Celebrex Capsules
(Celecoxib)

NDA 20-998/S-009

Medical Officer Review

Submission Date:	June 12, 2000
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Review Date:	September 20, 2000
Drug Name:	Celebrex™
Generic Name:	celecoxib
Chemical Name:	4-[5-(4-methylphenyl)-3-trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide
Applicant:	G.D. Searle & Co.
Related Reviews:	Statistics, Cardio-Renal, Gastrointestinal (HFD-550)
Pharmacologic category:	COX-2 inhibitor
Proposed Indication:	Label changes -Warnings (Clinically Significant UGI Events)
Dosage forms and route:	Oral capsule, 100 and 200 mg
Submission type:	Supplemental NDA
Materials Reviewed:	Primary-document N49-00-06-035_102

Orig NDA # 20-998
HFD-550/Div File
HFD-550/PM/Kong
HFD-550/Pharm/Yang
HFD-550/Chem/Bhavnagri
HFD-550/Biopharm/Bashaw
HFD-550/Statistics/Lin
HFD-550/MO/Witter/Goldkind

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(James Witter, M.D., Ph.D. Medical Officer)

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Table of Contents

Listing of Celecoxib sNDA (20-998) Review Tables

Clinical Background (Section 6):

Relevant Human Experience (Section 6.1):

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat chronic arthritic diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA). An important mechanism through which these agents are thought to act is via inhibition of the enzyme cyclooxygenase (COX). This enzyme is now known to exist in two isoforms: a mostly constitutive form (COX-1) and a mostly inducible form (COX-2). However, it is now appreciated that COX-2 can also be constitutively expressed in certain areas in the body. COX-1 is thought to be widely distributed throughout most body tissues and mediates synthesis of prostaglandins that have a diverse array of homeostatic physiological functions. One of these important functions is thought to include the maintenance of mucosal integrity in the upper gastrointestinal (UGI) tract. In contrast, COX-2 in most areas of the body, is thought to be expressed in low levels in tissues but is rapidly and highly induced at sites of inflammation.

Since "traditional" NSAIDs nonspecifically inhibit both COX isoforms, it has been postulated that their anti-inflammatory and analgesic benefits result from inhibition of COX-2 while the increased rate of UGI ulcers and complications commonly associated with NSAIDs result from inhibition of COX-1. The principal manifestations of ulcer complications are UGI bleeding, perforation, and gastric outlet obstruction. The UGI toxicity of NSAIDs has been well documented. For example, observational analysis of the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) database suggests that in a large population receiving NSAIDs over 10,600 patient-years, GI-related hospitalizations or deaths occurred at a rate of 1.3% per year. Most studies in this area, such as the one cited, have been observational cohort or retrospective case-control studies. In the only large, randomized, prospective trial of NSAID-related UGI ulcer complications (the MUCOSA trial), the annualized incidence was approximately 1.9% in 8843 RA patients followed for six months; the risk of UGI ulcer complications did not seem to diminish with continuing exposure.

This risk of UGI complications noted for NSAIDs resulted in the formation of a GI paragraph which has been included in the labeling of approved NSAIDs. The current labeling for Celebrex is as follows:

WARNINGS

Gastrointestinal (GI) Effects- Risk of GI Ulceration, Bleeding, and Perforation:

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

It is unclear, at the present time, how the above rates apply to CELEBREX. (See CLINICAL STUDIES-Special Studies.) Among 5285 patients who received CELEBREX in studies of 1 to 6 months duration, at a daily dose of 200

*mg or more in controlled clinical trials, 2 (0.04%) experienced significant upper GI bleeding at 14 and **22** days after initiation of dosing. Approximately **40%** of these 5285 patients were in studies that required them to be free of ulcers by endoscopy at study entry. (Thus this study population may have been at lower risk for significant gastrointestinal complications.) **Thus it is unclear if this study is representative of the general population.** Prospective, long-term studies required to compare the occurrence of serious clinically significant upper GI adverse events in patients taking CELEBREX vs. comparator NSAID products have not been performed.*

*NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal 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 for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.*

*Studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than 10-fold **higher** risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.*

An important hypothesis for development of selective inhibitors of COX-2 has been that they, by avoiding inhibition of COX-1, would spare the UGI tract toxicity while maintaining analgesic and anti-inflammatory efficacy. A corollary to this has been the impression that COX-2 agents may also be safer, overall, as compared to traditional NSAIDs. The original NDA for Celebrex included data on endoscopically-defined UGI endpoints, but insufficient data on clinical UGI outcomes to allow for any substantial modification of the GI Warning paragraph. **This sNDA, which consists basically of two large safety studies (protocols N49-98-02-035 and N49-98-02-102), seeks to address primarily the UGI clinical outcomes of celecoxib, a COX-2 selective agent, as compared to more traditional NSAIDs.** In particular, the incidence of clinically significant UGI events (CSUGIEs) associated with celecoxib was compared to that associated with ibuprofen or diclofenac during chronic administration (at least six months) in patients with OA or RA. The term "CSUGIE" represents a composite end point comprised of UGI bleeding, perforation, or gastric outlet obstruction. It should be noted that these companion protocols were prospectively designed with the intent to combine the results into a single study, pooling the celecoxib patients from both protocols into a single treatment group.

Clinical Studies (section 8):

This sNDA consists of two trials, N49-98-02-035 and N49-98-02-102. Owing to the similar nature of these trials, they will be described together with any important differences noted.
These two trials were submitted as a combined document (N49-00-06-035-102) entitled,

"A multicenter, double-blind, parallel group study comparing the incidence of clinically significant upper gastrointestinal events between Celecoxib 400 mg BID and Ibuprofen 800 mg TID or Diclofenac 75 mg BID : The Celecoxib Long-Term Arthritis Safety Study (CLASS)"

This study was conducted in compliance with **two protocols**:

(1) **Protocol N49-98-02-035**, entitled "A Multicenter, Double-Blind, Parallel Group Study Comparing the Incidence of Clinically Significant Upper Gastrointestinal Adverse Events Associated with SC-58635 400 mg BID to that of NSAID Treatment with Either Diclofenac 75 mg BID, Ibuprofen 800 mg TID or Naproxen 500 mg BID in Patients with Osteoarthritis or Rheumatoid Arthritis," dated 26 January 1998

(2) **Protocol N49-98-02-102**, entitled "A Multicenter, Double-Blind, Parallel Study Comparing the Incidence of Clinically Significant Upper Gastrointestinal Adverse Events Associated with SC-58635 400 mg BID to that of Diclofenac 75 mg BID and Naproxen 500 mg BID in Patients with Osteoarthritis or Rheumatoid Arthritis," dated 24 August 1998.

There were a total of **eight amendments or administrative changes to these two protocols**, described below. All of these changes were implemented while all patients' treatment assignments remained blinded.

- **Amendment No. 1 to N49-98-02-035, dated 16 July 1998, removed naproxen and diclofenac as NSAID comparators from the study; modified required laboratory testing; added a recommended algorithm for working up a suspected CSUGIE; and changed the clinical and medical monitors from Kenneth M. Verburg, PhD, and Richard C. Hubbard, MD, to David A. Callison, MS, and James B. Lefkowith, MD, respectively.**
- **Amendment No. 2 to N49-98-02-035, dated 18 August 1998, reduced the sample size required for the study from 6000 patients to 4000 patients, and specified that in the primary analysis, the celecoxib patients from the two companion studies would be pooled into a single treatment group.**
- **Amendment No. 1 to N49-98-02-102, dated 26 October 1998, removed naproxen as an NSAID comparator from the study; added to the required laboratory testing; clarified the definition of UGI bleeding and the algorithm for working up a suspected CSUGIE; expanded the planned statistical analysis and interim analysis; and expanded the recording of alcohol and tobacco use.**
- **Amendment No. 3 to N49-98-02-035, dated 9 November 1998, added to the required laboratory testing; clarified the definition of UGI bleeding and the algorithm for working up a suspected CSUGIE; expanded the planned statistical analysis and interim analysis; and expanded the recording of alcohol and tobacco use.**
- **Amendment No. 4 to N49-98-02-035, dated 6 July 1999, lengthened the study period by up to an additional three months, in order to reach the target number of CSUGIEs; and amended the phrase "ulcer or erosion" to "ulcer or large erosion" in the traditional and alternate definitions of UGI bleeding.**

- **Administrative Change No. 1 to N49-98-02-035, dated 4 August 1999, corrected one CRF.**
- **Administrative Change No. 1 to N49-98-02-102, dated 23 November 1999, changed and clarified censoring rules for CSUGIEs; amended the phrase "ulcer or erosion" to "ulcer or large erosion" in the traditional and alternate definitions of UGI bleeding; and changed the clinical monitor from Mary Lonien, MS, to T. Kirsten Kätz, BA, and the statistician from Shawn Yu, PhD, to William Zhao, PhD.**
- **Administrative Change No. 2 to N49-98-02-035, dated 24 November 1999, changed and clarified the censoring rules for analysis of CSUGIEs.**

The two protocols were originally planned to continue until the following criteria were fulfilled: (1) each patient had the opportunity to remain in the study for at least 26 weeks, and (2) at least 20 CSUGIEs occurred in each protocol, or a maximum of 45 CSUGIEs occurred in the two protocols combined. As of September 15, 1999, all patients had had the opportunity to participate for at least 26 weeks. As of November 24, 1999, a total of 40 CSUGIEs had been identified. Of these, 36 would be included in the analyses after application of the censoring rules (17 in protocol N49-98-02-035 and 19 in protocol N49-98-02-102). At that time, it was argued that the rate of CSUGIE development had deviated considerably 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. Therefore, in consultation with the Executive Committee, the GEC, and the Data Safety Monitoring Board, as well as with FDA, the Sponsor decided to conclude both protocols. All investigative sites were notified of this decision on December 9,1999, and asked to schedule final visits for all remaining patients to take place by January 7, 2000.

The Sponsor's rationale for modifying the analyses of UGI safety results by separately considering the first six months and the entire study period was as follows. Six months of exposure were felt to represent a clinically meaningful exposure for a comparison of GI safety end points and could be compared to available data from the only prospective, controlled, published trial (i.e. MUCOSA) noted earlier. Additionally, disproportionate withdrawal of patients with NSAID-associated risk factors was observed over the first six months of the study, and may have artificially decreased the observed rate of clinically significant events in the NSAID groups after six months (i.e., depletion of susceptible patients). The issue of unbalanced withdrawal of patients with NSAID-associated risk factors prompted the sponsor to discuss an adjustment for "informative censoring" for risk factor analysis (see page 35 of section 8.1.1.4.2 for details regarding informative censoring).

Study Objective (Section 8.1.1.1):

The Sponsor primarily is seeking modification of the GI Warning paragraph.

Study Design (Section 8.1.1.2):

This combined study was a Phase 3B/4, randomized, controlled, parallel, double-blind, multicenter (386 Investigators at 386 Study Sites in the United States and Canada) study conducted from September 23, 1998 - March 17, 2000.

Protocol (Section 8.1.1.3):

Population, procedures (Section 8.1.1.3.1)
Patients were randomly assigned to receive either celecoxib or the 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. Patients for inclusion or exclusion were selected according to the criteria noted below. 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.

Inclusion Criteria:
To qualify for study participation, candidates must have:

1. Been of legal age of consent or older;
2. For women of childbearing potential, had 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;
3. Had a documented clinical diagnosis of OA or RA of at least three months duration;
4. Required chronic NSAID therapy in the Investigator's opinion;
5. Been expected to be able to participate for the full duration of the study; and
6. Provided written informed consent.

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

1. Had an active malignancy of any type or history of malignancy. (Patients who had a history of basal cell carcinoma that had been treated were acceptable. Patients with a history of other malignancies that had been surgically removed and who had no evidence of recurrence for at least five years before study enrollment were also acceptable.);
2. 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;
3. Had active GI disease (e.g., inflammatory bowel disease);
4. Had a history of gastric or duodenal surgery other than simple oversew of an ulcer or perforation;
5. Had significant renal or hepatic dysfunction, or a significant coagulation defect considered by the Investigator to be clinically significant;
6. Had abnormal Screening laboratory test values >1.5 times the upper limit of normal (ULN) for either AST or ALT or any other laboratory abnormality at screening considered by the Investigator to be clinically significant;
7. Had a positive screening fecal occult blood test result;
8. Had a known hypersensitivity to COX-2 inhibitors, sulfonamides, ibuprofen (protocol-035) or diclofenac (protocol-102);
9. 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;

10. Had previously been admitted to either of these protocols or a prior study with celecoxib.

Selection of Doses in the Study:

For relief of the signs and symptoms of OA, the recommended, labeled dose of celecoxib is 200 mg per day administered as a single dose or as 100 mg BID; for relief of the signs and symptoms of RA in adults, the recommended dose is 100 to 200 mg BID. The dose of celecoxib evaluated in this study, 400 mg BID, was therefore two to four times the maximum recommended doses for RA and OA, respectively, and was chosen to ensure that the ulcerogenic potential of celecoxib was rigorously assessed.

Ibuprofen and diclofenac are indicated for the treatment of RA and OA. According to the prescribing information, the recommended dose of ibuprofen is 1200-3200 mg/day for both OA and RA; the recommended doses of diclofenac are 100-150 mg/day for OA and 150-200 mg/day for RA using a BID or TID dosing regimen. On this basis, the ibuprofen dose of 800 mg TID and the diclofenac dose of 75 mg BID were chosen for their respective protocols. These represent the most commonly prescribed doses of these two drugs for treating OA and RA.

Each protocol consisted of at least 26 weeks of treatment, with a maximum potential treatment period of 52 weeks (study-102) or 65 weeks (study-035). Patients underwent screening/baseline visits and follow-up visits scheduled for 4, 13, 26, 39, and 52 weeks (and 65 weeks in protocol -035 only) after the first dose of study medication. In protocol-035, all patients were instructed to take two capsules from bottle A (celecoxib 200 mg or placebo) and one tablet from bottle B (ibuprofen or placebo) with their morning and evening meals, and one tablet from bottle B only with their mid-day meal. In protocol-102, all patients took two capsules from bottle A (celecoxib 200 mg or placebo) and one tablet from bottle B (diclofenac 75 mg or placebo) with their morning and evening meals. All patients and study personnel remained blinded to each patient's treatment throughout the study.

The studies were planned to be conducted until at least 20 CSUGIEs occurred in each protocol, or a maximum of 45 CSUGIEs occurred in the two protocols combined. Minimum planned study participation for an individual patient was 26 weeks. Occurrences of suspected CSUGIEs were adjudicated and classified by an independent Gastrointestinal Events Committee (GEC), all of the members of which were blinded to each patient's study and treatment. The procedures performed in this combined study are shown in **Table 1**.

Table 1: Schedule of Observations and Procedures

	Pretreatment Period -7 to 0 Days		Treatment Period Weeks ± Days						Final Visit (b)	Early Term. (c)
	Screen	Baseline	4±5	13±5	26±5	39±5	52±5	65±5 (a)		
Informed Consent (d)	X									
Medical History (L)	X									
Physical Exam	X								X	X
Clinical Lab Tests (e)	X		X	X	X	X	X	X	X	X
Pregnancy Test (f)	X			X	X	X	X	X	X	X
Fecal Occult Blood Testing (m)	X								X	X
D/C Current NSAID/ anti-ulcer drugs (g)		X								
Arthritis Assessments (h)		X	X	X	X	X	X	X	X	X
Signs and Symptoms		X	X	X	X	X	X	X	X	X
Indirect Cost Assessment		X	X	X	X	X		X	X	X
Patient Satisfaction Questionnaire								X	X	X
QOL Assessments (i)		X			X			X	X	X
Health Status Assessments (j)		X	X	X	X		X		X	X
Dispense Study Med		X	X (k)	X	X	X	X (a)			
Dispense Concurrent Meds Diary Card		X	X	X	X	X	X (a)			
Retrieve Concurrent Meds Diary Card			X	X	X	X	X	X	X	X
Retrieve and Count Study Med			X	X	X	X	X	X	X	X

(a) Protocol 035 only.

(b) The Final Treatment Visit coincided with the Week 65 visit in protocol 035 or the Week 52 visit in protocol 102, or may have occurred at any time when the study officially concluded.

(c) Patients terminating early were contacted monthly for two months following their withdrawal or until the study officially concluded, whichever occurred first.

(d) Informed consent was obtained before any study-related procedures were performed.

(e) Clinical laboratory tests included: Hematology (WBC, hemoglobin, hematocrit, platelet count, MCV, MCHC, ferritin, iron, iron binding capacity; the latter five were performed after Screening only in the event of new-onset anemia), and Biochemistry (BUN, creatinine, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), creatine kinase (CK), sodium, potassium, chloride, phosphorus, bicarbonate). At Screening, serum FlexSure HP test for H. pylori status was also performed.

(f) For females of childbearing potential only.

(g) Current NSAID and any anti-ulcer drugs were discontinued at or before the Baseline Visit.

(h) Patient's Global Assessment of Arthritis and Patient's Assessment of Arthritis Pain-VAS.

(i) Protocol 035 only. Consisted of SF-36 Health Survey and Health Assessment Questionnaire (HAQ).

(j) Protocol 102 only. Consisted of Severity of Dyspepsia Assessment (SODA).

(k) At the Week 4 visit, patients brought back the kit dispensed at Baseline. Compliance was checked and the remaining medication from the Baseline kit redispensed.

(L) The information gathered in the medical history included date of birth, duration of OA or RA, duration of NSAID therapy, GI-related NSAID intolerance (defined as any history of NSAID-induced gastroduodenal ulcers, NSAID-induced erosive gastritis, or NSAID-induced UGI symptoms of sufficient severity to discontinue NSAID use), history of UGI bleeding, history of gastroduodenal ulcer disease (defined as a diagnosis by UGI barium x-ray or endoscopy or treatment by a physician for an ulcer diagnosed by clinical judgment and based on reliable patient history), history of cardiovascular disease, corticosteroid use, anticoagulant use, tobacco use, and alcohol use.

(m) All patients were tested for *H. pylori* antibodies using FlexSure HP serological testing.

At the end of the baseline visit, site personnel called the Interactive Voice-activated Response System (IVRS) utilized to randomize the patient into the study and receive the study medication allocation assignment. Study medication and a diary card were then dispensed to the patient. Patients returned to the study site at Weeks 4, 13, 26, 39, and 52 (and Week 65 in protocol 035 only) after the first dose of study medication. Study medication and concurrent medications diary cards were dispensed at all visits except the final visit, and previously dispensed study medication and completed diary cards were returned at each visit. Patients were queried about their alcohol and tobacco use at the week 26 and final (or early termination) visits.

At the final (or early termination) visit, patients underwent a complete physical examination, including weight and vital signs, and completed a patient satisfaction questionnaire. This questionnaire incorporates four questions regarding the patient's overall satisfaction with the efficacy and tolerability of their study medication.

Other Endpoints:

As noted in Table 1, the **arthritis assessments** consisted of a patient's global assessment of arthritis and a patient's assessment of arthritis pain. For the **patient's global assessment** of arthritis, patients answered the question: "Considering all the ways your arthritis affects you, how are you doing today?" Patients rated their condition using the following 5-point scale:

1	**Very Good - Asymptomatic and no limitation of normal activities**
2	**Good - Mild symptoms and no limitation of normal activities**
3	**Fair - Moderate symptoms and limitation of some normal activities**
4	**Poor - Severe symptoms and inability to carry out most normal activities**
5	**Very Poor - Very severe symptoms which are intolerable and inability to carry out all normal activities**

For the **patient's assessment of arthritis pain**, patients were asked to rate their arthritis pain on a 100-mm visual analog scale (VAS) between 0 (no pain) and 100 (most severe pain).

In protocol 035, Quality of Life (QOL) assessments consisted of the **SF-36** health survey and the Health Assessment Questionnaire Functional Disability Index **(HAQ**); both of these indices are widely used in arthritis clinical trials. These two assessments were completed before patients saw the investigator for arthritis assessments. The SF-36 Health Survey is a generic QOL instrument incorporating 36 items within eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The HAQ assesses eight areas of daily function, each with two to three activities. Patients indicated their ability to perform these activities on a scale of 0 to 3, as follows: without any difficulty, with some difficulty, with much difficulty, or unable to do, respectively, including whether or not help from another person or use of a device is required to perform these activities.

In protocol 102, patients completed the Severity of Dyspepsia Assessment (**SODA**) questionnaire. This questionnaire was developed for characterizing abdominal discomfort in a dyspepsia population, but is as yet unvalidated in an arthritis population. Patients also completed an **Indirect Cost Assessment** questionnaire at the baseline visit. This instrument contains a series of questions about how arthritis or the treatment of arthritis affects the patient's ability to work or carry out daily activities.

For the QOL, SODA, and Indirect Cost measures, after the patient completed the questionnaire, site personnel checked it for completeness. If an answer to any question was missing, the patient was asked to complete or clarify it.

Patients answered the following question during the visit: "**Do you currently have any symptoms that are not associated with your arthritis?**" (The information collected was used in the analyses of adverse events.) In addition, patients were asked to list any medication they had taken in the previous 30 days.

Removal of Patients from Therapy or Assessment

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
- Preexisting 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 found at an 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 a CSUGIE had occurred. What the sponsor considered reasonable attempts were made to contact each patient.

Prior and Concomitant Therapy:

No medications were prohibited prior to entering the study except the use of any investigational drug within 30 days prior to receiving the first dose. 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 30 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 H2 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; and
- Antineoplastics (other than methotrexate ≤ 25 mg/wk or azathioprine as treatment for RA).

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

Patients were instructed to record the drug name, dosage, regimen, reason for therapy, and therapy dates of any concomitant therapy on the concurrent medications diary card. The diary was reviewed with the patient at each visit and the information transcribed onto the appropriate CRF. Compliance was monitored by counting the number of unused tablets or capsules.

At each follow-up 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 a CSUGIE (i.e., bleeding, perforation, or gastric outlet obstruction, see section 8.1.1.3.2), the investigator called the CRO safety specialist immediately and initiated work-up of the potential event according to the algorithm (see section 8.1.1.3.2). Potentially suggestive signs or symptoms included, but were not limited to, abdominal pain, protracted nausea and vomiting, hematemesis, melena, and decreased hemoglobin or hematocrit.

Endpoints (Section 8.1.1.3.2)

The **primary objective of the study** was to compare the incidence of CSUGIEs (UGI bleeding, perforation, or gastric outlet obstruction) and CSUGIEs combined with gastroduodenal ulcers (CSUGIEs/GDUs) associated with celecoxib 400 mg BID to that associated with ibuprofen 800 mg TID (protocol 035) or diclofenac 75 mg BID (protocol 102) in patients with OA or RA.

The **secondary objectives of the study** were to:

1. Compare the chronic overall safety and tolerability of celecoxib versus ibuprofen and diclofenac;
2. Compare the effect of celecoxib versus ibuprofen and diclofenac on quality of life and patient satisfaction;
3. Compare the effect of celecoxib versus ibuprofen and diclofenac on direct and indirect costs;
4. Compare the chronic arthritis efficacy of celecoxib to that of ibuprofen and diclofenac;
5. Evaluate potential risk factors (e.g., age, gender, *Helicobacter pylori [H. pylor*i] infection, type of arthritis, cardiovascular disease, concurrent use of oral corticosteroids, history of peptic ulcer and/or gastrointestinal bleeding, alcohol, tobacco, and aspirin use) for their impact on the effect of treatment on outcome.

UGI SAFETY EVALUATION

For the two end points of primary interest, namely **CSUGIEs** (traditional definition) and CSUGIEs combined with gastroduodenal ulcers (**CSUGIEs/GDUs**).

Definitions of CSUGIEs

Two differing sets of definitions of CSUGIEs were employed and used in co-primary analyses; these are referred as "Traditional" and "Alternate" definitions. Both sets of definitions were prospectively devised.

Traditional Definitions

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

UGI Bleeding (Category 1)

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

- Hematemesis with a gastric or duodenal ulcer or large erosion proven by endoscopy or a UGI 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 UGI x-ray **(category 1C**);
- Hemoccult-positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or barium UGI x-ray and with bleeding as evidenced by a fall in hematocrit ≥5 percentage points or a reduction of hemoglobin of more than 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 UGI x-ray and with bleeding as evidenced both orthostasis (changes to postural vital signs: increase in pulse rate of ≥20 beats/min and/or a decrease in systolic blood pressure of ^{3}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 UGI x-ray and with bleeding as evidenced by a need for blood transfusion of two or more units **(category 1D-3)**; or
- Hemoccult-positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or barium UGI x-ray and with bleeding as evidenced by blood in the stomach as determined by endoscopy or nasogastric aspiration **(category 1D-4)**.

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 is unequivocal (free air, peritoneal irritation signs, etc.).

Gastric Outlet Obstruction (Category 3)
Occurrence of a gastric outlet obstruction was based on the opinion of the clinician with endoscopic or UGI barium x-ray documentation. Endoscopic evidence would include 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. UGI barium x-ray evidence of obstruction would include:

- 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; or
- severe narrowing and edema obstructing the outlet of the stomach.

Alternate Definitions of Bleeding Events

In the alternate set of definitions, the seven categories of UGI bleeding events were redefined into four categories that incorporated specific hemoglobin results and hypotension, as follows:

- **Category 1E**: hematemesis with a gastric or duodenal ulcer or large erosion proven by endoscopy or a UGI barium x-ray, and
  -a drop in hemoglobin >2 g/dL with adequate hydration or if urgent transfusion required, final hemoglobin (approximately 12-24 hours after the last urgent transfusion) pre-bleed hemoglobin (within assay variability) or
  -hypotension (defined as less than 90/60 mm Hg) or orthostatic hypotension;
- **Category 1F**: 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) and
  -a drop in hemoglobin >2 g/dL with adequate hydration or if urgent transfusion required, final hemoglobin (approximately 12-24 hours after the last urgent transfusion) pre-bleed hemoglobin (within assay variability) or
  -hypotension (defined as less than 90/60 mm Hg) or orthostatic hypotension;
- **Category 1G**: melena with a gastric or duodenal ulcer or large erosion proven by endoscopy or barium UGI x-ray and
  -a drop in hemoglobin >2 g/dL with adequate hydration or if urgent transfusion required, final hemoglobin (approximately 12-24 hours after the last urgent transfusion) pre-bleed hemoglobin (within assay variability) or
  -hypotension (defined as less than 90/60 mm Hg) or orthostatic hypotension;
- **Category 1H**: Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium x-ray and
  -a drop in hemoglobin >2 g/dL with adequate hydration or if urgent transfusion required, final hemoglobin (approximately 12-24 hours after the last urgent transfusion) pre-bleed hemoglobin (within assay variability) or
  -hypotension (defined as less than 90/60 mm Hg) or orthostatic hypotension.

Potential CSUGIEs, according to either set of definitions, were reviewed and adjudicated by an independent Gastrointestinal Events Committee (GEC) consisting of four expert gastroenterologists. In all of their activities related to reviewing and adjudicating potential CSUGIEs, all GEC members were blinded to all patients' study and treatment assignments.

As noted before, if during a visit, there were any signs or symptoms suggestive (in the investigator's opinion) of a CSUGIE, a work-up of the potential event was initiated according to the algorithm shown in **Table 2**. **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 2: Algorithm for Work-up of Suspected CSUGIEs

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 Kendle Safety Specialist immediately. Provide contact information.** • **Complete GI event case report forms (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; 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
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
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 Kendle 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: -n 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 uncertain	-Perform UGI endoscopy (test for H. pylori infection) - Lower GI work-up if bleeding source

If none of the base data (including the GI event CRFs and any source documentation) suggested a CSUGIE, then the case (information forwarded by Sponsor) was reviewed in a blinded fashion by a single member of the GEC (these cases were usually assigned to GEC members alphabetically by the patient's initials). The GEC member either confirmed that there was no evidence of a CSUGIE and the case was classified as a negative event, or chose (based upon potential evidence of a CSUGIE) to send the case material to the full GEC for adjudication.

If any base data or work-up results were suggestive of a CSUGIE, a narrative summary of the case was written by CRO personnel and forwarded to the Sponsor with other relevant documentation. All material on the case was then reviewed by all members of the GEC and discussed in a teleconference. The decision whether the case met the definition of a CSUGIE was reached by consensus. Those events that were adjudicated and considered by consensus not to meet the predetermined criteria are referred to as non-CSUGIEs. At any point during the review and adjudication process, the Investigator may have been **contacted to request further information or follow-up.**

Definitions of CSUGIEs/GDUs:
Symptomatic ulcer cases were those cases in which criteria for a CSUGIE were not met but in which a gastroduodenal ulcer was found by either endoscopy or upper gastrointestinal series, performed as a result of symptoms or signs. The combined category of these ulcers with the CSUGIEs was referred to as "**CSUGIEs/GDUs."** Of note, any patient with either a gastric or duodenal ulcer, or both, is counted as having a gastroduodenal ulcer.

Upper GI ulcers documented by endoscopy or UGI barium x-ray with no evidence of perforation, bleeding, or obstruction were categorized separately. Data on GI complaints and other GI adverse events, such as esophageal, small bowel, colonic, or rectal pathology, were also collected.

All analyses of GI safety/endpoints were carried out on the Intent-to-Treat Cohort, defined as all randomized patients who received at least one dose of study medication. For the two GI safety end points of interest, namely (1) CSUGIEs and (2) CSUGIEs combined with gastroduodenal ulcers (termed "CSUGIEs/GDUs" as noted above), the analyses were performed as follows:

· First Six Months of Treatment
    a. All Patients
    b. Patients not Taking Aspirin
    c. Patients Taking Aspirin
· Entire Study Period
    a. All Patients
    b. Patients not Taking Aspirin
    c. Patients Taking Aspirin

The rationale for separately considering the first six months and the entire study period has been discussed. The subgroup analyses of patients not taking aspirin and those taking aspirin were performed because of the confounding effect of aspirin (aspirin use at <325 mg/day was allowed during the study). The idea that aspirin has a confounding effect on assessment of UGI endpoints is supported by studies in the literature, as well as by the present study which included analysis of low-dose aspirin as an independent cause of CSUGIEs and ulcers among patients receiving celecoxib.

Statistical considerations (Section 8.1.1.3.3)

The two trials described in this sNDA were prospectively designed with the intent to combine the data into a pooled analysis. Therefore, except where otherwise noted, 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 the diclofenac 75 mg BID and ibuprofen 800 mg TID (i.e. NSAID) treatment groups. In most analyses the two NSAID groups are considered separately, but pooling was done for certain analyses.

Determination of Sample Size

The sample sizes for the combined protocols were determined based on the assumption that the probability of experiencing a CSUGIE is 0.3% per year with celecoxib and 1.2% per year with each of the NSAIDs. Assuming a withdrawal rate of 35%, a sample size of 4,000 patients (combining the two protocols) for the celecoxib group and 2,000 patients for each of the NSAID groups would be needed to detect this difference with approximately 85% power at a 5% significance level (two-sided). With the above assumptions and an enrollment period of approximately three months, it would be expected that a total of 40 CSUGIEs would occur in the combined study (eight in the combined celecoxib group and 16 in each NSAID group).

End point analyses

The primary end point in the GI safety analyses was the development of a CSUGIE (i.e., UGI bleeding, perforation, or obstruction). The **null hypothesis** being tested was that there is no difference between the incidence of **CSUGIEs** associated with celecoxib and that associated with either of the NSAID groups. Because of the association of development of an ulcer with an increased risk of experiencing a CSUGIE, all analyses of CSUGIEs in this study were repeated for patients who experienced either a CSUGIE or symptomatic gastroduodenal ulcer **(CSUGIE/GDU).**

The main 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. However, analyses were also carried out on the cohort of all randomized patients. For consistency with the GI safety

analyses, certain analyses of termination reasons, patient disposition, and baseline data were also analyzed for just the first six months of study participation, as well as being analyzed for the subgroups of patients taking and not taking **aspirin.** The reasons for these analyses are described elsewhere.

In the analyses of both CSUGIEs and CSUGIEs/GDUs, the events of interest were counted within each treatment group by time intervals. The event rates were summarized by time intervals (1, 4, 13, 26, 39, and 52 weeks), and **the log-rank test** was used to compare the time-to-event curves between celecoxib and the two NSAIDs combined, as well as between celecoxib and each of the NSAIDs separately as a stepwise procedure. Each test was performed at the alpha level of 0.05 (two-sided).

In this analysis, 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. Analyses of CSUGIEs based on the alternate definitions were also performed, both with and without the use of censoring as described elsewhere. Because patients receiving celecoxib from both protocols were pooled into a single group, the celecoxib results from the two protocols were also compared (numerically) to ensure homogeneity.

The numbers of patients randomized at each site, and the numbers of patients completing study participation or withdrawing for any reason, were summarized numerically by treatment group. Treatment duration was calculated for all completed patients, all withdrawn patients, and all patients in the Intent-to-Treat Cohort. Numbers of patients were summarized within each treatment group by the following intervals of treatment duration: 0 to 1 month, >1 to 3 months, >3 to 6 months, >6 to 9 months, >9 to 12 months, >12 to 15 months, and >15 months. In addition, mean duration of treatment as well as total patient-years of treatment were calculated.

Descriptive statistics for demographics and other baseline characteristics (height, weight, vital signs, GI risk factors, alcohol and tobacco use, and arthritis history) were calculated for all treatment groups. Categorical variables were summarized with frequency distributions and percentages. For continuous variables, mean values, standard deviations, median values, and ranges (minimum to maximum) were reported. The treatment groups were compared using Pearson's chi-square test for categorical variables and two-way analysis of variance (ANOVA) with treatment and study site as factors for continuous variables.

Because of the potential for certain medications to influence the risk of experiencing a CSUGIE, concurrent use of corticosteroids, anticoagulant agents, and aspirin during the study was compared among treatment groups using Pearson's chi-square test.

Baseline results on patient's global assessment of arthritis and patient's assessment of arthritis pain-VAS were summarized and compared among treatment groups using the Cochran-Mantel-Haenszel test stratified by center and two-way ANOVA with treatment and study site as factors, respectively.

Potential risk factors for the development of a CSUGIE were identified prior to analysis. These included demographic and disease characteristics (age, gender, disease type and duration, and baseline disease severity), GI history (positive Flexsure test for *H. pylori*, or history of UGI bleeding, gastroduodenal ulcer, or NSAID intolerance), concomitant medication use (including 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.

Efficacy and QOL Analysis

All efficacy (patient global, patient pain-VAS, and withdrawal due to lack of efficacy) and QOL analyses were carried out on the ITT cohort with missing values imputed by carrying forward the last observed value. For patient's global assessment and patient's assessment of arthritis pain-VAS, mean values with SD at each scheduled visit were summarized by treatment group. Least-squares means and 95% confidence intervals were created by visit, using ANCOVA with study site and treatment as factors and baseline score as the covariate. In addition, patient's global assessment scores were categorized based on changes from baseline as improved (reduction of at least one grade from baseline), unchanged, or worsened (increase of at least one grade from baseline). Percentages of patients in each category (and 95% confidence intervals) were calculated by scheduled visit and treatment group.

Incidences of withdrawal due to lack of arthritis efficacy were analyzed using the chi-square test. Times to withdrawal due to lack of arthritis efficacy were analyzed using the log-rank test. For the purpose of this analysis, patients who withdrew for other reasons were censored at the time of withdrawal; those who did not withdraw at any time were censored at the final scheduled visit. Similar analyses were performed for withdrawal due either to lack of arthritis efficacy or to an adverse event.

Quality of Life assessments were performed in protocol 035, and consisted of the HAQ and SF-36 health survey. For both of these instruments, mean values and SD at each scheduled visit were summarized by treatment group. Least-squares means and 95% confidence intervals were created by visit, using ANCOVA with study site and treatment as factors and baseline score as the covariate. Results on the patient satisfaction questionnaires and the SODA questionnaires were analyzed similarly. For the patient satisfaction questionnaires, least-squares means and 95% confidence intervals were created, using ANOVA with study site and treatment as factors. For the SODA, least-squares means, 95% confidence intervals, and p values were created by visit, using ANCOVA with study site and treatment as factors and baseline values as the covariate.

To verify homogeneity between the celecoxib groups in the two protocols, all of the summaries and analyses of patient disposition, reasons for termination, and baseline variables were repeated with the two celecoxib treatment groups from the two protocols analyzed separately. The same statistical tests were used as those described above.

Safety evaluation:
All patients who took at least one dose of study medication were included in all safety analyses. Adverse events (AE) were coded using W.H.O.a.r.t. terminology. 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 28 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. The incidences of treatment-emergent adverse events were also tabulated by severity and by the Investigator's attribution of the cause of the event.

Because of the long treatment period in this study, a separate analysis was performed in which adverse events were summarized by 90-day intervals (1 to 90 days, 91 to 180 days, 181 to 270 days, 271 to 360 days, 361 to 450 days, and 451 to 540 days). In this analysis, incidences and prevalences were summarized separately for each adverse event. Within each interval, events were counted under prevalence if they were new in that interval or continued from a previous interval, whereas incidence values included only events that were new within that interval.

For selected GI adverse events, time-to-event analyses were performed to assess the rates of the events by pre-specified time intervals (1, 4, 13, 26, 39, 52, and 65 weeks). 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 and each of the NSAIDs separately. Each test was performed at the alpha level of 0.05.

Times to withdrawal due to adverse events were analyzed using the log-rank test. In this analysis, patients who withdrew for other reasons were censored at the time of withdrawal; those who did not withdraw at any time were censored at the final scheduled visit.

Changes from baseline in clinical laboratory values at weeks 4, 13, 26, 39, 52, and the final visit were summarized as means and standard deviations (SD). The changes were compared among treatment groups by ANCOVA using pairwise treatment contrasts with baseline value as the covariate.

Incidences of extreme laboratory (and vital signs) values during the study were summarized by treatment group and compared among groups using Fisher's exact test. The values representing upper and lower extremes for each laboratory test were determined before the initiation of study conduct through discussions with external safety consultants, and were listed (Table 6.d, N49-00-06-035-102, p. 52/24295) and were utilized to construct shift tables. Contingency tables were also prepared showing numbers of patients whose post-treatment laboratory results met certain criteria for combinations of values or changes in values that might indicate hematologic, hepatobiliary, or renal effects. These criteria represented: decreases in both hemoglobin and hematocrit; increases in both creatinine and BUN; increases in both AST and ALT; increases in both alkaline phosphatase and total bilirubin; increases in both ALT and alkaline phosphatase; and increases in both ALT and total bilirubin. These tables showed numbers of patients shifting among various categories of increases and decreases according to predetermined cutoff values.

Results (Section 8.1.1.4):

Patient Disposition, comparability (Section 8.1.1.4.1)

As seen in **Table 3**, a total of **8059 patients were randomized** at 386 centers in the two protocols **4031 to the celecoxib** group, **2019 to the diclofenac** group, and **2009 to the ibuprofen** group. Ninety-one patients were determined never to have taken any study medication; those who did represent the Intent-to-Treat **(ITT) cohort** (i.e. patients who took at least one dose of study medication). Of these 91 subjects, the majority were randomized but were never entered into the study or dispensed study medication. Across the three treatment groups, 98 patients were found to have violated one or more entry criteria. These included 47 patients in the celecoxib group, 22 patients in the diclofenac group, and 29 patients in the ibuprofen group. These **violations** (Table 7.a, N49-00-06-035-102, p. 60) were mostly for past or active GI disease (including positive occult fecal blood), liver function test abnormalities, or hypersensitivity to the study medications (41 patients for celecoxib, 18 patients for diclofenac, 23 patients for ibuprofen). The seven patients entered into the study with violations of the inclusion/exclusion criteria were approved by the sponsor either prior to entry or upon discovery of the violation. Approval was given only if a review of the violation indicated that the patient could safely participate in the study and the violation was unlikely to affect the results of the study. Across the study, 50 patients were **withdrawn** for pre-existing protocol violations: 27 celecoxib patients, 11 diclofenac patients, and 12 ibuprofen patients.

The reasons for termination from the study within the first six months are shown in Table 3. A total of **4573 patients completed six months** (182 days or more): 2376 (60%) receiving celecoxib, 1148 (58%) receiving diclofenac, and 1049 (53%) receiving ibuprofen. A total of **3409 patients completed the study**: 1779 (45%) receiving celecoxib, 939 (47%) receiving diclofenac, and 691 (35%) receiving ibuprofen. The **majority of withdrawals in all treatment groups were due to protocol noncompliance, treatment failure, or an adverse event. No patients were lost to follow-up in any treatment group during the entire study.**

Across the entire study, **1147 patients were withdrawn** from the study for protocol noncompliance: 585 celecoxib patients, 197 diclofenac patients, and 365 ibuprofen patients (Table 3). These withdrawals occurred despite the study's objective to mimic standard medical practice so that minor protocol violations did not invariably lead to withdrawal during the study. Some examples of such violations included missing a protocol-required procedure (e.g., obtaining a blood sample for laboratory tests); missing the visit window established in the protocol and/or missing a visit altogether; intermittent use of proton pump inhibitors,H_2- antagonists, or NSAIDs; throwing out empty medication bottles; and misallocation of study medication by the site. However, prolonged use of non-study medications; compliance below 70% on more than one consecutive visit or sustained failure to comply with the required visit schedule; pregnancy; or receiving a treatment other than that assigned necessitated immediate withdrawal from the study.

In one case, a patient's treatment assignment was **unblinded** at the investigational site (the patient experienced a diverticular bleed). In two cases the treatment assignment was unblinded through the

IVRS randomization system by telephone. None of these three patients experienced a CSUGIE or ulcer, and in no instance was the patient's assigned treatment made known to sponsor or any members of the oversight committees.

Table 3: Patient Disposition-First Six Months and Entire Study Period[1]

Patients (%)	Total	Celebrex 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Randomized	8059	4031	2019	2009
Took medication (ITT)	7968	3987	1996	1985
Completed 6 months	4573	2376 (59.6)	1148 (57.5)	1049 (52.8)
Completed Study[2]	3409	1779 (44.6)	939 (47.0)	691 (34.8)
6 months				
Withdrawn	3395	1611 (40.4)	848 (42.5)	936 (47.2)
Lost to follow-up	0	0 (0)	0 (0)	0 (0)
Preexisting violation	46	25 (0.6)	10 (0.5)	11 (0.6)
Noncompliance	703	351 (8.8)	142 (7.1)	210 (10.6)
Treatment failure	1092	503 (12.6)	253 (12.7)	336 (16.9)
Adverse event	1554	732 (18.4)	443 (22.2)	379 (19.1)
Entire Study				
Withdrawn	4559	2208 (55.4)	1057 (53.0)	1294 (65.2)
Lost to follow-up	0	0 (0)	0 (0)	0 (0)
Preexisting violation	50	27 (0.7)	11 (0.6)	12 (0.6)
Noncompliance	1147	585 (14.7)	197 (9.9)	365 (18.4)
Treatment failure	1456	691 (17.3)	309 (15.5)	456 (23.0)
Adverse event	1906	905 (22.7)	540 (27.1)	461 (23.2)

1. From Figure 7.a and b (p. 57 and 59) and Table T2.1 and T2.3 (p. 247 and 250); N49-00-06-035-102.
2. Completed patients are those who completed the full scheduled treatment period or remained in the study at the time of study closure.

> ***Reviewer's comment: Considering the argument of disproportionate withdrawal of patients (i.e. informative censoring), during the first 6 months a higher proportion (compared to celecoxib) of patients in the diclofenac withdrew due to an adverse event while more patients in the ibuprofen group withdrew for noncompliance or treatment failure. This same general trend occurred in the entire study. Also, reasons for study termination (first 6 months) in patients taking ASA did not appear to differ substantially (Appendix 2.6.1, p. 2096/24295) in any treatment group from those noted in the table above. Total withdrawal, whether during the first 6 months or the entire study, was highest in the ibuprofen group.***

The duration of exposure to treatment in each group (all ITT patients, patients with aspirin) is shown for both the first six months and the entire study in **Table 4**. As can be seen, proportions of patients with at least three months of exposure to treatment ranged from 64% to 70% whereas for the entire study period, approximately 45% to 51% of patients in all treatment groups had at least nine months of exposure to treatment. Essentially all patients who completed the study had at least 9 months of exposure to treatment. **Exposure to medication for the entire study was estimated to be 2320 patient-years for celecoxib, 1081 patient-years for diclofenac, and 1122 patient-years for ibuprofen 800.**

Table 4: Treatment Duration-First Six Months and Entire Study[1]

Treatment Duration[2]	Celecoxib (N = 3987)	Diclofenac (N = 1996)	Ibuprofen (N = 1985)
First 6 months			
ITT-(Total)			
0 - 1 months	656 (16%)	328 (16%)	364 (18%)
1.1 - 3 months	546 (14%)	293 (15%)	351 (18%)
3.1 - 6 months[3]	2785 (70%)	1375 (69%)	1270 (64%)
Patient yrs.	1441.07	710.29	673.52
ITT-(non-ASA)	(n=3154)	(n=1567)	(n=1602)
0 - 1 months	527 (17%)	262 (17%)	309 (19%)
1.1 - 3 months	419 (13%)	222 (14%)	267 (17%)
3.1 - 6 months	2208 (70%)	1083 (69%)	1026 (64%)
Patient yrs.	1143.05	559.21	541.48
ITT-(ASA)	(n=833)	(n=429)	(n=383)
0 - 1 months	129 (15%)	66 (15%)	55 (14%)
1.1 - 3 months	127 (15%)	71 (17%)	84 (22%)
3.1 - 6 months	577 (69%)	292 (68%)	244 (64%)
Patient yrs.	298.02	151.07	132.04
Entire Study			
ITT-(Total)			
0 - 1 months	656 (16%)	328 (16%)	364 (18%)
1.1 - 3 months	546 (14%)	293 (15%)	351 (18%)
3.1 - 6 months	467 (12%)	262 (13%)	246 (12%)
6.1-9 months	291 (7%)	136 (7%)	130 (7%)
9.1-12 months	1442 (36%)	913 (46%)	415 (21%)
12.1-15 months	585 (15%)	64 (3%)	477 (24%)
>15 months	0 (0%)	0 (0%)	2 (0%)
Patient yrs.	2320.44	1080.55	1122.48
ITT-(non-ASA)	(n=3105)	(n=1551)	(n=1573)
0 - 1 months	527 (17%)	262 (17%)	309 (20%)
1.1 - 3 months	419 (13%)	222 (14%)	267 (17%)
3.1 - 6 months	357 (11%)	203 (13%)	206 (13%)
6.1-9 months	229 (7%)	97 (6%)	100 (6%)
9.1-12 months	1114 (36%)	717 (46%)	330 (21%)
12.1-15 months	459 (15%)	50 (3%)	359 (23%)
>15 months	0 (0%)	0 (0%)	2 (0%)
Patient yrs.	1803.46	841.16	873.80
ITT-(ASA)	(n=882)	(n=445)	(n=412)
0 - 1 months	129 (15%)	66 (15%)	55 (13%)
1.1 - 3 months	127 (14%)	71 (16%)	84 (20%)
3.1 - 6 months	110 (12%)	59 (13%)	40 (10%)
6.1-9 months	62 (7%)	39 (9%)	30 (7%)
9.1-12 months	328 (37%)	196 (44%)	85 (21%)
12.1-15 months	126 (14%)	14 (3%)	118 (29%)
>15 months	0 (0%)	0 (0%)	0 (0%)
Patient yrs.	516.98	239.39	248..68
Completed and Withdrawn-Entire Study			
	N=1779	N=939	N=691
Completed[4]			
0 - 1 months	0 (0%)	0 (0%)	0 (0%)
1.1 - 3 months	0 (0%)	0 (0%)	0 (0%)
3.1 - 6 months	0 (0%)	1 (0%)	0 (0%)
6.1-9 months	10 (1%)	6 (1%)	0 (0%)
9.1-12 months	1282 (72%)	868 (92%)	297 (43%)
12.1-15 months	487 (27%)	64 (7%)	392 (57%)
>15 months	0 (0%)	0 (0%)	2 (0%)
Patient yrs.	1640.68	812.87	698.69
	N=2208	N=1057	N=1294
Withdrawn			
0 - 1 months	656 (30%)	328 (31%)	364 (28%)
1.1 - 3 months	546 (25%)	293 (28%)	351 (27%)
3.1 - 6 months	467 (21%)	261 (25%)	246 (19%)
6.1-9 months	281 (13%)	130 (12%)	130 (10%)
9.1-12 months	160 (7%)	45 (4%)	118 (9%)
12.1-15 months	98 (4%)	0 (0%)	85 (7%)

>15 months	0 (0%)	0 (0%)	0 (0%)
Patient yrs.	679.76	267.68	423.79

1. From Table T2.2.1-3 and Table T2.4.1-3, N49-00-06-035-102, p. 247-253/24295; Appendix Table 2.3.1-.2, p2058-9.
2. Treatment duration is the time between first dose date and last dose date or last available visit date (if last dose date is not available).
3. Includes patients who withdrew during this interval or continued beyond 182 days.
4. Completed patients are those who completed the full scheduled treatment period or remained in the study at the time of study closure.

Reviewer's comment: Within treatment groups, either for the first six months or the entire study, use of ASA did not seem to substantially shorten treatment durations.

Baseline demographic characteristics are summarized in Table 5. Differences among the groups in mean age ($p=0.017$) and in distribution of race ($p<0.001$) were found to be statistically significant; these differences are of unclear clinical significance. Most patients enrolled in this study had OA and were elderly, white and female.

As seen in **Table 5**, fewer than 2% of patients in each treatment group had a history of UGI bleeding ($p=0.705$). History of gastroduodenal ulcers were not statistically significantly different among treatment groups ($p=0.543$), however, NSAID intolerance was different ($p<0.001$). Positive results on FlexSure testing for *H. pylori* was also similar among the groups ($p=0.989$).

The difference among treatment groups in self-reported alcohol use (Table 5) was statistically significant: 30.9% of celecoxib patients (when combined), 40.7% of diclofenac patients, and 19.4% of ibuprofen patients reported some alcohol use ($p<0.001$). Reported tobacco use was similar among the treatment groups ($p=0.455$).

Reviewer's comment: As can be seen in Table 5, the rates of self-reported alcohol use differed between protocol 035 and 102:

The duration of arthritis (Table 5) was similar between OA and RA, at approximately 10 to 11 years in all treatment groups. Regarding severity of arthritis symptoms, patients generally gave a global assessment of arthritis of fair, poor, or very poor (mean scores from 2.9-3.0) with mean VAS pain scores ranging from 50.3 to 51.7 on the 100-mm scale. The differences among the groups in these measures were not statistically significant ($p\geq0.956$ and 0.355 for global and pain, respectively).

As instructed, the majority of patients refrained from concurrent medication use, although these medications were not specifically prohibited by the protocols. The differences among the groups in any of the categories of use were not statistically significant. However, a noteworthy proportion of patients used aspirin during the trial; the incidence of aspirin use was approximately 21% among the three groups (Table 5).

The baseline demographic and concurrent medication data suggest that the two celecoxib protocols were essentially homogeneous with respect to these characteristics. The isolated statistically significant differences noted do not suggest any consistent pattern of disparity between the groups.

Table 5: Baseline demographic characteristics-ITT cohort[1]

Characteristic	Celecoxib (n=3987)		Diclofenac (n=1996)	Ibuprofen (n=1985)	p-value
	Study 035 (n=1990)	Study 102 (n=1997)			
Age (yrs)					0.017[4]
Mean	60.2	60.9	60.1	59.5	
Median	61.0	61.0	61.0	60.0	
Range (%)					
≤64	1226 (61.6)	1202 (60.2)	1234 (61.8)	1261 (63.5)	
65-74	510 (25.6)	562 (28.1)	526 (26.4)	507 (25.5)	
≥75	254 (12.8)	233 (11.7)	236 (11.8)	217 (10.9)	
Gender (%)					0.110[5]
Male	637 (32.0)	618 (30.9)	650 (32.6)	580 (29.2)	
Female	1353 (68.0)	1379 (69.1)	1346 (67.4)	1405 (70.8)	
Race/Ethnic Origin (%)					<0.001[5]
White	1730 (86.9)	1798 (90.0)	1784 (89.4)	1713 (86.3)	
Black	155 (7.8)	146 (7.3)	151 (7.6)	172 (8.7)	
Asian	14 (0.7)	15 (0.8)	19 (1.0)	9 (0.5)	
Hispanic	78 (3.9)	29 (1.5)	36 (1.8)	75 (3.8)	
Other	13 (0.7)	9 (0.5)	6 (0.3)	16 (0.8)	
Rheumatoid Arthritis (%)	548 (27.7)	523 (26.6)	536 (27.0)	542 (27.6)	
Duration of Disease, mean (SD)					
OA	10.07 (9.6)	10.43 (9.8)	10.35 (10.33)	9.94 (9.5)	0.734[4]
RA	11.20 (9.7)	11.26 (10.03)	10.51 (9.4)	10.94 (9.8)	0.465[4]
Potential Risk Factor (%)					
History GI bleed	31 (1.6)	37 (1.9)	30 (1.5)	28 (1.4)	0.705[5]
History gastroduodenal ulcer	159 (8.0)	175 (8.8)	170 (8.5)	151 (7.6)	0.543[5]
GI-related NSAID intolerance[2]	138 (6.9)	209 (10.5)	202 (10.1)	165 (8.3)	<0.001[5]
Cardiovascular disease	795 (39.9)	807 (40.4)	805 (40.3)	794 (40.0)	0.989[5]
H. pylori-Flexsure positive (%)	780 (39.2)	756 (37.9)	752 (37.7)	769 (38.7)	0.722[5]
Tobacco use (%)	320 (16.1)	309 (15.5)	311 (15.6)	284 (14.3)	0.455[5]
Alcohol use (%)	380 (19.1)	852 (42.7)	812 (40.7)	386 (19.4)	<0.001[5]
Pt global assessment, mean (SD)	2.9 (0.69)	3.0 (0.76)	3.0 (0.74)	2.9 (0.70)	0.965[6]
Pt pain-(0-100mm), mean (SD)	51.7 (23.1)	50.3 (25.1)	50.3 (25.2)	51.7 (23.6)	0.355[4]
Concurrent medications (%)					
ASA (≤325 mg/d)[3]	410 (20.6)	423 (21.2)	429 (21.5)	383 (19.3)	0.329[5]
Corticosteroids (any)	613 (30.8)	606 (30.3)	568 (28.5)	607 (30.6)	0.601[5]
Anticoagulants (any)	18 (0.9)	24 (1.2)	24 (1.2)	20 (1.0)	0.502[5]

1. From Appendix 2.2.3-2.2.10, N49-00-06-035-102, p. 2040-2047/24295; Table T6, p. 257/24295.
2. Defined as a history of NSAID-induced gastroduodenal ulcers, NSAID-induced erosive gastritis or NSAID-induced upper GI symptoms of sufficient severity to cause discontinuation of NSAID use.
3. Defined as **any** aspirin use during the first 6 months.
4. P-value from Two-Way Analysis of Variance with treatment group and center as factors.
5. P-value from Pearson's Chi-square test.
6. P-value from Cochran-Mantel-Haenszel (Row Mean Scores Differ) test stratified by center.

Efficacy endpoint outcomes (Section 8.1.1.4.2)

Endpoint of CSUGIE:

CSUGIEs-first 6 months:
A total of 1214 potential CSUGIEs (representing 1163 patients, not mutually exclusive across classifications), occurred within the **first six months** (182 days) of study participation and were worked up at the investigational sites with referral to one or all members of the GI events committee (GEC) for evaluation. The results (from Figure 8a, p. 66 of N49-00-06-035_102) can be summarized as follows:

- **Total potential CSUGIE** — **1214 (1163 patients)**
  - **Reviewed by single GEC member** — **955**
    - **Negative events** — **954 (912 patients)**
    - **Potential CSUGIE (forwarded)** — **1**
- **Reviewed by all GEC members** — **260**
  - **Non-CSUGIE** — **225 (224 patients)**
  - **CSUGIE** — **35 (35 patients)**

All of these cases were eventually classified as **negative event**s, **non-CSUGIE**s, or **CSUGIEs** (see section 8.1.1.3.2). It should be noted that the numbers of events exceeds the number of patients since some patients experienced more than one potential CSUGIE. However, **any patient who experienced a CSUGIE was withdrawn from the study**; therefore, no patient experienced more than one actual CSUGIE. The reported potential events classified as **negative cases** represented nonspecific GI symptoms (e.g., nausea, abdominal pain/cramping, etc.), decreases in hematocrit of unknown cause, non-GI symptoms (e.g., dizziness), non-localized minor GI bleeding episodes, and miscellaneous laboratory abnormalities without corresponding clinical events. The reported potential events classified as **non-CSUGIEs** included all of the ulcers (i.e. gastroduodenal), as well as esophageal disease, gastroduodenitis, small bowel/colonic/anorectal pathology, non-ulcer GI bleeding, anemia, and miscellaneous GI symptoms and findings.

The 35 CSUGIEs (traditional definition) found within the first six months are shown in **Table 6**. Thirteen (13) events occurred on celecoxib treatment, nine (9) events on diclofenac treatment, and thirteen (13) events on ibuprofen treatment. Four events (two in the celecoxib group and two in the ibuprofen group) were censored owing to the timing of their occurrence. All but one of the events (a gastric outlet obstruction in the celecoxib group) represented bleeding events in which an ulcer or large erosion was associated with either visual evidence of bleeding, melena, or hemoccult-positive stools and a decrease in hematocrit or hemoglobin. There were no UGI perforations**. A narrative summary of each event can be found in the Appendix .** Analyses and summaries of these events are shown in tables that follow.

Table 6: Distribution of CSUGIEs: Traditional Definitions -First Six Months [1]

Event Category	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
UGI Bleeding (Category 1)			
1A: Hematemesis with ulcer/large erosion	-	-	-
1B: Ulcer/large erosion with evidence of bleeding	**7**	**4**	**7**
1C: Melena with ulcer/large erosion	**3**[2]	**4**	**3**[3]
Hemoccult (+) stool with ulcer/large erosion and:			
1D-1: Hematocrit/Hemoglobin drop	**2**[2]	**1**	**3**
1D-2: orthostasis	-	-	-
1D-3: transfusion	-	-	-
1D-4: blood in stomach	-	-	-
UGI Perforation (Category 2)	-	-	-
Gastric Outlet Obstruction (Category 3)	**1**	-	-
Total	**13**	**9**	**13**
Total Uncensored	**11**	**9**	**11**

1. From Table 8b (p.67), Table T13 (p. 270), appendix 2.6.1 (p. 2123); N49-00-06-035-102.
2. One of these events censored from primary analysis.
3. Two of these events censored from primary analysis

Table 7 shows the rates (both crude and Kaplan-Meier) by time interval of all CSUGIEs that occurred within the 182-day period. These rates are in the entire ITT cohort. When all patients were included in the analysis, regardless of aspirin status, the uncensored events were shown to accrue in the ibuprofen group at a steady rate throughout the first six months. For celecoxib, seven of the 11 uncensored events occurred in the first three months. In the diclofenac group, all nine events occurred in the first 100 days, with a cluster of five events within the first 15 days and four more events occurring sporadically through approximately day 85. The cumulative event rates were lower at all time points (Weeks 1, 4, 13, and 26) for celecoxib than for either of the NSAID comparators. The p-values comparisons, as noted in the footnote of the table, are not statistically significantly different between celecoxib and either NSAID, or when they were pooled.

Table 7: CSUGIEs (Traditional-ITT)-First 6 months (Crude & Kaplan-Meier rates)[1,2]

	Celecoxib (n=3987)		Diclofenac (n=1996)		Ibuprofen (n=1985)	
Rates	+ censoring	- censoring	+ censoring	- censoring	+ censoring	- censoring
Crude						
Week 1 (1-7)	0.00%	0.03%	0.10%	0.10%	0.10%	0.15%
Week 4 (8-28)	0.03%	0.05%	0.25%	0.25%	0.20%	0.25%
Week 13 (29-91)	0.18%	0.23%	0.40%	0.40%	0.30%	0.40%
Week 26 (92-182)	0.28%	0.33%	0.45%	0.45%	0.55%	0.65%
Kaplan-Meier						
Week 1 (1-7)	0.01%	0.03%	0.10%	0.10%	0.12%	0.17%
Week 4 (8-28)	0.05%	0.07%	0.28%	0.28%	0.25%	0.31%
Week 13 (29-91)	0.24%	0.30%	0.51%	0.51%	0.47%	0.58%
Week 26 (92-182)	0.37%	0.42%	0.52%	0.52%	0.75%	0.86%

1. From Table T11.2 (p. 263); N49-00-06-035-102. Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval. Uncensored events were defined as those meeting either of the following two conditions: 1. Occurred after 48 hours past midnight of the first dosing day and before 48 hours following midnight of the last dosing day. 2. Occurred after 48 hours past midnight of the last dosing day and before 2 weeks following midnight of the last dosing day and were determined to be causally related to study drug by the GI events committee. Events were censored if they failed to meet either of these two conditions. For **censored events, log rank P-values** (Table T11.3, p. 264) of celecoxib vs. NSAIDs = 0.092, celecoxib vs. diclofenac = 0.264, celecoxib vs. ibuprofen = 0.073. **For uncensored events, log rank P-values** (Table T11.4, p. 265) of celecoxib vs. NSAIDs = 0.112, celecoxib vs. diclofenac = 0.445, celecoxib vs. ibuprofen = 0.053.

Table 8 shows the rates (both crude and Kaplan-Meier) by time interval of all CSUGIEs that occurred within the 182-day period in **the non-aspirin (ASA)** using ITT cohort. The p-values comparisons, as noted in the footnote of the table, suggest statistically significant differences between celecoxib and NSAIDs (p = 0.037 and 0.047 for censored and uncensored respectively) and celecoxib and ibuprofen (with or without censoring, p=0.005) but not between celecoxib and diclofenac.

Table 8: CSUGIEs without ASA (Traditional-ITT)-First 6 months (Crude & Kaplan-Meier rates)[1,2]

	Celecoxib (n=3154)		**Diclofenac (n=1567)**		**Ibuprofen (n=1602)**	
Rates	+ censoring	- censoring	+ censoring	- censoring	+ censoring	- censoring
Crude						
Week 1 (1-7)	0.00%	0.03%	0.06%	0.06%	0.12%	0.12%
Week 4 (8-28)	0.00%	0.03%	0.19%	0.19%	0.25%	0.25%
Week 13 (29-91)	0.13%	0.16%	0.26%	0.26%	0.37%	0.44%
Week 26 (92-182)	0.16%	0.19%	0.26%	0.26%	0.62%	0.69%
Kaplan-Meier						
Week 1 (1-7)	0.01%	0.04%	0.10%	0.10%	0.14%	0.14%
Week 4 (8-28)	0.03%	0.06%	0.22%	0.22%	0.32%	0.32%
Week 13 (29-91)	0.19%	0.23%	0.28%	0.28%	0.58%	0.65%
Week 26 (92-182)	0.20%	0.23%	-	-	0.81%	0.89%

1. From Table T12.2 (p. 267); N49-00-06-035-102. Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval. Uncensored and censored events as defined (Table 7 above).
2.For **censored events, log Rank P-values** (Table T12.3, p. 268) of celecoxib vs. NSAIDs = 0.037, celecoxib vs. diclofenac = 0.476, celecoxib vs. ibuprofen = 0.005. **For uncensored events, log Rank P-values** (Table T12.4, p. 269) of celecoxib vs. NSAIDs = 0.047, celecoxib vs. diclofenac = 0.651, celecoxib vs. ibuprofen = 0.005.

Reviewer's comment: Subset analysis looking at ASA status was not a prospectively defined endpoint in this trial.

CSUGIEs-Entire Study:

A total of 1670 potential CSUGIEs (representing 1527 patients, not mutually exclusive across classifications), occurred throughout the **full length of the study** participation and were worked up at the investigational sites with referral to one or all members of the GI events committee (GEC) for evaluation. The results (figure 8b, p. 71 N49-00-06-035-102), can be summarized as follows:

- **Total potential CSUGIE** **1670 (1527 patients)**
  - **Reviewed by single GEC member** **1287**
    - **Negative events** **1286 (1186 patients)**
    - **Potential CSUGIE (forwarded)** **1**
- **Reviewed by all GEC members** **384**
  - **Non-CSUGIE** **340 (337 patients)**
  - **CSUGIE** **44 (44 patients)**

All of these cases were eventually classified as **negative event**s, **non-CSUGIE**s, or **CSUGIEs** (see section 8.1.1.3.2). It should be noted that the numbers of events exceeds the number of patients since some patients experienced more than one potential CSUGIE. However, any patient who experienced a CSUGIE was withdrawn from the study; therefore, no patient experienced more than one actual CSUGIE.

The 44 events found to represent CSUGIEs through the entire study period are shown by treatment group and category in Table 9. Twenty events occurred on celecoxib treatment, 11 on diclofenac, and 13 on ibuprofen. This table includes all CSUGIEs that met the traditional definition, including those that were censored from the primary analysis owing to the timing of their occurrence (three in the celecoxib group, one in the diclofenac group, and 2 in the ibuprofen group). All events were classified into the same categories as those that occurred in the first six months, with the following exceptions: one bleeding event in the celecoxib group represented category 1A, and two UGI perforations occurred, one in the celecoxib group and one in the diclofenac group.

Table 9: Distribution of CSUGIEs: Traditional Definitions –Entire Study Period[1]

Event Category	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
UGI Bleeding (Category 1)			
1A: Hematemesis with ulcer/large erosion	**1**	-	-
1B: Ulcer/large erosion with evidence of bleeding	**8**	**4**	**7**
1C: Melena with ulcer/large erosion	**5**[3]	**4**	**3**[3]
Hemoccult (+) stool with ulcer/large erosion and:			
1D-1: Hematocrit/Hemoglobin drop	**3**[2]	**2**	**3**
1D-2: orthostasis	-	-	-
1D-3: transfusion	-	-	-
1D-4: blood in stomach	-	-	-
UGI Perforation (Category 2)	**1**	**1**[2]	-
Gastric Outlet Obstruction (Category 3)	**2**	-	-
Total	**20**	**11**	**13**
Total Uncensored	**17**	**10**	**11**

1 From Table 8e (p.72), Table T1 (p. 279), appendix 2.6.1 (p. 2123); N49-00-06-035-102.
2 One of these events censored from primary analysis.
3 Two of these events censored from primary analysis

Table 10 shows the rates (both crude and Kaplan-Meier) by time interval of all CSUGIEs that occurred within the entire study. These rates are in the entire ITT cohort. **When all patients were included in the analysis, regardless of aspirin status, the uncensored events were shown to continue to accrue in the celecoxib group at a generally steady rate from six months through the end of the study. In contrast, only one uncensored event occurred in the diclofenac group after 182 days, and none occurred in the ibuprofen group.** The curves for the two NSAIDs therefore become essentially flat in the second half of the study, with the result that the end points of the three curves are similar at the end of the study. As argued by the Sponsor, the decrease in accrual of events in patients taking NSAIDs suggests the possibility of depletion of patients at risk (depletion of susceptible patients, or informative censoring; see below). **The p-values comparisons, as noted in the footnote of the table, are not statistically significantly different between celecoxib and either NSAID, or when they were pooled.**

Table 10: CSUGIEs (Traditional-ITT)-Entire Study (Crude & Kaplan-Meier rates)[1,2]

	Celecoxib (n=3987)		**Diclofenac (n=1996)**		**Ibuprofen (n=1985)**	
Rates	+ censoring	- censoring	+ censoring	- censoring	+ censoring	- censoring
Crude						
Week 1 (1-7)	0.00%	0.03%	0.10%	0.10%	0.10%	0.15%
Week 4 (8-28)	0.03%	0.05%	0.25%	0.25%	0.20%	0.25%
Week 13 (29-91)	0.18%	0.23%	0.40%	0.40%	0.30%	0.40%
Week 26 (92-182)	0.28%	0.33%	0.45%	0.45%	0.55%	0.65%
Week 39 (183-273)	0.35%	0.43%	0.50%	0.50%	0.55%	0.65%
Week 52 (274-364)	0.43%	0.50%	0.50%	0.55%	0.55%	0.65%
Kaplan-Meier						
Week 1 (1-7)	0.01%	0.03%	0.10%	0.10%	0.12%	0.17%
Week 4 (8-28)	0.05%	0.07%	0.28%	0.28%	0.25%	0.31%
Week 13 (29-91)	0.24%	0.30%	0.51%	0.51%	0.47%	0.58%
Week 26 (92-182)	0.40%	0.45%	0.58%	0.58%	0.75%	0.86%
Week 39 (183-273)	0.54%	0.65%	0.62%	0.71%	-	-
Week 52 (274-364)	0.68%	0.78%	-	0.73%	-	-

1. From Table T12.2 (p. 267); N49-00-06-035-102. Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval. Uncensored and censored events were previously defined (Table 7 above).
2.For **censored events, log Rank P-values** (Table T14.3, p. 273) of celecoxib vs. NSAIDs = 0.450, celecoxib vs. diclofenac = 0.640, celecoxib vs. ibuprofen = 0.414. **For uncensored events, log Rank P-values** (Table T14.4, p. 274) of celecoxib vs. NSAIDs = 0.474, celecoxib vs. diclofenac = 0.752, celecoxib vs. ibuprofen = 0.372.

Table 11 shows the rates (both crude and Kaplan-Meier) by time interval of all CSUGIEs that occurred during the entire study. These rates are in the non-aspirin (ASA) using ITT cohort. The p-values comparisons, as noted in the footnote of the table **do not suggest statistically significantly difference between celecoxib and NSAIDs (both censored and uncensored results) nor between celecoxib and diclofenac (with or without censoring) but do between celecoxib and ibuprofen (p = 0.037 and 0.033 with and without censoring, respectively).**

Table 11: CSUGIEs without ASA (Traditional-ITT)-Entire Study (Crude & Kaplan-Meier rates)[1,2]

	Celecoxib (n=3105)		Diclofenac (n=1551)		Ibuprofen (n=1573)	
Rates	+ censoring	- censoring	+ censoring	- censoring	+ censoring	- censoring
Crude						
Week 1 (1-7)	0.00%	0.03%	0.06%	0.06%	0.13%	0.13%
Week 4 (8-28)	0.00%	0.03%	0.19%	0.19%	0.25%	0.25%
Week 13 (29-91)	0.13%	0.16%	0.26%	0.26%	0.38%	0.45%
Week 26 (92-182)	0.16%	0.19%	0.26%	0.26%	0.64%	0.70%
Week 39 (183-273)	0.23%	0.26%	0.26%	0.26%	0.64%	0.70%
Week 52 (274-364)	0.26%	0.29%	0.26%	0.26%	0.64%	0.70%
Kaplan-Meier						
Week 1 (1-7)	0.01%	0.04%	0.10%	0.10%	0.15%	0.15%
Week 4 (8-28)	0.03%	0.06%	0.23%	0.23%	0.32%	0.32%
Week 13 (29-91)	0.20%	0.23%	0.28%	0.28%	0.59%	0.67%
Week 26 (92-182)	0.25%	0.29%	-	-	0.83%	0.91%
Week 39 (183-273)	0.35%	0.38%	-	-	-	-
Week 52 (274-364)	0.41%	0.44%	-	-	-	-

1. From Table T15.2 (p. 276); N49-00-06-035-102. Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval. Uncensored and censored events were previously defined (Table 7 above).
2. For **censored events, log Rank P-values** (Table T15.3, p. 277) of celecoxib vs. NSAIDs = 0.185, celecoxib vs. diclofenac = 0.972, celecoxib vs. ibuprofen = 0.037. **For uncensored events, log Rank P-values** (Table T15.4, p. 278) of celecoxib vs. NSAIDs = 0.204, celecoxib vs. diclofenac = 0.870, celecoxib vs. ibuprofen = 0.033.

CSUGIEs (Alternate Definition) Entire Study:

As shown above, 40 of the 44 CSUGIEs that occurred during the entire study period were UGI bleeding events according to the traditional definition. Of these 40, 31 met one of the more restrictive alternate definitions of UGI bleeding (see section 8.1.1.3.2). These 31 uncensored events, along with the perforations and gastric outlet obstructions, are shown by category in Table 12. **No statistical analysis of the data were performed**. The profile of the events, however, is similar to that for CSUGIEs according to the traditional definition. The event rates were generally similar between the groups for the first six months of the study. Thereafter, events continued to accrue in the celecoxib group but not in the two NSAID groups. The difference between celecoxib and the NSAIDs was augmented by the fact that all of the uncensored traditional CSUGIEs in the celecoxib group met one of the alternate definitions, whereas this was true for only half of the events in the diclofenac group and nine of the 11 events in the ibuprofen group.

Table 12: CSUGIEs: Alternate Definitions-Entire Study Period[1]

Event Category	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
UGI Bleeding (Category 1)			
1E: Hematemesis with ulcer/large erosion and either hemoglobin drop or hypotension	1	-	-
1F: Ulcer/large erosion with evidence of bleeding and either hemoglobin drop or hypotension	8	2	6
1G: Melena with ulcer/large erosion and either hemoglobin drop or hypotension	5[2]	2	2[3]
1H: Hemoccult-positive stool with ulcer/large erosion and either hemoglobin drop or hypotension.	2	1	2
UGI Perforation (Category 2)	1	1[3]	-
Gastric Outlet Obstruction (Category 3)	2	-	-
Total	19	6	10
Total Uncensored	17	5	9
Week 52 crude rate (censoring rule applied)	0.43%	0.25%	0.45%

1. From Table 8u (p. 157) and 8v (p. 158); N49-00-06-035-102.
2. Two of these events censored from primary analysis.
3. One of these events censored from primary analysis.

Summary-CSUGIEs for 6 months and entire study:

Table 13 summarizes the incidence of CSUGIEs and the results during the first six months in the ITT population. The p-value comparisons are for uncensored events.

Table 13: Summary of CSUGIE Incidence (Traditional definition) - First Six Months (ITT)[1]

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celecoxib vs. Diclofenac	Ibuprofen	Both
All Patients						
	n = 3987	n = 1996	n = 1985			
No. of CSUGIEs						
Uncensored	11	9	11			
Censored[2]	2	0	2			
Total	13	9	13			
Week 26 crude rate[3]	0.28%	0.45%	0.55%	**0.264**	**0.073**	**0.092**
No. per 100 pt-yrs	0.76	1.27	1.63			
Patients not Taking Aspirin						
	n = 3154	n = 1567	n = 1602			
No. of CSUGIEs						
Uncensored	5	4	10			
Censored	1	0	1			
Total	6	4	11			
Week 26 crude rate[3]	0.16%	0.26%	0.62%	**0.476**	**0.005**	**0.037**
No. per 100 pt-yrs	0.44	0.72	1.85			

1 From T11.1 & T12.1, N49-00-06-035-102, p. 262 and 266/24295.

2 Occurred before 48 hours after midnight of the first dose day or more than 48 hours after midnight of the last dose day (unless occurred within two weeks after last dose and was determined by GEC to be treatment-related).

3 Rates and p-values based upon uncensored events.

Table 14 summarizes the incidence of CSUGIEs and the results during the entire study in the ITT population. The p-value comparisons are for uncensored events.

Table 14: Summary of CSUGIE Incidence (Traditional definition) - Entire Study Period (ITT)[2]

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celecoxib vs. Diclofenac	Ibuprofen	Both
All Patients						
	n = 3987	n = 1996	n = 1985			
No. of CSUGIEs						
Uncensored	17	10	11			
Censored[1]	3	1	2			
Total	20	11	13			
Week 52 crude rate[3]	0.43%	0.50%	0.55%	**0.640**	**0.414**	**0.450**
No. per 100 pt-yrs	0.73	0.93	0.98			
Patients not Taking Aspirin						
	n = 3105	n = 1551	n = 1602			
No. of CSUGIEs						
Uncensored	8	4	10			
Censored	1	0	1			
Total	9	4	11			
Week 52 crude rate	0.26%	0.26%	0.62%	**0.972**	**0.037**	**0.185**
No. per 100 pt-yrs	0.44	0.48	1.14			

1 Occurred before 48 hours after midnight of the first dose day or more than 48 hours after midnight of the last dose day (unless occurred within two weeks after last dose and was determined by GEC to be treatment-related).
2. From Table T14.1 & T15.1, N49-00-06-035-102, p. 271 & 275/24295.
3. Rates and p-values based upon uncensored events.

Censored events and informative censoring:

Censored events

As noted in Table 15, six of the events were censored from the primary analysis for the entire study period; therefore this also includes the four censored events described for the first 6 months (Table 13). **Uncensored events** were defined as those meeting either of the following two conditions (i.e. events were censored if they failed to meet either of these two conditions:

1. Occurred after 48 hours past midnight of the first dosing day and before 48 hours following midnight of the last dosing day.
2. Occurred after 48 hours past midnight of the last dosing day and before 2 weeks following midnight of the last dosing day and were determined to be causally related to study drug by the GI events committee.

In these analyses, **onset of a CSUGIE was defined as the day on which signs or symptoms first occurred that were suggestive of a potential CSUGIE**; onset of an ulcer was defined as the day of the endoscopy that disclosed the ulcer. When these censored cases were included in the analysis

along with the uncensored cases, the trends and comparisons shown in the Tables above were repeated; this includes the statistically significant difference between celecoxib and ibuprofen event rates in the non-aspirin-taking cohort.

Table 15 shows the reasons for censoring of CSUGIEs during the study. **Case 1029** started therapy (ibuprofen) on 12/4/98, noted GI symptoms on the second day (12/5,98) and discontinued ibuprofen the following day (12/6/98). On study day five (12/9/98), the patient was noted with a heme positive stool (12/9/98) and had endoscopy (12/11/98). **Case 1056** started therapy (celecoxib) on 12/11/98 (which may have been her last day of naproxen sodium), developed a rash on study day 9 (12/19/98) or 11 (12/21/98) when therapy was stopped; the patient also had complaints of abdominal pain at that time. By patient request, endoscopy was not done until 1/29/99. As typed summary in the CRF for case 1029 states "it is believed patient began having black stools on 12/12/98".

Table 15: Reasons for Censoring of CSUGIEs - Entire Study Period

Case No.	Patient No.	Treatment	Event Type	Reason for Censoring
1029	US0417-035-20397	Ibuprofen	1C	Event onset on day 2
1056	US0114-035-11573	Celecoxib	1C	Event onset on day 2
1201	US0039-035-21235	Celecoxib	1D1	Onset 19 days after D/C
1245	US0328-102-11895	Celecoxib	1C	Onset 8 days after D/C; use of ketorolac
1297	US0591-102-10168	Diclofenac	2	Onset 35 days after D/C
1383	CA0484-035-12170	Ibuprofen	1C	Onset 18 days after D/C

Reviewer's comment: One could argue that case 1056 does not fulfill the spirit of the censoring rules.

Homogeneity between the two protocols was addressed by comparing the counts and rates of CSUGIEs for celecoxib separately. There were 8 (2 censored) events in protocol 035 and 12 events (1 censored) in protocol 102. By log rank testing with censoring applied to the traditional endpoint definition, there was no statistically significant difference (p =0.237; page 2052, N49-00-06-035-102,) noted between these protocols which suggests these trials were homogeneous with respect to assessment of this endpoint.

Informative censoring

Univariate analyses of potential risk factors for both end points of primary interest (CSUGIEs and CSUGIEs/GDUs) showing a statistically significant factor effect within either the celecoxib or pooled NSAID group are summarized in **Table 16**.

The common risk factor for both end points (CSUGIEs and CSUGIEs/GDUs) in both the celecoxib and NSAID treatment groups was advanced age ≥75 years). Additional risk factors specific to NSAIDs for both end points were a history of UGI bleeding and a history of gastroduodenal ulcer. For celecoxib, the common risk factors for both end points were a history of cardiovascular disease and aspirin use. The risk factor common to celecoxib and NSAIDs for CSUGIEs/GDUs alone was a history of NSAID intolerance.

Table 16: Univariate Analysis of Risk Factors for CSUGIEs and CSUGIEs/GDUs[1]

Factor	Relative Risk			
	CSUGIEs		CSUGIEs/GDUs	
	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 (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 positive H. pylori serology	6.9 (p=0.002)	1.6 (p=0.240)	2.5 (p=0.002)	1.6 (p=0.048)
Aspirin use	0.7 (p=0.460)	2.2 (p=0.072)	1.1 (p=0.423)	2.0 (p=0.005)
	4.0 (p=0.005)	1.8 (p=0.211)	3.7 (p<0.001)	2.3 (p=0.002)

1 From Table 8.1 (p. 147), Table T23.1 (p. 303), Table T23.3 (p. 305), Table T24.1 (p. 307), Table T24.3 (p. 309), Table T25.1 (p. 311) and Table T 25.3 (p. 313);N49-00-06-035-102.

Multivariate regression for the risk factors for CSUGIEs/GDUs common to celecoxib and NSAIDs are shown in **Table 17**. Risk factors for CSUGIEs/GDUs were similar between celecoxib and NSAIDs, although their relative contribution differed between the two groups. For celecoxib, aspirin use appeared as the most important risk factor, and age the least important. For NSAIDs, the order was reversed, with age the most important risk factor and aspirin use the least important.

Table 17: Multivariate Analysis of Risk Factors for CSUGIEs/GDUs[1]

Treatment Group	Factor	Odds Ratio (p Value)
Celecoxib	Aspirin use	2.9 (p<0.001)
	History of GD ulcer	2.5 (p=0.018)
	Age ≥75 years	2.4 (p=0.012)
NSAIDs	Age ≥75 years	3.3 (p<0.001)
	History of GD ulcer	2.6 (p=0.004)
	Aspirin use	2.1 (p=0.006)

1 From Table 8.m (p. 148); N49-00-06-035-102.

Withdrawal in Patients with Risk Factors

The analyses above seem to confirm what is generally accepted that in GI safety studies in NSAID-treated patients, there are some risk factors (such as age, history of GI ulcer, GI bleeding, and cardiovascular disease) that are associated with GI outcomes. **Table 18** addresses, and seems to confirm, the generally accepted idea that patients falling into one or more of these categories have a greater chance to develop GI ulcers or complications than patients without such risk factors when treated with NSAIDs. It should be noted that this table contains all ITT patients in all treatment groups.

Table 18: Number of CSUGIEs or CSUGIE/GDU by Number of Risk Factors [1]

Number of Risk Factors	Number of Patients	CSUGIE N (%)	CSUGIE/GDU N (%)	Withdrawal N (%)
0	4073	6 (0.1)	25 (0.6)	2184 (54)
1	2993	14 (0.5)	43 (1.4)	1760 (59)
≥2	902	18 (2.0)	37 (4.1)	615 (68)

1. From Table 4 (p. 1985); N49-00-06-035-102.

A more detailed examination of the distribution CSUGIEs ± GDUs by treatment group is shown in **Table 19.**

Table 19: Number of CSUGIEs or CSUGIE/GDU by Treatment and Risk Factors [1]

Number of Risk Factors	Number of Patients (%)	CSUGIE N (%)	CSUGIE/GDU N (%)	Withdrawal N (%)
Celecoxib				
0	2029 (51)	6 (<0.1)	7 (0.3)	1045 (52)
1	1497 (38)	8 (0.5)	20 (1.3)	856 (57)
≥2	461 (12)	8 (1.7)	16 (3.5)	307 (67)
Diclofenac				
0	1019 (51)	0 (0.0)	2 (0.2)	485 (48)
1	738 (37)	4 (0.5)	13 (1.8)	416 (56)
≥2	239 (12)	6 (2.5)	11 (4.6)	156 (65)
Ibuprofen				
0	1025 (52)	5 (0.5)	16 (1.6)	654 (64)
1	758 (38)	2 (0.3)	10 (1.3)	488 (64)
≥2	202 (10)	4 (2.0)	10 (5.0)	152 (75)

1. From Table 5 (p. 1986); N49-00-06-035-102.

Reviewer's comment: In general, the endpoints of CSUGIE ±GDU and withdrawals increase with the number of risk factors in all treatment groups. However, when considering risk factors, there does not appear to be a consistent pattern of withdrawal (i.e. resulting in less patients at risk) when comparing celecoxib against ibuprofen and diclofenac. Patients receiving celecoxib appear more likely to withdraw at any given risk category than that of diclofenac but not ibuprofen. An association of endpoints with withdrawal does not seem evident when comparing across treatments.

Withdrawal in Patients with Symptoms

Since many patients showed the occurrence of GI symptoms (specifically, the development of abdominal pain, diarrhea, dyspepsia, nausea, or vomiting) as part of the evolution of the case, the question arose as to whether these GI symptoms represented an additional risk factor for a CSUGIE or CSUGIE/GDU. Results of this analysis by the Sponsor are summarized in Table 20. The results indicate that patients with these GI symptoms have an increased risk of a CSUGIE ± GDU.

Table 20: Risk for CSUGIEs and CSUGIEs/GDUs in Patients With/Without GI Symptoms[1]

	No. with Event/Total	Incidence	Relative Risk
CSUGIEs			
With GI symptoms[2]	18/1483	1.21%	3.9
Without GI symptoms	20/6485	0.31%	
CSUGIEs/GDUs			
With GI symptoms[2]	62/1483	4.2%	6.3
Without GI symptoms	43/6485	0.7%	

1 From Table 8.n (p. 149) and appendix 2.4.17.4 (p. 2085); N49-00-06-035-102.

2 Symptoms are moderate or severe abdominal pain, dyspepsia, nausea, diarrhea or vomiting. Total events for celecoxib = 699 (17.5%), diclofenac = 448 (22.4%) and ibuprofen = 336 (16.9%). Events are non-censored.

If symptomatic GI adverse events represent risk factors for clinically important events, withdrawals due to these GI symptoms could represent the loss of patients at risk. This depletion of susceptible individuals, or "**informative censoring**" as argued by the Sponsor, could result in misleading analyses, particularly if withdrawal due to GI adverse events were not similar among the treatment groups. As noted in **Table 21**, a higher proportion of patients receiving diclofenac withdrew as a result of some GI adverse events which represented the most common GI adverse events: abdominal pain, dyspepsia, nausea, diarrhea, and flatulence during the entire study. The overall incidence of withdrawal due to an adverse event was statistically significantly lower for celecoxib than for diclofenac as were several individual events. For example, the differences between celecoxib and diclofenac for three of the GI events (abdominal pain, nausea, and diarrhea) and the three hepatic events (elevations of liver enzyme levels) were statistically significant in favor of celecoxib. Between celecoxib and ibuprofen, the only statistically significant differences were in diarrhea, gastric ulcer, and rash; the incidence of rash with celecoxib was also significantly different than that seen with diclofenac.

Table 21: Adverse Events Causing Withdrawal with Incidence ³1%: Entire Study Period

Adverse Event (%)	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Any event	22.4	26.5[2]	23.0
Abdominal pain	4.3	6.5[2]	4.9
Dyspepsia	3.8	4.4	3.9
Rash	2.1	0.7[2]	1.3[2]
Nausea	1.7	2.8[2]	1.8
Diarrhea	1.4	2.7[2]	0.8[2]
Flatulence	1.2	1.8	1.4
Gastric ulcer	0.3	0.7	1.0[2]
SGOT increased	0.1	2.1[2]	0.1
SGPT increased	0.1	2.3[2]	0.1
Hepatic function abnormal	<0.1	1.1[2]	<0.1

1. From Table 10d (p. 180) and Table T 42.1 (p. 469); N49-00-06-035-102.
2. P<0.05 vs. celecoxib.

As noted (Table T42.4, p. 498, N49-00-06-035-102), the incidences of adverse events leading to withdrawal in the first six months of the study were in most cases identical to, or slightly below, those in the entire study period. This indicates that **almost all patients withdrawing due to adverse events did so within six months of beginning the study.**

To address whether informative censoring with respect to CSUGIEs ± GDUs was observed in patients who dropped out due to GI-related adverse events (i.e. dyspepsia, abdominal pain, nausea, diarrhea, and vomiting), the rates of these events were compared (**Table 22**). There are no statistically significant differences between ibuprofen and celecoxib with regards to overall withdrawal and withdrawal due to any particular GI adverse event. However, there does appear to be a difference between celecoxib and diclofenac in the overall withdrawal rate and those associated with (moderate to severe) diarrhea, abdominal pain and nausea.

Table 22: Incidence of Withdrawal for Moderate to Severe GI adverse events[1]

	Celecoxib N=3987	**Diclofenac N=1996**	**Ibuprofen N=1985**
Any GI adverse event	699	448	336
Withdrawal	298 (7.5%)	191 (9.6%)[2]	149 (7.5%)
Diarrhea	35 (0.9%)	40 (2.0%)[2]	13 (0.7%)
Vomiting	19 (0.5%)	7 (0.4%)	5 (0.3%)
Abdominal pain	140 (3.5%)	101 (5.1%)[2]	80 (4.0%)
Dyspepsia	122 (3.1%)	60 (3.0%)	58 (2.9%)
Nausea	49 (1.2%)	35 (1.8%)[2]	25 (1.3%)

1. From Table 1 (p. 1980) and Appendix 2.4.17.5 (p. 2086);N49-00-06-035-102.
2. P values from Fischer's exact test. For celecoxib vs. diclofenac withdrawal p=0.006; diarrhea p<0.001; abdominal pain p=0.005; nausea p=0.129. All other p-values >0.20 or could not be calculated.

To address whether patients who experienced GI adverse events had a higher incidence of CSUGIEs ± GDUs than patients who did not report GI adverse events, the rates of events were compared (Table 23).

Table 23: CSUGIE ± GDU rates and relative risks with/without 5 GI symptoms[1]

	Celecoxib N=3987		**Diclofenac N=1996**		**Ibuprofen N=1985**	
	Sponsor	MO[2]	Sponsor	MO	Sponsor	MO
CSUGIE						
With AE	5/699	12/699	8/448	7/448	5/336	6/336
Without AE	12/3288	5/3288	2/1548	3/1548	6/1649	5/1649
Relative Risk	1.96	11.5	13.82	8.2	4.09	5.9
CSUGIE/GDU						
With AE	22/699		20/448		20/336	
Without AE	21/3288		6/1548		16/1649	
Relative Risk	4.93		11.52		6.13	

1 From Table 2 (p. 1981) ; N49-00-06-035-102. Symptoms included dyspepsia, abdominal pain, nausea, diarrhea, and vomiting (moderate to severe). CSUGIEs or CSUGIE/GDU are those uncensored during the entire study.

2 Per medical officer review of case summaries of CSUGIEs. All patients were withdrawn from the trial. All patients had the GI symptoms noted in the summaries without regard to rating of severity (i.e. mild, moderate, severe). The CSUGIE/GDU cases for celecoxib were also reviewed; a relative risk of 12.83 (vs. 4.93) was obtained.

Reviewer's comment: There is a difference in adjudication of CSUGIEs between the sponsor and the medical officer; these differences can change the inferences that can be drawn from these data. The relative risk of a CSUGIE ± GDU in patients with an AE appears greater with celecoxib than with ibuprofen or diclofenac. This observation would tend not to support the importance of informative censoring in the outcomes. It

does appear that, in all treatment arms, CSUGIEs tend to be found more commonly in patients with the five GI symptoms listed above than without these AEs.

The Sponsor argued that withdrawals of susceptible individuals (i.e. "informative censoring") due to GI adverse events represent the loss of patients at risk. This loss suggests that standard analyses of risk may be misleading, particularly because incidences of withdrawal due to GI adverse events were not similar among the treatment groups. A higher proportion of patients receiving diclofenac withdrew as a result of GI signs or symptoms as discussed above.

To address this issue, incidences of events that could not occur because of withdrawals for GI adverse events were imputed based on risk calculations with a time-adjusted method (Appendix 1.9, N49-00-06-035-102). In brief, incidences were calculated for patients who experienced GI symptoms but continued in the study. The incidences were then applied to patients who discontinued due to GI symptoms. **As shown in Table 24, the adjusted rates suggested there would be differences between treatment groups for both end points within the first six months and for the entire study period had informative censoring been an important issue in influencing outcomes.**

Table 24: Crude Incidence Rates and Comparisons for CSUGIEs ± GDUs Adjusted for Withdrawals for GI Adverse Events[1]

	Celecoxib (n=3987)	**Diclofenac (n=1996)**	**Ibuprofen (n=1985)**	**Celecoxib vs. Diclofenac**	**Celecoxib vs. Ibuprofen**
First six months					
CSUGIE	15 (0.4%)	16 (0.8%)	16 (0.8%)	P=0.036	P=0.035
CSUGIE/GDU	44 (1.1%)	34 (1.7%)	44 (2.2%)	P=0.069	P=0.001
Entire Study					
CSUGIE	25 (0.6%)	23 (1.2%)	21 (1.1%)	P=0.044	P=0.084
CSUGIE/GDU	76 (1.9%)	58 (2.9%)	73 (3.7%)	P=0.016	P<0.001

1. From Table 8o (p. 150); N49-00-06-035-102

Endpoint of CSUGIE/GDU for first 6 months:

As discussed earlier (section 8.1.1.3.2), symptomatic ulcer cases were those cases in which criteria for a CSUGIE were not met but in which a gastroduodenal ulcer was found by either endoscopy or upper gastrointestinal series, performed as a result of symptoms or signs. The combined category of these ulcers with the CSUGIEs was referred to as "**CSUGIEs/GDUs."** Of note, any patient with either a gastric or duodenal ulcer, or both, is counted as having a gastroduodenal ulcer.

As noted above, a total of 1214 potential CSUGIEs occurred within the first six months of these studies. After GEC review, 225 of the 260 potential CSUGIEs were found to be non-CSUGIEs, and 954 were found to be negative events. Of these 225 non-CSUGIEs, 48 were cases of symptomatic gastroduodenal ulcers (from figure 8c p. 100, N49-00-06-035-102).

Table 25 shows that within the first six months of study, a total of 83 CSUGIEs/GDUs were found: 32 occurred on celecoxib treatment, 20 on diclofenac, and 31 on ibuprofen. Included in this

total are all CSUGIEs/GDUs regardless of censoring. None of the symptomatic ulcer cases within the first six months was censored; thus all ulcers are included in the CSUGIE/GDU analyses.

Table 25: Distribution of CSUGIEs/GDU: Traditional Definitions –First Six Months [1]

Event Category	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
UGI Bleeding (Category 1)			
1A: Hematemesis with ulcer/large erosion	-	-	-
1B: Ulcer/large erosion with evidence of bleeding	7	4	7
1C: Melena with ulcer/large erosion	3[2]	4	3[3]
Hemoccult (+) stool with ulcer/large erosion and:			
1D-1: Hematocrit/Hemoglobin drop	2[2]	1	3
1D-2: orthostasis	-	-	-
1D-3: transfusion	-	-	-
1D-4: blood in stomach	-	-	-
UGI Perforation (Category 2)	-	-	-
Gastric Outlet Obstruction (Category 3)	1	-	-
Symptomatic Ulcers			
Gastroduodenal	19	11	18
Gastric	13	8	17
Duodenal	7	5	1
Total	32	20	31
Total Uncensored	30	20	29

1 From Table 8h (p.101), Table T17.1 (p. 281), appendix 2.6.1 (p. 2123); N49-00-06-035-102. Any patient with both gastric and duodenal ulcers is counted once in the "Gastroduodenal" row.
2 One of these events censored from primary analysis.
3 Two of these events censored from primary analysis

Table 26 summarizes the results for the incidences and comparisons of CSUGIE/GDU during the first 6 months of the study for the ITT population. The differences in times to event over the first 26 weeks achieved statistical significance between celecoxib and NSAIDs pooled, as well as between celecoxib and ibuprofen. When only the patients not taking aspirin were included in the analysis, the event rate for celecoxib over the first 26 weeks was again statistically significantly lower than the rate for NSAIDs combined ($p=0.017$) as well as that for ibuprofen ($p<0.001$).

Table 26: Summary of CSGUIE/GDU Incidence – First Six Months

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celecoxib vs. Diclofenac	Ibuprofen	Both
All Patients						
	n = 3987	n = 1996	n = 1985			
No. of CSUGIE/GDUs						
Uncensored	30	20	29			
Censored[1]	2	0	2			
Total	32	20	31			
Week 26 crude rate[3]	0.75%	1.00%	1.46%	**0.308**	**0.005**	**0.023**
No. per 100 pt-yrs	2.08	2.82	4.31			
Patients not Taking Aspirin						
	n = 3154	n = 1567	n = 1602			
No. of CSUGIE/GDUs						
Uncensored	16	9	23			
Censored	1	0	1			
Total	17	9	24			
Week 26 crude rate	0.51%	0.57%	1.44%	**0.760**	**<0.001**	**0.017**
No. per 100 pt-yrs	1.40	1.61	4.25			

1. Occurred before 48 hours after midnight of the first dose day or more than 48 hours after midnight of the last dose day (unless occurred within two weeks after last dose and was determined by GEC to be treatment-related).
2. From Table T17.1 & T18.1, N49-00-06-035-102, p. 281 & 285/24295.
3. Rates and p-values based on uncensored data.

Table 27 shows the rates (both crude and Kaplan-Meier) by time interval of all CSUGIEs/GDU during the first six months of the study. These rates are in the entire ITT cohort. The p-values comparisons, as noted in the footnote of the table suggest statistically significantly different between celecoxib and the pooled NSAID results, or when compared against ibuprofen (p=0.005 and 0.004 with censored and uncensored cases, respectively) but not against diclofenac.

Table 27: CSUGIEs/GDU-First 6 months (Crude & Kaplan-Meier rates)[1,2]

	Celecoxib (n=3987)		**Diclofenac (n=1996)**		**Ibuprofen (n=1985)**	
Rates	+ censoring	- censoring	+ censoring	- censoring	+ censoring	- censoring
Crude						
Week 1 (1-7)	0.03%	0.05%	0.10%	0.10%	0.10%	0.15%
Week 4 (8-28)	0.18%	0.20%	0.25%	0.25%	0.30%	0.35%
Week 13 (29-91)	0.53%	0.58%	0.65%	0.65%	0.91%	1.01%
Week 26 (92-182)	0.75%	0.80%	1.00%	1.00%	1.46%	1.56%
Kaplan-Meier						
Week 1 (1-7)	0.04%	0.06%	0.10%	0.10%	0.12%	0.17%
Week 4 (8-28)	0.20%	0.23%	0.31%	0.31%	0.32%	0.37%
Week 13 (29-91)	0.65%	0.70%	0.82%	0.82%	1.24%	1.35%
Week 26 (92-182)	0.97%	1.02%	1.30%	1.30%	2.05%	2.16%

1.From Table T17.2 (p. 282); N49-00-06-035-102. Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval. Uncensored and censored events were previously defined (Table 7 above).

2. For **censored events, log Rank P-values** (Table T17.3, p. 283) of celecoxib vs. NSAIDs = 0.023, celecoxib vs. diclofenac = 0.308, celecoxib vs. ibuprofen = 0.005. **For uncensored events, log Rank P-values** (Table T17.4, p. 284) of celecoxib vs. NSAIDs = 0.026, celecoxib vs. diclofenac = 0.421, celecoxib vs. ibuprofen = 0.004.

Table 28 shows the rates (both crude and Kaplan-Meier) by time interval of all CSUGIEs/GDU during the first six months of the study in patients not taking ASA. These rates are in the entire ITT cohort. The p-values comparisons, as noted in the footnote of the table, suggest (as noted earlier with the CSUGIE results) statistically significantly differences between celecoxib and the pooled NSAID results, or when compared against ibuprofen ($p<0.001$ and 0.001 with censored and uncensored cases, respectively) but not against diclofenac.

Table 28: CSUGIEs/GDU-First 6 months without ASA (Crude & Kaplan-Meier rates-ITT)[1,2]

	Celecoxib (n=3154)		Diclofenac (n=1567)		Ibuprofen (n=1602)	
Rates	+ censoring	- censoring	+ censoring	- censoring	+ censoring	- censoring
Crude						
Week 1 (1-7)	0.03%	0.06%	0.06%	0.06%	0.12%	0.12%
Week 4 (8-28)	0.13%	0.16%	0.19%	0.19%	0.37%	0.37%
Week 13 (29-91)	0.35%	0.38%	0.45%	0.45%	0.87%	0.94%
Week 26 (92-182)	0.51%	0.54%	0.57%	0.57%	1.44%	1.50%
Kaplan-Meier						
Week 1 (1-7)	0.04%	0.07%	0.10%	0.10%	0.14%	0.14%
Week 4 (8-28)	0.14%	0.17%	0.26%	0.26%	0.39%	0.39%
Week 13 (29-91)	0.44%	0.48%	0.54%	0.54%	1.21%	1.28%
Week 26 (92-182)	0.65%	0.68%	0.74%	0.74%	2.00%	2.08%

1. From Table T18.2 (p. 286); N49-00-06-035-102. Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval. Uncensored and censored events were previously defined (Table 7 above).
2.For **censored events, log rank P-values** (Table T18.3, p. 287) of celecoxib vs. NSAIDs = 0.017, celecoxib vs. diclofenac = 0.760, celecoxib vs. ibuprofen < 0.001. **For uncensored events, log rank P-values** (Table T18.4, p. 288) of celecoxib vs. NSAIDs = 0.019, celecoxib vs. diclofenac = 0.872, celecoxib vs. ibuprofen < 0.001.

Endpoint of CSUGIE/GDU for entire study:

As noted earlier, throughout the full length of the study, a total of 1670 potential CSUGIEs were worked up with 384 reviewed by all members of the GEC. Of these, 44 were found to be CSUGIEs, 340 were found to be non-CSUGIEs, and 1286 were found to be negative events. Of the 340 non-CSUGIEs, 67 represented symptomatic gastroduodenal ulcers, for a total of 111 CSUGIEs/GDUs (i.e. 44 plus 67) occurring throughout the entire study period.

Table 29 shows all CSUGIEs/GDUs by treatment group and category. Forty-six CSUGIEs/GDUs occurred on celecoxib treatment, 27 on diclofenac, and 38 on ibuprofen. Included in these totals are all CSUGIEs and symptomatic ulcers regardless of censoring. Three CSUGIEs in the celecoxib group, one CSUGIE in the diclofenac group, and two CSUGIEs in the ibuprofen group were censored. None of the ulcer cases was censored; therefore, all of the ulcers are included in the CSUGIE/GDU analysis.

Table 29: Distribution of CSUGIEs/GDU: Traditional Definitions –Entire Study[1]

Event Category	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
UGI Bleeding (Category 1)			
1A: Hematemesis with ulcer/large erosion	**1**	**-**	**-**
1B: Ulcer/large erosion with evidence of bleeding	**7**	**4**	**7**
1C: Melena with ulcer/large erosion	**5**[2]	**4**	**3**[3]
Hemoccult (+) stool with ulcer/large erosion and:			
1D-1: Hematocrit/Hemoglobin drop	**3**[2]	**2**	**3**
1D-2: orthostasis	**-**	**-**	**-**
1D-3: transfusion	**-**	**-**	**-**
1D-4: blood in stomach	**-**	**-**	**-**
UGI Perforation (Category 2)	**1**	**1**	**-**
Gastric Outlet Obstruction (Category 3)	**2**	**-**	**-**
Symptomatic Ulcers (all patients)			
Gastroduodenal	**26**	**16**	**25**
Gastric	**18**	**13**	**22**
Duodenal	**10**	**5**	**3**
Symptomatic Ulcers (not taking aspirin)	**(n=3105)**	**(n=1561)**	**(n=1573)**
Gastroduodenal	**13**	**6**	**18**
Gastric	**8**	**5**	**16**
Duodenal	**6**	**2**	**2**
Total	**46**	**27**	**38**
Total Uncensored	**43**	**26**	**36**

1 From Table 8j (p.105), Table 8r (p. 154) and appendix 2.6.1 (p. 2123); N49-00-06-035-102. Any patient with both gastric and duodenal ulcers is counted once in the "Gastroduodenal" row.
2 One of these events censored from primary analysis.
3 Two of these events censored from primary analysis

Table 30 summarizes the results for the incidences and comparisons of CSUGIE/GDU during the entire study for the ITT population. The cumulative times to event were significantly lower through the entire study period for celecoxib than for the NSAID comparators pooled (p=0.040) and ibuprofen individually (p=0.017). When only patients not taking aspirin were included in the analysis, the celecoxib event rate over 52 weeks was statistically significantly lower than the rate for the NSAIDs pooled (p=0.020) and the rate for ibuprofen individually (p<0.001). When both censored and uncensored cases were included in the analysis, the trends and comparisons shown above were repeated (Table 20.4, p. 295; and Table 21.4, p. 299 of N49-00-06-035-102), including the statistically significant difference between celecoxib and ibuprofen event rates in the patients not taking aspirin. Celecoxib was not statistically significantly different from diclofenac for any comparison.

Table 30: Summary of CSGUIE/GDU Incidence (Traditional Definitions) – Entire Study Period

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celecoxib vs. Diclofenac	Ibuprofen	Both
All Patients						
	n = 3987	n = 1996	n = 1985			
No. of CSUGIE/GDUs						
Uncensored	43	26	36			
Censored[1]	3	1	2			
Total	46	27	38			
Week 52 crude rate[3]	1.05%	1.30%	1.76%	**0.296**	**0.017**	**0.040**
No. per 100 pt-yrs	1.85	2.41	3.21			
Patients not Taking Aspirin						
	n = 3105	n = 1551	n = 1573			
No. of CSUGIE/GDUs						
Uncensored	21	10	28			
Censored	1	0	1			
Total	22	10	29			
Week 52 crude rate	0.68%	0.64%	1.72%	**0.992**	**<0.001**	**0.020**
No. per 100 pt-yrs	1.16	1.19	3.20			

1. Occurred before 48 hours after midnight of the first dose day or more than 48 hours after midnight of the last dose day (unless occurred within two weeks after last dose and was determined by GEC to be treatment-related).
2. From Table T20.1 & T21.1, N49-00-06-035-102, p. 292 & 296/24295.
3. Rates and p-values from uncensored data.

Table 31 shows the rates (both crude and Kaplan-Meier) by time interval of all CSUGIEs/GDU during the entire study. These rates are in the entire ITT cohort. The p-values comparisons, as noted in the footnote of the table, suggest again statistically significantly differences between celecoxib and the pooled NSAID results, or when compared against ibuprofen (p=0.017 and 0.016 with censored and uncensored cases, respectively) but not against diclofenac.

Table 31: CSUGIEs/GDU-Entire Study-ITT (Crude & Kaplan-Meier rates)[1,2]

	Celecoxib (n=3987)		Diclofenac (n=1996)		Ibuprofen (n=1985)	
Rates	+ censoring	- censoring	+ censoring	- censoring	+ censoring	- censoring
Crude						
Week 1 (1-7)	0.03%	0.05%	0.10%	0.10%	0.10%	0.15%
Week 4 (8-28)	0.18%	0.20%	0.25%	0.25%	0.30%	0.35%
Week 13 (29-91)	0.53%	0.58%	0.65%	0.65%	0.91%	1.01%
Week 26 (92-182)	0.75%	0.80%	1.00%	1.00%	1.46%	1.56%
Week 39 (183-273)	0.83%	0.90%	1.25%	1.25%	1.61%	1.71%
Week 52 (274-364)	1.05%	1.13%	1.30%	1.35%	1.76%	1.86%
Kaplan-Meier						
Week 1 (1-7)	0.04%	0.06%	0.10%	0.10%	0.12%	0.17%
Week 4 (8-28)	0.20%	0.23%	0.31%	0.31%	0.32%	0.37%
Week 13 (29-91)	0.65%	0.70%	0.82%	0.82%	1.24%	1.35%
Week 26 (92-182)	1.00%	1.05%	1.31%	1.31%	2.06%	2.17%
Week 39 (183-273)	1.14%	1.24%	1.83%	1.86%	2.43%	2.54%
Week 52 (274-364)	1.95%	2.05%	1.91%	2.02%	2.84%	2.94%

1. From Table T20.2 (p. 293); N49-00-06-035-102. Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval. Uncensored and censored events were previously defined (Table 7 above).
2. For **censored events, log rank P-values** (Table T20.3, p. 294) of celecoxib vs. NSAIDs = 0.040, celecoxib vs. diclofenac = 0.296

celecoxib vs. ibuprofen = 0.017. **For uncensored events, log rank P-values** (Table T20.4, p. 295) of celecoxib vs. NSAIDs = 0.045, celecoxib vs. diclofenac = 0.349, celecoxib vs. ibuprofen = 0.016.

Table 32 shows the rates (both crude and Kaplan-Meier) by time interval of all CSUGIEs/GDU during the entire study in patients not taking ASA. These rates are in the entire ITT cohort. The p-values comparisons, as noted in the footnote of the table, suggest again (as noted earlier with the CSUGIE results) statistically significantly differences between celecoxib and the pooled NSAID results, or when compared against ibuprofen ($p<0.001$ and 0.001 with censored and uncensored cases, respectively) but not against diclofenac.

Table 32: CSUGIEs/GDU-Entire Study without ASA-ITT (Crude & Kaplan-Meier rates)[1,2]

	Celecoxib (n=3105)		Diclofenac (n=1551)		Ibuprofen (n=1573)	
Rates	+ censoring	- censoring	+ censoring	- censoring	+ censoring	- censoring
Crude						
Week 1 (1-7)	0.03%	0.06%	0.06%	0.06%	0.13%	0.13%
Week 4 (8-28)	0.13%	0.16%	0.19%	0.19%	0.38%	0.38%
Week 13 (29-91)	0.35%	0.39%	0.45%	0.45%	0.89%	0.95%
Week 26 (92-182)	0.52%	0.55%	0.58%	0.58%	1.46%	1.53%
Week 39 (183-273)	0.58%	0.61%	0.58%	0.58%	1.65%	1.72%
Week 52 (274-364)	0.68%	0.71%	0.64%	0.64%	1.72%	1.78%
Kaplan-Meier						
Week 1 (1-7)	0.04%	0.07%	0.10%	0.10%	0.15%	0.15%
Week 4 (8-28)	0.14%	0.18%	0.26%	0.26%	0.40%	0.40%
Week 13 (29-91)	0.45%	0.48%	0.54%	0.54%	1.24%	1.31%
Week 26 (92-182)	0.71%	0.74%	0.75%	0.75%	2.07%	2.14%
Week 39 (183-273)	0.80%	0.84%	0.89%	0.89%	2.55%	2.63%
Week 52 (274-364)	1.13%	1.16%	0.92%	0.92%	3.00%	3.07%

1. From Table T21.2 (p. 297); N49-00-06-035-102. Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval. Uncensored and censored events were previously defined (Table 7 above).
2. For **censored events, log rank P-values** (Table T21.3, p. 298) of celecoxib vs. NSAIDs = 0.020, celecoxib vs. diclofenac = 0.992, celecoxib vs. ibuprofen < 0.001. **For uncensored events, log rank P-values** (Table T21.4, p. 295) of celecoxib vs. NSAIDs = 0.022, celecoxib vs. diclofenac = 0.907, celecoxib vs. ibuprofen < 0.001.

Summary of GI endpoint results:

Table 33 summarizes the log-rank p-values for the endpoints of CSUGIEs and CSUGIEs/GDU for both the first six months and for the entire study in the ITT population both with and without the use of ASA.

During the first 6 months, analysis of the CSUGIE data in the entire cohort showed a numerical trend toward a decrease in the incidence with celecoxib compared to NSAIDs combined; these trends were not statistically significant. When the observed rates were analyzed in the subgroup of patients not taking aspirin, there was a statistically significant decrease in the incidence of CSUGIEs observed with celecoxib relative to pooled NSAIDs (Table 13). Although the reduction in CSUGIEs was not statistically significant in the entire study population at 6 months, the reduction in symptomatic ulcers combined with CSUGIEs (CSUGIEs/GDUs) was significant

(Table 26). This analysis also showed a significant difference in patients not receiving aspirin for celecoxib and NSAIDs.

In terms of individual comparisons with ibuprofen and diclofenac, all comparisons significant for celecoxib vs. NSAIDs combined were significant for celecoxib vs. ibuprofen. In contrast to the results for ibuprofen, no differences were seen between celecoxib and diclofenac for any of the end points.

Analysis of the entire study period showed that the difference between celecoxib and pooled NSAIDs for CSUGIEs in the entire study population was not statistically significant. Statistical significance was also not achieved when patients not taking aspirin were analyzed specifically (Table 14). This absence of statistical significance appeared to reflect a decline in the NSAID event rate between six months and the end of the study; this decline was argued to be attributable to the phenomenon of depletion of susceptible patients. When the combined end point of CSUGIEs/GDUs was analyzed, the difference between celecoxib and pooled NSAIDs became statistically significant. A statistically significant difference between celecoxib and the pooled NSAIDs was also noted when the confounding effects of low-dose aspirin use were removed from the analysis (Table 30).

With respect to specific comparisons, all differences that were statistically significant between celecoxib and the pooled NSAIDs were also significant for celecoxib versus ibuprofen. Consistent with the six-month analysis, the differences between celecoxib and diclofenac were not statistically significant for any of the endpoints. Again, it was argued that the absence of statistical significance may be a function of the larger proportion of patients withdrawing from the diclofenac group because of GI adverse events.

Table 33: Overall summary of log-rank p-values (CSUGIEs and CSUGIES/GDU-ITT)[1]

Endpoint (Traditional Definition)	Celecoxib vs.		
	NSAIDs	Diclofenac	Ibuprofen
CSUGIE-First 6 months			
Censored	0.092	0.264	0.073
Uncensored	0.112	0.445	0.053
CSUGIE-First 6 months without ASA			
Censored	0.037	0.476	0.005
Uncensored	0.047	0.651	0.005
CSUGIE-Entire study			
Censored	0.450	0.640	0.414
Uncensored	0.474	0.752	0.372
CSUGIE-Entire Study without ASA			
Censored	0.185	0.972	0.037
Uncensored	0.204	0.870	0.033
CSUGIE/GDU-First 6 months			
Censored	0.023	0.308	0.005
Uncensored	0.026	0.421	0.004
CSUGIE/GDU-First 6 months without ASA			
Censored	0.017	0.760	<0.001
Uncensored	0.019	0.872	<0.001
CSUGIE/GDU-Entire Study			
Censored	0.040	0.296	0.017
Uncensored	0.045	0.349	0.016
CSUGIE/GDU-Entire Study without ASA			
Censored	0.020	0.992	<0.001
Uncensored	0.022	0.907	<0.001

1. From sNDA 20-998 (S-009) review tables 7, 8, 10, 11, 13, 14, 26, 27, 28, 30, 31 & 32.

Reviewer's comment: These results tend to emphasize that celecoxib was not able to demonstrate it was statistically superior to diclofenac in terms of the clinically important UGI endpoints and conditions as defined in this study. The same is not true when comparisons are made to ibuprofen.

Arthritis Efficacy and QOL:

Patient global

The patient's global assessment of arthritis was based on a scale of 1 (very good) to 5 (very poor) and was assessed at baseline, weeks 4,13, 26, 39, and 52, and the final visit. The observed mean scores (not shown, Table T31.1, p. 329, N49-00-06-035-102) were nearly identical for the celecoxib, diclofenac, and ibuprofen treatment groups at baseline (ranging from 2.9 to 3.0). Maximal efficacy was evident at the first post-baseline assessment for all treatment groups, with mean scores decreasing to 2.6 or 2.7. The degree of arthritis efficacy was identical at week 26 and the final visit within all treatment groups. At these time points, the mean score for celecoxib fell from 3.0 to 2.7. Similarly, the mean score for diclofenac decreased from 3.0 to 2.6, while the mean score for ibuprofen fell from 2.9 to 2.8. As seen in **Table 34**, based on analysis of least square means, there were generally no differences among the three treatment groups with respect to changes from baseline. Although not compared statistically, least square mean analysis also indicated no differences among post-baseline scores within any of the three treatment groups, suggesting that the maximal efficacy achieved was maintained through the end of the study.

Also noted in Table 34, the percentages of patients who reported an improvement, worsening, or no change were similar between the celecoxib and diclofenac treatment groups at week 26 and the final visit. However, comparison of confidence intervals indicated differences between the celecoxib and ibuprofen treatment groups. At week 26, the percentage of celecoxib patients who reported an improvement in arthritis status was higher than that for ibuprofen patients. In addition, the percentage of celecoxib patients who reported a worsening in arthritis status was lower than for ibuprofen patients. At the final visit, the percentage of patients who reported an improvement in arthritis status was higher for the celecoxib group than for the ibuprofen group. These results suggest that celecoxib was comparable to diclofenac and ibuprofen (at the doses studied in these trials) in treating the signs and symptoms of OA and RA, as measured by the patient's global assessment of arthritis; no inferences regarding superiority or equivalence can be drawn.

Table 34: Summary of Patient's Global Assessment Results[2]

	Celecoxib (n=3987)	**Diclofenac (n=1996)**	**Ibuprofen (n=1985)**
Mean (95% CI)[1]			
Baseline	2.96 (2.93-2.98)	2.95 (2.91-2.99)	2.96 (2.92-3.00)
Week 26	2.68 (2.65-2.71)	2.71 (2.67-2.76)	2.73 (2.68-2.78)
Final	2.71 (2.68-2.74)	2.72 (2.67-2.77)	2.76 (2.71-2.81)
Categorical analysis, % (95% CI)			
Week 26			
Improved[3]	38 (37-40)	40 (38-42)	32 (30-34)
No Change	46 (45-48)	43 (41-45)	48 (46-50)
Worsened	16 (15-17)	17 (15-18)	20 (18-21)
Final			
Improved	37 (35-38)	40 (38-43)	31 (29-33)
No Change	46 (44-47)	42 (40-44)	48 (46-50)
Worsened	18 (16-19)	18 (16-19)	21 (19-23)

1. Means are least square means. Decreases represent improvements. Global scale ranged from 1 (very good) to 5 (very poor).
2. From Table 9a (p. 169); T31.2 (p 330); T31.3 (p. 331), N49-00-06-035-102. All results based on LOCF approach.
3. Improved or worsened is defined as a reduction or increase, respectively, of at least one grade from baseline.

Patient's Assessment of Arthritis Pain-VAS:

The patient's assessment of arthritis pain was assessed on a visual analog scale from 0 mm (no pain) to 100 mm (most severe pain) and was evaluated at baseline, weeks 4, 13, 26, 39, and 52, and the final visit. Although not shown (Table T32.1, p. 332, N49-00-06-035-102) observed mean scores showed improvements in arthritis pain relative to baseline at all post-baseline time points in each treatment group. Decreases in pain scores ranged from 6.5 to 12.9 mm. Comparable improvements in arthritis status were observed between the celecoxib and diclofenac groups at week 26 (decreases of 8.3 mm and 10.1 mm, respectively) and the final visit (decreases of 7.2 mm and 9.5 mm, respectively). Compared with ibuprofen, celecoxib appeared to provide pain relief at both week 26 (decrease of 8.3 mm-celecoxib versus 3.9 mm-ibuprofen) and the final visit (decrease of 7.2 mm -celecoxib versus 3.1 mm-ibuprofen).

Although not compared statistically, least square mean analysis indicated similar changes from baseline among the three treatment groups, based on comparison of confidence intervals. Results at week 26 and the final visit are shown in **Table 35.** While post-baseline least square mean values for each treatment group increased over the course of the study, overlapping of confidence intervals within groups suggested that the efficacy of each treatment was constant during the study. These results suggest that celecoxib was comparable to diclofenac and ibuprofen (at the doses studied in these trials) in treating the signs and symptoms of OA and RA, as measured by the patient's assessment of arthritis pain; no inferences regarding superiority or equivalence can be drawn.

Table 35: Patient's Assessment of Arthritis Pain - VAS

	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Mean (95% CI)			
Baseline	50.7 (49.9-51.6)	50.8 (49.6-52.1)	50.6 (49.3-51.9)
Week 26	42.9 (42.0-43.7)	43.4 (42.0-44.8)	45.0 (43.6-46.4)
Final	44.0 (43.1-44.9)	44.2 (42.7-45.6)	45.9 (44.5-47.4)

1. Means are least square means. Decreases represent improvements.
2. From Table 9b (p. 170), N49-00-06-035-102.

Reviewer's comment: While these protocols were not primarily intended to address effectiveness, it is disappointing that celecoxib at four times and twice the upper recommended dose for OA and RA, respectively, appeared to offer no substantial therapeutic gains.

QOL Results:

Quality of Life measures were performed in protocol N49-98-02-035 only, and consisted of the Health Assessment Questionnaire (HAQ) and the SF-36 Health Survey. Both the HAQ and the SF-36 Health Survey were conducted at Baseline, Week 26, and the Final Visit.

As summarized in **Table 36**, observed mean HAQ scores were identical for patients in the celecoxib and ibuprofen treatment groups at Baseline (0.9 on the scale of 0 to 3). Celecoxib-treated patients reported slightly less disability at Week 26 (0.8 versus 0.9 for ibuprofen) and the same degree of disability at the Final Visit (0.9 in both groups). Although statistical comparisons were

not done, least square mean analysis indicated that the treatments were similar and were maintained through the final visit.

Table 36: HAQ-Observed Means, Least Square Means and 95% Confidence Intervals[1]

	Celecoxib (N= 1990)	Ibuprofen (N= 1985)
Baseline		
N	1986	1981
Mean (SD)	0.9 (0.62)	0.9 (0.6
LS Mean and 95% CI	0.93 (0.90-0.96)	0.92 (0.89-0.95)
Week 26		
N	1990	1985
Mean (SD)	0.8 (0.65)	0.9 (0.65)
LS Mean and 95% CI	0.85 (0.83-0.87)	0.88 (0.86-0.90)
Final		
N	1990	1985
Mean (SD)	0.9 (0.66)	0.9 (0.66)
LS Mean and 95% CI	0.86 (0.84-0.88)	0.89 (0.87-0.91)

1. Based on LOCF data. HAQ scores range from 0-3 with lower scores indicating less disability. From Table T33 (p. 334), N49-00-06-035-102.
2. From analysis of covariance with treatment and center as factors and baseline (for visit other than baseline) value as covariate.

Results of selected SF-36 Health Survey at baseline, week 26, and the final visit are summarized in **Table 37**. In the celecoxib group, improvements relative to baseline were observed at week 26 and the final visit in three SF-36 domains: bodily pain, physical function, and role-physical. In the vitality domain, celecoxib also produced an improvement compared to baseline at week 26 only. In the ibuprofen group, improvements relative to baseline at week 26 and the final visit were observed in only one domain, bodily pain. Although statistical comparisons were not done between celecoxib than ibuprofen, the confidence intervals suggested that the treatments were similar in the effect of treatment.

Table 37: Summary of Results in Selected SF-36 Health Survey Domains[1]

SF-36 Health Survey Domain	Celecoxib (n=1990)	Ibuprofen (n=1985)
Bodily Pain		
Baseline	39.5 (38.6-40.4)	39.9 (39.0-40.8)
Week 26	46.0 (45.1-46.9)	44.8 (43.9-45.8)
Final	45.9 (45.0-46.9)	44.7 (43.8-45.7)
Physical Function		
Baseline	48.3 (47.1-49.5)	48.6 (47.4-49.9)
Week 26	51.4 (50.5-52.3)	50.4 (49.4-51.3)
Final	50.8 (49.9-51.7)	50.1 (49.2-51.0)
Vitality		
Baseline	45.4 (44.3-46.4)	46.1 (45.0-47.1)
Week 26	47.6 (46.7-48.4)	46.9 (46.0-47.7)
Final	47.0 (46.1-47.8)	46.3 (45.5-47.1)
Role-Physical		
Baseline	37.9 (35.9-39.8)	38.4 (36.4-40.3)
Week 26	42.6 (40.8-44.4)	41.0 (39.2-42.8)
Final	42.1 (40.4-43.9)	41.0 (39.2-42.8)

1. From Table 9c (p. 171), N49-00-06-035-102. All values are least square means (95% confidence intervals). Scales range from 0-100 with lower scores as worse.

Patient Satisfaction Questionnaire:

The patient satisfaction questionnaire (administered at the final visit) evaluated patient satisfaction in the following four domains: satisfaction with pain relief, improvement with walking and bending, stomach discomfort or problems, and overall performance of study medication. Observed mean scores (data not shown, Table T35, p. 343, N49-00-06-035_102) were generally similar among the three treatment groups. For the three measures in which higher scores indicated greater satisfaction, the scores for ibuprofen were lower than for celecoxib and diclofenac; however, comparison of confidence intervals did not suggest a difference. For stomach discomfort or problems, celecoxib and ibuprofen were similar, while diclofenac patients indicated more dissatisfaction. Again, the confidence intervals did not confirm the difference.

SODA Results:

The Severity of Dyspepsia Assessment (SODA) was administered only in protocol N49-98-02-102 and consisted of three domains (Pain Intensity, Non-Pain Symptoms, and Satisfaction). The SODA was administered at baseline, weeks 4, 13, 26, and 52 or the final visit. At baseline (Table 9d, p.172, N49-00-06-035_102), there were no statistically significant differences in observed mean scores between the celecoxib and diclofenac treatment groups in any of the three SODA domains ($p \geq 0.204$). With respect to pain intensity and satisfaction, all observed mean changes from baseline associated with diclofenac were statistically significantly higher (i.e., worse) than those associated with celecoxib ($p < 0.001$). With respect to non-pain symptoms, diclofenac produced a statistically significantly higher mean change relative to baseline than celecoxib only at week 4 ($p = 0.005$).

Withdrawal Due to Lack of Arthritis Efficacy:

Times to and incidences of withdrawal due to lack of arthritis efficacy (Table T37.1-.2, p.350-1, N49-00-06-035_102) revealed a total of 1456 patients withdrew due to treatment failure (number of patients, ITT):

- Celecoxib (n=3987) - 691 (17%)
- Diclofenac (n=1996)- 309 (15%)
- Ibuprofen (n=1985) - 456 (23%)

Based on this comparison, the withdrawal incidences of the celecoxib and diclofenac treatment groups were similar. However, ibuprofen was associated with a higher incidence of withdrawal than either celecoxib or diclofenac. The percentages of celecoxib and diclofenac patients who withdrew from the study due to lack of arthritis efficacy were generally similar over time: the ibuprofen group had a slightly higher withdrawal than that for either the celecoxib or diclofenac group. When withdrawals due to lack of arthritis efficacy or adverse events (see Table 40) were combined, a total of 3362 patients withdrew for one of these two reasons as follows:

- 1596 (40%) in the celecoxib group
- 849 (43%) in the diclofenac group
- 917 (46%) in the ibuprofen group

As before, celecoxib and diclofenac were similar, but the incidence was higher for ibuprofen than for celecoxib.

Overview of Safety (Section 10):

Deaths (Section 10.1.1):

A total of 36 deaths (Appendix 2.9.1, p. 3918; N49-00-06-035-102) occurred during the study or during post-study follow-up: 19 in the celecoxib group, 9 in the diclofenac group, and 8 in the ibuprofen group. Not expectedly in the population studied, the majority of deaths (25 of 36, 69%) occurred in elderly patients (65 years old or older). **Most deaths were cardiovascular** in nature. Of note, **none of the deaths resulted from a GI or liver-related cause.**

In all cases except one, the principle investigator and the sponsor's safety monitor believed that the death had no relationship to study medication. The exception was a case in which the cause of death was cardiopulmonary arrest/hypertension, and the investigator attributed the relationship to study medication as uncertain (patient US0383-102-12691; DER no. 990629-CL696). In this case, the date of the patient's last dose could not be determined, but the death was believed to have occurred more than 28 days after the patient discontinued taking study medication.

Noted below (**Table 38**) is a summary of the 16 deaths that occurred either during or within 28 days of participation in the entire study.

Table 38: Summary of Deaths-Entire Study or within 28 days of Treatment[1]

Adverse Event[2]	**Celecoxib (n=3987)**	**Diclofenac (n=1996)**	**Ibuprofen (n=1985)**
Patient-years of Exposure[3]	2320	1080	1122
Myocardial infarction (MI)	3	-	1
Cardiac arrest	1	4	1
Accidental injury	1	-	-
Circulatory failure/MI	-	-	1
Sepsis	1	-	-
Carcinoma	1	-	-
Coronary artery disorder	-	1	-
Arrhythmia/MI	1	-	-
Total (No. per 100 pt-yr)	8 (0.34)	5 (0.46)	3 (0.27)

1. From Table 10.e (p 182); N49-00-06-035-102.
2. For cases in with no adverse event term , the event was classified by the cause of death listed in the end-of-study CRF.
3. Rounded estimates of pt.-yr exposures (p. 174, N49-00-06-035-102).

Reviewer's comment: Of the deaths noted above, there were 5 (0.22), 4 (0.46) and 3 (0.27) deaths that appear to be attributable to cardiovascular causes for celecoxib, diclofenac and ibuprofen, respectively. Numbers in () are calculations based on the rounded estimates of patient exposure as noted in the table above.

Noted below (**Table 39**) is a summary of the 20 deaths that occurred 28 days or more after participation in the study.

Table 39: Summary of Deaths Occurring more than 28 days after Treatment[1]

Adverse Event[2]	**Celecoxib (n=3987)**	**Diclofenac (n=1996)**	**Ibuprofen (n=1985)**
Myocardial infarction (MI)	2	-	1
Cardiac arrest	1	1	-
Cardiac arrest/tamponade	1	-	-
Pulmonary fibrosis/pneumonia/carcinoma	2	2	1
Accidental injury	-	-	1
Sepsis	1	-	-
Carcinoma	1	-	-
Coronary artery disorder	1	-	1
Aneurysm/subarachnoid hemorrhage	-	1	-
Cerebrovascular disorder	1	-	-
Cardiac failure	-	-	1
Cardiopulmonary arrest/hypertension	1	-	-
Total (No. per 100 pt-yr)[1]	11 (0.47)	4 (0.37)	5 (0.45)

1. From Table 10.f (p 183); N49-00-06-035-102. Pt-years as noted in Table 38.
2. For cases in with no adverse event term , the event was classified by the cause of death listed in the end-of-study CRF.

Reviewer's comment: The table below summarizes results after review of the deaths noted above. Overall, most of the deaths were cardiovascular in origin, with the exclusion of 2 cases of CHF. Where it was unclear in the CRF when study drug was stopped, these cases have been included as occurring < 28 days after trial; hence the difference with the Sponsor. It is unclear whether any of these cardiovascular deaths are directly related to the treatment. Given the relatively few deaths, no large excess mortality (total or cardiac, with or without ASA) is consistently evident for celecoxib as compared to controls.

	Celecoxib (n=3987/882/3105)[1] (pt-yrs: 2320/517/1803)	**Diclofenac (n=1996/445/1551) (pt-yrs: 1081/239/841)**	**Ibuprofen (n=1985/412/1573) (pt-yrs: 1122/249/874)**
Deaths-all causes	19 (.82)	9 (.83)	8 (.71)
ASA users	6 (1.2)	1 (.4)	4 (1.6)
Non-ASA users	13 (0.7)	8 (1.0)	4 (0.5)
Deaths-cardiac (entire study)	11 (0.5)	5 (.46)	5 (0.4)
ASA users	5 (1.0)	0	3 (1.2)
Non-ASA users	6 (0.3)	5 (.63)	2 (0.2)
Deaths-cardiac (during or <28 day after trial)	**10 (.43): 5 (0.2)[2]**	**5 (.46): 4 (0.4)**	3 (.27)
ASA users	**5 (1.0): 2 (0.4)**	0	2 (.8)
Non-ASA users	**5 (.27): 3 (0.2)**	**5 (.63): 4 (0.5)**	1 (.11)

1. n = number of patients in entire group/ASA users/ASA non-users, respectively. Pt-yrs (estimates) are in same order.
2. Numbers in () are rate/100 patient years. Numbers following : and underlined are per Sponsor.

Adverse Events Causing Withdrawal:

The most common adverse events causing withdrawal >1% in any treatment group) are shown in **Table 40**. The overall incidence of withdrawal (also see Table 3) due to an adverse event was statistically significantly lower for celecoxib than for diclofenac. Six of the 10 most common events were related to the GI system, five of which represented the most common GI adverse events described above: **abdominal pain, dyspepsia, nausea, diarrhea, and flatulence**. Three of the events (SGOT/SGPT increased, and hepatic function abnormal) were related to elevations in liver function test results; these events led to noteworthy incidences of withdrawals in the diclofenac group. The differences between celecoxib and diclofenac for three of the GI events (abdominal pain, nausea, and diarrhea) and the three hepatic events were statistically significant in favor of celecoxib. Rash led to withdrawal in more than 1% of patients in the celecoxib and ibuprofen groups with statistically significant differences between celecoxib and both ibuprofen and diclofenac.

Table 40: Adverse Events Causing Withdrawal (Incidence >1%) in Any Treatment Group-Entire Study

Adverse Event	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Any event (% of patients)	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***
SGOT increased	0.1	**2.1***	0.1
SGPT increased	0.1	**2.3***	0.1
Hepatic function abnormal	<0.1	**1.1***	<0.1

* p<0.05 vs. celecoxib. From Table 10d (p. 180), N49-00-06-035-102.

As noted in Table T42.4 (p. 498, N49-00-06-035-102, data not shown), the incidences of adverse events leading to withdrawal in the first six months of the study were in most cases identical to, or slightly below, those in the entire study period. This suggests that **almost all patients withdrawing due to adverse events did so within six months of beginning the study**.

Other Serious Adverse Events:

A total of 500 patients experienced **serious adverse events (SAE)** during or 28 days after study participation:

- 270 patients in the celecoxib group
- 111 patients in the diclofenac group
- 119 patients in the ibuprofen group

The most common SAEs are summarized in **Table 41**. As can be seen, the difference between any two treatment groups was no more than 0.6 per 100 patient-years. The highest rate seen 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. Although the results are similar to those shown for general adverse events, the patterns suggested by the general adverse events were not replicated exactly in the serious adverse events. This difference in pattern may reflect the fact that there were smaller numbers of serious events than general adverse events.

Table 41: Summary of Serious Adverse Events-Entire Study Period[1]

Adverse Event	Celecoxib (n=3987) 2320.4 pt-yrs	Diclofenac (n=1996) 1080.5 pt-yrs	Ibuprofen (n=1985) 1122.5 pt-yrs
Any serious event	270 (11.6)	111 (10.3)	119 (10.6)
Abdominal pain	6 (0.3)	6 (0.6)	2 (0.2)
Accidental fracture	10 (0.4)	4 (0.4)	9 (0.8)
Accidental injury	3 (0.1)	4 (0.4)	7 (0.6)
Angina pectoris	4 (0.2)	5 (0.5)	6 (0.5)
Atrial fibrillation	9 (0.4)	2 (0.2)	3 (0.3)
Back pain	15 (0.6)	3 (0.3)	9 (0.8)
Cardiac failure	9 (0.4)	2 (0.2)	9 (0.8)
Cellulitis	8 (0.3)	1 (<0.1)	1 (<0.1)
Cerebrovascular disorder	4 (0.2)	6 (0.6)	6 (0.5)
Chest pain	11 (0.5)	5 (0.5)	7 (0.6)
Coronary artery disorder	19 (0.8)	5 (0.5)	5 (0.4)
Deep thrombophlebitis	7 (0.3)	5 (0.5)	1 (<0.1)
GI hemorrhage	7 (0.3)	2 (0.2)	1 (<0.1)
Myocardial infarction	19 (0.8)	4 (0.4)	9 (0.8)
Pneumonia	14 (0.6)	5 (0.5)	5 (0.4)
Syncope	5 (0.2)	4 (0.4)	3 (0.3)
Unstable angina	8 (0.3)	4 (0.4)	0

1. From Table 10.g (p 184); N49-00-06-035-102. Owing primarily to the unequal randomization, results are displayed as normalized for length of exposure, rather than crude incidence rates. Table includes any event experienced by a total of at least 10 patients across the three treatment groups.

Reviewer's comment: Generally, these normalized incidences do not seem to suggest any important differences or obvious trends of specific target organ or organ-system involvement by any treatment group.

Other safety findings (Section 10.2):

ADR incidence (Section 10.2.1):

A total of 6493 patients reported at least one adverse event during study participation:

- 3260 (81.8%) in the celecoxib group
- 1654 (82.9%) in the diclofenac group
- 1579 (79.5%) in the ibuprofen group.

The most common adverse events occurring in any treatment group are shown in **Table 42**. The majority of the common adverse events were gastrointestinal or upper respiratory in nature. The **most common event in any treatment group was dyspepsia, followed by upper respiratory**

tract infection, headache, and abdominal pain. Of the GI adverse events shown in Table 42 (dyspepsia, abdominal pain, diarrhea, nausea, flatulence, vomiting, constipation), all but one event (vomiting) were statistically significant in favor of celecoxib vs. diclofenac. Adverse events relating to liver function tests (SGOT or SGPT increases) were also statistically significantly lower for celecoxib than for diclofenac

Other comparisons of note, peripheral edema, hypertension, and anemia were statistically significantly less common for celecoxib than for ibuprofen whereas the incidence of rash was statistically significantly higher for celecoxib than for either diclofenac or ibuprofen.

The incidences of the most common respiratory adverse events were similar among the three treatment groups. Symptoms suggest typical seasonal allergies and minor upper respiratory infections. The incidence of bronchitis was significantly higher for ibuprofen.

Table 42: Adverse Events with Incidence ³3%- 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 (% of patients)	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***
SGPT increased	1.0	**5.1***	1.2
SGOT increased	0.9	**4.3***	1.0

* $p<0.05$ vs. celecoxib. From Table 10.b (p 177) and Table T41.1 (p. 357), N49-00-06-035-102.

The majority of adverse events occurred during the first six months (182 days) of treatment (Table T41.4, p. 415; N49-00-06-035-102). In fact (Appendix 2.8.4, p. 3832; N49-00-06-035-102), the large majority of events occurred within the first 90 days. During the first 6 months,

events were reported for 3023 (75.8%) patients in the celecoxib group, 1564 (78.3%) in the diclofenac group, and 1488 (75.0%) in the ibuprofen group. Although the incidences of almost all events were slightly lower during the first six months than during the entire study period, the differences among the treatment groups were similar in magnitude to those in Table 42, particularly with respect to the GI system. The statistical comparisons were similarly maintained, despite the lower numbers of events. All of the statistically significant differences shown in Table 42 were also statistically significant within the first six months, with two exceptions (tooth disorder between celecoxib and ibuprofen, and urinary tract infection between celecoxib and diclofenac). Conversely, certain differences that were not shown to be statistically significant in Table 42 were significant at six months. The incidence of anemia between celecoxib and diclofenac (2.0% vs. 3.2%, respectively; p=0.009) and the incidence of BUN increased between celecoxib and diclofenac (0.7% vs. 1.6%, respectively; p=0.004) being examples.

Events that occurred with incidences above 2% in intervals after the first 90 days are summarized in **Table 43**. As discussed above, these events generally were similar to those occurring most commonly during the entire study. The declining incidences of most events over time could reflect adaptation as well as the withdrawal of susceptible patients. However, there are exceptions to this trend such as anemia or upper respiratory infections; the latter may reflect the background incidence of these common events. Of note, the incidences of events for diclofenac in the last interval may well be influenced by the fact that protocol 102 was not extended to 15 months. The 64 patients remaining after Day 360 were only in the study for a maximum of two additional weeks; the longest treatment duration in this group was 374 days (Table T2.4.1, p. 357; N49-00-06-035-102). Therefore, there was a decreased possibility for adverse events in this period, but when an event did occur, it caused a high incidence owing to the low sample size.

Table 43: Adverse Events with ³ 2% Incidence in Any Interval After the First 90 days[1]

Adverse Event	**91-180 Days**			**181-270 Days**			**271-360 Days**			**361-450 Days**		
No. who entered interval												
Celecoxib (C) 400 mg BID	2836			2343			2028			585		
Diclofenac (D) 75 mg BID	1394			1127			977			64		
Ibuprofen (I) 800 mg TID	1297			1045			894			479		
	C	D	I	C	D	I	C	D	I	C	D	I
Dyspepsia	3.1	3.4	3.8	2.6	2.6	2.8	1.7	1.5	2.0	0.4	-	0.5
Headache	3.1	3.0	2.9	2.0	2.1	2.0	0.9	0.9	0.9	0.4	-	0.5
Upper respiratory. tract infection	2.8	3.1	4.7	2.4	3.7	2.8	4.2	3.5	3.0	3.1	3.8	2.5
Abdominal pain	2.7	5.2	3.0	2.2	2.2	2.2	1.3	1.7	1.4	1.1	-	0.7
Sinusitis	2.4	1.5	2.3	1.9	2.8	1.7	1.4	0.8	2.0	0.8	-	2.2
Diarrhea	2.3	3.7	1.7	1.5	1.8	1.8	1.3	1.1	1.2	1.0	-	0.2
Nausea	1.9	2.9	1.6	1.6	1.8	1.8	0.8	0.4	1.2	0.4	-	0.2
Flatulence	1.6	2.2	1.7	0.9	1.8	0.8	0.6	1.0	0.6	-	-	-
Anemia	1.3	2.3	3.4	1.4	1.7	2.2	2.7	2.7	3.5	2.0	1.7	2.8
SGOT increased	0.2	2.1	0.2	0.4	1.1	0.3	0.2	1.1	0.7	0.9	-	0.4
SGPT increased	0.2	2.1	0.3	0.3	1.3	0.3	0.3	1.2	0.8	0.7	-	0.8

1. From Table 10.c (p 179) and Appendix 2.8.4 (p. 3832), N49-00-06-035-102.

The majority of events were mild to moderate in severity (Appendix 2.8.1, p. 3627; N49-00-06-035-102). The **overall incidences of severe adverse events** were similar among the three treatment groups:

- 16.3% for celecoxib
- 18.1% for diclofenac
- 17.6% for ibuprofen.

Clinical Laboratory Evaluation (Section 10.2.2):

Table 44 summarizes the mean changes from baseline to the final visit for each standard laboratory test performed during the study. Although in most cases the change at the final visit does not represent the greatest change in laboratory values during the study, it includes the largest numbers of patients. Patients with at least one post-baseline laboratory result, including patients withdrawn owing to an abnormal result, are included in the final visit values.

Table 44: Mean Changes from Baseline to Final Visit in Laboratory Values[1]

Laboratory Test	Celecoxib	Diclofenac	Ibuprofen
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)

1. From Table 10.h (p 187); N49-00-06-035-102. All numbers are mean (SE) from baseline. (*) =$p<0.05$ vs. celecoxib.

Reviewer's Comment: Many differences among groups were statistically significant, owing to the large numbers of patients in each group. However, it is unclear if these differences were clinically meaningful; the LFT abnormalities associated with diclofenac may be the remarkable exception.

For most laboratory tests, incidences of extreme laboratory values (according to the predefined criteria) occurred in very few patients at any time. Those for which at least 20 patients across the three treatment groups had an extreme value are summarized in **Table 45**. The percentages of patients with extreme hemoglobin or hematocrit values were higher in the NSAID groups than for celecoxib. This data appears consistent with the adverse event (anemia) and mean laboratory data

noted previously. Two of the differences between celecoxib and diclofenac were statistically significant while the difference in minimum value between celecoxib and ibuprofen (hemoglobin) approached but did not achieve statistical significance (p=0.053).

Other differences of note were the incidences of extreme ALT and AST values. Although only the ALT results are shown in Table 45, differences in both of these tests (AST data, Table 45.1, p. 541; N49-00-06-035-102.) were statistically significant between celecoxib and diclofenac for both the final visit as well as for the maximum value measured during the study. Analysis of laboratory shift data (Appendix 2.12, p. 4214; N49-00-06-035-102) and scatter-plots (Appendix 2.13, p. 4230; N49-00-06-035-102) for the liver function tests (ALT and AST) also show that a higher proportion of patients in the diclofenac group experienced elevations at the final visit.

No difference was seen among the treatment groups in extreme high bicarbonate values (above 35 mmol/L), with incidences ranging from 0.2 to 0.4 in the three groups. Only one celecoxib patient and two diclofenac patients experienced extreme low bicarbonate values (below 15 mmol/L) at any time during the study. The only statistically significant difference in extreme laboratory values not shown in Table 45 was that between celecoxib and ibuprofen in potassium levels: 0.3% of celecoxib patients and 0.0% of ibuprofen patients had a maximum value above 6.0 mmol/L (p=0.021). Any trends for other laboratory data suggested in the means and extremes, and the differences among the groups, were not sufficiently robust to be detected by visual examination of these shift tables or the scatter-plots.

Table 45: Analysis of Extreme Laboratory Test Values: Entire Study Period[1]

Laboratory Test	Celecoxib	Diclofenac	Ibuprofen
Low			
Hemoglobin[2]			
Final visit	9/3708 (0.2)	9/1851 (0.5)	7/1805 (0.4)
Minimum value	12/3708 (0.3)	17/1851 (0.9) *	13/1805 (0.7)
Hematocrit[2]			
Minimum value	5/3701 (0.1)	12/1849 (0.6) *	6/1802 (0.3)
High			
ALT (SGPT) (>200 U/L)			
Final visit	2/3692 (<0.1)	22/1848 (1.2) *	0/1785 (0)
Maximum value	4/3692 (0.1)	29/1848 (1.6) *	1/1785 (<0.1)
Creatine kinase (>300 U/L)			
Final visit	67/3667 (1.8)	33/1840 (1.8)	27/1758 (1.5)
Maximum value	184/3667 (5.0)	83/1840 (4.5)	85/1758 (4.8)
BUN (>14.3 mmol/L)			
Final visit	17/3692 (0.5)	8/1849 (0.4)	12/1786 (0.7)
Maximum value	31/3692 (0.8)	20/1849 (1.1)	16/1786 (0.9)
Bicarbonate (>35 mmol/L)			
Maximum value	13/3689 (0.4)	7/1844 (0.4)	3/1782 (0.2)

1. From Table 10.j (p 189); N49-00-06-035-102. Data are expressed as No./total and percentage of patients. Includes all tests for which at least 20 patients had an extreme value. (*) =p<0.05 vs. celecoxib.
2. Hemoglobin-below 6.0 g/dL or 3.0 g/dL decrease from baseline. Hematocrit - below 0.25 or 0.10 decrease from baseline.

Contingency table analyses:

Contingency table analyses of patients whose post-treatment laboratory results met certain predefined criteria for combinations of values or changes in values included the following:

- Decreases in both hemoglobin and hematocrit
- Increases in both creatinine and BUN
- Increases in both AST and ALT
- Increases in both alkaline phosphatase and total bilirubin
- Increases in both ALT and alkaline phosphatase
- Increases in both ALT and total bilirubin.

Table 46 summarizes the results in those patients who experienced an extreme decrease in either hematocrit or hemoglobin at any time during the study. The results show that in all analyses, proportions of diclofenac or ibuprofen patients who had the specified decreases in hematocrit and/or hemoglobin were two- to three-fold higher than in patients receiving celecoxib. Here, the addition of aspirin increased the incidence rate in all treatment groups, but appeared to preserve the differences among the groups.

Table 46: Summary of Hemoglobin/Hematocrit Contingency Tables: Entire Study Period[1]

Patients with hemoglobin decrease >2 g/dL and/or hematocrit decrease ³0.10	**Celecoxib**	**Diclofenac**	**Ibuprofen**
All patients	87/3701 (2.4)[2]	82/1849 (4.4)	102/1802 (5.7)
Excluding CSUGIEs	83/3682 (2.3)[2]	81/1840 (4.4)	95/1792 (5.3)
Excluding CSUGIEs/ulcers	82/3659 (2.2)	78/1824 (4.3)	93/1768 (5.3)
Excluding all adjudicated potential CSUGIEs	73/3545 (2.1)	68/1753 (3.9)	81/1693 (4.8)
Excluding all reported potential CSUGIEs	41/3068 (1.3)	41/1490 (2.8)	42/1364 (3.1)
OA patients	63/2675 (2.4)[2]	48/1340 (3.6)	74/1299 (5.7)
RA patients	24/1026 (2.3)[2]	34/509 (6.7)	28/503 (5.6)
Patients not taking aspirin	53/2864 (1.9)[2]	53/1428 (3.7)	73/1414 (5.2)
Patients taking aspirin	34/837 (4.1)[2]	29/421 (6.9)	29/388 (7.5)

1. From Table 10.l (p 192); N49-00-06-035-102. Data are expressed as No./ total and percentage of patients.
2. p≤0.05 versus both other treatments by Fischer's Exact Test. Figures 10a-c, p 203-4; N49-00-06-035-102).

Table 47 summarizes the results of the hepatobiliary and renal laboratory contingency analyses. As with the hematocrit and hemoglobin analyses above, this table includes all patients who experienced either extreme laboratory value at any point during the study. The results are consistent with those reported above in adverse events and extreme laboratory values. Elevations in renal function tests were somewhat more frequent in the diclofenac group than in the celecoxib or ibuprofen group, and elevation in liver function tests were strikingly more frequent for diclofenac.

Table 47: Summary of Hepatobiliary and Renal Contingency Tables: Entire Study[1]

	Celecoxib	Diclofenac	Ibuprofen
Creatinine ≥159 µmol/L and/or BUN ≥14.3 mmol/L	47/3702 (1.3)[2]	39/1852 (2.1)	26/1807 (1.4)
AST and/or ALT ≥3xULN	14/3702 (0.4)	68/1851 (3.7)	13/1806 (0.7)
Alkaline phosphatase ≥3xULN and/or bilirubin ≥1.8xULN	4/3696 (0.1)	3/1851 (0.2)	0/1800 (0.0)
ALT and/or alkaline Phosphatase ≥3xULN	13/3696 (0.4)	62/1851 (3.3)	11/1800 (0.6)
ALT ≥3xULN and/or bilirubin ≥ 1.8xULN	15/3701 (0.4)	63/1851 (3.4)	11/1806 (0.6)

1. From Table 10.m (p 193); N49-00-06-035-102. Data are expressed as No./ total and percentage of patients.
2. p≤0.05 versus diclofenac by Fischer's Exact Test. Figure 10.d, p. 202:); N49-00-06-035-102.

Vital Signs and Physical Examination Results:

Group mean changes from baseline in blood pressure, pulse, and weight disclosed no obvious treatment effects, patterns or differences of clinical relevance among the groups. The only statistically significant difference was the change from baseline in weight in the subgroup of male patients with baseline weight above 90 kg: weight in the celecoxib group increased by 0.53 kg, while that for diclofenac decreased by 1.11 kg ($p<0.001$). The clinical significance of this finding is unknown.

Special studies-review of systems (Section 10.2.3):

Gastrointestinal Effects

The GI tolerability profiles of the three treatment groups in the study are summarized for these events by time interval (Table 48) or aspirin status (Table 49).

Table 48 demonstrates that the results at six months were quite similar to those for the entire study period. For the common GI adverse events, six-month incidences were all within 2% of the overall incidences; this was also true for withdrawals due to GI adverse events. In these GI adverse event measures, celecoxib appeared to be better tolerated than diclofenac and was generally similar to ibuprofen in tolerability. Most of these common GI adverse events were statistically significantly more frequent for diclofenac than for celecoxib. Statistically significant differences were seen between celecoxib and ibuprofen in only two types of events, one in favor of celecoxib (constipation) and one in favor of ibuprofen (diarrhea).

Table 48: Summary of GI Adverse Events by Time Interval[1]

Adverse Event	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Entire Treatment Period			
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**
First Six Months			
Any GI event	**40.3**	**49.9 ***	**40.5**
Dyspepsia	14.4	17.7 *	14.4
Abdominal pain	9.7	16.7 *	9.5
Diarrhea	9.4	13.6 *	6.0 *
Nausea	6.9	11.0 *	7.6
Flatulence	6.6	10.1 *	6.5
Tooth disorder	2.4	3.6 *	3.2
Vomiting	2.1	3.1*	2.3
Constipation	1.7	5.9 *	5.9 *
Any GI event causing withdrawal	**10.8**	**15.5 ***	**12.0**

1. From Table 10.n (p 196); N49-00-06-035-102. All numbers are percentages of patients. Includes any GI adverse event with incidence >3% in any treatment group. (*) =p<0.05 vs. celecoxib.

The incidence (data not shown) of diverticular disease (diverticulitis and diverticulosis) was lower for celecoxib than for ibuprofen. For these two events combined, the difference between the groups was 0.4% vs 1.0%. The difference was statistically significant for diverticulosis (0.2% vs. 0.6%; p=0.028).

The incidence 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 (**Table 49**). For the most part, the statistical relationships described above were maintained. Some variations (i.e. incidence of dyspepsia), however, could be seen in the analysis of patients taking aspirin. Several of the statistically significant differences between celecoxib and diclofenac did not retain significance in this analysis, most notably in overall incidence of a GI adverse event: 54.0% vs 59.1% (p=0.079). **In general, the use of aspirin appears to have increased incidences of GI adverse events across groups, and attenuated some of the differences between the treatment groups.**

As noted in Tables 48 and 49, there appears to be a difference in withdrawal rates from the treatment groups as a result of GI signs or symptoms. **Whether during the first six months or the entire study period, or whether patients were taking aspirin or not, significantly more patients withdrew from the diclofenac group than from the celecoxib group owing to GI adverse events.** The issue of differential dropouts for GI symptoms has been discussed under "Informative Censoring" above. Withdrawal due to a GI adverse event over the entire study period was 16.6% for diclofenac and 12.2% for celecoxib (p<0.001), and almost all of these withdrawals

took place in the first six months. For ibuprofen, GI withdrawals were numerically more frequent than for celecoxib, but the differences were not statistically significant.

Kaplan-Meier plots of cases (data not shown, Tables T55.1 through T55.4, p. 564-7; N49-00-06-035_102) of time to moderate/severe abdominal pain, dyspepsia, or nausea revealed that diclofenac was distinguished from celecoxib (for abdominal pain, nausea or all three) early during the study; this trend was maintained through the end of the study. In these three analyses, the differences between celecoxib and diclofenac were statistically significant ($p \leq 0.013$). However, no difference was found between celecoxib and diclofenac with regards to dyspepsia alone.

Table 49: Summary of GI Adverse Events by Aspirin Use-Entire Study[1]

Adverse Event	**Celecoxib (n=3987)**	**Diclofenac (n=1996)**	**Ibuprofen (n=1985)**
Patients not Taking Aspirin			
No. of patients	3105	1551	1573
Any GI event	**43.3**	**53.8 ***	**44.5**
Dyspepsia	15.6	19.5 *	15.6
Abdominal pain	10.9	17.3 *	10.7
Diarrhea	10.5	13.9 *	7.2 *
Nausea	8.0	11.6 *	8.5
Flatulence	7.1	10.8 *	7.5
Tooth disorder	2.3	4.1 *	3.9 *
Vomiting	2.4	3.4	3.0
Constipation	1.9	6.5 *	5.9 *
Any GI event causing withdrawal	**11.5**	**15.4 ***	**13.2**
Patients Taking Aspirin			
No. of patients	882	445	412
Any GI event	**54.0**	**59.1**	**52.7**
Dyspepsia	19.7	19.8	19.9
Abdominal pain	14.5	22.7 *	13.6
Diarrhea	12.1	18.6 *	8.3 *
Nausea	9.0	13.9 *	10.7
Flatulence	7.9	13.5 *	6.1
Tooth disorder	5.0	4.7	6.1
Vomiting	3.1	3.8	1.5
Constipation	3.3	7.9 *	9.0 *
Gastroenteritis	2.8	3.1	1.7
Gastroesophageal reflux	3.5	2.2	2.2
Hemoccult positivity	2.7	3.1	3.9
Any GI event causing withdrawal	**14.9**	**20.7 ***	**14.1**

1. From Table 10.o (p 197); N49-00-06-035-102. All numbers are percentages of patients. Includes any GI adverse event with incidence ≥3% in any treatment group. (*) =$p<0.05$ vs. celecoxib.

Renal Effects

Table 50 shows the incidences of selected renal adverse events occurring throughout the entire study period. In general, the incidences were low in all treatment groups, not suggesting any pronounced renal effects of any of these treatments. However, patients receiving ibuprofen experienced more edema and hypertension than celecoxib or diclofenac patients; these differences were statistically significant. Adverse events relating to increases in renal function laboratory values (BUN increased and NPN increased) were more frequent for diclofenac than for celecoxib. The differences were statistically significant when examined in the six-month analysis, but not over the entire treatment period.

Table 50: Selected Adverse Events Relating to Renal Function: Entire Study Period[1]

Adverse Event	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (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
NPN 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

1. From Table 10.q (p 201); N49-00-06-035-102. All numbers are percentages of patients. (*) =p<0.05 vs. celecoxib.

Reviewer's comment: For a more detailed analysis of the cardiovascular and renal effects of celecoxib and the comparator groups in this trial, the reader is referred to the review by Douglas Throckmorton, M.D.

Table 51 shows group mean changes and extreme changes in BUN and creatinine. Although the meaning is unclear, the results suggest an effect of diclofenac on mean creatinine values, and of celecoxib on BUN as compared to ibuprofen. Few patients experienced an extreme BUN value; the incidence appeared higher for ibuprofen than for the other two groups, but the difference was not statistically significant. When the extreme creatinine threshold of 265 µmol/L was used, only one patient in the entire study period experienced an extreme value. However, as noted above for the renal contingency tables, when the lower threshold of 159 µmol/L for creatinine with or without BUN changes was utilized, percent increases of 1.3 for celecoxib, 2.1 for diclofenac, and 1.4 for ibuprofen were noted. The difference between celecoxib and diclofenac was statistically significant.

Not shown in Table 51 was that between celecoxib and ibuprofen in elevated potassium levels: 0.3% of celecoxib patients and 0.0% of ibuprofen patients had a maximum potassium value above 6.0 mmol/L (p=0.021; Table 45.1,p. 535). Five of these 11 cases of extreme potassium levels in celecoxib patients were isolated increases that were bracketed by values within the normal range, and may be artifactual (i.e., due to hemolysis). One additional case was an isolated value drawn four days after discontinuation of study medication and is of uncertain clinical significance.

Table 51: Mean Changes from Baseline to Final Visit/Extreme Values in Specific Renal Laboratory Values[1]

Laboratory Test	Celecoxib	Diclofenac	Ibuprofen
Group Mean Changes from Baseline (Mean [SE])			
BUN, mmol/L	0.66 (0.027)	0.58 (0.041)	0.52 (0.039)[1]
Creatinine, µmol/L	0.8 (0.22)	2.4 (0.33)[1]	1.5 (0.33)
Incidence of Extreme Values (No./total [%])			
BUN (>14.3 mmol/L)			
Final visit	17/3692 (0.5)	8/1849 (0.4)	12/1786 (0.7)
Maximum value	31/3692 (0.8)	20/1849 (1.1)	16/1786 (0.9)
Creatinine (>265.2 µmol/L)			
Final visit	0/3692 (0.0)	0/1850 (0.0)	0/1786 (0.0)
Maximum value	1/3692 (<0.1)	0/1850 (0.0)	0/1786 (0.0)

1. From Table 10.r (p 202); N49-00-06-035-102. p<0.05 vs. celecoxib.

Vascular (Cardiac and Noncardiac) Effects

The incidences of cardiac and noncardiac vascular adverse events throughout the entire study period are shown in Table 52. The table shows that vascular events were rare in all treatment groups, and incidences were similar between celecoxib and the two NSAIDs. The only statistically significant difference in incidences was for cerebrovascular disorder between celecoxib (0.2%) and ibuprofen (0.5%).

Table 52: Incidences of Selected Cardiac/Noncardiac Vascular Adverse Events: Entire Study Period[1]

Adverse Event	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (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[1]
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

1. From Table 10.s (p 204); N49-00-06-035-102. Numbers are percentages. p<0.05 vs. celecoxib.

Reviewer's comment: There does not appear to be any clinically or statistically significant trend with celecoxib to suggest additional cardiovascular risks over the comparator drugs.

Incidences of the same group of adverse events are shown and statistically analyzed by aspirin status in **Table 53**. Patients in the two NSAID groups were pooled for this analysis. As might be expected, incidences of the cardiovascular-related events were higher in the patients taking aspirin, since these patients were more likely to have a significant cardiovascular medical history than the overall study population. The absence of statistical significance for any of the events suggest that the differences between celecoxib and NSAID were not markedly altered by the use of aspirin.

Table 53: Incidences of Selected Cardiac/Noncardiac Vascular Adverse Events with/without Aspirin Use: Entire Study[1]

	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

1. From Table 10.t (p 205); N49-00-06-035-102. Numbers are percentages. RD indicates risk reduction. None of the differences were statistically significant at $p<0.05$.

Table 54 (from Cardiorenal review, Doug Throckmorton, M.D.) shows selected cardiac adverse events reported during the trial according to aspirin use. For anginal disorders (especially the combined disorders), there seems to be a trend toward more events in those patients receiving celecoxib, regardless of aspirin use. However, for edema, there appears to be a trend toward more events in those patients receiving ibuprofen.

Table 54: Selected Cardiac Adverse Events Reported During CLASS According to ASA Use[a].

Adverse Event	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
ASA-Users	N=882	N=445	N=412
Edema			
Edema peripheral	35 (4.0%)	17 (3.8%)	**23 (5.6%)**
Edema (pooled reporting)[b]	38 (4.3%)	20 (4.5%)	**28 (6.8%)**
Angina			
Unstable Angina	8 (0.9%)	4 (0.9%)	1 (0.2%)
Angina Pectoris	13 (1.5%)	8 (1.8%)	6 (1.5%)
Coronary Artery Disorder	15 (1.7%)	3 (0.7%)	5 (1.2%)
Combined Anginal Disorders[c]	**36 (4.1%)**	**15 (3.4%)**	**12 (2.9%)**
Myocardial Ischemia	1 (0.1%)	2 (0.4%)	0 (0%)
Myocardial Infarction	13 (1.5%)	3 (0.7%)	7 (1.7%)
Hypertension	24 (2.7%)	14 (3.1%)	19 (4.6%)
Hypertension Aggravated	12 (1.4%)	2 (0.4%)	7 (1.7%)
Thrombophlebitis			
Thrombophlebitis, Deep	3 (0.2%)	2 (0.4%)	1 (0.2%)
Thrombophebitis, Combined[d]	3 (0.2%)	3 (0.4%)	1 (0.2%)
Vasculitis	1 (0.1%)	0 (0%)	0 (0%)
Non-ASA Users	N=3105	N=1551	N=1573
Edema peripheral	111 (3.6%)	53 (3.4%)	**81 (5.1%)**
Edema (pooled reporting)[b]	127 (4.1%)	61 (3.9%)	**96 (6.1%)**
Angina			
Unstable Angina	2 (<0.1%)	0 (0%)	1 (<0.1%)
Angina Pectoris	9 (0.3%)	2 (0.1%)	6 (0.4%)
Coronary Artery Disorder	10 (0.3%)	4 (0.3%)	1 (<0.1%)
Combined Anginal Disorders[c]	**21 (0.67%)**	**6 (0.38%)**	**8 (0.51%)**
Myocardial Ischemia	1 (<0.1%)	0 (0%)	0 (0%)
Myocardial Infarction	6 (0.2%)	2 (0.1%)	2 (0.1%)
Hypertension	54 (1.7%)	26 (1.7%)	42 (2.7%)
Hypertension Aggravated	20 (0.6%)	10 (0.6%)	17 (1.1%)
Thrombophlebitis			
Thrombophlebitis, Deep	9 (0.3%)	3 (0.2%)	0 (0%)
Thrombophlebitis, Combined[d]	14 (0.45%)	5 (0.3%)	4 (0.25%)
Vasculitis	1 (<0.1%)	0 (0%)	1 (<0.1%)

a. Data from electronic submission, NDA 20-998 supplement S-009, Table T41.1.
b. Includes edema, edema generalized, and edema peripheral.
c. Includes unstable angina, angina pectoris and coronary artery disorder.
d. Includes AEs reported under the following terms: phlebitis, thrombophlebitis, thrombophlebitis arm, thrombophlebitis deep, thrombophlebitis leg, thrombophlebitis leg deep, thrombophlebitis leg superficial.

Table 55 (from Cardiorenal review, Doug Throckmorton, M.D.) shows serious cardiac adverse events reported during the trial according to aspirin use. In the non-aspirin users, there appears to be a slight trend toward more events in those patients receiving celecoxib for combined atrial and anginal disorders; this does not appear to be the case for aspirin users.

Table 55: Serious Adverse Events (SAEs) per 100 Pt-Yrs Reported During CLASS by ASA Use[a].

Adverse Event	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
ASA Users	N=882 517 Pt-Yrs	N=445 N=239 Pt-Yrs	N=412 249 Pt-Yrs
Cardiac SAEs			
Atrial Arrhythmias			
Arrhythmia Atrial	2 (0.4%)	0 (0%)	1 (0.4%)
Bradycardia	0 (0%)	0 (0%)	0 (0%)
Fibrillation Atrial	4 (0.8%)	1 (0.4%)	3 (1.2%)
Tachycardia Supraventricular	1 (0.2%)	0 (0%)	0 (0%)
Combined Atrial SAEs [b]	7 (1.4%)	1 (0.4%)	4 (1.6%)
Angina			
Unstable Angina	6 (1.2%)	4 (1.7%)	0 (0%)
Angina Pectoris	3 (0.6%)	5 (2.1%)	4 (1.6%)
Coronary Artery Disorder	11 (2.1%)	2 (0.8%)	5 (2.0%)
Combined Anginal Disorders[c]	20 (3.9%)	11 (4.6%)	8 (3.2%)
Myocardial Infarction	13 (2.5%)	2 (0.8%)	7 (2.8%)
Thrombophlebitis Combined[d]	0 (0%)	2 (0.8%)	1 (0.4%)
Non-ASA Users	N=3105 1804 Pt-Yrs	N=1551 841 Pt-Yrs	N=1573 874 Pt-Yrs
Cardiac SAEs			
Atrial Arrhythmias			
Arrhythmia Atrial	0 (0%)	0 (0%)	0 (0%)
Bradycardia	2 (0.1%)	0 (0%)	0 (0%)
Fibrillation Atrial	5 (0.3%)	1 (0.1%)	0 (0%)
Tachycardia Supraventricular	2 (0.1%)	0 (0%)	0 (0%)
Combined Atrial SAEs [b]	**6 (0.3%)**	**1 (0.1%)**	**0 (0%)**
Angina			
Unstable Angina	2 (0.1%)	0 (0%)	0 (0%)
Angina Pectoris	1 (0.1%)	2 (0.2%)	0 (0%)
Coronary Artery Disorder	8 (0.4%)	3 (0.4%)	0 (0%)
Combined Anginal Disorders[c]	**10 (0.6%)**	**2 (0.2%)**	**0 (0%)**
Myocardial Infarction	6 (0.3%)	2 (0.2%)	2 (0.2%)
Thrombophlebitis Combined[d]	8 (0.4%)	4 (0.5%)	0 (0%)

a. Data from electronic data submission, Appendix 2.9.4 and 2.9.3.
b. Sum of atrial arrhythmia, atrial fibrillation, bradycardia and tachycardia.
c. Includes unstable angina, angina pectoris and coronary artery disorder.
d. Includes AEs reported under the following terms: phlebitis, thrombophlebitis, thrombophlebitis arm, thrombophlebitis deep, thrombophlebitis leg, thrombophlebitis leg deep, thrombophlebitis leg superficial.
e. These SAEs were not reported by investigators.

Hepatobiliary Effects

As has been noted previously in this review, the use of diclofenac was associated with increases in liver function values. These findings are summarized in **Table 56**. A consistent pattern of enzyme elevation was seen in diclofenac patients. The clinical significance of these elevations is indicated by the data on withdrawals: approximately half of diclofenac patients for whom liver enzyme elevations were reported as adverse events were withdrawn from the study as a result. Findings of statistically significant ($p<0.001$) increases of SGOT/SGPT for diclofenac (3.3%/3.9%, respectively) compared to celecoxib (0.5%/0.6% respectively) and ibuprofen (0.4%/0.5%, respectively) was also obvious at six months (Table T41.4, p.423). These findings are consistent

with the known hepatotoxic nature of diclofenac. Neither celecoxib nor ibuprofen had results obviously suggestive of a hepatic effect.

Table 56: Adverse Events and Laboratory Values Related to Hepatic Function: Entire Study[1]

Laboratory Test	Celecoxib	Diclofenac	Ibuprofen
Adverse Events (% of Patients)			
SGOT increased	0.9	4.3[1]	1.0
SGPT increased	1.0	5.1[1]	1.2
Hepatic function abnormal	0.3	1.6[1]	0.3
Adverse Events Causing Withdrawal (% of Patients)			
SGOT increased	0.1	2.1[1]	0.1
SGPT increased	0.1	2.3[1]	0.1
Hepatic function abnormal	<0.1	1.1[1]	<0.1
Changes from Baseline in Group Mean Laboratory Values (Mean [SE])			
AST (SGOT), U/L	0.3 (0.12)	5.0 (0.57)[1]	0.9 (0.16)
ALT (SGPT), U/L	-0.2 (0.18)	11.6 (1.1)[1]	1.3 (0.24)
Incidence of Extreme Values (No./total [%])			
AST (SGOT) (>200 U/L)			
Final visit	0/3692 (0.0)	7/1848 (0.4)[1]	0/1785 (0.0)
Maximum value	1/3692 (<0.1)	12/1848 (0.6)[1]	1/1785 (<0.1)
ALT (SGPT) (>200 U/L)			
Final visit	2/3692 (<0.1)	22/1848 (1.2)[1]	0/1785 (0.0)
Maximum value	4/3692 (0.1)	29/1848 (1.6)[1]	1/1785 (<0.1)

1. From Table 10.u (p 206); N49-00-06-035-102. Entries are No. (%) of patients. $p<0.05$ versus celecoxib.

Reviewer's comment: Of note, there were no deaths noted in any treatment group due to hepatic causes.

Dermatologic Effects:

As noted earlier and seen in **Table 57**, the incidence of rash (either within the first 28 days or for the entire study period) was statistically significantly higher for celecoxib than for either diclofenac or ibuprofen. The incidence of pruritus was also statistically significantly higher for celecoxib than for ibuprofen, but not diclofenac. Although not included here (Tables T41.4 and T42.4, p. 429 and 506, respectively) the results shown above were similar when examined for the first six months; these incidences of rash and pruritus were only slightly lower than in the entire study period, and the statistical comparisons were the same. Similarly, **all withdrawals due to pruritus, and all but five withdrawals due to rash, occurred within the first six months of treatment.** The percentage of patients withdrawing for either rash or pruritis was generally higher in the celecoxib group compared to the other treatments: approximately one half to one quarter of rash or pruritus events led to withdrawal. Cases of rash or pruritus in any treatment group tended to be either mild or moderate in severity versus severe; the proportions for severe rash were somewhat higher with celecoxib.

To assess the incidence of true drug-related rashes of clinical significance, those cases that were severe and caused early withdrawal from the study were examined. Of the 19 severe rashes in the celecoxib group, 13 led to withdrawal within the first 28 days of treatment. Using this index, the incidence of clinically significant rash associated with celecoxib would be estimated at 13 of 3987, or 0.33%. Performing a similar analysis on cases of pruritus, five events in the celecoxib group are

shown to have been rated as severe and to have led to early withdrawal. This yields an incidence of 0.13%. Events coded as erythematous, maculopapular, or psoriaform rash had incidences of 0.4% or less in any treatment group. None of these values were statistically significantly different between celecoxib and either of the NSAID treatment groups.

None of the rashes or any other dermatologic adverse events in the celecoxib group were serious. Only three serious adverse events relating to skin occurred: two were skin ulcerations, one each occurring in the diclofenac and ibuprofen groups, and one skin disorder occurred in the ibuprofen group.

Reviewer's comment: There were no cases of Stevens Johnson syndrome, toxic epidermal necrosis or erythema multiforme noted for any of the treatment groups.

Table 57: Characteristics of Rash and Pruritus Among the Three Treatment Groups [1]

	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
First 28 Days of Treatment			
Rash			
Overall incidence	149 (3.7)	24 (1.2)[1]	22 (1.1)[1]
Severity			
Mild	69 (1.7)	16 (0.8)	11 (0.6)
Moderate	64 (1.6)	8 (0.4)	9 (0.5)
Severe	15 (0.4)	0 (0.0)	2 (0.1)
Causing withdrawal	74 (1.9)	10 (0.5)[1]	9 (0.5)[1]
Pruritus			
Overall incidence	68 (1.7)	21 (1.1)	15 (0.8) *
Severity			
Mild	42 (1.1)	14 (0.7)	7 (0.4)
Moderate	21 (0.5)	7 (0.4)	7 (0.4)
Severe	5 (0.1)	0 (0.0)	1 (<0.1)
Causing withdrawal	27 (0.7)	6 (0.3)	4 (0.2)
Entire Study Period			
Rash			
Overall incidence	247 (6.2)	55 (2.8)[1]	75 (3.8)[1]
Severity			
Mild	126 (3.2)	35 (1.8)	42 (2.2)
Moderate	101 (2.5)	18 (0.9)	29 (1.5)
Severe	19 (0.5)	2 (0.1)	3 (0.2)
Causing withdrawal	85 (2.1)	13 (0.7)[1]	25 (1.3)[1]
Pruritus			
Overall incidence	97 (2.4)	38 (1.9)	28 (1.4)[1]
Severity			
Mild	61 (1.5)	23 (1.2)	15 (0.8)
Moderate	28 (0.7)	14 (0.7)	11 (0.6)
Severe	7 (0.2)	1 (<0.1)	2 (0.1)
Causing withdrawal	29 (0.7)	7 (0.4)	6 (0.3)[1]

1. From Table 10.v (p 207); N49-00-06-035-102. Numbers are percentages. $p<0.05$ versus celecoxib.

Respiratory, endocrine/metabolic, CNS/PNS, infectious disease safety:

Reviewer's comment: Since the original NDA review (including this sNDA and post-marketing data), there have been no new issues or clinically important concerns with regards to celecoxib and these general areas of safety.

Discussion/Conclusions (Section 12):

Discussion

The results of this CLASS trial, which represents the combination of two large safety trials, stands at any important juncture in the evolution of our understanding of the relative safety and efficacy of drugs that have been used for their analgesic and anti-inflammatory properties for more than 100 years. From the "black box" approach of employing extracts of willow bark, the precursor of acetylsalicylic acid, to "targeted" therapy of the recently discovered COX-2 enzyme with compounds such as celecoxib in this sNDA, the safety and efficacy of drugs in this important therapeutic area has been the topic of what is now an immense literature. One of the questions posed during the review of the original NDA was the consequences of "long-term, high-grade" inhibition of COX-2 and what types of compensatory mechanisms may come into play in this situation. This discussion will attempt to capture some of the "lessons learned" in this sNDA.

Efficacy/Effectiveness

The efficacy of celecoxib was not a primary outcome for this sNDA. The original NDA (NDA 20-998, Review July 8, 1998) addressed the issue of efficacy with studies of pain/analgesia and trials in patients with OA and RA. The original approval of Celebrex included indications for OA and RA, but not pain. Since then, the indication for use in familial adenomatous polyposis (FAP) was added. Of note, the recommended dose for FAP is 400 mg BID which was the same dose employed in the CLASS trials. Interestingly, as noted in the open-label studies that followed the original NDA trials, up to 70% of patients (p. 121, NDA review July 8, 1998) increased their dose of celecoxib. This "dose creep" phenomenon for RA patients resulted in doses again similar to those employed in this sNDA. Therefore, are there any lessons learned regarding the efficacy or effectiveness of celecoxib from the CLASS trial?

Unfortunately, the incomplete assessment of efficacy in the CLASS trial limits any detailed understanding of the efficacy of celecoxib at 400 mg BID, noted to be 2-4 times the recommended (i.e. currently labeled) dose for RA and OA, respectively. However, the patient global (Table 34), patient assessment of pain (Table 35), HAQ scores (Table 36), SF-36 results (Table 37) and patient disposition (i.e. withdrawals for treatment failure, Table 3) would seem to allow some general statements in this area. If one looks at withdrawals from the CLASS trial for arthritis treatment failure, either during the first 6 months or during the entire study, there is no clear trend that celecoxib offers any consistent advantage over the "conventional" doses of NSAIDs, represented here as diclofenac and ibuprofen. At best, it could be argued that celecoxib appears comparable to diclofenac and generally better than ibuprofen in this regard. It is of interest to note that the withdrawal rates for treatment failure in the CLASS trial were lower than the 12-week trials in OA or RA in the original NDA. Withdrawals for treatment failure in the original NDA ranged from 21-35% for the various doses of celecoxib compared to 18-26% for naproxen in OA (p 176, July 8, 1998); withdrawals ranged from 21-40% for the various doses of celecoxib compared to 29-30% for naproxen in RA (p.210, July 8, 1998). If one looks at the combination of treatment failure and noncompliance (as another estimate of treatment failure), the comments noted above seem to hold. Comparisons of celecoxib to the NSAIDs regarding the patient global assessment, assessment of arthritis pain, HAQ and SF-36 scores suggest that celecoxib was comparable to diclofenac and ibuprofen with no consistent and clear trends suggesting superiority. Therefore, based upon these variables as endpoint estimates, it would appear that celecoxib (even at multiples of doses for

labeled indications) does not offer a consistent advantage over the comparator NSAIDs in terms of efficacy or effectiveness in OA or RA.

Safety

In contrast to efficacy, the CLASS trial was designed to assess safety endpoints of celecoxib relative to the NSAIDs, diclofenac and ibuprofen. In so doing, arguments were made that this trial was also testing the COX-2 safety hypothesis; this hypothesis being (in general terms) that if COX-2 is not present in any particular organ or cell, drugs targeting COX-2 should not be a problem. Safety may be considered more from the molecular understanding of receptor structure and function, and less so from the prospective of a xenobiotic with its potentially unknown (and non-mechanism based) safety hazards.

The central clinical trial feature in CLASS that tested this hypothesis was the bona fide use of twice to four-fold the highest doses for two FDA-approved labeled indications, RA and OA respectively. As noted by the Sponsor, the multiples of dosing employed for celecoxib was to make comparisons of safety in a "robust" fashion. A safety trial, with "NSAIDs" at similar multiples of their respective labeled doses for OA and RA has not yet been conducted despite the long history of usage of these important and widely used drugs. Unfortunately, the fact that such multiples of the NSAIDs selected for this trial were not included ultimately confounds all discussions and/or conclusions of this CLASS trial.

While some might comment that these multiples were not robust enough (i.e. should be 10X), it appears clear that the dosing, sample size, and selection of safety endpoints all contributed to the highly unique and progressive character of the CLASS trial. Certainly, pushing the envelope in terms of safety has the potential for improvements in safety at both the patient and population levels. As noted, one of the unique aspects of the CLASS trial was the selection of the primary UGI safety endpoint. The gastrointestinal toxicity of NSAIDs, particularly to the upper GI tract, has long been felt by many to be one of the most important iatrogenic adverse events associated with modern drug therapies.

Gastrointestinal events

(*More details of GI events are found in the review by Larry Goldkind, M.D)*

Arguments have been made that the selection of CSUGIEs as a safety endpoint was attempting to address the endpoints of safety with the same rigor usually attributed to the assessment of efficacy. **The primary end point in the GI safety analyses was the development of a CSUGIE** (i.e., UGI bleeding, perforation, or obstruction with important clinical manifestations). The primary endpoint was a safety endpoint. The **null hypothesis** being tested was that there was no difference between the incidence of **CSUGIEs** associated with celecoxib and that associated with NSAIDs, pooled and then individually. When the endpoint of CSUGIEs in all ITT patients during either the first 6 months or the entire study was analyzed, **celecoxib did not exhibit a statistically significant difference from the NSAIDs studied in this trial, either singly or combined.** The CSUGIE event rate for the entire study period (Table 12), as defined by the alternate definition, reinforces the observation that celecoxib did not show significant differences from either NSAID. However, the trends (Table 13 and 14) for CSUGIEs in all patients during either the first 6 months or the

entire study period did favor celecoxib. Of importance though, at no time in the CLASS trial, and without regard to endpoint or aspirin use, was celecoxib superior to diclofenac.

The representative NSAIDs for this trial, ibuprofen and diclofenac, turned out to be useful comparators. Of note, when the confounding effects of aspirin use were addressed, or the endpoint was expanded to include gastric or duodenal ulcers (i.e. GDU) that were not felt to be clinically important enough to be classified as a CSUGIEs, celecoxib did demonstrate differences from ibuprofen, but not from diclofenac. This was seen during both the first 6 months (Table 13) and the entire study period (Table 14) for CSUGIEs/GDUs. Undoubtedly, the comparisons with ibuprofen accounted for the results of NSAIDs as pooled events; Table 33 may best illustrate these points. In any trial of safety, one could argue that superiority should always be the goal; the safety of drugs developed today should (ideally) be better than drugs developed years ago. Therefore, particularly for making drug class (i.e. COX-2 vs. NSAIDs) comparisons, it could be argued that beating one NSAID does not mean you beat them all, but losing to one NSAID (or failing to beat it) is losing to them all.

Why was celecoxib, as given under these exaggerated dosing multiples, not able to show statistical superiority to diclofenac? Certainly, there are a variety of possible explanations. One explanation could be that the use of the multiples of the "x" dose of celecoxib resulted in more clinically important UGI adverse events than would have occurred with the x dose alone. This result, unfortunately, was not testable in this trial but may well nullify the safety hypothesis of COX-2 had it occurred.

Among other possibilities for the results with celecoxib versus diclofenac could be that the event rates for diclofenac where not at their usual "NSAID" pace. In the CLASS trial, these clinically important UGI events seemed to occur early for diclofenac with rates seeming to level off at later time points in the trial while UGI events for celecoxib continued to occur at a steady rate (see below). Could a process of "differential adaptation" to the daily biochemical/biological insult of these drugs have played a role?

To help interpret and understand the comparisons with regards to diclofenac, one possible explanation that was brought forward by the Sponsor, and discussed in detail, was the idea of "informative censoring" as it relates to the GI adverse events. Such censoring, if it occurred, could influence the clinical outcomes provided these influences were not balanced in all treatment arms. In particular, the five adverse event symptoms of dyspepsia, abdominal pain, nausea, diarrhea and vomiting were cited as important contributors to the confounding effects of informative censoring with the consequence of removing at-risk patients from the diclofenac treatment arm. However, it is unclear that the potential for informative censoring represented a significant bias in assessment of the outcome of the CSUGIEs as defined in this trial. For example, if the symptoms as specified by the Sponsor (i.e. moderate to severe) are considered, it appears that informative censoring may be an important confounder. However, if the less restrictive definitions of symptoms (i.e. to include mild) as reasons for the withdrawal of the susceptible patient are applied, then such censoring may not have an important role (Table 23).

The timing of UGI events may also hold clues to understanding any role for informative censoring. For example, both crude and Kaplan-Meier event rates in the first 6 months (Tables 7) showed that

for celecoxib, seven of the 11 uncensored events occurred in the first three months. However, in the diclofenac group, all nine events occurred in the first 100 days, with a cluster of five events within the first 15 days and four more events occurring sporadically through approximately day 85. One could argue (as noted above) that this pattern might suggest a "shift to the right" for events associated with the use of celecoxib as compared to diclofenac. If this shift were real, than any loss of at-risk patients may influence the celecoxib CSUGIE rate more than that for diclofenac. Any shifting of events to a later point in time could also be one reason for the lack of CSUGIEs noted during the entire trial (Table 10) of NSAIDs as compared to celecoxib whose rates tended to increase at a generally steady pace with time. Therefore, although it does seem that more patients dropped out of the diclofenac group due to GI symptoms, this does not seem to be an adequate explanation for the observed UGI results between diclofenac and celecoxib.

When comparisons with ibuprofen are made, the importance of any censoring as an explanation for the results in the diclofenac group as compared to celecoxib become less evident. For example, in the entire population studied, only one uncensored event occurred in the diclofenac group after 182 days and none in the ibuprofen group; yet celecoxib was able to demonstrate statistical superiority to ibuprofen in certain settings as noted above. Similarly, when the overall withdrawal pattern was considered, and not just those due to adverse events, rates are highest in the ibuprofen group (Table 3) versus diclofenac or celecoxib. Further, when viewed from the prospective of risk factors (Table 19), patients receiving celecoxib appear more likely to withdraw at any given risk category than that of diclofenac, but not ibuprofen. Therefore, a consistent association of endpoints with patterns of withdrawal does not seem evident when comparing across treatments.

Was informative censoring an important component in the CLASS trial? One way to attempt to answer this question is with a clinical trial designed to do so. The hypothesis-generating conclusion that the confounding effect of UGI informative censoring is important in the outcomes of large clinical trials can be tested in prospectively-designed trials for confirmation and validation.

The absence of GI-related deaths in the CLASS trial is noteworthy. This might be attributable to the heightened vigilance for GI events maintained throughout the study since the occurrence of GI signs and symptoms related to the primary end points of this study. Therefore, events that if left untreated may have progressed to clinically significant events were identified early and these patients were treated and/or discontinued from study medication. On the other hand, it may suggest that prior estimates of GI-related deaths from NSAIDs have been over estimates.

During the first six months, all but one of the events (a gastric outlet obstruction in the celecoxib group) represented bleeding events in which an ulcer or large erosion which was associated with either visual evidence of bleeding, melena, or hemoccult-positive stools and a decrease in hematocrit or hemoglobin. There were no UGI perforations (Table 6). During the entire trial, all events were classified into the same categories as those that occurred in the first six months, with these exceptions: one bleeding event in the celecoxib group represented category 1A, and two UGI perforations occurred, one in the celecoxib group and one in the diclofenac group (Table 9).

Not unexpectedly, since this had been seen in the original NDA endoscopy trials, **aspirin use did seem to influence the gastrointestinal results in this trial**. For example, as seen in Table 13, it appears that use of aspirin tended to increase the overall CSUGIE event rate for celecoxib and

diclofenac but not for the ibuprofen group. This same differential pattern also seems evident in the CSUGIE event rate for the entire study (Table 14). While it would be clinically useful to understand whether UGI events are more problematic when added to one treatment regimen versus another, this trial was not able to address (i.e. issues of powering, etc.) the issue of aspirin co-administration in any great detail. Once again, it may be that specific trials need to be designed and conducted to understand these important interactions.

Cardiovascular events

(More details of cardiovascular events are found in the review by Douglas Throckmorton, M.D.)

When considering the deaths and other serious adverse events that occurred in this trial, they appear to be consistent in nature and frequency with those that would be expected in a long-term trial in this patient population. For example, most patients enrolled had several concomitant illnesses or significant medical histories, and many were elderly. As noted (Table 5) the median age was approximately 61 years, with about 11% of patients in each group ≥ 75 years. Approximately 40% of patients in each treatment group had a self-reported history of cardiovascular disease and approximately 20% took ASA prophylactically.

While serious adverse events and deaths related to cardiovascular disorders were not unexpected, was there evidence in the CLASS trial that any treatment group had an excess of these types of events relative to the other groups? For example, concerns have been raised about the possibility that COX-2 selective agents may predispose to thromboembolic events (i.e. myocardial infarction, deep venous thrombosis, pulmonary emboli, cerebrovascular accidents, etc.) owing to their preferential inhibition of endothelial prostacyclins relative to platelet thromboxanes. Further, literature reports of trials (i.e. VIGOR) of other COX-2 selective agents have also raised this possibility.

In the original NDA, myocardial infarction was noted to occur at a higher rate in celecoxib-treated as compared to placebo-treated patients. In the long-term trial (Trial 024) that was included in the NDA submission, the predominate (>90%) cause of death for patients taking celecoxib at any dose was cardiovascular. The majority of these deaths were felt to represent progression of previously known cardiovascular disease. Examination of Kaplan-Meier survival curves for both the controlled and long-term trials in the NDA did not support the conclusion that there was a relationship between any given duration of exposure to celecoxib and increased mortality. There were suggestions of a dose-response relationship (Table 60, NDA 20-998; 100 mg BID celecoxib, 0% crude mortality rate vs. 400 mg BID celecoxib, 0.64% crude mortality rate) between cardiovascular mortality and celecoxib use that could not be adequately addressed by the data. However, the cardiovascular mortality rates with celecoxib were lower than those seen with the active controls employed in the NDA, which confounded interpretation of these data. Of note, there was no suggestion, in the original NDA, of any rare or unusual cardiac toxicities.

In the CLASS trial, it is not possible to examine any dose-response relationships, rather, only comparisons of drugs at the doses employed and in the population studied. Given these caveats, there was no apparent, consistent adverse effect of celecoxib in the reported parameters of cardiovascular safety when compared to either diclofenac or ibuprofen (Table 52). When these

events were examined with or without aspirin use, these relationships did not appear to change (Table 53) in any significant way. However, as expected since they are at higher risk, patients taking aspirin had a higher incidence of cardiac ischemic events in all three treatment groups as compared to those not taking aspirin. Of note, discontinuations for thrombotic cardiac events were not significantly different in the treatment groups (Table T41.1, sNDA and 2.1.d.1, Cardiorenal Consult).

When cardiac adverse events (Table 54) or serious cardiac adverse events (Table 55) and the relationship of **aspirin use** are analyzed in more detail, some differences appear to emerge. For example, examination of selected cardiac adverse events (Table 54) reported during the trial suggests that anginal disorders (especially the combined disorders) was numerically higher in those patients receiving celecoxib, regardless of aspirin use. In the patients not receiving aspirin, the rate of myocardial infarction was also slightly higher in the celecoxib group (0.2%) compared with the other two drugs (0.1%). Of note, for edema and hypertension, there appears to be a trend toward more events in those patients receiving ibuprofen regardless of aspirin use.

For serious cardiac adverse events (Table 55) in the non-aspirin users, there appears to be a trend toward more events in those patients receiving celecoxib for atrial events and anginal disorders, especially when combined; this does not appear to be the case for aspirin users. The importance of any of these differences are difficult to interpret especially since the trial randomization was not stratified for aspirin use, any comparisons of the aspirin or non-aspirin users has limited power to detect only large differences between these groups. This difficulty in interpretation is also evident in considering cardiovascular mortality rates (Table 39 and comment). Overall though, these findings would not seem to support a conclusion that celecoxib has a large adverse effect on cardiovascular mortality compared to the non-selective NSAIDs. If the incidence rates for adverse events (including serious) is confirmed in trials designed to specifically address these important issues, it may be that the degree of loss of blood flow may be a factor in understanding these events, compared to mortality.

Renal events

(More details of renal events are found in the review by Douglas Throckmorton, M.D.)

As noted in the original NDA, the overall findings with celecoxib were that renal events were more like the comparator NSAIDs than the placebo controls. For example, there was an association between celecoxib administration and the development of clinically significant edema (i.e. peripheral), sodium retention, worsened hypertension in susceptible individuals, hypophosphatemia, hyperchloremia, and elevations of serum creatinine and BUN with proteinuria as was noted in the comparator NSAIDs. There were not clear signals, however, for serious renal events such as bony fractures (suggesting significant acid-base changes), renal stone formation, nephrotic syndrome, acute renal failure requiring dialysis, papillary necrosis, or interstitial nephritis. However, there were patients on celecoxib that were withdrawn from the long-term, open-label trial (Trial 024) because of renal adverse events, including acute renal failure. One outstanding issue was whether celecoxib altered the acid-base balance since no measurements (e.g. serum bicarbonate, arterial pH) were performed as part of the original NDA.

Regarding the issue of acid-base balance, serum HCO_3 was measured in the CLASS trial and adverse events possibly related to changes in acid-base balance were collected. Between 1 and 2% of the subjects in all three treatment groups had a measured HCO_3 <20 meq/dl during the study after starting with a normal baseline >25 mg/dl. The rate for celecoxib, however, was less than that of the two comparator drugs. In addition, there was no increase in reported clinical adverse events related to changes in acid-base balance (such as bony fractures which could indicate chronic acidosis with demineralization, Table T41.1, sNDA) in the celecoxib group although such adverse events were quite rare in the database for all three drugs. Overall, then, the rate of clinically-relevant changes in acid-base balance was similar for celecoxib, diclofenac and ibuprofen.

Regarding the comparative incidence of reported clinical renal adverse events between the three treatment groups, there was no consistent adverse effect of celecoxib in the reported parameters of renal safety when compared with either diclofenac or ibuprofen. In particular, the reported rates of uremia, nephrotic syndrome and severe hyperkalemia in CLASS were all less than 1 per 1000 patient-years of exposure for all three drugs. Celecoxib use was also not apparently associated with an increase in hypertension or edema compared with diclofenac and ibuprofen (Table 50).

When renal adverse events related to laboratory measurements were examined, celecoxib did not appear to have a striking adverse effect with regard to any renal parameter measured, compared with diclofenac or ibuprofen (Tables 47, 50). The incidence of hyperkalemia, assessed as clinical events and as changes in lab measurements, was consistently more common in the celecoxib group than in either of the comparators, although the difference did not achieve nominal statistical significance for any measure (Table T 41.1 sNDA and 2.1.c.1 and 2.1.c.2, Cardiorenal Consult).

Regarding changes in renal laboratory parameters, **when examined as mean changes** from baseline, no clinically relevant differences between the three treatment groups were seen at any time point for the changes in mean BUN, serum creatinine, phosphate, bicarbonate and chloride. The reported differences, some of which achieved nominal statistical significance, were quite small and of no apparent clinical relevance (Table T44.1, sNDA). Use or not of aspirin did not seem to influence these particular results.

Of note, it does appear that patients who used **aspirin** in all three treatment groups had a higher incidence of increases in BUN than patients who did not use aspirin. Hyperkalemia as an AE was somewhat higher in the celecoxib group, regardless of aspirin use (Table T 41.2 and T41.3, sNDA and 2.1.c.2, Cardiorenal Consult). For the renal SAEs (Table T43, sNDA and 2.1.b.1, Cardiorenal Consult), too few (i.e. none in any treatment group for hyper- or hypokalemia, acidosis, nephrotic syndrome, edema, uremia-1 case for ibuprofen, or renal calculus-4 cases for celecoxib, 2 for ibuprofen) were reported to analyze according to the use of aspirin.

Hepatic events

In the original NDA, it was noted that celecoxib did not appear to significantly alter liver or biliary function as determined primarily by elevations of enzymes and other laboratory measurements (i.e.

ALT, AST, bilirubin, alkaline phosphatase). Serious adverse events were rare. However, cases of liver failure have been reported in post-marketing data.

The data in the CLASS trial appear to confirm that long-term use of high doses of celecoxib is not associated with significant elevations of enzymes or serious hepatic adverse events. However, diclofenac was associated with significant elevations of liver enzymes requiring withdrawal of approximately half of these patients. Of interest, there were no deaths from hepatobiliary causes in any treatment group in the CLASS trial.

Dermatologic events

In the original NDA, it was noted that rashes and related cutaneous reactions were among the more frequently noted adverse events associated with celecoxib treatment. The rashes were generally mild in severity, and often associated with urticaria or pruritis. Rash was the single most common reason for withdrawal from study treatment. There was an increase in incidence of rash at higher celecoxib doses (the highest being the dose used in this trial) that suggested a dose-response relationship. Importantly, there were no serious cutaneous reactions associated with celecoxib treatment.

In the CLASS database, the results appear to be similar to those of the original NDA. The incidence of rash (generally mild or moderate, none were serious) was statistically significantly higher for celecoxib than for either diclofenac or ibuprofen. The incidence of pruritis was also statistically significantly higher for celecoxib than ibuprofen, but not diclofenac. The incidence of clinically significant rash with celecoxib was estimated to be 0.13%. The percentage of patients withdrawing for either rash or pruritis was generally higher in the celecoxib group. Of note, there were no cases of Stevens Johnson syndrome, toxic epidermal necrosis or erythema multiforme noted for any of the treatment groups in this trial.

Overall Safety of Celebrex

The results presented in this sNDA with celecoxib at the supratherapeutic doses studied, support the overall safety of celecoxib. While adverse events for celecoxib during the entire study period were statistically greater than those of the comparator drugs (Table 42), this did not seem to translate into more withdrawals for celecoxib versus ibuprofen or diclofenac (Table 3). Also, although serious adverse events were numerically higher for celecoxib (Table 41), there were no obvious trends to suggest any specific safety risks. Similarly, the death rate and pattern (Tables 38 and 39) did not suggest any obvious safety risks for celecoxib. Interestingly, no deaths in the celecoxib group occurred for GI, hepatic, renal or dermatologic causes, but the same was true for the comparators.

Conclusions:

As noted earlier, the CLASS trial was a robust testing of the safety of Celebrex at doses 2-4 times those currently labeled for RA or OA, respectively. The NSAID comparators, ibuprofen and diclofenac, were given at their commonly prescribed (not maximum) doses. Therefore, any conclusions regarding the relative safety or efficacy of Celebrex needs to be viewed in this context. However, the following are some conclusions from this CLASS trial:

1. Celecoxib does not appear to be more effective for treating the signs and symptoms of OA or RA than the NSAID comparators.

2. Celecoxib did not demonstrate statistical superiority to NSAIDs (pooled) or either comparator (diclofenac and ibuprofen) with regards to the primary safety endpoint of CSUGIEs at any point in the trial although there were trends that favored celecoxib. However, when the use of aspirin was considered or the definition of the UGI endpoints was expanded to include ulcer events not deemed to be CSUGIEs (i.e. GDUs), celecoxib did demonstrate statistical superiority to pooled NSAIDs, and to ibuprofen, during this trial. However, celecoxib did not demonstrate statistical superiority to diclofenac regardless of selection of endpoint or aspirin use during any point in the trial.

3. Aspirin use appears to influence event rates for gastrointestinal, renal and possibly cardiac outcomes. However, owing to the nature of this trial, particularly that use of aspirin would indicate a higher level of pre-existing cardiovascular disease and aspirin use was not stratified, it is unclear how aspirin impacts these outcomes among the treatment groups evaluated in this trial.

4. The CLASS trial contains no evidence for an adverse effect of celecoxib on acid-base balance relative to either diclofenac or ibuprofen. All groups rarely had changes in this renal parameter.

5. The CLASS trial data do not support a large adverse effect of celecoxib on cardiovascular mortality or on serious adverse events related to thrombosis relative to either diclofenac or ibuprofen. The data do not exclude a less apparent effect, reflected in the relative rates of cardiac adverse events related to ischemia.

6. The CLASS trial data do not support a large adverse effect of celecoxib on renal or cardiac adverse events relative to either diclofenac or ibuprofen. This includes adverse events reported by investigators (*e.g.*, hypertension, uremia) and those detected through routine laboratory or blood pressure measurements (*e.g.*, increased BUN/ serum creatinine or systolic blood pressure).

7. Hyperkalemia, however measured, was consistently more frequent in patients taking celecoxib than for diclofenac or ibuprofen, but these differences were small and not reflected in an increase in serious adverse events related to hyperkalemia.

8. The CLASS trial data do not support the conclusion that serious hepatic adverse events are more frequent in those patients taking celecoxib than diclofenac or ibuprofen. In fact, hepatic enzyme elevations and withdrawals for these elevations were significantly and consistently reduced compared to diclofenac.

9. The incidence of rash (generally mild or moderate, none were serious) was statistically significantly higher for celecoxib than for either diclofenac or ibuprofen. The incidence of pruritis was also statistically significantly higher for celecoxib than ibuprofen, but not diclofenac. The incidence of clinically significant rash with celecoxib was estimated to be 0.13%. The percentage of patients withdrawing for either rash or pruritis was generally higher in the celecoxib group.

10. There were no deaths from gastrointestinal, hepatic, renal or dermatologic causes in any treatment group during the time period of the CLASS trial.

11. No new safety issues were apparent regarding respiratory, endocrine/metabolic, CNS/PNS or infectious disease safety.

12. Celecoxib was generally safe and well tolerated at the supratherapeutic doses employed in this CLASS trial.

Appendix (CSUGIEs)

A narrative summary was prepared for each CSUGIE and symptomatic ulcer. The data for these summaries were derived from the CRFs and any additional medical records resulting from the work-up. The narrative summaries for all CSUGIEs that occurred at any time during study participation are included below. These are sorted by case number (case numbers were assigned chronologically in order of the reporting of potential CSUGIEs).

Case 1000

Patient US0293-035-10579 was a 69-year-old female with a history of hypertension, right-sided mastectomy, hysterectomy, non-insulin-dependent diabetes mellitus, and OA. Concomitant medications included atenolol, enalapril, and trazadone. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID**.

After 13 days of treatment the patient began experiencing intermittent black stools followed by frank blood in the toilet for two days with associated epigastric discomfort. On day 18 of treatment the patient presented to the emergency room after an episode of uncertain hematemesis; **study medication was discontinued at this time**. Significant findings at this time included melena and a hemoglobin of 8.8 g/dL compared with a baseline hemoglobin of 14.1 g/dL and a hematocrit of 25.4% compared with a baseline hematocrit of 41%. The patient was admitted to the hospital and an endoscopy performed the following day revealed an actively oozing ulcer in the gastric cardia with blood emanating from the ulcer margins and from friable underlying mucosa. Hemostasis was achieved using multiple injections of epinephrine in and around the ulcer. Antral biopsies revealed chronic gastritis but were negative for *H. pylori,* although the patient had been *H. pylori* positive at baseline. The patient ultimately received 3 units of packed red blood cells and was discharged from the hospital 48 hours later. The patient was to be treated with acid suppression and undergo a repeat endoscopy in 4 to 5 weeks to document healing. This event was classified as: **gastric ulcer; GI bleed (traditional, 1B; alternate, 1F).**

Case 1016

Patient US0242-035-11377 was a 51-year-old female with a history of intermittent stress headaches, dizziness, hysterectomy, bilateral salpingo-oophorectomy, stress incontinence, L4-5 spinal fusion with Harrington rod insertion, skin fibroids, dermatitis, thyroidectomy, and OA. A GI history was significant for peptic ulcer disease and esophageal reflux. Concomitant medications included levothyroxine, acetaminophen, and conjugated estrogens. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID.**

After 4 days of treatment the patient began to complain of epigastric pain and nausea. **Study medication was discontinued on day 7**. On study day 8, the patient reported a black stool and was admitted to the hospital. Significant findings at this time included Hemoccult-positive stools and a hemoglobin of 14.9 g/dL compared with a baseline hemoglobin of 16.2 g/dL and a hematocrit of 44.8%, compared with a baseline hematocrit of 49.0%. An endoscopy performed on the following day revealed a tiny ulcer in the gastric cardia and multiple antral ulcers, the largest measuring 0.75 cm in diameter. Specific locations for these ulcers were noted to be at the angularis, antrum, and prepyloric area. There was adherent clot in the prepyloric region that could not be washed off. This area was injected with 6 mL of epinephrine and no active bleeding was noted. Two additional ulcers, the larger of which measured 0.5 cm in diameter, were identified in the duodenal bulb. CLOtest was reported as negative although the patient had a positive *H. pylori* serology at baseline. The patient was discharged from the hospital on the same day and was to be treated with acid suppression and undergo a repeat endoscopy in 6 to 8 weeks. Follow-up endoscopy was performed and revealed healing antral ulcers of 0.5 cm and 0.2 cm in diameter. The duodenal bulb appeared normal. At this time the patient reported that she had not completed a full course of acid suppression and additionally reported a small amount of hematochezia. Colonoscopy was recommended and acid suppression was restarted. This event was classified as: **gastric ulcer; GI bleed and duodenal ulcer (traditional, 1B; alternate, 1F).**

Case 1018

Patient US0330-035-11159 was an 85-year-old female with a history of cataract surgery, herpes zoster, multiple arthralgias, hypertension, chronic pedal edema, obesity, and OA. Concomitant medications included multivitamin, Equate, and Tums. Voltaren was discontinued one day prior to start of study drug. The patient was enrolled in protocol N49-98-02-035 and randomized to **celecoxib 400 mg BID**.

After 43 days of treatment the patient began experiencing abdominal pain and dyspepsia. On study day 48 the patient was seen in the clinic and she continued to report dyspepsia and lower abdominal pain. Stool hemoccults on days 51, 52, and 53 were negative, and a hemoglobin on day 54 was 12.4 g/dL compared with a baseline hemoglobin of 13.6 g/dL and a hematocrit on day 54 was unchanged from a baseline of 38.0%. Study medication was discontinued on day 62 because of progressively worsening symptoms and an outpatient UGI endoscopy was scheduled for study day 63. The patient, however, presented to the emergency room later on study day 62 with dyspnea and melena. Nasogastric lavage produced dark maroon material and a hematocrit was now 16.0%. An endoscopy was done as an inpatient on day 63 revealing a 1.5 x 1.5 x 1.0-cm ulcer in the duodenal bulb with adherent clot. After the procedure the patient developed hematemesis and was transferred to the intensive care unit. Repeat endoscopy was performed on day 64, again revealing the large, deep ulcer in the apex of the duodenal bulb. On this exam a visible vessel was identified in the ulcer base which was injected with epinephrine. Immediate re-bleeding required repeat injections of epinephrine, and tenuous hemostasis was ultimately achieved. Baseline serology for *H. pylori* had been negative. On study day 66 the patient had a surgical oversew of the lesion and ultimately recovered. She received a total of 9 units of packed red blood cells during the hospitalization. This event was classified as: **duodenal ulcer; GI bleed (traditional, 1B; alternate, 1F).**

Case 1022

Patient US0268-102-10193 was a 73-year-old female with a history of sinusitis, hyperopia, myopia, migraines, hypertension, colon polyps, cholecystectomy, inflamed ovary, breast cancer with no recurrence, leg cramps, intermittent elevation of liver enzymes, allergy to penicillin, and OA. Concomitant medications included hydrochlorothiazide, potassium, and calcium carbonate. The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID.**

After 8 days of treatment the patient began experiencing melena, abdominal pain and distention, nausea, dyspnea, and syncope. On study day 10 the patient was found to have a hemoglobin of 12.8 g/dL compared with a baseline hemoglobin of 13.4 g/dL and a hematocrit of 37.5% compared with a baseline hematocrit of 40.0%. **Study medication was discontinued on day 10**. Baseline serology for *H. pylori* had been positive. On study day 15 an endoscopy was performed revealing two gastric ulcers in the antrum measuring 0.3 cm and 0.2 cm. Also seen were superficial gastric erosions and streaking erythema in the distal body and one duodenal bulb erosion. This event was classified as: **gastric ulcer; GI bleed (traditional, 1C; alternate, none).**

Case 1025

Patient US0425-035-11153 was an 85-year-old female with a history of sleep disorder due to chronic pain, mild Parkinson's disease, diastolic dysfunction, upper respiratory infection/sinusitis, restrictive/obstructive lung disease, bleeding secondary to constipation, colon cancer, rectal bleeding due to constipation, diverticulosis, gastroesophageal reflux disease, hiatal hernia, urinary tract infection, bladder dysfunction, hysterectomy, osteoporosis, low back pain, excision of basal cell carcinoma, hypothyroidism, hyperlipidemia, anemia, intermittent mild thrombocytopenia, allergy to metoclopramide hydrochloride, and OA. Concomitant medications included levothyroxine, atorvastatin, diltiazem, aspirin, Darvocet N-100, oxybutynin, alendronate, multivitamin, and Citrucel. The patient was enrolled in protocol N49-98-02-035 and randomized to **celecoxib 400 mg BID** .

On study day 67 the patient presented to the clinic with a one-day history of passing melenic stools and complaints of lightheadedness and abdominal pain that had begun on that day. Findings at this time included hemoccult-negative stool, significant orthostatic changes in both systolic and diastolic blood pressure, and a hemoglobin of 12.0 g/dL compared with a baseline of 15.0 g/dL and a hematocrit of 36% compared with a baseline of 45%. The patient was admitted to the hospital and subsequently transferred to the intensive care unit after she became more hypotensive and tachycardia. The patient was transfused 2 units of packed red blood cells and an endoscopy was performed on study day 68. Endoscopic findings included a deep gastric ulcer with a visible vessel in the antrum measuring 0.5 cm in its longest length, duodenitis with multiple areas of submucosal hemorrhaging, and a superficial duodenal bulb ulcer measuring 1.5 cm at its longest length. Due to mechanical failure, thermal coagulation of the visible vessel was unsuccessful. On study day 70 the patient's hemoglobin had fallen to 8.9 g/dL and the hematocrit had fallen to 26.9%. A repeat endoscopy was performed. This exam revealed similar findings to the previous endoscopy with the additional finding of a 1.0-cm clean-based postbulbar ulcer. Again, no active bleeding was present and the gastric ulcer with

visible vessel was treated with several applications of Gold Probe coagulation. Biopsies obtained for *H. pylori* from the antrum were negative, as was the baseline serology. Over the next several days the patient stabilized and was discharged on study day 73; **study medication had been discontinued on day 62**. This event was classified as: **gastric ulcer; GI bleed and duodenal ulcer (traditional, 1B; alternate, 1F).**

Case 1026

Patient US0080-035-12446 was a 75-year-old female with a history of splenectomy, hysterectomy, onychomycosis of both feet, water retention, hypothyroidism, and OA. Concomitant medications included estradiol, levothyroxine, and spironolactone hydrochlorothiazide. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID**.

After 5 days of treatment the patient developed melenic stools. Black, tarry stools continued into study day 6 and on study 7 the patient was seen in the investigator's office. Significant findings at this time included hemoccult-positive stools and a hemoglobin of 14.2 g/dL compared with a baseline of 15.0 g/dL and a hematocrit of 42.1% compared with a baseline of 45.0%. On study day 8 an endoscopy was performed revealing mild esophagitis, a 2.0-cm hiatal hernia, and a 1.0 x 1.0-cm ulcer on the superior wall of the duodenal bulb with adherent clot. An antral biopsy was negative for pathology and *H. pylor*i; Baseline serology for *H. pylori* had also been negative**. Study medication had been discontinued on day 6**. This event was classified as: **duodenal ulcer; GI bleed (traditional, 1B; alternate, none).**

Case 1027

Patient US0415-035-21191 was a 53-year-old female with a history of asthma, fluid retention, hypertension, and RA. Concomitant medications included methotrexate, folic acid, albuterol, and hydrochlorothiazide. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID**.

On day 17 of treatment the patient developed emesis, abdominal cramping, nausea, diarrhea, and dizziness. At this time she **discontinued her study medication**. She also reported experiencing ongoing nonspecific fatigue over the previous 9 days. On study day 18 she presented to the clinic with strongly hemoccult-positive black stools. At this time a hemoglobin was 10.3 g/dL compared with a baseline of 13.3 g/dL and a hematocrit was 30.3% compared with a baseline of 41%. An endoscopy was performed on study day 19 revealing approximately 12 petechial lesions in the body and three linear erosions, each measuring approximately 0.6 cm, in the antrum. Hemoccult-positive black stools persisted at least through study day 22 and the hematocrit fell to 27.6% at this time. The patient was treated for *H. pylor*i; the baseline serology had been positive This event was classified as: **gastric erosion (traditional, 1C; alternate, 1G).**

Case 1028

Patient US0144-035-20966 was an 80-year-old female with a history of sleep disturbance, hypertension, left foot bunion, peptic ulcer disease, and RA. Concomitant medications included Tylenol PM, glucosamine, and metoprolol. The patient was enrolled in protocol N49-98-02-035 and randomized to **celecoxib 400 mg BID**.

On study day 41 the patient reported that she had experienced a near syncopal episode and "fell over a sofa." Paramedics responding to her call were not informed of the near syncope and evaluated her for a fall. Because of stable vital signs and no other symptoms reported, the paramedics did not transport the patient to the hospital. Later in the day the patient experienced coffee ground-like emesis which she attributed to tea that she had previously consumed. At approximately 6:00 pm the patient began to feel weak and dizzy and passed a large black/burgundy colored diarrheal stool. Paramedics were again called and this time transported her to the emergency room. Significant findings in the emergency room included postural changes in blood pressure, specifically 113/65 mm Hg, 80 bpm (supine) and 105/64 mm Hg, 102 bpm (standing). Laboratory tests revealed a hemoglobin of 9.0 g/dL compared with a baseline of 12.1 g/dL and a hematocrit of 26.2% compared with a baseline of 37.0%. Baseline serology for *H. pylori* had been positive. The patient was transfused with 2 units of packed red blood cells. An endoscopy performed on study day 42 revealed antral linear erosions in the stomach and a 1.0 x 2.0-cm inferior duodenal ulcer without active bleeding or visible vessel. Study medication had been discontinued on day 40. The patient was treated with acid-suppressive therapy and was **discontinued from the study**. This event was classified as: **duodenal ulcer; GI bleed (traditional, 1C; alternate, 1G).**

Case 1029 (Censored)

Patient US0417-035-20397 was a 67-year-old female with a history of tonsillectomy, adenoidectomy, fatigue, depression, hypertension, hemorrhoidectomy, hematuria, fractured toes, basal cell carcinoma, psoriasis, hypercholesterolemia and RA. Concomitant medications included Prempro, triamterene/hydrochlorothiazide, methotrexate, aspirin, multivitamins, folic acid, cod liver oil, vitamin E, vitamin C, and calcium. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID** which started 12/4/98**.**

[On the second day 12/5/98] of treatment, the patient complained of stomach "churning," nausea, and "not feeling right." Study medication was discontinued on day 3 [12/6/98]. On study day 6 [12/9/98] the patient noticed black stools for the first time and a rectal examination detected hemoccult-positive stool. Additional significant findings at this time included a hematocrit of 41.8% compared with a baseline hematocrit of 43.0%. On study day [7, 12/11/98] the patient had an upper endoscopy performed revealing three gastric ulcers and a hiatal hernia. Two of these ulcers were located near the gastroesophageal junction and measured 0.5 x 0.1 cm and 1.0 x 0.1 cm, respectively. A third ulcer, 1.0 cm in diameter, was found in the prepyloric area. None of the ulcers had stigmata of recent bleeding and no fresh blood was seen. Finally, the gastric mucosa appeared generally inflamed and the antrum was described as "abnormal." A CLOtest biopsy was negative for *H. pylor*i, as was the baseline serology. The **patient was terminated from the study and treated with acid suppression**. A follow-up endoscopy done approximately six weeks later revealed a 0.5-cm antral ulcer approximately 3 to 4 cm from the pylorus. CLOtest was again negative. This event was classified as: **gastric ulcer; GI bleed (traditional, 1C; alternate, none).**

Reviewer's comment: The dates/comments in this summary that appear in* [] *were added after review of the CRF.

Case 1036

Patient US0017-102-10032 was an 80-year-old male with a history of impaired hearing, cataracts in right and left eyes, Parkinson's disease, anxiety, right carotid endarterectomy, hypertension, bilateral common carotid angiography, appendectomy, peptic ulcer in 1988, heartburn, rash under right breast, and OA. Concomitant medications included enalapril maleate, Darvocet-N, amantadine hydrochloride, isradipine, and clonazepam. The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID.**

After 66 days of treatment the patient began experiencing diarrhea and very dark black stool. Significant findings at this time included hemoccult-positive stool and a hemoglobin of 14.3 g/dL compared with a baseline of 14.5 g/dL and a hematocrit of 44% compared with a baseline of 43%. On study day 72, an upper endoscopy revealed fewer than 25 red- and white-based erosions scattered in the gastric body and antrum, but most prominently located in the prepyloric area. There was also a white-based linear ulceration measuring 0.3 cm in length on the posterior wall of the pylorus. The duodenal bulb and sweep were remarkable for patchy areas of inflammation. Also seen was a small sliding hiatal hernia. There was no evidence of esophagitis. Serology for *H. pylori* was negative, as was the baseline serology. **Study medication was discontinued on day 66.** This event was classified as: **gastric ulcer; GI bleed (traditional, 1C; alternate, none).**

Case 1037

Patient US0386-102-10294 was a 71-year-old female with a history of a right wrist ganglion, migraine headaches and intermittent headaches, dizziness, transient ischemic attack, hypertension, carotid artery stenosis, peripheral vascular disease, aortofemoral bypass, emphysema, dyspepsia, duodenal ulcer, gastric ulcer, esophagitis, chronic constipation, hemorrhoids, intermittent rectal bleeding, cystocele repair, hysterectomy, compound fracture of the 4th lumbar vertebra, back pain, left small toe fracture, hypercholesterolemia, osteoporosis, and OA. Concomitant medications included nifedipine slow release, lisinopril, dipyridamole, and hydrochlorothiazide. The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID.**

After nine days of treatment the patient began experiencing epigastric pain, nausea, and heartburn. At this time the patient was found to have hemoccult-positive stool. Endoscopic evaluation performed on study day 30 revealed a 1.0-cm duodenal bulb ulcer with a clot**. Study medication was discontinued** at this time. Serology for *H. pylori* was negative, as was the Baseline serology. This event was classified as: **duodenal ulcer; GI bleed (traditional, 1B; alternate, none).**

Case 1040

Patient US0024-102-20702 was a 73-year-old male with a history of hearing loss, tonsillectomy, chronic sinusitis, septal deviation, concha bullosa deformities of both middle turbinates, arcuate defects of both eyes, numbness and tingling in left leg, appendectomy, hemorrhoids, benign prostatic hyperplasia, muscle weakness, low back pain, fracture of the right ankle, shrapnel scars, bruising easily, lips burning, anemia, hepatitis, hyperuricemia, hypercholesterolemia, OA, and RA. Concomitant medications included hydrocodone bitartrate with acetaminophen, prednisone, methotrexate, hydrochlorothiazide with triamterene, diphenhydramine hydrochloride cream, aspirin, Tums, multivitamins, and Folic acid. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

After 17 days of treatment the patient began experiencing heartburn, mild epigastric pain, black vomitus, and black tarry stool. **Study medication was discontinued** at this time. Significant findings at this time included a hemoglobin of 9.4 g/dL compared with a baseline of 12.7 g/dL, a hematocrit of 27.2% compared with a baseline of 38.0%, and hemoccult-positive stool. Because of these findings the patient underwent an upper endoscopy. This revealed approximately 5.0 to 6.0 cm of Barrett's esophagus and a deep posterior duodenal bulb ulcer with a large clot in its base. The ulcer measured approximately 2.0 cm and was identified as the source of bleeding. The ulcer base was injected with 6.5 mL of epinephrine. Serology for *H. pylori* was negative, as was the baseline serology. The patient ultimately received 1 unit of packed red blood cells. This event was classified as: **duodenal ulcer; GI bleed (traditional, 1B; alternate, 1F).**

Case 1041

Patient US0112-035-10077 was an 81-year-old male with a history of a tonsillectomy, hypertension, heart murmur, hyperlipidemia, diverticulitis, cholecystectomy, benign prostatic hypertrophy, back pain, gout, right inguinal hernia repair, skin cancer, and OA. Concomitant medications included allopurinol, gemfibrozil, lisinopril, and hydrochlorothiazide. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID.**

After 85 days of treatment the patient was found to have a a hemoglobin of 12.1 g/dL compared with a baseline of 15.8 g/dL and a hematocrit of 36.0% compared with a baseline of 48.0%. **Study medication was discontinued on day 104**. On study day 105 a UGI endoscopy was performed revealing multiple superficial and full thickness ulcers measuring from 0.3 to 0.8 cm. One or two of the lesions appeared to have been oozing around the edge. Antral biopsies for *H. pylori* were positive, as was the baseline serology. This event was classified as: **gastric ulcer; GI bleed (traditional, 1B; alternate, 1F).**

Case 1052

Patient US0544-102-20398 was a 66-year-old male with a history of right hearing loss, coronary artery disease with six-vessel bypass, hyperlipidemia, GI intolerance to NSAIDs, right knee surgery, OA, and RA. Concomitant medications included Lipitor, procardia, atenolol, gold injections, multivitamins, and aspirin. The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID**.

On the first day of treatment the patient began taking Maalox every other day for heartburn. Between study days 8 and 41 the patient only used Maalox nightly at bedtime; however after day 41 this frequency was increased to BID due to increasingly symptomatic heartburn. **Study medication was discontinued on day 48**. On study day 49 the patient experienced several episodes of melena that recurred on day 50 but had stopped by day 51. A UGI endoscopy was performed on study day 56, revealing a 5.0-cm hiatal hernia, mild nonerosive duodenitis, and a 1.0 to 1.5-cm duodenal bulb ulcer with moderate surrounding erythema and edema. A biopsy for *H. pylori* was negative, as was the baseline serology. A rectal examination produced hemoccult-positive stool. Laboratory evaluation performed on study day 57 revealed a hemoglobin of 7.5 g/dL compared with a baseline of 13.3 g/dL and a hematocrit of 21.9% compared with a baseline of 41.0%. The patient was treated for *H. pylori* and with acid suppression and **discontinued from the study**. This event was classified as: **duodenal ulcer; GI bleed (traditional, 1C; alternate, 1G).**

Case 1055

Patient US0279-102-12815 was a 66-year-old male with a history of hiatal hernia and gastric ulcer (1991), hypertension, congestive heart failure, gout, cardiomegaly, obesity, hypercholesterolemia, esophageal reflux, angina,

rhinitis, psoriasis, bronchitis, arteriosclerotic cardiovascular disease, peptic ulcer disease (1988), esophagitis, chronic renal insufficiency, degenerative joint disease (right hip and bilateral shoulder replacement), seasonal allergies, OA, and RA. Concomitant medications included digoxin, isosorbide, sublingual nitroglycerin, aspirin, furosemide, lisinopril, metoprolol, prazosin, diphenhydramine, cetrizine, colchicine, probenecid, calcium carbonate, Maalox, hydrocortisone, Thymol, triamcinolone, and Entex-LA. The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID**.

After 7 days of treatment the patient began experiencing nausea and epigastric and abdominal pain. **Study medication was discontinued at this time**. On study day 11 the patient was seen in the clinic and reported multiple episodes of black tarry stools, which had begun that day. Significant findings at this time included hemoccult-positive stool and an orthostatic change in pulse rate from 83 bpm in a sitting position to 104 bpm in a standing position. The patient was admitted to the hospital and an upper endoscopy was performed on study day 12 revealing a duodenal bulb ulcer. Biopsy was negative for *H. pylori,* as was a Baseline serology. The patient was treated with acid suppression and was **discontinued from the study.** This event was classified as: **duodenal ulcer; GI bleed (traditional, 1C; alternate, 1G).**

Case 1056 (Censored)

Patient US0114-035-11573 was a 72-year-old female with a history of myopia, hyperopia, sinus infection, glaucoma, tonsillitis, temporal mandibular joint dysfunction, stress headaches, depression, migraines, hypertension, hypercholesterolemia, pneumonia, bronchitis, hiatal hernia, urinary tract infection, menorrhagia, benign bilateral breast cysts, shattered humerus, dehydration and OA. Concomitant medications included Levo Bunolol, medroxyprogesterone acetate, conjugated estrogen, triamterene, verapamil hydrochloride, fluoxetine hydrochloride, Fioricet, Calcium with Vitamin D, Darvocet, Vitamin C, and loratadine. The patient was enrolled in protocol N49-98-02-035 and randomized to **celecoxib 400 mg BID**.

[The patient started therapy on 12/11/98. This may also be the last day of her prior naproxen sodium therapy]. After 2 [rash was noted first on study day 9-12/19/98 or study day 11-12/21/98] days of treatment the patient developed itching, a whole body rash, and black stools [melena was first noted by the patient 12-19-98 at which time she was found to be heme +, a typed addition to the CRF states that "it is believed patient began having black stools on 12/12.98"]. From study day 10 through study day 16 the patient complained of GI upset. **Study medication was discontinued on day 10 [day 11-12/21/98]**. At this time the patient was given a prescription for cimetidine and a steroid dose pack. She refused further work-up until "after the holidays" and ultimately returned for a termination visit on day 27 [1/6/99]. Significant findings at this time included a hemoglobin of 10.2 g/dL compared with a baseline of 12.3 g/dL, a hematocrit of 29.0% compared with a baseline of 37.0%, and hemoccult-positive stool. A UGI endoscopy was performed on day 50 [1/29/99] revealing 0.5-cm and 0.3-cm clean-based antral ulcers, and an erosion on the greater curve in the mid-body of the stomach. A biopsy for *H. pylori* was negative, as was the baseline serology. Of note, the patient did not take any NSAIDs between study drug discontinuation and the endoscopy. This event was classified as: **gastric ulcer; GI bleed (traditional, 1C; alternate, 1G).**

> ***Reviewer's comment: The dates/ comments in this summary that appear in* [] *were added after review of the CRF.***

Case 1057

Patient US0268-102-10196 was a 60-year-old male with a history of tinnitus, decreased hearing in right ear, hypertension, mild restrictive lung disease, hiatal hernia, colon polyps, rotator cuff injury of the right shoulder, bilateral ankle and groin rash secondary to dermatitis, and OA. Concomitant medications included amlodipine besylate, levothyroxine sodium, diazepam, Tylenol PM, fluoxetine hydrochloride, Tylenol with Codeine, and nizatidine. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

After 56 days of treatment the patient began experiencing severe epigastric pain. **Study medication was discontinued on day 62.** On study day 65 the patient underwent an UGI endoscopy revealing a large hiatal hernia and a 1.0 to 1.2-cm duodenal bulb ulcer with adherent clot in the base. Serology for *H. pylori* was negative, as was the baseline serology. The patient was **discontinued from the study** and treated with acid suppression.
This event was classified as: **duodenal ulcer; GI bleed (traditional, 1B; alternate, 1F).**

Case 1058

Patient US0118-102-20035 was a 56-year-old female with a history of hysterectomy, multiple fractures as a result of an automobile accident, *Staphylococcus* infection, and RA. Concomitant medications included hydroxychloroquine sulfate, conjugated estrogens, and sulfasalazine. The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID**.

After 6 days of treatment the patient began experiencing nausea and moderate to severe abdominal pain. **Study medication was discontinued on day 19.** On study day 20 the patient underwent an upper endoscopy revealing six antral ulcers, the largest measuring 0.6 x 0.2 cm with a small overlying clot. The remaining five ulcers measured 0.2 to 0.4 cm. A small hiatal hernia, ulcerative esophagitis, and duodenitis were also reported. A biopsy for *H. pylori* was positive, as was the baseline serology. The patient was **discontinued from the study** and treated with acid suppression. This event was classified as: **gastric ulcer; GI bleed (traditional, 1B; alternate, none).**

Case 1060

Patient US0253-035-20258 was a 58-year-old male with a history of hypertension, hiatal hernia, gastroesophageal reflux disease, UGI bleeding, vasectomy, carpal tunnel release of left wrist, anemia, and RA. Concomitant medications included lisinopril and ferrous sulfate. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID.**

After 92 days of treatment, at the scheduled week 13 visit, the patient was found to have a hemoglobin of 12.2 g/dL compared with a baseline of 14.5 g/dL and a hematocrit of 39.0% compared with a baseline of 45.0%. On study day 94 a stool sample was found to be hemoccult-positive and a repeat hematocrit was 34.0%. **Study medication was discontinued on day 100**. A UGI endoscopy was performed on study day 101 revealing a hiatal hernia, ulcerative esophagitis, severe erosive gastritis with multiple deep linear erosions in the upper body of the stomach, minor antral petechiae and edema, and scant coffee ground material. The erosions were further characterized as 1.0 to 2.0 cm in length with a depth of 0.1 to 0.2 cm. A CLOtest was negative for *H. pylori* as was a baseline serology. This event was classified as: **gastric erosion; GI bleed (traditional, 1D1; alternate, 1H).**

Case 1073

Patient US0066-035-13004 was a 70-year-old male with a history of mild hypertension, hypercholesterolemia, mild benign prostatic hyperplasia, GI-related NSAID intolerance, and OA. Concomitant medications included aspirin, atorvastatin, niacin, vitamin E and C, glucosamine, and chondroitin. The patient was enrolled in protocol N49-98-02-035 and randomized to **celecoxib 400 mg BID**.

After 65 days of treatment the patient reported having a formed black stool. Formed black stool recurred on study day 66 and the patient presented to the clinic. **Study medication was discontinued at this time.** Significant findings at this time included hemoccult-positive stool and a hemoglobin of 15.2 g/dL compared with a baseline of15.8 g/dL and a hematocrit of 44.0%, compared with a baseline of 47.0%. The patient was admitted to the hospital and a follow-up hemoglobin done at midnight of study day 66 was 13.3 g/dL with a hematocrit of 39.3%. A UGI endoscopy was performed on study day 66 revealing two 0.5-cm stellate, clean-based ulcers on the angularis, a 1.3-cm antral ulcer oozing bright red blood, and a normal duodenum. Hemostasis was achieved using both epinephrine injection and bicap cautery. A CLOtest was positive for *H. pylori,* as was the baseline serology. The patient was treated with acid suppression and discontinued from the study. This event was classified as: **gastric ulcer; GI bleed (traditional, 1B; alternate, 1F).**

Case 1075

Patient US0585-102-11251 was a 79-year-old female with a history of peripheral vascular atherosclerotic disease with claudication, hypercholesterolemia, bradycardia, ulcers, and OA. Concomitant medications included atrovastin, cimetidine, aspirin, and hydrochlorothiazide with triamterene. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID**.

After 34 days of treatment the patient began experiencing epigastric pain. On day 36 the pain became more severe and the patient took cimetidine. On study day 37 the patient went to the emergency room after experiencing two episodes of tarry black stool and coffee ground emesis. **Study medication was discontinued at this time**. She also reported orthostatic symptoms at this time. A nasogastric lavage produced 600 mL of coffee ground material and fresh blood.

Significant laboratory findings at this time included hemoccult-positive stool and a hematocrit of 34.9% compared with a baseline hematocrit of 45.0%. The patient was admitted to the hospital and an UGI endoscopy was performed revealing a 0.8 x 1.0-cm pyloric channel ulcer with a pulsatile, actively bleeding visible vessel in its base. Additional ulcers were seen in the pyloric channel and duodenal bulb as well. Hemostasis was achieved using epinephrine injection and monopolar electrocautery. Biospy for *H. pylori* was positive, as was the baseline serology. Ultimately, the patient received 4 units of packed red blood cells and was treated with acid suppression. She was **discontinued from the study**. This event was classified as: **gastric ulcer; GI bleed; duodenal ulcer (traditional, 1B; alternate, 1F).**

Case 1078

Patient US0387-102-10181 was a 60-year-old male with a history of left lower leg reconstruction with left total knee replacement, left leg reconstruction with metal plate insertion, and OA. Concomitant medications included aspirin, darvocet, calcium, and multiple vitamins. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

After 107 days of treatment the patient began experiencing dyspnea on exertion, diaphoresis, hematochezia, and melena. **Study medication was discontinued** on day 108. On study day 113 the patient presented to the clinic and was admitted to the hospital. Significant findings at this time included a hematocrit of 25.3% compared with a baseline hematocrit of 38.0%. The patient received 2 units of packed red blood cells. Upper GI endoscopy performed the next day, study day 114, revealed a deep linear ulcer in the prepyloric antrum with surrounding edema. There was also a deep, round duodenal bulb ulcer 1.0 cm in diameter. Both ulcers had an exudative base without stigmata of recent bleeding. A CLOtest was negative for *H. pylori,* as was the baseline serology. The patient was treated with acid suppression. This event was classified as: **gastric ulcer, duodenal ulcer; GI bleed (traditional, 1C; alternate, 1G).**

Case 1084

Patient US0052-102-10549 was an 84-year-old female with a history of dry eyes secondary to Sjogren's syndrome, appendectomy, flatulence, irritable bowel syndrome, lysis of intestinal adhesions, incontinence, hysterectomy, chronic urinary tract infections, osteoporosis, left shoulder tendonitis, right hip replacement, bilateral hammertoe repair, hair loss, and OA. Concomitant medications included conjugated estrogens, multivitamins, calcium carbonate, loperamide, and aspirin. The patient was enrolled in Study N49-98-02-102 and randomized to **diclofenac 75 mg BID.**

After 93 days of treatment the patient was seen in the clinic for a scheduled week 13 visit and found to have a hemoglobin of 9.6 g/dL compared with a baseline of 11.9 g/dL and a hematocrit of 28.0% compared with a baseline of 37.0%. On study day 97 a stool sample was found to be hemoccult-positive. **Study medication was discontinued at this time.** On study day 98 a UGI endoscopy was performed revealing four very shallow erosions in the prepyloric antrum and a 1.0-cm shallow to moderately deep ulcer in the distal duodenal bulb. The ulcer had a clean base but a small amount of blood was noted to ooze from the periphery of the lesion. A biopsy for *H. pylori* was negative despite a positive baseline serology. The patient was treated with acid suppression and **discontinued from the study.** This event was classified as: **duodenal ulcer; GI bleed (traditional, 1B;**
alternate, 1F).

Case 1085

Patient US0110-035-11139 was a 67-year-old male with a history of Meniere's disease, hyperlipidemia, chronic obstructive pulmonary disease, cerebrovascular accident, asthma, anserine bursitis of right knee, central laminectomy, type II diabetes mellitus, thoracic outlet syndrome, rib resection, right knee arthroscopy, right tennis elbow, seasonal and environmental allergies, allergy to penicillin, and OA. Concomitant medications included pravastatin, meclizine, metformin, Asthmacort, albuterol, aspirin, methylprednisolone, and loratadine. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID**.

After 168 days of treatment the patient called the principal investigator because he was feeling weak and dizzy. He also reported black stools and leg cramps. Because the patient felt too sick to see the investigator, he presented to the emergency room. The patient repeated his concerns about orthostatic symptoms and reported persistent melena.
Significant findings at this time included pallor, tachycardia with a heart rate of approximately 130 to 140 bpm, and black, hemoccult-positive stool. A nasogastric lavage produced "coffee ground" material. A hemoglobin was 13.0 g/dL

compared with a baseline 15.3 g/dL and a hematocrit was 40.1% compared with a baseline of 45.0%. The patient was admitted to the hospital and a UGI endoscopy performed that evening revealed old blood but no active bleeding, a linear distal esophageal ulcer, a group of shallow antral ulcers, and a pyloric channel ulcer with a visible vessel. The visible vessel was cauterized with a heater probe. No *H. pylori* testing was done, but the baseline serology had been positive for *H. pylor*i. **Study medication was discontinued** and the patient was treated with acid suppression. This event was classified as: **gastric ulcer; GI bleed (traditional, 1B; alternate, 1F).**

Case 1113

Patient US0112-035-10235 was an 84-year-old female with a history of coronary artery bypass graft secondary to coronary artery disease, hypertension, benign heart murmur, hiatal hernia, colon resection secondary to infection, hysterectomy, osteoporosis, left knee replacement, psoriasis, and OA. Concomitant medications included alendronate sodium, diltiazem hydrochloride, aspirin, furosemide, vitamin B12, vitamin D, fluvastatin sodium, isoxsuprine hydrochloride, calcium carbonate, and potassium chloride. The patient was enrolled in protocol N49-98-02-035 and randomized to **celecoxib 400 mg BID.**

After 209 days of treatment the patient developed nausea, anorexia, and right upper quadrant pain. On study day 210 the patient presented to her primary care physician and a work-up including an abdominal ultrasound and abdominal CT was performed. The ultrasound revealed a small amount of fluid in Morrison's pouch and the CT revealed a prominent gallbladder with pericholecystic fluid. An x-ray revealed free air in the right upper quadrant and an exploratory laparotomy revealed a perforated pyloric channel ulcer. A Graham closure was performed and the patient recovered without incident. The baseline serology had been negative for *H. pylor*i. **Study medication was discontinued** on day 211. This event was classified as: **gastric ulcer; perforation (traditional, 2; alternate, 2).**

Case 1122

Patient US0448-035-11767 was a 68-year-old female with a history of bilateral cataract removal with lens implants, heartburn, back and neck pain, arthroscopic right knee surgery, psoriasis, sun sensitivity, and OA. Concomitant medications included conjugated estrogen, medroxyprogesterone acetate, carisoprodol, calcium, vitamins, Pain Free herbal supplement, acetaminophen, and l-lysine. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID** .

After 123 days of treatment the patient began experiencing abdominal pain. She reported that on study day 124 she vomited for 5 hours but obtained some relief from Mylanta. On study day 126 the patient presented to her physician and was found to be hemoccult-positive. **Study medication was discontinued** at this time. A hemoglobin at this time was 11.3 g/dL compared with a baseline of 12.3 g/dL and a hematocrit was 33.7% compared to a baseline of 37.0%. On study day 129 the patient underwent UGI endoscopy revealing four posterior wall antral ulcers, the largest of which was 0.8 cm x 1.0 cm, three proximal antral ulcers between 0.3 cm and 0.6 cm located along the lesser curvature, a 0.2 x 1.5-cm greater curvature erosion, multiple punctate erosions, a 0.6-cm to 0.7-cm pyloric channel ulcer, and a normal duodenum to the third portion. The endoscopist felt that there was no evidence of outlet obstruction but that the pyloric channel ulcer may have contributed to a partial outlet obstruction. Biopsy for *H. pylori* was negative, as was the baseline serology. This event was classified as: **gastric ulcer; GI bleed (traditional, 1D1; alternate, none).**

Case 1132

Patient US0371-035-12217 was a 78-year-old female with a history of cataract removal with lens implant, memory loss, internal hemorrhoids, colo-vesicular fistula, gastroesophageal reflux, appendectomy, coronary artery disease, angina pectoris, family history of colon carcinoma, sigmoid resection for chronic diverticulitis, hiatal hernia, urinary incontinence, degenerative joint disease, right inguinal hernia repair, fibrocystic breast disease, obesity, allergy to eggs, and OA. Concomitant medications included Centrum vitamins. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID.**

After 25 days of treatment the patient began experiencing epigastric pain and reflux. She was found to have a hemoglobin of 10.2 g/dL compared with a baseline of 12.3 g/dL and a hematocrit of 30.0% compared with a baseline of 36.0%. Stool hemoccults were negative and on study day 30 a UGI series revealed a large hiatal hernia with reflux. The patient remained in the study and on study day 81 she had a colonoscopy revealing hemorrhoids, an anastomotic stricture and diverticulosis. On a routine study visit on study day 92 the patient was found to have a persistently low hemoglobin of 9.7 g/dL with a hematocrit of 31.0% and on study day 99 the stool was hemoccult-positive for the first time. **Study medication was discontinued** on day 141 and on study day 149 a UGI endoscopy revealed a hiatal hernia and a 0.3 to 0.4-cm gastric ulcer in the proximal body with associated black spot or blood clot. Biopsy for *H. pylori* was

positive, as was the baseline serology. The patient was treated with antibiotics and acid suppression. This event was classified as: **gastric ulcer; GI bleed (traditional, 1B; alternate, 1F).**

Case 1133

Patient US0182-102-11142 was a 66-year-old female with a history of angina, heart attack, hypertension, constipation, hemorrhoid, hysterectomy, osteoporosis, total right and left hip arthroplasty, redone total left hip arthroplasty, and OA. Concomitant medications included lisinopril, diltiazem hydrochloride, conjugated estrogens, vitamin supplement, Vitamin C, Vitamin E, and docusate sodium. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

After 96 days of treatment the patient returned for a scheduled visit and was found to have a hemoglobin of 11.3 g/dL compared with a baseline of 14.0 g/dL and a hematocrit of 35.0% compared with a baseline of 41.0%. Follow-up stool hemoccults were found to be positive on study days 106, 108, and 118. **Study medication was discontinued** on day 127. Upper GI endoscopy was performed on study day 131, revealing three non-bleeding superficial antral ulcers with distinct depth. The largest lesion had a diameter of 0.6 cm in its longest axis. A biopsy for *H. pylori* was negative, as was the baseline serology. The patient was **discontinued from the study** and treated with acid suppression. This event was classified as: **gastric ulcer; GI bleed (traditional, 1D1; alternate, 1H).**

Case 1145

Patient US0448-035-11011 was an 81-year-old female with a history of cataract removal, hypercholesterolemia, duodenal ulcer disease (1976), heartburn, nocturia, postmenopausal hormone replacement therapy, occasional constipation, chronic low back pain, osteoporosis, sciatica, and OA. Concomitant medications included glucosamine, conjugated estrogens, medroxyprogesterone acetate, unspecified multivitamins, calcium, vitamins B, C, and E, iron, and acetaminophen. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID.**

After approximately 124 days of treatment the patient began experiencing sporadic epigastric pain and heartburn. On study day 158 the patient was found to have a hemoglobin of 11.1 g/dL compared with a baseline of 14.1 g/dL and a hematocrit of 34.0% compared with a baseline of 44.0%. Follow-up hemoglobin and hematocrit on study day 183 were again low at 11.1 g/dL and 33.0%, respectively. Stools were hemoccult-negative at this time. **Study medication was discontinued** on day 189. On study day 196 the patient underwent UGI endoscopy and colonoscopy. The colonoscopy revealed a 1.0-cm sessile sigmoid polyp and the endoscopy was remarkable for a hiatal hernia and esophageal erosions, an edematous pyloric channel, and a 1.5 x 2.0-cm duodenal bulb ulcer with a "dirty" necrotic base. The area around the ulcer was described as friable and bled with minimal manipulation. Because of surrounding edema and friability, the endoscope could not be passed into the descending duodenum. Biopsy for *H. pylori* was negative, as was the baseline serology. This event was classified as: **duodenal ulcer; GI bleed (traditional, 1B; alternate, 1F).**

Case 1146

Patient US0595-102-12252 was an 84-year-old male with a history of heart murmur, macular degeneration, ankle edema, left total knee surgery (twice), left carpal tunnel release, left lower leg cramps, right thumb lock, angina with exertion, bilateral cataract surgery, vitrectomy, scleral buckle, chronic obstructive pulmonary disease, gallstones, coronary artery disease, atrial fibrillation (nonrecurrent since 1993), arteriosclerotic cardiovascular disease, benign prostatic hypertrophy, polymyalgia rheumatica (nonrecurrent since 1989), aortic sclerosis, degenerative disc disease, partial tear of the right rotator cuff, and OA. Concomitant medications included diltiazem hydrochloride, bumetanide, aspirin, ocuflox, and Pred Forte. The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID.**

After 11 days of treatment the patient began experiencing heartburn and chest pain that was relieved with antacids. Later that day he developed severe epigastric burning and tightness with radiation to the chest. After medicating himself with three aspirin, one Prilosec, four nitroglycerin and an unknown medication and experiencing no relief, he presented to the hospital and was admitted. **Study medication was discontinued** at this time. Significant findings at this time included hemoccult-positive stool and a hemoglobin of 11.3 g/dL compared with a baseline of 13.2 g/dL and a hematocrit of 33.0% compared with a baseline of 38.0%. Additionally, a troponin level was 1.2 ng/mL. Myocardial infarction was ruled out and on study day 15 a UGI endoscopy revealed two to three small nonbleeding gastric antral

ulcers and antral gastritis. A biopsy for *H. pylori* was negative, as was the baseline serology. On study day 18 the patient underwent a cardiac catheterization that demonstrated triple vessel disease. The patient elected medical management of his cardiovascular disease and was treated with acid suppression for his ulcer disease. This event was classified as: **gastric ulcer; GI bleed (traditional, 1D1 alternate, none).**

Case 1148

Patient US0279-102-12965 was a 78-year-old male with a history of dizziness, cerebrovascular accident, hypertension, atrial fibrillation, cardiovascular disease, cardiac dysrhythmia, congestive heart failure, tobacco use, diverticulosis, hyperacidity, benign prostatic hypertrophy, rotator cuff sprain, lumbago, non-insulin-dependent diabetes mellitus, obesity, constipation, total right hip replacement (twice), and OA. Concomitant medications included aspirin, sublingual nitroglycerin, topical nitroglycerin, docusate sodium, albuterol, glyburide, levofloxacin, quinidine, terazosin, furosemide, lisinopril, metoprolol, and ipratropium. The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID.**

After 82 days of treatment the patient was hospitalized for dyspnea. A cardiac work-up was initiated and ultimately led to a cardiac catheterization and subsequent coronary artery bypass grafting on study day 92. **Study medication was discontinued on day 91**. Upon admission to the hospital on study day 82, the patient was found to have hemoglobin of 13.2 g/dL compared with a baseline of 15.1 g/dL and a hematocrit of 38.4% compared to a baseline of 46.0%, although a **GI work-up was not performed**. The patient was discharged from the hospital on study day 99 after an uneventful postoperative recovery. On study day 102, however, the patient was readmitted to the hospital after he presented to the emergency room with recurrent dyspnea and chest pain. He was transferred to another hospital and subsequently developed hypotension and melena and was placed in the intensive care unit. Upper GI endoscopy revealed a large amount of blood in the fundus and a 1.0 x 2.0-cm duodenal bulb ulcer with an adherent clot. No active bleeding was noted. The patient received 6 units of packed red blood cells as the hemoglobin and hematocrit had fallen to 8.0 g/dL and 23.0% by midnight of study day 102. At approximately this time the patient developed hematemesis and underwent a second endoscopy. On this examination pulsatile bleeding was noted from the duodenal ulcer. Heater probe cautery and injection sclerotherapy was unsuccessful and the patient required emergency surgery consisting of vessel ligation and vagotomy. He received an additional 3 units of packed red blood cells and ultimately stabilized and was discharged from the hospital. Biopsy for *H. pylori* was negative, despite a positive baseline serology. Medications included his cardiac regimen as well as acid suppression. This event was classified as: **duodenal ulcer: GI bleed (traditional, 1B; alternate, 1F).**

Case 1149

Patient US0134-035-20749 was a 60-year-old male with a history of ventral hernia repair and RA. Concomitant medications included methotrexate, hydrocodone, Cosamin DS, and acetaminophen. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID.**

After 31 days of treatment the patient was asymptomatic but noted to have a hemoglobin of 11.2 g/dL compared with a baseline of 12.3 g/dL and a hematocrit of 34.0% compared with a baseline of 39.0%. On study day 43, the patient was still asymptomatic but found to have a hemoglobin and hematocrit of 9.6 g/dL and 29.0%, respectively. Study **medication was discontinued** at this time and on study day 46 the patient was found to have a hemoccult-positive stool. Upper GI endoscopy was performed on study day 47 revealing greater than 25 gastric petechiae and 7 gastric erosions 0.2 to 0.3 cm in diameter predominantly located in the pre-pyloric antrum. The pylorus was also noted to be edematous and the duodenal bulb was remarkable for petechiae and edema. Baseline serology for *H. pylori* had been positive. This event was classified as: **gastric erosions; GI bleed (traditional, 1D1; alternate, 1H).**

Case 1186

Patient US0421-035-10266 was a 74-year-old male with a history of atrial arrhythmia, hypertension, nocturia, benign prostatic hypertrophy, appendectomy, and OA. Concomitant medications included verelan and "baby aspirin." The patient was enrolled in protocol N49-98-02-035 and randomized to **celecoxib 400 mg BID.**

After 292 days of treatment the patient passed two black stools followed by profuse red diarrhea. The patient also described one episode of hematemesis. Because of these symptoms and a feeling of weakness, the patient presented to the emergency room. **Study medication was discontinued**, and significant findings at this time included orthostatic symptoms, resting tachycardia to 110 bpm, hemoccult-positive stools, and a hemoglobin of 11.3 g/dL compared with a baseline of 14.4 g/dL and a hematocrit of 32.4% compared with a baseline of 42.0%. The patient was hydrated and

admitted to the intensive care unit. Shortly thereafter, he had recurrent hematemesis of fresh blood and clots. Emergent UGI endoscopy revealed a 1.0-cm prepyloric ulcer with two visible vessels. The ulcer base and vessels were injected with epinephrine with apparently adequate hemostatic effect. The patient ultimately received 2 units of packed red blood cells and was discharged from the hospital on study day 295 with a hemoglobin and hematocrit of 8.7 g/dL and 25.6%. Biopsy for *H. pylori* was positive, as was the baseline serology. This event was classified as: **gastric ulcer; GI bleed (traditional, 1B; alternate, 1F).**

Case 1189

Patient US0147-102-11341 was an 84-year-old female with a history of sinusitis, epistaxis, cataract, depression, atrial fibrillation, coronary artery disease, abdominal aortic aneurysm, angioplasty, asthma, cholecystectomy, bilateral inguinal hernia repair, constipation, anal incontinence, hiatal hernia, sigmoid diverticulitis, pyloric channel gastritis, duodenitis, hysterectomy, urinary incontinence, uterine prolapse, left renal cyst mass, osteoporosis, vertebral compression fracture, rib fracture, incisional hernia repair, lichen planus of the lip, mouth ulcers, hypertriglyceridemia, and OA. Concomitant medications included valsartan, calcium, felodipine, hydrocodone, nitroglycerine, and aspirin. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

After 150 days of treatment the patient began experiencing intermittent nausea, vomiting, and abdominal pain. On study day 163, because of progression of these symptoms, the patient presented to the emergency room. Significant findings at this time included a blood pressure of 78/46 mm Hg and a hemoglobin of 11.7 g/dL compared with a baseline of 12.5 g/dL and a hematocrit of 35.3% compared with a baseline of 39.0%. After a prolonged emergency room stay and intravenous hydration, the patient was discharged. **Study medication was discontinued on day 171.** The patient continued to have abdominal pain and intermittent nausea and vomiting. On study day 178 she was found to have a hemoglobin of 9.4 g/dL and a hematocrit of 29.0%. On day 179 she was treated in the emergency room for severe constipation. On study day 183 the patient underwent an UGI endoscopy revealing presbyesophagus with a mild stricture and ulceration at the gastroesophageal junction, and a 6.0 to 8.0-cm hiatal hernia. There were also five smaller gastric ulcers in the body of the stomach and a 3.0-cm ulcer on the lesser curvature with hemosiderin type lesions in the base, and two to five gastric erosions. Biopsies of the large lesion were negative for malignancy and biopsies were negative for *H. pylor*i, as was the baseline serology. The patient was treated with acid suppression and **discontinued from the study**. This event was classified as: **gastric ulcer; GI bleed (traditional, 1B; alternate, 1F).**

Case 1201 (Censored)

Patient US0039-035-21235 was a 74-year-old female with a history of seasonal allergies, spinal stenosis, peripheral neuropathy, dependent edema, left carpal tunnel surgery, first degree atrioventricular block, chronic bronchitis, right kidney surgery, left medial malleolus skin ulcer, gastroesophageal reflux disease, hemorrhoidal bleeding, asthma, hypertension, diverticulosis, cholelithiasis, oral carcinoma, rhinitis, tonsillectomy, appendectomy, hemorrhoidectomy, hysterectomy, benign breast cysts, sinus surgery, left eye cataract, anemia, and RA. Concomitant medications included prednisone, conjugated estrogens, "baby aspirin," lisinopril, pentoxyfylline, Tylox, famotodine, ipatropium, aurothioglucose, nedocromil sodium, fish oil, calcium carbonate, and fexofenadine. The patient was enrolled in protocol N49-98-02-035 and randomized to **celecoxib 400 mg BID.** Study medication was discontinued on day 29 because the patient began taking high-dose prednisone (day 23) for vasculitic toe lesions.

On approximately study day 42, the patient began experiencing weakness, polyuria, and fatigue. On day 48 she presented to the emergency room with significant findings included hyperglycemia, anemia, and hemoccult-positive stool. Specifically, her blood glucose was 317 g/dL and her hemoglobin was 9.8 g/dL compared with a baseline of 10.6 g/dL and a hematocrit was 31.8% compared with a baseline of 36.0%. She was admitted to the hospital and a UGI endoscopy performed on day 52 revealed a 1.0 x 1.0-cm "punched-out" appearing ulcer with edematous margins located on the posterior wall of the antrum. Biopsies were negative for *H. pylori,* as was the baseline serology. Her hemoglobin fell to a low of 8.9 g/dL and her hematocrit fell to 27.7% but she was not transfused. The patient was treated with acid suppression and discharged. This event was classified as: **gastric ulcer; GI bleed (traditional, 1D1; alternate, none).**

Case 1206

Patient US0518-102-20349 was a 69-year-old male with a history of ear surgery, recurrent headaches, hypertension, diverticulosis, cholecystectomy, duodenal polyp, GI NSAID intolerance, strained back, adult-onset diabetes, thrombocytopenia with transfusion, and RA. Concomitant medications included prednisone, penicillamine, nifedipine, and folic acid. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID**.

After 199 days of treatment the patient began experiencing loose melenic stools and left-sided abdominal pain. On study day 200 the patient was admitted to the hospital. **Study medication was discontinued**, and significant findings at this time included melena and a hemoglobin of 14.6 g/dL compared with a baseline of 15.8 g/dL and a hematocrit of 44.0% compared with a baseline of 46.0%. On study day 202 the hemoglobin and hematocrit had fallen to 12.5 g/dL and 35.5%, respectively. The patient underwent both upper endoscopy and colonoscopy. The upper endoscopy revealed a 1.5-cm ulcer on the posterior wall of the duodenal bulb without stigmata of recent bleeding. A CLOtest was negative for *H. pylori* despite positive baseline serology. The colonoscopy revealed marked sigmoid diverticulosis. The patient was **discontinued from the study** and treated with acid suppression. This event was classified as: **duodenal ulcer; GI bleed (traditional, 1C; alternate, 1G).**

Case 1242

Patient US0304-102-12176 was a 76-year-old female with a history of eye infection, fluid behind the eyes, myocardial infarction, arteriosclerotic heart disease, peripheral vascular disease, congestive heart disease, hyperlipidemia, diverticulitis, sigmoid colectomy, peptic ulcer disease, colon polyps, colorectal anastomosis, chronic low back pain, lumbar stenosis, lumbosacral spine fusion, onychomycosis, non-insulin-dependent diabetes mellitus, GI-related NSAID intolerance, and OA. Concomitant medications included chlorpropamide, lisinopril, potassium chloride, furosemide, "baby aspirin," multivitamins, and propoxyphene hydrochloride. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

After 139 days of treatment the patient began experiencing heartburn, epigastric pain, diarrhea, and dark stools. The patient interrupted study medication on days 143 through 145. On study day 145, the patient was examined in the office and diagnosed with viral gastroenteritis. Significant findings at this time were limited to a 28 mm Hg orthostatic change in systolic blood pressure. On day 153, the patient was again evaluated for persistent diarrhea and several episodes of emesis. On day 159 the patient was admitted to the hospital for persistent epigastric pain, nausea, and vomiting. Work-up on the day of admission included an ultrasound of the gallbladder with normal results. A hemoglobin at this time was 12.1 g/dL compared with a baseline of 15.2 g/dL and a hematocrit was 35.6% compared with a baseline of 43.0%. Stools remained hemoccult-negative.

An endoscopy performed on study day 161 revealed an enlarged stomach, abnormal duodenal mucosa, and a stricture of the duodenum just beyond the bulb. The stricture did not allow passage of the endoscope into the distal duodenum. Duodenal biopsies of the strictured area revealed mild acute duodenitis with slight villous blunting. Following the endoscopy, on the same day, the patient underwent a UGI series that revealed a slight narrowing of the second portion of the duodenum possibly representing a nonobstructive stricture. Additional work-up included a negative stool culture for *Clostridium difficil*e. Biopsy for *H. pylori* was negative, as was the baseline serology. Treatment medication included Unasyn, meperidine hydrochloride, promethazine hydrochloride, and famotidine. **Study medication was discontinued at the time of hospital admission on day 159.** The patient was discharged from the hospital on study day 162 with a diagnosis of "duodenal stricture - probably peptic." At a follow up visit on day 177, the patient offered no GI complaints and was placed on **rofecoxib 25 mg QD**. At an office visit on day 191 the patient reported having intermittent diarrhea. A follow-up endoscopy was performed on day 264 demonstrating a significantly improved duodenal stricture. The scope was able to pass and there was no evidence of mucosal abnormality other than some structural distortion consistent with prior duodenal ulcer disease. It was the endoscopist's impression that the stricture had been caused by an ulcer. This event was classified as: **gastric outlet obstruction (traditional, 3; alternate, 3).**

Case 1245 (Censored)

Patient US0328-102-11895 was a 75-year-old male with a history of angioplasty, hypertension, cardiovascular disease, prostate biopsy, removal of skin lesions, hyperlipidemia, transient ischemic attacks, inguinal herniorrhaphy, ear surgery, peptic ulcer disease (in his 20s), colon polyps, and OA. Concomitant medications included atenolol, aspirin, nitroglycerin, vitamin C, and Maxzide. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID**.

After 199 days of treatment the patient began experiencing severe left knee pain and was hospitalized for septic arthritis. **Study drug was discontinued at this time**. On study day 200 the patient underwent incision and drainage of the left knee and received one dose of **ketorolac 30 mg intravenously**. Additionally, **celecoxib 200 mg QD was apparently administered beginning on study day 205.** On study day 207 the patient experienced slight epigastric pain, witnessed melena, and a decreased hematocrit. Specifically, the hemoglobin was 10.0 g/dL compared with a baseline of 16.1 g/dL and a hematocrit was 29.3% compared with a baseline of 45.0%. At this time the patient related having dark stools for weeks prior to this event but was not able to determine the date they began. On the same day (study day 207) the patient underwent UGI endoscopy revealing four antral ulcers with exudative bases. These ulcers appeared chronic and measured 0.3 to 0.5 cm with pliable margins and stigmata of recent bleeding. Biopsies of the margins revealed chronic gastritis and no evidence of *H. pylori* despite a positive baseline serology. The patient ultimately received a total of 2 units of packed red blood cells and was discharged from the hospital. This event was classified as: **gastric ulcer; GI bleed (traditional, 1C; alternate, 1G).**

Case 1246

Patient US0125-102-10012 was a 71-year-old female with a history of right eye cataract, insomnia, hypertension, hiatal hernia, hemorrhoids, endometriosis, left total knee replacement, dislocated right shoulder, hypercholesterolemia, and OA. Concomitant medications included aspirin, fluvastatin, furosemide, multivitamins, and calcium carbonate. The patient was enrolled in protocol N49-98-02-102 and randomized to celecoxib 400 mg BID.

After 276 days of treatment the patient was asymptomatic but was found to have a decreased hemoglobin and hematocrit. Specifically, the hemoglobin was 10.7 g/dL compared with a baseline of 13.8 g/dL and the hematocrit was 36.0% compared with a baseline of 43.0%. The ensuing work-up revealed hemocult-positive stools on study days 283, 284, 285 and, 286. **Study medication was discontinued on day 295**. Upper GI endoscopy on study day 297 revealed a linear ulcer in the distal esophagus, esophageal erosions, a hiatal hernia, and a 0.5 x 2.0 to 3.0-cm linear antral ulcer on the lesser curvature. The antral ulcer was described as having some depth and slightly raised margins. A CLOtest for *H. pylori* was negative, as was the baseline serology. The patient was **withdrawn from the study**, treated with acid suppression, and scheduled for a follow-up endoscopy to document healing. This event was classified as: **gastric ulcer; GI bleed (traditional, 1D1; alternate, 1H).**

Case 1294

Patient US0531-102-11559 was an 80-year-old male with a history of tonsillectomy, constipation, insomnia, diabetes, hypertension, and OA. Concomitant medications included aspirin, tolbutamide, fosinopril, glucosamine sulfate, Metamucil, and Tylenol PM. The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID.**

After approximately 253 days of treatment the patient began experiencing intermittent abdominal bloating and flatulence. **Study medication was discontinued on day 259**. On study day 261 the patient experienced pain in the lower abdomen with radiation to the right shoulder, orthostatic symptoms, and fatigue. He also reported having a dark stool. On study day 263 the patient passed another dark stool and reported nausea without emesis. At this point the patient was hospitalized for further work-up. On admission the patient was found to have slight lower abdominal tenderness and hemoccult-positive dark brown stool. Laboratory findings revealed hemoglobin of 7.7 g/dL compared with a baseline of 10.9 and a hematocrit of 25.3% compared with a baseline of 35.0%. A nasogastric lavage performed in the emergency room was negative for blood. On study day 264 the patient received 2 units of packed red blood cells. On day 268 the patient underwent an endoscopy revealing grade III erosive esophagitis, evidence of chronic gastritis, and a single 1.0-cm duodenal bulb ulcer without stigmata of recent hemorrhage. A biopsy specimen was negative for *H. pylori* by CLOtest and histology despite a positive baseline serology. The patient was treated with acid suppression and **discontinued from the study**. This event was classified as: **duodenal ulcer; GI bleed (traditional, 1D1; alternate, 1H).**

Case 1297 (Censored)

Patient US0591-102-10168 was a 71-year-old male with a history of atrial fibrillation, bilateral inguinal hernia repair, bilateral repair of shoulder joints, removal of multiple basal cell carcinoma lesions, bilateral total knee replacements, and OA. Concomitant medications included lidocaine, propoxyphene hydrochloride, glucosamine, chondroitin, warfarin sodium, atenolol, triamcinolone, multivitamins, antioxidant, methylsulfanylmethane, and low-dose aspirin

(initiated on study day 253). The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID.**

After 277 days of treatment the patient began experiencing severe abdominal pain and was hospitalized with an acute abdomen. Of note, the patient had previously been hospitalized on study day 265 for elective bilateral total knee replacement and **study drug had been discontinued on study day 242**. On study day 278 the patient underwent an exploratory laparotomy revealing a perforated ulcer. The ulcer was noted to be 2.0 cm in diameter and located on the anterior surface of the prepyloric region. Also noted was an abscess in the right upper quadrant and a large amount of dark fluid within the colon that was felt to be old blood. Surgical repair of the lesion and appropriate drainage was performed. Significant laboratory findings at this time included a hemoglobin of 7.1 g/dL compared with a baseline of 13.4 g/dL and a hematocrit of 20.5% compared with a baseline hematocrit of 41.0%. The patient received 2 units of packed red blood cells on study days 278 and 280. On day 284 the patient had a witnessed black diarrheal stool that was found to be hemoccult-positive. Colonoscopy performed on study day 286 revealed multiple diverticuli in the sigmoid colon and a poor preparation in the right colon. No bleeding was identified on this examination. Baseline serology for *H. pylori* had been positive. This event was classified as: **gastric ulcer; perforation (traditional, 2; alternate, 2).**

Case 1343

Patient US0514-102-12391 was a 61-year-old female with a history of nasal fracture, tonsillectomy, depression, hypercholesterolemia, seasonal allergies, dyspnea, cholecystectomy, occasional heartburn, hiatal hernia, esophageal sphincter stenosis surgery, gastric ulcer oversew, surgical removal of gastric scar tissue, duodenal ulcer, bulimia, diverticulosis (inactive), appendectomy, hysterectomy, fibrocystic breast disease, fractured pelvis, back pain, thin dry skin on arms, lipoma removal, chronic anemia, and OA. Concomitant medications included vitamin B12, trazodone hydrochloride, bupropion, diazepam, conjugated estrogens, Tylenol Sinus, St. Johns Wort, Tums, and Darvocet N-100. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

After 261 days of treatment, at a routine visit, she was found by the Investigator to have epigastric tenderness and a hemoglobin of 9.8 g/dL compared with a baseline of 12.7 g/dL and a hematocrit of 32.0%, compared with a baseline of 41.0%. **Study medication was discontinued at this time**. In addition, on study day 249, stool was reported as hemoccult-positive. Baseline serology for *H. pylori* had been negative. On study day 262 an endoscopy revealed grade II nonerosive esophagitis and evidence of a partial gastrectomy. There was food residue in the stomach and a high-grade strictured region with erosive, friable, and white mucosa at the body of the stomach. The anastomotic area mucosa was friable, but no obvious old or new bleeding was seen. The endoscope could not be passed through the stenotic anastamosis. On study day 268, the patient underwent repeat endoscopy for vomiting, weight loss, and nausea. During balloon dilatation of the anastamosis a perforation occurred in the stomach requiring discontinuation of the procedure and hospitalization. The patient was transferred to the hospital for management of the perforation. Computerized tomography confirmed a perforated viscus with free peritoneal air. The patient underwent an emergency laparotomy, lysis of adhesions, and stricturoplasty with repair of perforation and patch. The patient received 2 units of blood perioperatively. Postoperative recovery was uneventful. This event was
classified as: **gastric outlet obstruction (traditional, 3; alternate, 3).**

Case 1356

Patient US0321-102-10761 was a 72-year-old female with a history of cardiovascular disease, recurrent sore throat, laryngitis, hypertension, hypercholesterolemia, II/IV systolic ejection murmur, bilateral leg varicosities, pneumonia, external hemorrhoids, menopause, left hip and leg pain, angioma of the right buttock, lumbar spondylosis, and OA. Concomitant medications included atenolol, hydrochlorothiazide, and acetaminophen. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

After 307 days of treatment the patient began experiencing nausea, vomiting, and diarrhea. On study day 316, the patient was admitted to the hospital with complaints of nausea, coffee ground emesis, burning in her throat, a bad taste in her mouth, diarrhea, and fever. **Study medication was discontinued**, and significant findings at this time included a hemoglobin of 9.7 g/dL compared with a baseline of 12.1 g/dL and a hematocrit of 28.0%, compared with a baseline of 36.0%, and hemoccult-positive stool. On study day 317, the patient developed right upper quadrant abdominal and epigastric discomfort and a temperature elevation to 103.7°F. On day 318, the patient underwent abdominal ultrasound with normal results. On day 319, the patient underwent an endoscopy that revealed a hiatal hernia, grade I esophagitis,

atrophic gastropathy, multiple dispersed erosions with stigmata of recent bleeding, evidence of dark blood in the incisura, antrum, and prepyloric region, two nonbleeding linear antral ulcers, and a normal duodenum. The largest dimension of the gastric ulcers was 0.7 cm. Baseline serology for *H. pylori* had been negative. The patient was treated with acid suppression and **discontinued from the study** with a work-up planned to determine the etiology of the fever. This event was classified as: **gastric ulcer; GI bleed (traditional, 1A; alternate, 1E).**

Case 1383 (Censored)

Patient CA0484-035-12170 was a 62-year-old male with a history of hypertension, ischemic heart disease, tachyarrythmias, cholecystectomy, peptic ulcer disease, elevated liver enzymes, diffuse idiopathic skeletal hyperostosis, gout, rotator cuff surgery, headaches, renal dysfunction, and OA. Concomitant medications included allopurinol, atenolol, Cytotec, vitamin E, calcium, and magnesium. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID.**

After 18 days of treatment the patient began experiencing diffuse abdominal pain, bloating, acid regurgitation, and severe retrosternal burning. **Study medication was discontinued at this time**. After study medication was discontinued on day 18, the patient took **indomethacin SR 75 mg from study day 22 to day 34**. On day 21 stool was hemoccult-negative. On study day 29 a hemoglobin was unchanged from baseline at 14.5 g/dL and a hematocrit was 44.0% compared with a baseline of 42.2%. On study day 36 the patient developed black tarry stools and weakness. On study day 43 an endoscopy was performed revealing a slight laxity at the diaphragmatic pinch, and a linear, 1.0-cm duodenal bulb ulcer. According to the endoscopist, the ulcer appeared to be healing. A biopsy for *H. pylori* was negative, despite a positive baseline serology. A hemoglobin and hematocrit on the day of endoscopy was 12.4 g/dL and 36.0%, respectively. Additionally, stools were hemoccult positive on study days 41 and 42. The patient was treated with acid suppression and for *H. pylori* and **discontinued from the study**. This event was classified as: **duodenal ulcer; GI bleed (traditional, 1C; alternate, 1G).**