease. Hierarchical statistical testing demonstrated that saxagliptin was non-inferior ($P < 0.001$) but not superior ($P = 0.99$) to placebo for the primary composite outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal ischemic stroke (hazard ratio = 1.00; 95% CI, 0.89 to 1.12). However, hospitalization for heart failure was more commonly reported for patients in the saxagliptin group than for patients in the placebo group (3.5% versus 2.8%; hazard ratio = 1.27 [95% CI, 1.07 to 1.51]; $P = 0.007$).²⁵

When added to ongoing therapy with metformin and a sulfonylurea, treatment with saxagliptin was associated with a statistically significant improvement in A1C relative to placebo (−0.66% [95% CI, −0.86 to −0.47]). The National Institute for Health and Clinical Excellence (NICE) and the US Food and Drug Administration (FDA) have indicated that reductions from baseline in A1C as small as −0.5% and −0.7%, respectively, have clinical importance.^{26,27} Hence, the effect size of saxagliptin appears to satisfy the FDA and NICE criteria for minimal clinical importance.

The effect of saxagliptin on A1C (−0.66%) in Study 06 was similar to that reported for linagliptin (−0.62%)¹⁵ and was slightly less than that reported for sitagliptin (−0.89%).²⁸ Differences in the glycemic response of the placebo groups appear to underlie the larger effect size observed with sitagliptin. Patients in the placebo groups of the saxagliptin and linagliptin RCTs demonstrated small improvements in A1C (−0.05% and −0.1%, respectively), whereas, the placebo group in the sitagliptin trial showed a deterioration of 0.3%. The manufacturer conducted an indirect comparison comparing saxagliptin against sitagliptin or linagliptin as add-on therapy to metformin and a sulfonylurea in patients with type 2 diabetes, and found no significant differences. CADTH's updated agent-level NMA also found no differences between these drugs with respect to A1C.

Many patients with type 2 diabetes are overweight or obese. Therefore, changes in body weight associated with antidiabetes therapy may be important for both patients and health care professionals. In CADTH's review of third-line antidiabetes therapies,⁶ DPP-4 inhibitors and alpha-glucosidase inhibitors were weight-neutral, GLP-1 analogues were associated with statistically significant weight loss, and insulins and TZDs were associated with weight gain (range: 1.9 kg to 5.0 kg). When provided in combination with metformin and a sulfonylurea, saxagliptin was associated with a minimal increase in body weight (0.8 kg) relative to placebo. This difference was primarily attributable to a slight decrease in the body weight of placebo-treated patients (−0.6 kg). A difference of 0.8 kg corresponds to a change in body weight of approximately 1% in the study population. This is not likely to be clinically relevant based on the 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children,²⁹ which define a clinically important weight change as ≥ 5% of total body weight.

Due to the progressive nature of type 2 diabetes, many patients ultimately require initiation of insulin therapy because optimal glycemic control can no longer be achieved with oral drugs alone. In Canada, saxagliptin and sitagliptin are currently indicated for use in combination with insulin.³⁰⁻³² Interestingly, the specific indication for both drugs is in combination with premixed or long or intermediate-acting insulin (with or without metformin) when premixed or long or intermediate-acting insulin (with or without metformin) used alone, with diet and exercise, does not provide adequate glycemic control. For saxagliptin, this indication is based on the findings of an RCT (CV181-057), which demonstrated that the addition of saxagliptin (5 mg once daily) to insulin with or without metformin provided a statistically significant improvement in A1C compared with placebo (mean difference = −0.4% [95% CI, −0.6 to −0.2]).

Rizos et al. (2012)³³ conducted a systematic review investigating the use of DPP-4 inhibitors combined with insulin and reported that DPP-4 inhibitors were associated with a reduction in A1C of approximately 0.5%, which is consistent with the 0.4% reported for Study 57. Reductions in A1C of 0.4% to 0.5% are relatively modest based on commonly cited, minimal clinically important differences (MCIDs) (e.g., 0.5% to 0.7%). Clinical practice guidelines typically recommend intensification of an insulin regimen for most patients who are inadequately controlled with basal insulin;³⁴⁻³⁶ however, there is limited evidence comparing the addition of a DPP-4 inhibitor versus intensified insulin.³⁷ Combination use of a DPP-4 inhibitor with insulin would likely be associated with significant costs, and the comparative cost-effectiveness of combining DPP-4 inhibitors with insulin versus insulin intensification is unknown.³⁸ It remains to be seen whether the addition of DPP-4 inhibitors to existing insulin regimens gains favour in clinical practice over time. However, in practical terms, the combined use of saxagliptin with insulin is unlikely for patients who would meet the requested listing criterion from the manufacturer (i.e., those for whom insulin is not an option).

The efficacy and safety of saxagliptin in patients with renal impairment (i.e., CrCl < 50 mL/min) has been studied in one RCT (Study D1680C00007). This study demonstrated that saxagliptin was superior to placebo for reducing A1C, and there were no adverse effects on renal function.³² The DPP-4 inhibitors approved for use in Canada differ with respect to usage and dosage adjustments in patients with renal impairment. Saxagliptin appears to have the least restrictive criteria and can be used without dosage adjustment (i.e., 5 mg once daily) in patients with mild renal impairment or with a single dosage adjustment (i.e., 2.5 mg once daily) in patients with moderate or severe renal impairment.³² The clinical expert consulted by the CDR identified gliclazide, sitagliptin, and insulins as additional treatments that are routinely used by patients with renal impairment, and indicated that such patients do not have a substantial unmet clinical need.

4.2.2 Harms

Overall, the harms data from Study 06 were consistent with the RCTs that were previously reviewed in the initial CDR review of saxagliptin. There were more AEs, SAEs, and WDAEs in the placebo group of Study 06 than in the saxagliptin group. The incidence of hypoglycemia was numerically greater in patients treated with saxagliptin compared with those treated with placebo (10% versus 6%). The majority of events were “suggestive,” meaning that there were no symptoms, and there were no cases of severe hypoglycemia. It is noteworthy that the product monograph states that a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia when used in combination with saxagliptin.³²

Similar to A1C, the manufacturer conducted an indirect comparison for hypoglycemia by comparing saxagliptin against sitagliptin and linagliptin as add-on therapy to metformin and a sulfonylurea. The manufacturer reported that there was no statistically significant difference between saxagliptin and linagliptin (odds ratio = 0.99). However, the results suggested a lower incidence of hypoglycemic events with saxagliptin compared with sitagliptin (odds ratio = 0.08 [95% CI, 0.008 to 0.718]). Due to the large confidence intervals, the manufacturer did not assume any significant difference in hypoglycemia between saxagliptin and sitagliptin. The three trials differed with respect to the proportion of patients in the placebo group who experienced hypoglycemia: 0.9% in the sitagliptin trial, 6.3% in the saxagliptin trial, and 14.8% in the linagliptin trial. In addition, definitions of hypoglycemia were not reported in the published trials for sitagliptin²⁸ and linagliptin.¹⁵ These limitations make it difficult to accurately compare the risk of hypoglycemia across these three trials, and suggest that the results of the indirect comparison for this end point should be interpreted with caution. CADTH’s review of third-line pharmacotherapy did not include indirect comparisons for hypoglycemia, due to the substantial between-study variation in the incidence of hypoglycemia in placebo-treated patients as well as the lack of reported definitions for hypoglycemia end points.³⁹

All of the DPP-4 inhibitors approved for use in Canada carry a warning in their respective product monographs regarding the risk of pancreatitis.³⁰⁻³² In Study 06, a single event of pancreatitis occurred in one saxagliptin-treated patient and none occurred in placebo-treated patients. In the large SAVOR-TIMI trial, acute pancreatitis was reported for 0.3% of patients in the saxagliptin group and for 0.2% in the placebo group ($P = 0.77$). Chronic pancreatitis was reported for 0.02% in the saxagliptin group and for 0.07% in the placebo group ($P = 0.18$).

5. CONCLUSIONS

One double-blind, 24-week, RCT demonstrated that the addition of saxagliptin to ongoing treatment with metformin and a sulfonylurea was statistically superior to placebo for reducing A1C in patients who were inadequately controlled on combination therapy with metformin and a sulfonylurea. The effect of saxagliptin on A1C (-0.66%) was in the range considered clinically significant, and was aligned with effects of other DPP-4 inhibitors in the third-line setting. Saxagliptin was not associated with clinically important changes in body composition compared with placebo. AEs, SAEs, and WDAEs were more commonly reported with placebo than with saxagliptin. The proportion of patients with hypoglycemia was numerically greater in patients treated with saxagliptin compared with those treated with placebo (10% versus 6%), but most events were asymptomatic and there were no events of severe hypoglycemia. Hence, the likelihood of clinically significant hypoglycemia events with saxagliptin appears to be low. There was no evidence regarding the effects of saxagliptin added to metformin and sulfonylurea on the macrovascular and microvascular complications of diabetes, specifically in patients who were unable to use insulin.

APPENDIX 1: PATIENT INPUT SUMMARY

No patient group input was received regarding this CDR submission for Onglyza.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW

Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 25, 2013
Alerts:	Weekly search updates until October 16, 2013
Study Types:	No search filters were applied
Limits:	Date limit: 2012 to present No language limits were used. Conference abstracts were excluded.

SYNTAX GUIDE

/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words that are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.nm	Name of Substance Word
.ot	Original title
.pt	Publication type
.rn	CAS registry number
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oomezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

- 1 (onglyza* or saxagliptin* or bms477118 or (bms adj "477118")).ti,ot,ab,sh,rn,hw,nm.
- 2 945667-22-1.rn,nm.
- 3 1 or 2
- 4 3 use pmez
- 5 *saxagliptin/
- 6 (onglyza* or saxagliptin* or bms477118 or (bms adj "477118")).ti,ab.
- 7 5 or 6
- 8 7 not conference abstract.pt.
- 9 8 use oemezd
- 10 4 or 9
- 11 remove duplicates from 10
- 12 limit 11 to yr="2012 -Current"

OTHER DATABASES

PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and other)	Same keywords, limits used as per MEDLINE search.

Grey Literature

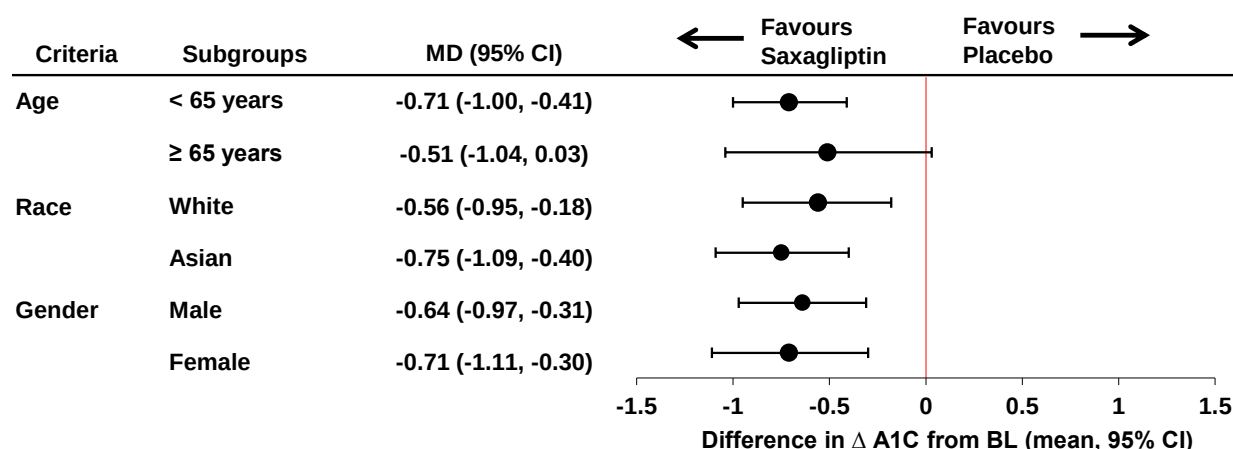
Date of Search:	June 17, 2013
Keywords:	saxagliptin (Onglyza), Diabetes mellitus, type 2
Limits:	Date: January 2012 to present, no language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Databases (free).

APPENDIX 3: DETAILED OUTCOME DATA

FIGURE 4: SUBGROUP ANALYSES FOR A1C FROM STUDY 06



Δ = change; A1C = glycated hemoglobin; BL = baseline; CI = confidence interval; MD = mean difference.

TABLE 15: SUMMARY OF ADVERSE EVENTS OCCURRING IN $\geq 2\%$ OF PATIENTS FROM STUDY 06

Adverse Events	SAX + MET + SU (N=129) n (%)	PL + MET + SU (N=128) n (%)
Total subjects with an AE	77 (59.7)	89 (69.5)
Nasopharyngitis	8 (6.2)	12 (9.4)
Diarrhea	7 (5.4)	5 (3.9)
Hypertension	7 (5.4)	2 (1.6)
Upper respiratory tract infection	6 (4.7)	6 (4.7)
Dyslipidemia	5 (3.9)	7 (5.5)
Urinary tract infection	4 (3.1)	8 (6.3)
Hyperglycemia	4 (3.1)	4 (3.1)
Headache	4 (3.1)	3 (2.3)
Cough	4 (3.1)	1 (0.8)
Flatulence	4 (3.1)	0 (0.0)
Gastritis	3 (2.3)	3 (2.3)
Dizziness	3 (2.3)	2 (1.6)
Peripheral neuropathy	3 (2.3)	0 (0.0)
Nausea	2 (1.6)	4 (3.1)
Pain in extremity	2 (1.6)	4 (3.1)
Arthralgia	2 (1.6)	3 (2.3)
Rash	2 (1.6)	3 (2.3)
Anemia	1 (0.8)	5 (3.9)
Back pain	1 (0.8)	4 (3.1)
Constipation	1 (0.8)	3 (2.3)

Adverse Events	SAX + MET + SU (N=129) n (%)	PL + MET + SU (N=128) n (%)
Oral candidiasis	0 (0.0)	3 (2.3)
Pharyngitis	0 (0.0)	3 (2.3)
Insomnia	0 (0.0)	3 (2.3)
Serious Adverse Events		
Patients with an SAE	3 (2.3)	7 (5.5)
Lower respiratory tract infection	1 (0.8)	0 (0.0)
Influenza	0 (0.0)	1 (0.8)
Osteomyelitis	0 (0.0)	1 (0.8)
Laryngeal cancer	1 (0.8)	0 (0.0)
Squamous cell carcinoma	0 (0.0)	1 (0.8)
Hepatitis	1 (0.8)	0 (0.0)
Cartilage injury	0 (0.0)	1 (0.8)
Arthritis	0 (0.0)	1 (0.8)
Musculoskeletal stiffness	0 (0.0)	1 (0.8)
Renal colic	0 (0.0)	1 (0.8)
Asthma	0 (0.0)	1 (0.8)
Adverse Events Leading to Discontinuation of IP		
AE leading to discontinuation	1 (0.8)	3 (2.3)
Headache	1 (0.8)	0 (0.0)
Abdominal distension	0 (0.0)	1 (0.8)
T2DM inadequate control	0 (0.0)	1 (0.8)
Asthma	0 (0.0)	1 (0.8)

AE = adverse event; IP = investigational product; MET = metformin; n = number of patients with event; N = total number of patients in analysis; PL = placebo; SAE = serious adverse event; SAX= saxagliptin; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

Source: Data from Study 06 Clinical Study Report.⁷

APPENDIX 4: SUMMARY OF COMPARATORS

Objective

To validate results from the manufacturer's indirect comparison comparing saxagliptin against sitagliptin or linagliptin as add-on therapy to metformin and a sulfonylurea in patients with type 2 diabetes.

Approach

The indirect treatment comparison (ITC) was conducted utilizing the ITC calculator developed and made publicly available by CADTH, which is based on methodology reported by Bucher et al. (1997).⁴⁰ CDR reviewers examined the comparisons and confirmed the following:

- All studies included in the indirect comparisons were sufficiently homogenous.
- No other relevant clinical studies were missing from the analysis.
- All data were accurately entered.
- All indirect comparison estimates could be replicated.

Included Studies

The manufacturer's indirect comparison included three placebo-controlled trials investigating the use of saxagliptin (Study 06), linagliptin (Owens et al., 2011),¹⁵ and sitagliptin (Hermansen et al., 2007).²⁸ All of the trials were 24 weeks in duration and all specified the change in A1C from baseline as the primary end point. Study 06 and the RCT by Hermansen (2007) were similar in size with study populations of 257 and 229, respectively. The study by Owens (2011) was considerably larger, with a total population of 1,055 patients. The patient characteristics were generally similar with the exception of mean body weight at baseline, which ranged from approximately 77 kg in Owens (2011) to 87 kg in Hermansen (2011). Additional study and patient characteristics are summarized in Glycated Hemoglobin (A1C).

Glycated Hemoglobin (A1C)

All of the DPP-4 inhibitors demonstrated statistically significant improvements in A1C from baseline to 24 weeks compared with placebo (Figure 5). The effect size was greatest with sitagliptin, which demonstrated a mean difference of -0.89% compared with -0.66% for saxagliptin and -0.62% for linagliptin. This resulted in an indirect estimate of effect favouring sitagliptin over saxagliptin of 0.23% (95% CI, -0.057 to 0.517); however, the difference was not statistically significant (Figure 5).⁴¹ There was no difference between saxagliptin and linagliptin with respect to changes in A1C. The larger effect size for sitagliptin appears to be driven by a deterioration of 0.3% in the placebo group, compared with improvements of 0.05% and 0.1% in the placebo groups of saxagliptin and linagliptin, respectively (Table).

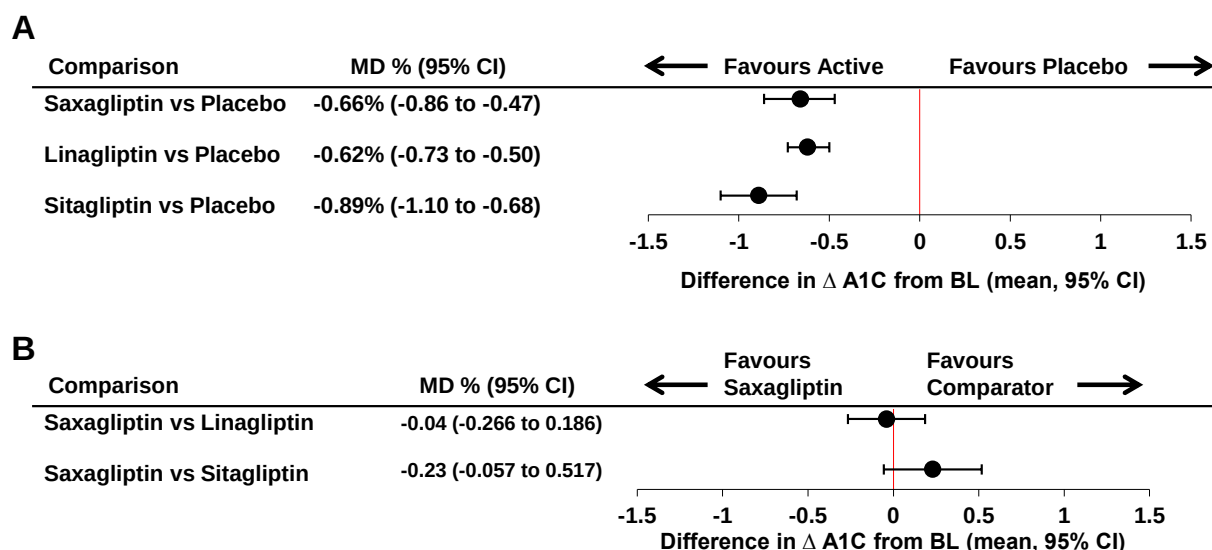
TABLE 16: CHARACTERISTICS OF RCTs INCLUDED IN THE MANUFACTURER-SUBMITTED INDIRECT COMPARISON

Characteristics	Study 06	Owens et al. (2011)	Hermansen et al. (2007)
Comparators (n)	SAX (129) PL (128)	LIN (792) PL (263)	SIT (116) PL (113)
Study design	DB RCT	DB RCT	DB RCT
Primary end point	Δ A1C from BL to 24 weeks	Δ A1C from BL to 24 weeks	Δ A1C from BL to 24 weeks
Follow-up	24 weeks	24 weeks	24 weeks
Inclusion criteria	• ≥ 18 years with T2DM • uncontrolled on MET + SU • A1C ≥ 7% to ≤ 10% • BMI ≤ 40 kg/m²	• ≥ 18 years and ≤ 80 years with T2DM • uncontrolled on MET + SU • A1C ≥ 7.0% to ≤ 10.0% • BMI ≤ 40 kg/m²	• ≥ 18 years and ≤ 75 years with T2DM • taking glimepiride alone or with MET, or another drug in monotherapy or combination therapy • A1C ≥ 6.5% to ≤ 10.5%
Baseline A1C, % (SD or SE)	SAX: 8.38 (0.85) PL: 8.19 (0.83)	LIN: 8.15 (0.03) PL: 8.14 (0.05)	SIT: 8.27 (0.73) PL: 8.26 (0.68)
Baseline body weight, kg (SD)	SAX: 82.4 (19.9) PL: 80.3 (18.5)	LIN: 76.5 (16.8) PL: 76.8 (16.8)	SIT: 87.2 (19.7) PL: 86.7 (21.1)
Baseline mean age, years (SD)	SAX: 57.2 (9.55) PL: 56.8 (11.49)	LIN: 58.3 (9.9) PL: 57.6 (9.7)	SIT: 56.8 (8.8) PL: 57.7 (8.9)
Sex, (% M/F)	SAX: (62/38) PL: (58/42)	LIN: (47/53) PL: (48/52)	SIT: (53/47) PL: (52/48)

Δ = change; A1C = glycated hemoglobin; BL = baseline; BMI = body mass index; DB = double-blind; F = female; LIN = linagliptin; M = male; MET = metformin; RCT = randomized controlled trial; SAX = saxagliptin; SIT = sitagliptin; SD = standard deviation; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

Source: Data from Saxagliptin Economic Analysis.⁴²

FIGURE 5: CHANGE IN A1C WITH DPP-4 INHIBITORS IN COMBINATION WITH METFORMIN AND A SULFONYLUREA



Δ = change; A1C = glycated hemoglobin; BL = baseline; CI = confidence interval; MD = mean difference.

TABLE 17: CHANGE IN A1C WITHIN AND BETWEEN TREATMENT GROUPS

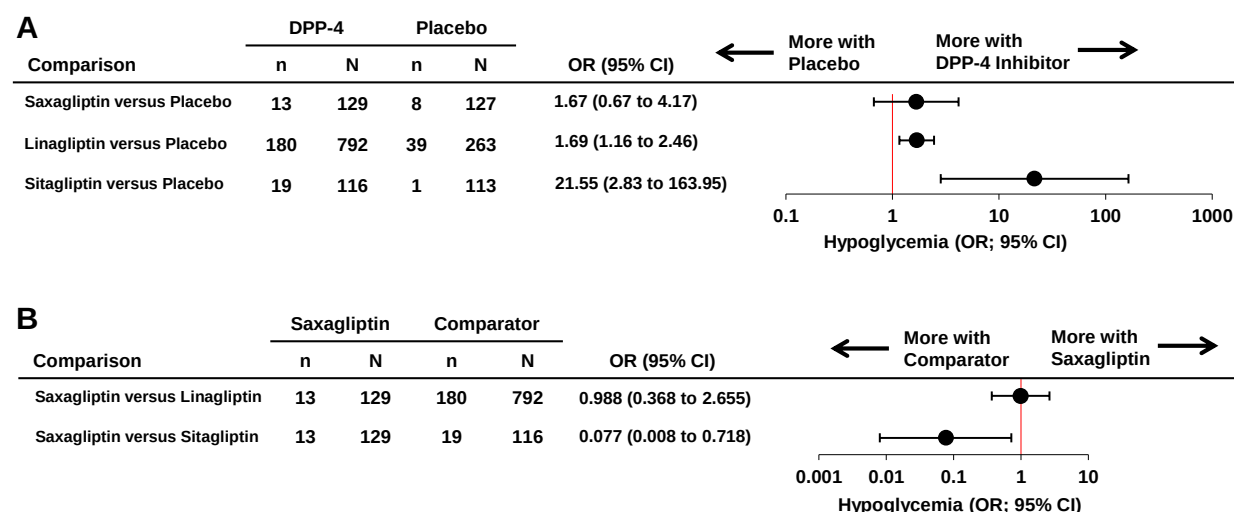
Study	Treatment	Mean Δ from BL in A1C (%)		DPP-4 versus PL
		DPP-4	PL	
Owens (2011) ¹⁵	Linagliptin	-0.72	-0.10	-0.62 (-0.73 to -0.50)
Hermansen (2007) ²⁸	Sitagliptin	-0.59	0.30	-0.89 (-1.10 to -0.68)
Study 06	Saxagliptin	-0.74	-0.05	-0.66 (-0.86 to -0.47)

Δ = change; A1C = glycated hemoglobin; BL = baseline; DPP-4 = dipeptidyl peptidase-4; PL = placebo.

Hypoglycemia

Both saxagliptin and linagliptin were associated with an increased risk of hypoglycemia compared with placebo, with odds ratios of 1.67 (95% CI, 0.67 to 4.17) and 1.69 (95% CI, 1.16 to 2.46), respectively (Figure 6). In contrast, sitagliptin was associated with a large increase in hypoglycemia relative to placebo (16.4% versus 0.9%) (odds ratio = 21.55 [95% CI, 2.83 to 163.95]). The three trials differed with respect to the risk of hypoglycemia in the placebo group, which was 0.9% in the sitagliptin trial, 6.3% in the saxagliptin trial, and 14.8% in the linagliptin trial. Clear definitions of hypoglycemia were not reported in the Owens (2011) and Hermansen (2007) articles; therefore, it is unclear why the risk of hypoglycemia in the placebo groups varied across the three trials. With respect to the indirect comparisons (Figure 6), there was no statistically significant difference between saxagliptin and linagliptin (odds ratio = 0.99 [95% CI, 0.37 to 2.66]). However, the results suggested a lower incidence of hypoglycemic events with saxagliptin compared with sitagliptin (odds ratio = 0.08 [95% CI, 0.01 to 0.72]). Due to the imprecision of the result, the manufacturer did not assume any significant difference in hypoglycemia between saxagliptin and sitagliptin.

FIGURE 6: HYPOGLYCEMIA WITH DPP-4 INHIBITORS IN COMBINATION WITH METFORMIN AND A SULFONYLUREA



CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; n = number of patients with hypoglycemia; N = total number of patients in analysis; OR = odds ratio.

Critical Appraisal

The manufacturer's indirect comparison of saxagliptin, linagliptin, and sitagliptin was well reported and was conducted using an appropriate methodology. CDR reviewers were able to replicate the manufacturer's indirect estimates of effect for saxagliptin relative to sitagliptin and linagliptin. In addition, CADTH's updated agent-level NMA also suggested that there are no significant differences between these drugs with respect to A1C. A literature search indicated that there were no relevant studies missing from the manufacturer's analysis. The RCTs that were included in the indirect comparison appear to be sufficiently homogenous, based on information available in the peer-reviewed publications for linagliptin and sitagliptin. The lack of clear definitions for hypoglycemia in the Owens (2011) and Hermansen (2007) articles is a limitation. It is unclear if the difference in the risk of hypoglycemia in the placebo groups (range: 0.9% to 14.8%) could be attributable to differences in the definition of this safety end point. Overall, the differences in baseline risk of hypoglycemia across trials limit the validity of this analysis and suggest that the findings of the indirect comparison for hypoglycemia should be interpreted with caution.

Summary

The manufacturer's indirect comparison included three placebo-controlled trials investigating the use of saxagliptin, linagliptin, and sitagliptin. There were no significant differences in change in A1C from baseline between saxagliptin and linagliptin or between saxagliptin and sitagliptin. With respect to hypoglycemia, there was no statistically significant difference between saxagliptin and linagliptin (odds ratio = 0.99 [95% CI, 0.37 to 2.66]). However, the results suggest a lower incidence of hypoglycemic events with saxagliptin compared with sitagliptin (odds ratio = 0.08 [95% CI, 0.01 to 0.72]). The most important limitation of the analysis is the lack of clear definitions for hypoglycemia in the linagliptin and sitagliptin studies. As such, it is unclear if the differences in the risk of hypoglycemia across placebo groups (range: 0.9% to 14.8%) could be attributable to the definition of this end point in each study.

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