CLASS

Celecoxib Long-term Arthritis Safety Study

Agenda

Introduction

Philip Needleman, Ph.D.
Senior Executive Vice President
Chief Scientist and Chairman
Research and Development

UGI Safety Profile of NSAIDs and
Celecoxib: Rationale for CLASS Study

G. Steven Geis, Ph.D., M.D.
Vice President
Arthritis Clinical R&D

Safety Profile of Celecoxib:
CLASS, Long Term Safety Trial

James Lefkowith, M.D.
Senior Director
Arthritis Clinical R&D

Summary

Fred Silverstein, M.D.
Chairman
CLASS Executive Committee
Introduction

Philip Needleman, Ph.D.
Pharmacia
Research and Development
The COX-2 Hypothesis: ca. 1990
Mechanism-Based Drug Targeting

**Arachidonic Acid**

- **COX-1** (Constitutive)
  - Stomach
  - Intestine
  - Kidney
  - Platelet

- **COX-2** (Inducible)
  - Inflammation
  - Pain

NSAIDs

(-)

celecoxib
Clinical Efficacy of Celecoxib in RA Patients

Reduction in Number of Swollen Joints

Change from Baseline (Mean ± SEM)

![Graph showing reduction in swollen joints](image)

Incidence of Gastroduodenal Ulcers

![Graph showing incidence of ulcers](image)

* Significantly different from 0 mg; \( P \leq 0.05 \)

* \( P < 0.001 \) vs other treatments

Celecoxib NDA Perspective

• Advisory Committee unanimously recommended approval of celecoxib (Celebrex) for signs and symptoms of OA and adult RA; approved Dec 29, 1998 by FDA.

• Celebrex demonstrated greater UGI safety than conventional NSAIDs

• Key unresolved issue:

  Would the decrease in endoscopic ulcers with celecoxib translate into improved, clinically meaningful GI safety in a large, well controlled outcomes trial?
CLASS Trial Design: Collaboration with FDA

• Primary objective: assess GI safety profile of Celebrex; may provide insight into other COX-related safety issues

• Rigorous trial of OA and RA patients that mimicked clinical practice – allowed cardioprotective aspirin

• Utilized two NSAIDs, including ibuprofen, at commonly used doses

• Studied Celebrex at 2 to 4 times the maximally effective therapeutic doses in arthritis
The COX-2 Hypothesis
2001

Arachidonic Acid

**COX-1**
(Constitutive)

- Stomach
- Intestine
- Kidney
- Platelet
- Endothelium

**COX-2**
(Inducible)

- (-)
- Celebrex

- NSAIDs
- Inflammation/Pain
- Tumors
- Kidney
- Central Nervous System
- Female Reproduction
- Endothelium?

NSAIDs
Areas where CLASS data may shed light on the roles of COX-1 and COX-2

• **Definitely:**
  – GI events
  – Blood loss

• **Possibly:**
  – Effects of Low Dose Aspirin
  – Renal
  – Cardiovascular/Thrombosis

• **Unlikely:**
  – Female Reproduction
  – Central Nervous System
  – Cancer
Low Dose Aspirin

• Aspirin covalently inhibits platelet COX-1, providing cardioprotection and increased bleeding potential
  – NSAIDs transiently inhibit platelet COX-1

• Aspirin causes direct damage to the GI mucosa

• Low dose aspirin shown to increase risk of GI ulcer complications (Lanas et al., NEJM 2000; 343: 834)

CLASS data can provide insight into the GI effects of aspirin
Renal COX-1/COX-2

- Both COX isoforms are expressed constitutively
- Localization in laboratory animals is distinct from that in primate
- NDA database did not distinguish Celebrex from NSAIDs

*CLASS database may provide further insight*
Cardiovascular/Thrombosis

- Low dose aspirin reduces risk of a myocardial infarction by inhibiting platelet COX-1
  - Clear benefit during an acute MI, unstable angina, and in secondary prevention of MI
  - Marginal benefit in primary prevention of MI

- Blood vessels and endothelium produce PGI2 predominantly by COX-1

- Endothelium also produces the potent anti-thrombotic nitric oxide (NO)
Celecoxib NDA Study 065

Platelet Aggregation

*\textit{p} <0.05 vs placebo
# Effect of Celecoxib on Human Urinary PGI$_2$ Metabolites: Potential for COX-2 and the Endothelium?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PGI-M (pg/mg creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>117 +/- 49</td>
</tr>
<tr>
<td>Celecoxib, 400 mg</td>
<td>34 +/- 7</td>
</tr>
<tr>
<td>Celecoxib, 800 mg</td>
<td>23 +/- 9</td>
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<td>Ibuprofen, 800 mg</td>
<td>51 +/- 19</td>
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### Effect of Celecoxib on Human Urinary PGI$_2$ Metabolites

*Potential for COX-2 and the Endothelium?*

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- PGI$_2$ is a potent vasodilator and inhibits platelet aggregation

- McAdam et al. suggested that the endothelium is the source of the COX-2 and PGI$_2$

• NSAIDs inhibit both COX-1 and COX-2
  • No net effect on thrombosis
• COX-2 inhibitors allow unopposed production of TxA₂
  • Potential for increased risk for thrombotic events

*If the hypothesis is correct, the expected effect would be similar to that of not taking aspirin in an “at risk” population*
CLASS Trial: Potential for assessing CV risk

• The cardioprotective benefits of aspirin in reducing primary CV event (MI) - or for a COX-2 inhibitor to cause a CV event - requires a sample size of >20,000 patients, treated for five years (NEJM 321:129,1989)

• Therefore, the CLASS trial (~4000 pts) was not large enough to detect small CV effects due to COX-2 inhibition of endothelial PGI₂ production

• However, the CLASS trial was large enough to establish the general CV safety profile of Celebrex
Summary

• The preponderance of the clinical data supports the safety of the COX-2 inhibitor – Celebrex compared to NSAIDs
  – Endoscopy
  – Evaluation of ulcers and complications
  – Post-marketing surveillance

• Evaluation of exaggerated doses of Celebrex in a large controlled trial revealed no new safety signals.

• Celebrex did not increase thromboembolic events when compared to NSAIDs, in the absence or presence of aspirin.
# CLASS

## Celecoxib Long-term Arthritis Safety Study

### Agenda

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Upper GI Safety Profile of NSAIDs and Celecoxib:

Rationale for CLASS Study

G. Steven Geis, PhD MD
Vice President, Arthritis Clinical R&D
Overview

- NSAID-associated upper GI toxicity
- Prospective trials to evaluate upper GI safety
- Upper GI safety of celecoxib
Overview

• **NSAID-associated upper GI toxicity**
  – Definition
  – Incidence
  – Patients at Risk

• Prospective trials to evaluate upper GI safety

• Upper GI safety of celecoxib
Clinical Evidence of NSAID-Related Upper GI Injury

- Symptomatic ulcers
- Ulcer complications
  - Perforation
  - Bleeding
  - Outlet obstruction
Symptomatic Ulcer
Ulcer with Visible Vessel
Bleeding Ulcer
Ulcer Perforation
Spectrum of NSAID-Related Upper GI Injury

Symptomatic Ulcer → Ulcer Complication
Clinical Evidence of NSAID-Related Upper GI Injury

- Symptomatic ulcers
- Ulcer complications
  - Perforation
  - Bleeding
  - Outlet obstruction

POB

PUB
Magnitude of NSAID-Related Upper GI Toxicity

• Observational cohort and retrospective cohort or case control studies
  – Examined hospital records for diagnoses of:
    • Symptomatic ulcers
    • Ulcer complications
Magnitude of NSAID-Related Upper GI Toxicity

Overall Incidence 2-4% per yr

Symptomatic Ulcers

Complicated Ulcers
Incidence of Ulcer Complications

Incidence (cases/100 pt-yr)

**NSAIDs**
- GI Hospitalizations: 1.31%
- Bleeding/Perforation: 1.66%

**Non-NSAIDs**
- GI Hospitalizations: 0.28%
- Bleeding/Perforation: 0.25%

### NSAIDs: GI Morbidity and Mortality

<table>
<thead>
<tr>
<th></th>
<th>Patient Years</th>
<th>Hospitalizations</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (Rate*)</td>
<td>No. (Rate*)</td>
<td>No. (Rate*)</td>
</tr>
<tr>
<td><strong>Tennessee</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicaid- ≥65 yrs¹ (est.)</td>
<td>2,340,000</td>
<td>41,000 (17.5)</td>
<td>3,300 (1.41)</td>
</tr>
<tr>
<td>Aramis² (est.)</td>
<td>13,000,000</td>
<td>107,000 (8.2)</td>
<td>16,500 (1.27)</td>
</tr>
</tbody>
</table>

* Per 1000 patient-years

## Risk Factors for NSAID-Related Symptomatic Ulcers/Ulcer Complications

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing Age</td>
<td>+++</td>
</tr>
<tr>
<td>Female</td>
<td>+</td>
</tr>
<tr>
<td>Concomitant Disease</td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>++</td>
</tr>
<tr>
<td>CV Disease</td>
<td>++</td>
</tr>
<tr>
<td>History of Ulcer or GI Bleed</td>
<td>+++</td>
</tr>
<tr>
<td>Alcohol or Smoking</td>
<td>+</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>High dose, long-term NSAIDs</td>
<td>+++</td>
</tr>
<tr>
<td>Low dose ASA</td>
<td>+++</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>++</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>+</td>
</tr>
</tbody>
</table>
### Odds Ratios for Ulcer Complications: Effect of NSAID Use and Age

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>15-59</th>
<th>60-79</th>
<th>≥80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Nonusers</td>
<td>1.0</td>
<td>3.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Female NSAID Users</td>
<td>4.9</td>
<td>16.6</td>
<td>57.2</td>
</tr>
<tr>
<td>Male Nonusers</td>
<td>2.0</td>
<td>4.8</td>
<td>18.4</td>
</tr>
<tr>
<td>Male NSAID Users</td>
<td>10.4</td>
<td>19.4</td>
<td>50.6</td>
</tr>
</tbody>
</table>

Perez-Gutthan et al. Epidemiology 1997;8:18-24
Risk of Upper GI Bleeding Related to Prophylactic Aspirin

* CI - Confidence interval

Weil et al. BMJ 1995;310:827-830

Aspirin (Daily Dose)

Odds Ratio

- 75 mg: CI* 1.2-4.4
- 150 mg: CI 1.7-6.8
- 300 mg: CI 2.5-6.3
## Risk of Upper GI Bleeding – Meta Analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1.8 (1.4-2.3)</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>2.2 (1.2-4.1)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>2.2 (1.7-2.9)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>2.5 (1.5-4.1)</td>
</tr>
<tr>
<td>Sulindac</td>
<td>2.1 (1.6-2.7)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>3.8 (2.7-5.2)</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>4.2 (2.7-6.4)</td>
</tr>
</tbody>
</table>

Henry et al. BMJ;1996 312:1563-1566
Conclusions: NSAID-Related Upper GI Toxicity

• Symptomatic ulcers and ulcer complications are on a continuum of GI toxicity
• All NSAIDs are associated with symptomatic ulcers and ulcer complications
• Approximately 16,500 deaths/year due to NSAID GI toxicity
Overview

• **NSAID-associated upper GI toxicity**

• **Prospective trials to evaluate upper GI safety**
  – Endoscopic ulcers
  – Ulcer complications

• **Upper GI safety of celecoxib**
Definitions: NSAID-Related Upper GI Toxicity

- **Symptomatic ulcers**
  - GI toxicity encountered in clinical practice
  - Identified by “for cause” endoscopy

- **Endoscopic ulcers**
  - Measure of GI toxicity in clinical investigations
  - Identified by scheduled endoscopy in a clinical trial
Prevalence of Endoscopic Gastroduodenal Ulcers in NSAID Users

*Cefuroxime, sulindac, flurbiprofen, etodolac, ketoprofen, aspirin

Prevalence of Endoscopic Ulcers in NSAID Users

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Gastric Ulcer (%)</th>
<th>Duodenal Ulcer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheatum et al.</td>
<td>1826</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Nobunaga et al.</td>
<td>1008</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Roth et al.</td>
<td>239</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Farah et al.</td>
<td>18</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Collins et al.</td>
<td>150</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>Sontag et al.</td>
<td>140</td>
<td>30</td>
<td>10</td>
</tr>
</tbody>
</table>
Prevalence of Endoscopic Gastrointestinal Ulcers by Age in NSAID Users

Patients with Ulcer (%)

30-39: n=186
40-49: n=382
50-59: n=127
60-69: n=129
70-79: n=67

Endoscopic Ulcers: Surrogates for Ulcer Complications?
Endoscopic Ulcers: Surrogates for Ulcer Complications?

• **Rationale:**
  – NSAIDs reduce mucosal prostaglandins and cause ulcers
  – Ulcers can result in bleeding, perforation or outlet obstruction

• **Development program for misoprostol (synthetic prostaglandin) investigated the relationship**
Design: 52-Week Endoscopy Study

- **Osteoarthritis or Rheumatoid Arthritis**
  - NSAID + placebo
  - NSAID + misoprostol

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy</td>
<td>X</td>
<td>X</td>
<td>X</td>
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- NSAID + misoprostol
- NSAID + placebo
- Osteoarthritis or Rheumatoid Arthritis
- Endoscopy

**Design:** 52-Week Endoscopy Study

**Osteoarthritis or Rheumatoid Arthritis**
- NSAID + placebo
- NSAID + misoprostol

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<td>X</td>
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Incidence of Endoscopic Gastroduodenal Ulcers Developing Over One Year


- NSAIDs + misoprostol (n=102)
- NSAIDs + placebo (n=102)

p = 0.018
MUCOSA: A Study of Relevant Outcomes

- Prospective randomized double-blind trial
- Primary endpoint
  - Ulcer complications (bleeding, perforation, obstruction)
MUCOSA: Trial Design

- The design paralleled normal medical practice
- No scheduled endoscopy
Ulcer Complications: MUCOSA Definitions

1. Perforation
2. Gastric outlet obstruction
3. Lesion + hematemesis
4. Lesion + melena
5. Lesion + evidence of bleeding (active bleeding, signs of recent hemorrhage, blood in the stomach)
6. Lesions + hemoccult positive stool + evidence of recent bleed (drop in hematocrit, orthostasis)
7. Hematemesis without identified lesion; no alternate cause
8. Melena plus hemoccult positive stool
MUCOSA
Ulcer Complications: Time to Event Analysis

Placebo + NSAIDs (n=4439)
Misoprostol + NSAIDs (n=4404)

Incidence (% per 6 mo)

Time (Days)

p = 0.031

Conclusions: Prospective GI Safety Trials

- Endoscopic ulcers and ulcer complications are reliable endpoints for investigating GI safety
- Endoscopic ulcers are predicative of ulcer complications
  - Exogenous prostaglandins reduce both endoscopic ulcers and ulcer complications by ~50%1,2

Overview

- NSAID-associated upper GI toxicity
- Prospective Trials to Evaluate Upper GI Safety
- Upper GI Safety of Celecoxib
NDA: Celecoxib Endoscopy Studies

- Endoscopies in over 4,700 arthritis patients
- Incidence of upper GI ulcers
  - similar to placebo in replicate studies
  - statistically lower compared to:
    - naproxen
    - diclofenac
    - ibuprofen
NDA: Incidence of Gastroduodenal Ulcers
3 Month Endoscopy Trials

ND = Not Done
* Significantly different from all other treatments; p < 0.05
NDA: Incidence of Gastroduodenal Ulcers
6-Month Endoscopic Study

Patients with Ulcer (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib 200 mg BID (n=212)</td>
<td>4</td>
</tr>
<tr>
<td>Diclofenac SR 75 mg BID (n=218)</td>
<td>16</td>
</tr>
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* Significantly different from celecoxib; p <0.001
NDA: Prospective Evaluation of GI Effects

- Endoscopy findings
  - 5 arthritis trials
- Analyses of upper GI ulcer complications
Methods: Analyses of Ulcer Complications

- 14 randomized controlled trials and one open-label trial of OA and RA patients
- Criteria for upper GI ulcer complications were prospectively developed
- Cases were adjudicated by Events Committee
  - Blinded to the trial and
  - Blinded to the study drug
Upper GI Ulcer Complications - Definitions

- Upper GI Perforation
- Gastric Outlet Obstruction
- Upper GI Bleeding
## NDA: Ulcer Complications

<table>
<thead>
<tr>
<th></th>
<th>Controlled Trials</th>
<th>Open Label Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>11,008</td>
<td>5155</td>
</tr>
<tr>
<td>Duration</td>
<td>12 weeks</td>
<td>2 years</td>
</tr>
<tr>
<td>Primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib Doses</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>200 – 400 mg /day</td>
<td></td>
</tr>
</tbody>
</table>
NDA: Incidence of Ulcer Complications

* Significantly different from all other treatments; p < 0.05
Goldstein et al. Am J Gastroenterol 2000;95:1681-1690
NDA Conclusions: GI Effects of Celecoxib

• **Incidence of endoscopic ulcers**
  – Similar to placebo
  – Lower than NSAIDs

• **Endoscopic ulcer data were predictive of ulcer complication results**

• **Incidence of ulcer complications**
  – Lower than NSAIDs
Clinical Relevance

• The generalizability of the ulcer complications analysis was uncertain:

  – About 40% of patients were ulcer free by endoscopy at study entry
  – Most studies were 3 months in duration
Rationale for CLASS

• Rigorous assessment of upper GI safety of celecoxib:
  • Using clinically relevant outcomes
  • In patients that fully represent the intended population
  • With chronic exposure
CLASS Design

- Large prospective randomized study
- Mirror usual medical practice
  - Endoscopy performed “for cause”
- Included:
  - OA and RA patients
  - High risk patients
  - Low dose ASA
- Celecoxib 400 mg BID (4X OA dose; 2X highest RA dose)
- Longer duration of exposure (up to 15 mo)
The End
Safety Profile of Celecoxib:

CLASS

Celecoxib Long-term Arthritis Safety Study

James B. Lefkowith, MD
Sr. Director, Arthritis Clinical R&D
CLASS Design Overview

• “Real world” study
  – Clinical practice conditions
  – Low dose aspirin allowed
  – RA and OA patients included

• Stringent test of safety
  – Celecoxib: 2-4x RA and OA doses
  – NSAID Comparators: Ibuprofen, Diclofenac
CLASS Design

• Objectives
• Study design
• Analysis plan
• Oversight committees
Objectives

Celecoxib vs. NSAIDs (ibuprofen, diclofenac)

• Compare the incidence of:
  – ulcer complications
  – symptomatic ulcers
• Evaluate impact of risk factors on outcome: ASA
• Compare general safety and tolerability
CLASS Design

- Objectives
- Study design
- Analysis plan
- Oversight committees
CLASS Trial

**Design:**
- Double-blind, randomized, parallel group
- Two protocols - pooled analysis
- Minimum 6 months exposure

**Inclusions:**
- OA and RA patients

**Exclusions:**
- History of:
  - recent or active GI disease
- Labeled contraindications
CLASS Trial

**Co-Meds:**
- **Permitted:**
  - ASA ≤ 325 mg/d
  - limited antacid use
- **Excluded:**
  - anti-ulcer drugs (H₂RAs, PPIs)
  - NSAIDs

**Treatments:**
- Celecoxib 400 mg BID
- Diclofenac 75 mg BID
- Ibuprofen 800 mg TID
CLASS Trial

- Power calculation:
  - Ulcer complication rate:
    - celecoxib vs. NSAIDs
      0.3 vs. 1.2 events/100 pt-yrs
    - assumptions:
      constant incidence rates
      ASA use ~ 12%
    - 40 total events; 8000 patients
      - 4000 celecoxib
      - 4000 NSAIDs (2000 per comparator)
CLASS Design

- Objectives
- Study design
- Analysis plan
- Oversight committees
Analysis Plan

• **Endpoints analyzed**
  – Ulcer complications
  – Symptomatic ulcers/ulcer complications

• **Statistics**
  – Intent-to-Treat Analysis
  – Log-rank test of time-to-event
  – Step-wise comparison
    • Celecoxib vs. NSAIDs combined
    • Celecoxib vs. each NSAID
Analysis Plan

• Risk Factors
  • ASA use
  • Risk factors defined by MUCOSA
    • Age $\geq 75$ y
    • History of ulcer
    • History of GI bleeding
    • Cardiovascular disease
  • Others (e.g., alcohol intake, smoking)
CLASS Design

- Objectives
- Study design
- Analysis plan
- Oversight committees
CLASS Committees

Executive Committee
- Fred Silverstein, M.D (Chair)
- Lee Simon, M.D.
- Gerald Faich, M.D.

GI Events Committee
- Jay Goldstein, M.D. (Chair)
- Naurang Agrawal, M.D.
- William Stenson, M.D.
- Glenn Eisen, M.D.

Data Safety Monitoring Board
- Gerald Faich, M.D. (Chair)
- Robert Makuch, Ph.D.
- Andrew Whelton, M.D.
- Theodore Pincus, M.D.
CLASS Committee Charters

- **GI Events Committee - GEC**
  - Review potential GI events

- **Data Safety Monitoring Board - DSMB**
  - Evaluate safety data

- **Executive Committee - EC**
  - Monitor and administer study conduct
Algorithm for Work-Up of Suspected Events by Investigator

Monitor for signs and/or symptoms of ulcer complications (e.g., dyspepsia, abdominal pain, anemia or melena)

If Present

Obtain further clinical data
- stool heme x 3
- Hct and Hgb
- orthostatic vital signs

If Indicated

Endoscope or contrast x-ray

Clinical follow-up as appropriate
Algorithm for Work-Up of Suspected Events by Investigator

Monitor for signs and/or symptoms of ulcer complications (e.g., dyspepsia, abdominal pain, anemia or melena)

If Present
- Obtain further clinical data
  - stool heme x 3
  - Hct and Hgb
  - orthostatic vital signs

If Indicated
- Endoscopy or contrast x-ray

Clinical follow-up as appropriate

Report Case to GEC
Evaluation Process

Potential Events Reported

GEC Review

Ulcer Complication
Symptomatic Ulcer
Other Diagnosis*

*Other diagnoses: esophagitis, gastritis, duodenitis, anemia etc
Ulcer Complications

Prospectively defined:

- Bleeding
- Perforation
- Gastric Outlet Obstruction

*All ulcer complications required endoscopic/contrast x-ray evidence of an ulcer or large erosion*
Ulcerc Complications: Bleeding

1A. Hematemesis + lesion
1B. Active bleeding/stigmata + lesion
1C. Melena + lesion
1D. Hemoccult positive stool + lesion + clinical evidence of blood loss
Symptomatic Ulcers

Prospectively defined:

- Mucosal break with unequivocal depth
- Found on “for cause” work-up (to investigate a sign or symptom)

All ulcers required endoscopic/contrast x-ray evidence
## CLASS Results

### GI Outcomes
- Study population
- GI Outcomes
  - Intent-to-treat
  - Risk Factors
  - Effect of ASA Use
  - RA vs OA
- Sources of Bias

### General Safety
- Overall Safety
- Analysis by System
  - GI
  - Renal
  - Hepatic
  - CV/Thromboembolic
- Analysis in ASA users
- Analysis by Age
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 400 mg BID (n=3987)</th>
<th>Diclofenac 75 mg BID (n=1996)</th>
<th>Ibuprofen 800 mg TID (n=1985)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs, mean)</td>
<td>60.6</td>
<td>60.1</td>
<td>59.5</td>
</tr>
<tr>
<td>Female (%)</td>
<td>69</td>
<td>67</td>
<td>71</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>88.5</td>
<td>89.4</td>
<td>86.3</td>
</tr>
<tr>
<td>Black</td>
<td>7.5</td>
<td>7.6</td>
<td>8.7</td>
</tr>
<tr>
<td>Other</td>
<td>4.0</td>
<td>3.1</td>
<td>5.1</td>
</tr>
<tr>
<td>OA (%)</td>
<td>72.7</td>
<td>72.8</td>
<td>72.2</td>
</tr>
</tbody>
</table>
## Baseline Risk Factors for Ulcer Complications

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 400 mg BID (n=3987)</th>
<th>Diclofenac 75 mg BID (n=1996)</th>
<th>Ibuprofen 800 mg TID (n=1985)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥75 years (%)</td>
<td>12.2</td>
<td>11.8</td>
<td>10.9</td>
</tr>
<tr>
<td>Hx GI Bleed (%)</td>
<td>1.7</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Hx of Ulcer (%)</td>
<td>8.4</td>
<td>8.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Hx of CV Dz (%)</td>
<td>40.2</td>
<td>40.3</td>
<td>40.0</td>
</tr>
</tbody>
</table>
## Concurrent Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Celecoxib 400 mg BID (n=3987)</th>
<th>Diclofenac 75 mg BID (n=1996)</th>
<th>Ibuprofen 800 mg TID (n=1985)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA (%)</td>
<td>22.1</td>
<td>22.3</td>
<td>20.8</td>
</tr>
<tr>
<td>Steroids(^1) (%)</td>
<td>30.6</td>
<td>28.5</td>
<td>30.6</td>
</tr>
<tr>
<td>Anticoagulants (%)</td>
<td>1.1</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>OTC NSAIDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen (%)</td>
<td>4.4</td>
<td>4.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Naproxen (%)</td>
<td>1.8</td>
<td>1.3</td>
<td>1.5</td>
</tr>
</tbody>
</table>

1. Includes oral, IA, IM, topical and inhaled steroids
# Treatment Exposure

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 400 mg BID (n=3987)</th>
<th>Diclofenac 75 mg BID (n=1996)</th>
<th>Ibuprofen 800 mg TID (n=1985)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Duration</strong></td>
<td>212</td>
<td>197</td>
<td>206</td>
</tr>
<tr>
<td><strong>(days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maximum Exposure</strong></td>
<td>446</td>
<td>374</td>
<td>456</td>
</tr>
<tr>
<td><strong>(days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Exposure</strong></td>
<td>2320</td>
<td>1081</td>
<td>1123</td>
</tr>
<tr>
<td><strong>(pt-yrs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Demographics - OA

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 400 mg BID (n=2898)</th>
<th>Diclofenac 75 mg BID (n=1453)</th>
<th>Ibuprofen 800 mg TID (n=1434)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs, mean)</td>
<td>62.4</td>
<td>62.0</td>
<td>60.9</td>
</tr>
<tr>
<td>Female (%)</td>
<td>67</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>Duration (yrs)</td>
<td>10.3</td>
<td>10.4</td>
<td>9.9</td>
</tr>
<tr>
<td>Prior NSAID use (%)*</td>
<td>71</td>
<td>71</td>
<td>73</td>
</tr>
</tbody>
</table>

*Excluding ASA
Demographics - RA

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 400 mg BID (n=1089)</th>
<th>Diclofenac 75 mg BID (n=543)</th>
<th>Ibuprofen 800 mg TID (n=551)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs, mean)</td>
<td>55.8</td>
<td>55.1</td>
<td>55.8</td>
</tr>
<tr>
<td>Female (%)</td>
<td>71</td>
<td>65</td>
<td>74</td>
</tr>
<tr>
<td>Duration (yrs)</td>
<td>11.3</td>
<td>10.5</td>
<td>10.9</td>
</tr>
<tr>
<td>Prior NSAID use (%)*</td>
<td>76</td>
<td>74</td>
<td>78</td>
</tr>
<tr>
<td>Steroid use (oral, %)</td>
<td>45</td>
<td>43</td>
<td>48</td>
</tr>
<tr>
<td>Methotrexate use (%)</td>
<td>44</td>
<td>46</td>
<td>39</td>
</tr>
</tbody>
</table>

*Excluding ASA
Patient Disposition

Completers

Adverse Event

Treatment Failure

Other

Lost to Follow Up

 withdrawal

Celecoxib 400 mg BID (n=3987)

Diclofenac 75 mg BID (n=1996)

Ibuprofen 800 mg TID (n=1985)

Percent of Patients

* p < 0.05 versus celecoxib
Study Population - Summary

- Representative OA/RA cohort
  - ASA use: 22%
- No lost to follow up patients
- Substantial exposure: up to 15 months
- Higher incidence of withdrawals vs. celecoxib:
  - ibuprofen: treatment failure
  - diclofenac: adverse events
# CLASS Results

## GI Outcomes
- Study population
- GI Outcomes
  - Intent-to-treat
  - Risk Factors
  - Effect of ASA Use
  - RA vs OA
- Sources of Bias

## General Safety
- Overall Safety
- Analysis by System
  - GI
  - Renal
  - Hepatic
  - CV/Thromboembolic
- Analysis in ASA users
- Analysis by Age
Evaluation Process

Potential Events Reported
(n = 1527)

GEC Review
(n = 1527)

Ulcuer Complication
38 Uncensored
6 Censored
44 Total

Symptomatic Ulcer
(n = 67)

Other Diagnosis*
(n = 1254)

*Other diagnoses: esophagitis, gastritis, duodenitis, anemia etc
Ulcer Complications

Incidence (Events/ 100 pt-yrs)

p = 0.45

p value by log rank test

Celecoxib (n=3987)

NSAIDs (n=3981)
Symptomatic Ulcers/Ulcer Complications

Incidence
(Events/100 pt-yrs)

Celecoxib (n=3987)

NSAIDs (n=3981)

p=0.040

p value by log rank test
Incidence of Symptomatic Ulcers/Ulcer Complications

- Celecoxib 400 mg BID (n=3987)
- NSAIDs (n=3981)

Log Rank p-value
Celecoxib vs. NSAIDs 0.04
Symptomatic Ulcer/Ulcer Complications

Incidence (Events/100 pt-yrs)

- Celecoxib (n=3987)
- Diclofenac (n=1996)

p value by log rank test: p=0.296
Symptomatic Ulcer/Ulcer Complications

Celecoxib (n=3987)
Ibuprofen (n=1985)

\[ p = 0.017 \]

\[ \text{Incidence (Events/100 pt-yrs)} \]

\[ p \text{ value by log rank test} \]
Incidence of Symptomatic Ulcers/ Ulcer Complications

<table>
<thead>
<tr>
<th>Days</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Celecoxib 400 mg BID (n=3987)</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen 800 mg TID (n=1985)</td>
</tr>
</tbody>
</table>

Log Rank p-value
Celecoxib vs. Ibuprofen  0.017
UGI Outcomes - Summary

• Celecoxib vs. NSAIDs:
  – Lower incidence of symptomatic ulcers/ulcer complications

• Celecoxib vs. ibuprofen:
  – Lower incidence of symptomatic ulcers/ulcer complications
CLASS Results

GI Outcomes

• Study population
• GI Outcomes
  – Intent-to-treat
  – Risk Factors
  – Effect of ASA Use
  – RA vs OA
• Sources of Bias

General Safety

• Overall Safety
• Analysis by System
  – GI
  – Renal
  – Hepatic
  – CV/Thromboembolic
• Analysis in ASA users
• Analysis by Age
Prespecified Risk Factor Analyses

• **Demographics:**
  – Age, Gender, Alcohol or Tobacco use

• **Disease:**
  – OA vs. RA, Duration, Severity

• **Concomitant medications:**
  – ASA, Steroids, Anti-coagulants

• **History of:**
  – UGI Bleed, GD Ulcer, CV Disease

• **Positive *H. pylori* serology**
Risk Factors for Symptomatic Ulcers/Ulcer Complications

• Significant:
  – Age $\geq$ 75 yrs
  – History of ulcer disease
  – History of UGI bleeding
  – ASA use (CV disease)

• Significant effect on treatment outcome:
  – ASA
Risk Factors for Symptomatic Ulcers/Ulcer Complications

• Not significant:
  – Gender
  – Alcohol
  – Tobacco use
  – Arthritis type (OA vs RA) or duration
  – Steroid use
Risk Factors - Summary

• Data confirm MUCOSA study risk factor analysis

• ASA use affects analysis of UGI outcomes
CLASS Results

GI Outcomes

• Study population
• GI Outcomes
  – Intent-to-treat
  – Risk Factors
  – Effect of ASA Use
• RA vs OA
• Sources of Bias

General Safety

• Overall Safety
• Analysis by System
  – GI
  – Renal
  – Hepatic
  – CV/Thromboembolic
• Analysis in ASA users
• Analysis by Age
Symptomatic Ulcer/Ulcer Complications

Incidence (Events/100 pt-yrs)

ASA

- Celecoxib: (n=882)
- NSAIDs: (n=867)

p = 0.618

Non-ASA

- Celecoxib: (n=3105)
- NSAIDs: (n=3124)

p = 0.02

p value by log rank test
Symptomatic Ulcer/Ulcer Complications

Incidence (Events/100 pt-yrs)

ASA

Non-ASA

p=0.001

p=0.462

p value by log rank test

Celecoxib

Ibuprofen

(n=882) (n=412) (n=3105) (n=1573)
Incidence of Symptomatic Ulcers/ Ulcer Complications

- **Celecoxib 400 mg BID (n=3105)**
- **Ibuprofen 800 mg TID (n=1573)**

Log Rank p-value
Celecoxib vs. Ibuprofen <0.001
Non-ASA

Ulcer Complications

Incidence
(Events/100 pt-yrs)

p = 0.037

Celecoxib 400 mg BID (n=3105)

Ibuprofen 800 mg TID (n=1573)

p value by log rank test
ASA Use and UGI Outcomes - Summary

• **Non-ASA users:**
  – Lower incidence of symptomatic ulcers/ulcer complications vs. NSAIDs and ibuprofen

• **ASA users:**
  – No difference in symptomatic ulcers/ulcer complications vs. NSAIDs and ibuprofen
# CLASS Results

## GI Outcomes
- Study population
- GI Outcomes
  - Intent-to-treat
  - Risk Factors
  - Effect of ASA Use
  - RA vs OA
- Sources of Bias

## General Safety
- Overall Safety
- Analysis by System
  - GI
  - Renal
  - Hepatic
  - CV/Thromboembolic
- Analysis in ASA users
- Analysis by Age
Incidence of Symptomatic Ulcers/ Ulcer Complications

- Celecoxib 400 mg BID (n=3987)
- NSAIDs (n=3981)

OA: Incidence (Events/100 pt-yrs) = 2
RA: Incidence (Events/100 pt-yrs) = 3

$p = 0.086$ for OA
$p = 0.04$ for RA
Incidence of Symptomatic Ulcers/Ulcer Complications

- Celecoxib 400 mg BID (n=3105)
- NSAIDs (n=3124)

RA

Incidence (Events/100 pt-yrs)

OA

p = 0.088

p = 0.02
Incidence of Symptomatic Ulcers/
Ulcer Complications

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA</td>
<td>(n=2989)</td>
<td>(n=1434)</td>
</tr>
<tr>
<td>RA</td>
<td>(n=1089)</td>
<td>(n=581)</td>
</tr>
</tbody>
</table>

Incidence (Events/100 pt-yrs)

- OA: p = 0.112
- RA: p = 0.017

p value by log rank test
Incidence of Symptomatic Ulcers/ Ulcer Complications

Non-ASA

- OA
  - Celecoxib: (n=2172) 1.5 events/100 pt-yrs
  - Ibuprofen: (n=1104) 2.5 events/100 pt-yrs
  - p = 0.017

- RA
  - Celecoxib: (n=933) 2.0 events/100 pt-yrs
  - Ibuprofen: (n=469) 3.0 events/100 pt-yrs
  - p < 0.001

p value by log rank test
Incidence of Symptomatic Ulcers/Ulcer Complications - RA

- **Celecoxib 400 mg BID (n=933)**
- **Ibuprofen 800 mg TID (n=469)**

Log Rank p-value
Celecoxib vs. Ibuprofen <0.001
Analysis of UGI Outcomes in OA/RA - Summary

OA vs. RA:

• Similar incidence of symptomatic ulcers/ulcer complications

• Similar treatment differences between celecoxib and NSAIDs

• Similar treatment differences between celecoxib and ibuprofen
CLASS Results

GI Outcomes

- Study population
- GI Outcomes
  - Intent-to-treat
  - Risk Factors
  - Effect of ASA Use
  - RA vs OA
- Sources of Bias

General Safety

- Overall Safety
- Analysis by System
  - GI
  - Renal
  - Hepatic
  - CV/Thromboembolic
- Analysis in ASA users
- Analysis by Age
Sources of Bias In Ulcer Complications Analysis

• ASA use
• Withdrawal of patients with symptomatic ulcers
Potential Source of Bias

Treatment Initiation → Ulcer Complications
Potential Source of Bias

- Treatment Initiation
- Symptomatic Ulcers
- Ulcer Complications
- Withdrawn

Potential Source of Bias
Incidence of Symptomatic Ulcers

Incidence (Events/100 pt-yrs)

- Celecoxib (n=3987)
- NSAIDs (n=3981)

p=0.045
Sources of Bias - Summary

• **Celecoxib vs. NSAIDs:**
  – Lower incidence of symptomatic ulcers

• **Withdrawals of symptomatic ulcers may bias the analysis of ulcer complications**
CLASS Results

GI Outcomes

• Study population
• GI Outcomes
  – Intent-to-treat
  – Risk Factors
  – Effect of ASA Use
  – RA vs OA
• Sources of Bias

General Safety

• Overall Safety
• Analysis by System
  – GI
  – Renal
  – Hepatic
  – CV/Thromboembolic
• Analysis in ASA users
• Analysis by Age
## Deaths and Serious Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 400 mg BID (2320 pt yrs)</th>
<th>Diclofenac 75 mg BID (1081 pt yrs)</th>
<th>Ibuprofen 800 mg TID (1123 pt yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Deaths</td>
<td>0.8</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.5</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Overall Serious AEs</td>
<td>11.6</td>
<td>10.3</td>
<td>10.6</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2.1</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Gastrointestinal*</td>
<td>1.9</td>
<td>2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>0.0</td>
<td>&lt;0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Renal</td>
<td>0.4</td>
<td>&lt;0.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Includes all esophageal, gastric, intestinal, colonic, and pancreatic SAEs.
## Common Adverse Events (≥ 5%)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Celecoxib 400 mg BID (n=3987)</th>
<th>Diclofenac 75 mg BID (n=1996)</th>
<th>Ibuprofen 800 mg TID (n=1985)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>81.8</td>
<td>82.9</td>
<td>79.5</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>16.5</td>
<td>19.5*</td>
<td>16.5</td>
</tr>
<tr>
<td>Headache</td>
<td>13.9</td>
<td>16.6*</td>
<td>13.0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11.7</td>
<td>18.5*</td>
<td>11.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.9</td>
<td>15.0*</td>
<td>7.5*</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.2</td>
<td>12.1*</td>
<td>9.0</td>
</tr>
<tr>
<td>Flatulence</td>
<td>7.3</td>
<td>11.4*</td>
<td>7.2</td>
</tr>
</tbody>
</table>

*p <0.05 versus celecoxib
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Celecoxib 400 mg BID (n=3987)</th>
<th>Diclofenac 75 mg BID (n=1996)</th>
<th>Ibuprofen 800 mg TID (n=1985)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>81.8</td>
<td>82.9</td>
<td>79.5</td>
</tr>
<tr>
<td>Rash</td>
<td>6.2</td>
<td>2.8*</td>
<td>3.8*</td>
</tr>
<tr>
<td>Anemia</td>
<td>4.4</td>
<td>5.3</td>
<td>8.7*</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4.0</td>
<td>4.1</td>
<td>5.1*</td>
</tr>
<tr>
<td>Edema Peripheral</td>
<td>3.7</td>
<td>3.5</td>
<td>5.2*</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.2</td>
<td>6.8*</td>
<td>6.5*</td>
</tr>
<tr>
<td>ALT increased</td>
<td>1.0</td>
<td>5.1*</td>
<td>1.2</td>
</tr>
</tbody>
</table>

* p <0.05 versus celecoxib
### Adverse Events Causing Withdrawal ≥1%

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Celecoxib 400 mg BID (n=3987)</th>
<th>Diclofenac 75 mg BID (n=1996)</th>
<th>Ibuprofen 800 mg TID (n=1985)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>22.4</td>
<td>26.5*</td>
<td>23.0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4.3</td>
<td>6.5*</td>
<td>4.9</td>
</tr>
<tr>
<td>Rash</td>
<td>2.1</td>
<td>0.7*</td>
<td>1.3*</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.7</td>
<td>2.8*</td>
<td>1.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.4</td>
<td>2.7*</td>
<td>0.8*</td>
</tr>
<tr>
<td>Gastric Ulcer</td>
<td>0.3</td>
<td>0.7</td>
<td>1.0*</td>
</tr>
<tr>
<td>AST increased</td>
<td>0.1</td>
<td>2.1*</td>
<td>0.1</td>
</tr>
<tr>
<td>ALT increased</td>
<td>&lt;0.1</td>
<td>2.3*</td>
<td>0.1</td>
</tr>
<tr>
<td>Hepatic function abn</td>
<td>&lt;0.1</td>
<td>1.1*</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

* p <0.05 versus celecoxib
Celecoxib General Safety - Summary

• Celecoxib is well tolerated at 400 mg BID

• No dose- or duration-related increases in adverse events except non-serious rash
CLASS Results

GI Outcomes
- Study population
- GI Outcomes
  - Intent-to-treat
  - Risk Factors
  - Effect of ASA Use
  - RA vs OA
- Sources of Bias

General Safety
- Overall Safety
- Analysis by System
  - GI
  - Renal
  - Hepatic
  - CV/Thromboembolic
- Analysis in ASA users
- Analysis by Age
## GI Adverse Events (%)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Celecoxib 400 mg BID (n=3987)</th>
<th>Diclofenac 75 mg BID (n=1996)</th>
<th>Ibuprofen 800 mg TID (n=1985)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>45.6</td>
<td>55.0*</td>
<td>46.2</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>16.5</td>
<td>19.5*</td>
<td>16.5</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>11.7</td>
<td>18.5*</td>
<td>11.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.2</td>
<td>12.1*</td>
<td>9.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.9</td>
<td>15.0*</td>
<td>7.5*</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.2</td>
<td>6.8*</td>
<td>6.5*</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>12.2</td>
<td>16.6*</td>
<td>13.4</td>
</tr>
</tbody>
</table>

* p <0.05 versus celecoxib
Clinically Significant Changes in Hct/Hgb (Decreases in Hct ≥10 % points and/or Hgb >2 g/dL)

* p <0.05 versus celecoxib
Mean Change From Baseline of Iron / Total Iron Binding Capacity

CELECOXIB (n=143)  DICLOFENAC (n=81)  IBUPROFEN (n=100)

* p <0.05 versus celecoxib
Celecoxib GI Safety - Summary

- Lower incidence of:
  - GI adverse events and withdrawals than diclofenac
  - Clinically significant reductions in Hgb/Hct than ibuprofen and diclofenac
- Decreases in iron stores and Hgb/Hct suggest chronic GI blood loss
CLASS Results

GI Outcomes

• Study population
• GI Outcomes
  – Intent-to-treat
  – Risk Factors
  – Effect of ASA Use
  – RA vs OA
• Sources of Bias

General Safety

• Overall Safety
• Analysis by System
  – GI
  – Renal
  – Hepatic
  – CV/Thromboembolic
• Analysis in ASA users
• Analysis by Age
## Renal Adverse Events ≥1%

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 400 mg BID (n=3987)</th>
<th>Diclofenac 75 mg BID (n=1996)</th>
<th>Ibuprofen 800 mg TID (n=1985)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>8.9</td>
<td>9.0</td>
<td>11.7*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.0</td>
<td>2.0</td>
<td>3.1*</td>
</tr>
<tr>
<td>Hypertension aggr.</td>
<td>0.8</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Edema generalized</td>
<td>0.5</td>
<td>0.6</td>
<td>1.0*</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>3.7</td>
<td>3.5</td>
<td>5.2*</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>1.3</td>
<td>1.9</td>
<td>1.2</td>
</tr>
<tr>
<td>BUN increased</td>
<td>1.1</td>
<td>1.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>1.6</td>
<td>1.3</td>
<td>1.7</td>
</tr>
</tbody>
</table>

* p <0.05 versus celecoxib
Clinically Significant Renal Lab Abnormalities
(BUN $\geq 40$ mg% and/or Cr $\geq 1.8$ mg%)

Percent of Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Lowering</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>400 mg BID</td>
<td>0.5</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>75 mg BID</td>
<td>2.0</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>800 mg TID</td>
<td>1.3</td>
</tr>
</tbody>
</table>

* $p <0.05$ versus celecoxib
Celecoxib Renal Safety - Summary

• Lower incidence of:
  – Hypertension and edema than ibuprofen
  – Clinically significant increases in creatinine and/or BUN than diclofenac
## CLASS Results

### GI Outcomes
- Study population
- GI Outcomes
  - Intent-to-treat
  - Risk Factors
  - Effect of ASA Use
  - RA vs OA
- Sources of Bias

### General Safety
- Overall Safety
- Analysis by System
  - GI
  - Renal
  - Hepatic
  - CV/Thromboembolic
- Analysis in ASA users
- Analysis by Age
Clinically Significant Elevations in Hepatic Transaminases (3x ULN)

* p <0.05 versus celecoxib

- Celecoxib 400 mg BID (n=3987)
- Diclofenac 75 mg BID (n=1996)
- Ibuprofen 800 mg TID (n=1985)
Celecoxib Hepatic Safety - Summary

• Lower incidence of clinically significant transaminase elevations than diclofenac
CLASS Results

GI Outcomes

• Study population
• GI Outcomes
  – Intent-to-treat
  – Risk Factors
  – Effect of ASA Use
  – RA vs OA
• Sources of Bias

General Safety

• Overall Safety
• Analysis by System
  – GI
  – Renal
  – Hepatic
  – CV/Thromboembolic
• Analysis in ASA users
• Analysis by Age
<table>
<thead>
<tr>
<th>Event</th>
<th>Celecoxib (n=3987)</th>
<th>Diclofenac (n=1996)</th>
<th>Ibuprofen (n=1985)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>2.5</td>
<td>2.1</td>
<td>2.2</td>
</tr>
<tr>
<td>MI</td>
<td>0.5</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Angina</td>
<td>0.6</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>CAD</td>
<td>0.6</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>0.3</td>
<td>0.2</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>CVA</td>
<td>0.2</td>
<td>0.5</td>
<td>0.5*</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>0.8</td>
<td>0.7</td>
<td>0.8</td>
</tr>
</tbody>
</table>

1. Includes all arterial and venous thromboembolic events

*p <0.05 versus celecoxib
<table>
<thead>
<tr>
<th>Event</th>
<th>Celecoxib (n=3105)</th>
<th>Diclofenac (n=1551)</th>
<th>Ibuprofen (n=1573)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>1.5</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>MI</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Angina</td>
<td>0.3</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>CAD</td>
<td>0.3</td>
<td>0.3</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>&lt;0.1</td>
<td>0.0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>CVA</td>
<td>&lt;0.1</td>
<td>0.3*</td>
<td>0.3</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>0.6</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

1. Includes all arterial and venous thromboembolic events

* p <0.05 versus celecoxib
## Other Cardiac Adverse Events (%)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib (n=3987)</th>
<th>Diclofenac (n=1996)</th>
<th>Ibuprofen (n=1985)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial Arrhythmias</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>0.4</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Atrial Arrhythmia</td>
<td>&lt;0.1</td>
<td>0.0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>&lt;0.1</td>
<td>0.0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>SVT</td>
<td>&lt;0.1</td>
<td>0.0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>&lt;0.1</td>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td>0.3</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>0.1</td>
<td>&lt;0.1</td>
<td>0.3</td>
</tr>
</tbody>
</table>
## Other Cardiac Adverse Events (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Celecoxib (n=3105)</th>
<th>Diclofenac (n=1551)</th>
<th>Ibuprofen (n=1573)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial Arrhythmias</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>0.3</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Atrial Arrhythmia</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0.1</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>SVT</td>
<td>&lt;0.1</td>
<td>0.0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>&lt;0.1</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td>0.2</td>
<td>0.1</td>
<td>0.3*</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>&lt;0.1</td>
<td>0.0</td>
<td>0.3*</td>
</tr>
</tbody>
</table>

* p <0.05 versus celecoxib
Celecoxib CV Safety - Summary

• Compared to ibuprofen or diclofenac:
  – No difference in thromboembolic events
  – No difference in atrial arrhythmias or CHF
CLASS Results

GI Outcomes

- Study population
- GI Outcomes
  - Intent-to-treat
  - Risk Factors
  - Effect of ASA Use
  - RA vs OA
- Sources of Bias

General Safety

- Overall Safety
- Analysis by System
  - GI
  - Renal
  - Hepatic
  - CV/Thromboembolic
- Analysis in ASA users
- Analysis by Age
### ASA Users

#### GI and Renal Adverse Events (%)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 400 mg BID (n=882)</th>
<th>Diclofenac 75 mg BID (n=445)</th>
<th>Ibuprofen 800 mg TID (n=412)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Event</td>
<td>54.0</td>
<td>59.1</td>
<td>52.7</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>14.9</td>
<td>20.7*</td>
<td>14.1</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Event</td>
<td>10.8</td>
<td>11.2</td>
<td>14.8*</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>1.4</td>
<td>1.8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

* * p <0.05 versus celecoxib
Clinically Significant Changes in Hct/Hgb
(Decreases in Hct $\geq 10\%$ points and/or Hgb $>2\, \text{g/dL}$)

* $p < 0.05$ versus celecoxib

* $p < 0.05$ versus celecoxib
Clinically Significant Renal Lab Abnormalities

(BUN ≥40 mg% and/or Cr ≥1.8 mg%)

* p < 0.05 versus celecoxib
Clinically Significant Elevations in Hepatic Transaminases (3x ULN)

Non-ASA Users

ASA Users

* p ≤ 0.05 versus celecoxib
Celecoxib Safety in ASA Users - Summary

• Similar safety profile to patients not on ASA:
  – GI
  – Renal
  – Hepatic
<table>
<thead>
<tr>
<th>GI Outcomes</th>
<th>General Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Study population</td>
<td>• Overall Safety</td>
</tr>
<tr>
<td>• GI Outcomes</td>
<td>• Analysis by System</td>
</tr>
<tr>
<td>– Intent-to-treat</td>
<td>– GI</td>
</tr>
<tr>
<td>– Risk Factors</td>
<td>– Renal</td>
</tr>
<tr>
<td>– Effect of ASA Use</td>
<td>– Hepatic</td>
</tr>
<tr>
<td>– RA vs OA</td>
<td>– CV/Thromboembolic</td>
</tr>
<tr>
<td>• Sources of Bias</td>
<td>• Analysis in ASA users</td>
</tr>
<tr>
<td></td>
<td>• Analysis by Age</td>
</tr>
</tbody>
</table>
### Safety by Body System (%)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 400 mg BID (n=1599)</th>
<th>Diclofenac 75 mg BID (n=762)</th>
<th>Ibuprofen 800 mg TID (n=724)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI - Any AE</td>
<td>47.3</td>
<td>58.0*</td>
<td>47.7</td>
</tr>
<tr>
<td>Hct/Hgb Decreases</td>
<td>2.8</td>
<td>5.4*</td>
<td>6.5*</td>
</tr>
<tr>
<td>Renal - Any AE</td>
<td>10.2</td>
<td>9.8</td>
<td>13.8*</td>
</tr>
<tr>
<td>BUN/Cr Increases</td>
<td>2.3</td>
<td>4.0*</td>
<td>3.3</td>
</tr>
<tr>
<td>Hepatic - Any AE</td>
<td>1.3</td>
<td>7.2*</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* p <0.05 versus celecoxib
Celecoxib Safety by Age - Summary

• Similar safety profile in patients in all age groups:
  – Patients $\geq 65$ years
### CLASS SUMMARY:
GI Safety Advantages of Celecoxib

<table>
<thead>
<tr>
<th>Symptomatic Ulcers/</th>
<th>NSAIDs Combined</th>
<th>Diclofenac 75 mg BID</th>
<th>Ibuprofen 800 mg TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer complications</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GI Blood Loss*</th>
<th>NSAIDs Combined</th>
<th>Diclofenac 75 mg BID</th>
<th>Ibuprofen 800 mg TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GI Tolerability*</th>
<th>NSAIDs Combined</th>
<th>Diclofenac 75 mg BID</th>
<th>Ibuprofen 800 mg TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>

* Similar results in ASA users
## CLASS SUMMARY:
General Safety Advantages of Celecoxib

<table>
<thead>
<tr>
<th></th>
<th>Diclofenac</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75 mg BID</td>
<td>800 mg TID</td>
</tr>
</tbody>
</table>

### Renal Safety*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diclofenac</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema/Hypertension</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Increased Creatinine/BUN</td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>

### Hepatic Safety*

- √

* Similar results in ASA users

**Similar safety profile in all age groups**

**No increased risk of cardiac or thromboembolic events**

* Similar results in ASA users
Summary

• Trial Design
• Clinical Results
• Confirmation of Antecedent Trials
• Safety
• Conclusion
Ulcer Complication Rate

Incidence (events/100 pt-yrs)

- **Celecoxib**
- **NSAIDs**

- All Patients
  - (n=3987)
  - (n=3981)
  - $p = 0.45$

- Non-ASA
  - (n=3105)
  - (n=3124)
  - $p = 0.185$
Gastrointestinal Safety Analyses

• Outcomes evaluated:
  – Ulcer complications (primary)
  – Symptomatic ulcers (secondary)
## Baseline NSAID Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Incidence (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MUCOSA(^1) 1990</td>
</tr>
<tr>
<td>RA patients</td>
<td>100</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>16.0</td>
</tr>
<tr>
<td>History of GI Bleed</td>
<td>6.5</td>
</tr>
<tr>
<td>History of ulcer</td>
<td>14.5</td>
</tr>
<tr>
<td>History of CVD</td>
<td>54.6</td>
</tr>
</tbody>
</table>

2. Silverstein et al. JAMA 2000; 284:1247-1255
Baseline NSAID Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Incidence (% of Patients)</th>
<th>NDA (14 RCTs)</th>
<th>CLASS 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA patients</td>
<td></td>
<td>33.3</td>
<td>27.4</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td></td>
<td>10.8</td>
<td>11.6</td>
</tr>
<tr>
<td>History of GI Bleed</td>
<td></td>
<td>2.1</td>
<td>1.5</td>
</tr>
<tr>
<td>History of ulcer</td>
<td></td>
<td>11.6</td>
<td>8.2</td>
</tr>
<tr>
<td>History of CVD</td>
<td></td>
<td>51.2</td>
<td>40.2</td>
</tr>
<tr>
<td>Aspirin Use</td>
<td></td>
<td>12.0</td>
<td>22.0</td>
</tr>
</tbody>
</table>

2. Silverstein et al. JAMA 2000; 284:1247-1255
## GI Event Surveillance

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>8843</td>
<td>7968</td>
</tr>
<tr>
<td>Patient Years</td>
<td>--</td>
<td>4523</td>
</tr>
<tr>
<td>Reported</td>
<td>--</td>
<td>1527</td>
</tr>
<tr>
<td>Full GI Work-up</td>
<td>242</td>
<td>384</td>
</tr>
<tr>
<td>Crude Rate*</td>
<td>2.7%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

* Number with full GI work-up/patients

2. Silverstein et al. JAMA 2000; 284:1247-1255
Ulcer Complication and Symptomatic Ulcer Rate

- **Celecoxib 400 mg BID**
- **NSAIDs (n=3169)**

<table>
<thead>
<tr>
<th>Incidence (events/100 pt-yrs)</th>
<th>All Patients</th>
<th>Non-ASA</th>
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</thead>
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Summary

- Trial Design
- Clinical Results
- Confirmation of Antecedent Trials
- Safety
- Conclusion