

FDA Arthritis Advisory  
Committee - April 20, 1999

VIOXX<sup>®</sup> (Rofecoxib)

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Regulatory Affairs

Merck Research Laboratories

# Proposed Indication

VIOXX<sup>®</sup> is indicated for:

- Acute and chronic treatment of the signs and symptoms of osteoarthritis
- Relief of pain
- Treatment of primary dysmenorrhea

# Major Conclusions of the Rofecoxib Development Program

- Rofecoxib is a COX-2 specific inhibitor
- Rofecoxib has efficacy comparable to NSAIDs in the treatment of both OA and acute pain
- Rofecoxib's GI safety profile is significantly superior to NSAIDs
- Rofecoxib is generally safe and well tolerated

# Agenda

## Rofecoxib – A COX-2 Specific Inhibitor

- Program Hypotheses                      Beth Seidenberg, MD
- COX-2 Specificity
- Efficacy in Osteoarthritis
- Efficacy in Acute Analgesia
  
- Human Gastrointestinal Safety        Thomas Simon, MD
  
- General Safety & Tolerability            Beth Seidenberg, MD
- Summary & Conclusions

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# Rofecoxib: A COX-2 Specific Inhibitor

## Introduction

# 1994: Hypotheses Rofecoxib Development Program

- Rofecoxib, a COX-2 specific inhibitor will be an effective anti-inflammatory and analgesic agent with a substantially reduced risk of GI toxicity
  - Efficacy will be
    - Comparable to NSAIDs
  - GI mucosal injury will be
    - Less than NSAIDs

# Rofecoxib Clinical Development Program

## Approximately 10,000 Patients/Subjects

- Clinical pharmacology
  - 36 studies
- Osteoarthritis
  - 9 Phase II/III studies
  - 4 ongoing double-blind, NSAID controlled extension studies
- Acute analgesia
  - 9 Phase II/III studies
  - 3 distinct models of pain, single and multiple dose
- Ongoing Phase III rheumatoid arthritis program

# Rofecoxib Clinical Doses

- Osteoarthritis - chronic dosing

- Primary dose 12.5 mg once daily

- Some patients may receive additional benefit from 25 mg once daily

- Acute analgesia (1 to 5 day studies)

- Primary dose 50 mg once daily

- After the first dose, some patients may receive relief from acute pain with 25 mg once daily

Rofecoxib: A COX-2 Specific Inhibitor

Specificity

# Rofecoxib Is COX-2 Specific No COX-1 Inhibition in Subjects

Phase I Study of the Effect of Rofecoxib on Platelet Function and Bleeding Time in Healthy Subjects

- Serum TxB<sub>2</sub> & bleeding time
- PG synthesis in GI biopsies
- Platelet aggregation

## Doses of Rofecoxib

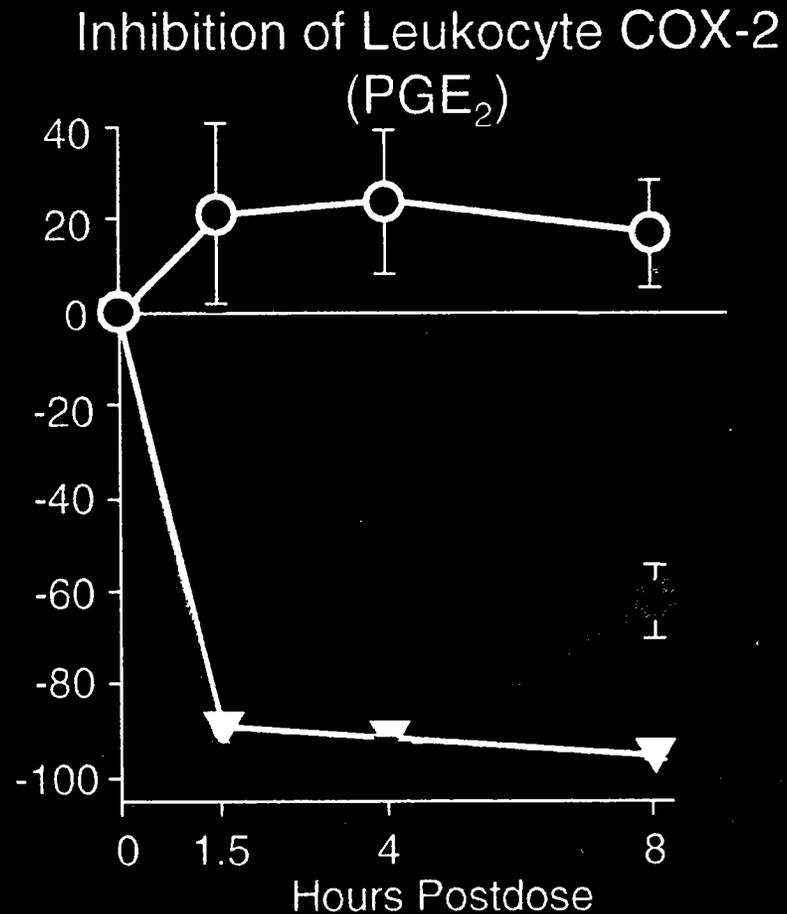
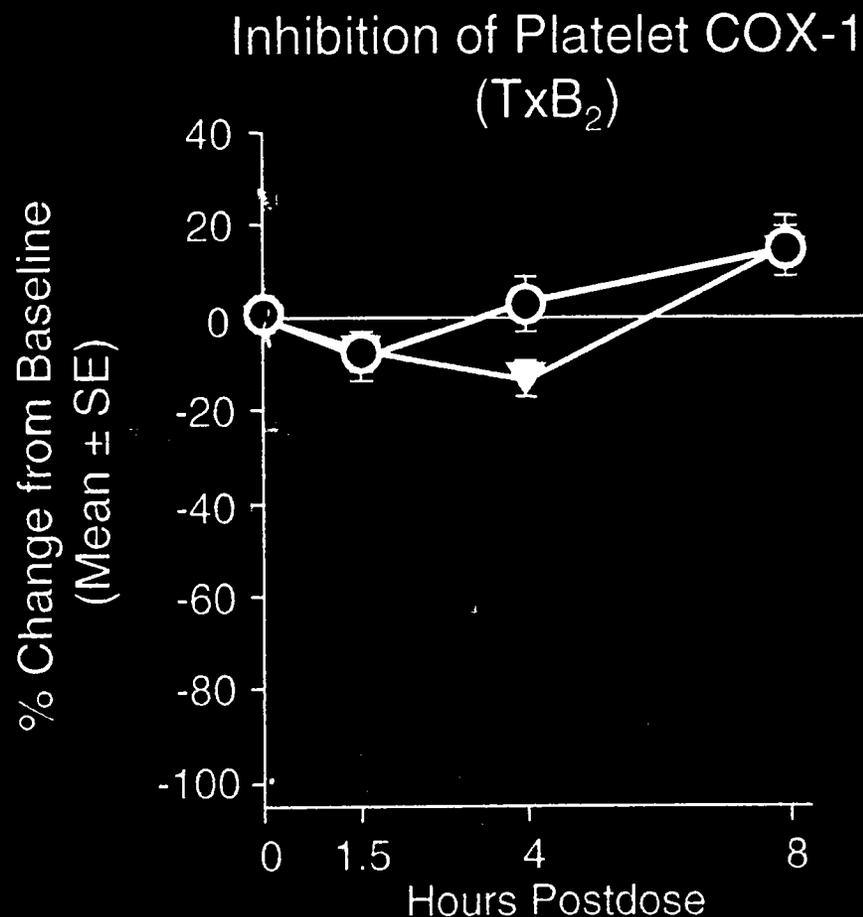
1000 mg single dose  
375 mg x 14 days

25 mg x 5 days  
50 mg x 5 days

25 mg x 14 days  
50 mg x 4 days

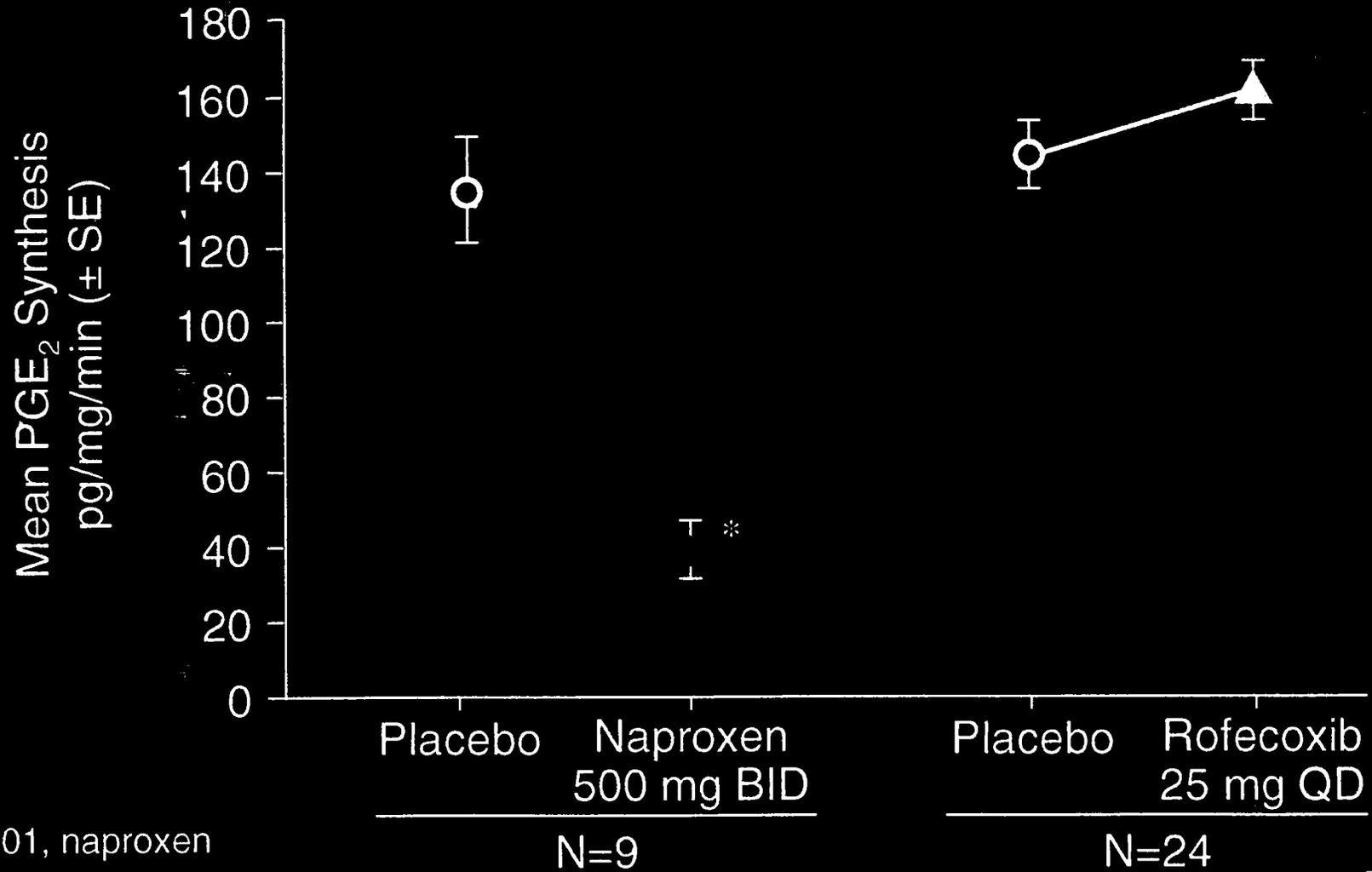
# COX-2 Specificity

## Subjects Received Rofecoxib 1000 mg Single Dose



▼ Rofecoxib 1000 mg N=6      Indomethacin 75 mg N=9      ○ Placebo N=16

# PGE<sub>2</sub> Synthesis in Gastric Biopsies at Steady State Subjects Received Rofecoxib 25 mg QD x 5 Days



\*p < 0.001, naproxen compared with placebo.

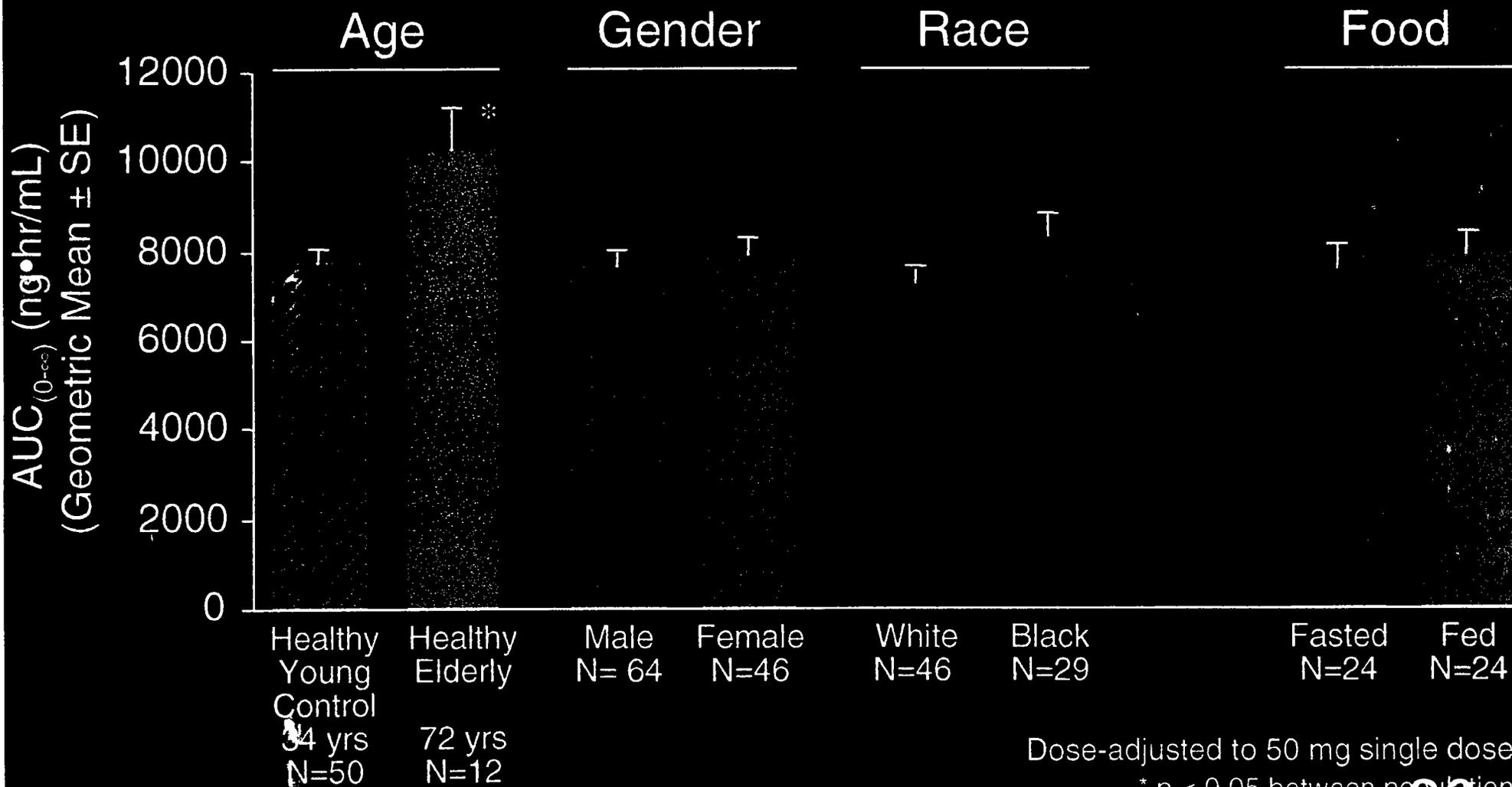
# Rofecoxib Pharmacokinetics

- General Pharmacokinetics
- Pharmacokinetics in special populations
- Drug Interaction studies

# Rofecoxib: Pharmacokinetics

- High bioavailability: 92 and 93% (12.5 mg and 25 mg, respectively)
- $T_{max}$ : 2 to 3 hours
- Accumulation half-life: 17 hours
  - Supports once-daily dosing
- *In vivo*, elimination is primarily by hepatic metabolism
  - Dominant pathway is cytosolic reduction (non-P450)
  - Secondary pathway oxidation by multiple P450 enzymes
  - Metabolites primarily excreted in urine
- Identified metabolites, no meaningful COX inhibitory activity
- *In vitro*, no inhibition of hepatic P450 isozymes

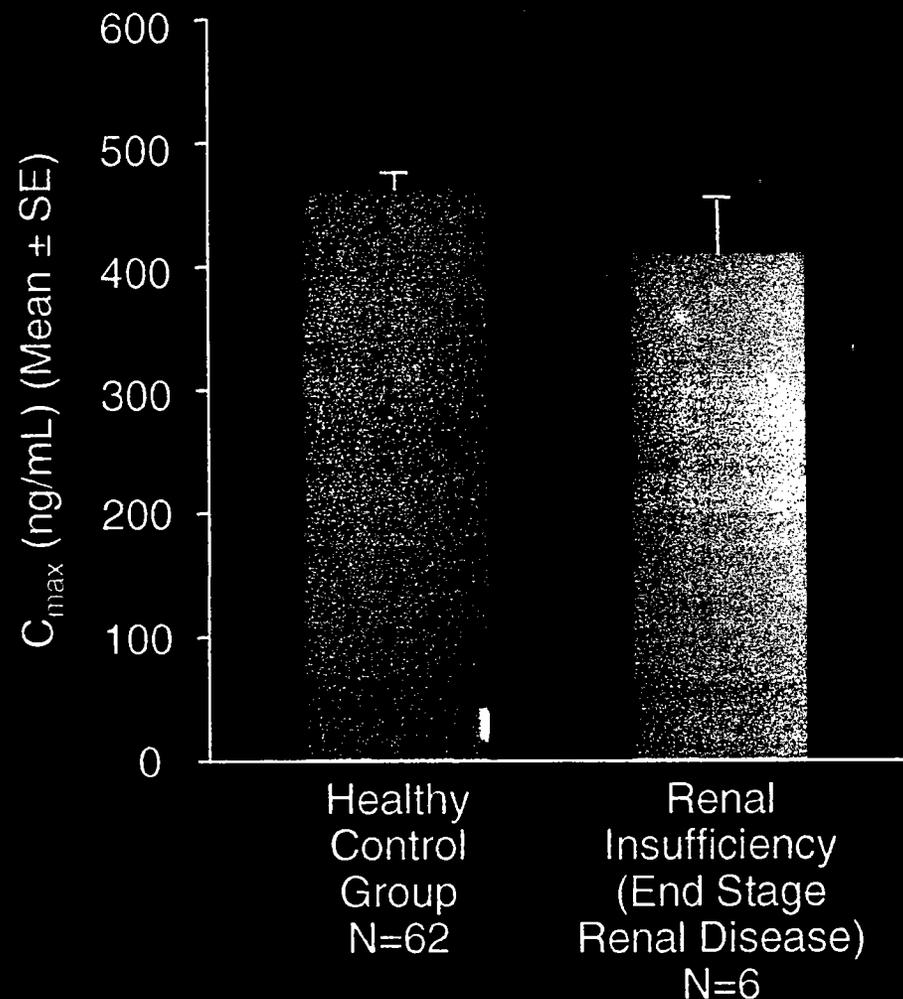
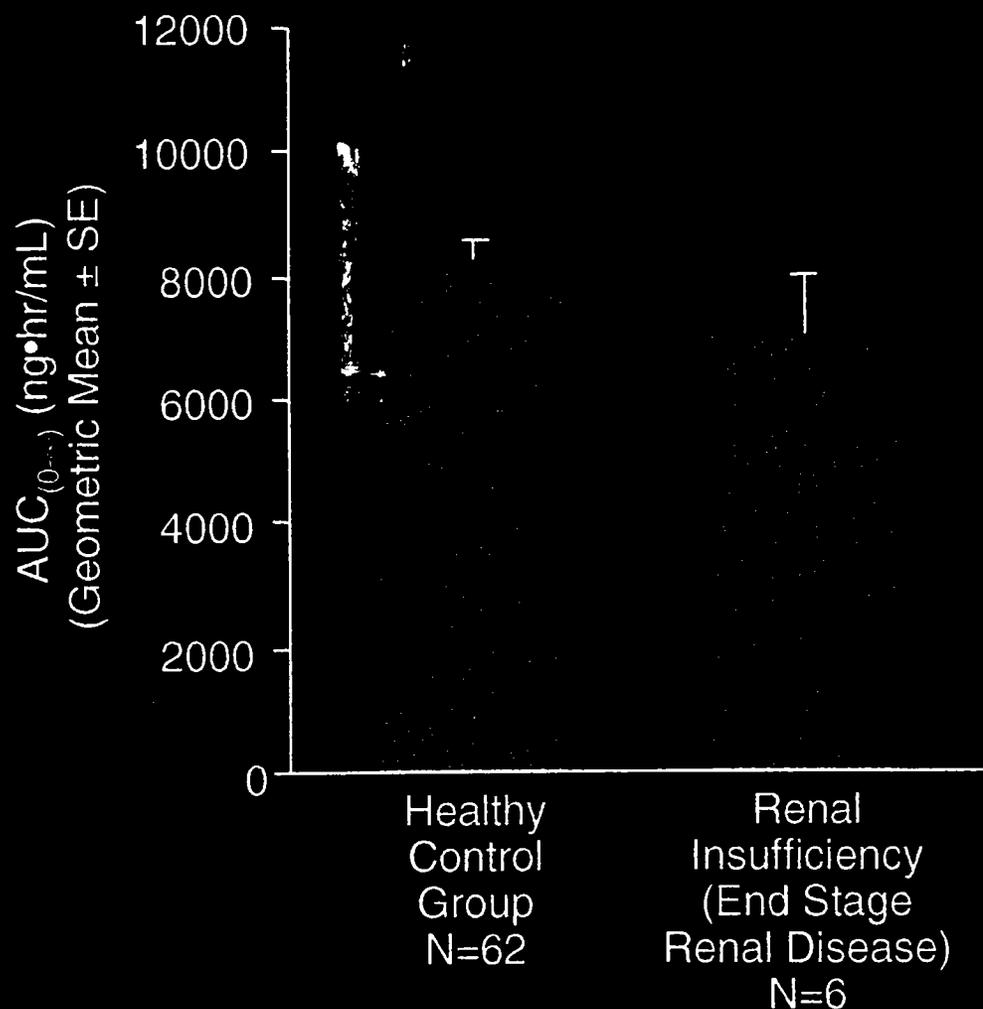
# Rofecoxib Pharmacokinetics



Dose-adjusted to 50 mg single dose.

\* p < 0.05 between population.

# Rofecoxib Pharmacokinetics Influence of Renal Insufficiency

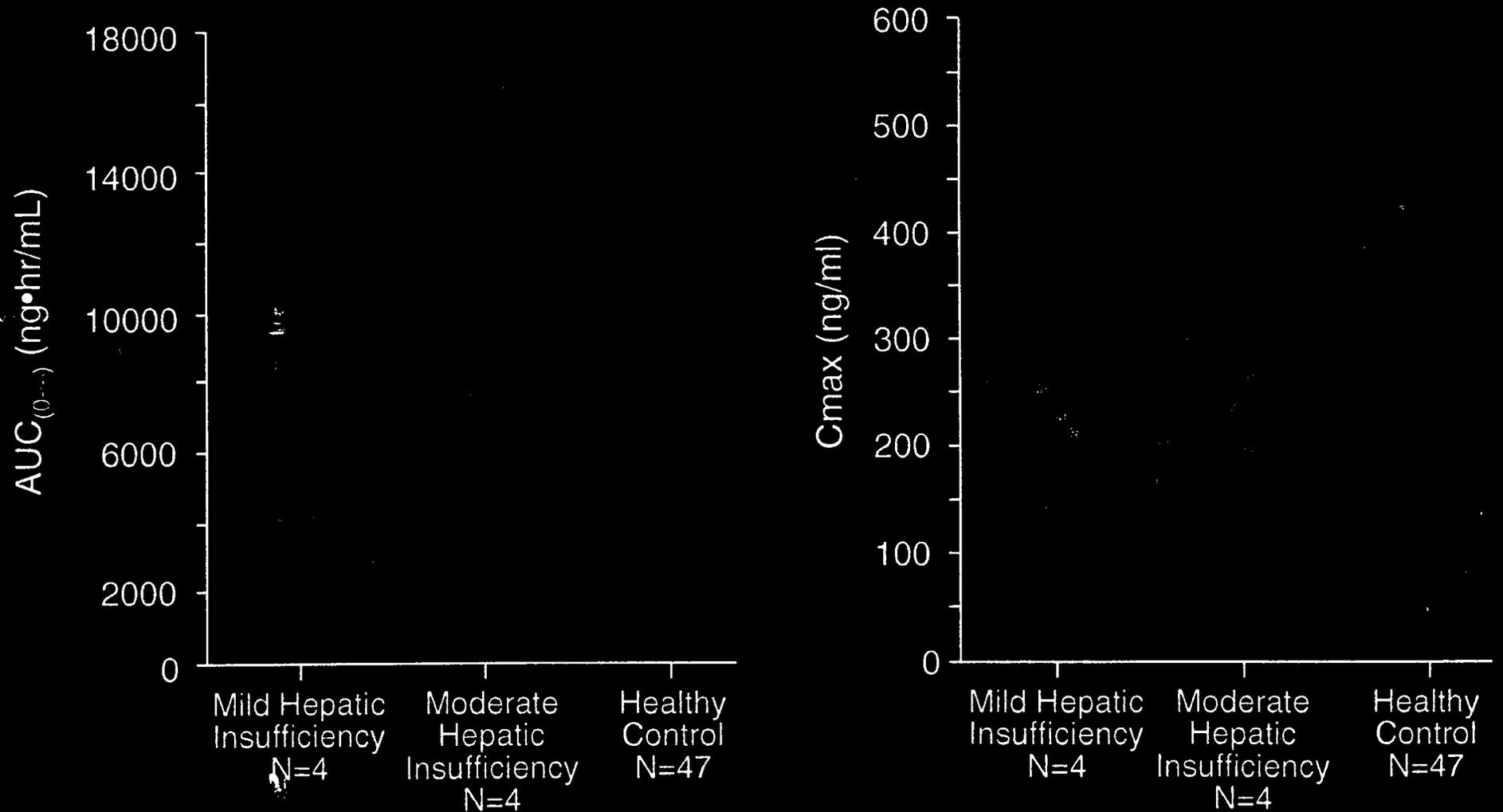


p = NS between groups.

Dose-adjusted to 50 mg single dose.

Protocol 076

# $AUC_{(0-\infty)}$ & $C_{max}$ for Patients with Mild and Moderate Hepatic Insufficiency Compared to Healthy Subjects



Dose-adjusted to 25 mg single dose.

Protocol 057  
**22**

# Rofecoxib Drug Interaction Studies

- Rofecoxib has no clinically significant effect on:
  - Prednisone
  - Oral contraceptives
  - Digoxin
  - Low dose aspirin - rofecoxib 50 mg x 10 days
- No clinically significant effect on rofecoxib pharmacokinetics
  - Antacids
  - Cimetidine

# Rofecoxib

## Drug Interaction Studies

- Warfarin administered with rofecoxib 25 mg
  - Prothrombin time, INR 8% higher with rofecoxib compared to placebo
  - Monitor prothrombin time, INR as usually recommended for patients receiving warfarin therapy
- Methotrexate administered with rofecoxib 75 mg
  - Methotrexate levels ~23% increase in AUC
  - No change in dose
  - No change in the standard guidelines for monitoring drug therapy in RA, American College of Rheumatology. \*

\* *Arthritis & Rheumatism*, 1996 Vol. 39 (5), 723-731

# Efficacy in Osteoarthritis

- Scope of the Phase IIb and III efficacy program
- 6 week efficacy compared to placebo and ibuprofen
- 12 month efficacy compared to diclofenac
- Rationale for the dosing recommendation