

Combined Analysis of Osteoarthritis Trials

• Types of Osteoarthritis

• Meta-analysis of randomised trials (RCTs)

• Cohort studies

• Case reports

• Systematic reviews

Sensitivity analyses

• Meta-analysis of RCTs

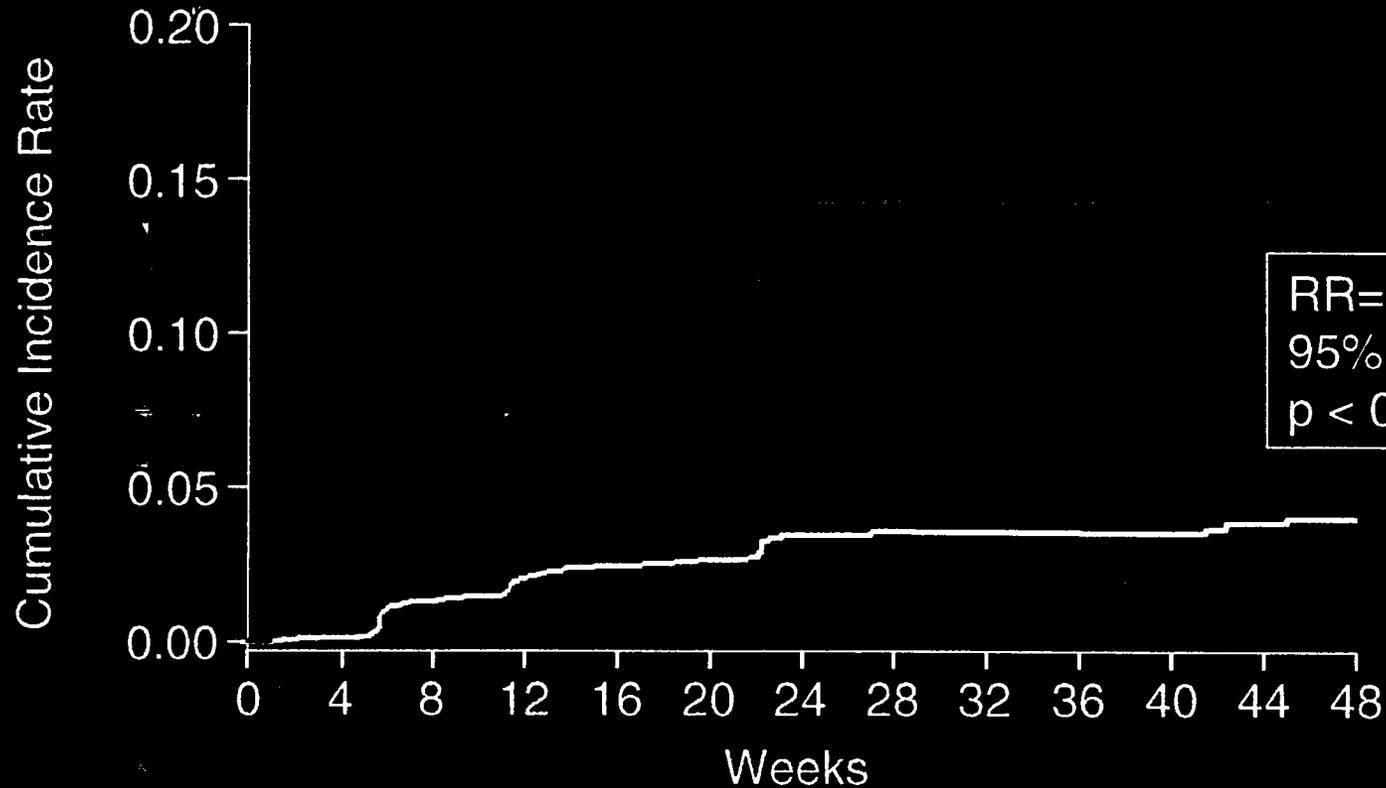
Rationale for Including Endoscopy Studies

- Substantial exposure to test drug
 - 28% of total patients
 - 53% of rofecoxib 50 mg patient-years
 - 68% of ibuprofen patient-years

Counting “PUBs” in Endoscopy Studies

- Assessment of PUBs biased against rofecoxib in endoscopy studies:
 - Treatment discontinued for ulcers $\geq 3\text{mm}$
Prevents progression to PUB
 - Risk factors for endoscopic ulcer and PUB are similar, e.g., history of PUB
 - This bias remains in combined analyses
- Must separate “endoscopic” ulcers [surveillance] from symptomatic clinical ulcers

Observed Events: Endoscopic Ulcers, P_UBs (=Symptomatic Ulcers + P_OBs)



Scheduled Endoscopies

X

X

X

—

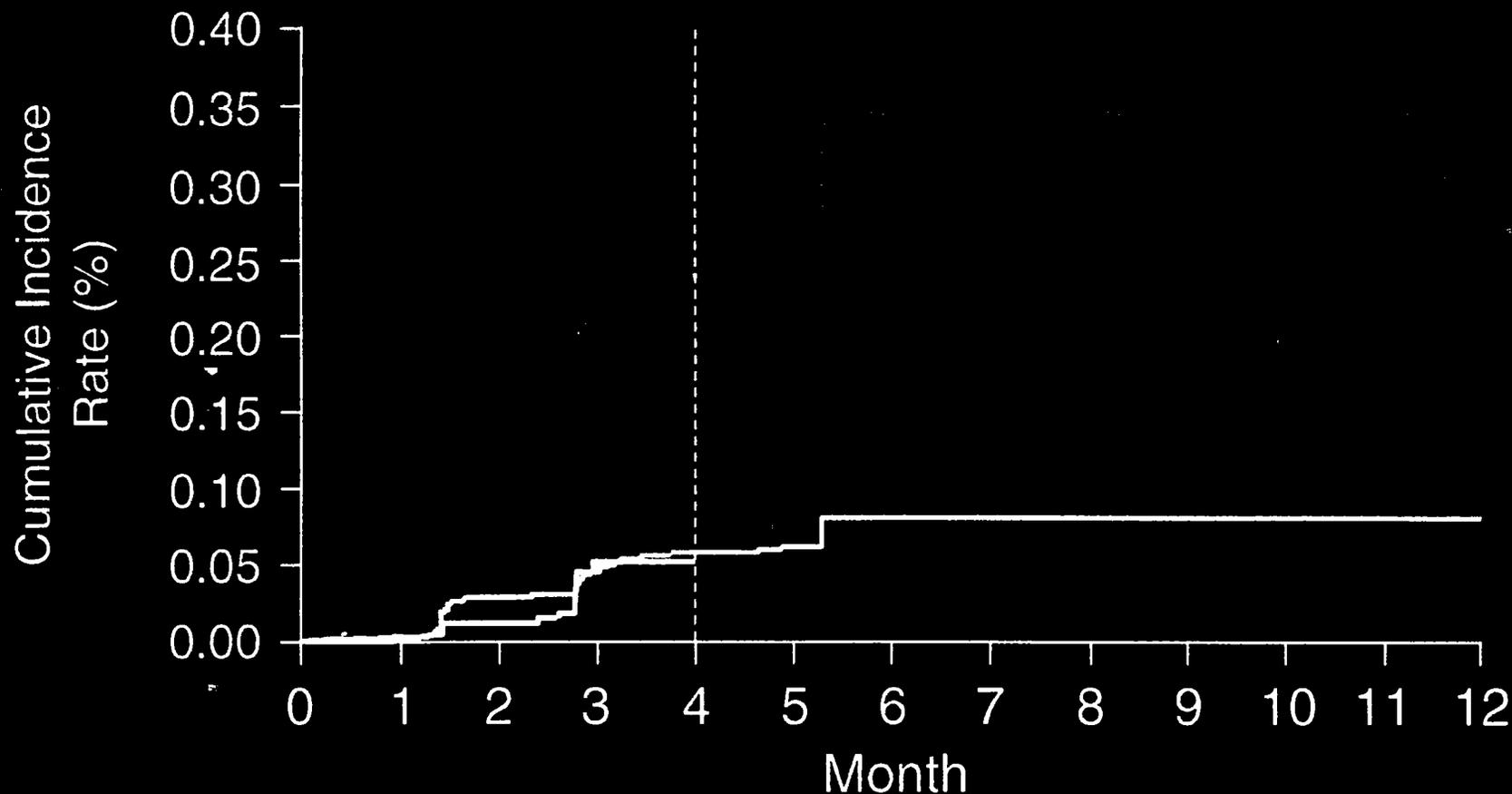
Rofecoxib

--- NSAID Comparators

Protocol 069

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Observed Events: Endoscopic Ulcers, PUBs (=Symptomatic Ulcers + POBs), Placebo Controlled Studies



— Rofecoxib N=1701

NSAID N= 847

— Placebo N= 514

Protocols 033, 040, 44, 045

Prespecified Exclusion Windows

- Purpose: eliminate endoscopic ulcers from PUB end point, by an objective method

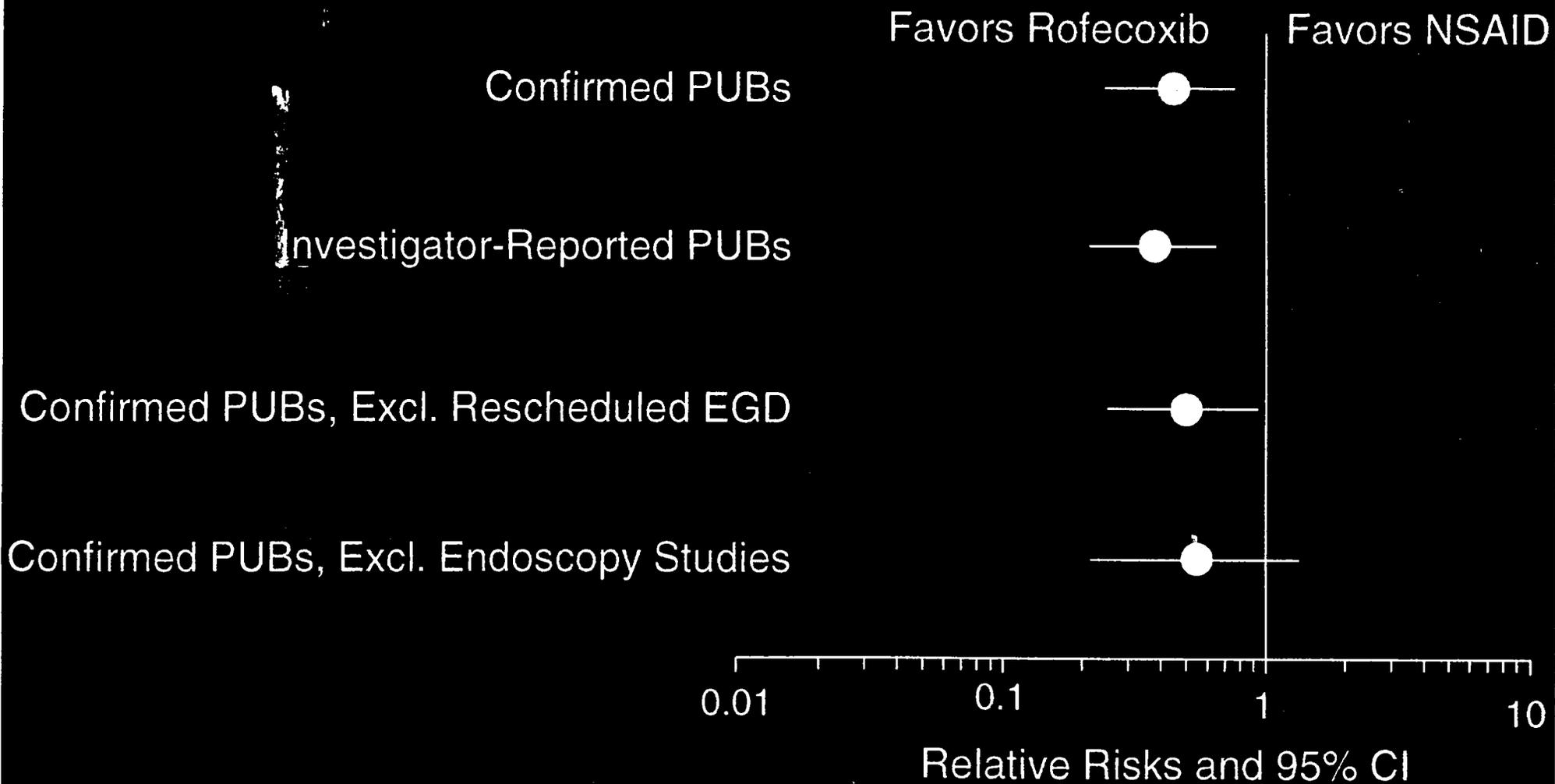


- Adverse experiences of POB always *included*
- Limitation: introduces error
 - Removes symptomatic clinical ulcers inside window
 - Windows may have been enriched for symptomatic ulcers

Rescheduled Endoscopies

- Endoscopy outside of exclusion window
 - GI sign or symptom, discontinuation for non-GI adverse event, rescheduled for administrative reason
- Planned analyses include all ulcers found outside of exclusion window, regardless of reason for procedure
 - No subjective determination of reason for endoscopy by investigator or sponsor
 - All ulcers outside scheduled time point assumed found for clinical cause
- Sensitivity analysis after removing “rescheduled endoscopies” (EGD)
 - Discontinuation due to non-GI adverse event, administrative

Consistency of Relative Risk: Rofecoxib vs. NSAIDs



Conclusions - Predefined Analyses of PUBs

- In predefined analyses, the incidence of PUBs (symptomatic ulcers + POBs) is lower with rofecoxib than with NSAIDs
 - Sensitivity analyses consistent

Combined Analysis of Osteoarthritis Trials

• Review of literature

• Particular concerns, biases (POBs)

• Database

• Search

• Predefined analysis

• Sensitivity analysis

Post hoc analyses of POBs

Spectrum of NSAID-Induced Upper GI Injury

• Ulcers (≥ 5 mm) detected during endoscopic surveillance

• Hemorrhagic ulcers

• Gastric mucosal disease

“PUB”

- Ulcer complications: Perforations (rare), obstructions (rare), bleeding [“POB”]

Patients with Perforation, Obstruction, or Bleed N=18

- 17 bleeds
 - 9 confirmed
 - 5 complicated
 - 8 Unconfirmed
 - 3 complicated
- 1 gastric outlet obstruction
- No perforations

Confirmed, Complicated Upper GI Bleeds

Cumulative Number of Events (Crude %)

Treatment	Up to 4 months	Up to 6 months	Up to 12 months
Rofecoxib N=3357	1 (0.03%)	1 (0.03%)	2 (0.06%)
NSAID N=1564	2 (0.13%)	3 (0.19%)	3 (0.19%)
Placebo N=514	0	--	--

Confirmed, Complicated POBs

Cumulative Number of Events (Crude %)

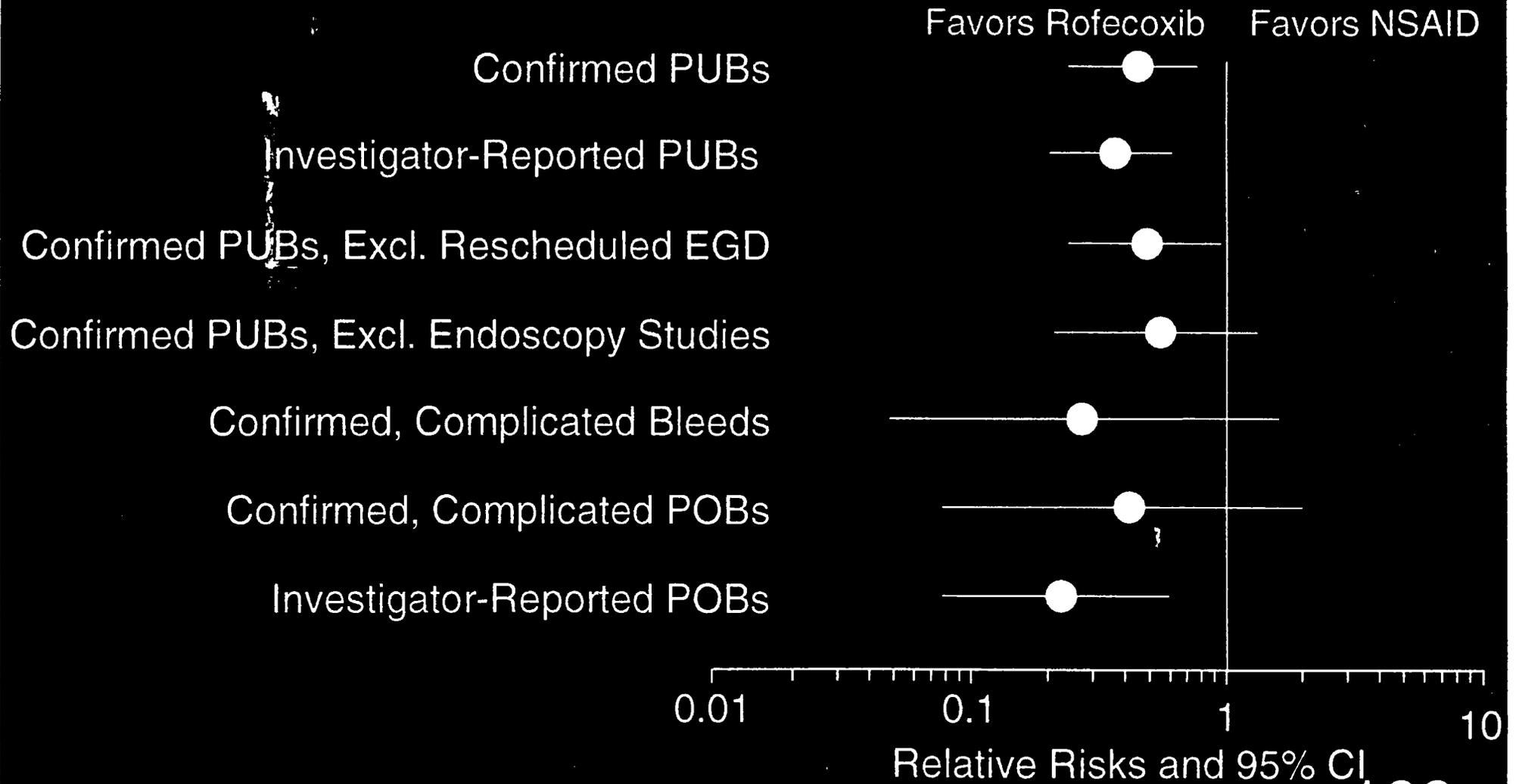
Treatment	Up to 4 months	Up to 6 months	Up to 12 months
Rofecoxib N=3357	1 (0.03%)	2 (0.06%)	3 (0.09%)
NSAID N=1564	2 (0.13%)	3 (0.19%)	3 (0.19%)
Placebo N=514	0	--	--

Investigator-Reported POBs

Cumulative Number of Events (Crude %)

Treatment	Up to 4 months	Up to 6 months	Up to 12 months
Rofecoxib N=3357	4 (0.12%)	5 (0.15%)	6 (0.18%)
NSAID N=1564	8 (0.51%)	11 (0.70%)	11 (0.70%)
Placebo N=514	1 (0.19%)	--	--

Consistency of Relative Risk: Rofecoxib vs. NSAIDs



Overall Conclusions - Combined Analysis, OA Studies

- UGI Symptoms (spontaneous adverse events)
 - Placebo < rofecoxib < NSAID comparators
- Combined Analyses of OA Studies
 - Perforations, symptomatic ulcers, bleeds
 - Superior to NSAID comparators (predefined)
 - Perforation, obstruction, bleed (investigator-reported)
 - Superior to NSAID comparators
- Observed magnitudes of risk reduction probably underestimate the clinical advantage of rofecoxib, due to methodology

Key Results of GI Studies

- Combined estimates of difference vs placebo for endoscopic gastroduodenal ulcer
 - Rofecoxib 25 mg: approximately 2.5% below placebo
 - met pre-specified equivalence criteria
 - Rofecoxib 50 mg: 1% above placebo
 - Ibuprofen: 21% above placebo
- Statistically significant risk reduction for PUBs vs. comparator NSAIDs

Conclusion

- Gastrointestinal safety of rofecoxib differentiated from nonspecific NSAID
 - Biochemical, clinical evaluation of gastrointestinal safety
 - Superiority to NSAIDs at equally efficacious doses
 - Endoscopy, special GI safety studies, PUBs, UGI symptom adverse events
 - Corroborated by analysis of POBs
 - Statistical equivalence to placebo
 - Red blood cell loss, intestinal permeability
 - Endoscopic gastroduodenal ulcers

Rofecoxib: General Safety and Tolerability

General Safety & Tolerability Overview of the Presentation

- Safety Database
- General Safety Overview
 - Rofecoxib 12.5 and 25 mg
 - Rofecoxib 50 mg
- Specific topics
 - Renal
 - Liver
 - Cardiovascular

Safety Database

Exposure & Patient Population

- Large safety database approximately 10,000 patients/subjects
 - 5435 patients/subjects received rofecoxib
- Primary Osteoarthritis studies - 5431 patients
 - 3595 patients rofecoxib (all doses)
 - 1385 for 6 months or longer; 818 for 1 year or longer
 - 1565 patients NSAIDs
- Many elderly patients were treated with rofecoxib
 - 1881 patients > 65 years of age, 406 patients > 75 years
 - Octogenarian study
 - 341 total patients
 - 61 patients on rofecoxib used cardioprotective low dose ASA

General AE Profile of Rofecoxib

Clinical AE's 6 Week Osteoarthritis Studies

Incidence of 3.0% in Any Treatment Group

Adverse Experience	Placebo	Rofecoxib		Ibuprofen
	N=412 %	12.5 mg N=725 %	25 mg N=735 %	2400 mg N=470 %
Headache	6.3	2.2	4.5	4.3
Upper resp. inf.	5.8	5.0	5.9	2.8
Diarrhea	5.8	4.6	5.7	4.9
Abdominal pain	1.7	2.1	3.0	3.8
Dyspepsia	1.5	1.8	2.6	3.8 *
Epigastric discomfort	0.0	2.2 *	2.9 *	5.3 *
Nausea	1.9	3.7	5.0 *	4.9 *
Lower ext. edema	1.0	3.3 *	3.4 *	4.0 *

* p ≤ 0.05 vs. placebo.

Protocols 010,029,033,040,058

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