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1. ABSTRACT

Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat inflammatory diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA). Well-established limitations of NSAID therapy, however, include the risk of significant injury to the upper gastrointestinal (GI) tract due to inhibition of cyclooxygenase (COX), specifically the COX-1 isoform.

Celecoxib, a COX-2 specific inhibitor that spares COX-1 at therapeutic and supratherapeutic doses, is indicated for the relief of the signs and symptoms of OA and RA in adults. Data submitted with the original NDA establish that celecoxib is associated with a lower incidence of endoscopic ulcers and, in a combined analysis of the data, fewer ulcer complications than conventional NSAIDs. The objective of the Celecoxib Long-term Arthritis Safety Study (CLASS) was to provide further evidence of the GI safety profile of celecoxib by determining whether celecoxib is associated with a lower incidence of significant upper GI toxic effects (ulcer complications and symptomatic ulcers) and other adverse effects compared to conventional NSAIDs in a prospective double-blind, randomized, controlled trial.

In the CLASS trial, patients with OA or RA were randomly assigned to receive celecoxib 400 mg twice daily or a conventional NSAID comparator (ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily). The trial was comprised of two protocols, each employing one of the two comparator NSAIDs, which were designed to be analyzed as one study as agreed upon with the FDA. The dose of celecoxib chosen was two- to four-fold greater than the maximum and recommended doses for the treatment of RA and OA, respectively, to rigorously assess the safety of celecoxib as requested by the FDA. Comparator NSAIDs were administered at commonly used doses for the OA and RA population. Ibuprofen was chosen based on evidence suggesting that it is the safest of the conventional NSAIDs, and diclofenac was chosen due to its worldwide use. Use of ibuprofen was also requested by the FDA.

The CLASS trial was constructed to replicate clinical practice and employed nonrestrictive inclusion and exclusion criteria. Accordingly, aspirin use for cardiovascular prophylaxis ($\leq$325 mg per day) was permitted during the study. The primary outcome measure was the incidence of prospectively defined ulcer complications

(bleeding, perforation, and obstruction). Other safety outcomes specified in the protocol included symptomatic ulcers and other adverse events. An analysis of potential risk factors for GI toxicity was also included in the protocol to determine their impact on outcomes and to address sources of confounding or bias in the data. Risk factors specified in the protocol included aspirin use and previously identified NSAID risk factors such as GI intolerance, a history of ulcer disease, a history of GI bleeding, and age. The minimum planned study participation was six months as agreed upon with the FDA.

Three independent committees comprised of external experts provided trial oversight. The GI Events Committee adjudicated cases of suspected ulcer complications. The Data Safety Monitoring Board assessed overall trial safety in terms of confirmed ulcer complications and serious adverse events. The Executive Committee reviewed the proceedings of the other two committees and made recommendations regarding the conduct of the trial. All committees were blinded to study treatment during the trial. In their supervisory roles, the combined committees noted a marked decrease, and then a cessation, in the accrual of ulcer complications at the point where all patients had an opportunity to complete six months of treatment. They consequently unanimously agreed that no additional useful medical or scientific information would be gained from continuing the study past this point and therefore recommended ending the study.

A total of 8059 patients were enrolled into the study. Of these, 7968 patients received at least one dose of study medication, and 4573 patients received treatment for six months. For all treated patients, the incidence rates of upper GI ulcer complications for celecoxib and comparator NSAIDs were 0.76 versus 1.45 events per 100 patients years of exposure, respectively, ($p=0.09$). The rates for upper GI ulcer complications combined with symptomatic ulcers for celecoxib versus comparator NSAIDs were 2.08 and 3.54 events per 100 patients years of exposure, respectively, ($p=0.02$).

Consistent with the literature, aspirin was an independent cause of ulcer complications. Thus, analysis was performed in the non-aspirin-taking cohort. For patients not taking aspirin, the incidence rates of upper GI ulcer complications alone for celecoxib and comparator NSAIDs were 0.44 versus 1.27 events per 100 patients years of exposure, respectively, ($p=0.04$). For upper GI ulcer complications and symptomatic ulcers, the

rates for patients not taking aspirin on celecoxib and comparator NSAIDs were 1.40 versus 2.91 events per 100 patients years of exposure, respectively, (p=0.02).

Analyses identified risk factors for upper GI toxicity associated with conventional NSAIDs similar to those identified in previous studies: age, history of ulcer disease or GI bleeding, and cardiovascular disease. A progressive and differential loss of high-risk patients (i.e., those with two or more such risk factors) over low-risk patients was also observed during the entire study. This loss of high-risk patients corresponded to the overall marked decrease in events in the study after six months.

With respect to comparisons with the individual NSAIDs, celecoxib was associated with significantly fewer ulcer complications and symptomatic ulcers than ibuprofen at six months. For patients not taking aspirin, the incidence rates of upper GI ulcer complications associated with celecoxib and ibuprofen were 0.44 versus 1.85 events per 100 patients years of exposure, respectively (p=0.005). For all treated patients, the incidence rates of upper GI ulcer complications combined with symptomatic ulcers for celecoxib versus ibuprofen were 2.08 versus 4.31 events per 100 patients years of exposure (p=0.005), respectively. For patients not taking aspirin, the incidence rates of upper GI ulcer complications combined with symptomatic ulcers were 1.40 versus 4.25 events per 100 patients years of exposure, respectively, (p<0.001).

Celecoxib was associated with fewer ulcer complications alone or combined with symptomatic ulcers than diclofenac at six months, although the difference did not reach statistical significance. However, withdrawals due to GI intolerance were significantly greater in the diclofenac group than in the other treatment groups. Moreover, GI intolerance was identified as a risk factor for ulcer complications and symptomatic ulcers. Therefore, the greater withdrawal rate of patients with GI intolerance from the diclofenac cohort prematurely removed a high-risk group for ulcer complications and symptomatic ulcers from this treatment arm and progressively biased the observed event rates over time. Statistical analysis of this source of confounding indicated that the observed rates of GI endpoint events in the diclofenac group were underestimated.

In the general safety assessments, the safety profile of supratherapeutic doses of celecoxib was generally the same as for therapeutic doses of celecoxib. No dose- or duration-

dependent toxicities were observed with the exception of a higher incidence of nonserious rash. Of specific note, celecoxib was associated with a significantly lower incidence of clinically important decreases in hematocrit and hemoglobin, likely due to chronic GI blood loss, relative to comparator NSAIDs. In terms of renal safety, celecoxib was associated with a significantly lower incidence of edema and hypertension relative to ibuprofen and a lower incidence of clinically important changes in BUN/creatinine relative to diclofenac. Celecoxib was also associated with a significantly lower incidence of clinically important changes in liver function tests compared to diclofenac. No difference in the incidence of thromboembolic cardiovascular events was seen between celecoxib and comparator NSAIDs regardless of aspirin use. Definitions of clinically important changes in laboratory tests were specified in the protocol and requested by the FDA.

In order to further explore the safety profile of celecoxib, the FDA requested an analysis of the data from the long-term open-label safety trial (Study 024) and the first year of postmarketing surveillance. In terms of GI toxicity, the ulcer complication rate from Study 024 was 0.23%, and the reporting rate of ulcer complications from postmarketing surveillance was <0.02%. These estimates are consistent with the incidence rates from the CLASS study. No dose- or duration-dependent toxicities have emerged from either Study 024 or postmarketing surveillance.

In sum, the CLASS study combined with the NDA, long-term open-label trial, and postmarketing surveillance support the conclusion that celecoxib is associated with a significantly lower incidence of clinically significant upper GI toxicity relative to conventional NSAIDs and ibuprofen specifically. Moreover, no safety issue has emerged with long-term and widespread use to compromise this safety advantage.

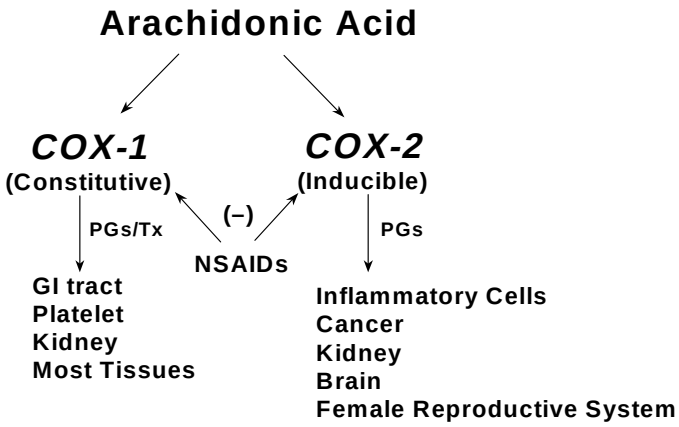
2. INTRODUCTION

2.1. Overview

Conventional NSAIDs are an important component of the standard of care for OA and RA. (1) These agents provide analgesic and anti-inflammatory effects via their inhibition of COX, the enzyme that catalyzes the conversion of arachidonic acid into prostaglandins and thromboxane, autacoids that mediate pain and inflammation. (2) Conventional NSAIDs as a class of drugs, however, exhibit a common adverse effect profile. Many of these adverse effects are mechanism-based and result from the inhibition of prostaglandin and thromboxane biosynthesis: specifically, GI toxicity, inhibition of platelet function, and renal dysfunction. Other common adverse effects of conventional NSAIDs are less clearly mechanism-based, and include effects such as GI intolerance, hepatotoxicity, and dermatologic reactions. (3)

Several years ago, two distinct isoforms of COX were identified and designated COX-1 and COX-2. COX-1 is constitutively expressed in most tissues throughout the body, including the GI tract, kidney, and platelets. COX-2 is normally found in very low amounts in healthy tissue but is rapidly and highly induced in inflamed tissues by inflammatory mediators (4) The therapeutic benefits of conventional NSAIDs are largely due to the inhibition of COX-2 at inflammatory sites, while the GI toxicity and platelet effects result from inhibition of COX-1. Because both COX-1 and COX-2 are expressed in the kidney, the mechanism of the renal effects of conventional NSAIDs is somewhat complex, but toxicity is in part COX-1-mediated. (5)

Figure 2.a. Roles of COX-1 and COX-2 and Mechanism of Action of Conventional NSAIDs



Note: PG = prostaglandin; Tx = thromboxane

This advance in understanding of the roles of the COX isoforms led to the development of celecoxib, a COX-2 specific inhibitor. The rationale behind the development of celecoxib was to provide comparable therapeutic benefit to conventional NSAIDs via COX-2 inhibition, without the attendant COX-1-mediated toxicities inherent to the mechanism of conventional NSAIDs. The data submitted with the original celecoxib New Drug Application (NDA 20,998) demonstrated that celecoxib is safe and effective in treating the signs and symptoms of both OA and RA, as well as the potential safety advantage of celecoxib. (6-10) Specifically, celecoxib was shown to be associated with statistically significantly lower incidences of endoscopically detected gastroduodenal ulcers and fewer ulcer complications than conventional NSAIDs.

In order to further establish the correlation between reduced ulcer incidences and a lowered number of associated ulcer complications, the CLASS trial was performed in a prospective, controlled, double-blind fashion to compare the incidence of clinically significant upper GI toxicity between celecoxib and comparator NSAIDs (diclofenac and ibuprofen) under clinical practice conditions (i.e. a broad patient population with extended use). It is worth noting, however, that the prospective, controlled, double-blind study design is not impervious to bias relating to patient withdrawal, changes in clinical care patterns, and cotherapies.

This Briefing Document will review the CLASS study results in the context of the original NDA, the recently completed long-term safety trial (Study 024), and ongoing postmarketing surveillance in order to provide a comprehensive and current review of the safety of celecoxib.

2.2. NSAID Toxicity

Conventional NSAIDs exhibit a number of mechanism-based toxicities derived from their inhibition of COX-1, the principal such toxicity being GI in nature. (11,12) Conventional NSAIDs cause symptomatic gastroduodenal ulcers and ulcer complications (upper GI bleeding, perforation, and obstruction) at a rate of two to four cases per 100 patient years, the occurrence of ulcer complications alone being between one and two cases per 100 patient years. (13,14) Ulcer complications specifically are a substantial source of conventional NSAID-associated morbidity and mortality, with an estimated 107,000 hospitalizations and 16,500 deaths attributable to this class of drugs annually in the United States. (14) The occurrence of ulcer complications is common to all conventional NSAIDs, is dose-dependent, and has been observed even in patients taking low-dose aspirin for cardiovascular prophylaxis. (15,16) The risk of conventional NSAID-associated ulcer complications also appears to remain constant over time. (17)

Patients most at risk for conventional NSAID-mediated ulcers and ulcer complications are the elderly, those with a history of GI ulcers or GI bleeding, and those with a history of cardiovascular disease. (18) Other potential risk factors include general debility, smoking, alcohol, NSAID intolerance, concurrent use of corticosteroids or anticoagulants, and possibly concomitant infection with *Helicobacter pylori*. (14,19,20)

Conventional NSAIDs may also cause small and large intestinal toxicity. NSAID enteropathy most often manifests as asymptomatic anemia but may include intestinal ulcers, perforations, or strictures. (21) The incidence of such events is difficult to determine as these toxic effects often go unrecognized.

In addition to pathologic effects on the GI tract mucosa, conventional NSAIDs also produce GI intolerance, which manifests as nonspecific symptoms such as dyspepsia, abdominal pain, and nausea. (3) Because such symptoms often occur in the absence of ulcers or ulcer complications, these symptoms are not necessarily predictive of serious GI

toxicity. However, the occurrence of GI intolerance is a risk factor for more serious GI outcomes, indicating that GI tolerability and toxicity are interrelated. (14)

Another mechanism-based toxicity of conventional NSAIDs is platelet dysfunction. (22) Because platelet aggregation depends on COX-1-mediated production of thromboxane, conventional NSAIDs produce the potential for a bleeding diathesis by inhibiting COX-1 activity. (22) This effect is clinically evident in the context of surgery or accidental injury and may contribute to GI toxicity as well. This property of conventional NSAIDs also complicates the concomitant use of anticoagulant agents such as warfarin.

Renal dysfunction is also a side effect of chronic conventional NSAID therapy. This may manifest as either acute alterations in renal function (e.g., a decline in glomerular filtration or sodium retention leading to congestive heart failure, edema, or hypertension) or more chronic syndromes (e.g., interstitial nephritis or papillary necrosis). (23) The incidence of serious renal dysfunction is lower than that of GI toxicity; it has been estimated that the incidence of hospitalization for acute renal failure secondary to conventional NSAIDs is on the order of 15 to 20 per 100,000 patient years. (24)

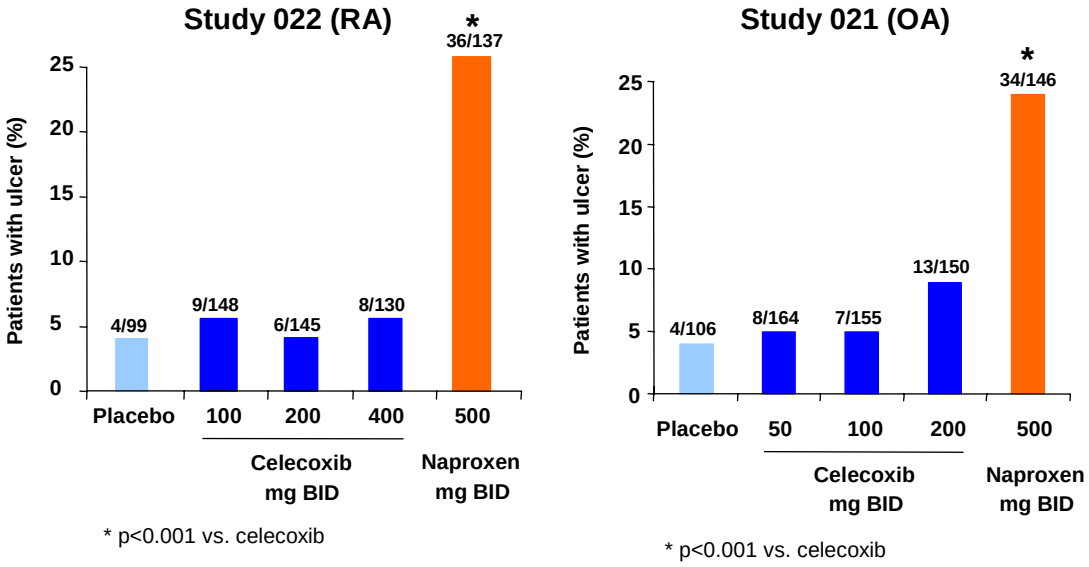
Finally, conventional NSAIDs are associated with a variety of adverse effects that are not mechanism-based but are more likely idiosyncratic or immunologic in nature. The more common of these effects are hepatotoxicity and cutaneous reactions (25,26), although occurrence of more serious forms of these reactions such as hepatic failure or exfoliative dermatitis (e.g., Stevens-Johnson syndrome) is rare. (25,27)

2.3. Celecoxib Safety Profile Derived from the Original NDA

The celecoxib NDA contained data from 51 completed clinical studies involving over 13,000 unique patients or healthy volunteers, of which over 9400 received celecoxib. These trials established that celecoxib is safe and effective in the treatment of OA (maximally effective and recommended daily dose of 200 mg) and adult RA (maximally effective and recommended daily dose of 200-400 mg), and is comparably effective to full therapeutic doses of conventional NSAIDs (naproxen, ibuprofen, and diclofenac). (9,10)

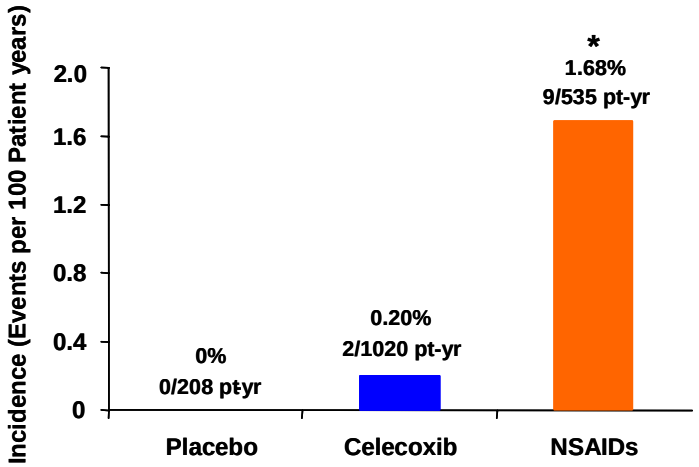
The GI safety profile of celecoxib was established in six endoscopy trials. (9) The results from the two pivotal OA and RA trials that included endoscopy are shown in Figure 2.b. These studies established that celecoxib up to 800 mg daily is associated with an incidence of gastroduodenal ulcers over 12 weeks that is similar to placebo and significantly less than that observed with typical therapeutic doses of naproxen. Similar results were derived from serial endoscopic studies comparing celecoxib at 400 mg daily to standard therapeutic doses of naproxen, ibuprofen, and diclofenac, and from an additional endoscopic study comparing celecoxib with diclofenac that did not require a baseline endoscopy.

Figure 2.b. Gastroduodenal Ulcer Incidences over 12 Weeks in Pivotal OA and RA Trials: Original Celecoxib NDA



A prospective blinded review of all potential clinically significant upper GI events (ulcer complications consisting of bleeding, perforation, and gastric outlet obstruction) from the controlled arthritis trials by an independent GI Events Committee was also performed. As shown in Figure 2.c, the derived annualized rates were 0%, 0.20%, and 1.68% in patients receiving placebo, celecoxib (50-800 mg daily), and conventional NSAIDs, respectively. (9)

Figure 2.c. Annual Incidence of Ulcer Complications in Controlled Clinical Trials: Original Celecoxib NDA



*p<0.05 vs. celecoxib

In terms of overall GI tolerability, celecoxib was well tolerated, with significantly higher incidences of dyspepsia, diarrhea, and flatulence than placebo (Table 2.a). Celecoxib was generally better tolerated than conventional NSAIDs, with significantly lower incidences of dyspepsia, abdominal pain, nausea, constipation, and flatulence.

Table 2.a. Analysis of GI Adverse Events between Celecoxib and Either Placebo or NSAIDs: Original Celecoxib NDA

Adverse Event	Celecoxib*	Placebo	p Value	Celecoxib*	NSAID	p Value
No. treated	3512	1864		2890	2098	
Any GI event	23.5	18.5	<0.001	27.7	35.4	<0.001
Dyspepsia	8.4	6.2	0.004	9.9	12.0	0.021
Diarrhea	5.4	3.8	0.008	6.2	6.1	-
Abdominal pain	3.5	2.8	-	4.9	8.2	<0.001
Nausea	3.6	4.2	-	3.8	5.6	0.002
Flatulence	2.1	1.0	0.003	2.2	3.7	0.003
Constipation	1.8	1.9	-	1.9	4.1	<0.001
Tooth disorder	1.7	1.5	-	1.9	2.2	-
Vomiting	0.9	0.5	-	1.3	1.6	-

Derived from Celecoxib Integrated Summary of Safety Information. (9) Data represent percentages of patients unless otherwise indicated.
*Includes celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.

Five previously reported clinical studies were undertaken to compare the effects of celecoxib on platelet function with those of conventional NSAIDs. (9) The results of two studies employing a dose of 1200 mg daily demonstrated that celecoxib at six times the maximally effective OA dose and three times the maximally effective RA dose did not

inhibit platelet aggregation or increase bleeding time. A subsequent study performed with celecoxib doses up to 2400 mg daily confirmed these results. (28)

The incidence of renal adverse effects of celecoxib reported in the original NDA was low but discernibly greater than placebo. (9) The most common renal adverse event was peripheral edema. Overall, the incidence was similar to conventional NSAIDs, but no dose-related increase was observed. Celecoxib was not associated with measurable changes in glomerular filtration in subgroups that are considered susceptible to the renal effects of conventional NSAIDs (i.e., the elderly and those with renal insufficiency). However, transient reductions in urinary sodium excretion were evident with celecoxib that were comparable in degree to conventional NSAIDs. The data from the NDA thus did not establish a clear safety benefit between celecoxib and conventional NSAIDs with respect to renal effects.

Hepatic adverse events and elevated liver function tests were uncommon with celecoxib. (9) Incidence rates were similar to or less than placebo and significantly less than conventional NSAIDs.

Cutaneous reactions to celecoxib were observed at a rate not significantly greater than that observed in the placebo or conventional NSAID group. (9) A small but statistically significant increase in withdrawals due to rash was noted relative to comparator NSAIDs.

3. CLASS TRIAL: STUDY DESIGN AND PATIENT DISPOSITION

3.1. Study Objectives

The primary objective of the CLASS trial was the following:

- To compare the incidence of ulcer complications (upper GI bleeding, perforation, or gastric outlet obstruction) associated with celecoxib 400 mg BID to that associated with ibuprofen 800 mg TID (protocol N49-98-02-035) or diclofenac 75 mg BID (protocol N49-98-02-102) in patients with OA or RA.

The secondary safety objectives of the study were the following:

- To compare the chronic overall safety and tolerability of celecoxib versus ibuprofen and diclofenac (hereafter collectively referred to as "NSAIDs").
- To evaluate potential risk factors (e.g., age, gender, *H. pylori* infection, type of arthritis, cardiovascular disease, concurrent use of oral corticosteroids, history of peptic ulcer and/or GI bleeding, alcohol, tobacco, and aspirin use) for their impact on the effect of treatment on outcome.

An assessment of the incidence of symptomatic ulcers was included in the protocol as part of the evaluation of GI safety as requested by the FDA. The evaluation of risk factors for GI outcome events was included as a safety objective not only to identify potential risk factors, but to facilitate the evaluation of GI safety in the event that bias was introduced by such risk factors. Of particular concern to the FDA was the use of low-dose aspirin.

3.2. Investigational Plan and Endpoints

3.2.1. Study Design

Patients were randomly assigned to receive either celecoxib 400 mg BID or comparator NSAID (ibuprofen 800 mg TID in protocol N49-98-02-035 or diclofenac 75 mg BID in protocol N49-98-02-102) in a balanced randomization that was stratified by OA/RA status. These two separate protocols were designed to run contemporaneously and to be analyzed as a single study as agreed upon with the FDA.

The dose of celecoxib evaluated in this study (400 mg BID) was two to four times the maximally effective and recommended doses for RA and OA, respectively, and was

chosen to ensure that the ulcerogenic potential of the drug was rigorously assessed. The use of a supratherapeutic dose was requested by the FDA.

Ibuprofen was chosen as a comparator NSAID because it is generally regarded as the safest conventional NSAID (29) and its inclusion was requested by the FDA. Diclofenac was chosen as the other comparator NSAID because of its widespread use throughout the world. The ibuprofen dose of 800 mg TID and the diclofenac dose of 75 mg BID were chosen, since these represent the most commonly prescribed doses of the two drugs for treating OA and RA. (30) Total combined enrollment was planned to reach approximately 4000 patients receiving celecoxib and 2000 patients receiving each NSAID comparator, for a total of 8000 patients. Patients underwent Screening/Baseline visits and follow-up visits scheduled at 4, 13, 26, 39, and 52 weeks (and 65 weeks in protocol N49-98-02-035 only) after the first dose of study medication. The minimum planned study participation was six months as agreed upon with the FDA.

Three independent oversight committees comprised of external experts supervised the conduct of the trial:

- The GI Events Committee (GEC), comprised of Drs. Jay L. Goldstein (chair), Naurang M. Agrawal, William Stenson, and Glenn Eisen, adjudicated suspected ulcer complications reported by the participating investigators.
- The Data Safety Monitoring Board, comprised of Drs. Gerald Faich (chair), Robert Makuch, Theodore Pincus, and Andrew Whelton, monitored the ongoing incidences of confirmed ulcer complications and serious adverse events.
- The Executive Committee, comprised of Drs. Fred Silverstein (chair), Lee Simon, and Gerald Faich, reviewed the proceedings of the other two committees and made recommendations regarding conduct of the trial.

All committees were blinded to treatment assignment during the study.

3.2.2. Study Population

3.2.2.1. Inclusion Criteria

To qualify for study participation, candidates must have:

- Been of legal age of consent or older;
- For women of childbearing potential, been using adequate contraception since last menses and agreed to continue to use adequate contraception during the study, not

been lactating, and had a negative serum pregnancy test within seven days before receiving the first dose of study medication;
- Had a documented clinical diagnosis of OA or RA of at least three months duration;
- Required chronic NSAID therapy in the Investigator's opinion;
- Been expected to be able to participate for the full duration of the study; and
- Provided written informed consent.

3.2.2.2. Exclusion Criteria

Candidates were excluded from participation if they satisfied any of the following criteria:

- Had an active malignancy of any type or history of malignancy (except basal cell carcinoma that had been treated, or a history of other malignancies that had been surgically removed without recurrence for at least five years);
- Had been diagnosed as having or had received treatment for esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days prior to receiving the first dose of study medication;
- Had active GI disease (e.g., inflammatory bowel disease);
- Had a history of gastric or duodenal surgery other than simple oversew of an ulcer or perforation;
- Had significant renal or hepatic dysfunction, or a significant coagulation defect considered by the Investigator to be clinically significant;
- Had abnormal Screening laboratory test values >1.5 times the upper limit of normal (ULN) for either aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) or any other laboratory abnormality at Screening considered by the Investigator to be clinically significant;
- Had a positive screening fecal occult blood test result;
- Had a known hypersensitivity to COX-2 inhibitors, sulfonamides, ibuprofen (protocol N49-98-02-035) or diclofenac (protocol N49-98-02-102);
- Had received any investigational medication within 30 days before the first dose of study medication or was scheduled to receive an investigational drug other than celecoxib during the course of the study;
- Had previously been admitted to either of these protocols or a prior study with celecoxib.

At each visit after the Baseline Visit, patients answered the following question: "Since your last visit, have you experienced or do you currently have any symptoms that are not associated with your arthritis?" If any sign or symptom was suggestive, in the Investigator's opinion, of an ulcer complication (i.e., upper GI bleeding, perforation, or gastric outlet obstruction), the Investigator was to initiate a work-up of the potential event according to the algorithm shown in Table 3.a. Potentially suggestive signs or symptoms included, but were not limited to, abdominal pain, protracted nausea and vomiting, hematemesis, melena, and decreased hemoglobin or hematocrit. Study personnel were instructed that clinical judgment and the administration of standard medical care should take precedence over the algorithm in the evaluation and treatment of any patient in the study.

Table 3.a. Algorithm for Work-up of Suspected Ulcer Complications

Presentation	Initial Evaluation	Work-up
Clinical situations requiring emergent or urgent attention **For all patients with the following presentations:** • **Obtain base data (hematocrit, stool heme x3, and postural vital signs) as part of initial evaluation.** • **Test for *H. pylori* infection as part of work-up (Meretek UBT, CLOtest or H&E).** • **Notify Searle medical monitor and Safety Specialist immediately. Provide contact information.** • **Complete GI event CRFs.**		
Severe acute abdominal pain/acute abdomen	EMERGENT: • Evaluation for perforating ulcer including base data	• Documentation of perforation by surgery or by laparoscopy with radiographic evidence of free air in abdomen • Test for *H. pylori* infection
Intractable abdominal pain with nausea/vomiting	EMERGENT: • Evaluation for gastric outlet obstruction including base data	• Documentation of gastric outlet obstruction with UGI study (radiographic or endoscopic) • Test for *H. pylori* infection
Hematemesis or melena	EMERGENT: • Evaluation for GI bleeding source including base data	• Documentation of bleeding source by UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain
Acute hypovolemia/hypotension	EMERGENT: • Evaluation for acute GI blood loss including base data	• If GI evaluation positive (e.g., blood in nasogastric aspirate, heme positive stool, or hematocrit decreased by 5% or more [absolute change]), investigate source with UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain
Current/recent (<14 days) history of: • melena (black tarry stool) or • black stool which is a change in normal pattern	IMMEDIATE: • Obtain base data	• If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain • If work-up negative, retest stool for heme and repeat hematocrit in 1-2 weeks
Development of: • postural dizziness or lightheadedness • syncope	IMMEDIATE: • Obtain base data • If patient orthostatic, evaluate for acute GI blood loss	• If GI evaluation positive (e.g., blood in nasogastric aspirate, heme positive stool, or hematocrit decreased by 5% or more [absolute change]), investigate source with UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain

Presentation	Initial Evaluation	Work-up
Clinical situations requiring prompt attention **For all patients with the following presentations:** • **Obtain base data (hematocrit, stool heme x3, and postural vital signs) as soon as possible.** • **Test for *H. pylori* infection as part of work up (Meretek UBT, CLOtest or H&E)** • **Notify Safety Specialist as soon as possible.** • **Complete GI event CRFs.**		
History of dark stool: • >14 days previously, or • vaguely characterized, or • with concurrent iron/bismuth ingestion	ASAP: • Obtain base data	• If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain
History of : • hematochezia, or • anal/rectal bleeding after elimination	ASAP: • Obtain base data	• Perform colonoscopy • UGI endoscopy at Investigator's discretion (test for *H. pylori* infection)
Development of: • New anemia, or • Drop in hematocrit of 5% or more (absolute change)	ASAP: • Obtain base data including ferritin, iron, iron binding capacity, MCV, MCHC	• If stools heme positive or studies indicate iron deficiency, perform UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain
Development of: • Dyspepsia, or • Abdominal pain, or • Nausea/vomiting	ASAP: • Obtain base data	• If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for *H. pylori* infection) • Additional studies as indicated by "ordinary care"
Development of: • Heme-positive stools	ASAP: • Obtain base data	• Perform UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain

CRF represents case report form; H&E, hematoxylin-eosin; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration.

3.2.3. Adjudication Process for Potential Ulcer Complications

Potential ulcer complications were reviewed and adjudicated as outlined in Figure 3.a by the GEC. In all of their activities related to reviewing and adjudicating potential ulcer complications, all GEC committee members were blinded to all patients' study and treatment assignments.

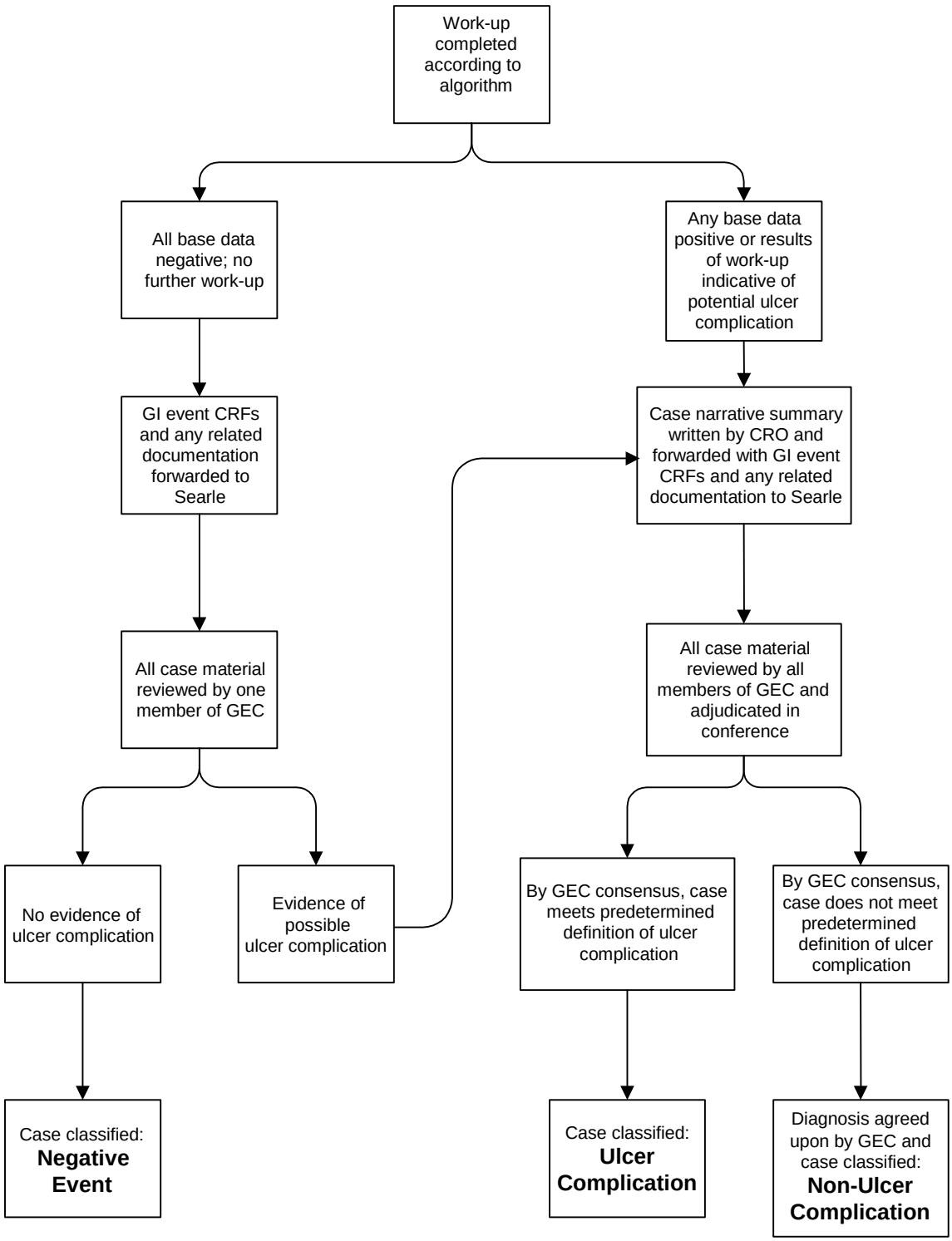
In brief, all data on potential ulcer complications, including the GI event case report forms and any source documentation (e.g., laboratory reports, endoscopy reports and photographs, radiology reports, and hospital discharge summaries), were forwarded to Searle from the site. If none of the base data suggested an ulcer complication, then the case was reviewed in a blinded fashion by a single member of the GEC (these cases were assigned to GEC members alphabetically by the patient's initials). The GEC member

either confirmed that there was no evidence of an ulcer complication and the case was classified as a negative event, or chose to send the case material to the full GEC for adjudication.

If any base data or work-up results were suggestive of an ulcer complication, a narrative summary of the case was written. This summary and other relevant documentation were then reviewed by all members of the GEC. The decision whether the case met the definition of an ulcer complication was reached by unanimous consensus. Those events that were adjudicated and considered by unanimous consensus not to meet the predetermined criteria are referred to as non-ulcer complications.

At any point during the review and adjudication process, the Investigator may have been contacted to request further information or follow-up.

Figure 3.a. Data Flow and Adjudication of Potential Ulcer Complications



3.2.3.1. Pre-specified Definitions of An Ulcer Complication

The definitions listed below were based on those used in the MUCOSA trial (18) and in the celecoxib NDA.

3.2.3.1.1. UGI Bleeding (Category 1)

Upper GI bleeding was categorized as one of the following seven clinical presentations:

- Hematemesis with a gastric or duodenal ulcer or large erosion proven by endoscopy or an upper GI barium x-ray (category 1A).
- A gastric or duodenal ulcer or large erosion proven by endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or attached clot to base of an ulcer; category 1B).
- Melena with a gastric or duodenal ulcer or large erosion proven by endoscopy or barium upper GI x-ray (category 1C).
- Hemoccult-positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or barium upper GI x-ray and with bleeding as evidenced by a fall in hematocrit ≥5 percentage points or a reduction of hemoglobin >1.5 g/dL from Baseline (category 1D-1).
- Hemoccult-positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or barium upper GI x-ray and with bleeding as evidenced by orthostasis (changes to postural vital signs: increase in pulse rate of ≥20 beats/min and/or a decrease in systolic blood pressure of ≥20 mm Hg and/or diastolic blood pressure of ≥10 mm Hg; category 1D-2).
- Hemoccult-positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or barium upper GI x-ray and with bleeding as evidenced by a need for blood transfusion of two or more units (category 1D-3).
- Hemoccult-positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or barium upper GI x-ray and with bleeding as evidenced by blood in the stomach as determined by endoscopy or nasogastric aspiration (category 1D-4).

3.2.3.1.2. UGI Perforation (Category 2)

Upper GI perforation was defined as an opening in the wall of the stomach or duodenum requiring surgery or laparoscopic repair, but only if the evidence was unequivocal (free air, peritoneal irritation signs, etc.).

3.2.3.1.3. Gastric Outlet Obstruction (Category 3)

Occurrence of a gastric outlet obstruction was based on the opinion of the clinician with endoscopic or upper GI barium x-ray documentation. Endoscopic evidence included a tight edematous pylorus with an ulcer in the pyloric channel, inability to pass the endoscope tip into the duodenal bulb or descending duodenum, or retained fluid/food in the stomach. Upper GI barium x-ray evidence of obstruction included:

- A dilated stomach.
- A slowly emptying stomach in a patient with clinical evidence of outlet obstruction and in some instances with an ulcer in the channel or duodenal bulb.
- Severe narrowing and edema obstructing the outlet of the stomach.

3.2.3.2. Categorization of Patient Participation

Patients who took study medication for the full scheduled Treatment Period or were continuing to take study medication when the trial officially concluded were considered to have completed the study. Patients terminating study participation before completing the full Treatment Period and before the trial officially concluded were considered to have withdrawn. Reasons for withdrawal were classified as follows:

- Lost to follow-up
- Pre-existing violation of entry criteria
- Protocol noncompliance (failure to comply with the requirements of the protocol, e.g., failure to take at least 70% of the study medication in any 13-week dispensing interval)
- Treatment failure (arthritis signs and symptoms were not controlled)
- Adverse sign or symptom (including an ulcer detected by endoscopy)

Patients found to have a gastric or duodenal ulcer were required to be withdrawn from the study and treated according to the clinical judgment of the Investigator.

Patients terminating early from the study were contacted by telephone monthly for two months or until the official conclusion of the study, whichever occurred first, to gather pharmacoeconomic information as well as to determine if an ulcer complication had occurred. Reasonable attempts were made to contact each patient.

3.2.3.3. Prior and Concomitant Therapy

No medications were prohibited prior to entering the study except the use of any investigational drug within thirty days prior to receiving the first dose of study medication. No NSAID washout period was performed.

Patients were instructed to avoid the use of any medication other than the drugs provided, if at all possible, during the Treatment Period. The following drugs were specifically excluded:

- NSAIDs, either prescription or nonprescription. Patients taking ≤325 mg aspirin per day for reasons other than arthritis, for at least thirty days before the first dose of study medication, were allowed to continue the same dose regimen for the duration of the study.
- Anti-ulcer drugs (including H_2 antagonists, proton pump inhibitors, sucralfate, and misoprostol), either prescription or nonprescription. Short-term use of antacids (up to seven days of more than one dose per day each month) and daily use of calcium-containing antacids as a calcium supplement (e.g., for osteoporosis) was permitted.
- Antibiotics (i.e., amoxicillin, clarithromycin, azithromycin, tetracycline, metronidazole, or bismuth) used alone or combined with omeprazole, lansoprazole, or ranitidine specifically as treatment for *H. pylori* infection.
- Antineoplastics (other than methotrexate ≤25 mg per week or azathioprine as treatment for RA).

Acetaminophen (≤2 g per day, alone or in combination with propoxyphene hydrochloride or napsylate, hydromorphone hydrochloride, oxycodone hydrochloride, or codeine phosphate) was permitted as necessary throughout the study. Oral, intramuscular, and intra-articular corticosteroids were also allowed.

3.2.4. Statistical Methods Planned in the Protocol

The two trials described in this Briefing Document were prospectively designed with the intent (and the FDA's agreement) to combine the data into a pooled analysis. Therefore, the statistical analyses described in this section were performed on a single, combined data set in which celecoxib patients from both protocols were pooled into a single treatment group for comparison with patients in the diclofenac 75 mg BID and ibuprofen 800 mg TID treatment groups. The statistical analysis plan for the upper GI safety results in this study was developed in discussion with FDA representatives and submitted to the FDA prior to study closure.

3.2.4.1. Analyses of Baseline Data

Analyses of Baseline data were performed on the Intent-to-Treat Cohort, defined as all randomized patients who received at least one dose of study medication. Statistical tests were performed as appropriate using continuous or categorical methods.

3.2.4.2. GI Safety Analyses

All analyses of GI safety were carried out on the Intent-to-Treat Cohort.

For the two GI safety endpoints, (i) ulcer complications and (ii) ulcer complications combined with symptomatic ulcers, the analyses were performed for the following categories of patients: all patients and patients not taking aspirin. These analyses were based on the assessment of aspirin as a risk factor prespecified in the protocol (see Section 4.3). Results are presented as normalized incidence rates (events normalized for patient exposure) and Kaplan-Meier plots of time to events.

The GI safety data presented are for the six-month treatment timepoint based on the analysis of risk factors prespecified in the protocol. In brief, a disproportionate withdrawal of patients at high risk of an ulcer complication from the entire study was observed after six months (depletion of susceptibles). Additionally, a significantly greater withdrawal of patients on diclofenac for GI intolerance occurred during the initial six months of the study. The withdrawal of patients for GI intolerance prematurely removed a group at high risk for ulcer complications and symptomatic ulcers from the diclofenac treatment arm (informative censoring). These issues are detailed in Sections 4.3 and 4.5.

The primary endpoint in the GI safety analyses was the development of an ulcer complication (i.e., upper GI bleeding, perforation, or obstruction). The null hypothesis being tested was that there is no difference between the incidence of ulcer complications associated with celecoxib and that associated with either of the NSAID groups. Because the development of an ulcer is a necessary precursor to the development of an ulcer complication, all analyses of ulcer complications in this study were repeated for patients who experienced either an ulcer complication or symptomatic ulcer.

In the analyses of ulcer complications and ulcer complications/symptomatic ulcers, events not considered to be possibly related to study drug were censored as follows. Events occurring before 48 hours after midnight of the first dose day were censored and not included in the analysis (no NSAID washout period was performed). Similarly, any event occurring more than 48 hours after midnight of the last dose day was censored from the analysis, unless it occurred within two weeks after the last dose of study medication *and* the GEC determined that it was treatment-related (i.e., it was unlikely to be related to any intervening confounding factors). In these analyses, onset of an ulcer complication was defined as the day on which signs or symptoms first occurred that were suggestive of a potential ulcer complication; onset of an ulcer was defined as the day of the endoscopy that disclosed the ulcer.

In the analyses of both ulcer complications and ulcer complications/symptomatic ulcers, the log-rank test was used to compare the time-to-event curves between celecoxib 400 mg BID and the two NSAIDs combined, as well as between celecoxib 400 mg BID and each of the NSAIDs separately as a stepwise procedure. Each test was performed at the alpha level of 0.05 (two-sided). In these analyses, patients completing the study without the event of interest were censored at the Final Visit, and patients who withdrew from the study for reasons other than occurrence of an event were censored at the time of withdrawal.

Potential risk factors for the development of an ulcer complication were identified prior to analysis. These included demographic and disease characteristics (age, gender, disease type and duration, and Baseline disease severity), GI history (positive *H. pylori* serology, or history of upper GI bleeding, gastroduodenal ulcer, or NSAID intolerance), concomitant medication use (particularly aspirin use), alcohol use, and tobacco use. For

each of these factors, factor effect and treatment-by-factor interaction, as well as within-group effects, were assessed based on time to event with a COX proportional hazards model. All of these risk factor analyses were performed with the NSAID groups examined separately as well as with pooling of the two NSAID groups.

Additional multivariate analyses of risk factors were performed, as was modeling of the results to adjust for study-emergent imbalances between groups at risk for developing an ulcer or ulcer complication.

3.2.4.3. General Safety Analyses

All patients who took at least one dose of study medication were included in all safety analyses.

The incidences of treatment-emergent adverse events were tabulated by treatment group and body system, and compared pairwise between treatment groups using Fisher's Exact test. Events occurring more than twenty-eight days after the last dose of study medication were excluded from all analyses.

Adverse events causing withdrawal were similarly analyzed. Serious adverse events were tabulated by treatment group and body system, but no statistical analysis was performed.

Mean changes from Baseline in clinical laboratory values were summarized by treatment group and compared pairwise by analysis of covariance with Baseline value as the covariate.

Contingency tables were prepared showing numbers of patients whose posttreatment laboratory results met certain criteria for combinations of values or changes in values that indicated clinically important hematologic, hepatobiliary, or renal effects. These criteria represented decreases in both hemoglobin and hematocrit, increases in both creatinine and BUN, and increases in both AST and ALT. These tables showed the numbers of patients whose laboratory values shifted among various categories of increases and decreases according to predetermined cutoff values provided by the FDA.

3.2.4.4. Changes in the Conduct of the Study

The two protocols were originally planned to continue until the following criteria were fulfilled: (i) each patient had the opportunity to remain in the study for at least six months, and (ii) at least 20 ulcer complications occurred in each protocol, or a maximum of 45 ulcer complications occurred in the two protocols combined. As of September 15, 1999, all patients had had the opportunity to participate for at least six months. As of November 24, 1999, a total of 36 ulcer complications had been identified (17 in protocol N49-98-02-035 and 19 in protocol N49-98-02-102). At this time, the rate of ulcer complication development had considerably deviated from the predicted rate of approximately one per month. In protocol N49-98-02-035, no events had occurred in the previous three months, and in protocol N49-98-02-102, only a single event had occurred in the previous two months. It was considered unlikely that the above criteria for study discontinuation would be met within the following six months. The Executive Committee, the GEC, and the Data Safety Monitoring Board therefore concluded that continuation of the trial would provide no useful medical or scientific information. Upon their recommendation, the study was stopped.

3.3. Patient Disposition

A total of 8059 patients were randomized at 386 centers in the two protocols. Ninety-one patients were determined never to have taken any study medication. In the majority of these cases, the patients were assigned a randomization number and treatment before completing the screening procedures. These patients were never entered into the study or dispensed study medication. All subsequent tables and figures in this document, including all subgroup analyses, include or represent subsets of the Intent-to-Treat Cohort, which included only those patients who took at least one dose of study medication.

3.3.1. Reasons for Termination

The reasons for termination from the study and patient disposition within the first six months are summarized in Table 3.b and Figure 3.b. A total of 4573 patients completed six months (182 days or more): 2376 (59.6%) receiving celecoxib 400 mg BID, 1148 (57.5%) receiving diclofenac 75 mg BID, and 1049 (52.8%) receiving ibuprofen 800 mg TID. The significant majority of withdrawals in all treatment groups were due to protocol

noncompliance, treatment failure, or an adverse event. No patient was lost to follow-up and thus no endpoint outcomes were missed because of lost to follow-up patients

Table 3.b. Reasons for Withdrawal: First Six Months

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Completed	59.6	57.5	52.8
Withdrawn	40.4	42.5	47.2
Lost to follow-up	0.0	0.0	0.0
Pre-existing violation	0.6	0.5	0.6
Protocol noncompliance	8.8	7.1	10.6
Treatment failure	12.6	12.7	16.9
Adverse event	18.4	22.2	19.1

Data represent percentages of patients.

Figure 3.b. Disposition of Patients: First Six Months

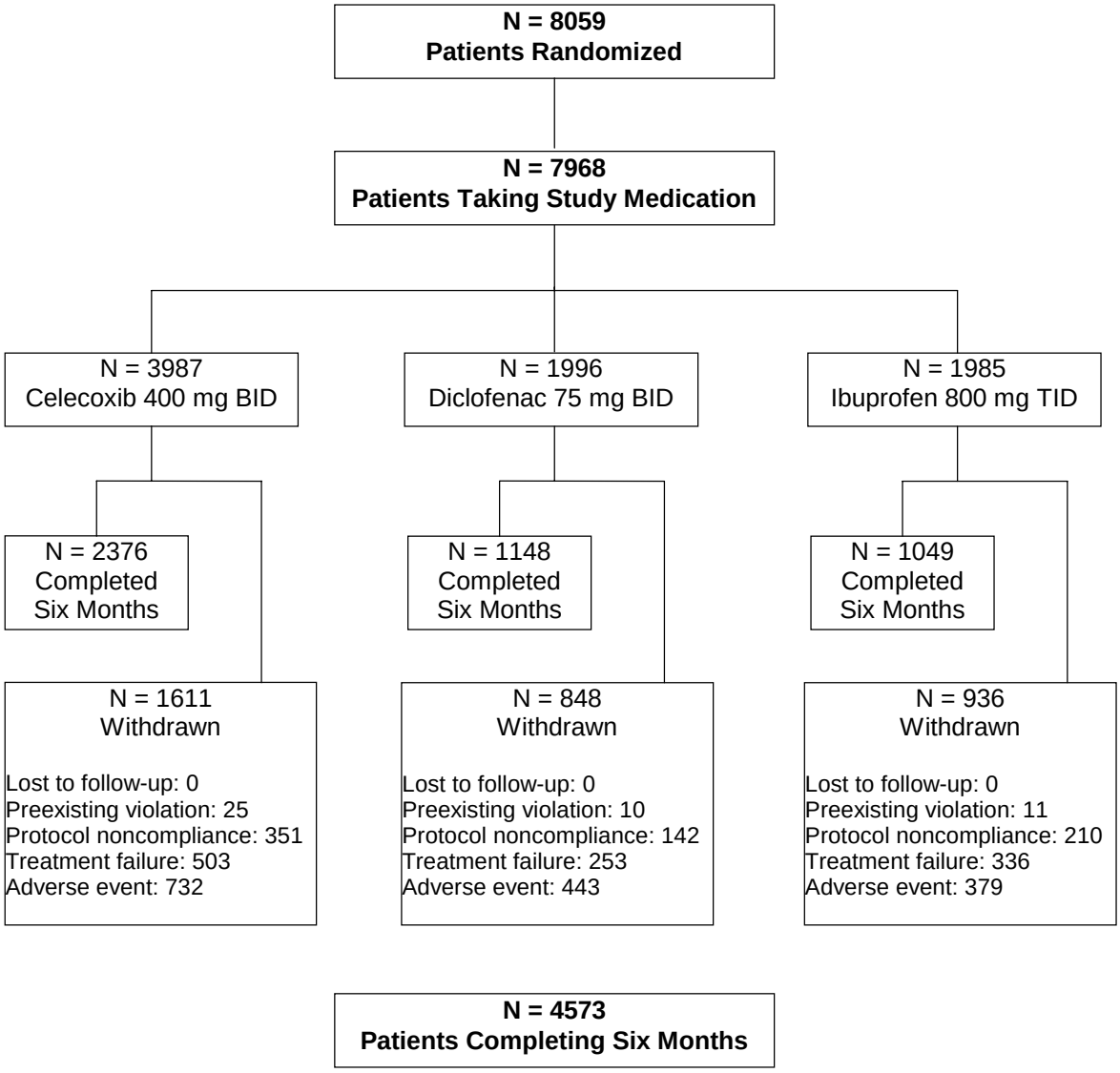


Table 3.c displays the duration of exposure to treatment for all patients and patients not taking aspirin. The proportions of patients with between three and six months of exposure to treatment ranged from 64% to 70%.

Table 3.c. Duration of Exposure: First Six Months

Treatment Duration	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
All Patients			
3 to 6 months (%)	70	69	64
Total patient-years	1441.07	710.29	673.52
Patients not taking aspirin			
3 to 6 months (%)	70	69	64
Total patient-years	1143.05	559.21	541.48

3.3.2. Demographics and Other Baseline Characteristics

Baseline characteristics of all patients in the study are summarized in Table 3.d. While the three treatment groups were generally similar with respect to most Baseline parameters, statistically significant differences in age and distribution by race were observed. These small differences are likely due to the large group size and are not clinically meaningful.

Table 3.d. Demographic and Other Baseline Characteristics: All Patients

Characteristic	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Age*,			
mean (range), y	60.6 (20-89)	60.1 (21-90)	59.5 (18-90)
>65 (%)	39.1	38.2	36.5
>75 (%)	12.2	11.8	10.9
Women (%)	68.5	67.4	70.8
Race/ethnicity* (%)			
White	88.5	89.4	86.3
Black	7.5	7.6	8.7
Other	4.0	3.1	5.0
Primary RA (%)	27.3	27.2	27.8
Duration of disease, mean, y			
OA	10.3	10.4	10.0
RA	11.3	10.5	10.9
NSAID therapy at Baseline (%)	81.4	81.0	81.3
Risk factor (%)			
History of upper GI bleeding	1.7	1.5	1.4
History of GI ulcer	8.4	8.5	7.6
Positive *H. pylori* serology	38.5	37.7	38.7
History of cardiovascular disease	40.2	40.3	40.0
Concurrent medication (%)			
ASA (≤325 mg daily)	22.1	22.3	20.8
Corticosteroids	30.6	28.5	30.6

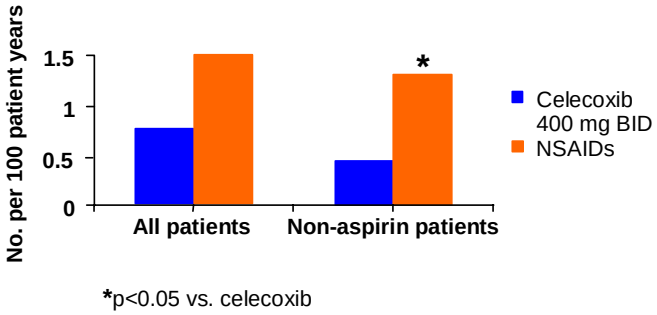
*Statistically significantly different among treatment groups at $p<0.05$ (p value from two-way analysis of variance with treatment group and center as factors).

4. CLASS TRIAL: GI SAFETY BENEFITS

4.1. Ulcer complications

The ulcer complication data in the entire cohort and the cohort of patients not on aspirin over six months based on the uncensored patients are shown in Figure 4.a (expressed as events per 100 patient years of exposure to study medication). The statistical comparisons are derived from log-rank tests of the time-to-event curves that are shown in Figures 4.b and 4.c.

Figure 4.a. Annualized Incidences of Ulcer Complications



*p<0.05 vs. celecoxib

Figure 4.b. Kaplan-Meier Plot of Time to Ulcer Complication: All Patients

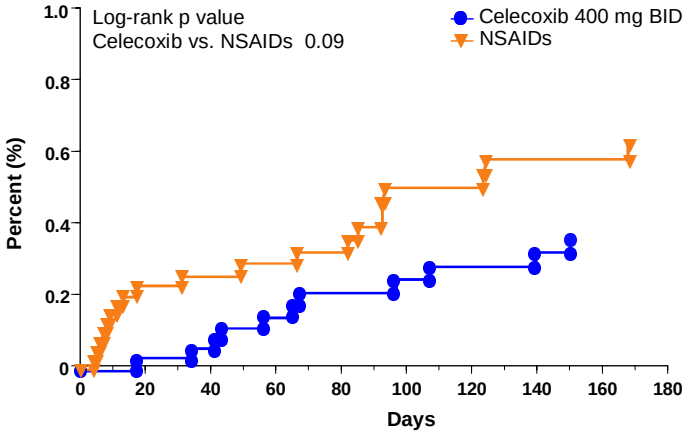
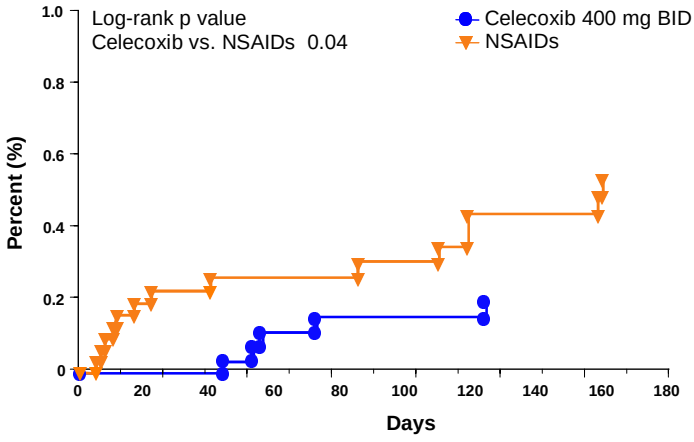


Figure 4.c. Kaplan-Meier Plot of Time to Ulcer Complication: Patients not Taking Aspirin



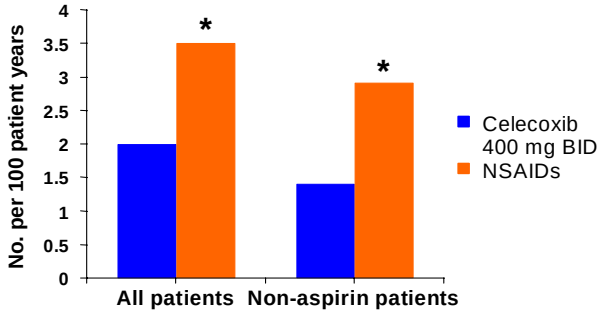
These data showed a strong numerical trend toward a reduction in the incidence of ulcer complications on celecoxib compared to NSAIDs combined. The lack of statistical significance was largely a function of the higher than expected observed event rate in the celecoxib group relative to the rate for celecoxib in the controlled clinical trials reported in the original NDA (0.76 vs. 0.20 events per 100 patient years). (12) The observed NSAID rate (1.45 events per 100 patient years), in contrast, was comparable to that seen in the original celecoxib trials (1.68 events per 100 patient years), as well as in the previously published MUCOSA trial and the ARAMIS database (1.96 and 1.58 events per 100 patient years, respectively). (14,18)

Analyses of risk factors for celecoxib and NSAIDs showed that aspirin was a significant risk factor for ulcer complications for patients on celecoxib (RR=4.5, p=0.01) but not for NSAIDs (RR=1.7, p=0.29). Therefore, an analysis of the non-aspirin using cohort was performed. In the non-aspirin using cohort, there was a statistically significant decrease in the incidence of ulcer complications observed with celecoxib relative to pooled NSAIDs (0.44 vs. 1.27 events per 100 patient years; Figures 4.a and 4.c). The incidence rate for celecoxib of 0.44 events per 100 patient years (95% CI, 0.06-0.82 events per 100 patient years) was similar to the rate of 0.2 events per 100 patient years previously reported for celecoxib, and close to the background rate of ulcer complications in non-NSAID users, which has been estimated to be approximately 0.1 to 0.4 events per 100 patient years (varying as a function of patient age). (14,31)

4.2. Symptomatic Ulcers and Ulcer Complications

The ulcer complication/symptomatic ulcer data in the entire cohort and the cohort of patients not on aspirin at six months based on the uncensored patients are shown in Figure 4.d (expressed as events per 100 patient-years of exposure to study medication). The statistical comparisons are derived from log-rank tests of the time-to-event curves, which are shown in Figures 4.e and 4.f.

Figure 4.d. **Annualized Incidences of Ulcer Complications/Symptomatic Ulcers**



*p<0.05 vs. celecoxib

Figure 4.e. **Kaplan-Meier Plot of Time to Ulcer Complication/Symptomatic Ulcer: All Patients**

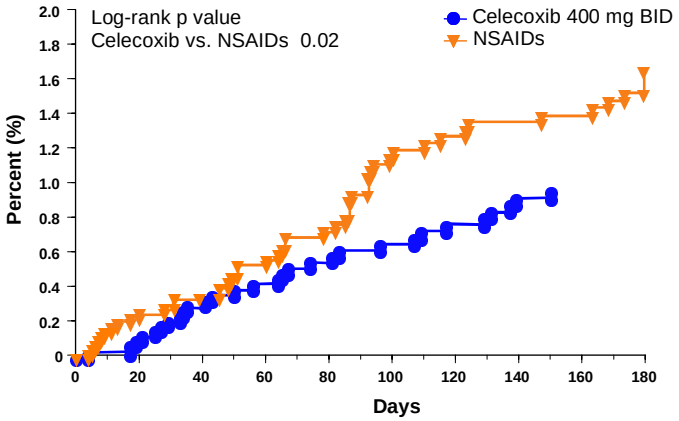
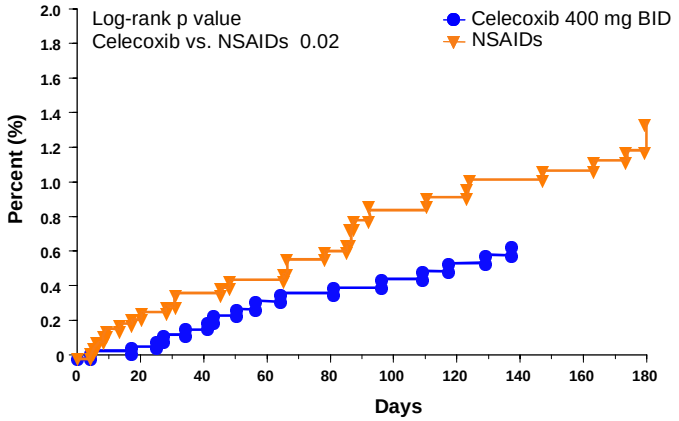


Figure 4.f. **Kaplan-Meier Plot of Time to Ulcer Complication/Symptomatic Ulcer: Patients not Taking Aspirin**



The incidence of ulcer complications/symptomatic ulcers was significantly lower in the celecoxib treatment group versus the NSAID treatment group: 2.08 and 3.54 events per 100 patient years for celecoxib and NSAIDs, respectively. This analysis also showed a significant difference in the incidences of ulcer complications/symptomatic ulcers in patients not receiving aspirin: 1.40 and 2.91 events per 100 patient years, respectively, for celecoxib and NSAIDs (Figures 4.d and 4.f).

Kaplan-Meier curves for the NSAID and celecoxib groups (entire cohort and patients not receiving aspirin) for the six-month period and the entire study are provided in Appendix 1 along with the statistical analysis.

4.3. Risk Factor Analysis and Basis of Six-Month Analyses

Univariate risk factor analysis (Table 4.a) indicated that there were five common risk factors for ulcer complications/symptomatic ulcers for celecoxib and NSAIDS: age ≥75 years, history of upper GI bleeding, history of gastroduodenal ulcer, history of cardiovascular disease, and aspirin use. The first four risk factors were the same conventional NSAID risk factors identified in the MUCOSA study. (18) Risk factors not significant by univariate analysis included disease type (OA versus RA), disease duration, corticosteroid use, and tobacco or alcohol use.

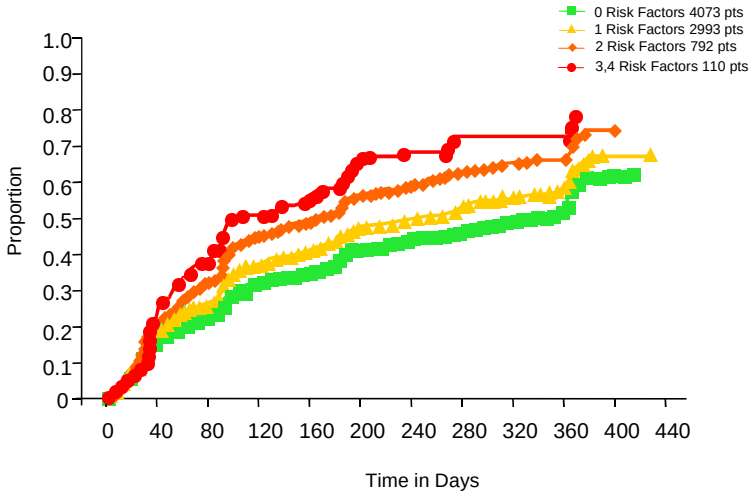
Multivariate regression established that aspirin use was the most important risk factor for celecoxib and the least important risk factor for NSAIDS. The association of NSAID risk factors with celecoxib may have resulted in part from concomitant aspirin use.

Table 4.a. Univariate Analysis of Risk Factors for Ulcer Complications and Ulcer Complications/Symptomatic Ulcers

Factor	Relative Risk			
	Ulcer Complications		Ulcer Complications/ Symptomatic Ulcers	
	Celecoxib 400 mg BID	NSAIDs	Celecoxib 400 mg BID	NSAIDs
Age ≥75 years	5.0 (p<0.001)	5.8 (p<0.001)	3.5 (p<0.001)	3.7 (p<0.001)
Patient's Global Assessment (Baseline)	2.5 (p=0.037)	2.4 (p=0.045)	1.4 (p=0.202)	1.4 (p=0.144)
History of UGI bleeding	3.6 (p=0.144)	7.1 (p=0.006)	4.3 (p=0.006)	3.4 (p=0.019)
History of GD ulcer	1.5 (p=0.509)	3.6 (p=0.009)	2.9 (p=0.002)	2.7 (p<0.001)
History of NSAID intolerance	2.2 (p=0.183)	2.3 (p=0.105)	3.2 (p=0.001)	1.9 (p=0.037)
History of CV disease	6.9 (p=0.002)	1.6 (p=0.240)	2.5 (p=0.002)	1.6 (p=0.048)
Positive *H. pylori s*erology	0.7 (p=0.460)	2.2 (p=0.072)	1.1 (p=0.423)	2.0 (p=0.005)
Aspirin use	4.0 (p=0.005)	1.8 (p=0.211)	3.7 (p<0.001)	2.3 (p=0.002)

A marked withdrawal of patients with the aforementioned NSAID risk factors (i.e., age ≥75 years, history of GI bleeding, history of GI ulcer, or history of CV disease) occurred during the initial six months of the study (Figure 4.g). Withdrawal rates were higher in patients with two or more risk factors, thus differentially removing the high-risk patients (i.e., those most likely to develop endpoint events) from the trial during this interval (i.e., depletion of susceptible patients, in statistical terms). This depletion of susceptible patients was reflected in the cessation of ulcer complications in the study noted by the oversight committees and prompted their recommendation to terminate the trial. Confounding due to this differential loss of high-risk patients from the study is minimized in the six-month analysis.

Figure 4.g. **Kaplan-Meier Plot of Time to Withdrawal by Number of Risk Factors: Age >75 Years, History of Upper GI Bleeding, History of GI Ulcer, or History of Cardiovascular Disease**



4.4. Comparisons of Event Rates Between Celecoxib and Individual NSAID Comparators

The individual comparisons with ibuprofen and diclofenac for ulcer complications and ulcer complications/symptomatic ulcers are shown in Table 4.b. All comparisons that were significant for celecoxib versus NSAIDs combined were also significant for celecoxib versus ibuprofen. For the non-aspirin using cohort, celecoxib was associated with significantly fewer ulcer complications and symptomatic ulcers/ulcer complications combined versus ibuprofen. For the entire cohort, celecoxib was associated with significantly fewer symptomatic ulcers/ulcer complications combined versus ibuprofen.

Numerical trends were noted between celecoxib and diclofenac cohorts for both of the endpoints. The absence of significant differences between these two groups, however, was likely a function of the high withdrawal rate for GI adverse events in patients receiving diclofenac (i.e., informative censoring) outlined in the following section.

Table 4.b. Incidences of Ulcer Complications/Symptomatic Ulcers for Individual Treatment Groups (Events per 100 Patient-Years of Exposure)

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank p Values for Celecoxib vs.		
				Diclo	Ibu	Both
All Patients						
Ulcer Complications	0.76	1.27	1.63	0.264	0.073	0.092
Ulcer Complications/ Symptomatic Ulcers	2.08	2.82	4.31	0.308	0.005	0.023
Patients not Taking Aspirin						
Ulcer Complications	0.44	0.72	1.85	0.476	0.005	0.037
Ulcer Complications/ Symptomatic Ulcers	1.40	1.61	4.25	0.760	<0.001	0.017

4.5. Informative Censoring

A fundamental assumption of a survival analysis is that subjects will not alter drug intake or withdraw from a study due to signs or symptoms that precede the study endpoint. (20) In statistical terms, the log-rank test statistic assumes that censoring is independent of the likelihood of an outcome event. Published data suggest that this assumption may not hold true in trials of conventional NSAID-associated risks (or in statistical terms, that informative censoring may alter conventional NSAID-associated event rates). (20) This assumption appears to have been violated in this trial, particularly within the diclofenac treatment arm.

Treatment-emergent GI symptoms (e.g., moderate-to-severe abdominal pain, diarrhea, dyspepsia, nausea, and vomiting) were identified as a risk factor in this study for both ulcer complications and ulcer complications/symptomatic ulcers, most notably so for diclofenac. The relative risk of an ulcer complication in patients with moderate-to-severe GI symptoms versus patients without moderate-to-severe GI symptoms was 3.9 overall and 13.8 for diclofenac individually. The relative risk of an ulcer complication/ symptomatic ulcer in patients with moderate-to-severe GI symptoms versus patients without moderate-to-severe GI symptoms was 6.3 overall and 11.5 for diclofenac individually.

Withdrawals due to moderate-to-severe GI symptoms were also significantly higher in the diclofenac group versus the other treatment arms (9.5% for diclofenac vs.7.5% for

celecoxib and ibuprofen, p<0.05 for diclofenac vs. celecoxib). This significantly higher withdrawal rate due to moderate-to-severe GI symptoms for the diclofenac group thus led to the early withdrawal of patients at risk of an endpoint event within this treatment arm, biasing the observed event rates associated with diclofenac (i.e., informative censoring). Therefore, standard analysis and interpretation of the event rates associated in this study with diclofenac may be misleading.

To adjust for this source of bias, an imputation of lost endpoint events was performed using the observed event rate in patients with GI symptoms who remained in the study and the calculated lost exposure due to dropouts for GI symptoms. (32-34) This analysis suggests that the observed event rates for diclofenac were likely to be significant underestimates (Table 4.c). Observed and imputed Kaplan-Meier curves are shown in Appendix 1.

Table 4.c. Crude Incidence Rates of Ulcer Complications and Ulcer Complications/Symptomatic Ulcers Adjusted for Withdrawals for GI Adverse Events: Six-Month Study Period

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	p Value	
				Celecoxib vs. Diclofenac	Celecoxib vs. Ibuprofen
Observed Rates					
Ulcer Complications	0.3%	0.5%	0.6%	0.264	0.073
Ulcer Complications + Symptomatic Ulcers	0.8%	1.0%	1.5%	0.308	0.005
Adjusted Rates					
Ulcer Complications	0.4%	0.8%	0.8%	0.036	0.035
Ulcer Complications + Symptomatic Ulcers	1.1%	1.7%	2.2%	0.069	0.001

4.6. GI Safety Conclusions

Based on these findings, it is thus concluded that:

- Celecoxib at 400 mg BID (two to four times the maximally effective and recommended doses for RA and OA) is associated with a lower rate of ulcer complications relative to conventional NSAIDs and ibuprofen specifically.
- Celecoxib is associated with a lower rate of ulcer complications/symptomatic ulcers relative to conventional NSAIDs and ibuprofen specifically.
- Aspirin use is an independent cause of ulcers in patients receiving celecoxib and reduces the GI benefit of celecoxib in terms of risk reduction.
- Celecoxib cannot be meaningfully compared to diclofenac with respect to ulcer complications or ulcer complications/symptomatic ulcers using standard survival analysis because diclofenac is associated with a higher withdrawal rate due to GI adverse events, which represent precursors to clinically significant events.

5. CLASS TRIAL: GENERAL SAFETY

5.1. Adverse Events

Adverse events are presented based on the entire study results. Analyses were generally the same when performed at six months, except where noted in the text.

Overall, the adverse event profile of celecoxib in this trial was similar to that reported in the original NDA. The most common adverse events that occurred in the CLASS trial are summarized in Table 5.a. Celecoxib was associated with lower incidence rates of GI, hepatic, and renal adverse events than comparator NSAIDs as discussed in detail in Sections 5.6 to 5.9.

Table 5.a. Adverse Events with Incidence ≥3% in Any Treatment Group: Entire Study Period

Adverse Event	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
Any event	81.8	82.9	79.5*
Dyspepsia	16.5	19.5*	16.5
URTI	15.4	14.7	15.8
Headache	13.9	16.6*	13.0
Abdominal pain	11.7	18.5*	11.3
Diarrhea	10.9	15.0*	7.5*
Sinusitis	8.8	8.6	9.5
Nausea	8.2	12.1*	9.0
Flatulence	7.3	11.4*	7.2
Rash	6.2	2.8*	3.8*
Influenza-like symptoms	5.4	5.6	6.1
Injury accidental	5.3	5.0	5.5
Anemia	4.4	5.3	8.7*
Coughing	4.4	3.5	4.6
Rhinitis	4.3	3.9	3.7
Bronchitis	4.0	4.1	5.1*
Back pain	3.7	3.3	4.0
Edema peripheral	3.7	3.5	5.2*
Insomnia	3.6	3.7	3.2
Dizziness	3.5	3.4	4.2
Tooth disorder	2.9	4.3*	4.4*
Pharyngitis	2.9	2.7	3.5
Urinary tract infection	2.8	1.8*	3.0
Vomiting	2.6	3.5	2.7
Hypertension	2.0	2.0	3.1*
Constipation	2.2	6.8*	6.5*
ALT increased	1.0	5.1*	1.2
AST increased	0.9	4.3*	1.0

Data represent percentages of patients.
*p<0.05 vs. celecoxib 400 mg BID.

Table 5.b displays the most common adverse events causing withdrawal in the study. The overall incidence of withdrawal due to an adverse event was statistically significantly lower for celecoxib than for diclofenac.

Table 5.b. Adverse Events Causing Withdrawal with Incidence ≥1% in Any Treatment Group: Entire Study Period

Adverse Event	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
Any event	22.4	26.5*	23.0
Abdominal pain	4.3	6.5*	4.9
Dyspepsia	3.8	4.4	3.9
Rash	2.1	0.7*	1.3*
Nausea	1.7	2.8*	1.8
Diarrhea	1.4	2.7*	0.8*
Flatulence	1.2	1.8	1.4
Gastric ulcer	0.3	0.7	1.0*
AST increased	0.1	2.1*	0.1
ALT increased	0.1	2.3*	0.1
Hepatic function abnormal	<0.1	1.1*	<0.1

Data represent percentages of patients.
*p<0.05 vs. celecoxib 400 mg BID.

Adverse events that occurred after the first 90 days of the study were similar in nature to those most commonly occurring in the entire study. The incidences of most events declined over time, and thus there was no evidence of cumulative toxicity (i.e., duration-dependent toxicity).

5.2. Serious Adverse Events

Table 5.c summarizes serious adverse events in the CLASS trial. The highest rate for any serious adverse event was 0.8 per 100 patient years, seen in at least one treatment group for myocardial infarction, coronary artery disorder, accidental fracture, cardiac failure, and back pain. The incidences did not suggest any important differences among the treatment groups. These serious adverse events reflect common causes of morbidity in the arthritis patient population.

Table 5.c. Summary of Serious Adverse Events: Entire Study Period

Adverse Event	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
Patient-years	2320.4	1080.5	1122.5
Any serious event	11.6	10.3	10.6
Abdominal pain	0.3	0.6	0.2
Accidental fracture	0.4	0.4	0.8
Accidental injury	0.1	0.4	0.6
Angina pectoris	0.2	0.5	0.5
Atrial fibrillation	0.4	0.2	0.3
Back pain	0.6	0.3	0.8
Cardiac failure	0.4	0.2	0.8
Cellulitis	0.3	<0.1	<0.1
Cerebrovascular disorder	0.2	0.6	0.5
Chest pain	0.5	0.5	0.6
Coronary artery disorder	0.8	0.5	0.4
Deep thrombophlebitis	0.3	0.5	<0.1
GI hemorrhage[†]	0.3	0.2	<0.1
Myocardial infarction	0.8	0.4	0.8
Pneumonia	0.6	0.5	0.4
Syncope	0.2	0.4	0.3
Unstable angina	0.3	0.4	0.0

Data represent number of patients (number per 100 patient-years). Table includes any event experienced by a total of at least 10 patients across the three treatment groups.
[†]Category includes investigator-defined episodes of GI hemorrhage often not classifiable under a more specific term (e.g., GI bleed of unknown origin, lower GI bleed).

5.3. Deaths

A total of 16 deaths occurred during the study or during post-study follow-up up to 28 days (Table 5.d): 8 in the celecoxib 400 mg BID group, 5 in the diclofenac 75 mg BID group, and 3 in the ibuprofen 800 mg TID group. Adjustment for duration of exposure shows similar rates of deaths in the three treatment groups.

Table 5.d. Summary of Deaths Occurring During Treatment or Within Twenty-Eight Days After Discontinuation of Treatment

Adverse Event	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
Myocardial infarction	3	-	1
Cardiac arrest	1	4	1
Accidental injury	1	-	-
Circulatory failure/Myocardial infarction	-	-	1
Sepsis	1	-	-
Carcinoma	1	-	-
Coronary artery disorder	-	1	-
Arrhythmia/Myocardial infarction	1	-	-
Total (No. per 100 pt-yr)	8 (0.34)	5 (0.46)	3 (0.27)

For cases in which no adverse event preferred term is available, the event is classified by cause of death listed on the end-of-study CRF.

5.4. Clinical Laboratory Evaluations

Clinical laboratory results are presented as group mean values over time by treatment groups. Table 5.e summarizes the mean changes from Baseline to the Final Visit for each standard laboratory test performed during the study. Many differences among groups were statistically significant, owing to the large numbers of patients in each group. Changes in mean laboratory values that were noteworthy were those in liver function tests, for which the statistically significant differences represent the known hepatic effects of diclofenac (28,33); creatinine changes, for which the group mean increase was statistically significantly higher for diclofenac than for celecoxib; and differences between groups in hematocrit and hemoglobin changes.

Table 5.e. Mean Changes from Baseline to Final Visit in Laboratory Values

Laboratory Test	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Hemoglobin, g/dL	-0.06 (0.013)	-0.26 (0.020) *	-0.37 (0.019) *
Hematocrit, %	-0.001 (0.0004)	-0.007 (0.0006) *	-0.012 (0.0007) *
Platelet count, $x10^9$/L	-2.3 (0.70)	10.0 (1.11) *	7.9 (0.94) *
WBC, $x10^9$/L	-0.09 (0.029)	0.06 (0.038) *	0.01 (0.041) *
Total bilirubin, µmol/L	0.0 (0.05)	0.1 (0.06)	-1.0 (0.07) *
Alkaline phosphatase, U/L	0.9 (0.23)	1.6 (0.38) *	-0.5 (0.31) *
AST, U/L	0.3 (0.12)	5.0 (0.57) *	0.9 (0.16)
ALT, U/L	-0.2 (0.18)	11.6 (1.10) *	1.3 (0.24)
Creatine kinase, U/L	-2.0 (1.17)	1.3 (2.18)	-0.1 (1.97)
Creatinine, µmol/L	0.8 (0.22)	2.4 (0.33) *	1.5 (0.33)
BUN, mmol/L	0.66 (0.027)	0.58 (0.041)	0.52 (0.039) *
Sodium, mmol/L	-0.1 (0.05)	-0.4 (0.07) *	0.0 (0.07)
Potassium, mmol/L	0.05 (0.007)	0.03 (0.010)	-0.03 (0.010) *
Chloride, mmol/L	0.7 (0.05)	0.4 (0.07) *	0.7 (0.07)
Bicarbonate, mmol/L	0.2 (0.04)	0.3 (0.06)	0.1 (0.06) *
Inorganic phosphorus, mmol/L	0.009 (0.0030)	-0.012 (0.0042) *	-0.003 (0.0046)

Data represent mean (SE) changes from Baseline.
*p<0.05 vs. celecoxib 400 mg BID.

Mean changes from Baseline in the special iron-related laboratory tests are summarized in Table 5.f. These tests were only required by the protocol in the event of new-onset anemia (obtained in approximately 3% in each treatment group). The decreases in iron and ratio of iron to iron-binding capacity in the NSAID groups are consistent with iron depletion, suggesting that the decreases seen in hematocrit and hemoglobin were secondary to occult GI blood loss.

Table 5.f. Mean Changes from Baseline to Final Visit in Special Laboratory Values

Laboratory Test	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
MCHC, g/L	-0.22 (0.060)	-0.30 (0.081)	0.01 (0.067) *
MCV, fL	0.4 (0.22)	1.4 (0.34) *	-0.2 (0.27)
Iron, µmol/L	0.5 (0.61)	-1.7 (0.61) *	-1.3 (0.52) *
Ferritin, pmol/L	13.56 (15.572)	62.38 (41.153)	-10.65 (8.418)
Iron-binding capacity, µmol/L	-2.51 (0.587)	-1.65 (0.654)	-0.65 (0.747) *
Ratio of iron to iron-binding capacity	0.014 (0.0116)	-0.026 (0.0120) *	-0.022 (0.0098) *

Data represent mean (SE) changes from Baseline.
*p<0.05 vs. celecoxib 400 mg BID.

5.5. GI Effects

The adverse events relating to the GI system are shown in Table 5.g. In all GI adverse event measures, celecoxib was better tolerated than diclofenac and generally similar to ibuprofen in tolerability. Almost all of the common GI adverse events were statistically significantly more frequent for diclofenac than for celecoxib.

Table 5.g. Summary of GI Adverse Events: Entire Study Period

Adverse Event	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
Any GI event	**45.6**	**55.0 ***	**46.2**
Dyspepsia	16.5	19.5 *	16.5
Abdominal pain	11.7	18.5 *	11.3
Diarrhea	10.9	15.0 *	7.5 *
Nausea	8.2	12.1 *	9.0
Flatulence	7.3	11.4 *	7.2
Tooth disorder	2.9	4.3 *	4.4 *
Vomiting	2.6	3.5	2.7
Constipation	2.2	6.8 *	6.5 *
Any GI event causing withdrawal	**12.2**	**16.6 ***	**13.4**

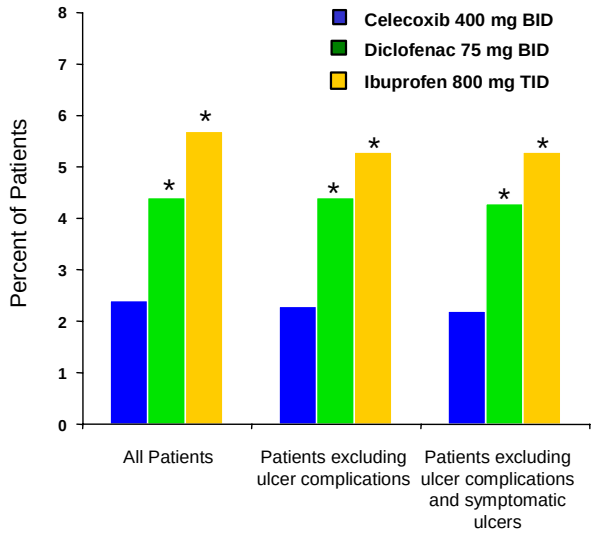
Data represent percentages of patients. Table includes any GI adverse event with incidence ≥3% in any treatment group.
*p<0.05 vs. celecoxib 400 mg BID.

The incidences of GI adverse events in patients not taking aspirin were similar to those in the overall population, though generally reduced by approximately 1% across treatment groups. The statistical relationships described above were maintained. In general, the use of aspirin increased incidences of GI adverse events across groups and attenuated some of the differences between celecoxib and the NSAIDs.

The occurrence of occult blood loss as indicated by clinically important decreases in hematocrit (≥10% points) and/or hemoglobin (>2 g/dL) represents an important adjunct measure of the GI mucosal effects of NSAIDs. This analysis was requested by the FDA and prespecified. Figures 5.a and 5.b shows the percentages of patients who experienced such decreases in hematocrit and/or hemoglobin, both in the overall population as well as in those patients who did not experience an ulcer complication or a symptomatic ulcer, patients with OA or RA, and patients taking or not taking aspirin. The proportions of

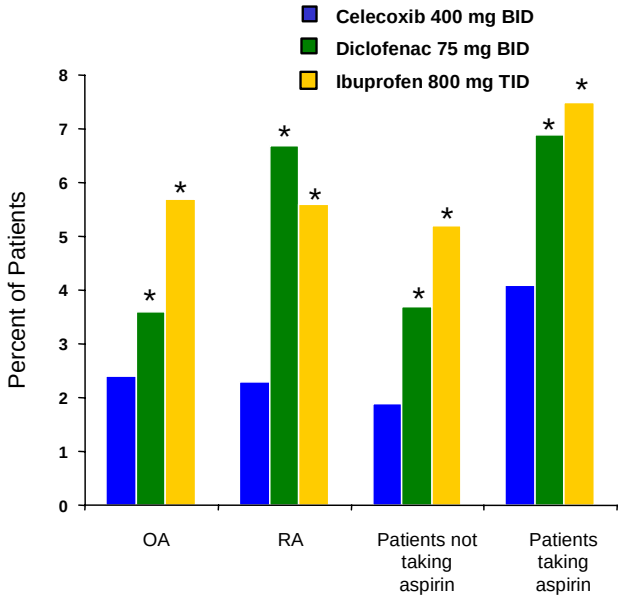
patients receiving diclofenac or ibuprofen who had such decreases in hematocrit and/or hemoglobin were consistently significantly higher than in patients receiving celecoxib.

Figure 5.a. **Incidences of Clinically Important Decreases in Hemoglobin/Hematocrit (>2 g/dL/≥10% Points): Entire Study Period**



*p<0.05 vs. celecoxib

Figure 5.b. **Incidences of Clinically Important Decreases in Hemoglobin/Hematocrit (>2 g/dL/≥10% Points): OA vs. RA Patients and Aspirin vs. Non-Aspirin Patients**



*p<0.05 vs. celecoxib

5.6. Renal Effects

Patients receiving ibuprofen experienced more edema (peripheral and generalized) and hypertension (new-onset and aggravated) than celecoxib or diclofenac patients. In three of these four categories the differences were statistically significant between celecoxib and ibuprofen (Table 5.h).

Table 5.h. Summary of Adverse Events Relating to Renal Function: Entire Study Period

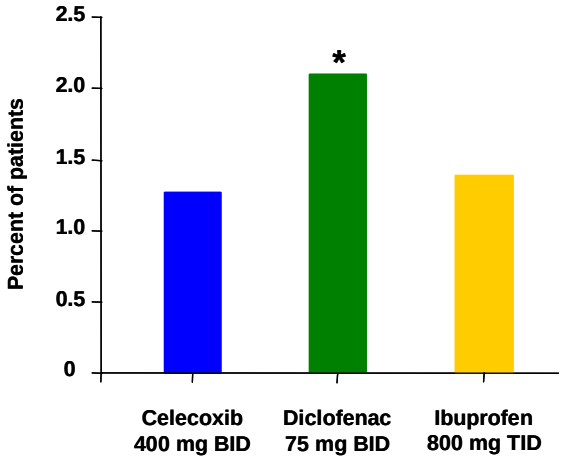
Adverse Event	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
Hypertension	2.0	2.0	3.1*
Hypertension aggravated	0.8	0.6	1.2
Edema generalized	0.5	0.6	1.0*
Edema peripheral	3.7	3.5	5.2*
Cardiac failure	0.3	0.2	0.5
BUN increased	1.1	1.7	0.9
Creatinine increased	1.3	1.9	1.2
Renal failure acute	0.0	<0.1	0.0
Renal function abnormal	<0.1	<0.1	0.1

Data represent percentages of patients.
*p<0.05 vs. celecoxib 400 mg BID.

Adverse events relating to increases in renal function laboratory values (BUN increased and creatinine increased) were more frequent for diclofenac than for celecoxib. The differences were statistically significant when examined in the six-month analysis.

When thresholds of 159 µmol/L for creatinine and 14.3 mmol/L for BUN were used in the laboratory analyses (1.8 mg/dL and 40 mg/dL, respectively) to define clinically important changes in these laboratory values (an analysis requested by the FDA and prespecified), incidences of either an elevated BUN or elevated creatinine value were 1.3% for celecoxib, 2.1% for diclofenac, and 1.4% for ibuprofen. The difference between celecoxib and diclofenac was statistically significant (Figure 5.c).

Figure 5.c. Incidences of Clinically Important Changes in BUN (≥14.3 mmol/L) and/or Creatinine (≥159 µmol/L)



*p<0.05 vs. celecoxib

5.7. Vascular Effects

Cardiac and noncardiac vascular adverse events were infrequent in all treatment groups, and incidences were similar between celecoxib and the two NSAIDs. As shown in Table 5.i, the only statistically significant difference in incidences was for cerebrovascular disorder between celecoxib and ibuprofen (0.2% vs. 0.5%, respectively; $p<0.05$).

Table 5.i. Incidences of Cardiac and Noncardiac Vascular Adverse Events: Entire Study Period

Adverse Event	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
Angina pectoris	0.6	0.5	0.6
Arteriosclerosis	<0.1	0.0	<0.1
Atherosclerosis	<0.1	<0.1	0.1
Carotid bruit	<0.1	0.1	<0.1
Carotid stenosis	<0.1	0.0	0.0
Cerebrovascular disorder	0.2	0.5	0.5*
Coronary artery disorder	0.6	0.4	0.3
Embolism	<0.1	0.0	0.0
Embolism pulmonary	0.1	<0.1	0.1
Myocardial infarction	0.5	0.3	0.5
Myocardial ischemia	<0.1	0.1	0.0
Peripheral gangrene	<0.1	0.0	0.0
Peripheral ischemia	0.1	0.0	0.1
Peripheral vascular disease	<0.1	0.0	<0.1
Phlebitis	<0.1	0.0	<0.1
Thrombophlebitis	<0.1	0.0	<0.1
Thrombophlebitis arm	<0.1	0.0	<0.1
Thrombophlebitis deep	0.3	0.3	<0.1
Thrombophlebitis leg	0.0	<0.1	<0.1
Thrombophlebitis leg deep	<0.1	<0.1	0.0
Thrombophlebitis leg superficial	<0.1	<0.1	0.0
Unstable angina	0.3	0.2	0.1

Data represent percentages of patients.
*p<0.05 vs. celecoxib 400 mg BID.

As was expected, the incidences of the cardiovascular-related events were higher in patients taking aspirin since these patients were more likely to have a significant cardiovascular medical history than the overall study population. However, there was no difference between celecoxib and NSAIDs in the incidence of vascular adverse events, regardless of the use of aspirin, as indicated by the lack of statistical significance (Table 5.j.).

Table 5.j. Incidences of Selected Cardiac and Noncardiac Vascular Adverse Events Analyzed According to Aspirin Use: Entire Study Period

	With Aspirin			Without Aspirin		
	Celecoxib (N=882)	NSAIDs (N=857)	RD*	Celecoxib (N=3105)	NSAIDs (N=3124)	RD*
Any thromboembolic event	6.1	5.7	0.4	1.5	1.2	0.3
Angina pectoris	1.5	1.6	-0.2	0.3	0.3	0.0
Arteriosclerosis	0.2	0.1	-	0.0	0.0	-
Atherosclerosis	0.1	0.2	-0.1	<0.1	<0.1	0.0
Carotid bruit	0.0	0.1	-0.1	<0.1	<0.1	0.0
Carotid stenosis	0.1	0.0	-	0.0	0.0	-
Cerebrovascular disorder	0.6	1.2	-0.6	<0.1	0.3	-0.2
Coronary artery disorder	1.7	0.9	0.8	0.3	0.2	0.2
Embolism	0.0	0.0	-	<0.1	0.0	-
Embolism pulmonary	0.1	0.0	0.1	<0.1	<0.1	0.0
Myocardial infarction	1.5	1.2	0.3	0.2	0.1	0.1
Myocardial ischemia	0.1	0.2	-0.1	<0.1	0.0	0.0
Peripheral gangrene	0.0	0.0	-	<0.1	0.0	-
Peripheral ischemia	0.3	0.1	0.2	<0.1	<0.1	0.0
Peripheral vascular disease	0.1	0.0	0.1	<0.1	<0.1	0.0
Phlebitis	0.0	0.0	-	<0.1	<0.1	-
Thrombophlebitis	0.0	0.0	-	<0.1	<0.1	-
Thrombophlebitis arm	0.0	0.0	-	<0.1	<0.1	-
Thrombophlebitis deep	0.3	0.4	0.0	0.3	<0.1	0.2
Thrombophlebitis leg	0.0	0.0	-	0.0	<0.1	-
Thrombophlebitis leg deep	0.0	0.0	-	<0.1	<0.1	-
Thrombophlebitis leg superficial	0.0	0.1	-0.1	<0.1	0.0	0.0
Unstable angina	0.9	0.6	0.3	<0.1	<0.1	0.0

Data represent percentages of patients unless otherwise indicted. None of the differences was statistically significant at $p \leq 0.05$.
*RD=risk difference.

5.8. Hepatobiliary Effects

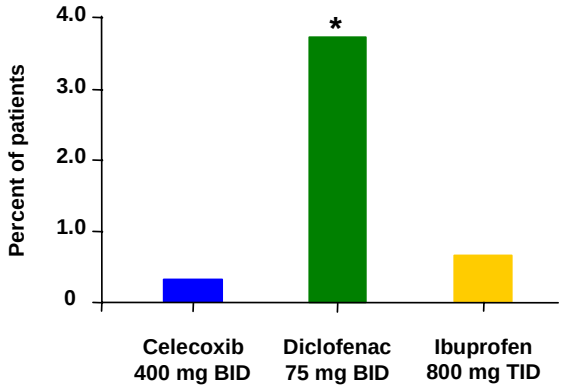
Diclofenac was associated with significantly more hepatic adverse events than celecoxib (Table 5.k). Diclofenac was also associated with significantly more frequent clinically important changes in ALT compared to celecoxib (analysis requested by the FDA and prespecified; Figure 5.d). The clinical significance of these elevations is indicated by withdrawals for hepatic adverse events: approximately half of diclofenac patients for whom liver enzyme elevations were reported as adverse events were consequently withdrawn from the study (Table 5.k).

Table 5.k Adverse Events and Laboratory Values Related to Hepatic Function: Entire Study Period

Parameter	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Adverse Events			
AST increased	0.9	4.3*	1.0
ALT increased	1.0	5.1*	1.2
Hepatic function abnormal	0.3	1.6*	0.3
Adverse Events Causing Withdrawal			
AST increased	0.1	2.1*	0.1
ALT increased	0.1	2.3*	0.1
Hepatic function abnormal	<0.1	1.1*	<0.1

Data represent percentages of patients.
*p<0.05 vs. celecoxib 400 mg BID.

Figure 5.d. Incidences of Clinically Important Increases in ALT (≥3 x Upper Limit of Normal)



*p<0.05 vs. celecoxib

5.9. Dermatologic Effects

In this study, the incidence of rash was statistically significantly higher for celecoxib than for either diclofenac or ibuprofen as previously shown in Table 5.a. The incidence of pruritus was statistically significantly higher for celecoxib than for ibuprofen (2.4% vs. 1.4%, p=0.009). Generally, drug-related rash and pruritus would be expected to occur within the first twenty-eight days of treatment; this analysis is shown in Table 5.l. For celecoxib, most cases of rash or pruritus within the first twenty-eight days (~90%) were mild or moderate.

Table 5.l. Characteristics of Rash and Pruritus Among Treatment Groups Within First Twenty-Eight Days of Treatment

Parameter	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Rash			
Overall incidence	3.7	1.2*	1.1*
Causing withdrawal	1.9	0.5*	0.5*
Pruritus			
Overall incidence	1.7	1.1	0.8*
Causing withdrawal	0.7	0.3	0.2*

Data represent percentages of patients.
*p<0.05 vs. celecoxib 400 mg BID.

No serious dermatologic adverse events occurred in patients receiving celecoxib. Only three serious adverse events relating to skin occurred: two skin ulcerations (one each occurring in the diclofenac and ibuprofen groups) and one skin disorder in the ibuprofen group.

5.10. General Safety Conclusions

The data from the CLASS study support the following conclusions for celecoxib 400 mg BID:

- No quantitative or qualitative changes were noted in the safety profile of celecoxib compared with that seen in previous celecoxib trials; specifically, no dose- or duration-dependent toxicity was observed with the exception of nonserious rash.
- Celecoxib is associated with a lower incidence of clinically important decreases in hematocrit and hemoglobin, likely due to chronic GI blood loss, compared with conventional NSAIDs.
- Celecoxib is associated with a lower incidence of GI adverse events relative to diclofenac.
- Celecoxib is associated with a lower incidence of edema and hypertension relative to ibuprofen.
- Celecoxib is associated with a lower incidence of clinically important changes in BUN and/or creatinine compared with diclofenac.
- Celecoxib is associated with a lower incidence of clinically important changes in liver function tests compared with diclofenac.

- No difference in the incidence of thromboembolic cardiovascular events was seen between celecoxib and conventional NSAIDs.

6. SAFETY UPDATE FROM THE OPEN-LABEL SAFETY TRIAL

As requested by the FDA, an analysis of the long-term safety trial, Study 024, was performed as part of the analysis of the CLASS study. This long-term safety trial provides data on exposures up to two years and is an additional source of safety information on the effects of celecoxib in OA and RA patients that can be used to place the CLASS results into context. (This study has recently been completed, and a final report is in preparation.) This study more closely approximates clinical practice than the controlled celecoxib trials in that drug treatment was not blinded and the dose of celecoxib could be titrated by the physician; however, the rigor of a clinical trial was maintained in terms of the collection of adverse events. The principal limitation of the data is that patients with significant medical problems excluded from the original controlled arthritis trials were not eligible to enroll in Study 024.

In this study, the mean age for RA patients was 54.9 years compared to 61.6 years for OA patients. There were similar distributions in ethnicity and gender for each group. Doses of celecoxib permitted in the study ranged from 100-400 mg BID. This trial provides approximately 7000 additional patient-years of exposure from which the safety of celecoxib can be assessed in a rigorous fashion.

As shown in Table 6.a, the incidences and types of adverse events from the long-term open-label trial were similar to those observed in the CLASS trial.

Table 6.a. Adverse Events with Incidence ≥3% in Celecoxib Patients: CLASS Trial and Long-term Open-label Trial (Study 024)

Adverse Event	CLASS Trial: Celecoxib 400 mg BID (N=3987)	Study 024: Celecoxib 100-400 mg BID (N=5157)
Any event	81.8	86.3
Dyspepsia	16.5	13.1
URTI	15.4	22.3
Headache	13.9	17.9
Abdominal pain	11.7	8.4
Diarrhea	10.9	10.0
Sinusitis	8.8	13.0
Nausea	8.2	7.3
Flatulence	7.3	3.2
Rash	6.2	5.5
Influenza-like symptoms	5.4	5.4
Injury accidental	5.3	11.7
Anemia	4.4	3.6
Coughing	4.4	5.6
Rhinitis	4.3	5.1
Bronchitis	4.0	7.2
Back pain	3.7	7.2
Edema peripheral	3.7	6.0
Insomnia	3.6	5.4
Dizziness	3.5	5.8
Pharyngitis	2.9	4.3
Tooth disorder	2.9	4.8
Urinary tract infection	2.8	5.4
Gastroesophageal reflux	2.7	3.2
Pain	2.6	3.7
Arthralgia	2.3	3.3
Constipation	2.2	3.0
Hypertension	2.0	4.2
Gastroenteritis	1.9	3.5
Neuralgia	1.8	3.6
Myalgia	1.7	3.5
Depression	1.6	3.3
Fatigue	1.6	3.3
Chest pain	1.3	3.1
Fracture accidental	1.3	3.3
Prostatic disorder	1.2	3.0

Derived from Celecoxib Integrated Summary of Benefits and Risks (Document No. N49-00-07-842). Data represent percentages of patients.

In general, incidence rates tended to be somewhat higher in Study 024 because of the longer duration of exposure. The higher incidence of GI symptoms in the CLASS trial may reflect the more intense surveillance for GI events in this study.

The most common serious adverse events that occurred in Study 024 are summarized in Table 6.b. In general, the incidences and types of serious adverse events between these two studies closely approximate one another and represent common causes of morbidity in the arthritis patient population.

Table 6.b. Serious Adverse Events in Celecoxib Patients: CLASS Trial and Long-term Open-label Trial (Study 024)

Adverse Event	CLASS Trial: Celecoxib 400 mg BID (N=3987)	Study 024: Celecoxib 100-400 mg BID (N=5157)
Patient years	2320.4	6965.3
Any serious event	11.6	9.8
Coronary artery disorder	0.8	0.5
Myocardial infarction	0.8	0.5
Back pain	0.6	0.5
Pneumonia	0.6	0.4
Chest pain	0.5	0.3
Accidental fracture	0.4	0.4
Atrial fibrillation	0.4	0.2
Cardiac failure	0.4	0.3
Cellulitis	0.3	0.2
Unstable angina	0.3	0.2
Abdominal pain	0.3	0.1
Breast neoplasm malignant	0.2	0.2
Angina pectoris	0.2	0.3
Cerebrovascular disorder	0.2	0.3
Cholecystitis	0.2	0.2
Accidental injury	0.1	0.3
Urinary incontinence	0.1	0.2
Carcinoma	<0.1	0.3
Cholelithiasis	<0.1	0.2
Hernia	<0.1	0.2
Implantation complication	<0.1	0.2
Basal cell carcinoma	0.0	0.3
Pulmonary carcinoma	0.0	0.2
Skin carcinoma	0.0	0.2

Derived from Celecoxib Integrated Summary of Benefits and Risks (Document No. N49-00-07-842).
Data represent number per 100 patient-years. Table includes any event experienced by a total of at least 10 patients in either study.

6.1. GI Safety

The overall incidence of ulcer complications in Study 024 was 0.23 per 100 patient years (a total of 16 events over 6965.3 patient-years of exposure). The rate of ulcer complications in Study 024, while similar to that derived during the NDA, is lower than that observed in the CLASS trial over six months (0.76 per 100 patient years), attributable to the difference in aspirin use between the two studies (approximately 14% in Study 024

vs. 22% in the CLASS trial) and reinforcing the conclusion that aspirin is an independent cause of ulcers for patients on celecoxib. Ulcer complications in 5 of the 16 cases occurred among patients on low-dose aspirin.

6.2. Safety Conclusions for Study 024

The safety data for Study 024 indicate the following:

- The incidences and types of adverse events from the long-term open-label trial were similar to those observed in the CLASS trial.
- The serious adverse event rates were similar between the CLASS and long-term open-label trials, and represent common causes of morbidity in the arthritis population.
- The rate of ulcer complications in the long-term open-label trial was similar to that reported in the NDA and lower than that observed in the CLASS trial. This difference is attributable to the increased aspirin use in the CLASS trial.

7. POSTMARKETING SURVEILLANCE SUMMARY

7.1. General Safety

The FDA also requested that data from postmarketing surveillance during 1999 be included as part of the analysis of CLASS. Such surveillance takes place under clinical practice conditions; however, the rigor and assiduousness of safety data collection is not comparable to that in clinical trials. Moreover, reporting rates are crude estimates of incidence rates, with the precision of the estimate varying as a function of the severity and rarity of the event. Despite these qualifications, the incidence of rare serious adverse events (annualized incidence of less than one per 10,000 patient years) can be estimated from this database.

The most commonly reported serious adverse events were GI in nature. The incidence of serious GI adverse events relating to ulcer complications was 19.9/100,000 patient years (or 0.02% per 100 patient years). The overall rate of serious GI events relating to ulcer complications was approximately $\geq$10-fold lower than the corresponding rates of such events derived from celecoxib clinical trials. Although it is difficult to estimate the degree of underreporting of such events during postmarketing surveillance, this rate appears consistent with the clinical trial experience.

Although quantitative analysis of GI mortality risk is not possible, qualitative analysis shows that of the 30 fatal GI events noted during 1999, most occurred in elderly patients with substantial comorbidities.

For serious renal, cardiovascular, hepatic, and dermatologic adverse events, postmarketing reporting rates were in general low (less than three per 100,000 patient years). Of specific note, the incidence of acute renal failure (too low to be estimated during clinical trials) was 3.9 per 100,000 patient years during postmarketing surveillance.

7.2. Rare Serious Adverse Events

To date, postmarketing surveillance reports have shown the occurrence of a number of rare serious adverse events. These events, and the reporting rates for the first year of postmarketing based on approximately 6.8 million treated patients and 1.8 million patient-years of exposure, are summarized in Table 7.a.

Table 7.a. Rare Serious Adverse Events Reported During Postmarketing Surveillance: December 31, 1998 through December 31, 1999

Event	Reporting Rate (Number per 100,000 Patient-Years)
Cardiovascular	
Vasculitis	0.4
Liver and biliary	
Hepatitis	0.5
Jaundice	1.5
Hepatic failure	0.4
Hemic and lymphatic	
Agranulocytosis	0.2
Aplastic anemia	0.3
Pancytopenia	0.4
Leukopenia	0.9
Metabolic	
Hypoglycemia	0.4
Renal	
Interstitial nephritis	0.2
Skin	
Erythema multiforme	0.3
Exfoliative dermatitis	0.2
Stevens-Johnson syndrome	0.3
Epidermal necrolysis	0.1
General	
Anaphylactoid reaction	1.1
Angioedema	1.9

The events listed in Table 7.a have been added to the "Adverse Reactions" section of the celecoxib product label. (8) No significant trends and no new medical issues have been since noted.

8. CONCLUSIONS

The safety data from the CLASS trial, the original NDA studies, the long-term open-label safety study (Study 024) encompassing 10,000 patient-years of exposure to celecoxib, and postmarketing surveillance (encompassing 1.8 million patient-years of exposure to celecoxib) support the following conclusions:

- Celecoxib at a supratherapeutic dose for OA and RA is associated with a lower rate of symptomatic ulcers and/or ulcer complications relative to conventional NSAIDs and ibuprofen specifically at therapeutic doses.
- Celecoxib is safe and well tolerated at doses four-fold and two-fold greater than those required for maximal efficacy in OA and adult RA, respectively.
- Celecoxib is not associated with dose- or duration-related increases in adverse effects with the exception of nonserious rash.
- Celecoxib at a supratherapeutic dose is associated with less frequent clinically important changes in hemoglobin or hematocrit than ibuprofen and diclofenac.
- Celecoxib at a supratherapeutic dose is associated with lower incidences of GI adverse events than diclofenac.
- Celecoxib at a supratherapeutic dose is associated with lower incidences of renal adverse events than conventional NSAIDs at therapeutic doses, hypertension and edema when compared to ibuprofen, and clinically important changes in BUN/creatinine when compared to diclofenac.
- Celecoxib at a supratherapeutic dose is associated with a lower incidence of hepatic adverse events than diclofenac.
- The risk of cardiovascular events associated with celecoxib at a supratherapeutic dose is similar to that of conventional NSAIDs

Addition of these data to the product label and modification of the GI warning are requested.

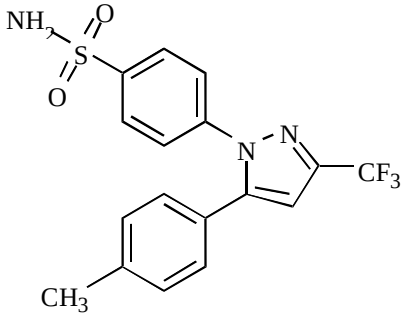
9. PROPOSED LABELING SECTION

DRAFT LABEL INCLUDING REVISIONS BASED ON CLASS STUDY

CELEBREX®
(celecoxib capsules)

DESCRIPTION

CELEBREX (celecoxib) is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl substituted pyrazole. It has the following chemical structure:



The empirical formula for celecoxib is $C_{17}H_{14}F_3N_3O_2S$, and the molecular weight is 381.38.

CELEBREX oral capsules contain 100 mg and 200 mg of celecoxib.

The inactive ingredients in CELEBREX capsules include: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, sodium lauryl sulfate and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: CELEBREX is a COX-2 specific inhibitor, a member of a larger class of nonsteroidal anti-inflammatory drugs, that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of CELEBREX is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, CELEBREX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. In animal colon tumor models, celecoxib reduced the incidence and multiplicity of tumors.

Pharmacokinetics:

Absorption
Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Under fasting conditions, both peak plasma levels (C_{max}) and area under the curve (AUC) are roughly dose proportional up to 200 mg BID; at higher doses there are less than proportional increases in C_{max} and AUC (see Food Effects). Absolute bioavailability studies have not been conducted. With multiple dosing, steady state conditions are reached on or before day 5.

The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in Table 1.

Table 1
Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects[1]

Mean (%CV) PK Parameter Values				
Cmax, ng/mL	**Tmax, hr**	**Effective t1/2, hr**	**Vss/F, L**	**CL/F, L/hr**
705 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)

[1] Subjects under fasting conditions (n=36, 19-52 yrs.)

Food Effects
When CELEBREX capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. Coadministration of CELEBREX with an aluminum- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in C_{max} and 10% in AUC. CELEBREX, at doses up to 200 mg BID can be administered without regard to timing of meals. Higher doses (400 mg BID) as recommended for FAP patients should be administered with food to improve absorption.

Distribution
In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, α_1-acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Metabolism
Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors. Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Excretion
Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Special Populations

Geriatric: At steady state, elderly subjects (over 65 years old) had a 40% higher Cmax and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib Cmax and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose.

***Pediatric*:** CELEBREX capsules have not been investigated in pediatric patients below 18 years of age.

***Race*:** Meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this finding is unknown.

***Hepatic Insufficiency*:** A pharmacokinetic study in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) hepatic impairment has shown that steady-state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, the daily recommended dose of CELEBREX capsules should be reduced by approximately 50% in patients with moderate (Child-Pugh Class II) hepatic impairment. Patients with severe hepatic impairment have not been studied. The use of CELEBREX in patients with severe hepatic impairment is not recommended.

***Renal Insufficiency*:** In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied.

Drug Interactions
Also see **PRECAUTIONS – Drug Interactions.**

General: Significant interactions may occur when celecoxib is administered together with drugs that inhibit P450 2C9. *In vitro* studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4.

Clinical studies with celecoxib have identified potentially significant interactions with fluconazole and lithium. Experience with nonsteroidal anti-inflammatory drugs (NSAIDs) suggests the potential for interactions with furosemide and ACE inhibitors. The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, methotrexate, phenytoin, tolbutamide have been studied *in vivo* and clinically important interactions have not been found.

CLINICAL STUDIES

Osteoarthritis (OA): CELEBREX has demonstrated significant reduction in joint pain compared to placebo. CELEBREX was evaluated for treatment of the signs and the symptoms of OA of the knee and hip in approximately 4,200 patients in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment with CELEBREX 100 mg BID or 200 mg QD resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, CELEBREX doses of 100mg BID and 200mg BID provided significant reduction of pain within 24-48 hours of initiation of dosing. At doses of 100 mg BID or 200 mg BID the effectiveness of CELEBREX was shown to be similar to that of naproxen 500 mg BID. Doses of 200 mg BID provided no additional benefit above that seen with 100 mg BID. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg BID or 200 mg QD.

Rheumatoid Arthritis (RA): CELEBREX has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. CELEBREX was evaluated for treatment of the signs and symptoms of RA in approximately 2,100 patients in placebo- and active-controlled clinical trials of up to 24 weeks in duration. CELEBREX was shown to be superior to placebo in these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and functional measures in RA.

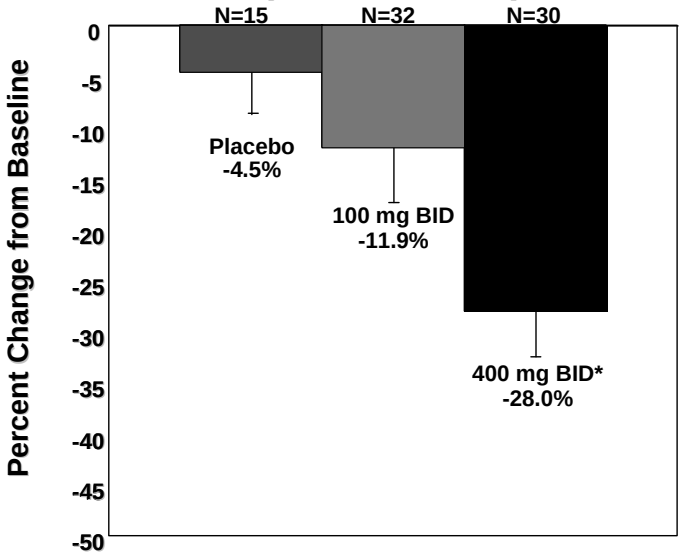
CELEBREX doses of 100 mg BID and 200 mg BID were similar in effectiveness and both were comparable to naproxen 500 mg BID.

Although CELEBREX 100 mg BID and 200 mg BID provided similar overall effectiveness, some patients derived additional benefit from the 200 mg BID dose. Doses of 400 mg BID provided no additional benefit above that seen with 100-200 mg BID.

Familial Adenomatous Polyposis (FAP): CELEBREX was evaluated to reduce the number of adenomatous colorectal polyps. A randomized double-blind placebo-controlled study was conducted in 83 patients with FAP. The study population included 58 patients with a prior subtotal or total colectomy and 25 patients with an intact colon. Thirteen patients had the attenuated FAP phenotype.

One area in the rectum and up to four areas in the colon were identified at baseline for specific follow-up, and polyps were counted at baseline and following six months of treatment. The mean reduction in the number of colorectal polyps was 28% for CELEBREX 400 mg BID, 12% for CELEBREX 100 mg BID and 5% for placebo. The reduction in polyps observed with CELEBREX 400 mg BID was statistically superior to placebo at the six-month timepoint (p=0.003). (See Figure 1)

Figure 1
Percent Change from Baseline in Number of Colorectal Polyps (FAP Patients)



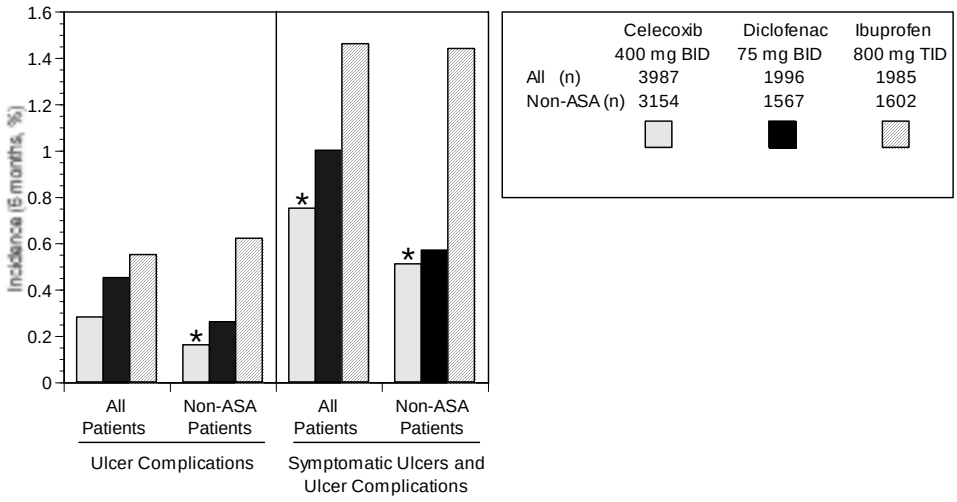
*** p=0.003 versus placebo**

Special Studies

Long Term Outcome Study:

The incidence of symptomatic GI ulcers and serious ulcer complications (bleeding, perforation or obstruction) was prospectively studied in approximately 5800 OA patients and 2200 RA patients. Patients received CELEBREX 400 mg BID (4-fold and 2-fold greater than the recommended OA and RA doses, respectively) or diclofenac 75 mg BID or ibuprofen 800 mg TID (common therapeutic doses). Approximately 22% of patients were on low dose aspirin (ASA) for cardiovascular disease prophylaxis. In the overall population CELEBREX was associated with a significantly lower incidence of symptomatic GI ulcers and ulcer complications vs. ibuprofen. In patients not taking low dose aspirin (non-ASA) a significantly lower incidence of ulcer complications vs. ibuprofen was observed (Figure 2). The incidence rates for diclofenac may be underestimated because of a higher incidence of early withdrawals due to GI adverse events than CELEBREX and ibuprofen.

Figure 2
Incidence of Symptomatic Ulcers and Ulcer Complications

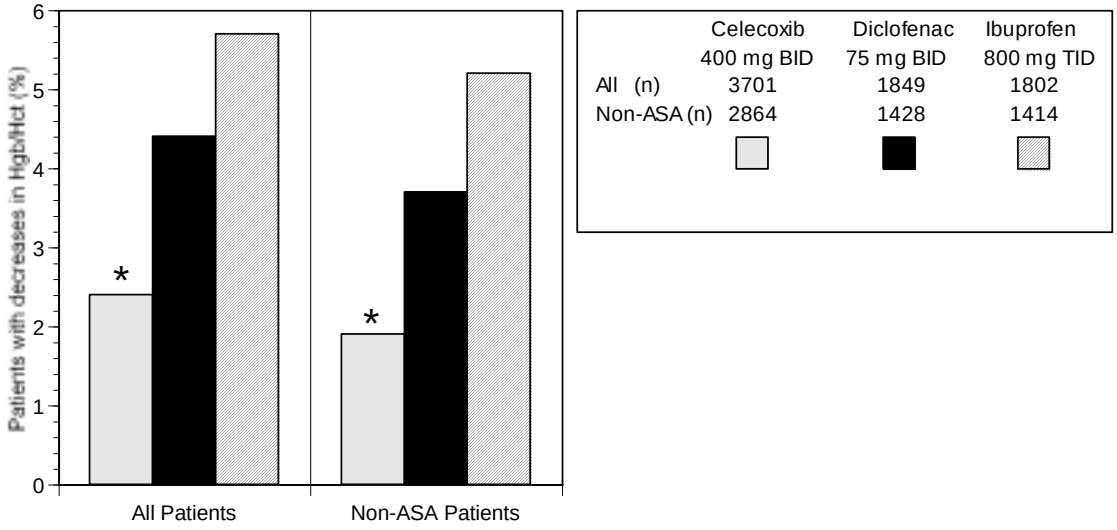


*p<0.05 vs ibuprofen

CELEBREX (4-fold and 2-fold greater than the recommended OA and RA doses, respectively) was also associated with a significantly lower incidence of clinically relevant decreases in hemoglobin (> 2 g/dl) or hematocrit ($\geq$10 points) than ibuprofen and diclofenac. (Figure 3). The pooled rates from other controlled arthritis trials (1 to 6 months duration, most of 3 months duration) were 0.4%, 0.9%, and 2.8% in placebo, celecoxib, and comparator NSAID groups, respectively. Celecoxib doses ranged from 50 mg BID to 400 mg BID.

The incidence of clinically relevant decreases in hemoglobin and hematocrit in CELEBREX patients was not affected by aspirin use.

Figure 3
Incidence of Clinically Relevant Decreases in Hemoglobinand/or Hematocrit



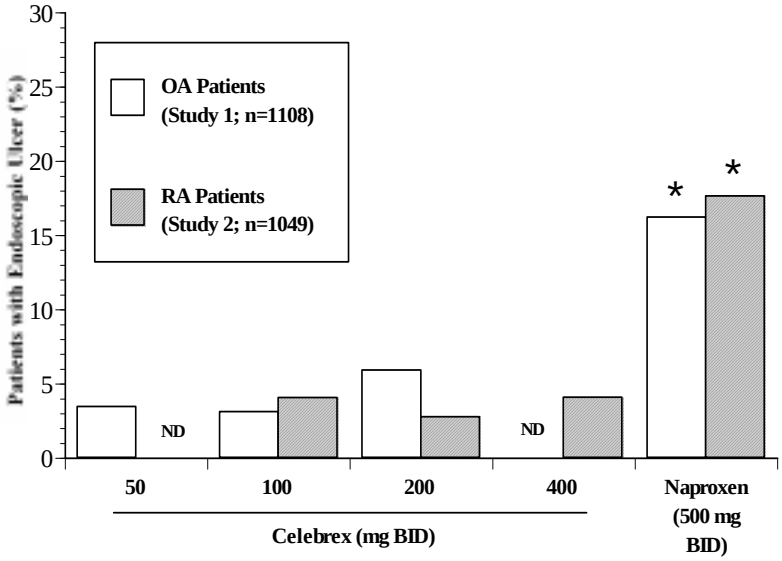
*p<0.05 vs ibuprofen and diclofenac

Endoscopic studies:
Scheduled upper GI endoscopic evaluations were performed in over 4,500 arthritis patients who were enrolled in five controlled randomized 12-24 week trials using active comparators, two of which also included placebo controls. Twelve-week endoscopic ulcer data are available on approximately 1,400 patients and 24 week endoscopic ulcer data are available on 184 patients on CELEBREX at doses ranging from 50-400 mg BID. In all three studies that included naproxen 500 mg BID, and in the study that included ibuprofen 800 mg TID, CELEBREX was associated with a statistically significantly lower incidence of endoscopic ulcers over the study period. Two studies compared CELEBREX with diclofenac 75 mg BID; one study revealed a statistically significantly higher prevalence of endoscopic ulcers in the diclofenac group at the study endpoint (6 months on treatment), and one study revealed no statistically significant difference between cumulative endoscopic ulcer incidence rates in the diclofenac and CELEBREX groups after 1, 2, and 3 months of treatment. There was no consistent relationship between the incidence of gastroduodenal ulcers and the dose of CELEBREX over the range studied.

Figure 4 and Table 2 summarize the incidence of endoscopic ulcers in two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers.

Figure 4

Incidence of Endoscopically Observed Gastroduodenal Ulcers after 12 Weeks of Treatment



ND = Not Done

* Significantly different from all other treatments; $p<0.05$.

Celebrex 100 mg BID and 200 mg QD, BID are the recommended doses.

These studies were not powered to compare the endoscopic ulcer rates of Celebrex vs. placebo.

Study 1: placebo ulcer rate = 2.3%

Study 2: placebo ulcer rate = 2.0%

Table 2
Incidence of Gastroduodenal Ulcers from Endoscopic Studies in OA and RA Patients

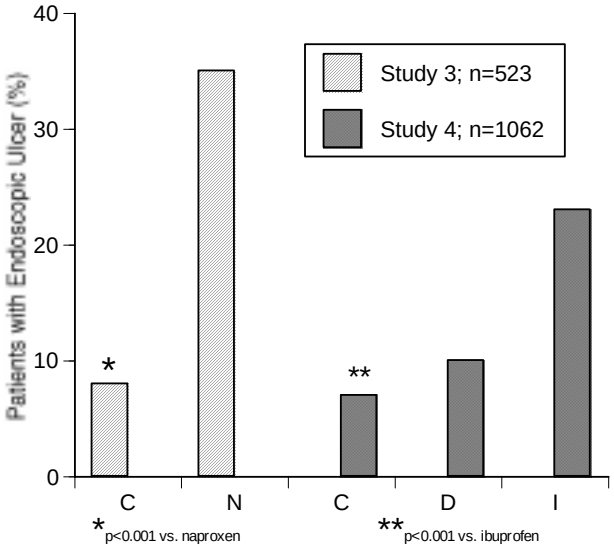
	3 Month Studies	
	Study 1 (n = 1108)	**Study 2 (n= 1049)**
Placebo	2.3% (5/217)	2.0% (4/200)
Celebrex 50 mg BID	3.4% (8/233)	---
Celebrex 100 mg BID	3.1% (7/227)	4.0% (9/223)
Celebrex 200 mg BID	5.9% (13/221)	2.7% (6/219)
Celebrex 400 mg BID	---	4.1% (8/197)
Naproxen 500 mg BID	16.2% (34/210)*	17.6% (37/210)*

* $p \leq 0.05$ vs all other treatments

Figure 5 and Table 3 summarize data from two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers. Patients underwent interval endoscopies every 4 weeks to give information on ulcer risk over time.

Figure 5

Cumulative Incidence of Gastroduodenal Ulcers Based on 4 Serial Endoscopies over 12 Weeks



C = Celecoxib 200 mg BID D = Diclofenac 75 mg BID
N = Naproxen 500 mg BID I = Ibuprofen 800 mg TID

Table 3
Incidence of Gastroduodenal Ulcers from 3-Month Serial Endoscopy Studies in OA and RA Patients

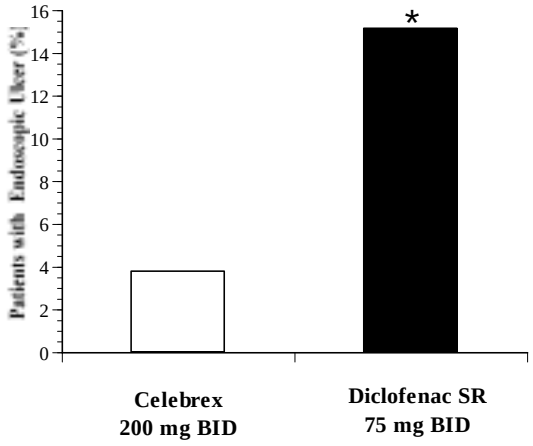
	Week 4	Week 8	Week 12	Final
Study 3 (n=523)				
Celebrex 200 mg BID	4.0% (10/252)*	2.2% (5/227)*	1.5% (3/196)*	7.5% (20/266)*
Naproxen 500 mg BID	19.0% (47/247)	14.2% (26/182)	9.9% (14/141)	34.6% (89/257)
Study 4 (n=1062)				
Celebrex 200 mg BID	3.9% (13/337)	2.4% (7/296)	1.8%(5/274)	7.0% (25/356)
Diclofenac 75 mg BID	5.1% (18/350)	3.3% (10/306)	2.9%(8/278)	9.7% (36/372)
Ibuprofen 800 mg TID	13.0% (42/323)	6.2% (15/241)	9.6% (21/219)	23.3% (78/334)

*p≤ 0.05 Celebrex vs. naproxen based on interval and cumulative analyses
 p≤ 0.05 Celebrex vs. ibuprofen based on interval and cumulative analyses

One randomized and double-blinded 6-month study in 430 RA patients was conducted in which an endoscopic examination was performed at 6 months. The results are shown in Figure 6.

Figure 6

Prevalence of Endoscopically Observed Gastroduodenal Ulcers after Six Months of Treatment in Patients with Rheumatoid Arthritis



* Significantly different from Celebrex; p<0.001

Use with Aspirin: Approximately 11% of patients (440/4,000) enrolled in 4 of the 5 endoscopic studies were taking aspirin (≤ 325 mg/day). In the CELEBREX groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than the endoscopic ulcer rates observed in the active comparator groups, with or without aspirin.

Approximately 22% of patients enrolled in the long term outcome study were taking aspirin (≤325 mg/day). In the CELEBREX patients the rate of ulcers and ulcer complications was higher in aspirin than in non-aspirin users.

Platelets: In clinical trials, CELEBREX at single doses up to 800 mg and multiple doses of 600 mg BID for up to 7 days duration (higher than recommended therapeutic doses) had no effect on platelet aggregation and bleeding time. Comparators (naproxen 500 mg BID, ibuprofen 800 mg TID, diclofenac 75 mg BID) significantly reduced platelet aggregation and prolonged bleeding time.

INDICATIONS AND USAGE

CELEBREX is indicated:

1) For relief of the signs and symptoms of osteoarthritis.

2) For relief of the signs and symptoms of rheumatoid arthritis in adults.

3) To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance , surgery). It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients . It is also not known whether the effects of CELEBREX treatment will persist after CELEBREX is discontinued. The efficacy and safety of CELEBREX treatment in patients with FAP beyond six months have not been studied (See CLINICAL STUDIES, WARNINGS and PRECAUTIONS sections).

CONTRAINDICATIONS

CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib.

CELEBREX should not be given to patients who have demonstrated allergic-type reactions to sulfonamides.

CELEBREX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS - Anaphylactoid Reactions, and PRECAUTIONS - Preexisting Asthma).

WARNINGS

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation: Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach or intestine has been observed in patients treated with CELEBREX albeit

infrequently. Physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms.

Among 5,285 patients who received CELEBREX in controlled clinical trials of 1 to 6 months duration (most were 3 month studies) at a daily dose of 200 mg or more, 2 (0.04%) experienced significant upper GI bleeding, at 14 and 22 days after initiation of dosing. Approximately 40% of these 5,285 patients were in studies that required them to be free of ulcers by endoscopy at study entry. Thus it is unclear if this study population is representative of the general population.

In a prospective randomized controlled long term outcome trial in 8000 OA and RA patients in which low dose aspirin use was allowed, approximately 0.28% of patients on CELEBREX 400 mg BID demonstrated upper GI ulcer complications (bleeding, obstruction, or perforation) over 6 months (see Special Studies: Long Term Outcome Study). In the absence of low dose aspirin use the rate was 0.16%. Patients most at risk of developing an ulcer complication were the elderly (≥75 years), patients in poor health or with cardiovascular disease, aspirin users and patients with a history of a GI ulcer or UGI bleeding .

Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. To minimize the potential risk of an ulcer complication, the lowest effective dose should be used.

Anaphylactoid Reactions
As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to CELEBREX. In post-marketing experience, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving CELEBREX. CELEBREX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS - Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease
No information is available regarding the use of CELEBREX in patients with advanced kidney disease. Therefore, treatment with CELEBREX is not recommended in these patients. If CELEBREX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS - Renal Effects).

Pregnancy
In late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus.

Familial Adenomatous Polyposis (FAP): Treatment with CELEBREX in FAP has not been shown to reduce the risk of gastrointestinal cancer or the need for prophylactic colectomy or other FAP-related surgeries. Therefore, the usual care of FAP patients should not be altered because of the concurrent administration of CELEBREX. In particular, the frequency of routine endoscopic surveillance should not be decreased and prophylactic colectomy or other FAP-related surgeries should not be delayed.

PRECAUTIONS

General: CELEBREX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of CELEBREX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Hepatic Effects: Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including CELEBREX. (See ADVERSE REACTIONS – post-marketing experience.) In controlled clinical trials of CELEBREX, the incidence of borderline elevations of liver tests was 6% for CELEBREX and 5% for placebo, and approximately 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo had notable elevations of ALT or AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with CELEBREX. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CELEBREX should be discontinued.

Renal Effects: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow,

which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with CELEBREX have shown renal effects similar to those observed with comparator NSAIDs.

Caution should be used when initiating treatment with CELEBREX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with CELEBREX. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS-Advanced Renal Disease).

Hematological Effects: Anemia is sometimes seen in patients receiving CELEBREX. In controlled clinical trials the incidence of anemia was 0.6 % with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. CELEBREX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not appear to inhibit platelet aggregation at indicated dosages (See CLINICAL STUDIES-Special Studies-Long Term Outcome Study and Platelets).

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking CELEBREX (see ADVERSE REACTIONS). Therefore, CELEBREX should be used with caution in patients with fluid retention, hypertension, or heart failure.

Pre-existing Asthma: Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, CELEBREX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients: CELEBREX can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, Risk of Gastrointestinal Ulceration, Bleeding and Perforation).

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, or edema to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus.

Patients with familial adenomatous polyposis (FAP) should be informed that CELEBREX has not been shown to reduce colo-rectal, duodenal or other FAP-related cancers, or the need for endoscopic surveillance, prophylactic or other FAP-related surgery. Therefore, all patients with FAP should be instructed to continue their usual care while receiving CELEBREX.

Laboratory Tests: Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. In controlled clinical trials elevated BUN occurred more frequently in patients receiving Celebrex compared with patients on placebo. This abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

Drug Interactions
General: Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of cytochrome P450 2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by P450 2D6.

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking CELEBREX concomitantly with ACE-inhibitors.

Furosemide: Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Aspirin: CELEBREX can be used with low dose aspirin. However, concomitant administration of aspirin with CELEBREX may result in an increased rate of GI

ulceration or other complications, compared to use of CELEBREX alone (see CLINICAL STUDIES - Special Studies Long term Outcome Study).

In the long term outcome study there was no difference in the incidence of thromboembolic events (MI and stroke) in CELEBREX patients compared to patients taking diclofenac or ibuprofen, regardless of aspirin use. Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis.

Fluconazole: Concomitant administration of fluconazole at 200 mg QD resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole (see Pharmacokinetics - Metabolism). CELEBREX should be introduced at the lowest recommended dose in patients receiving fluconazole.

Lithium: In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BID with CELEBREX 200 mg BID as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when CELEBREX is introduced or withdrawn.

Methotrexate: In an interaction study of rheumatoid arthritis patients taking methotrexate, CELEBREX did not have a significant effect on the pharmacokinetics of methotrexate.

Warfarin: Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing CELEBREX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anti-coagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2-5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin.

Carcinogenesis, mutagenesis, impairment of fertility: Celecoxib was not carcinogenic in rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-fold the human exposure as measured by the AUC_{0-24} at 200 mg BID) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC_{0-24} at 200 mg BID) for two years.

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in vivo* micronucleus test in rat bone marrow.

Celecoxib did not impair male and female fertility in rats at oral doses up to 600 mg/kg/day (approximately 11-fold human exposure at 200 mg BID based on the AUC_{0-24}.

Pregnancy

Teratogenic effects: Pregnancy Category C. Celecoxib at oral doses $\geq$150 mg/kg/day (approximately 2-fold human exposure at 200 mg BID as measured by AUC_{0-24}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses $\geq$30 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg BID) throughout organogenesis. There are no studies in pregnant women. CELEBREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Celecoxib produced pre-implantation and post-implantation losses and reduced embryo/fetal survival in rats at oral dosages $\geq$50 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg BID). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function, nor are they expected at clinical exposures. No studies have been conducted to evaluate the effect of celecoxib on the closure of the ductus arteriosus in humans. Therefore, use of CELEBREX during the third trimester of pregnancy should be avoided.

Labor and delivery: Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by the AUC_{0-24} at 200 mg BID). The effects of CELEBREX on labor and delivery in pregnant women are unknown.

Nursing mothers: Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CELEBREX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.

Geriatric Use
Of the total number of patients who received CELEBREX in clinical trials, more than 3300 were 65-74 years of age, while approximately 1300 additional patients were 75 years and over. While the incidence of adverse experiences tended to be higher in elderly patients, no substantial differences in safety and effectiveness were observed between these subjects and younger subjects**.** Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers.

ADVERSE REACTIONS

Of the CELEBREX treated patients in controlled trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and approximately 1,050 were patients with post-surgical pain. More than 8,500 patients have received a total daily dose of CELEBREX of 200 mg (100 mg BID or 200 mg QD) or more, including more than 400 treated at 800 mg (400 mg BID). Approximately 3,900 patients have received CELEBREX at these doses for 6 months or more; approximately 2,300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

Adverse events from controlled arthritis trials: Table 4 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving CELEBREX from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group.

Table 4
Adverse Events Occurring in ≥2% Of Celebrex Patients From Controlled Arthritis Trials

	Celebrex (100-200 mg BID or 200 mg QD) (N=4146)	Placebo (N=1864)	Naproxen 500 mg BID (N=1366)	Diclofenac 75 mg BID (N=387)	Ibuprofen 800 mg TID (N=345)
Gastrointestinal					
Abdominal pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a whole					
Back Pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central and peripheral nervous system					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis	2.3%	1.1%	1.7%	1.6%	2.6%
Rhinitis	2.0%	1.3%	2.4%	2.3%	0.6%
Sinusitis	5.0%	4.3%	4.0%	5.4%	5.8%
Upper respiratory tract infection	8.1%	6.7%	9.9%	9.8%	9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving CELEBREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of CELEBREX patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The adverse event profile from the long term outcomes trial (at 4- and 2-fold the recommended doses for OA and RA, respectively) was similar to those reported in the arthritis controlled trials.

The following adverse events occurred in 0.1 - 1.9% of patients regardless of causality.

Celebrex
(100 - 200 mg BID or 200 mg QD)

Gastrointestinal:	Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, tooth disorder, vomiting
Cardiovascular:	Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction
General:	Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain
Resistance mechanism disorders:	Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media
Central, peripheral nervous system:	Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo
Female reproductive:	Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage, vaginitis
Male reproductive:	Prostatic disorder
Hearing and vestibular:	Deafness, ear abnormality, earache, tinnitus
Heart rate and rhythm:	Palpitation, tachycardia
Liver and biliary system:	Hepatic function abnormal, SGOT increased, SGPT increased
Metabolic and nutritional:	BUN increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase
Musculoskeletal:	Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis
Platelets (bleeding or clotting):	Ecchymosis, epistaxis, thrombocythemia
Psychiatric:	Anorexia, anxiety, appetite increased, depression, nervousness, somnolence
Hemic:	Anemia
Respiratory:	Bronchitis**,** bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia
Skin and appendages:	Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria
Application site disorders:	Cellulitis, dermatitis contact, injection site reaction, skin nodule
Special senses:	Taste perversion
Urinary system:	Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection
Vision:	Blurred vision, cataract, conjunctivitis, eye pain, glaucoma

Other serious adverse reactions which occur rarely (estimated <0.1%), regardless of causality: The following serious adverse events have occurred rarely in patients, taking CELEBREX. Cases reported only in the post-marketing experience are indicated in italics.

Cardiovascular:	Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, *vasculitis*
Gastrointestinal:	Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus
Liver and biliary system:	Cholelithiasis, *hepatitis, jaundice, liver failure*
Hemic and lymphatic:	Thrombocytopenia, *agranulocytosis, aplastic anemia, pancytopenia, leukopenia*
Metabolic:	*Hypoglycemia*
Nervous system:	Ataxia, suicide
Renal:	Acute renal failure, *interstitial nephritis*
Skin:	*Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis*
General:	Sepsis, sudden death, *anaphylactoid reaction, angioedema*

Adverse events from the controlled trial in familial adenomatous polyposis: The adverse event profile reported for the 83 patients with familial adenomatous polyposis enrolled in the randomized, controlled clinical trial was similar to that reported for patients in the arthritis controlled trials. Intestinal anastomotic ulceration was the only new adverse event reported in the FAP trial, regardless of causality, and was observed in 3 of 58 patients (one at 100 mg BID, and two at 400 mg BID) who had prior intestinal surgery.

OVERDOSAGE

No overdoses of CELEBREX were reported during clinical trials. Doses up to 2400mg/day for up to 10 days in 12 patients did not result in serious toxicity.

Patients should be managed by symptomatic and supportive care following an overdose. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

DOSAGE AND ADMINISTRATION

For osteoarthritis and rheumatoid arthritis, the lowest dose of CELEBREX should be sought for each patient. These doses can be given without regard to timing of meals.

Osteoarthritis: For relief of the signs and symptoms of osteoarthritis the recommended oral dose is 200 mg per day administered as a single dose or as 100 mg twice per day.

Rheumatoid arthritis: For relief of the signs and symptoms of rheumatoid arthritis the recommended oral dose is 100 to 200 mg twice per day.

Familial adenomatous polyposis (FAP): Usual medical care for FAP patients should be continued while on CELEBREX. To reduce the number of adenomatous colorectal polyps in patients with FAP, the recommended oral dose is 400 mg (2 X 200 mg capsules) twice per day to be taken with food.

Special Populations
***Hepatic insufficiency*:** The daily recommended dose of CELEBREX capsules in patients with moderate hepatic impairment (Child-Pugh Class II) should be reduced by approximately 50% (see CLINICAL PHARMACOLOGY – Special Populations).

HOW SUPPLIED

CELEBREX 100-mg capsules are white, reverse printed white on blue band of body and cap with markings of 7767 on the cap and 100 on the body, supplied as:

NDC Number	Size
0025-1520-31	bottle of 100
0025-1520-51	bottle of 500
0025-1520-34	carton of 100 unit dose

CELEBREX 200-mg capsules are white, with reverse printed white on gold band with markings of 7767 on the cap and 200 on the body, supplied as:

NDC Number	Size
0025-1525-31	bottle of 100
0025-1525-51	bottle of 500
0025-1525-34	carton of 100 unit dose

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]

Rx only **Revised: Draft dated 22 May 2000**

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Caguas PR 00725

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APPENDIX 1: SUPPORTIVE STATISTICAL ANALYSES

Six months analyses:

Ulcer complications

A. Celecoxib vs NSAIDs combined - ITT

B. Celecoxib vs NSAIDs combined – Patients not taking Aspirin

Symptomatic ulcers and ulcer complications

C. Celecoxib vs NSAIDs combined - ITT

D. Celecoxib vs NSAIDs combined – Patients not taking Aspirin

Entire study period analysis:

Ulcer complications

E. Celecoxib vs NSAIDs combined - ITT

F. Celecoxib vs NSAIDs combined – Patients not taking Aspirin

Symptomatic ulcers and clinically significant ulcer complications

G. Celecoxib vs NSAIDs combined - ITT

H. Celecoxib vs NSAIDs combined – Patients not taking Aspirin

Comparisons between treatment groups – observed and adjusted for informative censoring (entire study):

Ulcer complications

I. Celecoxib vs Diclofenac and Ibuprofen - ITT

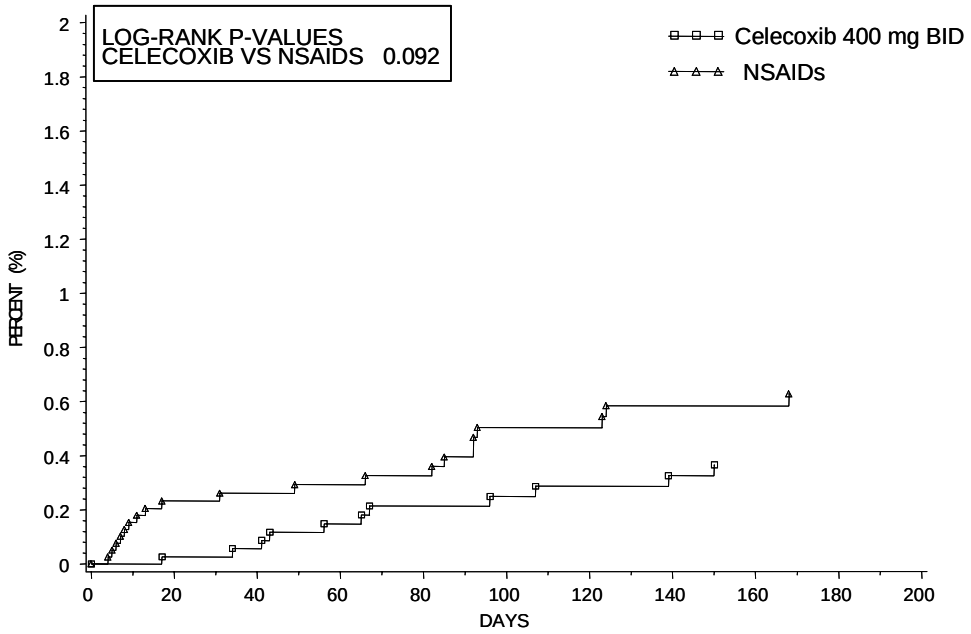
J. Celecoxib vs Diclofenac and Ibuprofen - ITT adjusted for informative censoring

Symptomatic ulcers and ulcer complications

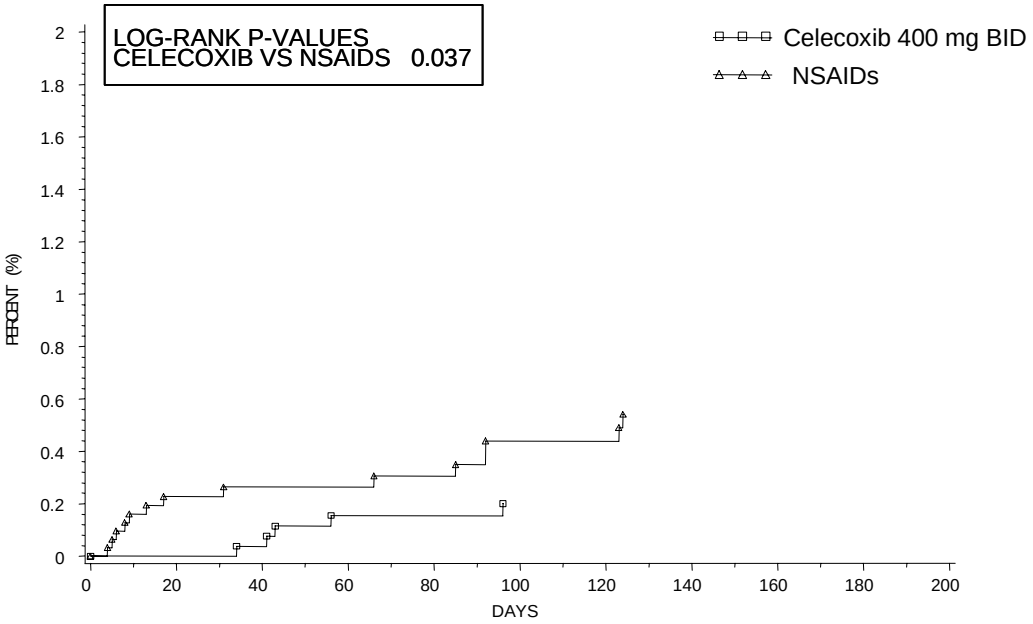
K. Celecoxib vs Diclofenac and Ibuprofen - ITT

L. Celecoxib vs Diclofenac and Ibuprofen - ITT adjusted for informative censoring

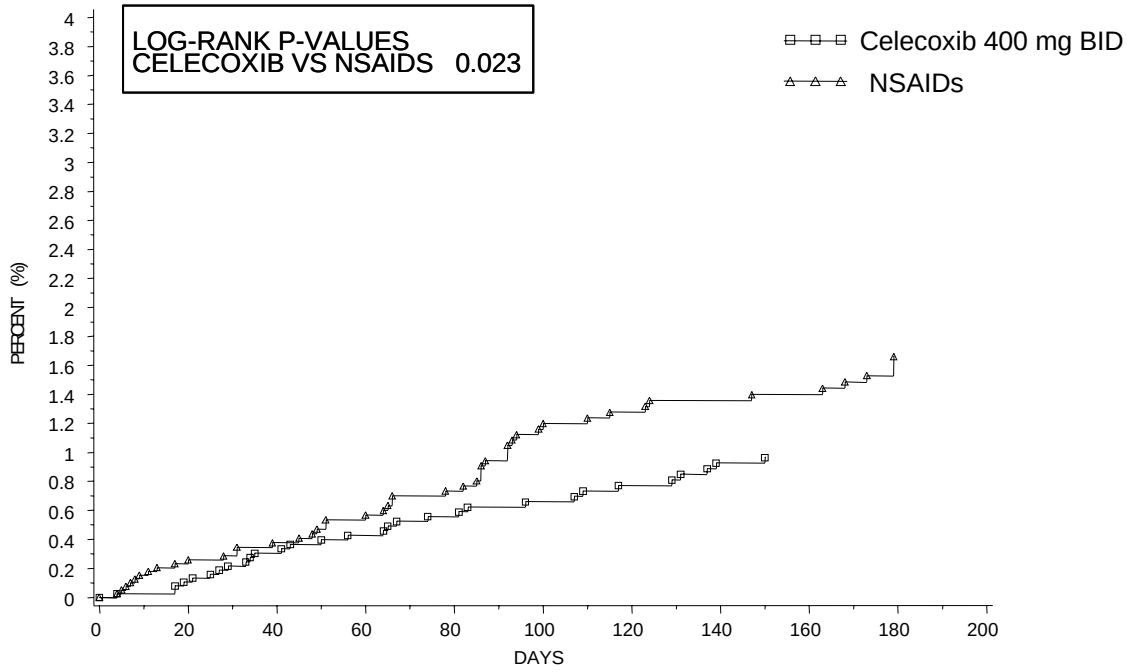
A. Six months – Ulcer complications: Celecoxib vs. NSAIDs - ITT



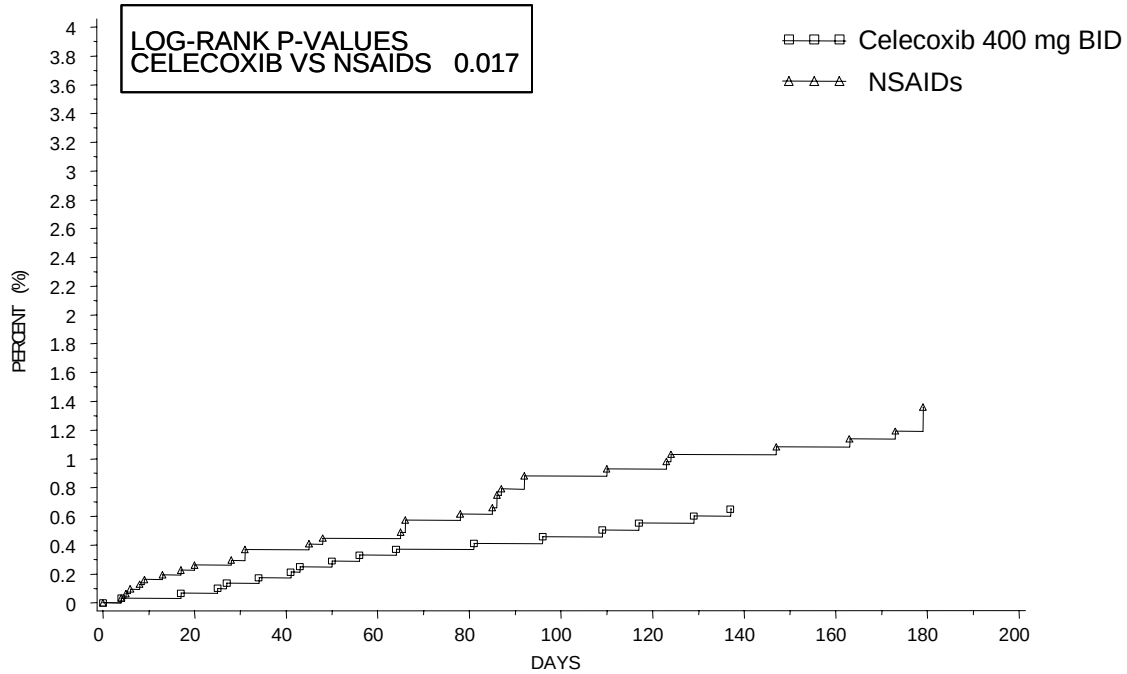
B. Six months – Ulcer complications: Celecoxib vs. NSAIDs – Patients not taking aspirin



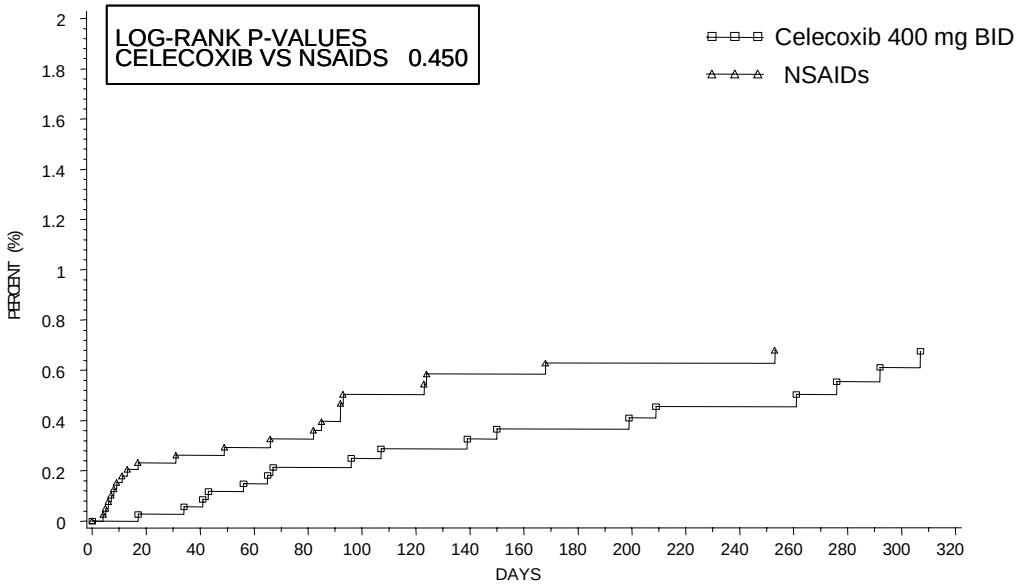
C. Six months – Symptomatic ulcers and ulcer complications: Celecoxib vs. NSAIDs – ITT



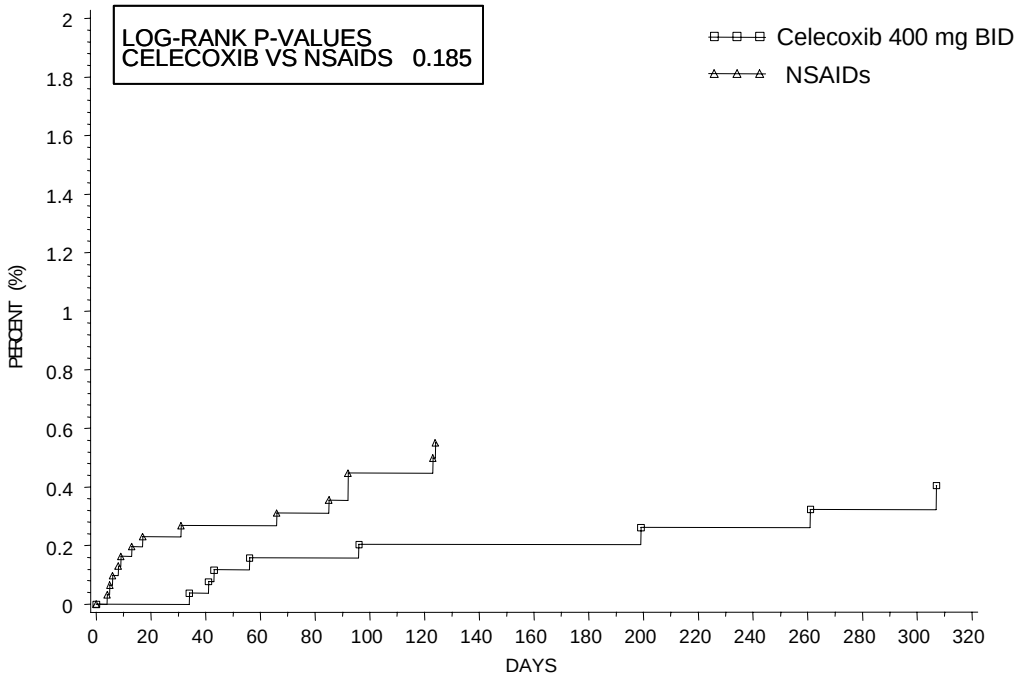
D. Six months – Symptomatic ulcers and ulcer complications: Celecoxib vs. NSAIDs – Patients not taking aspirin



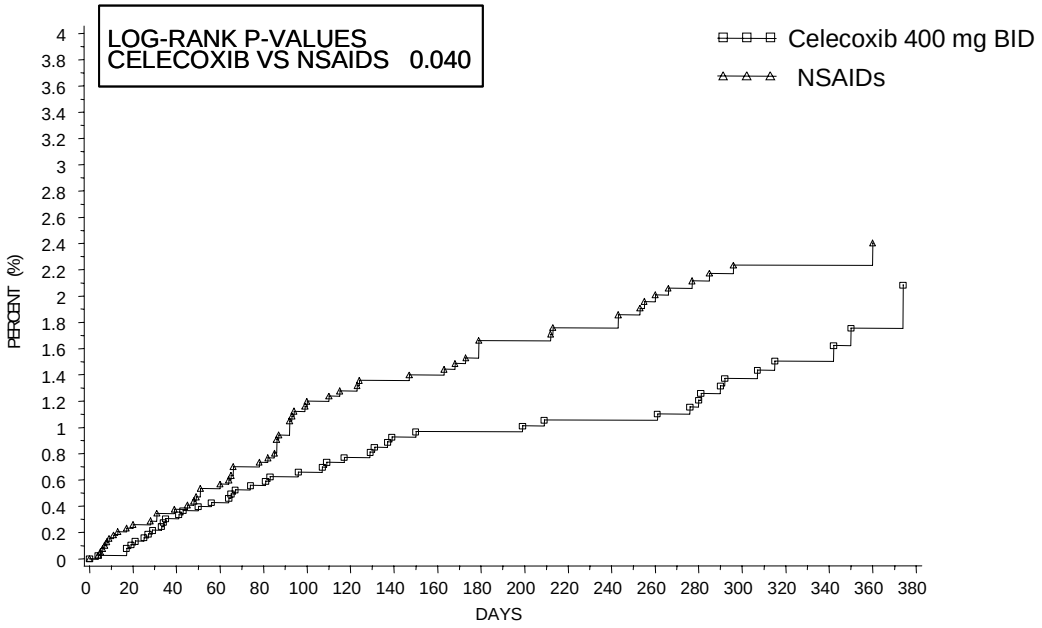
E. Entire study – Ulcer complications: Celecoxib vs. NSAIDs – ITT



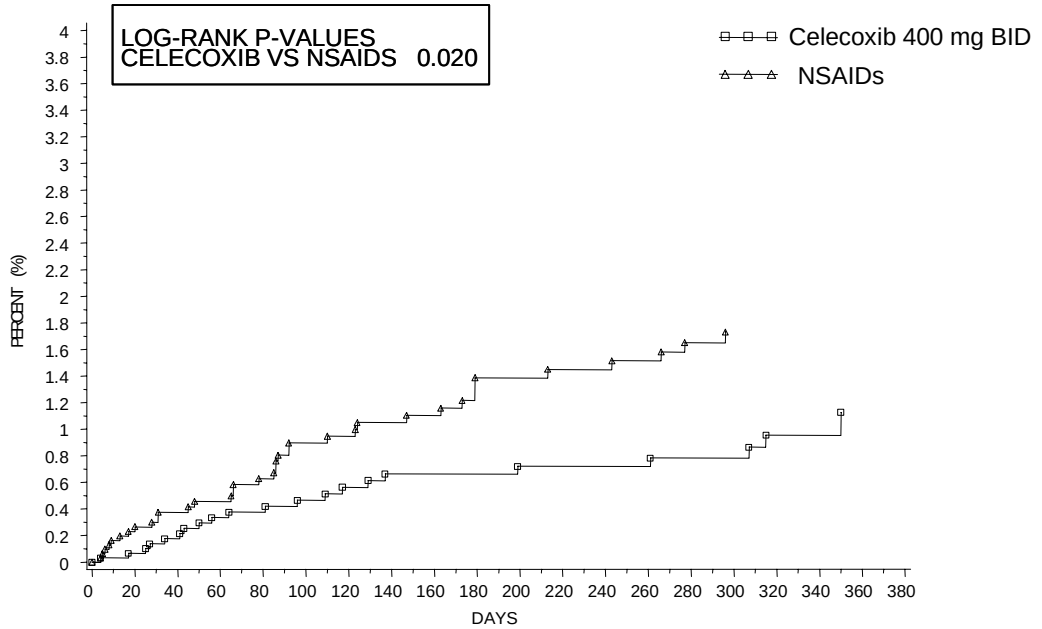
F. Entire study – Ulcer complications: Celecoxib vs. NSAIDs – Patients not taking aspirin



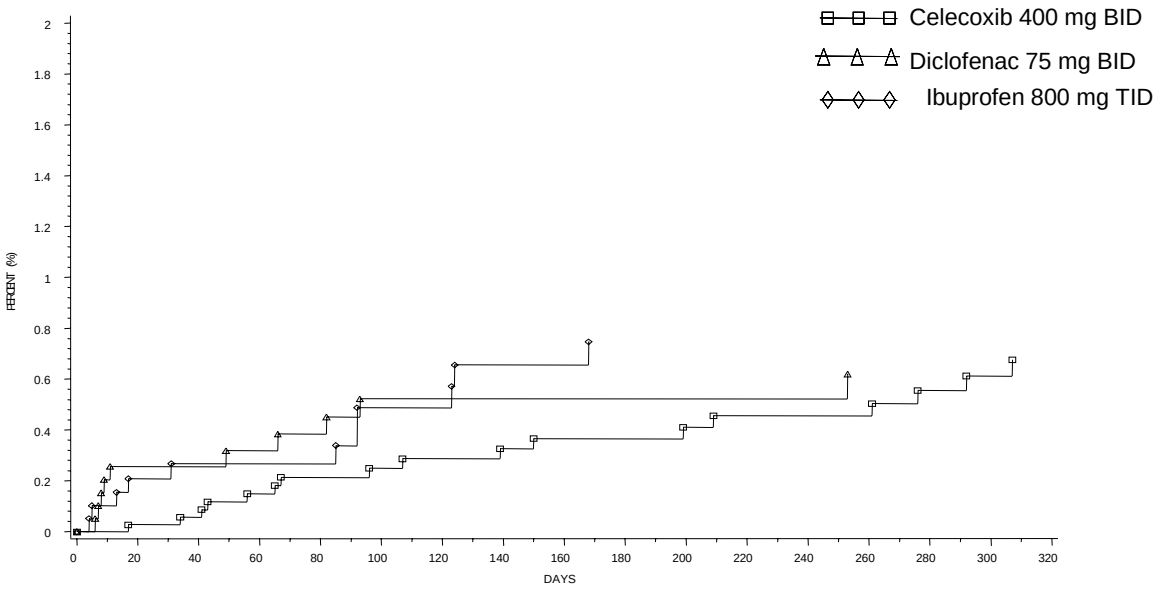
G. Entire study – Symptomatic ulcers and ulcer complications: Celecoxib vs. NSAIDs – ITT



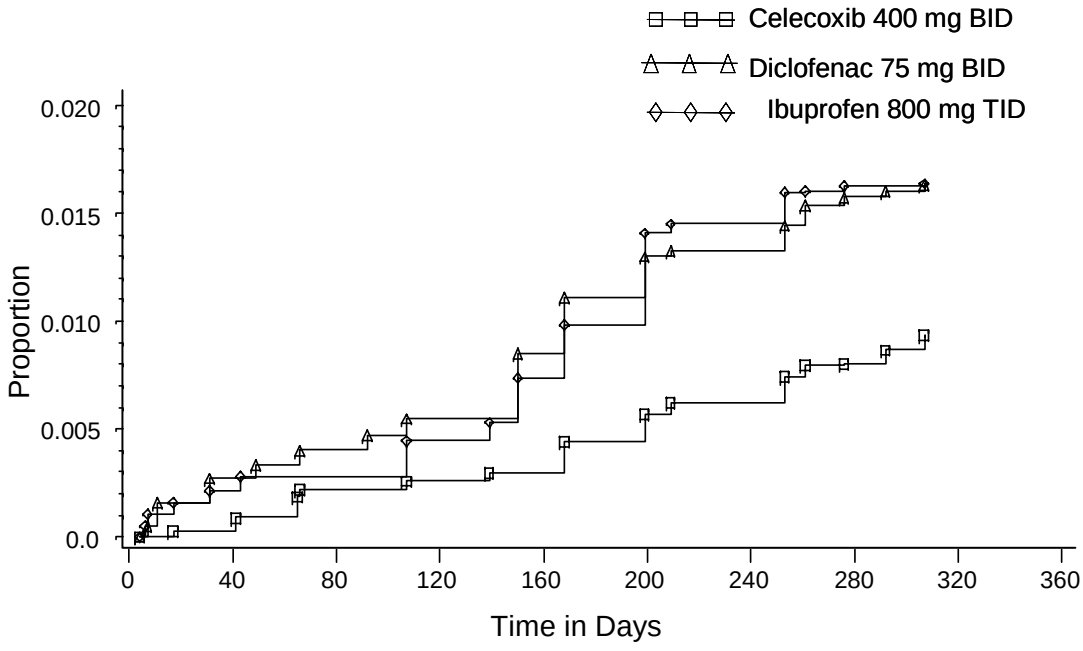
H. Entire study – Symptomatic ulcers and ulcer complications: Celecoxib vs. NSAIDs – Patients not taking aspirin



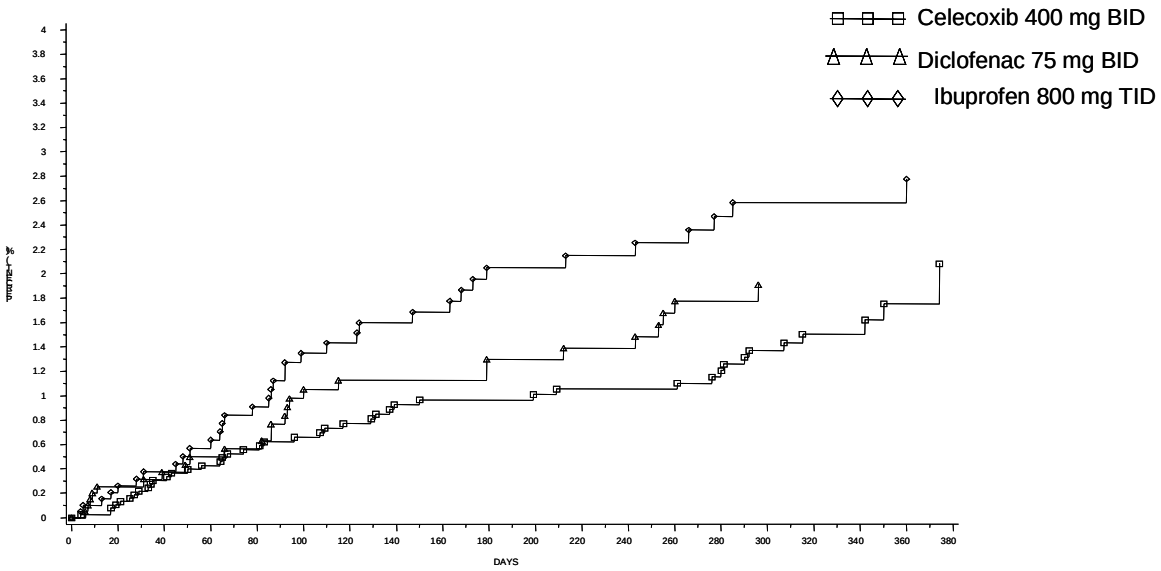
I. Entire study: Ulcer complications: Celecoxib vs. diclofenac and ibuprofen - Observed



J. Entire study: Ulcer complications: Celecoxib vs. diclofenac vs. ibuprofen – Adjusted for informative censoring



K. Entire study – Ulcer complications and symptomatic ulcers: Celecoxib vs. diclofenac vs. ibuprofen – Observed



L. Entire study – Ulcer complications and symptomatic ulcers: Celecoxib vs. diclofenac vs. ibuprofen – Adjusted for informative censoring