Once-Daily Saxagliptin Added to Metformin Provides Sustained Glycaemic Control and Is Well Tolerated Over 102 Weeks in Patients With Type 2 Diabetes

Ralph DeFronzo,[1] Miguel N. Hissa,[2] Alan J. Garber,[3] Jorge Luiz Gross,[4] Raina Yuyan Duan,[5] Shoba Ravichandran,[5] Roland Chen,[5] Ranjit Rasalam[6], Julie Newman[6], and Paul Slade[6]

[1]San Antonio, TX; [2]CE, Brazil; [3]Houston, TX; [4]Rio Grande Do Sul, Brazil; [5]Princeton, NJ; [6]Melbourne, Australia

ABSTRACT

- Diabetes is Australia's fastest growing chronic disease with approximately 890,000 patients currently diagnosed with diabetes.[1] By 2031 it is predicted that 3.3 million Australians will have type 2 diabetes mellitus,[2] thus increasing the demand for treatment. Saxagliptin (SAXA) is a potent selective DPP-4 inhibitor designed for extended inhibition of the DPP-4 enzyme. The long-term efficacy and safety of SAXA added to metformin were assessed in patients with T2D and inadequate glycaemic control (A1C ≥7.0% − ≤10.0%) on metformin alone. For the double-blind (DB) short-term (ST) treatment period 743 patients (baseline [BL] A1C 8.0%) were randomized and treated 1:1:1:1 to SAXA 2.5, 5, 10 mg or placebo od + stable metformin dose (1500−2500mg/d) for 24 weeks. Patients who met pre-specified glycaemic rescue criteria during ST treatment period received open-label pioglitazone 15-45 mg + blinded study medication and entered the DB 42-month long-term extension (LTE). Patients completing ST treatment period without rescue were also eligible to enter the 42mo LTE; pioglitazone rescue therapy was also available during the LTE based on prespecified glycaemic criteria.
- At 102 weeks placebo-subtracted A1C changes from BL (n/N) were -0.62, -0.72, and -0.52 for SAXA 2.5, 5, and 10mg, respectively. The proportion of patients (n/N) discontinued for lack of glycaemic control or rescued for meeting prespecified glycaemic criteria was lower for SAXA. SAXA + metformin was generally well tolerated; AE frequency was 89.6%, 78.0%, and 86.7% for SAXA 2.5, 5, and 10 mg vs. 78.8% for placebo + metformin. Proportion of patients with hypoglycaemia events (all) was 10.4%, 8.9%, and 11.0% for SAXA 2.5, 5, and 10mg vs. 10.1% for placebo + metformin and confirmed hypoglycaemia was infrequent.
- In summary, in patients with T2D inadequately controlled on metformin alone SAXA added to metformin provided sustained clinically meaningful glycaemic improvements over 102 weeks vs. control and was generally well tolerated with no increase in hypoglycaemia or weight.

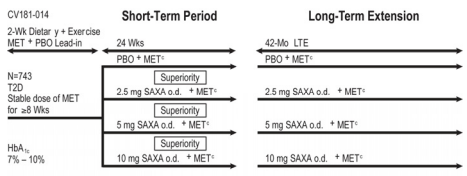
INTRODUCTION

- MET is considered standard first-line pharmacotherapy for T2D.
- MET reduces hepatic glucose production and improves insulin sensitivity; however, MET alone is frequently insufficient to maintain glycaemic goals in the face of progressive β-cell failure and increasing insulin resistance.
- SAXA is a potent, selective DPP-4 inhibitor specifically designed for extended inhibition of the DPP-4 enzyme.
- The CV181-014 trial evaluated the efficacy and safety of SAXA in combination with MET as add-on therapy in patients with T2D and inadequate glycaemic control on MET alone.[3]

METHODS

- **Study Design (CV181-014)**
  - **Design**: Randomised, double-blind, PBO-controlled, 4-arm, parallel-group, international, multicentre trial (Figure 1).
  - **Population**: Patients (aged 18-77 yrs) with T2D and inadequate glycaemic control (HbA1c ≥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, 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 MET for 24 wks (ST treatment period).

Figure 1. Study Design[a,b]



[a] The current report describes interim analysis at time of database lock (January 17, 2008).
[b] Total duration of ST treatment period + LTE = 48 mos.
[c] If rescue criteria met in ST treatment period, added PIO and entered LTE phase; PIO rescue also available in LTE.
LTE = long-term extension; MET = metformin; o.d. = once daily; PIO = pioglitazone; SAXA = saxagliptin; ST = short term.

- **LTE Entry (2 Routes)**:
  - Patients completing the ST treatment period without rescue therapy:
    - PIO rescue therapy available during the LTE based on prespecified glycaemic criteria (Table 1).
  - Patients who met prespecified glycaemic rescue criteria during the ST treatment period:
    - Open-label PIO 15 mg to 45 mg + blinded study medication.

METHODS *(continued)*

- Patients remained on the same treatment assigned in the ST treatment period throughout the LTE.
- Patients and study investigators remained blinded to study medication throughout the LTE.

Table 1. LTE Rescue Criteria for Lack of Glycaemic Control

Visit	Measurement
LTE	**HbA_{1c}**
Wks 30, 37, 50	>8.0%
Wks 63, 76	>7.5%
Wks 89-193	>7.0%

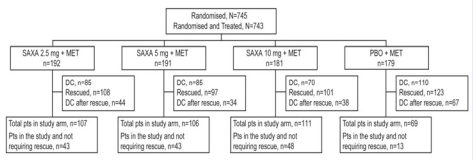
HbA_{1c} = glycated haemoglobin; LTE = long-term extension.

- **LTE Study Objectives**
  - Assess safety and tolerability of each dose of SAXA + MET when administered for up to 48 mos.
  - Assess safety and tolerability of each dose of SAXA + MET and PIO when administered for up to 42 mos.
  - For each SAXA treatment group, assess the glycaemic parameters in the LTE.
- **Statistical Analyses**
  - Efficacy analyses for continuous variables were performed using an ANCOVA model with treatment as an effect and baseline as the covariate, and with LOCF methodology.
  - Percentages of patients achieving target HbA_{1c} at wks 24, 50, 76, and 102 (LOCF) were compared between each combination treatment group vs the respective monotherapy group using the exact 95% CI on the difference between groups.
  - Efficacy analyses reflect data prior to rescue.
  - Safety analyses reflect data regardless of rescue.

RESULTS

- The patient disposition for this interim analysis is shown in Figure 2.
- Demographic and baseline characteristics are shown in Table 2.

Figure 2. Patient Disposition[a]



[a]Patient disposition at time of database lock for interim analysis (January 17, 2008). Rescued patients include all patients who were rescued in the ST or LTE. Rescued patients may later have discontinued from the study.
Pts = patients; SAXA = saxagliptin; DC = total number of patients who discontinued from the study.
Total pts in study arm = total number in study at database lock for the interim analysis.

Table 2. Demographic and Baseline Characteristics of Patients With T2D by Randomised Group: ST + LTE Treatment Period

	SAXA 2.5 mg + MET	SAXA 5 mg + MET	SAXA 10 mg + MET	PBO + MET
Characteristics	n=192	n=191	n=181	n=179
Age (yrs)[a]	54.7 (10.1)	54.7 (9.6)	54.2 (10.1)	54.8 (10.2)
≥65 yrs[b]	33 (17.2)	32 (16.8)	26 (14.4)	26 (14.5)
Gender[b]				
Male	83 (43.2)	103 (53.9)	95 (52.5)	96 (53.6)
Female	109 (56.8)	88 (46.1)	86 (47.5)	83 (46.4)
Race[b]				
Caucasian	153 (79.7)	159 (83.2)	144 (79.6)	150 (83.8)
Black/African American	8 (4.2)	11 (5.8)	14 (7.7)	7 (3.9)
Asian	8 (4.2)	3 (1.6)	5 (2.8)	4 (2.2)
Other	23 (12.0)	18 (9.4)	18 (9.9)	18 (10.1)
Body weight (kg)[a]	86.0 (17.6)	87.3 (17.0)	87.8 (18.9)	87.1 (17.8)
BMI (kg/m^2)[a]	31.7 (5.2)	31.2 (4.7)	31.1 (4.8)	31.6 (4.8)
Diabetes duration (yrs)[a]	6.7 (5.6)	6.4 (4.7)	6.3 (4.4)	6.7 (5.6)
HbA_{1c} (%)[a]	8.1 (1.0)	8.1 (0.8)	8.0 (1.0)	8.1 (0.9)
FPG (mg/dL)[a]	174 (44.3)	180 (47.7)	176 (50.2)	174 (43.5)

[a]Values are expressed as mean (SD). [b]Values are expressed as n (%).
BMI = body mass index; FPG = fasting plasma glucose.

Safety and Tolerability

- SAXA + MET was generally well tolerated (Table 3). The proportion of patients experiencing AEs was numerically higher in the SAXA + MET groups vs PBO + MET.
  - The higher incidence of AEs in the SAXA + MET groups needs to be interpreted in relation to the longer duration of exposure to study medication in patients randomised to SAXA + MET vs PBO + MET (Table 3).
  - No dose-related trends were observed.
  - There were 3 deaths reported, 1 in the SAXA 10 mg group (pulmonary embolism and lung neoplasm) and 2 in the PBO group (congestive heart failure; cardiogenic shock and MI).

RESULTS *(continued)*

Safety and Tolerability (continued)

- The proportion of patients with reported and confirmed hypoglycaemia is listed in Table 3.
- The most frequent AEs by dose at 102 wks are listed in Table 4.
- SAXA + MET was not associated with an increase in AEs pertaining to infections, localized oedema, or cardiovascular AEs vs PBO + MET.
- There was a numerically higher incidence of skin-related AEs in the SAXA + MET groups vs the PBO + MET group (15.6%, 13.6%, and 22.7% vs 11.2% for SAXA 2.5, 5, and 10 mg + MET vs PBO + MET, respectively).
  - There were no AEs with the preferred term of angioedema or Stevens-Johnson syndrome.

Table 3. Safety and Tolerability During ST + LTE Treatment Period by Treatment Group

	SAXA 2.5 mg + MET	SAXA 5 mg + MET	SAXA 10 mg + MET	PBO + MET
	n=192	n=191	n=181	n=179
Exposure (weeks)[a,b]	78 (32.3)	75 (34.1)	81 (31.1)	68 (35.3)
AEs[c]				
≥1 AE	172 (89.6)	149 (78.0)	157 (86.7)	141 (78.8)
≥1 related AE	50 (26.0)	56 (29.3)	61 (33.7)	50 (27.9)
Deaths	0	0	1 (0.6)	2 (1.1)
≥1 SAE	17 (8.9)	19 (9.9)	20 (11.0)	10 (5.6)
≥1 related SAE	0	1 (0.5)	1 (0.6)	0
Discontinuation due to AE	9 (4.7)	14 (7.3)	10 (5.5)	8 (4.5)
Discontinuation due to SAEs	3 (1.6)	3 (1.6)	5 (2.8)	0
Reported hypoglycaemia[c,d]	20 (10.4)	17 (8.9)	20 (11.0)	18 (10.1)
Confirmed hypoglycaemia[c,e]	2 (1.0)	2 (1.0)	2 (1.1)	1 (0.6)

[a] Exposure = Last dosing date (ST + LTE double-blind treatment) − first dosing (ST period) + 1.
[b] Values are expressed as mean (SD).
[c] Values are expressed as n (%).
[d] Reported hypoglycaemia was defined as events consistent with signs or symptoms of hypoglycaemia with or without documented blood glucose levels.
[e] Confirmed hypoglycaemia was defined by a fingerstick glucose value ≤50 mg/dL with associated symptoms.

Table 4. Most Frequent AEs by Dose for Each SAXA Treatment Group vs PBO at 102 Wks

AE[a]	SAXA 2.5 mg + MET	SAXA 5 mg + MET	SAXA 10 mg + MET	PBO + MET
	n=192	n=191	n=181	n=179
Nasopharyngitis	25 (13.0)	21 (11.0)	25 (13.8)	19 (10.6)
Influenza	20 (10.4)	22 (11.5)	23 (12.7)	23 (12.8)
URTI	23 (12.0)	17 (8.9)	19 (10.5)	14 (7.8)
UTI	19 (9.9)	15 (7.9)	17 (9.4)	12 (6.7)
Bronchitis	12 (6.3)	18 (9.4)	9 (5.0)	11 (6.1)
diarrhoea	27 (14.1)	14 (7.3)	17 (9.4)	12 (12.8)
Back Pain	15 (7.8)	15 (7.9)	9 (5.0)	16 (8.9)
Headache	26 (13.5)	17 (8.9)	22 (12.2)	20 (11.2)

[a]Values are expressed as n (%).
Five most frequent AEs by dose highlighted in purple.
URTI = upper respiratory tract infection; UTI = urinary tract infection.

- There was a decrease in the mean absolute lymphocyte count from baseline to wk 102 of small magnitude in all treatment groups including PBO with the maximal reduction seen in the SAXA 10 mg group.
  - There was no progressive decline in mean absolute lymphocyte count and values remained within the normal range in all treatment groups throughout the ST + LTE periods.
- There were no clinically meaningful drug effects on any laboratory safety parameter.

Efficacy

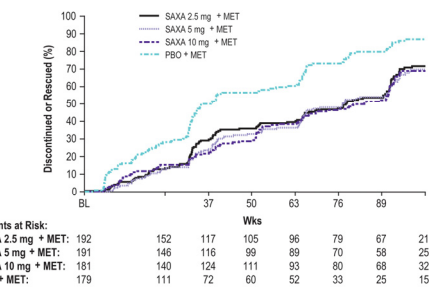
- More patients treated with PBO + MET were discontinued or rescued for lack of glycaemic control; rescue for meeting prespecified glycaemic criteria occurred earlier in the study in the PBO + MET group (Figure 3).
- SAXA was associated with greater reductions in HbA_{1c} in all treatment groups vs PBO through wk 102 (Figure 4).
  - The greatest HbA1c reduction was in the SAXA 5 mg group.
- SAXA added to MET produced sustained effects up to wk 102 in the wk 24 secondary end points relative to control (Table 5).
- Small decreases in mean body weight at wk 102 (before rescue, LOCF) vs baseline were observed in all treatment groups.
  - At wk 102, mean change from baseline was -1.0, -0.4, and -0.5 kg for SAXA 2.5, 5, and 10 mg + MET, respectively, vs -0.8 kg for the PBO + MET group.

RESULTS *(continued)*

Table 5. Main Efficacy Results at Wk 102 (LOCF) by Randomised Group

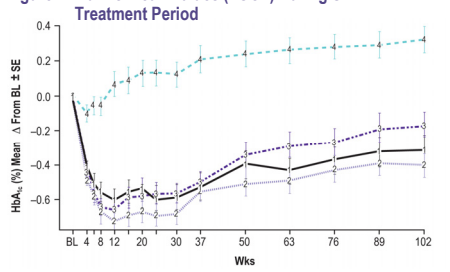
Efficacy Parameter	SAXA 2.5 mg + MET	SAXA 5 mg + MET	SAXA 10 mg + MET	PBO + MET
	n=192	n=191	n=181	n=179
HbA_{1c} (%)				
n observed	34	31	33	15
n for LOCF	181	184	177	172
Baseline mean (SE)	8.1 (0.07)	8.1 (0.06)	8.0 (0.08)	8.1 (0.07)
Adj mean Δ from baseline	-0.30	-0.40	-0.20	0.32
Diff vs PBO + MET	-0.62	-0.72	-0.52	
95% CI	(-0.84, -0.40)	(-0.94, -0.50)	(-0.74, -0.30)	
FPG (mg/dL)				
n observed	32	31	33	15
n for LOCF	183	184	178	173
Baseline mean (SE)	174 (3.3)	179 (3.5)	176 (3.8)	175 (3.3)
Adj mean Δ from baseline	-7.7	-11.3	-7.8	6.8
Diff vs PBO + MET	-14.6	-18.2	-14.6	
95% CI	(-22.7, -6.4)	(-26.3, -10.0)	(-22.8, -6.4)	
HbA_{1c} <7%,				
n/N (%)	44/181 (24.3)	56/184 (30.4)	58/177 (32.8)	20/172 (11.6)
Diff vs PBO + MET	12.7%	18.8%	21.1%	
95% CI	(4.7%, 20.7%)	(10.4%, 27.1%)	(12.6%, 29.6%)	
PPG AUC (mg*min/dL)				
n observed	58	44	51	23
n for LOCF	156	156	154	137
Baseline mean (SE)	48067 (879.2)	48606 (845.0)	44823 (869.5)	47607 (1041.6)
Adj mean Δ from baseline	-5732	-5820	-3285	-1146
Diff vs PBO + MET	-4586	-4673	-2139	
95% CI	(-6879, -2292)	(-6968, -2378)	(-4444, 166)	(-6879, -2292)
PPG at 120 min (mg/dL)				
n observed	58	46	50	24
n for LOCF	160	162	156	141
Baseline mean ± SE	292 (5.9)	293 (5.8)	273 (5.7)	292 (7.1)
Adj mean Δ from baseline	-40	-35	-23	-4
Diff vs PBO + MET	-36	-32	-20	
95% CI	(-51.8, -20.4)	(-47.5, -16.1)	(-35.6, -3.8)	

Figure 3. Kaplan-Meier Curve for Discontinuation for Lack of Glycaemic Control or Rescue for Failing to Achieve Glycaemic Targets During ST + LTE Treatment Period



Patients at Risk:								
SAXA 2.5 mg + MET:	192	152	117	105	96	79	67	21
SAXA 5 mg + MET:	191	146	116	99	89	70	58	25
SAXA 10 mg + MET:	181	140	124	111	93	80	68	32
PBO + MET:	179	111	72	60	52	33	25	15

Figure 4. HbA1C Mean Values (LOCF) During ST + LTE Treatment Period



1 = SAXA 2.5 mg + MET; 2 = SAXA 5 mg + MET; 3 = SAXA 10 mg + MET; 4 = PBO + MET.

STUDY LIMITATIONS

- There was a decreasing number of patients with pre-rescue HbA_{1c} measurements observed at later time points.
- For the interim analysis, only patients who received the first dose of study drug early enough to have the potential to reach a specific time point were included in the LOCF analysis for that time point.
- Because glycaemic parameters would be affected by the addition of rescue therapy, efficacy results obtained after the initiation of rescue treatment were not included in any efficacy analyses.

CONCLUSIONS

- In this interim analysis of patients with T2D inadequately controlled on MET alone, the overall profile of AEs associated with extended dosing of saxagliptin added to MET for up to 2 years was consistent with that seen at 24 weeks.
- Saxagliptin added to MET provided sustained clinically meaningful glycaemic improvements over 102 weeks vs PBO + MET and was generally well tolerated with no increase in hypoglycaemia or weight.

REFERENCES

1. Ref goes here
2. Ref goes here
3. DeFronzo R, Hissa M, Garber A, Gross J, Duan RY, Ravichandran S, Chen RS, and the Saxagliptin 014 Study Group. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes on metformin alone. *Diabetes Care*. Published ahead of print May 28, 2009. doi:10.2337/dc08-1984.

Disclosure Information: This study was funded by Bristol-Myers Squibb and AstraZeneca