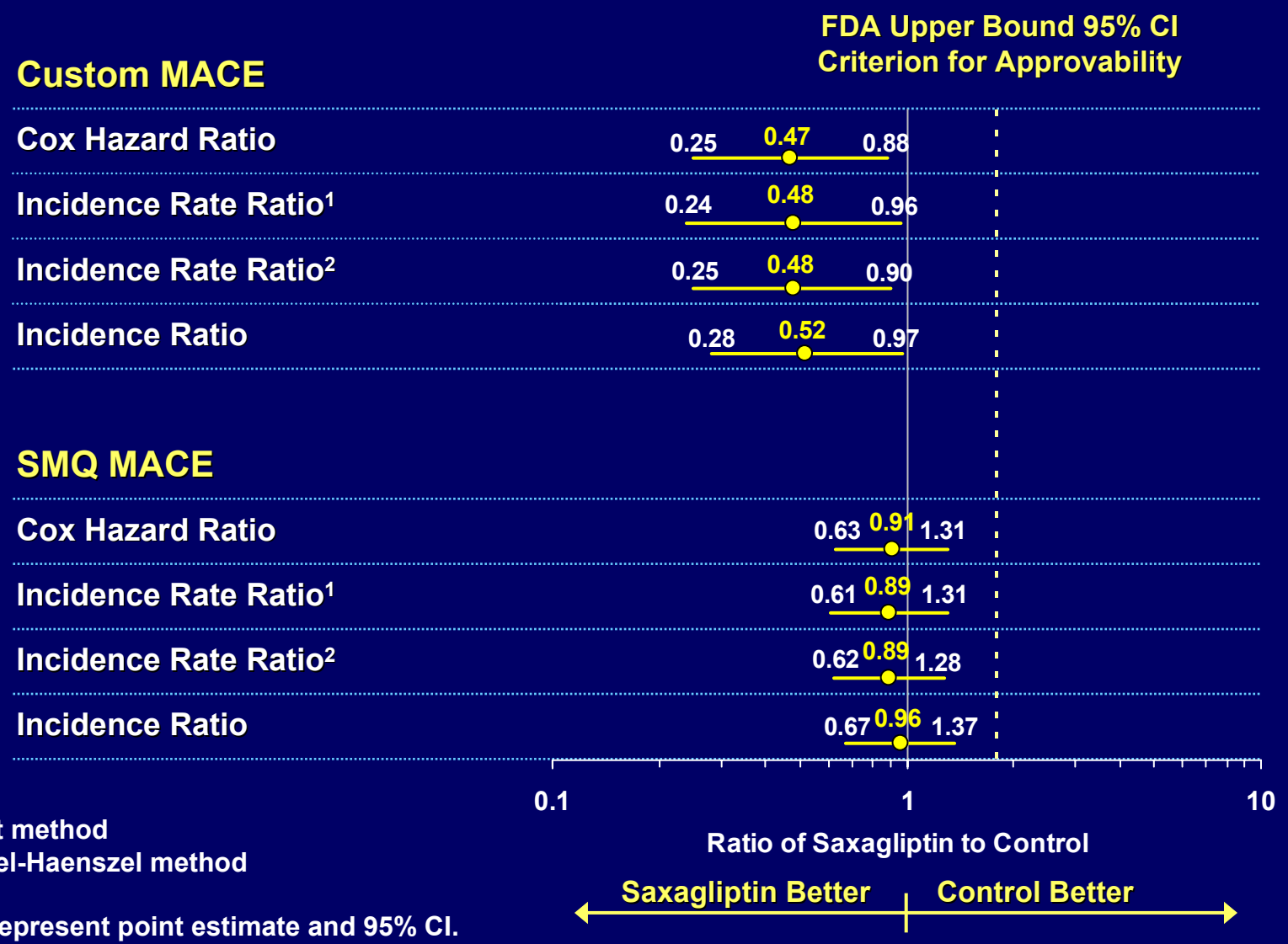
Stratified Analyses of FDA-defined MACE



[1]Exact method
[2]Mantel-Haenszel method

Data represent point estimate and 95% CI.

Use of Statins by Baseline History of Hypercholesterolemia

	n / N (%)				
	SAXA 2.5 mg N = 937	SAXA 5 mg N = 1269	SAXA 10 mg N = 1000	All SAXA* N = 3356	Control N = 1251
Baseline Hypercholesterolemia					
Yes	239 / 471 (50.7)	276 / 565 (48.9)	160 / 353 (45.3)	712 / 1475 (48.3)	282 / 566 (49.8)
No	49 / 403 (11.4)	38 / 581 (6.5)	34 / 483 (7.0)	120 / 1521 (7.9)	49 / 566 (8.7)

* Includes contribution from 20–100 mg saxagliptin in Phase 2b Study (-008).

Diabetes-Related Disease History

	Number (%) of Patients				
	SAXA 2.5 mg N = 937	SAXA 5 mg N = 1269	SAXA 10 mg N = 1000	All SAXA* N = 3356	Control N = 1251
Patients with at least one diabetes-related disease	181 (19.3)	216 (17.0)	130 (13.0)	547 (16.3)	219 (17.5)
Retinopathy	30 (3.2)	34 (2.7)	22 (2.2)	89 (2.7)	40 (3.2)
Neuropathy	115 (12.3)	144 (11.3)	75 (7.5)	349 (10.4)	145 (11.6)
Nephropathy	29 (3.1)	29 (2.3)	17 (1.7)	76 (2.3)	29 (2.3)
Microalbumnuria	58 (6.2)	62 (4.9)	39 (3.9)	164 (4.9)	67 (5.4)

* Includes contribution from 20–100 mg saxagliptin in Phase 2b Study (-008).

Adverse Events of Pancreatitis

	SAXA 2.5 mg N = 937	SAXA 5 mg N = 1269	SAXA 10 mg N = 1066	All SAXA N = 3422	Comp N = 1251
All AEs of Pancreatitis	1 (0.1%)	3 (0.2%)	2 (0.2%)	6 (0.2%)	2 (0.2%)
Pancreatitis PT	0	2 (0.2%)	1 (0.1%)	3 (0.1%)	1 (0.1%)
Acute Pancreatitis PT	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Chronic Pancreatitis PT	1 (0.1%)	0	0	1 (<0.1%)	1 (0.1%)

* Saxagliptin 2.5 and saxa 5 mg groups include subjects originally in these groups who were later uptitrated in Study CV181-038. The Saxa 10 mg group includes the Open Label cohort in Study -011. The All Saxa group includes data from higher-dose groups in Study -008; therefore, numbers across the rows are not additive.

† Combined placebo groups from all Phase 2b/3 studies, including the metformin monotherapy group from Study CV181039.

Higher Risk Population Identified in FDA December 2008 Guidance

	n (%)				
	SAXA 2.5 mg N = 937	SAXA 5 mg N = 1269	SAXA 10 mg N = 1000	All SAXA* N = 3356	Control N = 1251
Relatively Advanced Disease					
Duration of T2DM					
≥ 5 years	386 (41.2)	400 (31.5)	193 (19.3)	1005 (29.9)	388 (31.0)
≥ 10 years	150 (16.0)	145 (11.4)	53 (5.3)	356 (10.6)	151 (12.1)
Elderly Patients					
Age ≥ 65	154 (16.4)	185 (14.6)	146 (14.6)	506 (15.1)	193 (15.4)
Patients with Some Degree of Renal Impairment					
Creatine Clearance ≤ 80 mL/min	158 (16.9)	241 (19.0)	147 (14.7)	560 (16.7)	238 (19.0)

* Includes contribution from 20–100 mg saxagliptin in Phase 2b Study (-008).

Baseline Creatinine Clearance

	Number (%) of Patients				
(mL/min)	SAXA 2.5 mg N = 937	SAXA 5 mg N = 1269	SAXA 10 mg N = 1000	All SAXA N = 3356	Control N = 1251
<50	11 (1.2)	15 (1.2)	12 (1.2)	38 (1.1)	16 (1.3)
≥50 – <65	48 (5.1)	71 (5.6)	38 (3.8)	161 (4.8)	63 (5.0)
≥65 – ≤80	99 (10.6)	155 (12.2)	97 (9.7)	361 (10.8)	159 (12.7)
>80	779 (83.1)	1027 (80.9)	853 (85.3)	2795 (83.3)	1013 (81.0)

Use of Concomitant CV Medications

	Number (%) of Patients				
	SAXA 2.5 mg N = 937	SAXA 5 mg N = 1269	SAXA 10 mg N = 1000	All SAXA* N = 3356	Control N = 1251
ACE Inhibitors	291 (31.1)	390 (30.7)	303 (30.3)	1014 (30.2)	418 (33.4)
Angiotensin Receptor Blockers	108 (11.5)	111 (8.7)	73 (7.3)	311 (9.3)	118 (9.4)
Beta Blockers	129 (13.8)	170 (13.4)	150 (15.0)	465 (13.9)	193 (15.4)
Calcium Channel Blockers	128 (13.7)	134 (10.6)	110 (11.0)	390 (11.6)	123 (9.8)

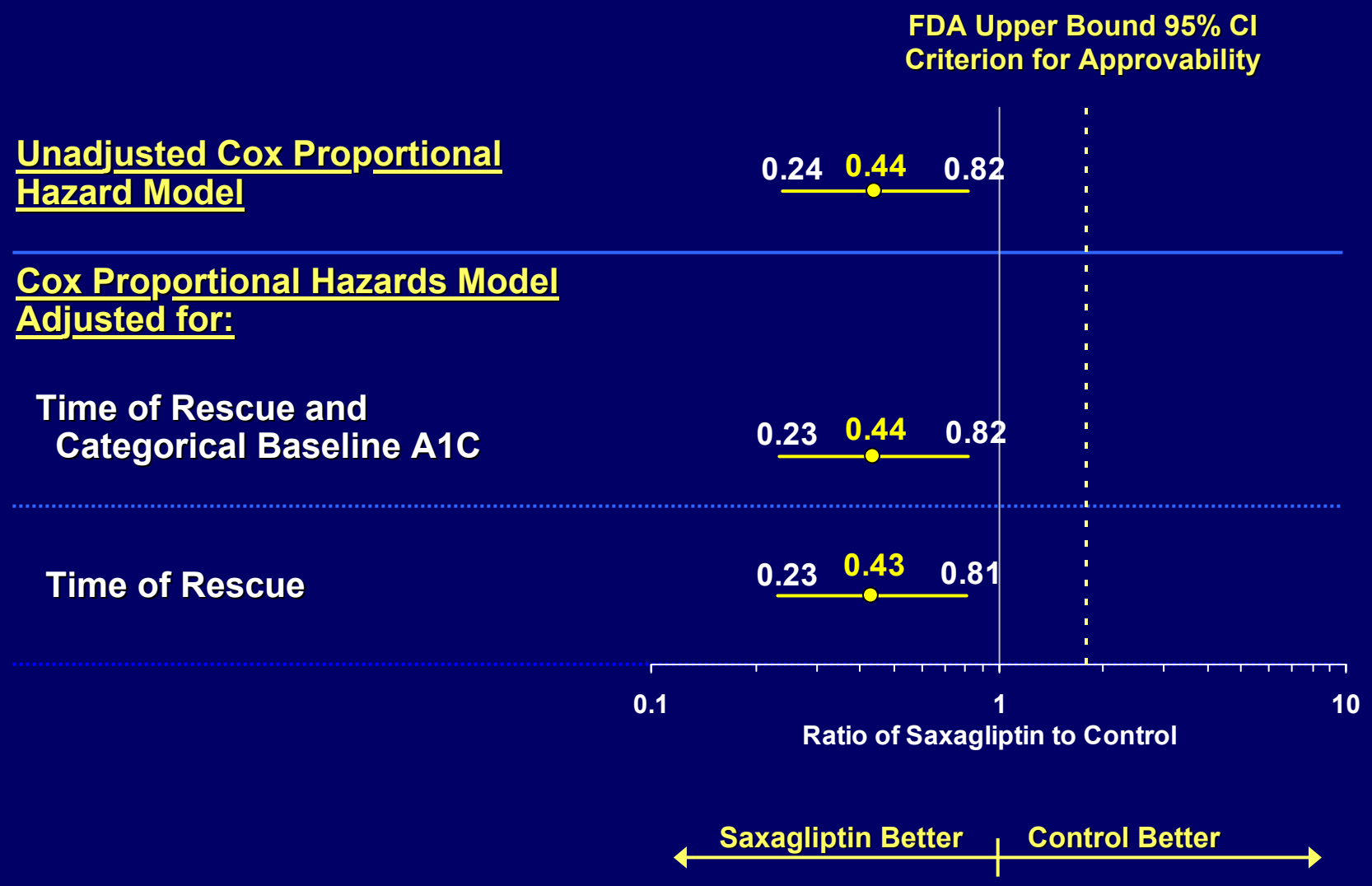
* Includes contribution from 20–100 mg saxagliptin in Phase 2b Study (-008).

Summary of Sponsor Defined MACE by Rescue

Summary	All SAXA	Comparator
Total number of events prior to rescue	18	13
Total number of events on or after rescue	5	5
Subject years of exposure prior to rescue	2921	905
Subject years of exposure on or after rescue	832	385

* Includes contribution from 20–100 mg saxagliptin in Phase 2b Study (-008).

Hazard Ratios of Sponsor-defined Primary MACE Using Cox Proportional Hazards Model Adjusted for Covariates



Data represent point estimate and 95% CI.

Pooled Analysis of Cardiovascular AEs Reported for Sitagliptin

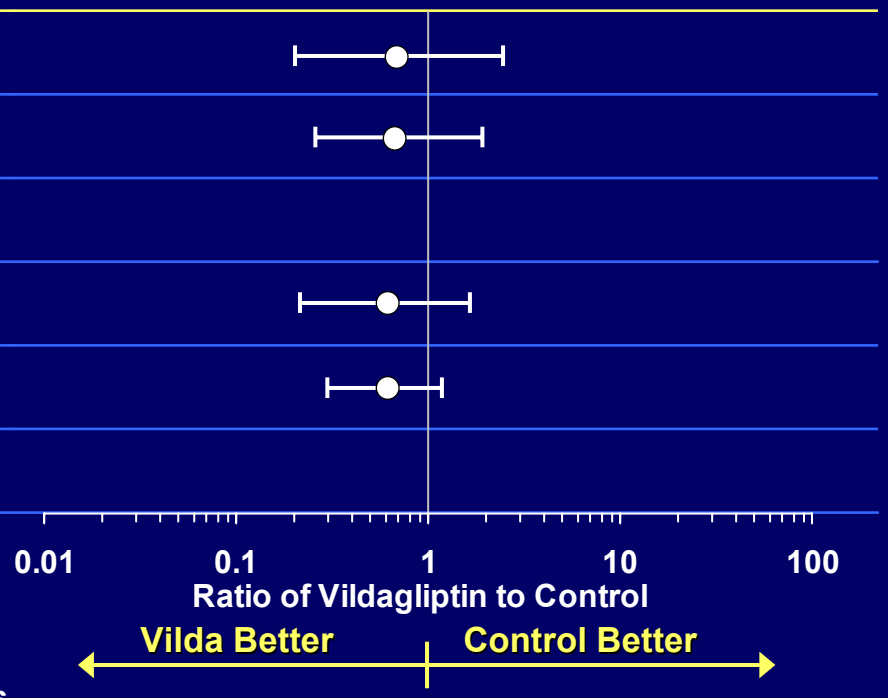
Cardiovascular Adverse Event	% Sitagliptin 100 mg (n=3415)	% Non-exposed (n=2724)	% Difference between Sitagliptin and Non-exposed (95% CI)
Cardiac Disorder AEs	4.0%	3.9%	0.1% (-0.9%, 1.1%)
Cardiac Disorder SAEs	1.2%	1.5%	-0.3% (-1.0%, 0.3%)
Ischemia-related AEs	2.0%	2.3%	-0.2% (-1.0%, 0.5%)
Ischemia-related SAEs	1.1%	1.5%	-0.4% (-1.0%, 0.2%)
Fatal Ischemia-related AEs	0.09%	0.26%	Not Reported

Source: EASD 2008 Poster, Diabetologia 2008;51 [Suppl 1]
Dataset: Data pooled from 12 studies, duration 18-106 weeks
Mean Duration of Exposure: Sitagliptin 100 mg 307.3 days; Non-exposed 293.6 days

Pooled Analysis of Cardiovascular SAEs Reported for Vildagliptin

Overall incidence and odds ratios for serious CV events by treatment (up to 24 week safety population)

Cardiovascular SAEs	Vilda n/N (%)	Odds Ratio
Vilda 50 mg Daily*	8/1469 (0.54)	0.79
Vilda 50 mg BID*	25/4594 (0.54)	0.79
Placebo	9/1304 (0.69)	
Vilda 50 mg Daily**	8/1469 (0.54)	0.70
Vilda 50 mg BID**	25/4594 (0.54)	0.70
All Comparators	34/4357 (0.78)	



* comparison vs. placebo ** comparison vs. all comparators
Comparators = all non-Vilda treatment groups.

Source: EASD 2008 Poster 915, *Diabetologia* 2008;51 [Supple 1]
Dataset: Data pooled from 19 studies, data truncated at 24 weeks
Mean Duration of Exposure: 20-22 weeks