CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-998/S-009

MEDICAL REVIEW(S)

Celebrex Capsules
(Celecoxib)

NDA 20-998/S-009

Medical Officer Review

Submission Date:	June 12, 2000
Received Date:	June 14, 2000
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)

Celecoxib
NDA # 20-998 /S-009

Table of Contents

Listing of Celecoxib sNDA (20-998) Review Tables

CLASS Executive Summary

Significant Issues/Highlights

- The Celecoxib Long-term Arthritis Safety Study (CLASS) represented the combination of two large safety studies (protocols N49-98-02-035 and N49-98-02-102) which addressed 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 in patients with OA or RA. Patients were allowed to take aspirin (ASA) for cardiovascular prophylaxis. The term "CSUGIE" represented a composite end point comprised of UGI bleeding, perforation, or gastric outlet obstruction. Those symptomatic UGI events deemed not to be CSUGIEs, were referred to as gastroduodenal ulcers (GDU).

- Data in the CLASS trial included information on serum bicarbonates and other estimates of potential effects on acid-base balance. This new data represented a fulfillment of a phase 4 commitment to study these issues since serum bicarbonates had not been measured in the original NDA.

- Overall, the CLASS trial represented a robust test of the safety of celecoxib as compared to the "traditional" NSAIDs of ibuprofen and diclofenac. The latter two compounds were at their "usual" therapeutic doses while celecoxib was given at a "2X" dose which represent twice the currently approved dosing for rheumatoid arthritis. This supratherapeutic dose is the also the currently recommended dose for the labeled indication of familial adenomatous polyposis (FAP).

- 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 (noted below) that favored celecoxib. When the subgroup of non-aspirin users 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 superiority to pooled NSAIDs, and to ibuprofen (only), during this trial. This superiority was not a pre-specified efficacy endpoint and was not corrected statistically for multiplicity. Celecoxib did not demonstrate statistical superiority to diclofenac regardless of selection of study endpoint or aspirin use during any point in the trial.

- 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.

- The CLASS trial data do not support an apparent 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.

- The CLASS trial data do not support an apparent 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).

- Overall safety, as defined by the endpoints of deaths, serious adverse events and withdrawals due to adverse events did not appear to be meaningfully or consistently different among the three treatment groups.

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.);
1. 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;
1. 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. ©
	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

1. 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.

© 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.

1. 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**
1. **Good – Mild symptoms and no limitation of normal activities**
1. **Fair – Moderate symptoms and limitation of some normal activities**
1. **Poor – Severe symptoms and inability to carry out most normal activities**
1. **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* 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 ³20 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
Clinical situations requiring PROMPT attention **For all patients with the following presentations:** **-Obtain base data (hematocrit, stool heme x3, and postural vital signs) as soon as possible.** **-Test for H. pylori infection as part of work up (Meretek UBT, CLOtest or H&E)** **-Notify ~~~ Safety Specialist as soon as possible.** **- Complete GI event CRFs.**		
History of dark stool: - >14 days previously, or - vaguely characterized, or - with concurrent iron/bismuth ingestion	ASAP: -Obtain base data	-If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for H. pylori infection) - Lower GI work-up if bleeding source uncertain
History of: -hematochezia, or -anal/rectal bleeding after elimination	ASAP: -Obtain base data	-Perform colonoscopy -UGI endoscopy at Investigator's discretion (test for H. pylori infection)
Development of: -New anemia, or - Drop in hematocrit of 5% or more (absolute change)	ASAP: -Obtain base data including ferritin, iron, iron binding capacity, MCV, MCHC	-If stools heme positive or studies indicate iron deficiency, perform UGI endoscopy (test for H. pylori infection) - Lower GI work-up if bleeding source uncertain
Development of: -Dyspepsia, or -Abdominal pain, or -Nausea/vomiting	ASAP: - Obtain base data	-If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for H. pylori infection) -Additional studies as indicated by "ordinary care"
Development of: -Heme-positive stools	ASAP: -Obtain base data 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
    1. All Patients
    b. Patients not Taking Aspirin
    c. Patients Taking Aspirin
- Entire Study Period
    1. 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 (see Table 7). 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.**

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– 3 months	546 (14%)	293 (15%)	351 (18%)
3 – 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– 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– 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%)
1-3 months	546 (14%)	293 (15%)	351 (18%)
3 – 6 months	467 (12%)	262 (13%)	246 (12%)
6-9 months	291 (7%)	136 (7%)	130 (7%)
9-12 months	1442 (36%)	913 (46%)	415 (21%)
12-15 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– 3 months	419 (13%)	222 (14%)	267 (17%)
3 – 6 months	357 (11%)	203 (13%)	206 (13%)
6-9 months	229 (7%)	97 (6%)	100 (6%)
9-12 months	1114 (36%)	717 (46%)	330 (21%)
12-15 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– 3 months	127 (14%)	71 (16%)	84 (20%)
3 – 6 months	110 (12%)	59 (13%)	40 (10%)
6-9 months	62 (7%)	39 (9%)	30 (7%)
9-12 months	328 (37%)	196 (44%)	85 (21%)
12-15 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 month	0 (0%)	0 (0%)	0 (0%)
1-3 months	0 (0%)	0 (0%)	0 (0%)
3– 6 months	0 (0%)	1 (0%)	0 (0%)
6-9 months	10 (1%)	6 (1%)	0 (0%)
9-12 months	1282 (72%)	868 (92%)	297 (43%)
12-15 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			
	656 (30%)	328 (31%)	364 (28%)
1– 3 months	546 (25%)	293 (28%)	351 (27%)
3 – 6 months	467 (21%)	261 (25%)	246 (19%)
6-9 months	281 (13%)	130 (12%)	130 (10%)
9-12 months	160 (7%)	45 (4%)	118 (9%)
12-15 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 ($p\geq 0.956$ 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 events, non-CSUGIEs,** 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 events**, **non-CSUGIEs**, 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).
1. 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 = 1573			
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 ketorola c
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	NSAIDs	Celecoxib	NSAIDs

	400 mg BID		400 mg BID	
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.	6.9 (p=0.002)	1.6 (p=0.240)	2.5 (p=0.002)	1.6 (p=0.048)
pylori serology	0.7 (p=0.460)	1.2 (p=0.072)	1.1 (p=0.423)	2.0 (p=0.005)
Aspirin use	4.0 (p=0.005)	1.8 (p=0.211)	3.7 (p<0.001)	2.3 (p=0.002)

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)
	902	18 (2.0)	37 (4.1)	615 (68)

≥2				

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)	1. (0.2)	485 (48)
1	738 (37)	1. (0.5)	13 (1.8)	416 (56)
≥2	239 (12)	6 (2.5)	11 (4.6)	156 (65)
Ibuprofen				
0	1025 (52)	1. (0.5)	16 (1.6)	654 (64)
1	758 (38)	1. (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			