Health Canada Advisory Committee Meeting

9 June 2005

Dr. Mark T Brown, Pfizer Inc.

Valdecoxib:

Cardiovascular Safety, Skin Reactions

&

Benefit-Risk Assessment

Valdecoxib - Background

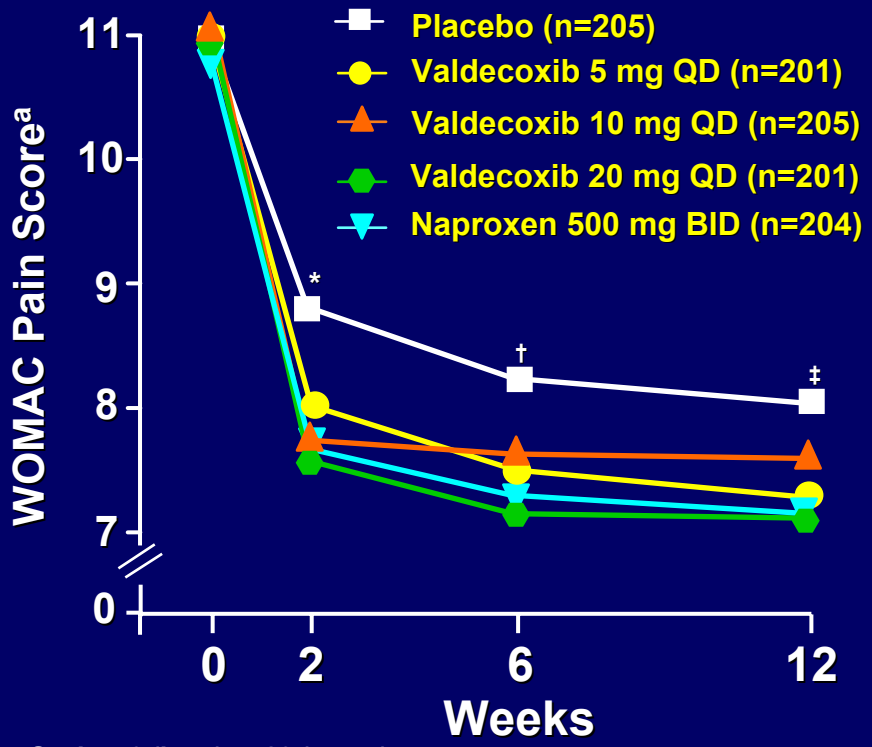
- Valdecoxib approved for OA and RA in US Nov 2001 (first approval) & in Canada in Dec 2002
- Approved dose = 10-20 mg once daily
- >15,000 individuals studied in the registration program = celecoxib
- Valdecoxib approved in 68 countries; Since April 2005, sales have been suspended in 48 countries
  - Due to concerns regarding severe cutaneous adverse reactions (SCAR)

Benefit-Risk of Valdecoxib - Conclusions

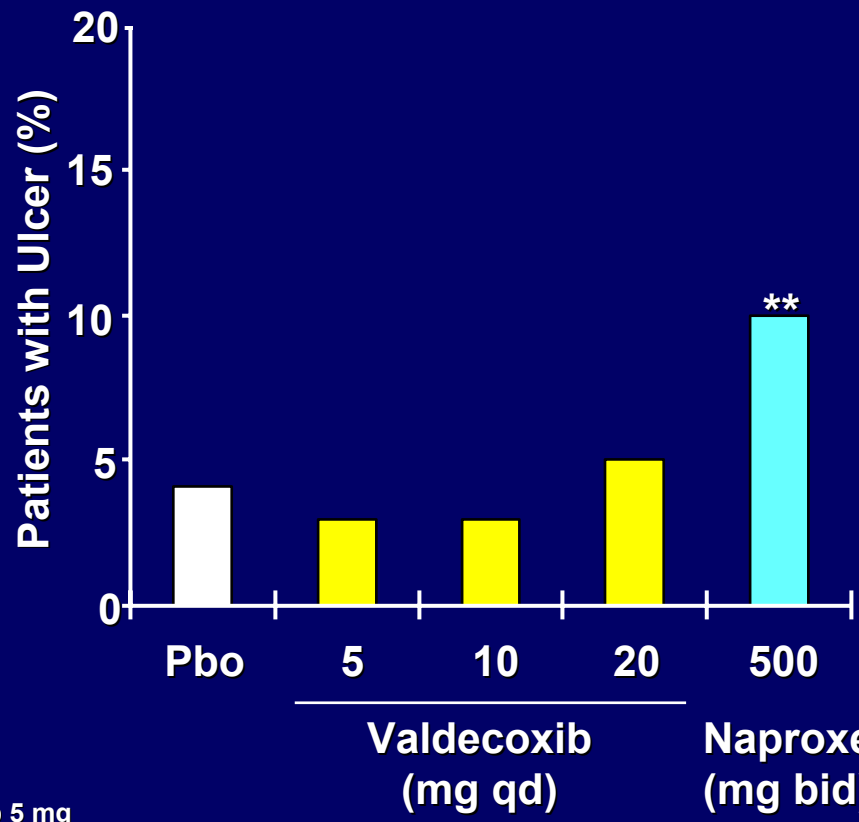
- Valdecoxib remains a viable treatment alternative for arthritis patients
  - Efficacy similar to NSAIDS
  - GI safety benefit superior to NSAIDs
  - CV safety profile comparable to NSAIDs
  - Higher rate of severe cutaneous adverse reactions compared to other COX-2 selective inhibitors

Clinical Effects of Valdecoxib in OA

Efficacy



Upper GI Safety



a. Scale = 0 (best) to 20 (worst)

* Placebo significantly different from all treatments; $p < 0.05$

† Placebo significantly different from all treatments except valdecoxib 5 mg and valdecoxib 10 mg; $p < 0.05$

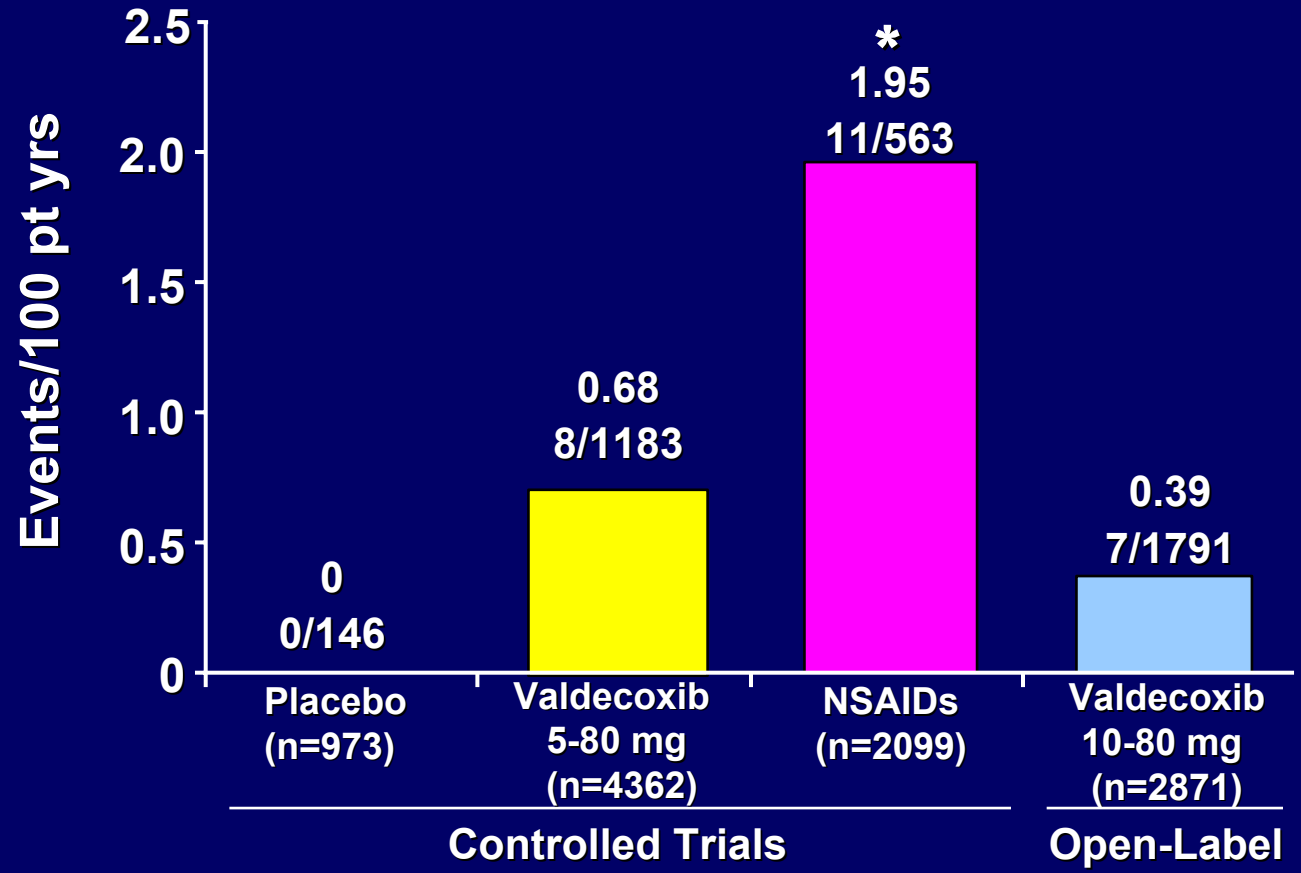
‡ Placebo significantly different from valdecoxib 20 mg and naproxen; $p < 0.05$

** Significantly different from placebo, valdecoxib 5 mg and 10 mg; $p < 0.05$

Kivitz et al. J Family Practice 2002:51;530-537

Incidence of Ulcer Complications

Pre-defined analysis of 8 randomized controlled trials (12-26 wks) & 3 open label studies up to 1 yr



* Significantly different from other treatments; $p < 0.05$

Goldstein et al. Alimentary Pharmacol Ther 2004;20:527-538

CV Safety of Valdecoxib

- Randomized controlled trials in arthritis
- Short-term acute pain studies with parecoxib followed by valdecoxib

Cardiovascular Safety of Valdecoxib:
Meta-analysis

- 19 randomized controlled trials and a total of 12,254 treated patients (>84% OA/RA)
  - 7,061 valdecoxib-treated patients
  - 2,235 placebo-treated patients
  - 2,958 patients treated with active comparators
- Study duration: 2 wks – 12 months
  - 11 studies ≥ 3 month duration
- Valdecoxib doses; 1 – 80 mg daily

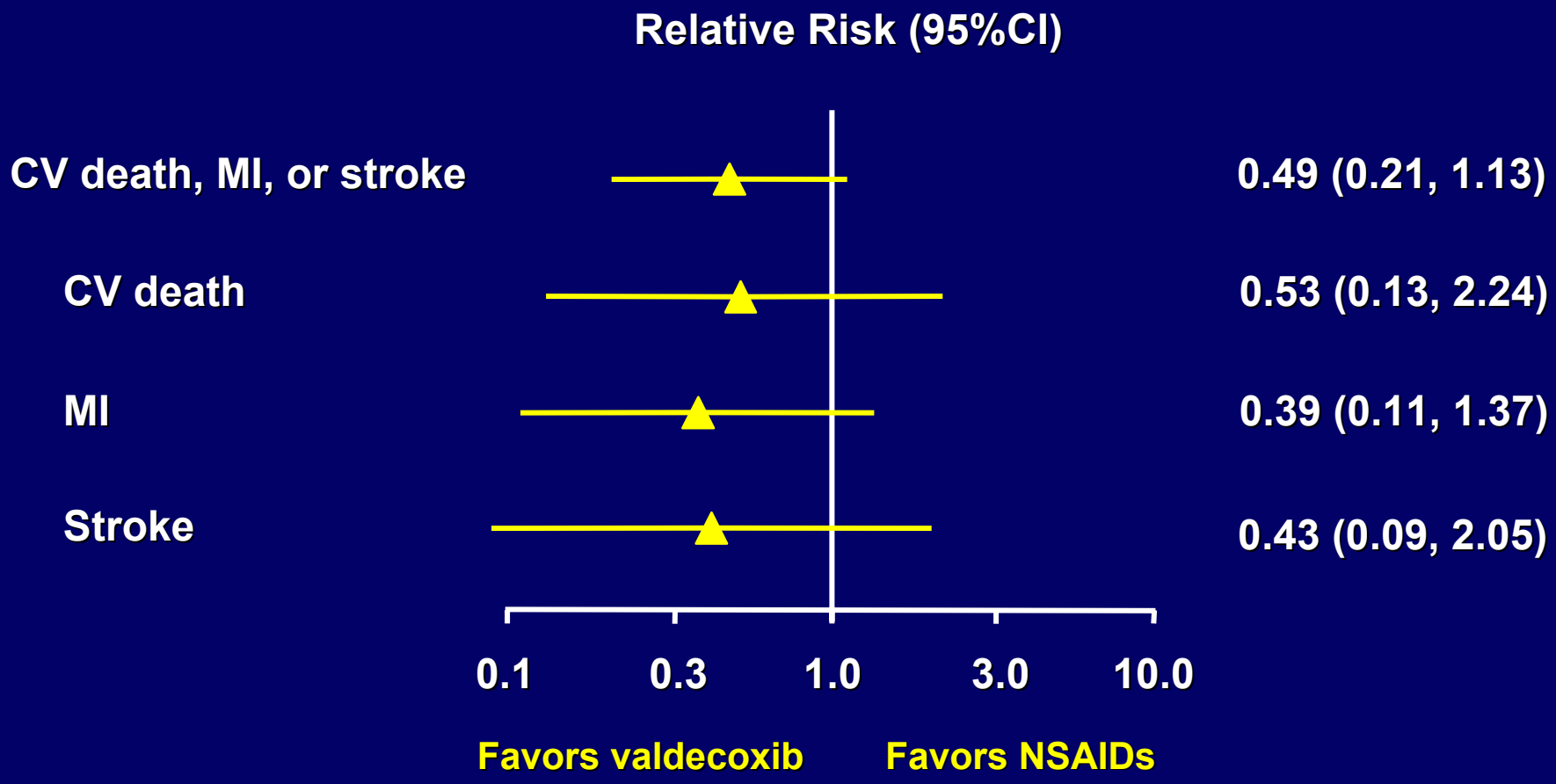
Valdecoxib exposure
≥ 3 months – 2714 (50%) of patients
≥ 6 months – 1176 (22%) of patients
≥ 1 yr – 211 (4%) of patients

CV Death, MI and Stroke:
Valdecoxib vs NSAIDs

	Valdecoxib ≥ 10 mg N=4591	NSAIDs N=2323
Patient-years	1346	662
Mean exposure/patient (mos)	3.5	3.4
CV death, MI, stroke	11 (0.8)	10 (1.5)
CV death	3 (0.2)	3 (0.5)
MI	5 (0.4)	5 (0.8)
Stroke	3 (0.2)	3 (0.5)

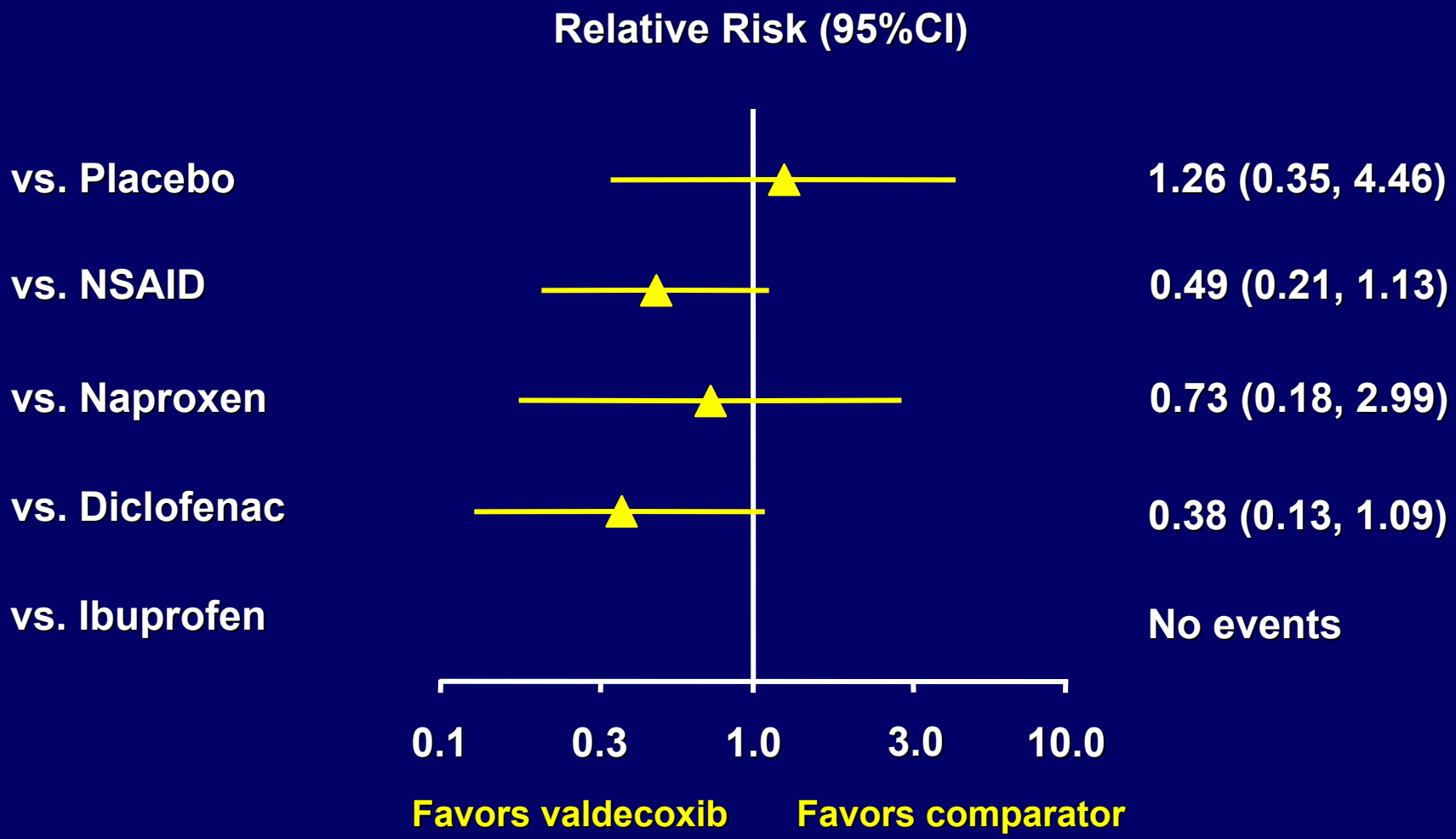
n (events per 100 patient-years)

CV Death, MI and Stroke:
Valdecoxib vs NSAIDs



Valdecoxib daily dose ≥ 10 mg

CV Death, MI and Stroke:
Valdecoxib vs Pbo, NSAIDs Combined & Individually



Valdecoxib daily dose ≥ 10 mg

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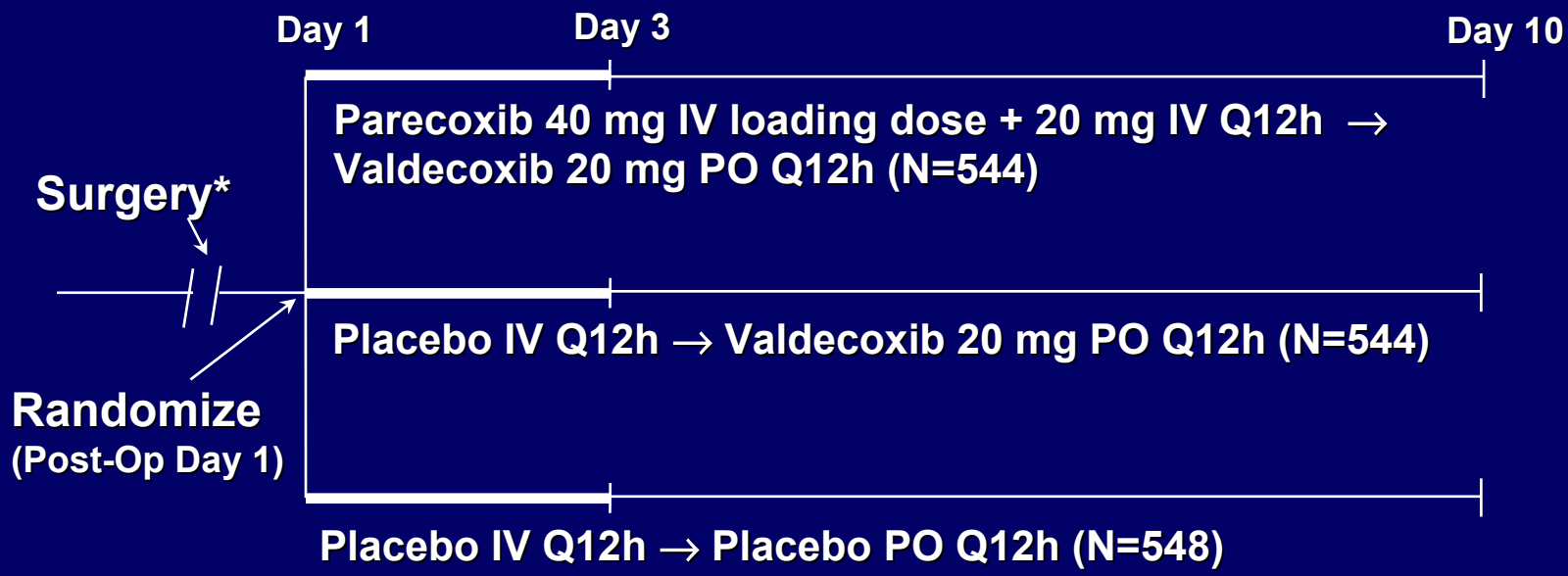
CV Safety of Valdecoxib

- Randomized controlled trials in arthritis
- Short-term acute pain studies with parecoxib followed by valdecoxib
  - Initial CABG study identified CV safety signal for parecoxib followed by valdecoxib
  - Two larger placebo-controlled studies further evaluated parecoxib + valdecoxib safety in CABG and General Surgery patients
  - Primary endpoints: Pre-specified adjudicated adverse events
    - CV thromboembolic events included myocardial, cerebrovascular, peripheral vascular and pulmonary embolism events

Study Design
CABG Surgery Study 071



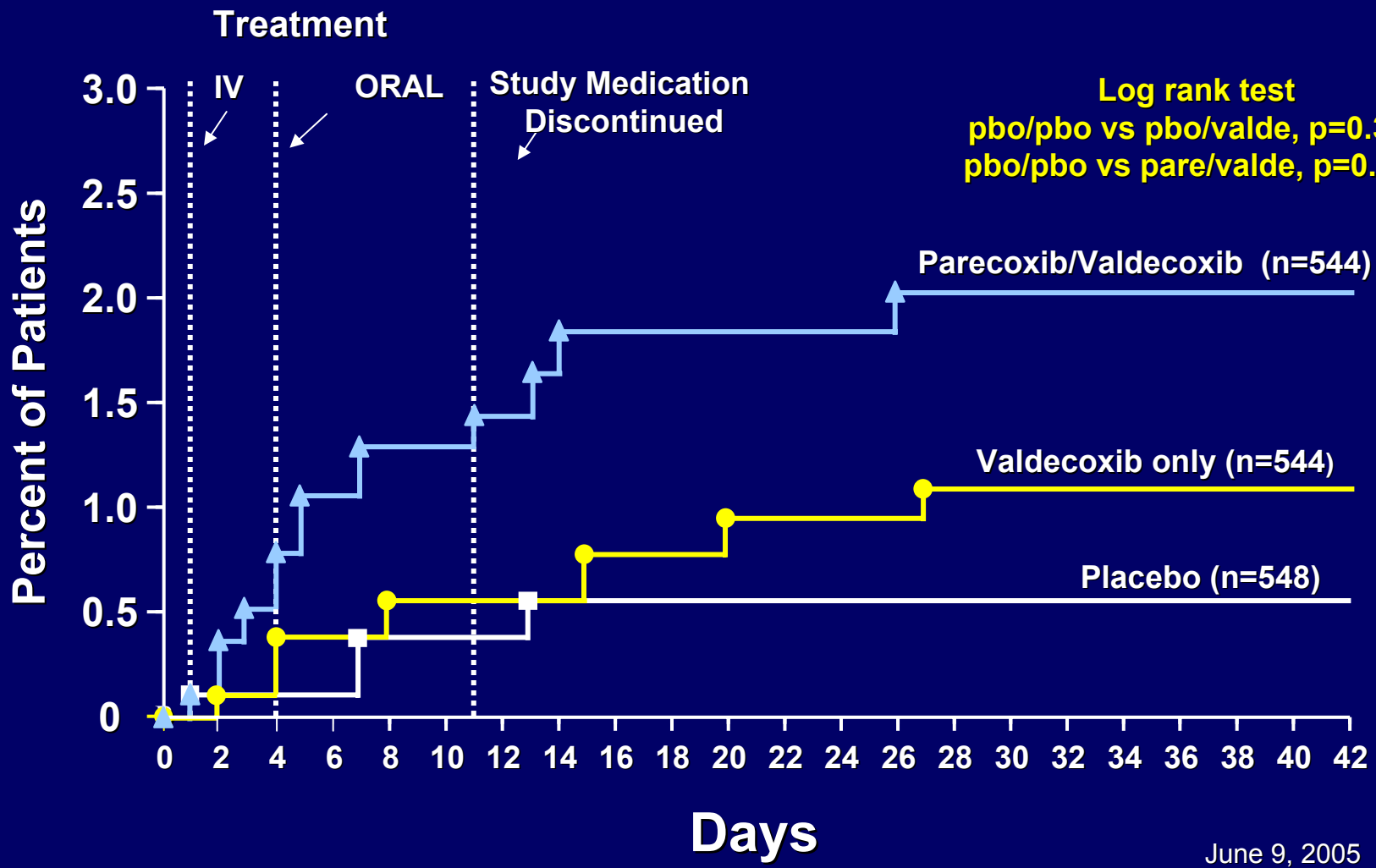
Both treatment groups receive: PRN Supplemental Analgesia (PCA morphine → oral APAP+codeine)

All patients received aspirin (75-325 mg daily)

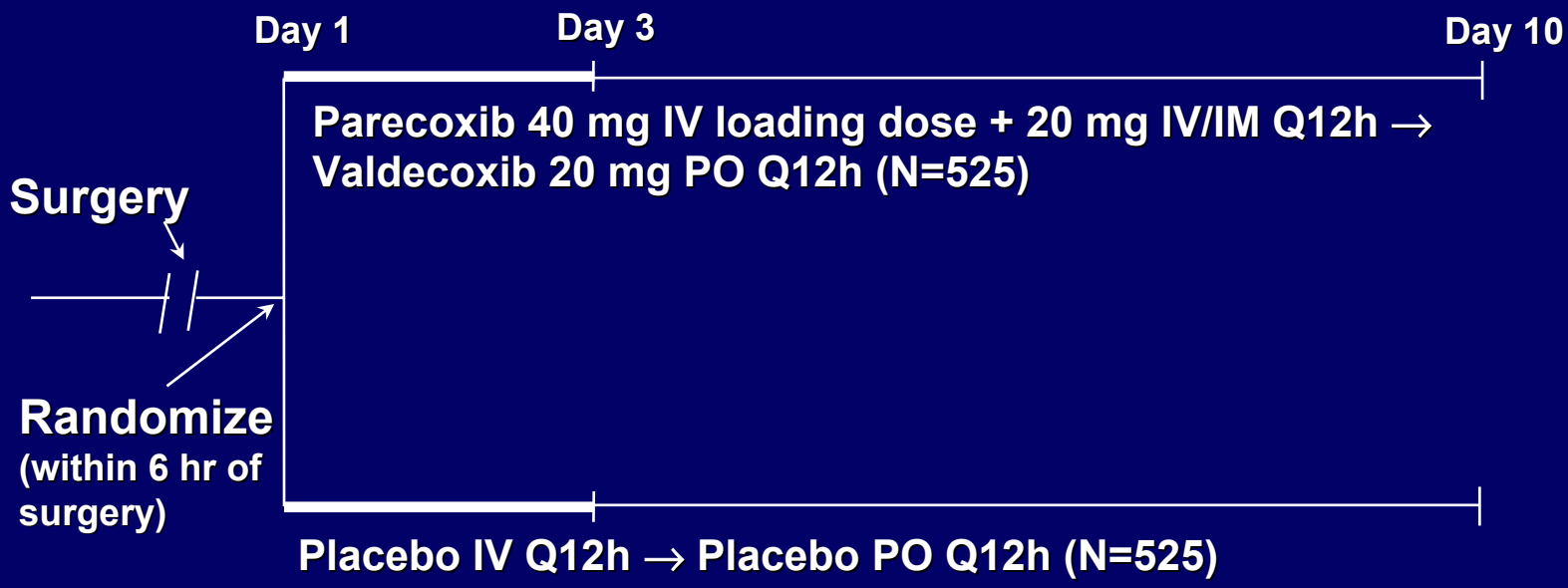
*all cases were cardiopulmonary bypass

Adjudicated Thromboembolic CV Events
CABG Surgery Study 071

Time to Event Analysis



Study Design
General Surgery Study 069



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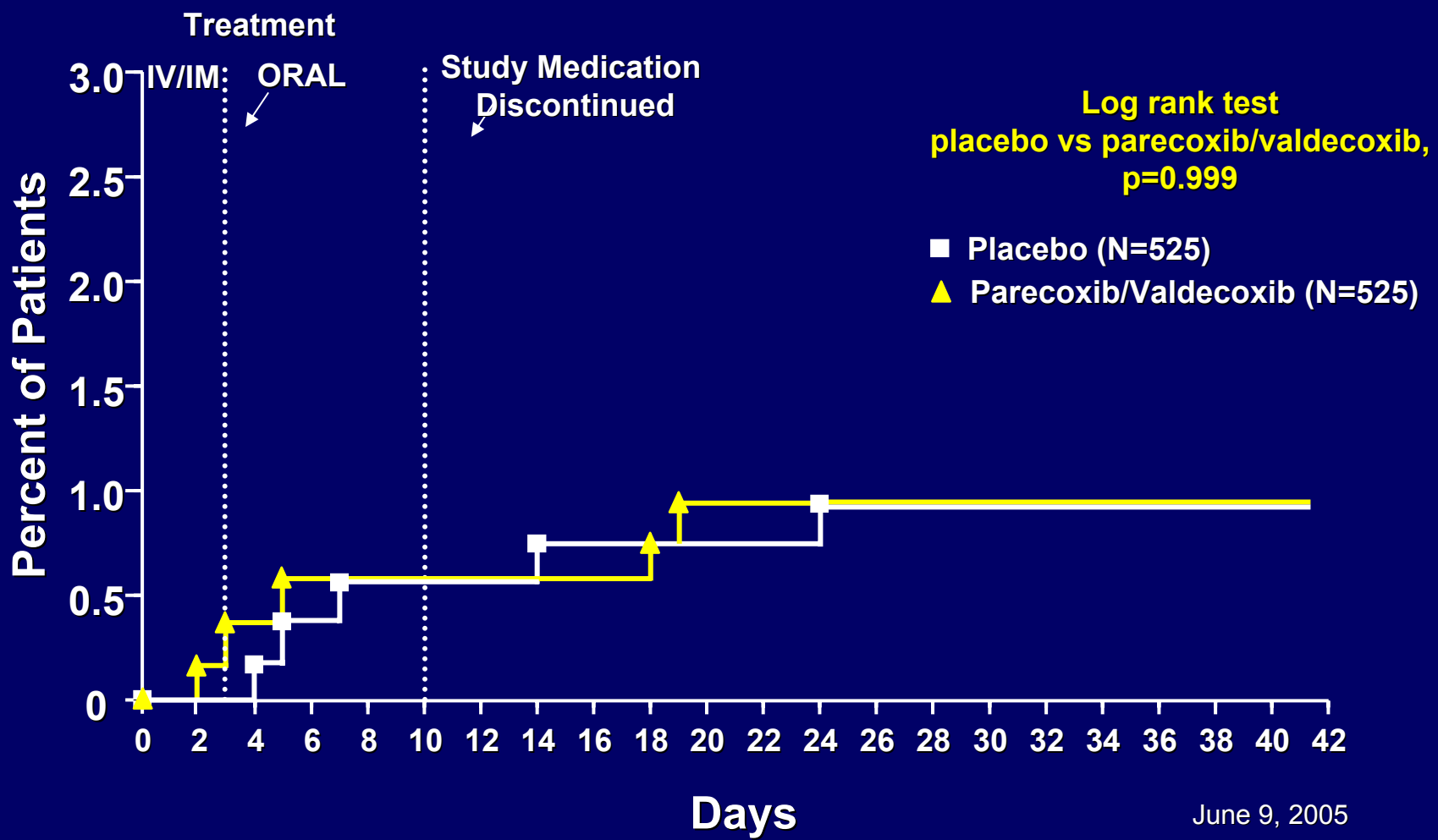
Adjudicated Thromboembolic CV Events
General Surgery Study 069

Time to Event Analysis



Valdecoxib CV Safety Conclusions

- Valdecoxib CV safety database is small relative to celecoxib; large relative to NSAIDs
- CV safety profile of valdecoxib is similar to NSAIDs for up to 6 months
- CV signal in high risk CABG surgery setting does not extrapolate to the general surgery or arthritis populations
- Limited data to evaluate the effects of NSAIDs in CABG surgery setting

Spontaneous SCAR Reports with Valdecoxib

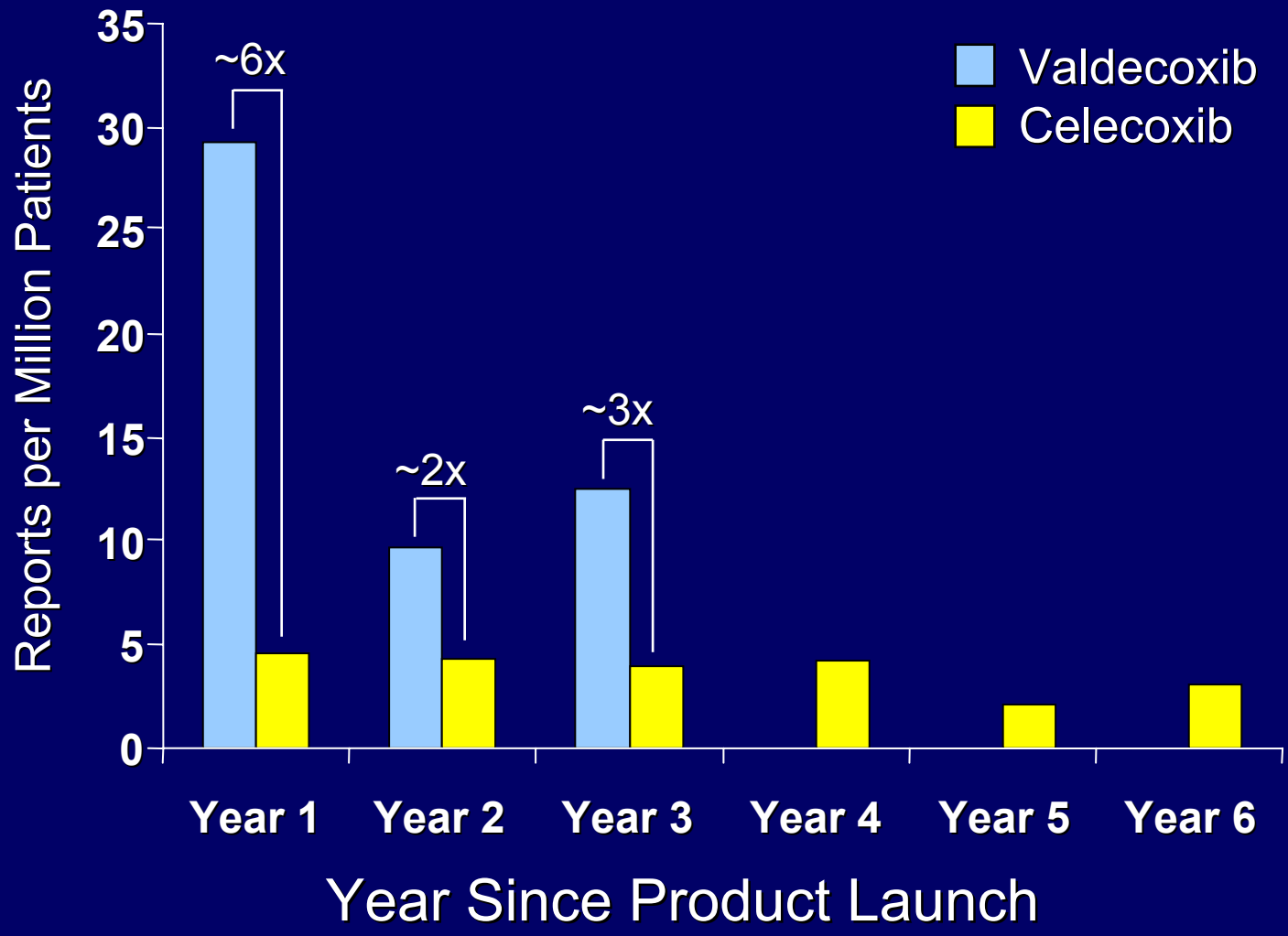
- SCAR Classification
  - Erythema Multiforme
  - Stevens-Johnson Syndrome
  - Toxic Epidermal Necrolysis
  - + (Exfoliative Dermatitis)
- As of 15 March 2005
  - estimated 12.9 million patients exposed
  - 227 total reports of SCAR
  - 188 reports of SCAR from HCP
  - 10 SCAR-related deaths

Valdecoxib: SCAR Reports
Safety Database Analysis

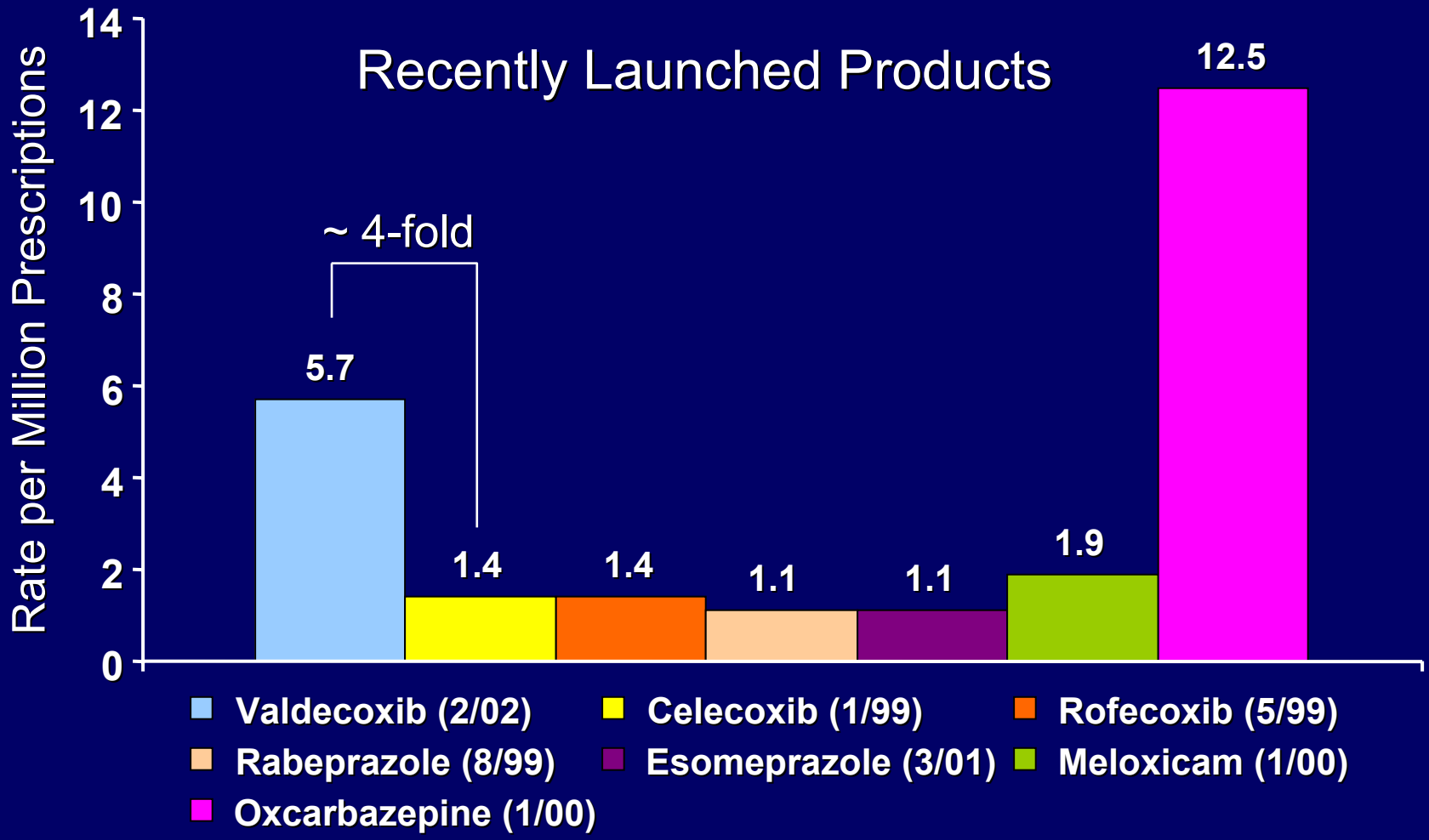
- Most reports occur early during the course of therapy
  - ~90% ≤1 month
  - 8 of 10 deaths within 20 days of starting treatment; 2 onset unknown
- 11% of reports in sulfonamide allergic patients
- 13% of reports in patients with history of drug allergy other than sulfonamide
- 11% of reports recorded with another suspect drug (anti-convulsant, MTX, NSAID)

HCP-Reported SCAR

Annual Reporting Rates

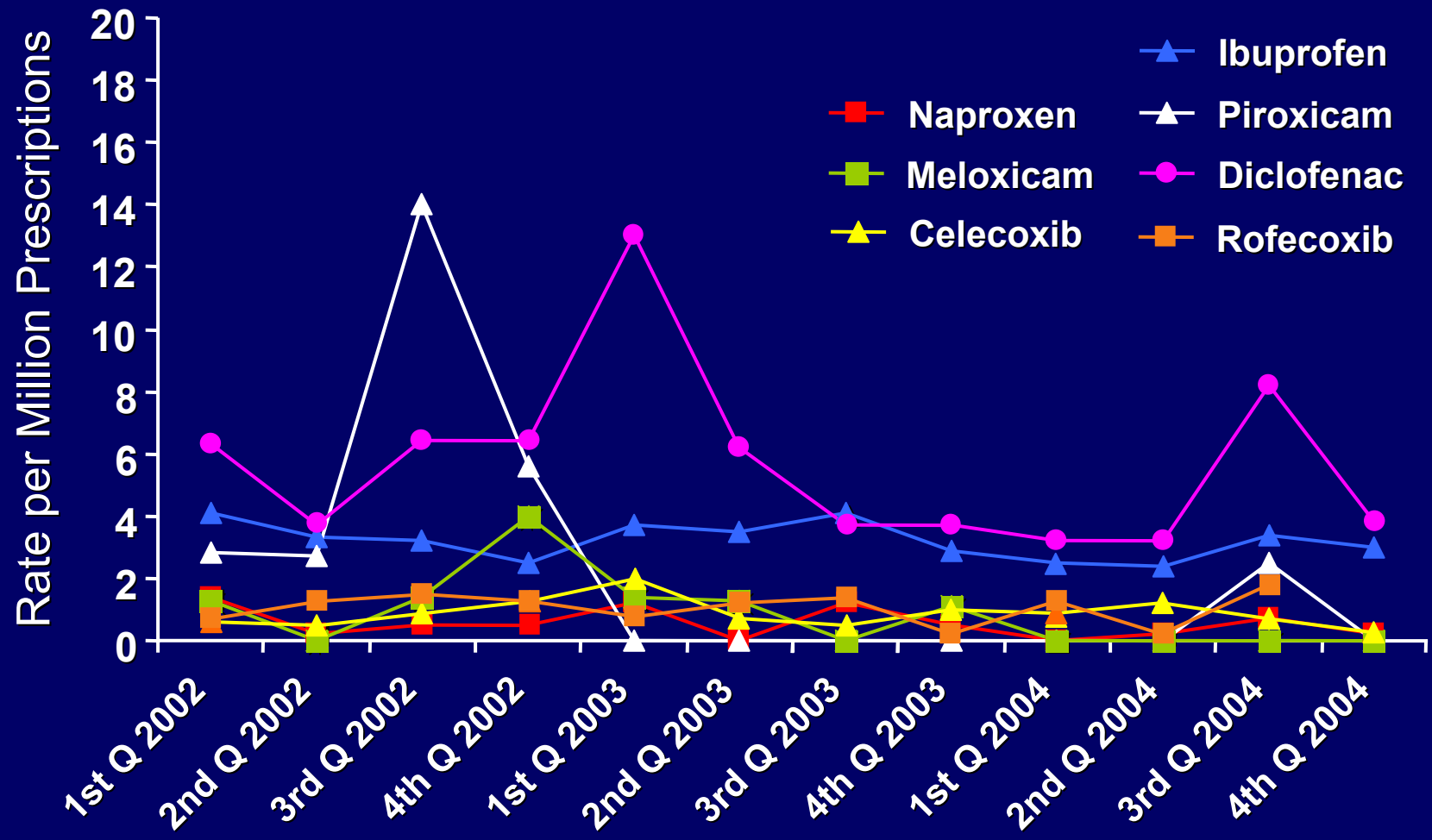


SCAR Reporting Rates from FDA AERS:
Cumulative Reporting Rates Since Product Launch



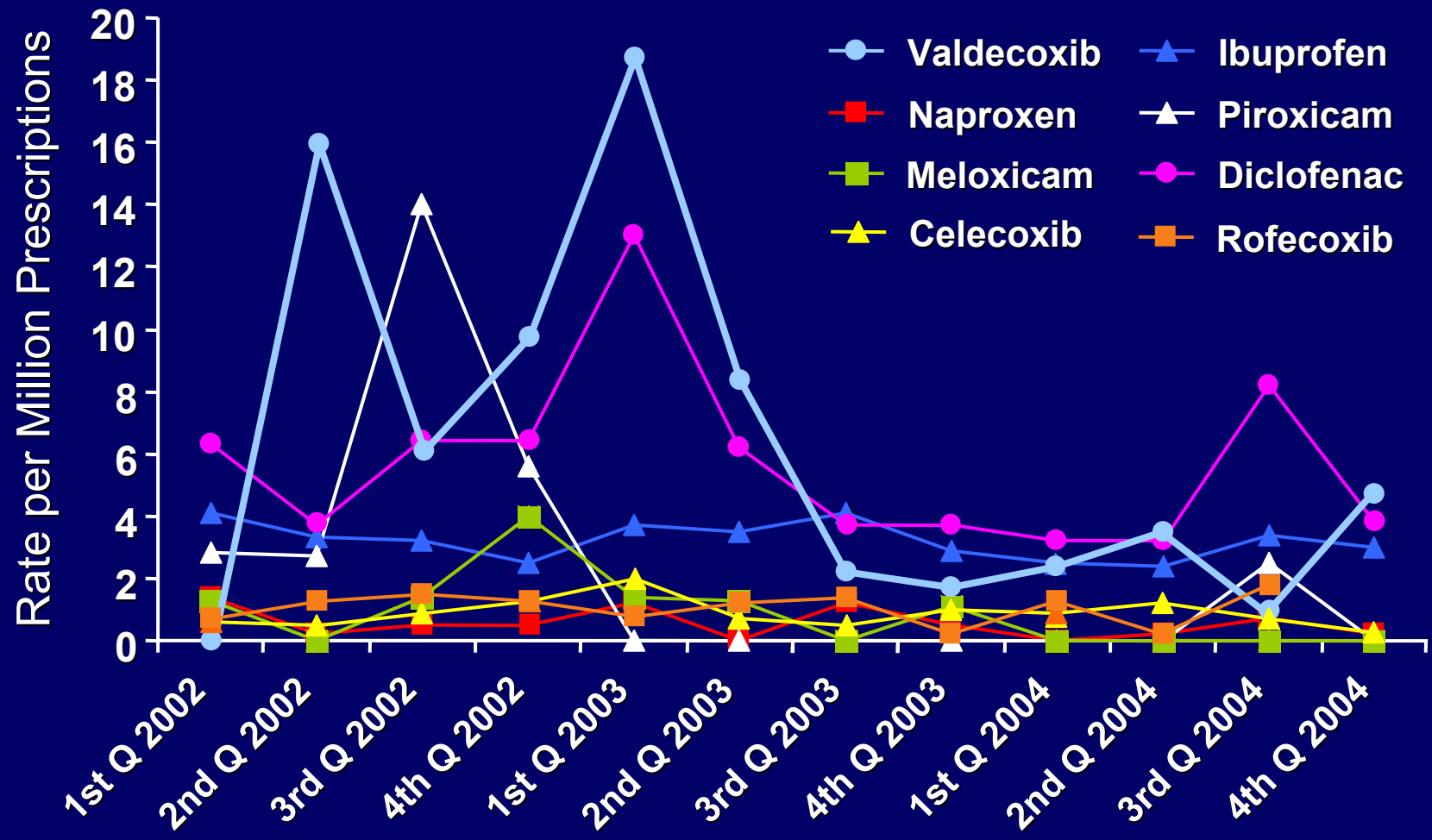
Adverse Event Reporting System, US FDA (launch date)

SCAR Reporting Rates from FDA AERS:
Reporting Rates by Quarter



Adverse Event Reporting System, US FDA

SCAR Reporting Rates from FDA AERS:
Reporting Rates by Quarter – Valdecoxib



Adverse Event Reporting System, US FDA

June 9, 2005

Conclusions

- The cumulative SCAR reporting rate with valdecoxib is higher than other COX-2 selective inhibitors;
  - only marginally worse than some other NSAIDs
  - dropped substantially since Year 1
  - excess attributable risk = 2 –10 per million

Future Action

- Pfizer is committed to continuing discussions with Health Canada and regulators worldwide to evaluate ways to make valdecoxib available to patients who really need it.