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

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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

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Celecoxib - Clinical Objectives

Indications
- Osteoarthritis
- Rheumatoid Arthritis
- Management of Pain

Differentiation
- Gastrointestinal
- Platelet
- General Safety

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Pivotal OA Studies

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

6

Design: 12-Week Studies

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

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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

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12-Week OA Studies

	Study No.			
Index Joint	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

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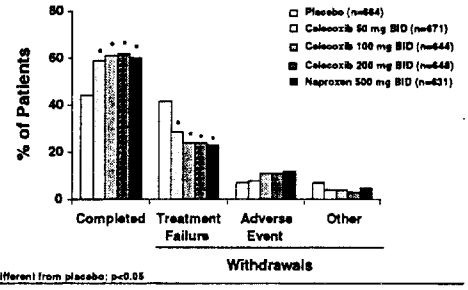
Patient Disposition: 12-Week Studies



Pooled data
* Significantly different from placebo: p<0.05

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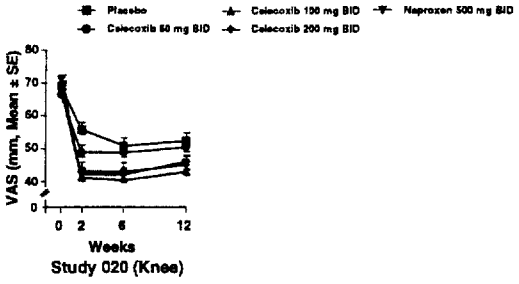
Patient's Assessment of Pain



Scale = 0-100

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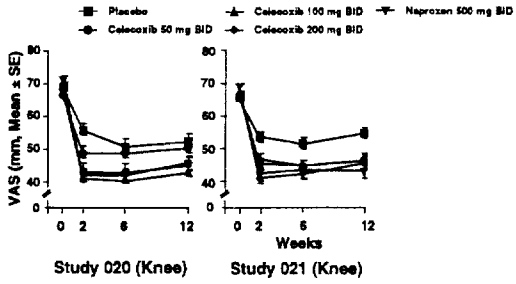
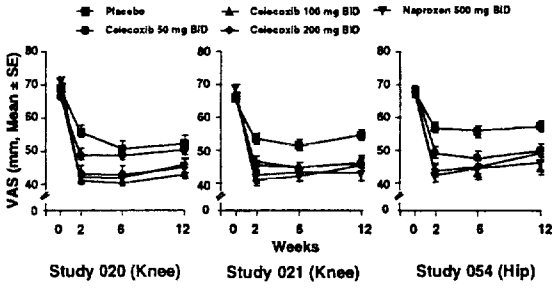
Patient's Assessment of Pain



Scale = 0-100

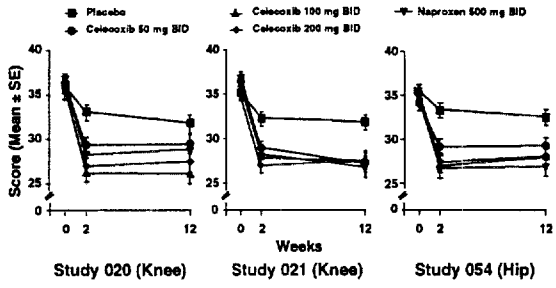
12

Patient's Assessment of Pain



Scale = 0-100

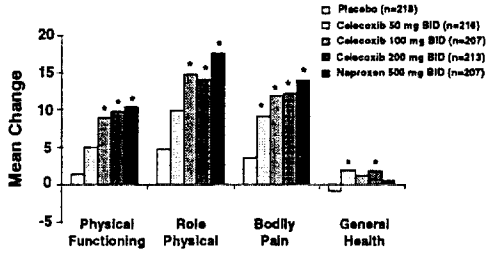
WOMAC - Physical Function



Score = 0 - 68

Hip OA Pivotal Study - 054

SF-36 - Physical Health Domains



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

Design: 6-Week Studies

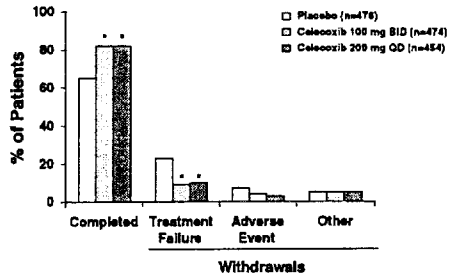
Osteoarthritis Flare	Placebo BID		
	Celecoxib 100 mg BID		
	Celecoxib 200 mg QD		
Week	0	2	6
Arthritis Assessments	X	X	X

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

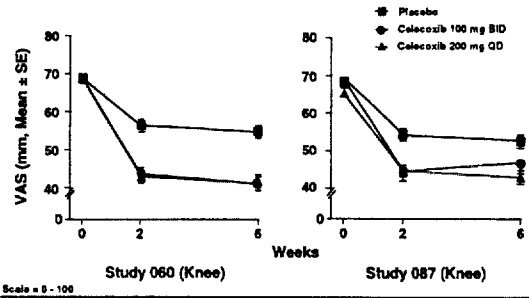
Planned sample size - 200/group

Patient Disposition: 6-Week Studies



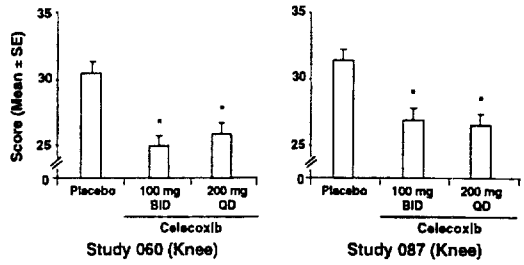
Pooled data
* Significantly different from placebo; p<0.05

Patient's Assessment of Pain



Scale = 0 - 100

WOMAC - Physical Function at Week 6



Score = 0 - 68

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

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

Celecoxib - Clinical Objectives

Indications

- Osteoarthritis
- Rheumatoid Arthritis
- Management of Pain

Differentiation

- Gastrointestinal
- Platelet
- General Safety

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

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

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

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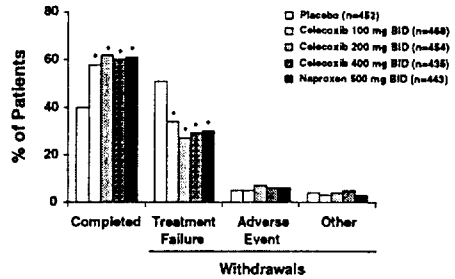
Patient Disposition: 12-Week Studies



Pooled data
* Significantly different from placebo: p<0.05

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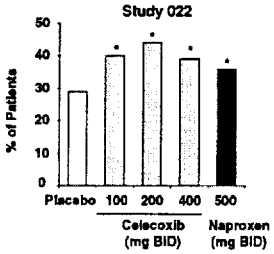
ACR-20 at Week 12



* Significantly different from placebo; p <0.05

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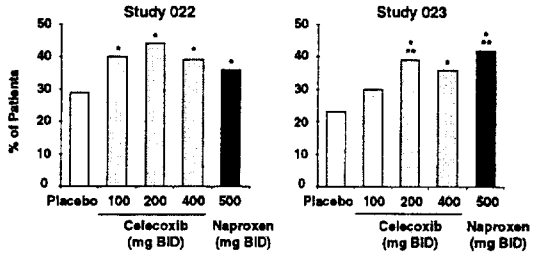
ACR-20 at Week 12



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

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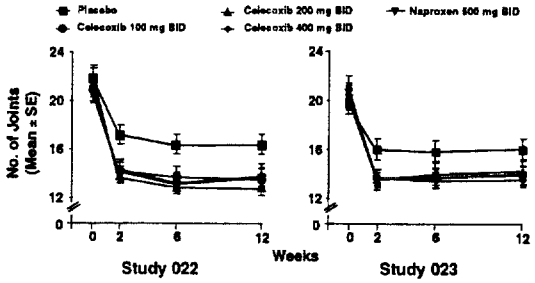
Number of Swollen Joints



68 joints examined (excludes hips)

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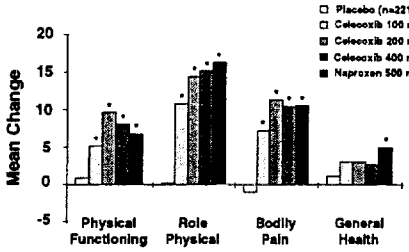
Pivotal RA Study - 023

SF-36 - Physical Health Domains



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

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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

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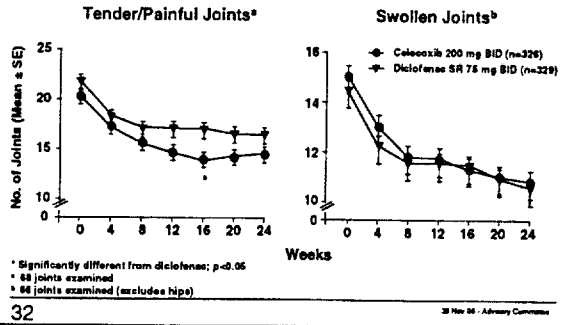
6-Month RA Study



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

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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)

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

Model # 2
SHORT TERM PAIN
(1 - 7 DAYS)

- OA flare
  - 3 pivotal studies
  - multiple dose

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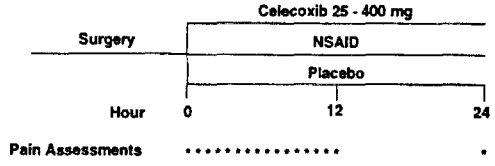
Model # 1

Design: Post-Dental Surgery Studies



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Model # 1
Measures of Efficacy

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

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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

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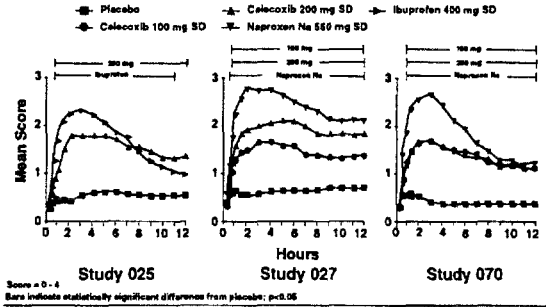
Model # 1
Time Specific Pain Relief



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

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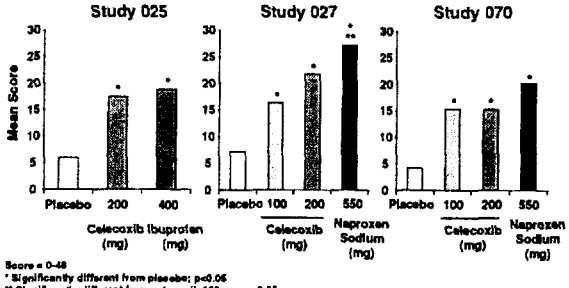
Model #1
TOTPAR (12) Scores



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

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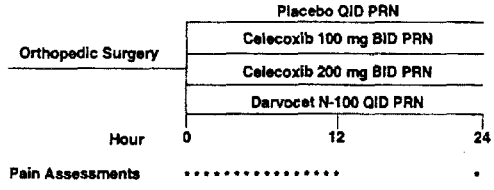
Model # 1 - Supporting Study
Design: Post-Orthopedic Surgery Study



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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

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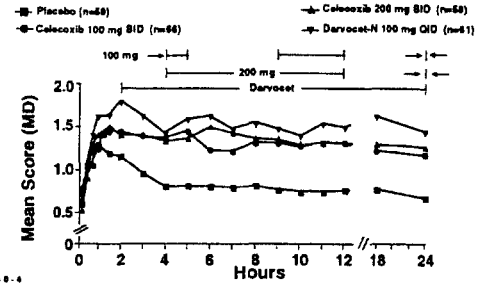
Model # 1
Time Specific Pain Relief



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

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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	

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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
Jansen, E.M., Ginsberg, F., *Drug Invest* 1994; 8:211-218

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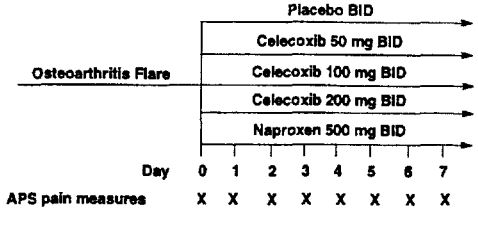
Model # 2
Design: Three Pivotal 12-Week OA Studies



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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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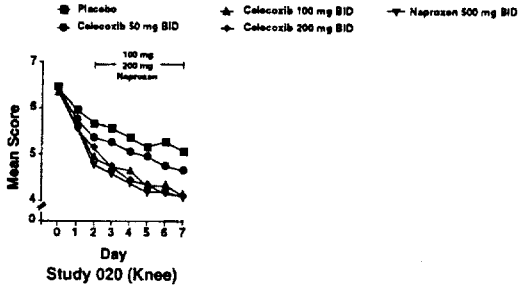
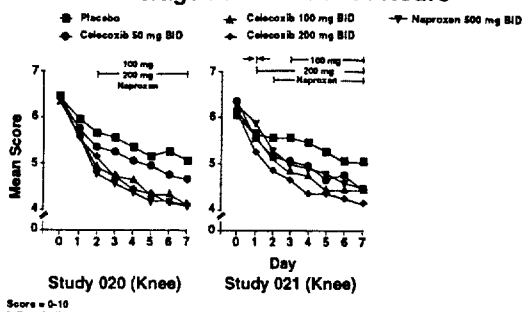
Model # 2
Average Pain in Past 24 Hours



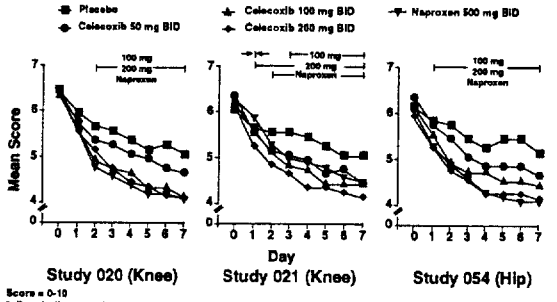
Score = 0-10
* Bars indicate statistically significant difference from placebo; $P < 0.05$

Model # 2
Average Pain in Past 24 Hours



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

Model # 2
Average Pain in Past 24 Hours



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

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

Celecoxib - Clinical Objectives

Indications

- Osteoarthritis
- Rheumatoid Arthritis
- Management of Pain

Differentiation

- Gastrointestinal
- Platelet
- General Safety

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

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

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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

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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

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Adverse Events With an Incidence ≥5%

Adverse Event	Incidence, % North American Arthritis Trials* (n=4146)	Incidence, % 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

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Laboratory Analyses

- Hepatic
- Renal

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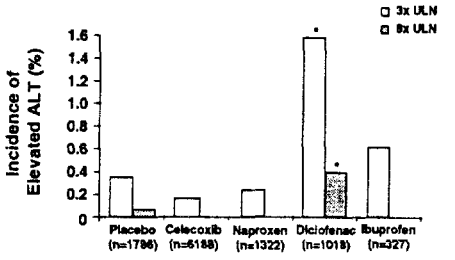
All Arthritis Trials

Incidence of Elevated ALT (%)



* Significantly different from celecoxib; p <0.05
All doses

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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 = 2066 - 2189; naproxen n = 979 - 1072

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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

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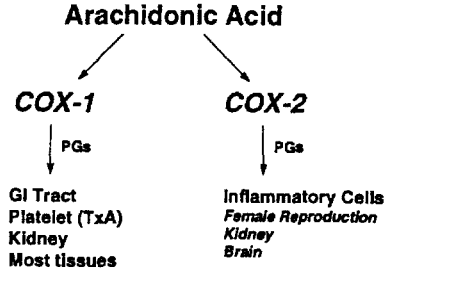
Two Forms of Cyclooxygenase



65

North American Arthritis Trials

Incidence of CNS/Psychiatric Adverse Events ≥0.5%

Adverse Event	Placebo (n=1864)	Celecoxib* (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

* 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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Effects on Renal Function

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

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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

		Blood Pressure (mm Hg)	
	n	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

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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

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Effects on Platelet Function

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

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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; $p < 0.05$

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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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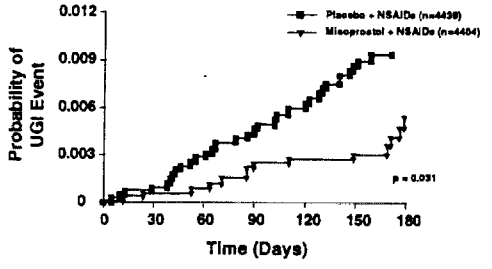
MUCOSA Trial



Derived from Silverstein et al., Ann Intern Med 1995;123:241-249

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Prospective Evaluation of GI Effects

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

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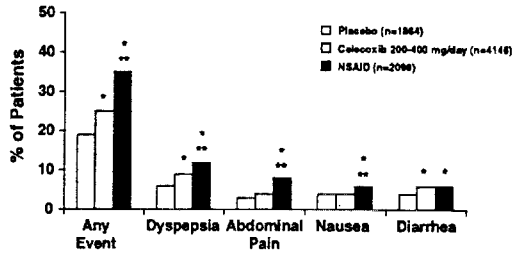
North American Arthritis Trials

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

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Prospective Evaluation of GI Effects

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

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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

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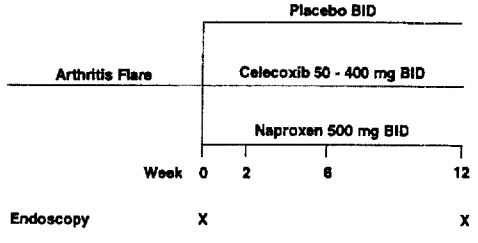
Design: 12-Week Studies



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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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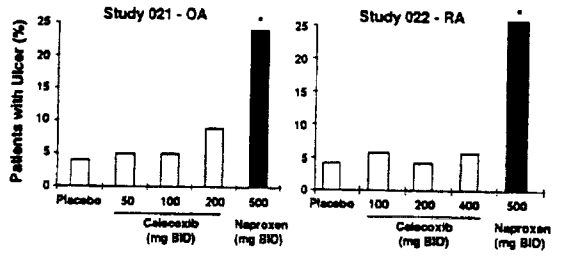
Incidence of Gastroduodenal Ulcers 12-Week Studies

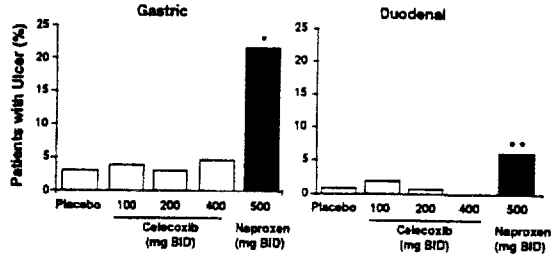


* Significantly different from all other treatments: p <0.001

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 ≤0.053

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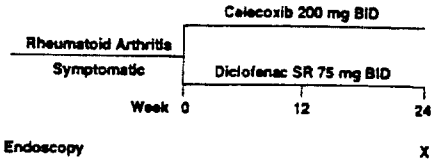
Design: 6-Month RA Study



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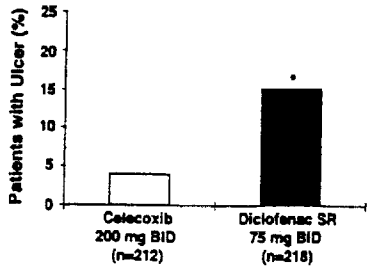
Incidence of Gastroduodenal Ulcers 6-Month Study



* Significantly different from celecoxib; p <0.001

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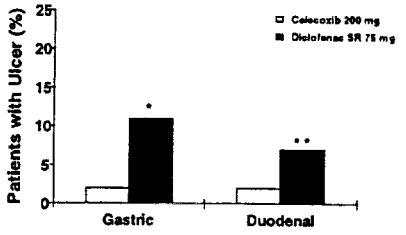
Incidence of Ulcers 6-Month Study



* 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

92

Design: 12-Week Serial Endoscopy Studies

Osteoarthritis or Rheumatoid Arthritis	Celecoxib 200 mg BID			
	NSAID			
Week	0	4	8	12
Endoscopy	X	X	X	X

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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

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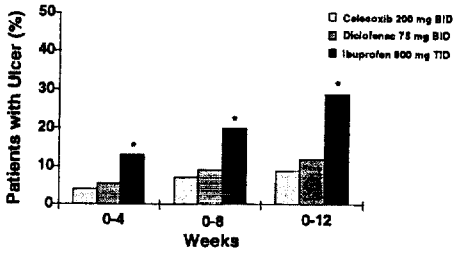
UGI Safety vs Diclofenac and Ibuprofen Study - 071

Cumulative Incidence of Gastroduodenal Ulcers



* Significantly different from celecoxib and diclofenac; p <0.001

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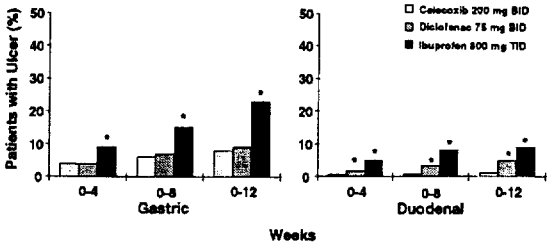
UGI Safety vs Diclofenac and Ibuprofen Study - 071

Cumulative Incidence of Gastric & Duodenal Ulcers



* Significantly different from celecoxib; p <0.05

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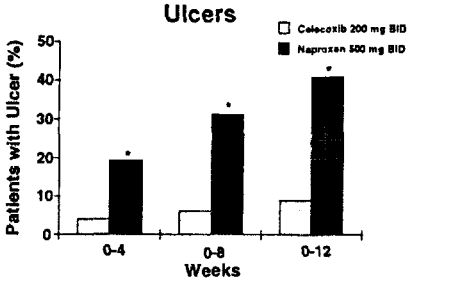
UGI Safety vs Naproxen Study - 062

Cumulative Incidence of Gastroduodenal Ulcers



* Significantly different from celecoxib; p <0.001

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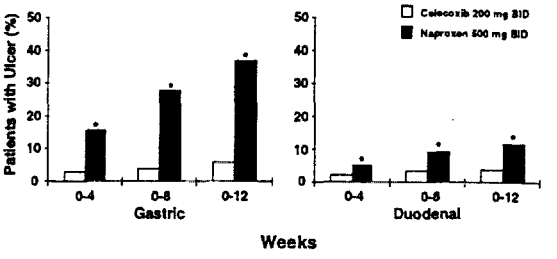
UGI Safety vs Naproxen Study - 062

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

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UGI Ulcer Complications Committee

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

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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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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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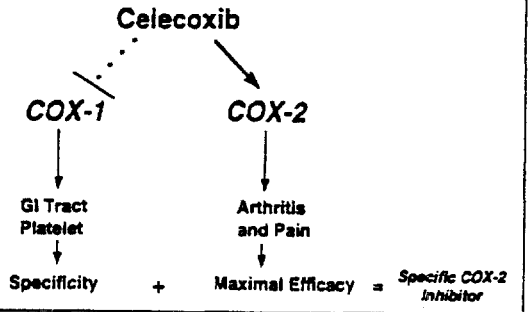
COX-2 Inhibitors: Mechanism Based Drug Targeting



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