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

Bristol-Myers Squibb

AstraZeneca

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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[2] 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=.035). In the fasting state during IV HC SAXA significantly increased %Δ insulin from BL (adj% difference of 27.9% vs PBO, p=.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=.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.

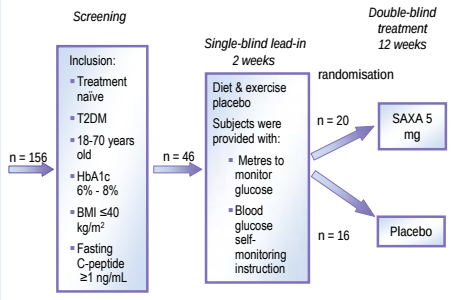
BACKGROUND

- 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

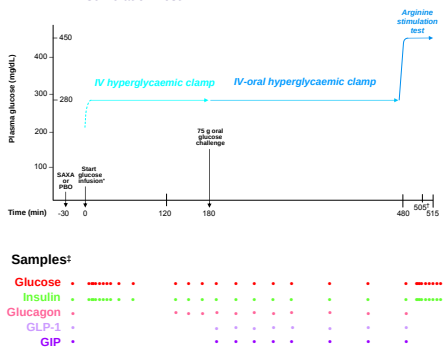


METHODS

- 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)*

Figure 2. Sequential IV-Oral Hyperglycaemic Clamp and Arginine Stimulation Test



*Glucose infusion to achieve and maintain hyperglycaemia = 280 mg/dL from 0 – 480 min. At 480 min, infusion adjusted to maintain hyperglycaemia = 450 mg/dL.
†Arginine 5 g (10% solution, 50 mL IV over 30 sec) administered at 505 min.
‡Samples drawn at protocol-specified intervals.

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

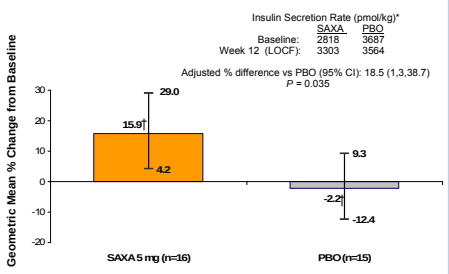
Table 1. Patient Demographics and Baseline Characteristics

	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/m², 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

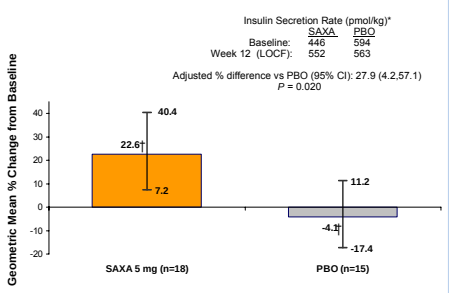
- At week 12, insulin secretion increased from baseline with SAXA but not with PBO:
  - In the postprandial state (**Primary endpoint – Figures 3 and 5**).
  - In the fasting state **(Secondary endpoint – Figures 4 and 5**).

Figure 3. Insulin Secretion Rate During IV-Oral Hyperglycaemic Clamp: Adjusted % Change from Baseline at Week 12 (LOCF)



*Values are geometric means.
†Adjusted % change from baseline, geometric mean and 95% CI (represented by bar).

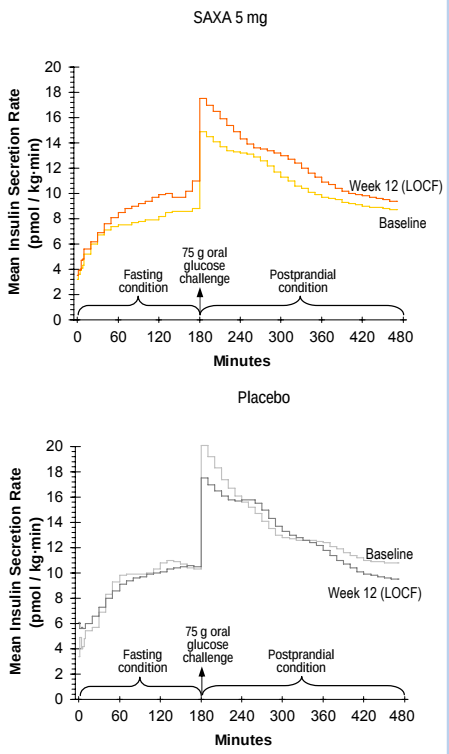
Figure 4. Insulin Secretion Rate During IV Hyperglycaemic Clamp: Adjusted % Change From Baseline at Week 12 (LOCF)



*Values are geometric means.
†Adjusted % change from baseline, geometric mean and 95% CI (represented by bar).

RESULTS *(continued)*

Figure 5. Insulin Secretion Rates During Hyperglycaemic Clamp in Fasting (0–180 min) and Postprandial Conditions (180–480 min) at Baseline and Week 12 (LOCF)



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

Insulin secretion in first 5 minutes following IV arginine	SAXA 5 mg	PBO
Acute insulin response, μU/mL	(n = 16)	(n = 14)
Baseline, median (Q1, Q3)	164 (107, 203)	204 (175, 268)
Week 12, 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)

*LOCF, last observation carried forward.
†P value vs PBO = 0.074 (Kruskal-Wallis test).

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**).

Figure 6. Active GLP-1 Concentrations During IV-Oral Hyperglycaemic Clamp at Baseline and Week 12 (LOCF)

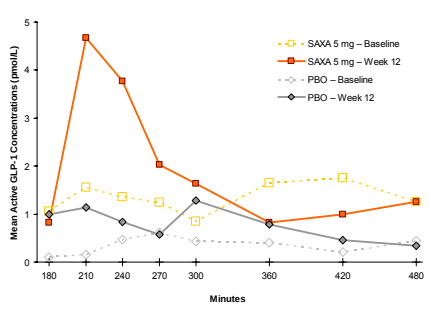
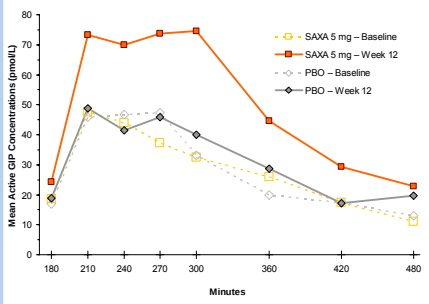


Figure 7. Active GIP Concentrations During IV-Oral Hyperglycaemic Clamp at Baseline and Week 12 (LOCF)



RESULTS *(continued)*

Glucagon Secretion

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

Parameter	SAXA 5 mg	PBO
Glucagon AUC during IV-oral clamp, pg*min/mL	(n = 17)	(n = 14)
Baseline mean (SE)	14279 (1228)	11177 (880)
Week 12 LOCF, 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	(n = 18)	(n = 15)
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)

AUC, area under the curve; LOCF, last observation carried forward, ANCOVA model.
*P value vs PBO = 0.031.

Glycaemic Control

- Glycaemic parameters are summarized in **Table 4.**

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 (-0.38, 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)

LOCF, last observation carried forward.

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), parasthesia (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 hypoglycaemic clamp.
  - Increased pancreatic **β**-cell responsiveness to glucose in the fasting state during IV hypoglycaemic 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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