CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ARTHRITIS DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 12/1/98

SLIDES

Arthritis Advisory Committee
Food and Drug Administration
Center for Drug Evaluation and Research

December 1, 1998

NDA 20-998, Celebrex™ (Celecoxib) Searle

CELEBREX™
(celecoxib)
Capsules

1

Indications

1. Acute or Chronic use in the Treatment of the Signs and Symptoms of Osteoarthritis and Rheumatoid Arthritis
2. Management of Pain

2

Agenda

I.	Introduction	Dr. Richard Spivey
II.	Overview	Dr. Philip Needleman
III.	Discovery & Pre-Clinical Development	Dr. Peter Isakson
IV.	Pharmacokinetics/ Pharmacodynamics	Dr. Aziz Karim
V.	Clinical Efficacy	Dr. G. Steven Geis
VI.	Clinical Safety	Dr. G. Steven Geis
VII.	Summary	Dr. Philip Needleman

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Major Conclusions

1. Celecoxib is effective in treating OA, RA, and Pain
2. In osteoarthritis, celecoxib given once daily or in divided doses is equally effective
3. Celecoxib is a specific COX-2 inhibitor that has an improved safety profile compared to mixed COX-1/COX-2 inhibitors
4. The clinically significant differences in GI effects compared to NSAIDs warrant specific changes in NSAID GI Class Labeling

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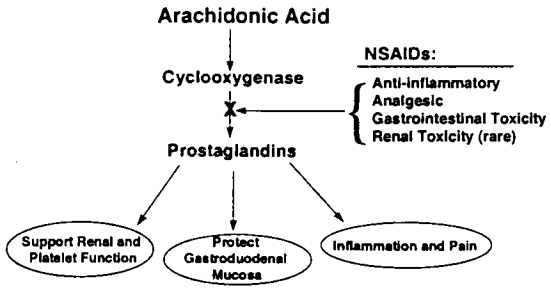
Mechanism of Action of NSAIDs: The Vane Hypothesis



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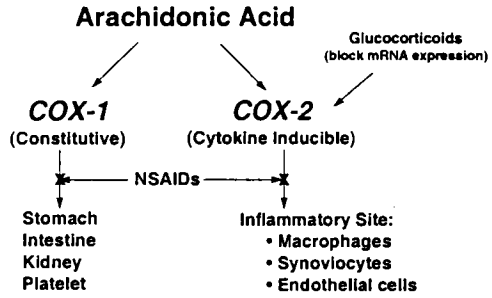
1990 Hypothesis: 2 COX Isoforms Exist



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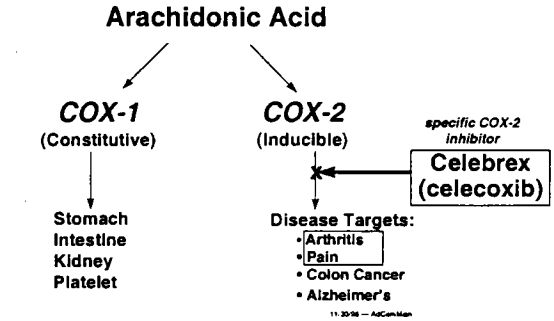
COX-2 Inhibitors: Mechanism Based Drug Targeting



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Breakthroughs in Anti-Inflammatory Therapy

- 1897 Invention of aspirin
- 1963 Development of NSAIDs
- 1971 Mechanism of aspirin
- 1990-91 Paradigm shift - Discovery of COX-2
- 1992 Rational drug development begins
- 1998 Delivery of a new class of drugs
  - Delivers the effectiveness of NSAIDs in arthritis and pain
  - Provides greater safety than the NSAIDs
  - Differentiated class with a clear therapeutic index

4

COX-2: Targeted Drug Discovery

Scientific Objectives:

- Mechanism of Specificity
- Evaluation of the COX-2 Hypothesis
- Efficacy and Safety Profile Consistent with COX-2 Specific Mechanism

→ **Clinical Evaluation**

5

Identification and Evaluation of COX-2 Inhibitors

- ***In vitro* pharmacology**
  - Recombinant human COX-1 and COX-2
  - Cells
- ***In vivo* pharmacology**
  - Selectivity
  - Anti-inflammatory and analgesic activity
- **Safety**
  - Acute and chronic

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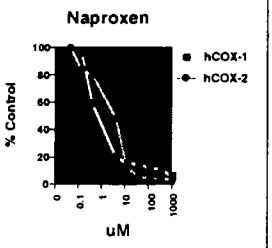
Enzyme Inhibition Profiles of Celecoxib and NSAIDS

Enzyme + Drug
↓
+ Arachidonate
↓
Measure
Prostaglandin

Recombinant human enzymes assayed *in vitro*



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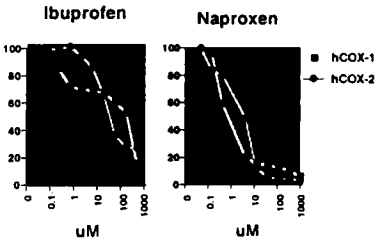
Enzyme Inhibition Profiles of Celecoxib and NSAIDS



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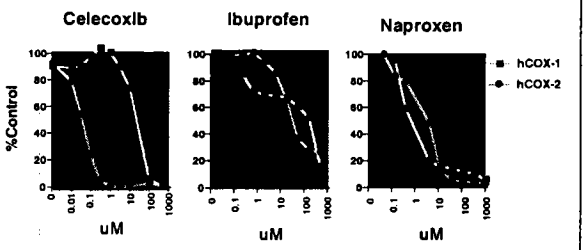
Enzyme Inhibition Profiles of Celecoxib and NSAIDS



Glerse et al, Biochem. J. 305:479, 1995
Penning et al, J.Med.Chem. 40:1347, 1997

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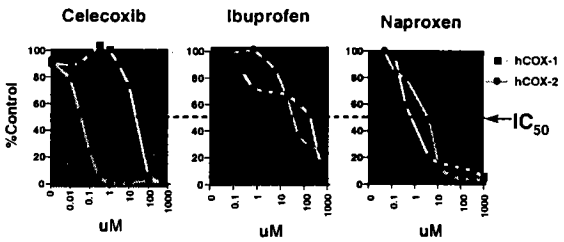
Enzyme Inhibition Profiles of Celecoxib and NSAIDS



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Inhibition of Cyclooxygenases *in vitro*

	IC_{50} (μM)		
	COX-1	COX-2	COX-1/COX-2
Diclofenac	0.03	0.01	3
Etodolac	>100	54	>2
Ibuprofen	38	117	0.4
Nabumetone (6-MNA)	82	>1000	<0.1
Naproxen	32	235	0.1

Glerse et al, Biochem. J. 305:479, 1995

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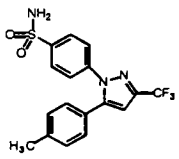
Inhibition of Cyclooxygenases *in vitro*

	IC_{50} (μM)		
	COX-1	COX-2	COX-1/COX-2
Celecoxib	15	0.04	375



Penning et al, J.Med.Chem. 40:1347, 1997

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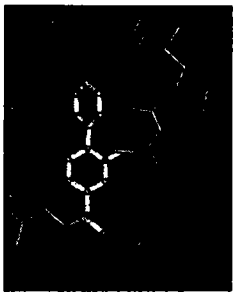
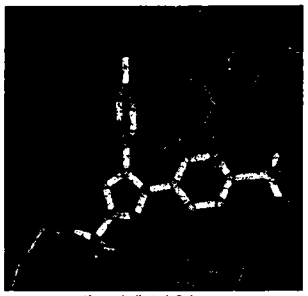
COX-1 with flurbiprofen in the active site



Picot, Loll and Garavito
Nature 367:243, 1994

COX-2 with celecoxib in the active site



Kurumbail et al, Science
(In press)

Mechanism of Celecoxib Enyzme Selectivity

- **Binds to a side pocket unique to the COX-2 active site**
- **Selectivity is due to a novel mechanism:**
  - Low affinity, competitive inhibition of COX-1
  - High affinity, non-competitive inhibition of COX-2; very slowly reversible

→ Duration of action longer than pharmacokinetic $T_{1/2}$

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Identification and Evaluation of COX-2 Inhibitors

- ***In vitro* pharmacology**
  - Recombinant human COX-1 and COX-2
  - Cells
- ***In vivo* pharmacology**
  - Selectivity
  - Anti-inflammatory and analgesic activity
- **Safety**
  - Acute and chronic

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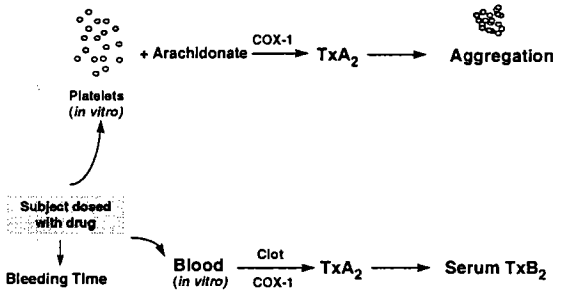
Assessment of Specificity with Human Platelets



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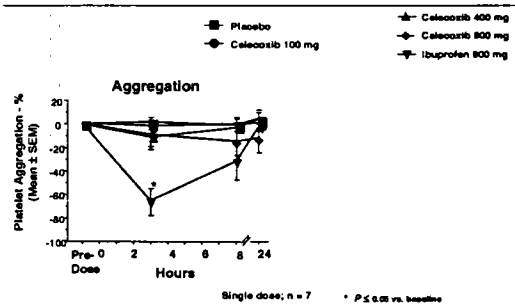
Effect of Single Dose Celecoxib on Human Platelet Aggregation and Serum TxB_2



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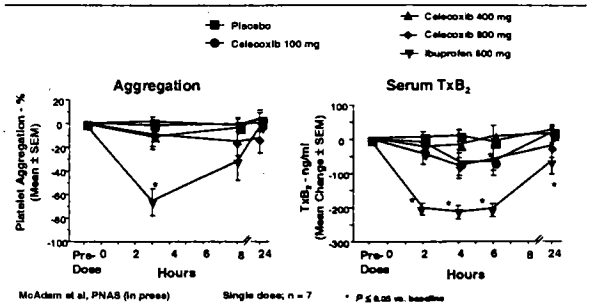

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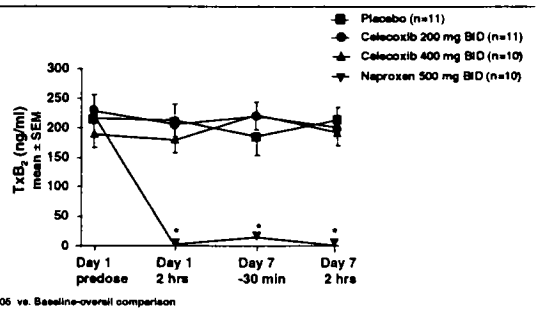
Effect of High Dose Celecoxib on Serum TxB_2



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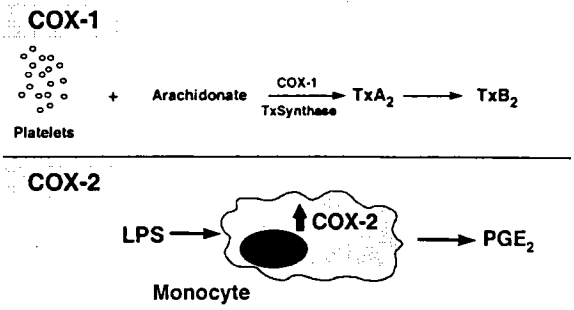
Whole Blood Assays of COX-1 and COX-2



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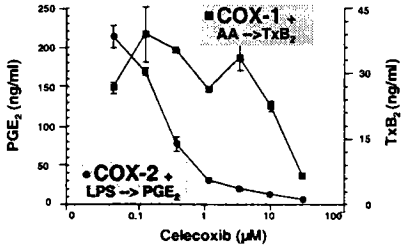
Whole Blood Assay of Celecoxib *ex vivo*



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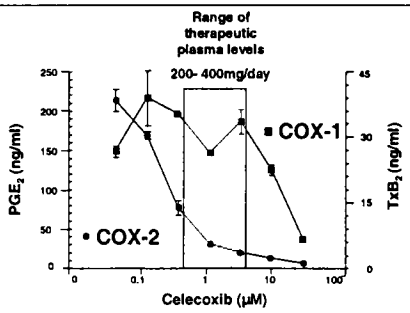
Relationship of COX Inhibition to Celecoxib Doses in Humans



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Celecoxib Platelet Effects

- **No effect of celecoxib at 2X the maximum therapeutic dose on:**
  - Platelet aggregation
  - TxB_2 production
  - → COX-1 sparing

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Identification and Evaluation of COX-2 Inhibitors

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  - Cells
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  - Selectivity
  - Anti-inflammatory and analgesic activity
- **Safety**
  - Acute and chronic

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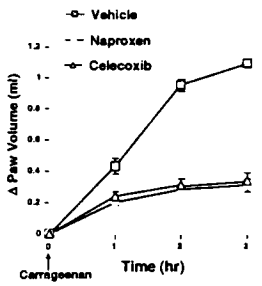
Effect of Celecoxib on Acute Inflammation



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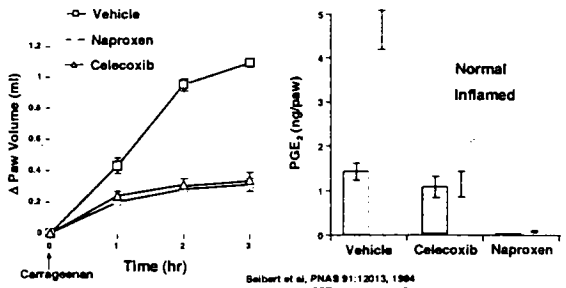
Effect of Celecoxib on Acute Inflammation



Seibert et al, PNAS 91:12013, 1994
Zhang et al, JPET 283:1069, 1997

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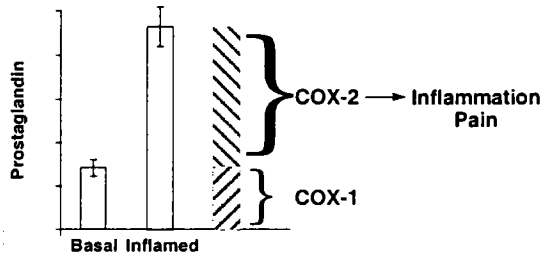
Cyclooxygenases in Acute Inflammation



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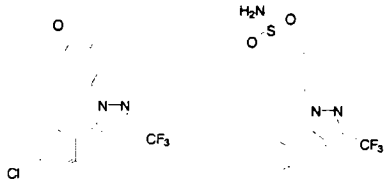
Specific COX-1 Inhibitor



		SC-560	Celecoxib
IC_{50}: (uM)	COX-1	0.009	15
	COX-2	6.3	0.04

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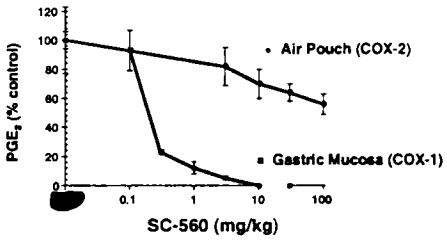
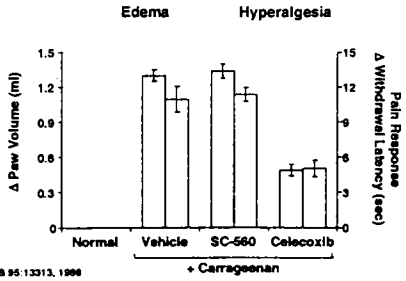
In vivo Specificity of SC-560



Smith et al, PNAS 95:13313, 1998

29

Inhibition of COX-1 is Not Anti-inflammatory or Analgesic



Smith et al, PNAS 95:13313, 1998

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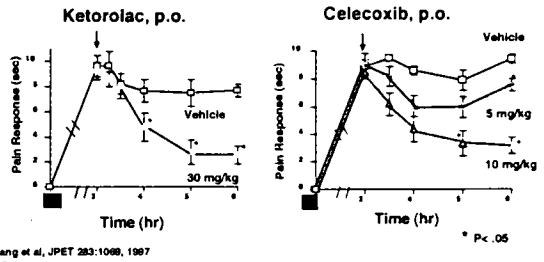
Rapid Reduction of Pain by Celecoxib



Zhang et al, JPET 283:1068, 1997

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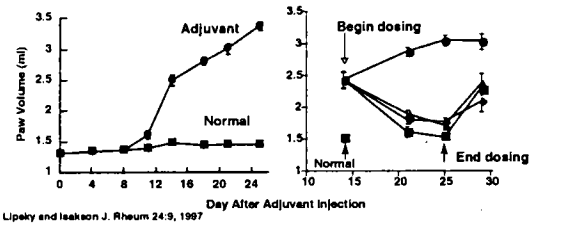
Rat Adjuvant Arthritis

- Mononuclear Cell Infiltrate
- COX-2 expression
- Marked PG Production
- Edema and Joint Destruction



Lipsky and Isakson J. Rheum 24:9, 1997

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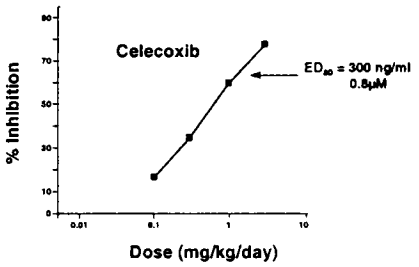
Effect of COX Inhibitors on Rat Adjuvant Arthritis



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Conclusions

- Specific inhibition of COX-2 by celecoxib results in the same maximal efficacy as inhibition of both COX-1 and COX-2 by NSAIDs
- *Therefore, in animal models COX-2 is the therapeutic target for NSAIDs*

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Identification and Evaluation of COX-2 Inhibitors

- *In vitro* pharmacology
  - Recombinant human COX-1 and COX-2
  - Cells
- *In vivo* pharmacology
  - Selectivity
  - Anti-inflammatory and analgesic activity
- Safety
  - Acute and chronic
    - Rat (6 months to 2 years)
    - Dog (1 year)

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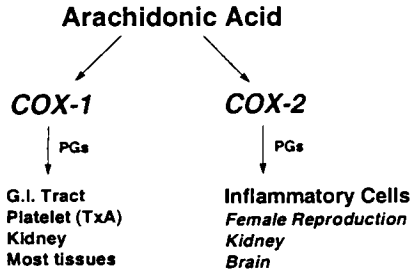
Two Forms of Cyclooxygenase



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Preclinical Toxicology of Celecoxib Relevant to Mechanism

- **Pregnancy**
  - No effect on ovulation or fertility
  - Effects on embryo viability (implantation) at exposures 6-12 fold therapeutic
- **No adverse effects related to:**
  - Bleeding
  - CNS
- **Renal**
  - No renal papillary necrosis
  - Transient anti-natriuresis in rats
- **Gastrointestinal**
  - Chronic safety established at exposures 3 to 6 fold therapeutic in sensitive species (rat and dog)

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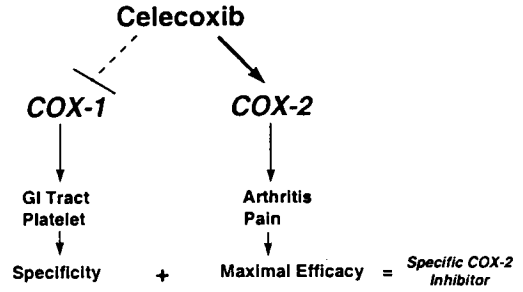
COX-2 Inhibitors: Mechanism Based Drug Targeting



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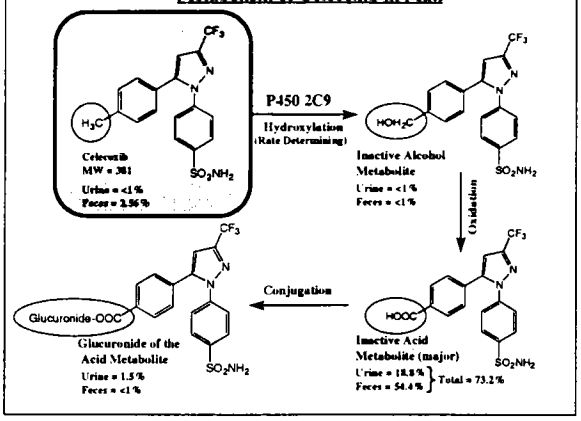
Celecoxib: Clinical PK

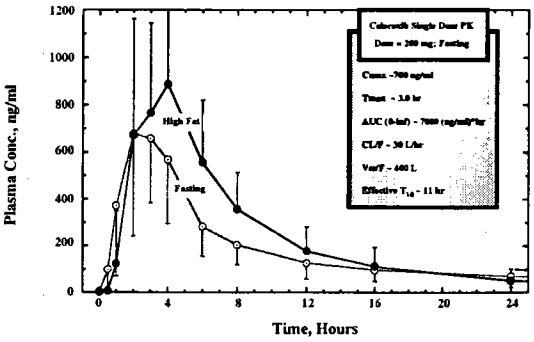
1. Basic PK Profile
2. PK in Special Populations
3. Drug-Drug Interactions
4. Population PK/PD Analysis of Pivotal Clinical Trial Data
5. Bioequivalency: Clinical Trial Batches vs. Commercial Formul.

Celecoxib PK Assessed in 1566 Subjects From 32 Studies

Metabolism of Celecoxib in Man



Mean (SD; N = 24) Plasma Concentrations of Celecoxib Following 200 mg Single Doses Given Under Fasting State or With High Fat Breakfast



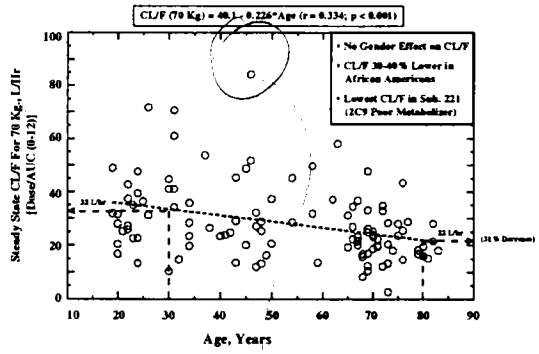
Celecoxib: Clinical PK

PK in Special Population

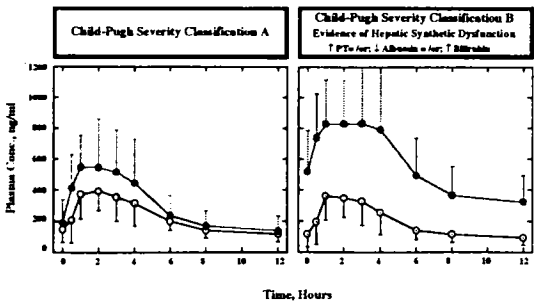
1. Effect of Age, Gender, Weight and Race
2. Effect of Hepatic Impairment
3. Effect of Chronic Renal Impairment
4. Effect of Diabetes (NIDDM)
5. Effect of Osteo- and Rheumatoid Arthritis

Relationship Between Celecoxib CL/F (Adjusted For 70 Kg) and Age (N=112)

[-010 Renal Elderly; -015 Young vs. Elderly PK; -017 MTX Interaction; -043 BID vs QD PK]



Mean (SD; N = 11-12) Steady State Plasma Conc.-Time Curves of Celecoxib in Hepatic Impaired Patients (●) and Matching Healthy Subjects (○) Following Celecoxib 100 mg BID



12/31 = same subject

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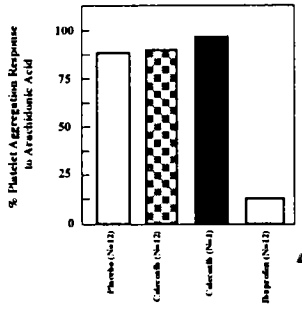
Six Subjects (Out of 1566) Showing Unusually High Exposure of Celecoxib

[redacted]									
221	-015	73	74.9	F	Caucasian	200 (7 days with food)	72.2	2.59	10.2
222	-015	68	79.3	F	Caucasian	200 (7 days with food)	21.4	8.25	3.20
[redacted]									
031	-072	33	70.1	M	Caucasian	200 (Single Dose)	54.6 (lqc)	3.66	2.84
827	-824	68	56.2	F	Afr. Amer.	100 (7-28 days)	NA	NA	2.39
461	-824	80	71.9	F	Afr. Amer.	200 (7-28 days)	NA	NA	5.97

Note: Subject #012, study -065 and subject #031, study -072 were the same subject participating in two different studies

Mean (N=12) Steady State COX-1 Mediated Pharmacodynamic Responses at Two Hours on Day 8 Following Celecoxib (600 mg BID), Ibuprofen (800 mg TID) or Placebo
Study N49-97-02-065



platelet aggregation

ibuprofen

Drug-Drug Interactions

NSAIDs Decrease Renal Blood Flow

Effect on Drugs Eliminated Mostly by the Kidney

- Methotrexate
- Lithium

NSAIDs Undergo Hepatic Metabolism

Effects on Drugs that are also Metabolized by the Liver (2C9)

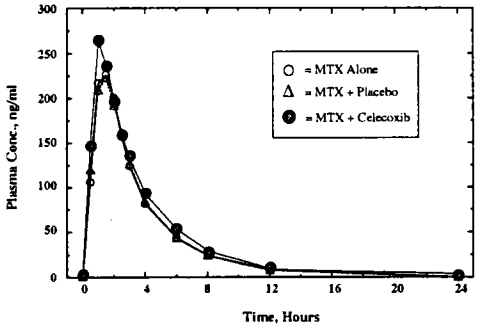
- Warfarin
- Tolbutamide
- Phenytoin

NSAIDs Are Highly Protein Bound

Protein Binding Displacements and Clearance of Other Drugs

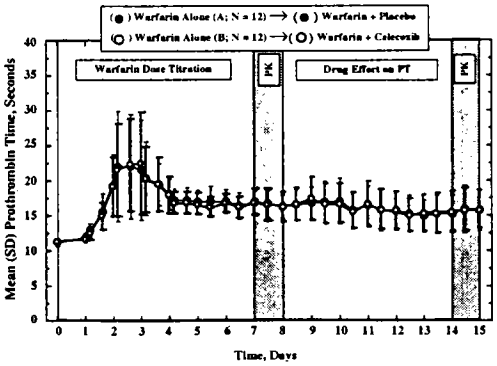
- Glyburide

Mean (N = 14) Methotrexate (MTX) Plasma Conc. In Patients Following Their Usual Therapeutic Doses of MTX (5-15 mg Weekly) Given Alone, and After 7-Day Treatments With Placebo (BID) or Celecoxib (200 mg BID)



no interaction w/ NSAID + MTX

Effect of Celecoxib 200 mg BID on Pharmacodynamic Response (Prothrombin Time) to Warfarin QD



no interaction with warfarin

Celecoxib: PK Summary

- Achiral, Low-Solubility-High-Permeability Drug With Systemic Availability of ~73%
- CL/F ~500 ml/min (~30 L/hr); Vss/F ~400 L; Effective $T_{1/2}$ ~11 hr; Extensive Hepatic Metabolism To Inactive Metabolites via P450 2C9; Protein Binding ~97% and Concentration Independent
- Advantages of Dosing With or Without Food and Potential For Once a Day Dosing
- Lower CL (higher AUC) in Elderly Women (Lower Body Weight), in Patients With Moderate to Severe Hepatic Impairment and in African Americans
- Lack of Drug-Drug Interactions Commonly Encountered With NSAIDs (MTX, Lithium, Warfarin, Phenytoin, Glyburide, Tolbutamide)

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Celecoxib Clinical Efficacy and Safety

1

Hypothesis

Specific inhibitors of COX-2 will be anti-inflammatory and analgesic without the typical side-effects of NSAIDs

2

Celecoxib - Clinical Objectives

Indications
- Osteoarthritis
- Rheumatoid Arthritis
- Management of Pain

Differentiation
- Gastrointestinal
- Platelet
- General Safety

3

Celecoxib Clinical Program Overview

- Studies: 51
- Patients/Subjects: 13,072
- Endoscopy: > 4,700 patients
- No. Patients with ≥ 1 Year Exposure:
  981 - NDA
  2,443 - Safety Update
- Patient Years: 3,283 - NDA
  5,005 - Safety Update

4

Celecoxib - Clinical Objectives

Indications
- Osteoarthritis
- Rheumatoid Arthritis
- Management of Pain

Differentiation
- Gastrointestinal
- Platelet
- General Safety

5

Pivotal OA Studies

3 - 12-week studies
- 2 knee
- 1 hip

2 - 6-week studies
- 2 knee

6

BEST POSSIBLE

Design: 12-Week Studies

Osteoarthritis Flare	Placebo BID			
	Celecoxib 50 mg BID			
	Celecoxib 100 mg BID			
	Celecoxib 200 mg BID			
	Naproxen 500 mg BID			
Week	0	2	6	12
Arthritis Assessments	X	X	X	X

7

Measures of OA Efficacy

- Patient's Assessment of Pain (VAS)
- WOMAC OA Index
  - Pain
  - Function
  - Stiffness
- Patient's Global Assessment
- Physician's Global Assessment
- SF-36 Health Survey

8

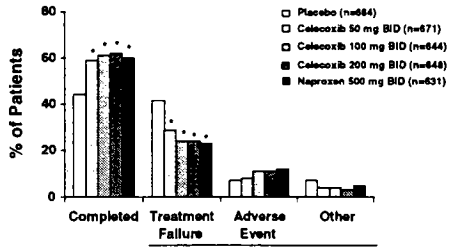
12-Week OA Studies

Index Joint	Study No. 020 Knee	021 Knee	054 Hip	Total
Treatment Group (n)				
Placebo	204	242	218	664
Celecoxib 50 mg BID	203	252	216	671
Celecoxib 100 mg BID	197	240	207	644
Celecoxib 200 mg BID	202	233	213	648
Naproxen 500 mg BID	198	226	207	631
Total	1004	1193	1061	3258

Planned sample size - 200/group

9

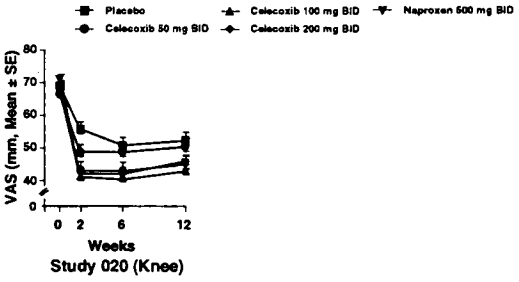
Patient Disposition: 12-Week Studies



Pooled data
* Significantly different from placebo; p<0.05

10

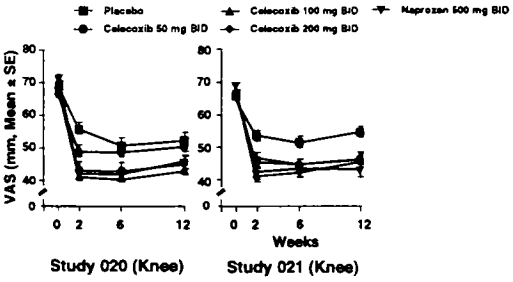
Patient's Assessment of Pain



Scale = 0-100

11

Patient's Assessment of Pain

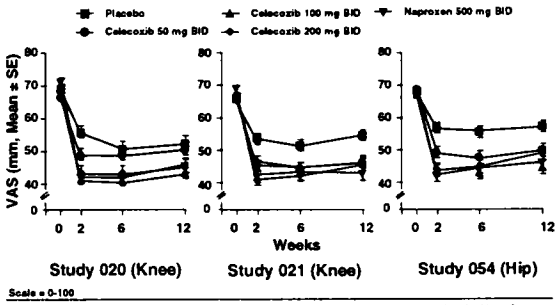


Scale = 0-100

12

BEST POSSIBLE

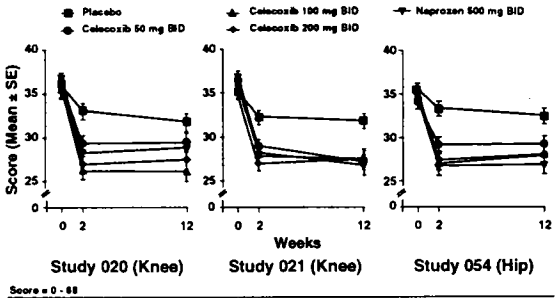
Patient's Assessment of Pain



Scale = 0-100

13

WOMAC - Physical Function

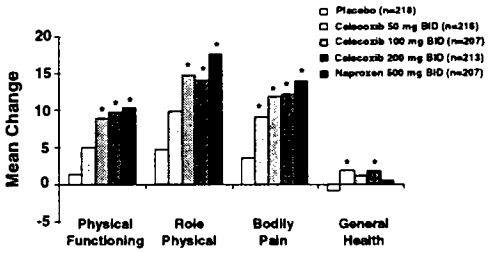


Score = 0 - 68

14

Hip OA Pivotal Study - 054

SF-36 - Physical Health Domains



Scale = 0 - 100

* Significantly different from placebo; p <0.05

15

Design: 6-Week Studies

Osteoarthritis Flare	Placebo BID		
	Celecoxib 100 mg BID		
	Celecoxib 200 mg QD		
Week	0	2	6
Arthritis Assessments	X	X	X

16

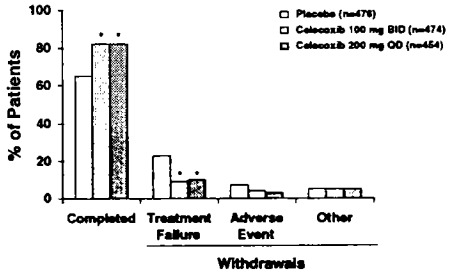
6-Week OA Studies

Index Joint	Study No. 060 Knee	Study No. 087 Knee	Total
Treatment Group (n)			
Placebo	232	244	476
Celecoxib 100 mg BID	231	243	474
Celecoxib 200 mg QD	223	231	454
Total	686	718	1404

Planned sample size - 200/group

17

Patient Disposition: 6-Week Studies



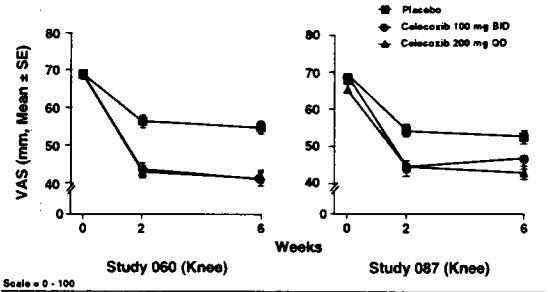
Pooled data

* Significantly different from placebo; p<0.05

18

BEST POSSIBLE

Patient's Assessment of Pain

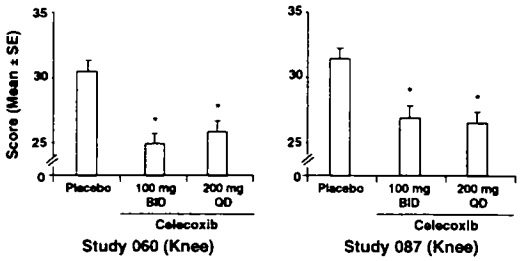


Scale = 0 - 100

19

30 Nov 98 - Advisory Committee

WOMAC - Physical Function at Week 6



Score = 0 - 68

* Significantly different from placebo based on change from Baseline; p <0.05

20

30 Nov 98 - Advisory Committee

Conclusions: Celecoxib in OA

- Effective in OA
- Recommended dose
  - 200 mg per day
  - Can be administered in single or divided doses
- Efficacy similar to naproxen

21

30 Nov 98 - Advisory Committee

Celecoxib - Clinical Objectives

Indications

- Osteoarthritis
- Rheumatoid Arthritis
- Management of Pain

Differentiation

- Gastrointestinal
- Platelet
- General Safety

22

30 Nov 98 - Advisory Committee

Design: 12-Week RA Studies

	Placebo BID			
	Celecoxib 100 mg BID			
Rheumatoid Arthritis Flare	Celecoxib 200 mg BID			
	Celecoxib 400 mg BID			
	Naproxen 500 mg BID			
Week	0	2	6	12
Arthritis Assessments	X	X	X	X

23

30 Nov 98 - Advisory Committee

Measures of RA Efficacy

- ACR-20
- Number of Swollen Joints
- Number of Tender/Painful Joints
- Patient's Global Assessment of Arthritis
- Physician's Global Assessment of Arthritis
- SF-36 Health Survey

24

30 Nov 98 - Advisory Committee

BEST POSSIBLE

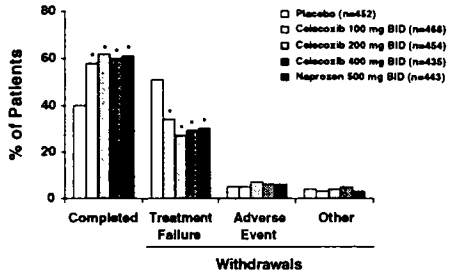
12-Week RA Studies

	Study No. 022	Study No. 023	Total
Treatment Group (n)			
Placebo	231	221	452
Celecoxib 100 mg BID	240	228	468
Celecoxib 200 mg BID	235	219	454
Celecoxib 400 mg BID	218	217	435
Naproxen 500 mg BID	225	218	443
Total	1149	1103	2252

Planned sample size - 200/group

25

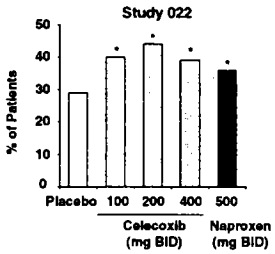
Patient Disposition: 12-Week Studies



Pooled data
* Significantly different from placebo; p<0.05

26

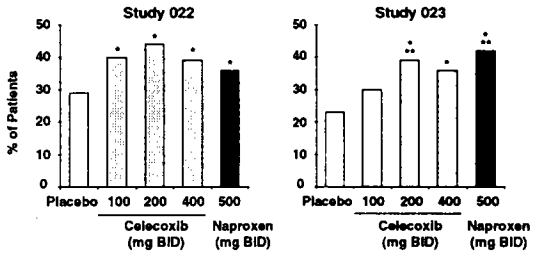
ACR-20 at Week 12



* Significantly different from placebo; p <0.05

27

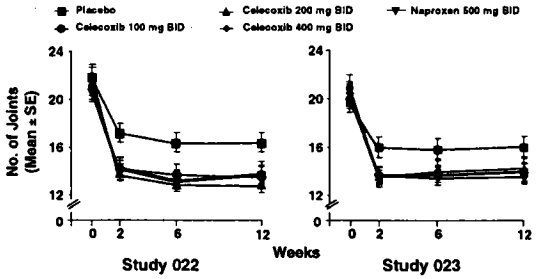
ACR-20 at Week 12



* Significantly different from placebo; p <0.05
** Significantly different from celecoxib 100 mg BID; p <0.05

28

Number of Swollen Joints

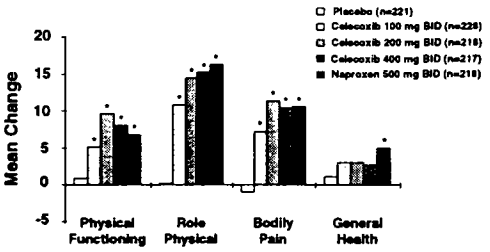


68 joints examined (excludes hips)

29

Pivotal RA Study - 023

SF-36 - Physical Health Domains



Scale = 0 - 100
* Significantly different from placebo; p <0.05

30

BEST POSSIBLE

Design: 6-Month RA Study

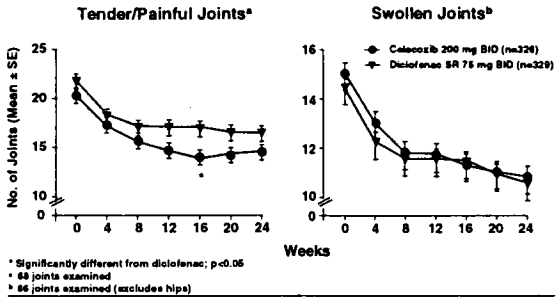
Rheumatoid Arthritis
Symptomatic

Celecoxib 200 mg BID
Diclofenac SR 75 mg BID

Week	0	4	8	12	16	20	24
Arthritis Assessments	X	X	X	X	X	X	X

31

6-Month RA Study



* Significantly different from diclofenac; p<0.05
[a] 68 joints examined
[b] 66 joints examined (excludes hips)

32

Conclusions: Celecoxib in RA

- Effective in RA
- Recommended dose
  - 100 mg BID
  - Some patients may benefit by increasing the dose to a maximum of 200 mg BID
- Efficacy similar to naproxen
- Sustained efficacy

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Celecoxib - Clinical Objectives

Indications

- Osteoarthritis
- Rheumatoid Arthritis
- Management of Pain
  - acute pain
  - short term pain
  - chronic arthritis pain

Differentiation

- Gastrointestinal
- Platelet
- General Safety

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Pain Program

Model # 1
ACUTE PAIN
(0 - 24 HOURS)

- Post-dental surgery
  - 3 pivotal studies
  - single dose
- Post-orthopedic surgery
  - 1 supporting study
  - repeat dose

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Pain Program

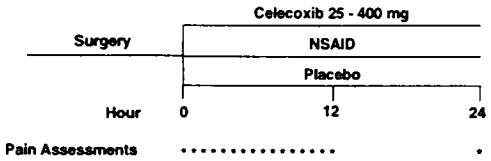
Model # 1 ACUTE PAIN (0 - 24 HOURS)	Model # 2 SHORT TERM PAIN (1 - 7 DAYS)
• Post-dental surgery - 3 pivotal studies – single dose	• OA flare - 3 pivotal studies – multiple dose
• Post-orthopedic surgery - 1 supporting study – repeat dose	

36

BEST POSSIBLE

Model # 1

Design: Post-Dental Surgery Studies



37

Model # 1
Measures of Efficacy

- Time to Onset of Pain Relief
- Time Specific Pain Relief
- Duration of Pain Relief

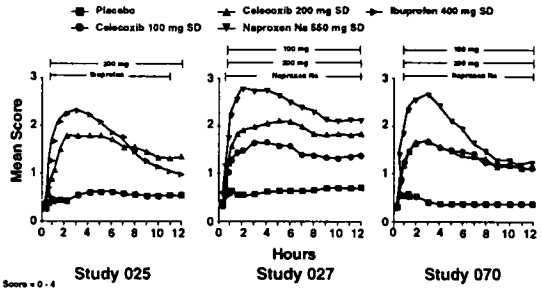
38

Model # 1
Post-Dental Surgery Studies

	Study No.			
	025	027	070	Total
Treatment Group (n)				
Placebo	50	55	50	155
Celecoxib 100 mg	--	55	50	105
Celecoxib 200 mg	50	56	50	156
Ibuprofen 400 mg	50	--	--	50
Naproxen Na 550 mg	--	54	35	89

39

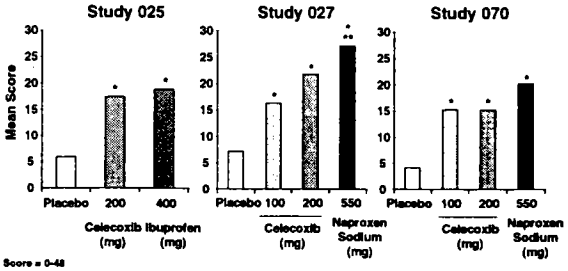
Model # 1
Time Specific Pain Relief



Score = 0 - 4
Bars indicate statistically significant difference from placebo; p<0.05

40

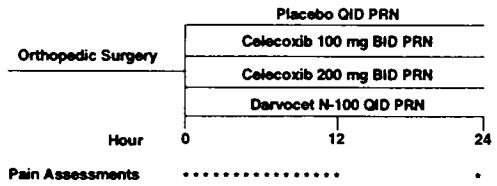
Model #1
TOTPAR (12) Scores



Score = 0-48
* Significantly different from placebo; p<0.05
** Significantly different from celecoxib 100 mg; p<0.05

41

Model # 1 - Supporting Study
Design: Post-Orthopedic Surgery Study



42

BEST POSSIBLE

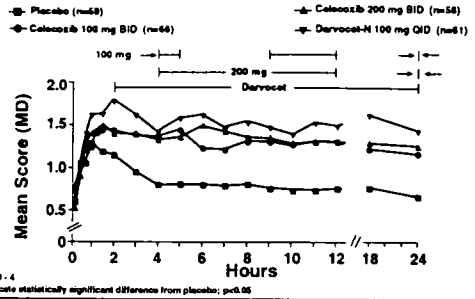
Model # 1
Dosing Regimen: Post-Orthopedic Surgery Study

	First Dose	Second Dose	Third Dose	Fourth Dose
Darvocet N-100	+	+	+	+
Celecoxib 200 mg	+	+	Pbo	Pbo
Celecoxib 100 mg	+	+	Pbo	Pbo
Placebo	Pbo	Pbo	Pbo	Pbo

Remedication was allowed ≥4 hours after the first dose of study medication

43

Model # 1
Time Specific Pain Relief



Score = 0 - 4
Bars indicate statistically significant difference from placebo; p<0.05

44

Pain Program

Model # 1 ACUTE PAIN (0 - 24 HOURS)	Model # 2 SHORT TERM PAIN (1 - 7 DAYS)
• Post-dental surgery - 3 pivotal studies – single dose	• OA flare - 3 pivotal studies – multiple dose
• Post-orthopedic surgery - 1 supporting study – repeat dose	

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Model # 2
Rationale: OA Flare Pain Model

- Pain is the primary symptom of OA
- Non-anti-inflammatory analgesics (e.g., acetaminophen and opiates) are efficacious in treating OA pain
- OA model has been used to evaluate the efficacy of a variety of analgesics including opiates and centrally acting analgesics

Bradley, JD, Brandt, KD, *N Engl J Med* 1991; 325:87-91
Jensen, E.M., Ginsberg, F., *Drug Invest* 1994; 8:211-218

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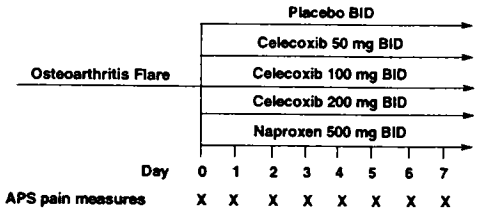
Model # 2
Design: Three Pivotal 12-Week OA Studies



47

Model # 2
American Pain Society (APS) Pain Measure

1. Have you experienced any pain in the last 24 hrs?
2. How much pain are you having right now?
3. Indicate the worst pain you have had in the past 24 hrs.
4. Indicate the average level of pain you have had in the past 24 hrs.
5. Indicate how pain has interfered with function.

JAMA, December 20, 1996, Vol. 274, No. 23

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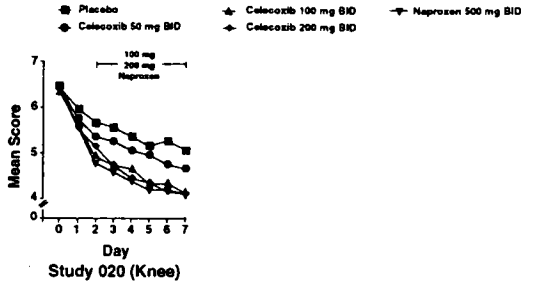
BEST POSSIBLE

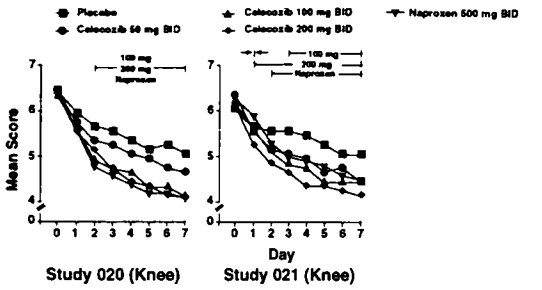
Model # 2
Average Pain in Past 24 Hours



Score = 0-10
* Bars indicate statistically significant difference from placebo; $P < 0.05$

49

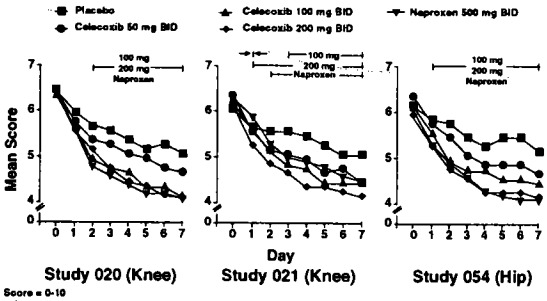
Model # 2
Average Pain in Past 24 Hours



Score = 0-10
* Bars indicate statistically significant difference from placebo; $P < 0.05$

50

Model # 2
Average Pain in Past 24 Hours



Score = 0-10
* Bars indicate statistically significant difference from placebo; $P < 0.05$

51

Celecoxib in Analgesia

- Efficacy was demonstrated by replicate studies:
  - Model # 1: acute pain - 3 post-dental surgery studies; single dose
  - Model # 2: short term pain - 3 OA flare studies; multiple dose over several days
- Recommended dose:
  - 100 mg or 200 mg BID
  - For acute pain, the second dose may be administered as early as 4 hrs

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Celecoxib - Clinical Objectives

Indications

- Osteoarthritis
- Rheumatoid Arthritis
- Management of Pain

Differentiation

- Gastrointestinal
- Platelet
- General Safety

53

Safety Database

	Placebo	Celecoxib	Active Control
Pharmacokinetic Studies	281	1,023	280
Analgesia Studies	305	748	295
North American Arthritis Trials	1,864	5,704	2,768
International Arthritis Trial	0	672	670
Long-term Open Label Arthritis	—	4,499	—
	2,450	12,646	3,343
Total		18,439*	

* 13,072 unique subjects/patients

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BEST POSSIBLE

General Safety Analyses

- Serious adverse events and deaths
- Incidence of adverse events and withdrawals:
  - North American Arthritis Trials
  - Long-term Open Label Arthritis Trial
- Laboratory results

55

Serious Adverse Events

	Placebo (n=2450)	Celecoxib* (n=12,646)	Active Control (n=3343)
SAEs Incidence, No. (%)	34 (1.4)	341 (2.7)	61 (1.8)
Events/100 patient-yrs	15.9	10.4	11.3
Gastrointestinal, No. (%)	6 (0.2)	39 (0.3)	10 (0.3)
Events/100 patient-yrs	2.8	1.2	1.9
Cardiovascular, No. (%)	7 (0.3)	53 (0.4)	4 (0.1)
Events/100 patient-yrs	3.3	1.6	0.7

* All doses

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Deaths

	Placebo (n=2450)	Celecoxib* (n=12,646)	Active Control (n=3343)
Deaths Incidence, No. (%)	0 (0.0)	22 (0.2)	4 (0.1)
Events/100 patient-yrs	0.0	0.5	0.7
Cardiovascular deaths, No. (%)	0 (0.0)	16 (0.1)	2 (0.1)
Events/100 patient-yrs	0.0	0.3	0.4

* All doses

57

North American Arthritis Trials

Adverse Events with ≥5% Incidence in Any Treatment

Adverse Event	Placebo (n=1864)	Celecoxib* (n=4146)	Celecoxib 400 mg BID (n=615)	NSAID (n=2098)
Any Event	54.6	60.4*	60.2	66.7* **
Headache	20.2	15.8*	14.5*	14.8*
Dyspepsia	6.2	8.8*	8.1*	12.0* **
URTI	6.7	8.1*	7.0	9.9
Diarrhea	3.8	5.6*	6.5*	6.1
Sinusitis	4.3	5.0	5.4	4.6
Abdominal Pain	2.8	4.1	3.3	8.2* **
Nausea	4.2	3.5	3.6	5.6* **

* Patients who received either celecoxib 100 mg BID, 200 mg BID or 200 mg QD
* Significantly different from placebo; p<0.05
** Significantly different from celecoxib 100 mg BID, 200 mg BID or 200 mg QD

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North American Arthritis Trials

Adverse Events Causing Withdrawal with Incidence ≥0.5%

Adverse Events	Placebo (n=1864)	Celecoxib* (n=4146)	Celecoxib 400 mg BID (n=615)	NSAID (n=2098)
Any Event	6.1	7.1	6.8	9.7*
Abdominal Pain	0.6	0.8	0.3	2.1* **
Dyspepsia	0.6	0.8	0.8	1.6*
Rash	0.6	0.8	1.1	0.3**
Diarrhea	0.3	0.3	0.3	0.4
Nausea	0.6	0.5	0.3	0.9
Pruritis	0.2	0.2	0.5	0.0
Esophageal Ulceration	0.0	<0.1	0.0	0.6*

* Patients who received either celecoxib 100 mg BID, 200 mg BID or 200 mg QD
* Significantly different from placebo; p<0.05
** Significantly different from celecoxib 100 mg BID, 200 mg BID or 200 mg QD

59

Adverse Events With an Incidence ≥5%

Adverse Event	Incidence, % North American Arthritis Trials* (n=4146)	Long-term Open Label Trial (n=4499)
Headache	15.8	16.0
URTI	8.1	14.1
Dyspepsia	8.8	10.1
Sinusitis	5.0	9.2
Diarrhea	5.6	7.7
Accidental Injury	2.9	7.2
Abdominal Pain	4.1	5.5
Nausea	3.5	5.4

* The column shows the incidence of adverse events for celecoxib 100 mg BID, 200 mg QD and BID

60

BEST POSSIBLE

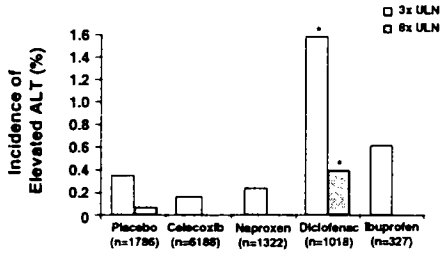
Laboratory Analyses

- Hepatic
- Renal

61

All Arthritis Trials

Incidence of Elevated ALT (%)



* Significantly different from celecoxib; p <0.05
All doses

62

North American 12-Week Placebo and Active-Controlled Arthritis Trials

Incidence of Abnormal Renal Lab Tests (%)

	Placebo	Celecoxib 100 and 200 mg BID	Naproxen 500 mg BID
Creatinine			
>1.8 mg/dL	0.1	0.1	0.0
>3.0 mg/dL	0.0	0.0	0.0
Potassium			
>5.5 mmol/L	0.3	0.4	0.8
>6.0 mmol/L	0.0	0.0	0.0
Uric Acid			
<148.7 µmol/L	0.5	0.8	0.7
<119 µmol/L	0.2	0.1	0.1

Placebo n = 1003 - 1080; celecoxib n = 2058 - 2189; naproxen n = 978 - 1072

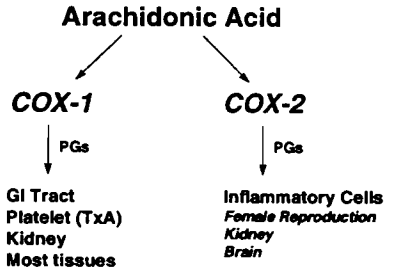
63

Conclusions: General Safety of Celecoxib

- Well tolerated
- Similar short and long term safety profiles
- Incidence of adverse events
  - less than NSAIDs
  - higher than placebo
- Laboratory tests results similar to placebo
- Incidence of elevated liver function tests lower than with diclofenac

64

Two Forms of Cyclooxygenase



65

North American Arthritis Trials

Incidence of CNS/Psychiatric Adverse Events ≥0.5%

Adverse Event	Placebo (n=1864)	Celecoxib[a] (n=4146)	NSAID (n=2098)
Any Event	28.4	25.4*	23.5*
Headache	20.2	15.8*	14.8*
Insomnia	2.3	2.3	2.3
Dizziness	1.7	2.0	2.3
Hypertonia	0.8	1.1**	0.2*
Anxiety	0.6	0.8	0.6
Migraine	1.1	0.7	0.7
Leg Cramps	0.5	0.7	0.9*
Somnolence	0.4	0.6	0.3
Paresthesia	0.4	0.5	0.3
Withdrawals:	0.7	1.1	0.7

[a] doses of 100 mg BID, 200 mg QD and BID
* significantly different from placebo; p <0.05 ** significantly different from NSAID; p <0.05

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BEST POSSIBLE

Effects on Renal Function

- Renal-related adverse events
- Effects on blood pressure
- Renal pharmacology studies
  - healthy elderly
  - chronic renal insufficiency

67

North American Arthritis Trials

Incidence of Renal Adverse Events ≥0.5%

Adverse Event	Placebo (n=1864)	Celecoxib* (n=4146)	NSAID (n=2098)
Any renal event	2.5	4.3*	4.1*
Generalized Edema	0.0	0.1	0.5
Peripheral Edema	1.1	2.1*	2.1*
Hypertension	0.3	0.8	0.7
Aggravated Hypertension	0.4	0.6	0.3
Withdrawals	0.2	0.3	0.3

* 100 mg BID and 200 mg QD or BID
* Significantly different from placebo; p <0.05

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Placebo- and Active-Controlled Arthritis Trials

Effects on Blood Pressure in 12-Week Arthritis Trials

	n	Blood Pressure (mm Hg) Baseline	Mean Change ± SE
Placebo	2194	132/79	-1.9 ± 0.3 / -1.0 ± 0.2
Celecoxib*	4410	132/79	-0.5 ± 0.3 / -0.4 ± 0.1
Naproxen	2150	133/79	-0.9 ± 0.3 / -0.5 ± 0.2

* doses of 50-400 mg BID
Treatments were not significantly different

69

Renal Pharmacology Studies

- Objectives:
  - Assess effects vs. placebo and naproxen
- Design:
  - Healthy elderly and patients with chronic renal insufficiency
  - Duration - 7 to 10 days
- Results:
  - No effects on GFR
  - Transient reduction in sodium excretion (24-48 hrs) similar to naproxen

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Conclusions: Celecoxib Renal Safety

- Renal adverse events - uncommon and similar to NSAIDs
- No effects on blood pressure
- Transient reduction in sodium excretion similar to naproxen
- Low incidence of edema
- No evidence of serious metabolic abnormalities with celecoxib or NSAIDs

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Celecoxib - Clinical Objectives

Indications

- Osteoarthritis
- Rheumatoid Arthritis
- Management of Pain

Differentiation

- Gastrointestinal
- Platelet
- General Safety

72

BEST POSSIBLE

Effects on Platelet Function

- Bleeding-related adverse events
- Platelet studies
  - single dose
  - multiple dose

73

North American Arthritis Trials

Incidence of Bleeding-Related Adverse Events ≥0.5%

Adverse Event	Placebo (n=1864)	Celecoxib[a] (n=4146)	NSAID (n=2098)
Any Bleeding-Related Event	1.6	1.8	3.8* **
Anemia	0.4	0.5	1.6* **
Ecchymosis	0.3	0.4	1.0* **
Withdrawals	0.0	<0.1	0.3

[a] 100 mg BID and 200 mg QD or BID
* Significantly different from placebo; p <0.05
** Significantly different from celecoxib; p <0.05

74

Platelet Studies

- Objectives:
  - Assess effects vs placebo and NSAIDs
- Design:
  - 5 studies in healthy volunteers
  - Duration - 1 to 10 days
- Results:
  - No effect at 2X the therapeutic dose:
    - platelet aggregation
    - TxB_2 production
    - bleeding time

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Conclusions: Celecoxib Effects on Platelet Function

- Bleeding-related adverse events - uncommon, significantly lower than NSAIDs and similar to placebo
- No effect on serum TxB_2 levels, platelet function or bleeding time at 2X the therapeutic dose
- Platelet studies supported the COX-1 sparing effect of celecoxib

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Celecoxib - Clinical Objectives

Indications

- Osteoarthritis
- Rheumatoid Arthritis
- Management of Pain

Differentiation

- Gastrointestinal
- Platelet
- General Safety

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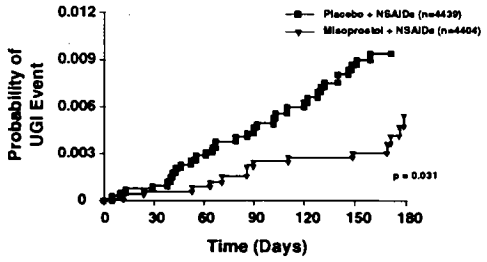
MUCOSA Trial



Derived from Silverstein et al., Ann Intern Med 1996;123:241-249

78

BEST POSSIBLE

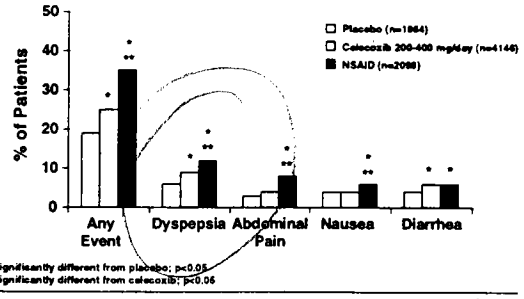
Prospective Evaluation of GI Effects

- GI symptoms
- Endoscopy findings
  - 5 arthritis trials
- Analyses of UGI ulcer complications

79

North American Arthritis Trials

GI Adverse Events



* Significantly different from placebo; p<0.05
** Significantly different from celecoxib; p<0.05

80

North American Arthritis Trials

GI Adverse Events Causing Withdrawal with an Incidence ≥0.5%

Adverse Event	Treatment Group: Placebo (n=1864)	Celecoxib[a] (n=4146)	NSAID (n=2098)
Any GI Event	2.0	2.7	6.3**
Abdominal Pain	0.6	1.0	2.1* **
Dyspepsia	0.6	0.8	1.6*
Diarrhea	0.3	0.3	0.4
Nausea	0.6	0.5	0.9
Esophageal Ulceration	0.0	<0.1	0.6**

a Patients who received either celecoxib 100 mg BID, 200 mg BID or 200 mg QD
* Significantly different from placebo; p<0.05
** Significantly different from celecoxib; p<0.05

81

Prospective Evaluation of GI Effects

- GI symptoms
- Endoscopy findings
  - 5 arthritis trials
- Analyses of UGI ulcer complications

82

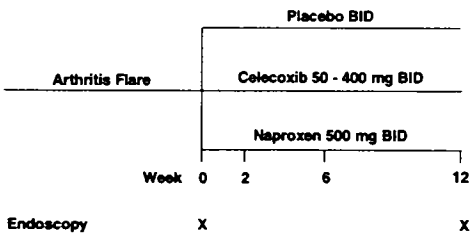
Endoscopic Ulcers are Surrogates for UGI Ulcer Complications

- Rationale:
  - NSAIDs reduce mucosal prostaglandins and cause ulcers
  - Ulcers can result in bleeding, perforation or outlet obstruction
  - Exogenous prostaglandins reduce both endoscopic ulcers and ulcer complications by ~50% over six months[a,b]

a Agrawal et al., *Dig Dis Sci* 1995; 40:1125-1131
b Silverstein et al., *Ann Intern Med* 1995; 123:241-249

83

Design: 12-Week Studies



84

BEST POSSIBLE

Mucosal Grading Scale

Grade	Description
0	No visible lesions (normal mucosa)
1	1-10 petechiae
2	>10 petechiae
3	1-5 erosions*
4	6-10 erosions
5	11-25 erosions
6	>25 erosions
7	Ulcer**

* An erosion is defined as any break in the mucosa without depth
** An ulcer is defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth

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12-Week Endoscopy Studies

	Study No. 021	Study No. 022	Total
Treatment Group (n)			
Placebo	247	231	478
Celecoxib 50 mg BID	258	–	258
Celecoxib 100 mg BID	240	240	480
Celecoxib 200 mg BID	237	235	472
Celecoxib 400 mg BID	–	218	218
Naproxen 500 mg BID	233	225	458
Total	1215	1149	2364

Planned sample size - 200/group

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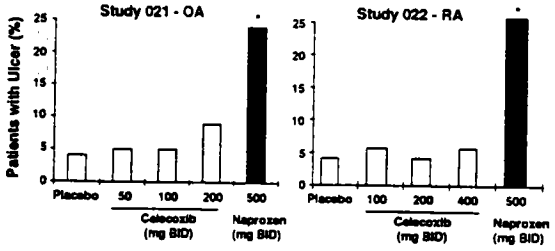
Incidence of Gastroduodenal Ulcers 12-Week Studies

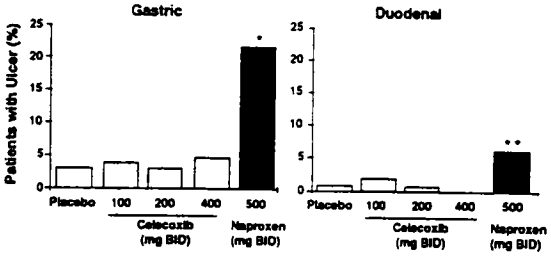


* Significantly different from all other treatments: p <0.001

87

RA and UGI Safety Study - 022

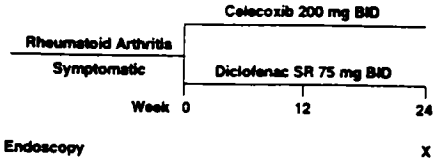
Incidence of Ulcers



* Significantly different from all other treatments: p ≤0.026
** Significantly different from placebo and celecoxib 200 and 400 mg BID: p ≤0.033

88

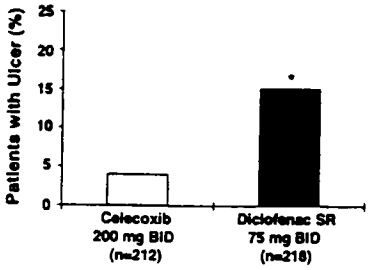
Design: 6-Month RA Study



89

Prevalence

Incidence of Gastroduodenal Ulcers 6-Month Study

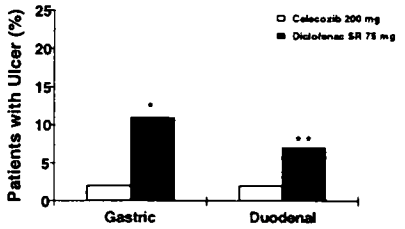


* Significantly different from celecoxib: p <0.001

90

BEST POSSIBLE

Incidence of Ulcers 6-Month Study



* Significantly different from celecoxib; P=0.002
** Significantly different from celecoxib; P=0.003

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Rationale for Serial Endoscopy Trials

- Asymptomatic ulcers may form and reheal without detection (with long intervals between endoscopies)
- Serial endoscopies might better estimate the true incidence of ulcers

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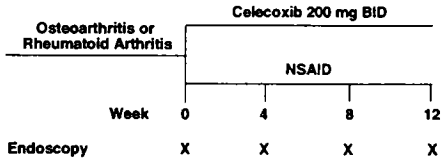
Design: 12-Week Serial Endoscopy Studies



93

12-Week Serial Endoscopy Studies

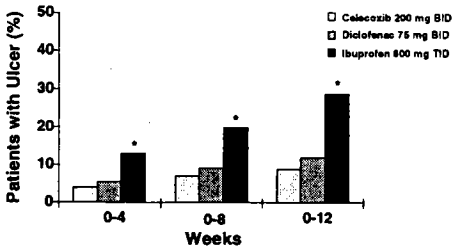
	Study No. 062	Study No. 071	Total
Treatment Group (n)			
Celecoxib 200 mg BID	270	366	636
Naproxen 500 mg BID	267	--	267
Diclofenac 75 mg BID	--	387	387
Ibuprofen 800 mg TID	--	346	346
Total	537	1099	1636

Planned sample size - 200 to 240/group

94

UGI Safety vs Diclofenac and Ibuprofen Study - 071

Cumulative Incidence of Gastroduodenal Ulcers

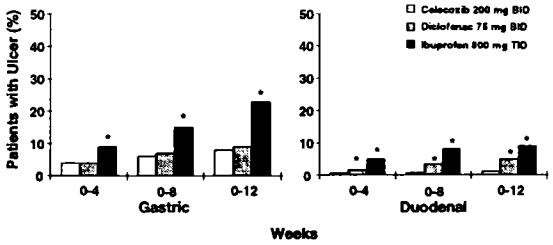


* Significantly different from celecoxib and diclofenac; p <0.001

95

UGI Safety vs Diclofenac and Ibuprofen Study - 071

Cumulative Incidence of Gastric & Duodenal Ulcers



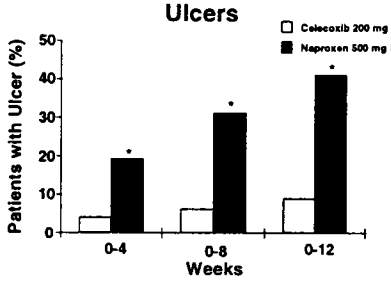
* Significantly different from celecoxib; p <0.05

96

BEST POSSIBLE

UGI Safety vs Naproxen Study - 062

Cumulative Incidence of Gastroduodenal Ulcers

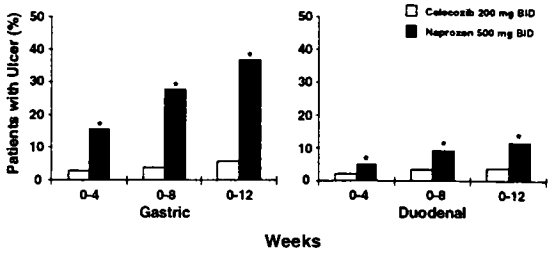


* Significantly different from celecoxib; p <0.001

97

UGI Safety vs Naproxen Study - 062

Cumulative Incidence of Gastric & Duodenal Ulcers



* Significantly different from celecoxib; p <0.05

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Celecoxib Endoscopy Studies

- Endoscopies in over 4,700 arthritis patients
- Incidence of UGI ulcers
  - similar to placebo in replicate studies
  - statistically lower compared to:
    - naproxen
    - diclofenac
    - ibuprofen

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Prospective Evaluation of GI Effects

- GI symptoms
- Endoscopy findings
  - 5 arthritis trials
- Analyses of UGI ulcer complications

100

Identifying UGI Ulcer Complications

- External Committee prospectively defined UGI ulcer complications
- Investigators reported potential cases from OA and RA trials
- Committee reviewed and adjudicated cases
- Committee was blinded to patient, study and treatment

101

UGI Ulcer Complications Committee

- Fred Silverstein, M.D.
- Naurang Agrawal, M.D.
- Jay Goldstein, M.D.

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BEST POSSIBLE

Categories of UGI Ulcer Complications

- Bleeding
- Perforation
- Gastric Outlet Obstruction

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UGI Ulcer Complications Program Overview

	Controlled Trials	Open Label Trial	
		NDA	Safety Update
No. Studies	14	1	-
No. Patients	11,008	4499	5155
No. Patient-Years	1763	2672	5002

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UGI Ulcer Complications Controlled Trials

Treatment	No. Patients	No. Events	K-M Est.*	Patient Years	Events/ 100 Pt. Yrs.	Annual Incidence
Placebo	1864	0	0	208	0	0.00%
Celecoxib	6376	2	0.036%	1020	0.20	0.20%
NSAIDs	2768	9	0.393%	535	1.68	1.68%**

* Estimates of cumulative event rate through 12 Weeks
** Significantly different from celecoxib and placebo; $p < 0.05$

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UGI Ulcer Complications Celecoxib Open-Label Study

	No. Patients	No. Events	K-M Est.*	Patient Years	Events/ 100 Pt. Yrs.	Annual Incidence
NDA	4499	7	0.219%	2672	0.26	0.26%
Safety Update	5155	9	0.226%	5002	0.18	0.18%

* Estimates of cumulative event rate through 18 Months

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UGI Ulcer Complications

	No. Patients	No. Events	K-M Est.*	Patient Years	Events/ 100 Pt. Yrs.	Annual Incidence
NDA	4499	7	0.219%	2672	0.26	0.26%
Safety Update	5155	9	0.226%	5002	0.18	0.18%
CONTROLLED TRIALS						
Celecoxib	6376	2	0.036%	1020	0.20	0.20%

* Estimates of cumulative event rate through 18 Months

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Conclusions: GI Effects of Celecoxib

- NSAID GI class labeling is obviated:
  - similar to placebo:
    - UGI ulcers
    - ulcer complications
  - compared to NSAIDs showed a significant reduction in:
    - GI symptoms
    - UGI ulcers
    - ulcer complications

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BEST POSSIBLE

Celecoxib - Differentiation Summary

NSAIDs	Celecoxib
Gastrointestinal	Gastrointestinal
– Ulcers	– Ulcers and complications similar to placebo
– Complications	– Reduction in ulcers and complications
– Symptoms	– Reduction in symptoms
Hemostasis	Hemostasis
– Inhibit platelets	– No effect on platelet function
Hepatic	Hepatic
– Elevated LFTs	– No elevation in LFTs

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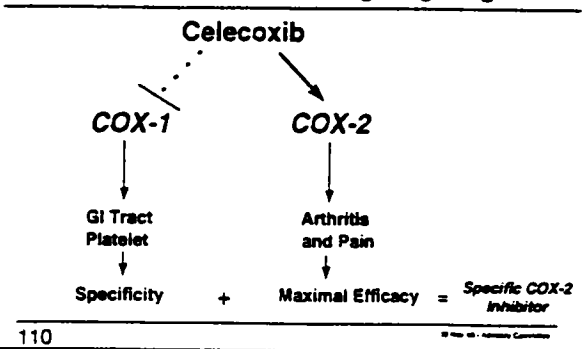
COX-2 Inhibitors: Mechanism Based Drug Targeting



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APPEARS THIS WAY ON ORIGINAL