Saxagliptin in Combination With Metformin or Sulfonylurea Achieved HbA_{1c} Goals

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ABSTRACT

Diabetes affects over 1.2 million people in Australia. Saxagliptin (SAXA) is a potent, selective dipeptidyl peptidase-4 (DPP-4) inhibitor. Three 24-week phase 3 studies assessed efficacy and safety of SAXA as add-on to Metformin (MET), as initial combination therapy with MET, or as add-on to the sulfonylurea (SU) glyburide (GLY) in patients (pts) with type 2 diabetes (T2D) and inadequate glycaemic control. In the add-on to MET study, 743 pts inadequately controlled on MET alone (HbA_{1c} 7.0%–10.0%; mean baseline (BL) HbA_{1c} 8.0%; mean T2D duration 6.5 yrs) were randomised to SAXA or placebo (PBO) with ongoing dose of MET. In the initial combination study, 1306 drug naïve pts (HbA_{1c} 8.0%–12.0%; mean BL HbA_{1c} 9.5%; mean T2D duration 1.7 yrs) were randomised to SAXA + MET, SAXA + PBO, or MET + PBO. In the add-on to SU study, 768 pts inadequately controlled on SU alone (HbA_{1c} 7.5%–10.0%; mean BL HbA_{1c} 8.4%; mean T2D duration 6.9 yrs) were randomised to SAXA or uptitrated GLY + PBO in addition to open-label GLY. Efficacy analyses used ANCOVA model. The proportion of patients reaching HbA_{1c} goals used Fisher exact test. HbA_{1c} goals were predefined for each study. In all three studies, statistically significantly greater proportions of SAXA-treated pts achieved HbA_{1c} goals of <7.0% and ≤6.5% vs. control at 24 wks (Table). Twice as many pts treated with SAXA added to MET or GLY achieved the HbA_{1c} goal of <7% and ≤6.5% relative to control at 24 wks. For all three studies, the frequency of adverse events (AEs) was generally similar for SAXA vs. control (Table). SAXA 5 mg + MET as either add-on or initial combination therapy, and SAXA 5 mg + SU significantly improved glycaemic control, was well tolerated and achieved predefined HbA_{1c} goals vs. control in more patients.

Efficacy and Safety Variables at Wk 24	MET Add-on		SAXA Given With MET as Initial Therapy		SU Add-on	
	SAXA 5 mg + MET	PBO + MET	SAXA 5 mg + MET	PBO + MET	SAXA 5 mg + GLY	PBO + UP-GLY
	n=191	n=179	n=320	n=328	n=253	n=267
Adjusted mean Δ from BL in HbA_{1c} (%), (SE)	−0.7 (0.1)*	0.1 (0.1)	−2.5 (0.1)*	−2.0 (0.1)	−0.6 (0.1)*	0.1 (0.1)
HbA_{1c} <7%, (%)	43.5*	16.6	60.3*	41.1	22.8*	9.1
HbA_{1c} ≤6.5%, (%)	22.0†	8.0	45.3*	29.0	10.4‡	4.5
Overall AEs, (%)	70.2	64.8	55.3	58.5	72.3	76.8

*P<.0001 vs PBO; †P=.0002 vs PBO; ‡P=.0117 vs PBO + UP-GLY. UP-GLY = up-titrated glyburide.

INTRODUCTION

- For patients with type 2 diabetes (T2D), monotherapy is frequently insufficient to achieve or maintain the American Diabetes Association/European Association for the Study of Diabetes1 and the American Association of Clinical Endocrinologists[2] recommended glycated haemoglobin (HbA_{1c}) goals (<7.0% and ≤6.5%, respectively) in the face of progressive β-cell failure and increasing insulin resistance.
- Metformin (MET) and sulfonylureas (SUs) are 2 of the most common first-line therapies used to treat T2D.
- Saxagliptin (SAXA) is a potent, selective dipeptidyl peptidase-4 (DPP-4) inhibitor, specifically designed for extended inhibition of the DPP-4 enzyme.
- Three multicenter, randomised, double-blind, 24-wk phase 3 trials assessed the efficacy and safety of SAXA as add-on to background MET (CV181-014), in combination with MET as initial therapy (CV181-039), or as add-on to the SU glyburide (GLY) (CV181-040) in patients with T2D and inadequate glycaemic control.[3-5]
- This report describes data for SAXA 5 mg as add-on or initial combination therapy vs control with a focus on the proportion of patients reaching predefined HbA_{1c} goals of <7.0% and ≤6.5%.

METHODS

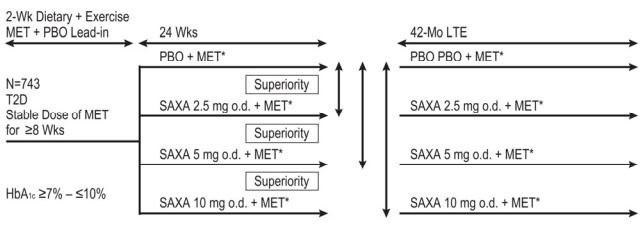
Study Design

- All 3 studies were randomised, double-blind, placebo- (PBO) or active-controlled, international, multicentre trials.

CV181-014 (Figure 1)

- **Population:** Previously treated patients (18 – 77 yrs) with T2D and inadequate glycaemic control (HbA_{1c} ≥7.0% – ≤10.0%) on a stable dose of MET for ≥8 wks prior to screening and with fasting C-peptide ≥1.0 ng/mL, body mass index (BMI) ≤40 kg/m^2.
- **Intervention:** 743 eligible patients were randomised and treated with SAXA 2.5 mg, SAXA 5 mg, SAXA 10 mg, or PBO in addition to their current dose of open-label (OL) MET for up to 24 wks (short-term [ST] treatment period).

Figure 1. CV181-014 Study Design

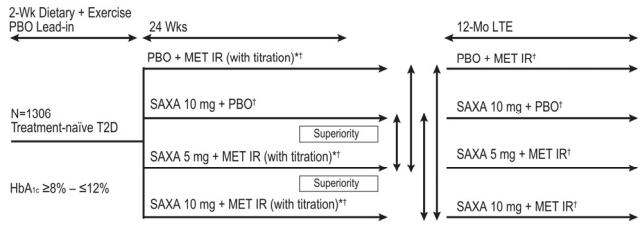


*If rescue criteria were met in ST treatment period, PIO was added and patients entered LTE; PIO rescue also available in LTE.LTE = long-term extension; o.d. = once daily; PIO = pioglitazone.

CV181-039 (Figure 2)

- **Population:** Treatment-naïve patients (18 – 77 yrs) with T2D and inadequate glycaemic control (HbA_{1c} ≥8.0% – ≤12.0%) and with fasting C-peptide ≥1.0 ng/mL, BMI ≤40 kg/m^2.
- **Intervention:** 1306 eligible patients were randomised and treated with SAXA 5 mg + MET, SAXA 10 mg + MET, SAXA 10 mg + PBO, or MET + PBO for up to 24 wks.
  - From wks 1 – 5, MET was up-titrated in 500 mg/d increments to a 2000 mg/d maximum in the SAXA 5 mg + MET, SAXA 10 mg + MET, and MET + PBO treatment groups.

Figure 1. CV181-014 Study Design



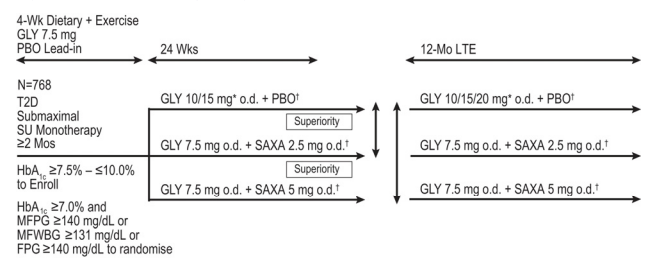
*MET IR titration: Forced titration from 500 mg – 1000 mg at wk 1, then elective titration at wks 2, 3, 4, and 5 to achieve mean FPG <110 mg/dL (maximum MET 2000 mg total daily dose).†If rescue criteria were met in ST treatment period, PIO 15 – 45 mg o.d. was added and patients entered LTE; PIO rescue also available in LTE.
MET IR = metformin immediate release.

METHODS *(continued)*

CV181-040 (Figure 3)

- **Population:** Previously treated patients (18 – 77 yrs) with T2D and inadequate glycaemic control (HbA_{1c} ≥7.5% – ≤10.0%) on a submaximal dose of an SU (GLY) for ≥2 mos prior to screening and with fasting C-peptide ≥1.0 ng/mL, BMI ≤40 kg/m^2.
- **Intervention:** 768 eligible patients were randomised and treated with SAXA 2.5 mg + OL GLY 7.5 mg or SAXA 5 mg + OL GLY 7.5 mg o.d. or PBO + blinded GLY 2.5 mg + OL GLY 7.5 mg o.d. (total daily dose [TDD] of GLY, 10 mg/d) for up to 24 wks.
  - Up-titration of blinded GLY (UP-GLY) was allowed in the GLY-only arm at wks 2 and 4 for mean fasting plasma glucose (MFPG) ≥100 mg/dL, to a maximum TDD of 15 mg (7.5 mg OL GLY + 7.5 mg blinded GLY).
  - The dose of OL GLY could be reduced one dose step at the discretion of the investigator for patients who developed hypoglycaemia.

Figure 3. CV181-040 Study Design



*Up-titration of blinded GLY allowed if MFPG ¯100 mg/dL or MFWBG ¯95 mg/dL at wk 2 or wk 4, or HbA_{1c} ¯7.0% at wk 30. Up-titration of GLY not permitted if down-titration previously occurred for hypoglycaemia. No titration of GLY allowed once rescued with metformin.
†If rescue criteria were met in ST treatment period, MET 500 mg – 2500 mg total daily dose was added and patients entered the LTE; MET rescue also available in LTE.
FPG = fasting plasma glucose; MFPG = mean fasting plasma glucose; MFWBG = mean fasting whole blood glucose.

- **Rescue Therapy:** Patients were eligible for rescue therapy based on progressively strict glycaemic control criteria.
- **Long-term Extension:** Patients who completed their respective 24-wk ST treatment period without rescue therapy, or those who were rescued in the first 24 wks were eligible to enter the respective LTE phase.

Study Objectives

- All 3 studies shared the same primary and key secondary objectives.
  - **Primary:** Change from baseline to wk 24 in HbA_{1c} with each SAXA combination therapy group vs the respective control group.
  - **Secondary:** Changes from baseline to wk 24 with each SAXA combination therapy group vs the respective control group in:
    - FPG
    - Percentages of patients achieving a therapeutic glycaemic response (HbA_{1c} <7.0% for all 3 studies and HbA_{1c} ≤6.5% for the SAXA given with MET as initial therapy study)
    - Postprandial glucose (PPG) response, as indicated by PPG-area under the curve (AUC) from 0 – 180 min during an oral glucose tolerance test (OGTT)
  - **Safety:** Assess safety and tolerability of each dose of SAXA combination therapy administered for up to 24 wks.

Statistical Analysis

- Efficacy analyses for continuous variables were performed using an analysis of covariance (ANCOVA) model with treatment as an effect and baseline as the covariate, and utilized last-observation-carried-forward (LOCF) methodology.
- Percentages of patients achieving a prespecified target glycaemic response (HbA_{1c} <7.0% or ≤6.5%) at wk 24 (LOCF) were compared between each combination treatment group vs the respective control group using the Fisher exact test.
- Statistical analyses were performed on hypoglycaemia data (reported and confirmed) for the SAXA + SU study only.
- Efficacy and safety measurements obtained after rescue were not included in any analyses.

RESULTS

- Demographic and baseline characteristics were generally balanced across treatment groups in the individual studies (Table 1).
- Differences in baseline characteristics across studies included:
  - Higher mean (SD) baseline HbA_{1c} (all treatment arms) in treatment-naïve patients in the SAXA given with MET as initial therapy study vs previously treated patients in the add-on studies
    - 9.5% (1.3%) for SAXA given with MET as initial therapy study
    - 8.0% (0.9%) for SAXA + MET and 8.4% (0.9%) for SAXA + SU studies
  - Longer mean (SD) duration of diabetes (all treatment arms) in previously treated patients in the add-on studies vs treatment-naïve patients in the SAXA given with MET as initial therapy study
    - 6.5 (5.1) yrs for SAXA + MET and 6.9 (5.8) yrs for SAXA + SU studies n 1.7 (3.1) yrs for SAXA given with MET as initial therapy study

Table 1. Demographic and Baseline Characteristics of Patients With T2D by Trial According to Randomised Group

Characteristic	MET Add-on		SAXA Given With MET as Initial Therapy		SU Add-on	
	SAXA 5 mg + MET	PBO + MET	SAXA 5 mg + MET	PBO + MET	SAXA 5 mg + GLY	PBO + UP-GLY
	n=191	n=179	n=320	n=328	n=253	n=267
Age, yrs*	54.7 (9.62)	54.8 (10.17)	52.0 (10.43)	51.8 (10.74)	54.9 (9.96)	55.1 (10.69)
≥65 yrs†	32 (16.8)	26 (14.5)	33 (10.3)	36 (11.0)	42 (16.6)	52 (19.5)
Gender†						
Male	103 (53.9)	96 (53.6)	165 (51.6)	163 (49.7)	110 (43.5)	123 (46.1)
Female	88 (46.1)	83 (46.4)	155 (48.4)	165 (50.3)	143 (56.5)	144 (53.9)
Race†						
White	159 (83.2)	150 (83.8)	246 (76.9)	251 (76.5)	151 (59.7)	152 (56.9)
Black/African American	11 (5.8)	7 (3.9)	7 (2.2)	4 (1.2)	7 (2.8)	7 (2.6)
Asian	3 (1.6)	4 (2.2)	51 (15.9)	52 (15.9)	46 (18.2)	51 (19.1)
Other	18 (9.4)	18 (10.1)	16 (5.0)	21 (6.4)	49 (19.4)	57 (21.3)
Body weight, kg*	87.3 (17.05)	87.1 (17.75)	82.1 (16.25)	82.8 (17.54)	76.2 (17.64)	75.6 (17.35)
BMI, kg/m^2*	31.2 (4.67)	31.6 (4.80)	29.9 (4.45)	30.2 (4.89)	29.2 (4.55)	28.8 (4.74)
Diabetes duration, yrs*	6.4 (4.7)	6.7 (5.6)	2.0 (3.6)	1.7 (3.1)	6.8 (5.8)	6.8 (5.7)
HbA_{1c}, %*	8.1 (0.8)	8.1 (0.9)	9.4 (1.2)	9.4 (1.3)	8.5 (0.9)	8.4 (0.9)
FPG, mg/dL*	180 (47.3)	174 (43.5)	199 (56.6)	198 (58.7)	175 (44.3)	175 (42.8)

*Values are expressed as mean (SD); †Values are expressed as n (%).

Efficacy

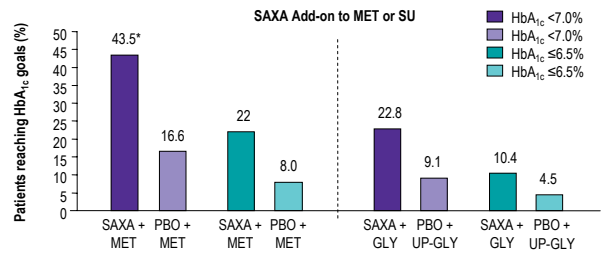
- SAXA added to MET or SU, or given with MET as initial combination therapy demonstrated statistically significantly greater decreases from baseline in HbA_{1c} vs control (Table 2).
- In all 3 studies, a statistically significantly greater percentage of SAXA-treated patients achieved HbA_{1c} goals of <7.0% and ≤6.5% vs control at 24 wks (Figure 4A and B).
- More than twice as many patients treated with SAXA added to MET or SU achieved the HbA_{1c} goals of <7.0% and ≤6.5% relative to control at 24 wks.

RESULTS *(continued)*

Table 2. HbA_{1c} Results by Trial According to Randomised Group

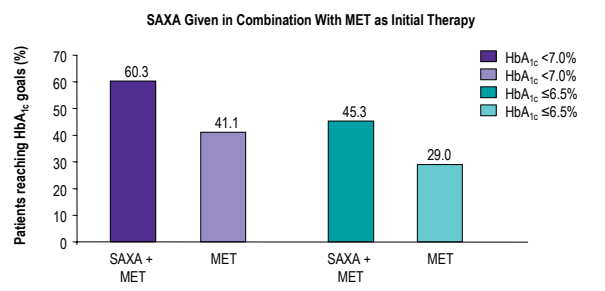
	MET Add-on		SAXA Given With MET as Initial Therapy		SU Add-on	
	SAXA 5 mg + MET	PBO + MET	SAXA 5 mg + MET	PBO + MET	SAXA 5 mg + GLY	PBO + UP-GLY
HbA_{1c} (%)	n=186	n=175	n=306	n=313	n=250	n=264
Baseline mean (SE)	8.1 (0.06)	8.1 (0.07)	9.4 (0.07)	9.4 (0.07)	8.5 (0.06)	8.4 (0.06)
Wk 24 mean (SE)	7.4 (0.08)	8.2 (0.09)	6.9 (0.07)	7.5 (0.08)	7.8 (0.07)	8.5 (0.08)
Adjusted mean Δ from baseline (95% CI)	−0.7 (−0.83, −0.56)	0.1 (−0.00, 0.27)	−2.5 (−2.66, −2.39)	−2.0 (−2.12, −1.85)	−0.6 (−0.76, −0.53)	0.1 (−0.03, 0.19)
P vs control	<.0001		<.0001		<.0001	

Figure 4A. Percentage of Patients Reaching HbA_{1c} Goals After 24 Wks of Treatment With SAXA 5 mg



*P<.0001 vs PBO + MET; †P=.0002 vs PBO + MET; ‡P<.0001 vs PBO + UP-GLY; §P=.0117 vs PBO + UP-GLY.

Figure 4B. Percentage of Patients Reaching HbA_{1c} Goals After 24 Wks of Treatment With SAXA 5 mg



*P<.0001 vs MET.

Safety

- SAXA added to MET or SU, or given with MET as initial combination therapy was generally well tolerated. In all 3 studies, the frequency of adverse events (AEs) was generally similar for SAXA vs control (Table 3).
- In the MET studies, the frequency of reported and confirmed hypoglycaemia was similar for SAXA compared with control. In the SU study, reported but not confirmed hypoglycaemia was higher for SAXA compared with control; the difference was not statistically significant (Table 3).

Table 3. Safety and Tolerability of SAXA 5 mg in Combination With MET or SU

	MET Add-on		SAXA Given With MET as Initial Therapy		SU Add-on	
	SAXA 5 mg + MET	PBO + MET	SAXA 5 mg + MET	PBO + MET	SAXA 5 mg + GLY	PBO + UP-GLY
	n=191	n=179	n=320	n=328	n=253	n=267
Overall (≥1) AE*	134 (70.2)	116 (64.8)	177 (55.3)	192 (58.5)	183 (72.3)	205 (76.8)
Reported hypoglycaemia*†	10 (5.2)	9 (5.0)	11 (3.4)	13 (4.0)	37 (14.6)§	27 (10.1)
Confirmed hypoglycaemia*‡	1 (0.5)	1 (0.6)	0	1 (0.3)	2 (0.8)‖	2 (0.7)

*Values are expressed as n (%).
† Reported hypoglycaemia was defined as events consistent with signs or symptoms of hypoglycaemia with or without documented blood glucose levels.
‡ Confirmed hypoglycaemia was defined by a fingerstick glucose value ≤50 mg/dL with associated symptoms.
§ P=.1417 vs PBO + UP-GLY.
‖ P=1.0000 vs PBO + UP-GLY.

CONCLUSIONS

- In patients with type 2 diabetes, saxagliptin 5 mg + MET, as add-on or given as initial combination therapy, and saxagliptin 5 mg + SU:
  - Provided clinically meaningful glycaemic improvements
  - Resulted in more patients achieving predefined HbA_{1c} goals vs control without significantly increasing hypoglycaemia
- Saxagliptin, in combination with MET or SU, was generally well tolerated.
- Saxagliptin may be a suitable combination partner for a broad range of patients with type 2 diabetes.

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