5. The incidence of drug related GI adverse events is significantly lower in patients treated with Vioxx than in patients treated with nonspecific cyclooxygenase inhibitors over twelve months.
6. Vioxx at doses of 25to 50mg a day is associated with significantly less fecal blood loss than ibuprofen 2400mg a day in healthy subjects. Vioxx associated fecal blood loss is no greater than placebo associated rates.
7. Vioxx at doses of 25 to 50 mg a day is not associated with increases in intestinal permeability compared to placebo in healthy subjects over a one-week period based on a ^{51}Cr-tagged EDTA study design.

Scope of Medical Officers safety review:

Studies 041, 044,045,050 and 069 as well as combined analysis of studies 044/045 outlined in protocol 044C will be reviewed to assess the claims related to gastrointestinal safety. Study 041 and 050 will be reviewed related to claims regarding intestinal permeability and GI blood loss respectively as surrogates for gastrointestinal safety. A review of primary source documents was undertaken as an external audit of endoscopic reports.

Evaluation of Endoscopic Ulcer Studies 044 and 045

Study 044 was a multicenter study including 34 sites within the U.S. Study 045 was a multicenter study including 31 international sites and 5 sites within the U.S. The protocol for both studies were identical except for the minimal differences in escape medication allowed for treatment of pain and upper gastrointestinal symptoms. At the U.S. sites acetaminophen was used and in the international sites paracetamol was used for escape pain when needed. In the U.S. Gelusil™ and Maalox-Plus ™ were used (both containing 200mg of magnesium hydroxide and 200mg of aluminum hydroxide per dose and simethicone. At the international sites Kompensan-S™ (dimethicone/dihydroxyaluminum sodium carbonate 340mg) was also used.

Statistical analysis of the results of the two studies was identical and there was a prespecified intention to combine the data from the two studies in the form of protocol 044C. The primary objective of this combined analysis was to compare the incidence of gastric and /or duodenal ulcers $\geq$ 3 mm in patients receiving placebo or Vioxx 25mg daily over 12 weeks. A secondary objective was to compare the endoscopic endpoints of gastric and/or duodenal ulcers($\geq$3mm, $\geq$5mm) and erosions following the administration of Vioxx 25mg a day, Vioxx 50mg a day, ibuprofen 2400 mg a day in 3 divided doses and placebo. An exploratory evaluation of esophageal scores among the treatment groups was also planned.

The design of the two studies will be described in a single section with results discussed separately before combining the data in the discussion of protocol 044C.

Study 044/045 Protocol

Title: A multicenter, randomized parallel-group, active and placebo controlled, double –blind study, conducted under in-house blinding conditions, to determine the incidence of gastroduodenal ulceration after 12 weeks of treatment with MK-0966, ibuprofen, or placebo with a 12-week continuation period.

"Primary Hypothesis

Compared to ibuprofen 800 mg t.i.d., the percentage of osteoarthritic patients who develop gastric and/or duodenal ulcers (≥3 mm) after 12 weeks of treatment will be lower with MK-0966 25 mg q.d.

Secondary Hypotheses

Gastric and/or Duodenal Ulcers (≥3 mm)

1) Compared to ibuprofen 800 mg t.i.d., the percentage of osteoarthritic patients who develop gastric and/or duodenal ulcers after 12 weeks of treatment will be lower with MK-0966 50 mg q.d.

2) Compared to ibuprofen 800 mg t.i.d., the percentage of osteoarthritic patients who develop gastric and/or duodenal ulcers after 12 weeks of treatment will be lower with placebo treatment.

Safety

3) MK-0966 25 mg q.d. and 50 mg q.d. will be well tolerated.

The expected proportions of patients with either a gastric and/or duodenal ulcer are 15% and 2.5% for ibuprofen 800 mg t.i.d. and placebo, respectively. For MK-0966 25 mg q.d. and 50 mg q.d., there are no data available on the occurrence of gastric and/or duodenal ulcers. The incidence rate of placebo, 2.5%, is assumed for the MK-0966 treatment groups [3.3.1].

Tertiary Hypotheses

Gastric and/or Duodenal Ulcers (≥3 mm)

1) Compared to ibuprofen 800 mg t.i.d., the percentage of osteoarthritic patients who develop gastric and/or duodenal ulcers after 24 weeks of treatment will be lower with MK-0966 25 mg q.d.

2) Compared to ibuprofen 800 mg t.i.d., the percentage of osteoarthritic patients who develop gastric and/or duodenal ulcers after 24 weeks of treatment will be lower with MK-0966 50 mg q.d.

Gastric and/or Duodenal Ulcers (≥5 mm)

3) Compared to ibuprofen 800 mg t.i.d., the percentage of osteoarthritic patients who develop gastric and/or duodenal ulcers ≥5 mm will be lower on MK-0966 25 mg, 50 mg, and/or placebo.

Erosions

4) Compared to ibuprofen 800 mg t.i.d., the percentage of osteoarthritic

patients who develop an increase in gastric and/or duodenal erosion after 12 weeks of treatment will be lower with MK-0966 25 mg q.d.
5) Compared to ibuprofen 800 mg t.i.d., the percentage of osteoarthritic patients who develop an increase in gastric and/or duodenal erosion after 12 weeks of treatment will be lower with MK-0966 50 mg q.d.
6) Compared to ibuprofen 800 mg t.i.d., the percentage of osteoarthritic patients who develop an increase in gastric and/or duodenal erosion after 12 weeks of treatment will be lower with placebo treatment.
7) Compared to ibuprofen 800 mg t.i.d., the percentage of osteoarthritic patients who develop an increase in gastric and/or duodenal erosion after 24 weeks of treatment will be lower with MK-0966 25 mg q.d.
8) Compared to ibuprofen 800 mg t.i.d., the percentage of osteoarthritic patients who develop an increase in gastric and/or duodenal erosion after 24 weeks of treatment will be lower with MK-0966 50 mg q.d.

b. Objectives

Exploratory Evaluations:
Other exploratory evaluations will include the effect of antacid consumption on the percentage of patients in each treatment group who develop gastric and/or duodenal ulcers, and between-group comparisons of the percentage of patients who develop erosions of the gastroduodenal mucosae."

Characteristics of the study population

Inclusion criteria:

1. Osteoarthritis with anticipated need for therapy of 6 months
2. Male or female over the age of 50 years
3. Ability to comply with protocol
4. Informed consent

Exclusion criteria:

1. Gastric, esophageal or duodenal ulceration, erosive esophagitis or endoscopically evident pyloric obstruction at baseline endoscopy
2. Positive fecal occult blood testing at baseline
3. History of bleeding diathesis or need for anticoagulant therapy
4. Unstable cardiovascular, renal or hepatic disease or uncontrolled diabetes
5. History of neoplastic disease within the past 10 years except for adequately treated basal cell carcinoma of the skin or carcinoma of the cervix in situ.
   (patients with a history of myeloproliferative diseases and malignancies were excluded regardless of disease free interval)
6. "Any illness that in the opinion of the investigator might confound the results of the study or pose additional risk to the patient"
7. allergy to acetominophen or hypersensitivity to or all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin, ibuprofen or other NSAIDs

8. Clinically significant complication of ibuprofen therapy
9. Usage of any dose of aspirin, anticoagulant or corticosteroids
10. One month after the study was initiated the protocol was amended to also exclude patients with:
    1. a history of active cerebrovascular disease within the prior two years
    2. those whose estimated creatinine clearance was $\leq$30 mL/min or whose serum creatinine was > 2.0 mg/dL
    3. those taking ticlopide or aspirin within one month of the study
    4. those previously exposed to MK-0966 in a clinical study

Study Design:

This was a randomized, double-blind (with in-house blinding), parallel-group, active- and placebo-controlled, multicenter study. Six hundred evaluable patients were required for the primary objective. Approximately 660 patients were expected to enroll over a 6-month period.

The study consisted of 12 visits: visit 1.0 (preliminary screening visit), visit 2.0 (baseline/randomization visit), visit 3.0 through 11.0 (treatment visits), and visit 12 (follow-up visit). The preliminary visit took place 12 to 16 days before randomization, followed by visits at Study Week 1 (Visits 2.0 and 3.0), and Study Weeks 3 through 26 (Visits 4.0 through 12.0). Treatment lasted for 16 to 24 weeks.

Patients who satisfied the selection criteria were assigned to one of the four treatment groups listed in Table 1 according to a computer-generated allocation schedule of random numbers supplied by Merck Research Laboratories.

Table 1

Planned Treatment Group Allocation

Group	Treatment	Planned No. of Patients Evaluable	Planned No. of Patients Enrolled
I	Placebo	150	165
II	MK-0966 25 mg once daily.	150	165
III	MK-0966 50 mg once daily.	150	165
IV	Ibuprofen 800 mg 3 times daily.	150	165
	TOTAL	600	660

Data Source: [3.2.1]

To maintain study blinding, there was a matching placebo medication for each

study medication. Enrollment was stratified by the presence or absence of a history of gastroduodenal mucosal disease (i.e., gastroduodenal ulceration, upper gastrointestinal hemorrhage, or upper gastrointestinal perforation) to ensure balance among treatment groups for this known risk factor among treatment groups. Patients with a history of gastroduodenal mucosal disease were randomized to the highest available allocation number while those without such a history or with an equivocal history were randomized to the lowest available allocation number.

Patients had a preliminary screening visit 2 weeks prior to the baseline visit in order to have laboratory assessments available at baseline. Endoscopy visits were scheduled for baseline, Weeks 6, 12, and 24.
Ninety-five percent of the placebo treatment group was scheduled to discontinue at Week 16; 5% of the placebo treatment group continued to the end of the study. To maintain study blinding, 5% of the patients in each nonplacebo treatment group were also scheduled to discontinue at Week 16. All patients in the study were scheduled for a poststudy visit 2 weeks after the last endoscopy.

Concomitant use of the following medications was prohibited during the entire study: NSAIDs, corticosteroids, warfarin or other anticoagulants, aspirin (including "low-dose" aspirin), and ticlopidine. Over-the-counter preparations that contain NSAIDs or aspirin were also prohibited (e.g. aspirin-containing cough or cold preparations).
Excluding aspirin optimized hypothesis testing about Cox-2 selectivity and gastroduodenal ulcers. It did leave the safety development program without information on potential interactions between even low dose nonselective cyclooxygenase inhibition and Cox-2 selective inhibition. This is an important question in view of the large population of patients in this country on low dose aspirin likely to be exposed to Cox-2 selective agents.

Furthermore, patients were not permitted to take anti-ulcer medications such as sucralfate, any H_2-receptor antagonist (e.g., cimetidine, ranitidine, nizatidine, roxatidine, famotidine), prostaglandin analogue (e.g., misoprostol), or proton pump inhibitors (e.g., omeprazole or lansoprazole). Antacids other than the GELUSIL™ provided were not permitted (antacid consumption was not a reason to exclude patients from data analysis). All concurrent therapy was recorded at each visit, including dosage regimen (formulation, route, dose in milligrams per day), duration of therapy, and reason for prescribing .

Endoscopic Evaluations

The protocol specified that endoscopies would be performed at Baseline, Week 6, Week 12, and at the time of discontinuation, should the patient discontinue early. Patients who did not undergo scheduled discontinuation at Week 16 had an endoscopy at Week 24. In addition, unscheduled endoscopy was undertaken if a patient developed moderate-to-severe upper gastrointestinal symptoms for 2 or more days, or other circumstances developed that would suggest the need for discontinuation.
At the baseline endoscopy visit, the endoscopic evaluation included biopsies for urease testing (CLOtest™) and histologic evaluation. Patients with erosive esophagitis, pyloric obstruction, or gastroduodenal ulceration were not randomized. At subsequent visits, patients with a gastric or duodenal ulcer at the time of endoscopy were discontinued with the ulcer data point carried forward in the cumulative life table design of the study.

Endoscopic endpoints

The incidence of ulcers ≥3 mm in either the stomach or duodenum was the primary endpoint, and the incidence of ulcers ≥5 mm was a secondary endpoint for this study. An ulcer was defined as a circumscribed mucosal break ≥3 mm (≥5 mm for ≥5 mm ulcers) in greatest dimension (length or width), as measured by close application of an open endoscopic biopsy forceps; the lesion also had to demonstrate unequivocal evidence of depth. Patients were to be ulcer free at baseline endoscopy when they entered the study. Photographs [redacted] were taken of gastroduodenal ulcers and retained in a workbooklet held by the investigators. Central storing of photographs was not planned, and the investigator retained responsibility for diagnosing ulceration correctly according to the protocol. The photographs were considered supportive. There was an audit by Merck of source documentation by the sponsor. The individual investigators however held all primary source documentation. Merck centrally stored only computerized transformed data retrieved from the investigator. This reviewer affirms that sponsors should have contemporaneous copies of source documents related to primary endpoints of study and related to major claims about the study drug when subjective interpretation of such data is needed.

Secondary Endpoint—Gastroduodenal Erosions
The patient's gastric and duodenal mucosa were examined separately by the endoscopist for erosive mucosal injury at baseline and after 6, 12, and 24 weeks of treatment. The number of gastric or duodenal erosions was counted discretely from 0 to 10 or recorded as >10. Values of >10 were set to 11 for statistical analysis because 11 and >11 were not considered clinically different. Change from baseline in the total of gastric and duodenal mucosal erosion numbers, at Week 12 as primary and at Week 24 as secondary were analyzed and compared among treatment groups. In addition, the incidence of an increase in gastroduodenal erosion number from baseline was analyzed.

Esophageal Erosion Scores
The esophagus was inspected at each endoscopy. The mucosa was graded

according to the predefined scale presented in Table 2.

Table 2

Score	Description
0	No mucosal abnormalities.
1	No macroscopic erosions, but erythema, hyperemia, or mucosal friability.
2	Superficial erosions involving <10% of the mucosal surface of the last 5 cm of esophageal squamous mucosa.
3	Superficial erosions or ulceration involving 10 to 50% of the mucosal surface of the last 5 cm of esophageal squamous mucosa.
4	Deep peptic ulceration anywhere in the esophagus or confluent erosion of >50% of the mucosal surface of the last 5 cm of esophageal squamous mucosa.

Taken from Hetzel DJ et al. Gastro 1988; 95:903-12

According to the exclusion criteria patients were to be randomized with an esophageal score less than 2 (Table 2). The incidence of developing an esophageal score of equal to or greater than 2 was the primary readout for the analysis of esophageal score. Change from baseline (at Week 12 and Week 24) was considered as a secondary readout for the analysis of esophageal score. No hypotheses were presented in relation to esophageal injury. These are however relevant safety data.

Statistical Hypothesis
The statistical null hypothesis was that, after a period of treatment, the cumulative incidence rates of patients with gastric and/or duodenal ulcers would be the same across treatment groups. The statistical alternative hypothesis was that there were differences in the rates between the Vioxx and the ibuprofen treatment groups or between the placebo and the ibuprofen treatment groups.

Power
With at least 150 evaluable patients completing the study in each treatment group, there would be 95% power to detect a difference in the cumulative incidence rate between Vioxx 25 or 50 mg once daily or placebo and ibuprofen 800 mg 3 times daily if the true incidence rates were 2.5, 2.5, 2.5 and 15% for the Vioxx 25 mg once daily, Vioxx 50 mg once daily, placebo, and ibuprofen treatment groups, respectively. This power calculation was based on a two-sided test with α=0.05.

Statistical Analysis

Intention-to-Treat Analysis (ITT)
Life-table analysis using an intention-to-treat approach was the primary analysis and was performed for all endpoints. The sponsor defined the intention to treat population as patients who had at least 1 treatment-phase measurement (and a baseline value for

change-from-baseline type analyses), including discontinuation or unscheduled measurement. This is a modified ITT. While valid as a sensitivity analysis, this modified ITT definition does introduce bias since the exclusion of patients withdrawing before follow-up does involve informed censoring. The protocol specified exit endoscopies. These exit endoscopies minimize the degree of bias potentially associated with this modified ITT by keeping to a minimum the amount of lost endoscopic information from early withdrawal. Exit endoscopies however were not universally done. The impact on safety data of using this analysis cannot be clearly stated. The magnitudes of statistical significance in the primary endpoint and sensitivity analyses provided are however, convincing that the ITT analysis used resulted in reliable results. The impact on placebo related conclusions is less certain.

Per-Protocol Analysis

Original protocol version:
"This will be performed as a secondary analysis for the primary endpoint only. Any patient who is identified as a major protocol violator will not be included. Major protocol violators will be defined based on a set of prespecified criteria. These criteria will be identified prior to unblinding the database."

Final protocol version:
"The per-protocol analysis population excluded patients and/or data points with clinically important deviations from prespecified criteria. The per-protocol analysis was performed only for the primary endpoint (incidence of gastroduodenal ulcers ≥3 mm). Patients who had part or all of their data excluded from the per-protocol analysis and the reasons for their exclusion are presented."

In the original protocol major protocol violations were to be defined based on the database involved before unblinding. In the final version there is no mention as to whether this was done before or after blinding. During the review process communication with the sponsor revealed that the data were indeed blinded when the violations were adjudicated for withdrawal.

Validation of Endoscopic Data: The records from 10 centers were reviewed for accuracy of information transfer from primary source to secondary source document. Most endoscopists had full endoscopy reports in addition to filling out a "worksheet" supplied by Merck. In cases where the worksheet was the only source document the endoscopist signed this form which did contain the necessary information for accurate ascertainment. No significant errors were found.

Results for Study 044

Baseline patient characteristics

1. Center allocation:

   None of the 35 participating centers accounted for more that 6% of the study population. The centers with relative imbalance in ascertainment are listed in table 3.

Table 3

Center #	%of total patients	% of total placebo ulcers	%of total Vioxx ulcers	% of total ibuprofen ulcers
004	3	0	6	6
006	5	0	3	**7.5**
017	3.5	0	0	6
019	4	18	9	**11**
032	6	9	9	**13**
033	5	9	0	**9**
035	2	0	0	**6**
044	2	18	6	**0**

There did not appear to be a single center driving the data or dominant treatment-center interaction.

2. Patient characteristics: Patients were well distributed by age with a mean age between 61-62% in all four groups. Race appeared randomly distributed with ranges of 81-84% White, 16-22% Black and 6-13% Hispanic among groups. Arthritis related global assessment of disease activity using the Likert Scale was similar with a mean range of 1.91-2.08 among groups. The median was identical among groups at 2.00 and the range was identical at 0.00-4.00. Gender was evenly distributed among groups with an overall preponderance of females who represented between 65-69% of all 4 groups.
   Alcohol intake was quantitated by the number of drinks per day, 0, 1-4, 5-7, 8-10, >11. The number of patients with 0 intake was similar among groups. The percent of patients in each intake category had a notable disparity in the 5-7-drink category. The other categories were varied such that a potential clinical effect would not be expected.

Tobacco use was noted by 51-65 % of patients among the 4 groups. H. pylori status based on urease and histopathology, prior NSAID use and prior history of ulcer complications were evenly distributed among the groups.
The distribution of baseline scores in terms of number of gastroduodenal erosions and presence or absence of erosions showed a numeric difference with higher scores weighted in the placebo group. The large standard deviations and median of 0 in the score category, however suggest that this may not represent a meaningful imbalance.

Table 4

Baseline Patient Characteristics

	Placebo	MK-0966		Ibuprofen[+]	Total[+]
		25 mg	50 mg	2400 mg	
Gastric and Duodenal Erosions					
N	177	195	186	183	741
=0, n (%)	150 (84.75)	176 (90.26)	157 (84.41)	162 (88.52)	645 (87.04)
>0, n (%)	27 (15.25)	19 (9.74)	29 (15.59)	21 (11.48)	96 (12.96)
Number of Gastric and Duodenal Erosions					
N	177	195	186	183	741
Mean (SD)	0.64 (2.07)	0.29 (1.12)	0.49 (1.62)	0.38 (1.46)	0.45 (1.60)
Median	0.00	0.00	0.00	0.00	0.00
Range	0.00 to 15.00	0.00 to 10.00	0.00 to 11.00	0.00 to 11.00	0.00 to 15.00
Number of Gastric Erosions					
N	177	195	186	183	741
Mean (SD)	0.54 (1.70)	0.20 (0.83)	0.31 (1.02)	0.36 (1.45)	0.35 (1.29)
Median	0.00	0.00	0.00	0.00	0.00
Range	0.00 to 11.00	0.00 to 5.00	0.00 to 8.00	0.00 to 11.00	0.00 to 11.00
Number of Duodenal Erosions					
N	177	195	186	183	741
Mean (SD)	0.11 (0.91)	0.09 (0.49)	0.18 (1.15)	0.02 (0.21)	0.10 (0.78)
Median	0.00	0.00	0.00	0.00	0.00
Range	0.00 to 11.00	0.00 to 5.00	0.00 to 11.00	0.00 to 2.00	0.00 to 11.00

Patient Accounting:
Table 5 indicates that withdrawals for lack of efficacy were highest in the placebo group and withdrawals for adverse experiences were highest in the Ibuprofen group.

Table 5

Patient Accounting

	Placebo	MK-0966		Ibuprofen	Total
		25 mg	50 mg	2400 mg	
ENTERED:	177	195	186	184	742[†]
Male (age range)[‡]	61 (49 to 76)	61 (49 to 81)	58 (49 to 76)	63 (49 to 80)	243 (49 to 81)
Female (age range)[‡]	116 (47 to 85)	134 (49 to 83)	128 (49 to 86)	121 (49 to 87)	499 (47 to 87)
	n (%)	n (%)	n (%)	n (%)	n (%)
COMPLETED:	119 (67.2)	136 (69.7)	122 (65.6)	72 (39.1)	449 (60.5)
DISCONTINUED:	58 (32.8)	59 (30.2)	64 (34.4)	112 (60.9)	293 (39.5)
Clinical adverse experience	12 (6.8)	20 (10.3)	22 (11.8)	21 (11.4)	75 (10.1)
Laboratory adverse experience	2 (1.1)	0 (0.0)	1 (0.5)	6 (3.3)	9 (1.2)
Lack of efficacy	16 (9.0)	6 (3.1)	4 (2.2)	9 (4.9)	35 (4.7)
Lost to follow up	1 (0.6)	3 (1.5)	0 (0.0)	3 (1.6)	7 (0.9)
Patient moved	1 (0.6)	3 (1.5)	0 (0.0)	0 (0.0)	4 (0.5)
Patient withdrew consent	7 (4.0)	13 (6.7)	14 (7.5)	11 (6.0)	45 (6.1)
Deviation from protocol	9 (5.1)	3 (1.5)	4 (2.2)	8 (4.3)	24 (3.2)
Study endpoint[§]	10 (5.6)	11 (5.6)	19 (10.2)	54 (29.3)	94 (12.7)

Fifty-two patients did not reach their first endoscopy. As specified in the sponsor's ITT definition these patients were excluded from the ITT analysis. This represents a loss of 7 percent of the true ITT group. These are unlikely to be truly randomly censored and this definition of ITT may bias to some extent the results. Table 6 shows the number of patients in the ITT analysis.

Table 6 (Modified ITT used)

Number of Patients Included in the Primary End Point Analyses

Treatment	Intention-to-Treat	Per-Protocol
	N = 689	N = 668
Placebo	158	153
MK-0966 25 mg	186	183
MK-0966 50 mg	178	175
Ibuprofen 2400 mg	167	157

Data Source: [4.2; 4.3; 4.10.1; 4.10.2]

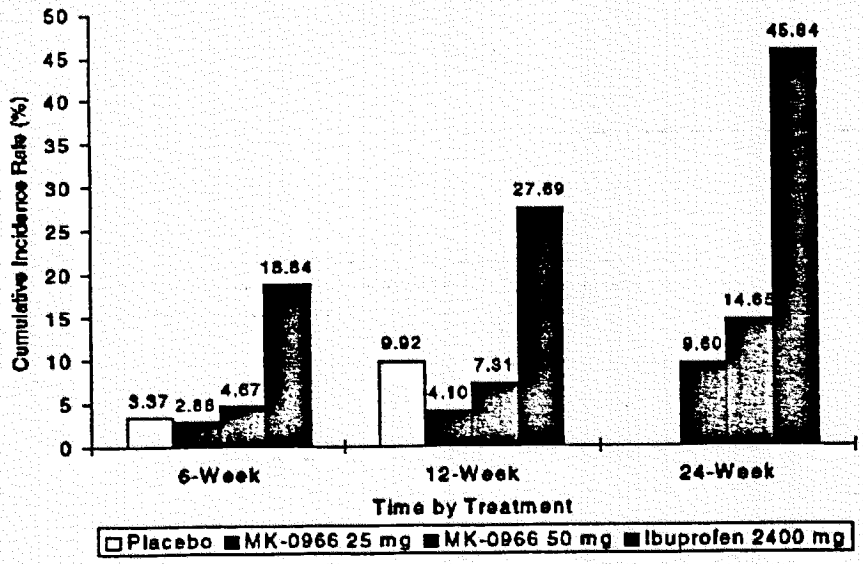
Endoscopic Results:

Figure 1 and table 7 shows the major endpoint results of this study. There was a statistically significant difference between both doses of Vioxx and Ibuprofen at all three time points studied. The comparisons to placebo revealed no significant differences at 12 weeks although this was not a prespecified comparison. No calculation was shown for comparisons at 6 weeks although the data indicate no significant numeric differences. There are serious concerns over the placebo data that will be detailed in the discussion section of study 044C.

Figure 1

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥3 mm

Intention-to-Treat



N=158 N=186 N=178 N=167

p<0.001 ibuprofen versus placebo, MK-0966 25 mg, MK-0966 50 mg at Week 6 and Week 12.

p<0.001 ibuprofen versus MK-0966 25 mg, MK-0966 50 mg at Week 24.

Data Source: [4.10.1; 4.10.2]