Program Goal

- Differentiate the gastrointestinal safety of rofecoxib from nonspecific NSAID
  - Biochemical, clinical evaluation of gastrointestinal safety
  - Compare to placebo for statistical equivalence (gastroduodenal ulcers)
  - Compare to NSAIDs for statistical superiority, at equally efficacious doses

Rofecoxib GI Safety Program

COX-2 Biochemistry *in vivo*

- Human Blood Cells
- Gastric Mucosa

COX-2 Biochemistry *in vivo*

- Human Blood Cells
- Gastric Mucosa

Combined GI, Efficacy Studies In OA Patients

- Upper GI Symptoms
- Upper GI Clinical Events (Prespecified Clinical Outcomes)

Key Results of GI Studies

- Combined estimates of difference vs. placebo for endoscopic gastroduodenal ulcer
  - Rofecoxib 25 mg: approximately 2.5% below placebo

    met prespecified equivalence criteria
  - Rofecoxib 50 mg: 1% above placebo
  - Ibuprofen: 21% above placebo
- Statistically significant risk reduction for PUBs vs. comparator NSAIDs

Placebo Controlled GI Studies

- Upper GI endoscopy - placebo controlled studies
  - 7-day treatment in healthy volunteers

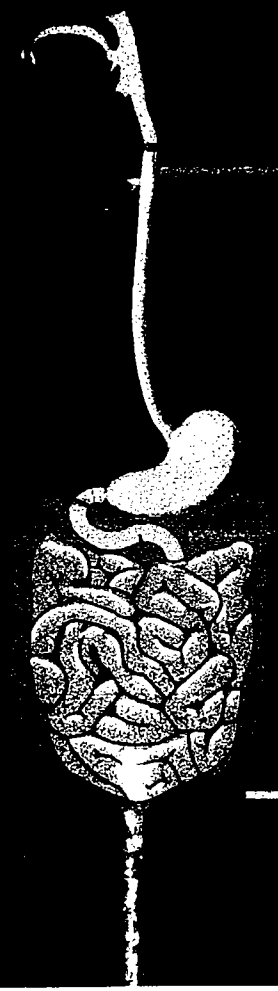
    250 mg once daily
  - 6-month treatment in osteoarthritis patients

    25 mg and 50 mg once daily
- Special GI safety studies
  - 25 mg and 50 mg once daily

    Intestinal permeability

    Fecal red blood cell loss

Extent of Investigation



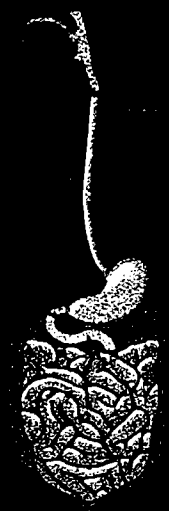
Upper Endoscopy

Intestinal Permeability

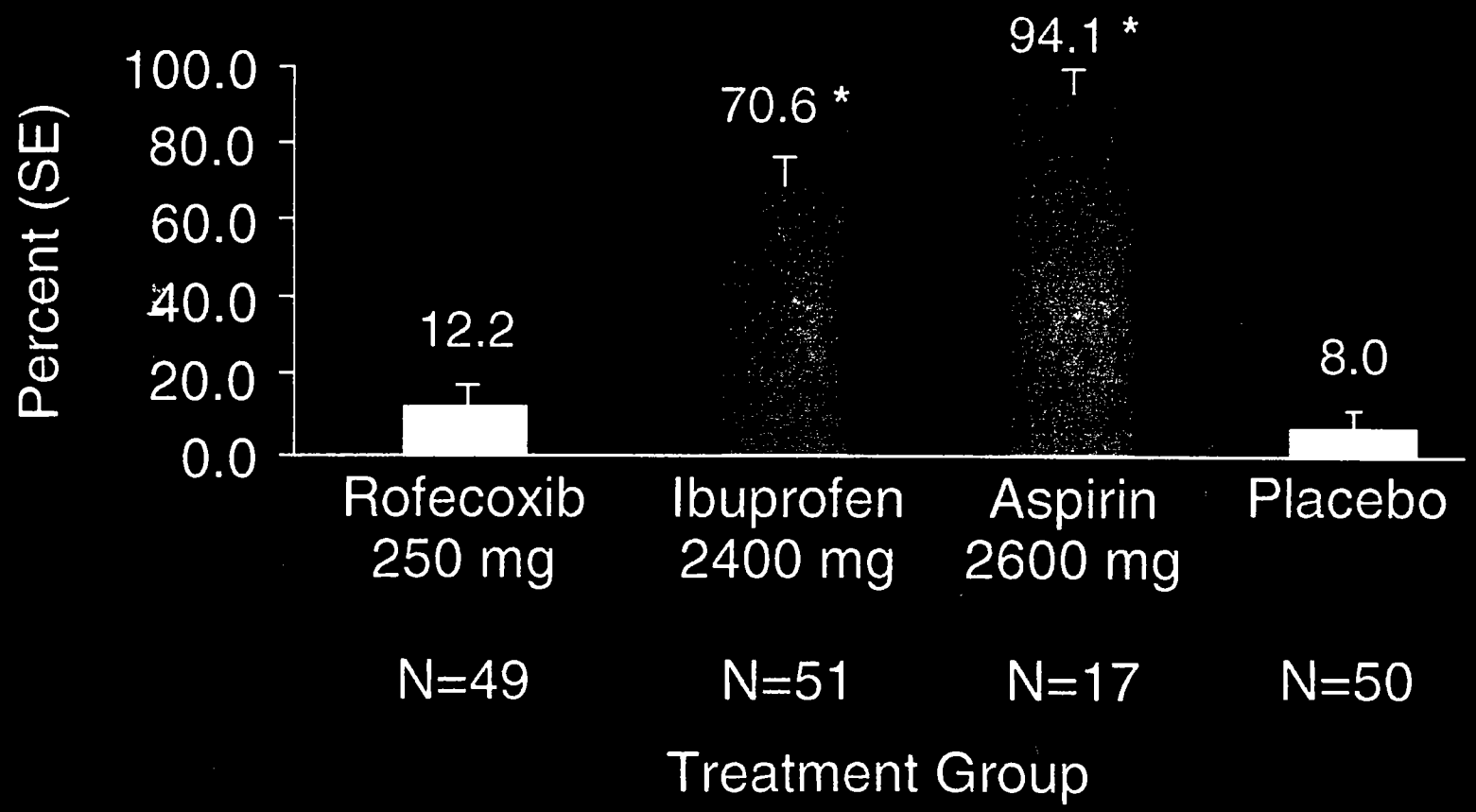
Fecal Red Blood Cell Loss

7-Day Placebo-Controlled Endoscopy Study

(250 mg)



Endoscopy in Healthy Subjects



*p < 0.001 vs. placebo and rofecoxib.

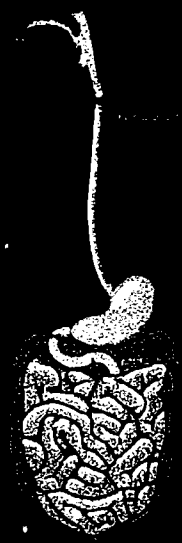
Protocol 009

Conclusions - 7-Day Endoscopy Study

- Rofecoxib 250 mg once daily was superior to ibuprofen 800 mg three times daily and aspirin 650 mg four times daily
- Rofecoxib 250 mg once daily (10 to 20 times the therapeutic dose) was similar to placebo

Two 6-Month Placebo-Controlled Endoscopy Studies in Osteoarthritis Patients

(25 mg and 50 mg)



Relationship Between Endoscopic Studies and Clinical Outcome Studies

Intervention	Endoscopy Studies	Clinical Outcome Studies
• H_2 receptor antagonists	↓ Duodenal ulcer recurrence	↓ Duodenal ulcer rebleeding
• *Helicobacter pylori* eradication	↓ Duodenal ulcer recurrence	↓ Duodenal ulcer rebleeding
• Oral prostaglandin with NSAIDs	↓ Endoscopic gastroduodenal ulcer	↓ Upper GI complication

Hypotheses

In each trial:

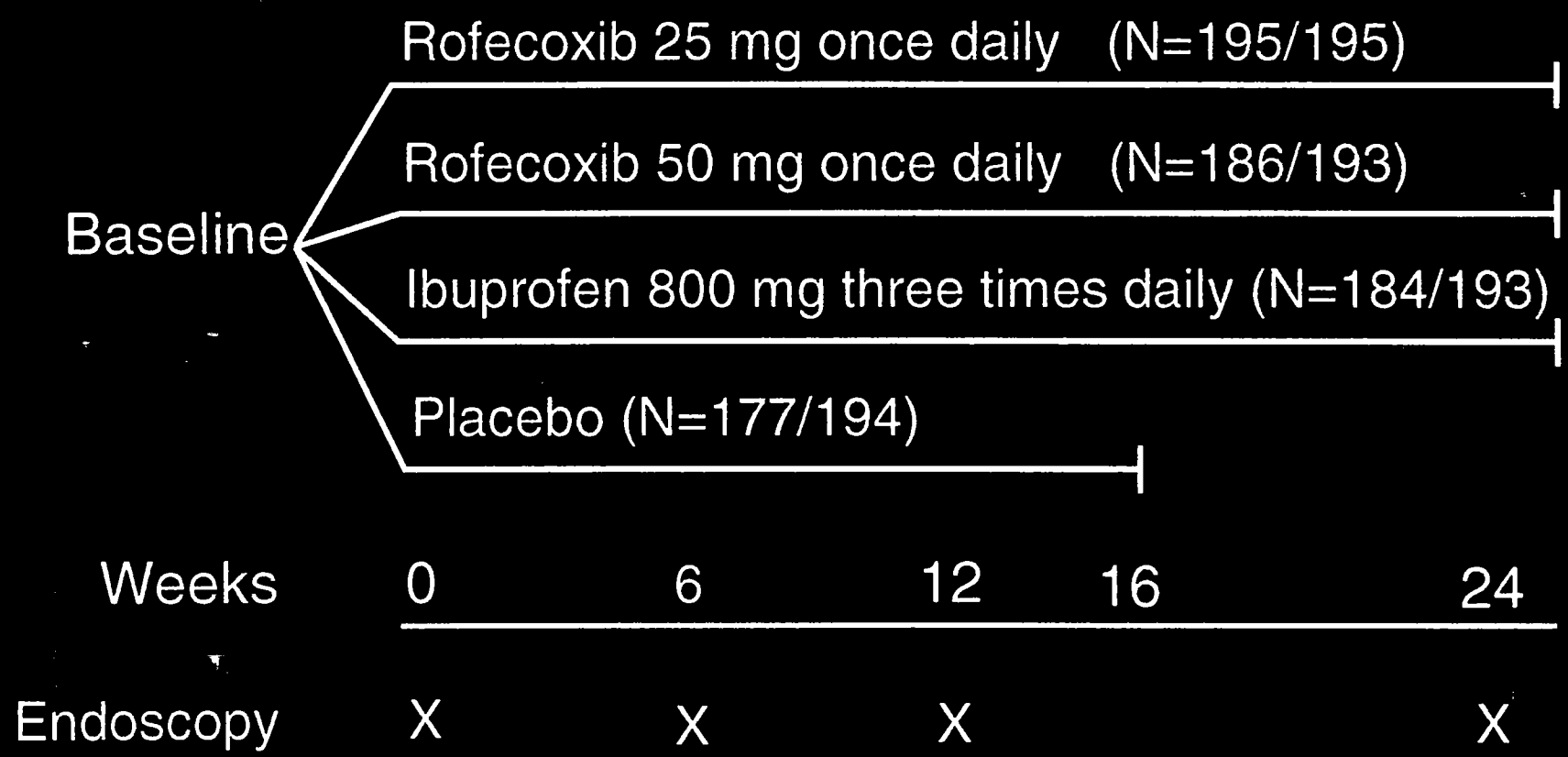
- Rofecoxib 25 mg once daily will be superior to ibuprofen 800 mg three times daily (gastroduodenal ulcers ≥ 3 mm, after 12 weeks)

Combined trials (predefined analysis):

- Rofecoxib 25 mg once daily and placebo will be statistically equivalent with respect to ulcer incidence (gastroduodenal ulcers ≥ 3 mm, after 12 weeks)
  - Upper bound of one-sided 95% confidence limit on difference < 4.0 percentage points

Protocols 044 and 045

Study Design



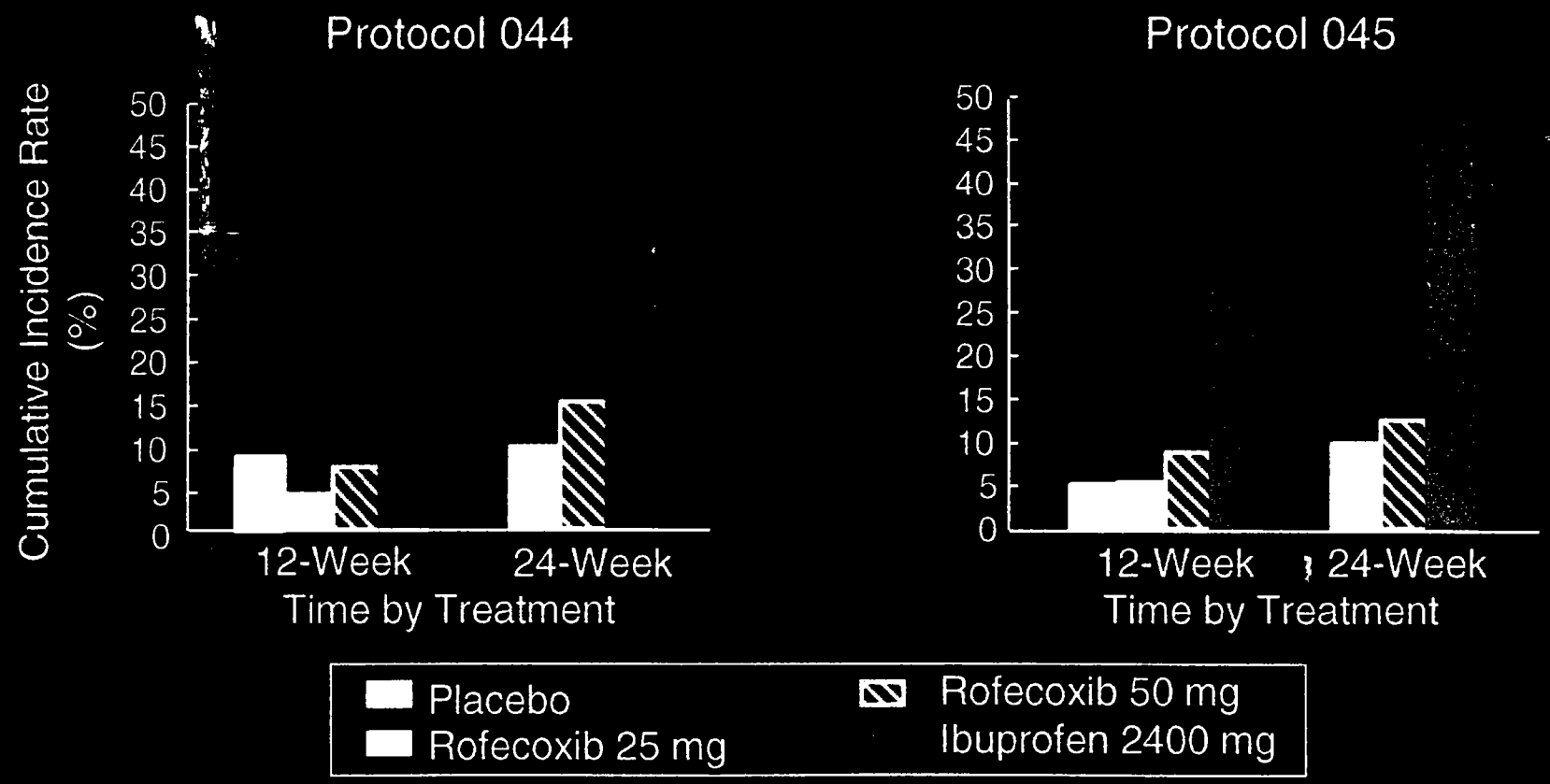
Protocols 044 and 045

Rofecoxib vs. Ibuprofen: Study Populations at Baseline

Category	Protocol 044	Protocol 045	Combined 044/045
Randomized patients	741	775	1516
Female (%)	67	75	71
Male (%)	33	25	29
Mean age (years)	62	62	62
Age range	47 to 87	49 to 88	47 to 88
Prior GI history (%)	19	11	15
H. pylori present	27	55	41
Erosions at baseline (%)	13	15	14
Prior NSAID use (%)	83	49	66

Protocols 044 and 045

Comparisons to Ibuprofen



$p < 0.001$ rofecoxib 25 mg, 50 mg, and placebo vs. ibuprofen.

Protocols 044 and 045

Conclusions - Rofecoxib vs. Ibuprofen

In each of two studies:

- Rofecoxib 25 mg once daily and 50 mg once daily superior to ibuprofen 800 mg three times daily, at 12 and 24 weeks
  - Incidence of gastroduodenal ulcers ≥ 3 mm
  - Incidence of gastroduodenal ulcers ≥ 5 mm

Protocols 044 and 045

Rofecoxib vs. Placebo: Study Populations at Baseline

Category	[illegible]	[illegible]	Combined 044/045
Randomized patients	[illegible]	[illegible]	1516
Female (%)	[illegible]	[illegible]	71
Male (%)	[illegible]	[illegible]	29
Mean age (years)	[illegible]	[illegible]	62
Age range	[illegible]	[illegible]	47 to 88
Prior GI history (%)	[illegible]	[illegible]	15
H. pylori present	[illegible]	[illegible]	41
Erosions at baseline (%)	[illegible]	[illegible]	14
Prior NSAID use (%)	[illegible]	[illegible]	66

Protocols 044 and 045

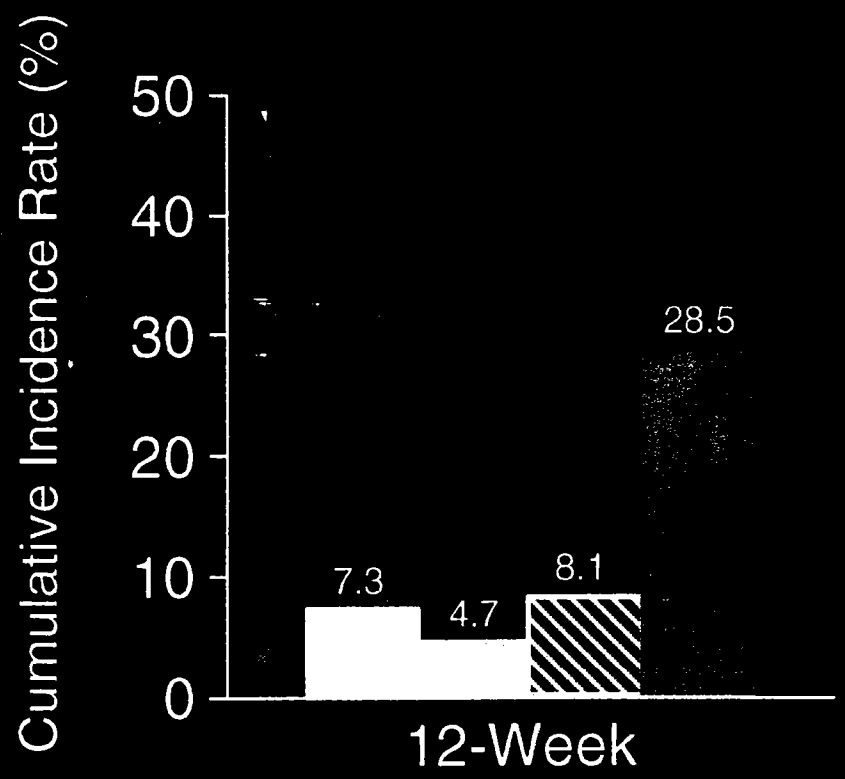
Hypothesis for Equivalence to Placebo

Prespecified analysis of gastroduodenal ulcers for protocols 044/045*

- Upper bound of the one-sided 95% confidence limit of the difference between rofecoxib and placebo will be < 4.0 percentage points

* Combined analysis, stratified by protocol.

Comparison to Placebo - Protocols 044 and 045

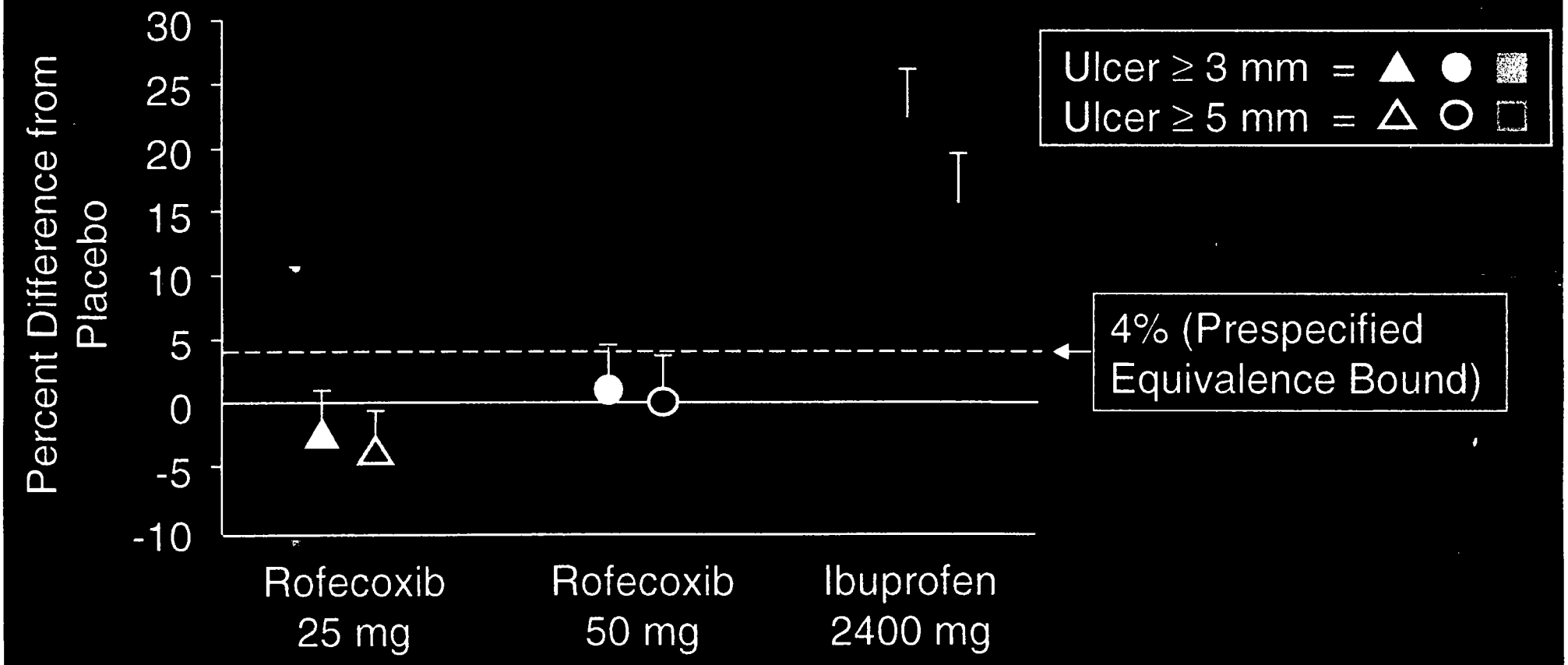


Placebo	N=340
Rofecoxib 25 mg	N=373
Rofecoxib 50 mg	N=360
Ibuprofen 2400 mg	N=354

p = 0.419 rofecoxib 25 mg vs. placebo.
p < 0.001 ibuprofen vs. rofecoxib 25 mg, 50 mg, and placebo.

Protocols 044 and 045

Prespecified Primary Comparison vs.Placebo Protocols 044 and 045 Combined



Ulceration on Placebo

- No historical precedent
- Key features of rofecoxib endoscopy studies
  - Placebo-controlled serial endoscopy
  - Prevalence of risk factors
  - Designed to minimize dropout from placebo group
    - Acetaminophen
    - Other non-ASA, non-NSAID (e.g., propoxyphene)
  - Calculations by survival method

Subgroup Analyses of Gastroduodenal Ulcer Incidence

- Similarity to placebo, superiority to ibuprofen
  - Gastroduodenal erosions at baseline
  - History of PUB
  - Age > 65
  - *Helicobacter pylori* infection

Esophageal Scoring Scale†

Score	Description
0	No mucosal abnormalities.
1	No macroscopic erosions, but erythema, hyperemia, or mucosal friability.
2	Superficial erosions involving < 10% of the mucosal surface of the last 5 cm of esophageal squamous mucosa.
3	Superficial erosions or ulceration involving 10 to 50% of the mucosal surface of the last 5 cm of esophageal squamous mucosa.
4	Deep peptic ulceration anywhere in the esophagus or confluent erosion of > 50% of the mucosal surface of the last 5 cm of esophageal squamous mucosa.

† Hetzel, et al., Gastroenterology 1988.

Protocol 044 and 045

Cumulative Incidence of Esophageal Score ≥2

(Life-Table, 12 Week)

Treatment	N		Rate (%)		Combined Rate (%) and 95% CI
	044	045	044	045	
Placebo	155	179	9.27	2.32	5.54 (2.63, 8.46)
Rofecoxib 25 mg	181	185	11.07	5.47	8.24 (5.27, 11.21)
Rofecoxib 50 mg	176	180	14.16	7.85	10.97 (7.49, 14.45)*
Ibuprofen 2400 mg	164	185	11.87	12.67	12.29 (8.30, 16.28)*

* $p < 0.05$ vs placebo.

Protocol 044 and 045

Esophageal Erosion Scores

- No prior serial endoscopic evaluation of esophagus in patients taking NSAID, or COX-2 specific inhibitor
- In combined database, rofecoxib between ibuprofen and placebo
  - Ibuprofen, rofecoxib 50 mg statistically different from placebo
- Epidemiologic relationship between NSAID and esophageal erosion uncertain
  - Not included in NSAID template warning

Conclusions - Rofecoxib vs. Placebo Endoscopy Studies

- Rofecoxib 25 mg once daily (highest therapeutic OA dose)
  - Gastroduodenal ulcers ≥ 3 mm, ≥ 5 mm

    Equivalent to placebo by prespecified criterion
- Rofecoxib 50 mg once daily (2 to 4 times the effective OA dose)
  - Gastroduodenal ulcers ≥ 3 mm

    1% above placebo
  - Gastroduodenal ulcers ≥ 5 mm

    Equivalent to placebo
- Epidemiologic significance of esophageal erosions uncertain for NSAID
  - Placebo < rofecoxib 25 mg < rofecoxib 50 mg < ibuprofen

Protocols 044 and 045