

β-Cell Stimulation by Saxagliptin in Patients with Type 2 Diabetes

Robert Henry¹, Steven Smith², Sherwin Schwartz³, James List⁴, Yuyan Duan⁴, Roland Chen⁴, Fred Fiedorek⁴, Ranjit Rasalam⁵, Julie Newman⁵, and Paul Slade⁵

¹San Diego, CA; ²Baton Rouge, LA; ³San Antonio, TX; ⁴Princeton, NJ; ⁵Melbourne, Australia

ABSTRACT

- Diabetes is Australia's fastest growing chronic disease with approximately 890,000 patients currently diagnosed with diabetes. By 2031 it is predicted that 3.3 million Australians will have type 2 diabetes¹ thus increasing the demand for prevention strategies and an emphasis on early diagnosis and treatment. Saxagliptin (SAXA) is a potent, selective DPP-4 inhibitor, specifically designed for extended inhibition of the DPP-4 enzyme. DPP-4 inactivates incretins that stimulate glucose-dependent insulin secretion and inhibit glucagon secretion. A proposed MOA of SAXA involves protecting incretins from DPP-4 degradation, thus improving β-cell response. This randomised, parallel-group, double-blind, PBO-controlled study (CV181-041) assessed SAXA's effect on β-cell function by intravenous hyperglycaemic clamp (IV HC) in T2DM patients.
- Patients were assessed at baseline (BL) and wk 12 in the fasting state (0–180min, IV HC) and after stimulating incretin secretion by orally ingesting 75g glucose (180–480min, IV-oral HC). HC infusions were adjusted to maintain plasma glucose at 280mg/dL. Insulin secretion was calculated by C-peptide deconvolution. Primary endpoint was %Δ from BL in total insulin secretion (%Δ insulin) during IV-oral HC (180–480min). Secondary endpoint was %Δ insulin during IV HC (120–180min). Patients were drug-naïve with T2DM aged 43–69yrs with BL A1C range 5.9%–8.1%. Twenty patients received SAXA 5mg od; 16 received PBO.
- After 12 wks, SAXA significantly increased %Δ insulin from BL during IV-oral HC (adj% difference of 18.5% vs PBO, p=0.035). In the fasting state during IV HC SAXA significantly increased %Δ insulin from BL (adj% difference of 27.9% vs PBO, p=0.020). At wk 12 insulin secretion increased from BL with SAXA but not with PBO (Fig). Glucagon AUC during IV-oral HC also improved from BL with SAXA (adj% difference of -21.8% vs PBO, p=0.031). SAXA was generally safe and well-tolerated.
- In conclusion, SAXA improved pancreatic β-cell function in the postprandial and fasting states and decreased postprandial glucagon concentration.

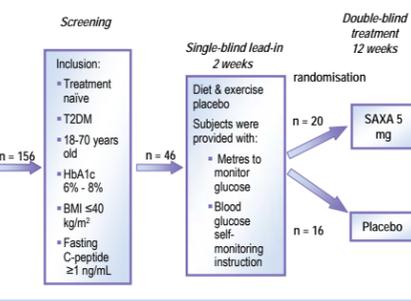
BACKGROUND

- The endogenous incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) regulate blood glucose via mechanisms that include stimulation of glucose-dependent insulin secretion and inhibition of glucagon secretion.
- GLP-1 and GIP are secreted in response to enteral nutrient loads, but are rapidly cleaved and inactivated by dipeptidyl peptidase-4 (DPP-4).
- Saxagliptin (SAXA) is a potent, selective DPP-4 inhibitor, specifically designed for extended inhibition of the DPP-4 enzyme.³
- Previously reported trials of SAXA in patients with type 2 diabetes mellitus (T2DM) have demonstrated efficacy and safety of SAXA as monotherapy and in combination with other oral antidiabetic agents.^{4,7}
- The proposed mechanism of action of SAXA involves protecting incretins from DPP-4 degradation, thereby improving β-cell response and decreasing glucagon secretion.
- This trial utilized a sequential intravenous and intravenous-oral hyperglycaemic clamp to study the mechanism of action of SAXA. Trial endpoints compared changes in β-cell responsiveness and insulin secretion rates in drug-naïve T2DM patients who received either SAXA 5 mg or placebo for 12 weeks (Trial # CV181-041).

STUDY DESIGN

- Three-centre, phase 3, randomised, parallel-group, double-blind, placebo-controlled trial with IV-oral hyperglycaemic clamp to assess the effect of SAXA on β-cell function in T2DM patients (Figure 1):
 - 2-week single-blind diet and exercise PBO lead-in phase.
 - 12-week double-blind treatment phase.
- Patients were randomised to receive once daily SAXA 5 mg or PBO.

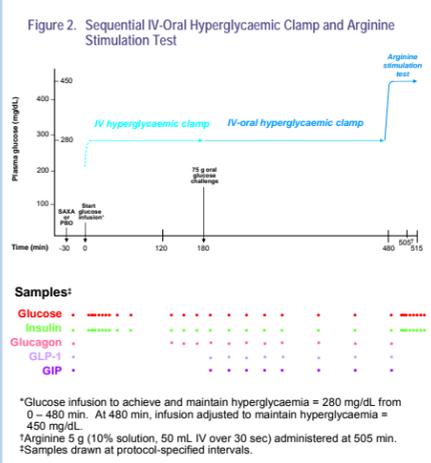
Figure 1: Phase 3 Study Design



METHODS

- Sequential IV-oral hyperglycaemic clamp and arginine stimulation tests performed on Day -1 and Day 84 (Figure 2):
 - IV Hyperglycaemic Clamp [0–180 min]:
 - SAXA or PBO administered 30 min before beginning of glucose infusion to achieve hyperglycaemia with plasma glucose = 280 mg/dL.
 - Plasma glucose then maintained at 280 mg/dL by adjusted glucose infusion rate.
 - IV-Oral Hyperglycaemic Clamp [180–480 min]:
 - 75 g glucose administered orally at 180 min.
 - Plasma glucose maintained at 280 mg/dL by adjusted glucose infusion rate.
 - Arginine Stimulation Test [480–515 min]:
 - Prior to start of arginine infusion, glucose infusion increased to achieve and maintain plasma glucose = 450 mg/dL.
 - Arginine 5 g (10% solution, 50 mL IV over 30 sec) administered at 505 min.
- Glucose, insulin, and glucagon measurements were drawn at designated intervals prior to starting and during the infusion process.
- Analytical technique for insulin secretion rate measured by C-peptide deconvolution.^{8–10}

METHODS (continued)



OBJECTIVES

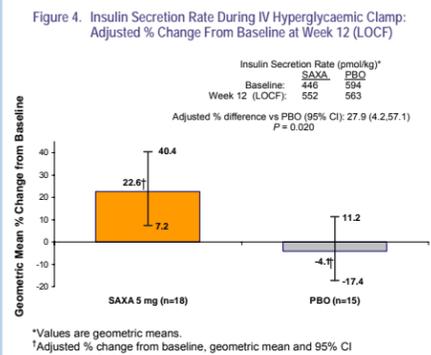
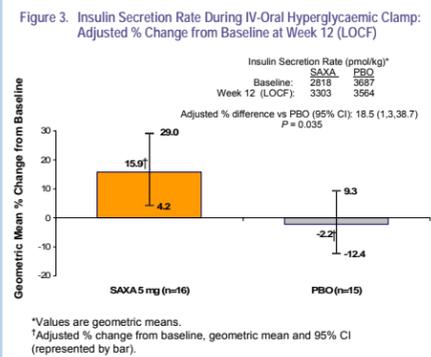
- Study objectives (SAXA 5 mg vs PBO at 12 weeks):
 - Primary:** Percent change from baseline in total insulin secretion during IV-oral hyperglycaemic clamp (180–480 min).
 - Secondary:** Percent change from baseline in total insulin secretion during IV hyperglycaemic clamp (120–180 min).
 - Tertiary:**
 - Percent changes from baseline in insulin secretion following IV arginine stimulation.
 - Changes from baseline in GLP-1 and GIP concentrations during IV-oral hyperglycaemic clamp.
 - Changes from baseline in glucagon assessments during IV-oral and IV hyperglycaemic clamp.
- Safety and tolerability of SAXA 5 mg.**
- Efficacy analyses were performed using an ANCOVA model utilising last observation carried forward (LOCF).

RESULTS

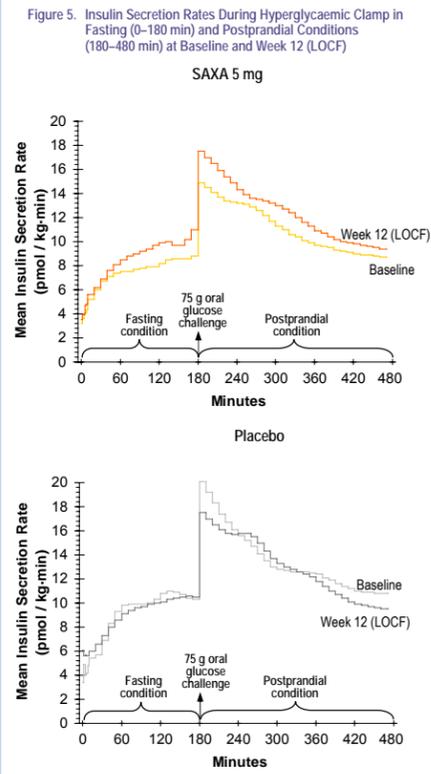
Table 1. Patient Demographics and Baseline Characteristics

	SAXA 5 mg (n=20)	PBO (n=16)
Age, y, mean (SD)	55.2 (8.6)	56.2 (6.9)
Gender, female, n (%)	12 (60.0)	10 (62.5)
Weight, kg, mean (SD)	95.0 (15.0)	92.5 (13.5)
BMI, kg/m ² , mean (SD)	33.5 (3.7)	32.2 (3.9)
T2DM duration, y, mean (SD)	2.7 (4.4)	3.7 (4.0)
HbA1c, %, mean (SD)	6.9 (0.5)	6.6 (0.6)
FPG, mg/dL, mean (SD)	131.5 (22.0)	124.7 (21.5)

- Insulin Secretion Rates During Postprandial and Fasting States
 - At week 12, insulin secretion increased from baseline with SAXA but not with PBO:
 - In the postprandial state (Primary endpoint – Figures 3 and 5).
 - In the fasting state (Secondary endpoint – Figures 4 and 5).



RESULTS (continued)

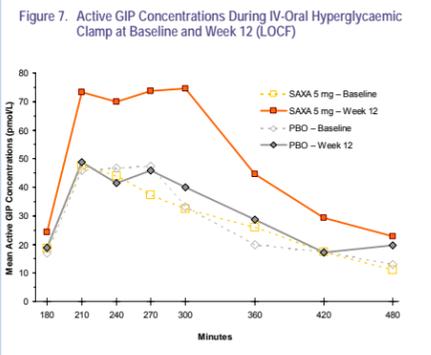
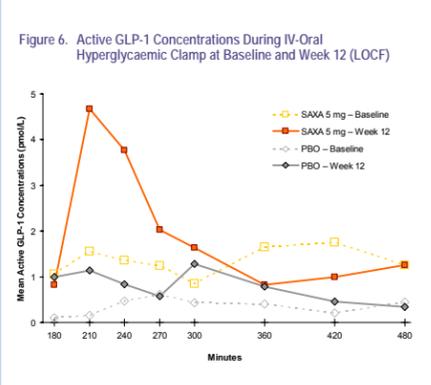


- Insulin Secretion Following Stimulation with IV Arginine
 - At week 12, percent changes in insulin secretion and acute insulin response to IV arginine were numerically greater for SAXA than PBO (Table 2), although not statistically significant.

Table 2. Insulin Secretion Following IV Arginine: Changes from Baseline at Week 12

	SAXA 5 mg (n=16)	PBO (n=14)
Insulin secretion in first 5 minutes following IV arginine		
Acute insulin response, μU/mL	164 (107, 203)	204 (175, 268)
Baseline, median (Q1, Q3)	172 (136, 228)	185 (147, 208)
Change from baseline*, median (Q1, Q3)	24.0* (-5.8, 71.5)	-21.7 (-52.3, 5.3)

- GLP-1 and GIP Concentrations During IV-Oral Hyperglycaemic Clamp
 - At week 12, SAXA increased peak concentrations of intact, active GLP-1 and GIP following oral glucose stimulation during IV-oral hyperglycaemic clamp (Figures 6 and 7).



RESULTS (continued)

Table 3. Glucagon Secretion: Changes from Baseline at Week 12

Parameter	SAXA 5 mg (n=17)	PBO (n=14)
Glucagon AUC during IV-oral clamp, pg·min/mL	14279 (1228)	11177 (880)
Baseline mean (SE)	11571 (1113)	12965 (1273)
Adjusted change from baseline, mean (95% CI)	-2191 (-4153, -229)	1161 (-1014, 3336)
Difference vs PBO, mean (95% CI)	-3352* (-6371, -333)	
Mean glucagon concentration during IV clamp, pg/mL		
Baseline, mean (SE)	50.2 (3.54)	36.8 (3.43)
Week 12 LOCF, mean (SE)	41.7 (3.75)	45.5 (3.95)
Adjusted change from baseline, mean (95% CI)	-5.7 (-12.6, 1.3)	5.5 (-2.2, 13.2)

- The change from baseline at week 12 in glucagon AUC during IV-oral hyperglycaemic clamp in the SAXA group was significantly different from the PBO group (Table 3).
- During IV hyperglycaemic clamp, mean glucagon concentration decreased in the SAXA group, and increased in the PBO group (Table 3).

Table 4. Glycaemic Control at Week 12

Glycaemic Parameters	SAXA 5 mg (n=18)	PBO (n=16)
HbA1c %		
Baseline, mean (SE)	6.9 (0.12)	6.6 (0.14)
Week 12 LOCF, mean (SE)	6.8 (0.16)	6.6 (0.17)
Adjusted change from baseline, mean (95% CI)	-0.14 (-0.30, 0.10)	0.02 (-0.23, 0.28)
FPG, mg/dL		
Baseline, mean (SE)	133.2 (5.29)	124.7 (5.37)
Week 12 LOCF, mean (SE)	134.6 (7.01)	138.2 (6.19)
Adjusted change from baseline, mean (95% CI)	2.4 (-8.5, 13.3)	12.4 (0.8, 23.9)

SAFETY

- SAXA 5 mg was well tolerated.
- There were no deaths, serious AEs, or discontinuations due to AEs.
- AEs reported for >1 subject per treatment group included headache (SAXA, n=3; PBO, n=1), muscle spasms (SAXA, n=3), sinusitis (SAXA, n=2), parosmia (SAXA, n=2), infusion site pain (SAXA, n=2), fatigue (PBO, n=2), cough (PBO, n=2), and sinus congestion (PBO, n=2).
- Compared with PBO, SAXA was not associated with a meaningful increase in hypoglycaemia, infections, localised oedema, or cardiovascular events.

CONCLUSIONS

- Compared to placebo, 12 weeks of treatment with SAXA 5 mg in drug-naïve T2DM patients:
 - Increased pancreatic β-cell responsiveness to glucose in the postprandial state during IV-oral hyperglycaemic clamp.
 - Increased pancreatic β-cell responsiveness to glucose in the fasting state during IV hyperglycaemic clamp.
 - Increased peak levels of intact, active GLP-1 and GIP following oral glucose stimulation.
 - Lowered postprandial glucagon secretion.
- Thus, saxagliptin improves glycaemic parameters in patients with T2DM by inhibiting the degradation of incretins and reducing postprandial glucagon secretion.
- Saxagliptin was generally well tolerated, with a safety profile consistent with that observed in prior large Phase 3 studies.

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