Saxagliptin Clinical Trials: Evaluation of CV Risk

R Rasalam[1], *Robert Wolf[2], Robert Frederich[2], Fred Fiedorek[2], Mark Donovan[2], Susan Harris[3], Roland Chen[2]*

[1]Bristol-Myers Squibb, Melbourne, VIC, Australia; [2]Bristol-Myers Squibb, Princeton, NJ, USA; [3]AstraZeneca, Wilmington, DE, USA

Ranjit Rasalam
Bristol-Myers Squibb
556 Princes Highway
Noble Park North, VIC 3174
Phone: 03-9213-4000
E-mail: ranjit.rasalam@bms.com

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. However, several diabetes, obesity, and lipid drug trials have had unexpected and unfavourable cardiovascular (CV) results. The saxagliptin (SAXA) phase 2b/3 program enrolled a range of patients with diabetes and included a controlled, long-term safety extension phase. SAXA is a potent, selective dipeptidyl peptidase-4 (DPP-4) inhibitor. In the SAXA clinical data, the primary endpoint, major adverse cardiovascular events (MACE; stroke, myocardial infarction or CV death, analysed post hoc) and acute cardiovascular events (ACE; acute, clinically significant events, including cardiac revascularisation procedures) were identified using selected MedDRA Preferred Terms. CV events were analysed in a comprehensive dataset: 8 randomised, double-blind, phase 2b/3 trials, which included 4607 patients (3206 randomised to SAXA 2.5, 5, or 10 mg; 150 randomised to SAXA 20, 40, or 100 mg; and 1251 randomised to placebo, metformin, or up-titrated glyburide). Overall exposure was 3758 patient-years on SAXA and 1293 patient-years on comparators. Within the SAXA population, 81% had at least 1 CV risk factor in addition to diabetes, with hypertension (52%), dyslipidaemia (44%), or history of smoking (39%) the most common; 12% had known prior CV disease. Comparator group had similar proportions. Numbers of patients with events are shown in Table. The Cox proportional hazard ratio for MACE was 0.44 (95% CI: 0.24–0.82) and for ACE was 0.59 (95% CI: 0.35–1.00). A series of sensitivity analyses using related endpoints and alternative analytic methods produced consistent results. Based on a >5000 patient-year clinical trial experience, there was no evidence of increased CV risk with SAXA treatment – as monotherapy or in combination with other oral antidiabetic agents. These data raise the hypothesis of a cardioprotective effect of SAXA, which will be studied in the SAVOR trial.

Event Type, n (%)	SAXA (n%) n=3356	Control (n%) n=1251
ACE	38 (1.1)	23 (1.8)
MACE	23 (0.7)	18 (1.4)
All Death	10 (0.3)	12 (1.0)
CV Death	7 (0.2)	10 (0.8)

CONTEXT FOR ASSESSMENT OF CV SAFETY OF SAXAGLIPTIN

There has been considerable scrutiny of the CV safety of some antidiabetic agents, including sulfonylureas and PPAR gamma agonists. Concerns regarding the safety of antidiabetic agents are based on data from randomised clinical trials and observational studies.

Based on data available prior to initiating the phase 2b/3 studies, there was no *a priori* concern that increased CV risk would be associated with saxagliptin. These data include:

- No microscopic evidence of cardiotoxicity in any nonclinical species.
- No indication of adverse CV effects based on *in vitro* (hERG, Purkinje) or *in vivo* (ECG, haemodynamic) assessments in rat, dog, or monkey.
- No adverse effect on lipid parameters, blood pressure, heart rate, or QTc in phase 1 studies.

METHODS

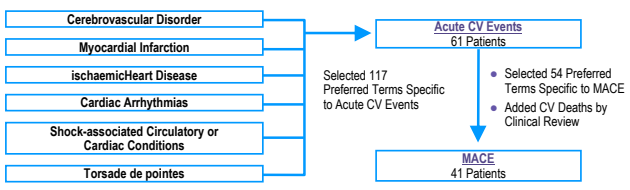
To evaluate CV risk in the saxagliptin phase 2b/3 clinical trials, two major composite end points were defined:

- Acute CV Events comprised ischaemic events that were acute and consequential, including both reversible and irreversible ischaemic events, as well as revascularisation procedures.
- Major Adverse Cardiovascular Events (MACE) encompassed CV death, nonfatal myocardial infarction, and nonfatal stroke.
- Acute CV Events and MACE were identified in the adverse event database of phase 2b/3 studies by searching for events that coded to particular terms in the Medical Dictionary for Regulatory Activities (MedDRA) using the methods described in **Figure 1**. For MACE, case identification was supplemented by clinical review of all deaths to ensure that each death with a CV aaetiology was counted.

A meta-analysis of Acute CV Events and MACE was performed by pooling data from randomised, controlled phase 2b/3 studies of saxagliptin in type 2 diabetes (T2D). Analytic methods are described below and the set of clinical studies included in the meta-analysis is described in **Figure 2**. The meta-analysis included patients exposed to doses of 2.5 – 100 mg of saxagliptin once daily; the proposed usual clinical dose is 5 mg once daily.

Figure 1. Process for Identifying Acute CV Events and MACE

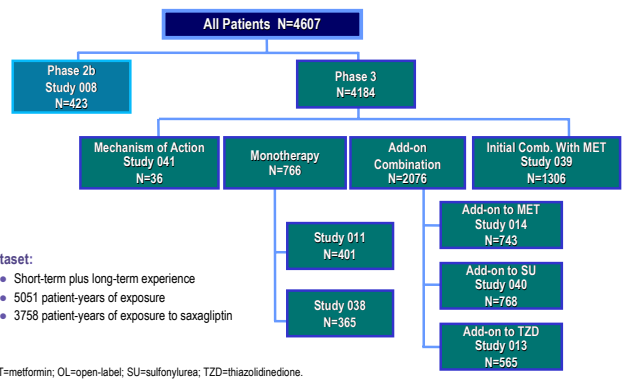
Source of Preferred Terms: Standard MedDRA Query Lists (SMQs)



ANALYTIC METHODS

- Summary of baseline characteristics:
  - Demographic, diabetes, CV risk, CV history
- Frequency of patients with events overall and by treatment group
- Incidence rates (adjusted for exposure) for combined saxagliptin groups overall, and within specified subgroups
- Assessment of risk ratios from controlled phase 2b/3 data (stratified by study):
  - Incidence Rate Ratio (adjusted for exposure)
    - Mantel-Haenszel (MH)
    - Exact method
  - Cox Proportional Hazards Model
  - Incidence Ratio (MH, not adjusted for exposure)
- Assessment of risk ratios overall, and in individual studies:
  - Individual: Incidence Rate Ratio with Bayesian credibility interval
  - Overall: Incidence Rate Ratio (MH)
- Time to first event by weighted Kaplan-Meier estimate:
  - Weights proportional to overall study sample size

Figure 2. Controlled Phase 2b/3 Clinical Studies Pooled to Assess CV Safety



Dataset:

- Short-term plus long-term experience
- 5051 patient-years of exposure
- 3758 patient-years of exposure to saxagliptin

MET=metformin; OL=open-label; SU=sulfonylurea; TZD=thiazolidinedione.

RESULTS

There was no evidence of increased risk of CV events:

- in the phase 2b/3 pooled population
- in subgroups of patients expected to be at higher risk
- in individual studies

Data presentations:

- Demographic and Baseline Characteristics (**Table 1**)
- CV Risk Factors (**Table 2**)
- Frequency of CV End Points (**Table 3**)
- Incidence Rate for MACE in Subgroups Expected to Be at Higher Risk (**Figure 3**)
- Incidence Rate Ratio of MACE in the Pooled Population and by Study (**Figure 4**)
- Stratified Analyses of MACE and Acute CV Events (**Figure 5**)
- Time to Onset of First MACE (**Figure 6**)
- Time to Onset of Death (**Figure 7**)

Controlled Phase 2b/3 Pooled Population

Table 1. Demographic and Baseline Characteristics

		SAXA 2.5 mg n=937	SAXA 5 mg n=1269	SAXA 10 mg n=1000	All SAXA[a] n=3356	Control[b] n=1251
Age	Mean (SD) yrs	54.6 (10.0)	53.7 (10.3)	52.7 (10.7)	53.6 (10.3)	53.9 (10.6)
Race	White, n (%)	650 (69)	902 (71)	775 (78)	2456 (73)	889 (71)
	Non-white, n (%)	287 (31)	367 (29)	225 (23)	900 (27)	362 (29)
Race, n (%)						
	White	650 (69.4)	902 (71.1)	775 (77.5)	2456 (73.2)	889 (71.1)
	Black	36 (3.8)	62 (4.9)	38 (3.8)	149 (4.4)	50 (4.0)
	Asian	155 (16.5)	206 (16.2)	125 (12.5)	493 (14.7)	195 (15.6)
	Other	96 (10.2)	99 (7.8)	62 (6.2)	258 (7.7)	117 (9.4)
Gender	Male, n (%)	444 (47)	625 (49)	495 (50)	1659 (49)	620 (50)
	Female, n (%)	493 (53)	644 (51)	505 (51)	1697 (51)	631 (50)
Body Mass Index (kg/m^2)	Mean	30.4	30.3	30.6	30.4	30.3
Duration of T2D	Mean (SD) yrs	5.1 (5.2)	4.1 (5.1)	2.5 (3.6)	3.8 (4.8)	4.1 (5.0)
HbA_{1c}	Mean (SD) %	8.1 (0.99)	8.5 (1.18)	9.0 (1.42)	8.5 (1.26)	8.4 (1.23)

[a] Includes 20, 40, and 100 mg experience from Study 008.
[b] Includes metformin monotherapy from Study 039.

Table 2. CV Risk Factors (in Addition to T2D)

	Number (%) of Patients				
	SAXA 2.5 mg n=937	SAXA 5 mg n=1269	SAXA 10 mg n=1000	All SAXA[c] n=3356	Control n=1251
Patients With at Least One CV Risk Factor in Addition to T2D	777 (83)	1015 (80)	803 (80)	2724 (81)	1035 (83)
Hypertension	519 (55)	655 (52)	510 (51)	1750 (52)	688 (55)
Hypercholesterolaemia[a]	471 (50)	565 (45)	353 (35)	1475 (44)	566 (45)
Smoking History	383 (41)	449 (35)	393 (39)	1301 (39)	471 (38)
First-degree Family Member With Premature Coronary Heart Disease	190 (20)	248 (20)	186 (19)	677 (20)	265 (21)
Patients With History of CV Disease[b]	118 (13)	150 (12)	118 (12)	404 (12)	165 (13)

[a] Includes mixed dyslipidaemia.
[b] Prior CV disease defined as previous myocardial infarction, congestive heart failure, hospitalisation for unstable angina, stable angina, percutaneous coronary intervention, coronary artery bypass graft, coronary artery disease, cerebrovascular disease, peripheral vascular disease.
[c] Includes 20, 40, and 100 mg experience from Study 008.

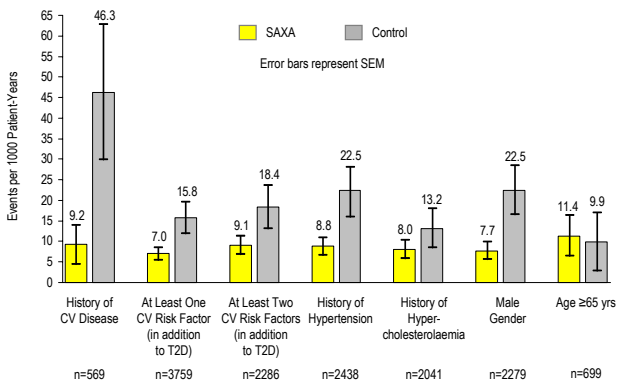
Table 3. Frequency of CV End Points

	SAXA 2.5 mg	SAXA 5 mg	SAXA 10 mg	All SAXA[a]	Control
N (Total Patients)	937	1269	1000	3356	1251
Total Patient-Years	1149	1462	1119	3758	1293
Mean Duration of Follow-up (yrs)	1.23	1.15	1.12	1.12	1.03
Number (%) With Event					
MACE	6 (0.6)	6 (0.5)	11 (1.1)	23 (0.7)	18 (1.4)
Acute CV Events	14 (1.5)	10 (0.8)	14 (1.4)	38 (1.1)	23 (1.8)
All Death	3 (0.3)	3 (0.2)	4 (0.4)	10 (0.3)	12 (1.0)
CV Death	1 (0.1)	2 (0.2)	4 (0.4)	7 (0.2)	10 (0.8)

[a] Includes 20, 40, and 100 mg experience from Study 008.

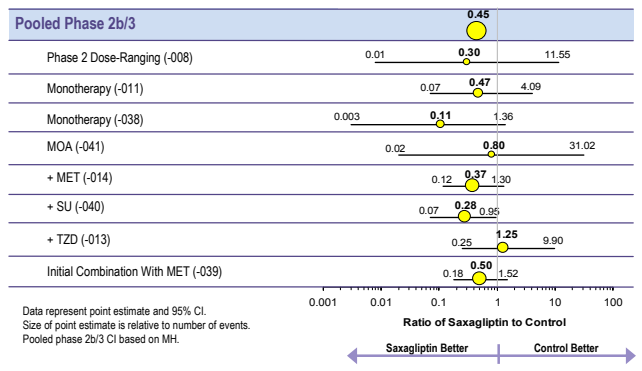
Controlled Phase 2b/3 Pooled Population

Figure 3. Incidence Rate for MACE in Subgroups Expected to Be at Higher Risk



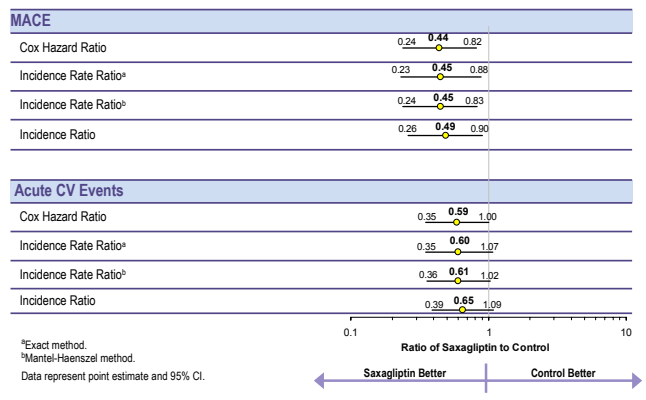
RESULTS *(continued)*

Figure 4. Incidence Rate Ratio of MACE in the Pooled Population and by Study



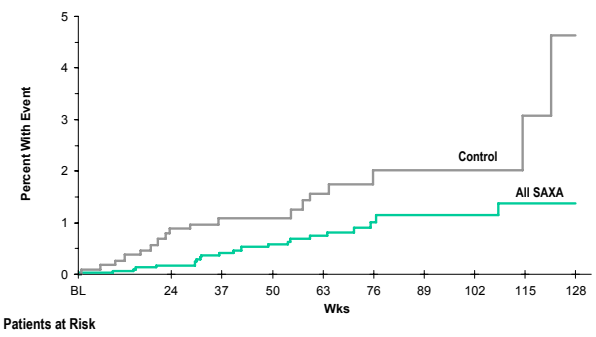
Data represent point estimate and 95% CI.
Size of point estimate is relative to number of events.
Pooled phase 2b/3 CI based on MH.

Figure 5. Stratified Analyses of MACE and Acute CV Events



[a]Exact method.
[b]Mantel-Haenszel method.
Data represent point estimate and 95% CI.

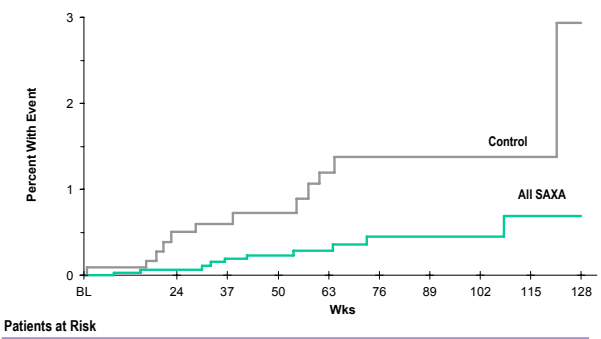
Figure 6. Time to Onset of First MACE



Patients at Risk

Control	1251	935	860	774	545	288	144	123	102	57
All SAXA	3356	2615	2419	2209	1638	994	498	436	373	197

Figure 7. Time to Onset of Death



Patients at Risk

Control	1251	937	863	777	547	290	145	124	103	59
All SAXA	3356	2617	2423	2213	1642	997	500	438	374	198

CARDIOVASCULAR SAFETY SUMMARY AND CONCLUSIONS

- Analysed multiple CV end points using multiple analytic techniques to assess consistency of results.
- Analysed CV end points in phase 2b/3 pooled population by subgroup and by study.
- No evidence of increased CV risk in patients with T2D exposed to saxagliptinfor up to 2.5 years.
- Data raise hypothesis of a cardioprotective effect of saxagliptin, which merits further study.

REFERENCES

1. Vos T et al. Australian Burden of Disease and Injury Study: Projected Health Care Costs Report. School of Population Health, University of Queensland and Australian Institute of Health and Welfare: Brisbane, 2005.
2. http://www.dfoa.com.au/ Understanding-Diabetes/Diabetes-in-Australia. Website accessed 2 August 2010.

Receive an electronic PDF of this poster using a QR reader on your mobile phone.

Download your free QR Reader App from the iTunes store if you use an iPhone or visit www.mobile-barcodes.com to find your phone and download the application.

Data presented previously at the 2010 American Diabetes Association.

2010 Australian Diabetes Society And Australian Diabetes Educators Association Annual Scientific Meeting, 1-3 September, Sydney, NSW

MedPos10_0131A