considered safe.

Subjects could not have used NSAIDs within 2 weeks of the study. NSAID use prior to that time was not specified. It is possible to have a chronic enteropathy that would affect the permeability of the small intestine even after a washout period. The use of baseline measurements for control in each patient minimizes the interindividual variability that would otherwise impact on such a study.

Intestinal permeability was measured before treatment (i.e., at the baseline visit on the day before Treatment Period 1 and on the day before Treatment Periods 2, 3, and 4) and after treatment (i.e., on Day 7 of each treatment period). Treatment periods were separated by a washout period lasting 7 to 10 days. Ratios of $^{51}$Cr EDTA/L-rhamnose values were computed for each subject before and after treatment in each period.
Subjects were required to abstain from alcoholic beverages, spicy foods, and smoking for 7 days prior to the start of the study and for the duration of the study; consumption of coffee (both caffeinated and decaffeinated) and other caffeinated beverages was limited to four 8-oz cups per day. Any use of alcohol or tobacco (as well as the average number of cups of caffeinated beverages consumed per day) was reported on the Case Report Form.





## Table 69

**Treatment Allocation Schedule**

| Planned Subjects/ Sequence | Treatment Period 1 | Treatment Period 2 | Treatment Period 3 | Treatment Period 4 |
|---|---|---|---|---|
| (N=6) | A | D | B | C |
| (N=6) | B | A | C | D |
| (N=6) | C | B | D | A |
| (N=6) | D | C | A | B |

Treatment A: Placebo.
Treatment B: MK-0966 25 mg once daily.
Treatment C: MK-0966 50 mg once daily.
Treatment D: Indomethacin 50 mg (2 x 25 mg) three times daily.

Data Source: [3.2]

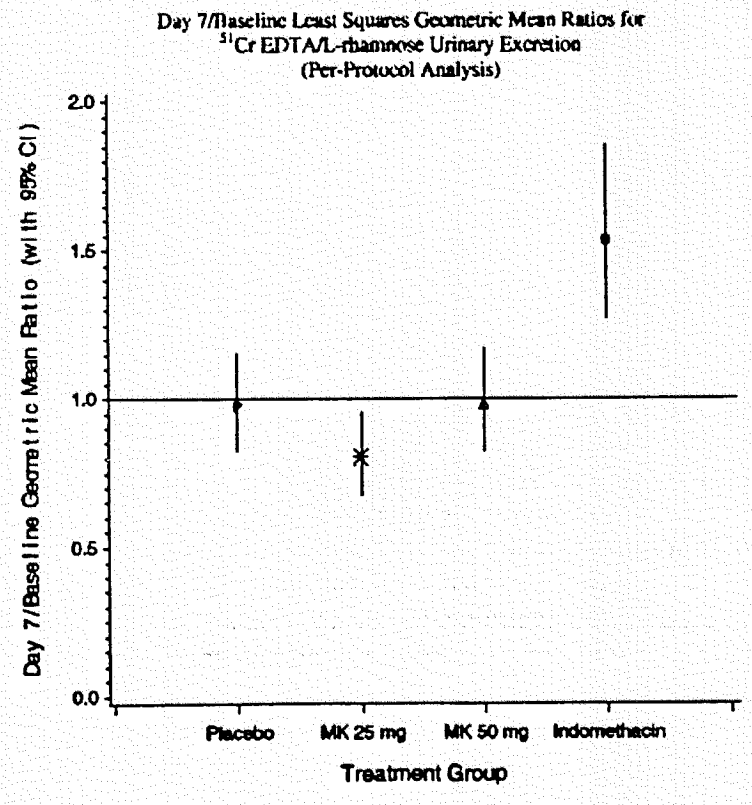
The sponsor did not specify in the original protocol whether intention to treat or per protocol would be the primary basis for analysis. In the final report the per-protocol was

defined as the primary analysis. A secondary analysis was performed on the intention to treat population. There were 9 subjects excluded because of major protocol violations (alcohol intake- which significantly and acutely affects the permeability of the small bowel). These subjects were replaced with other volunteers. Selected data on five other major protocol violators was excluded from the per-protocol analysis. There was no prespecified definition of major violations. All available data was included in the intention to treat analysis.

**Results:**



## Figure 13




Data Source: [4.9.2]

# Table 70

Least Squares (LS) Geometric Mean Ratios for $^{51}$Cr EDTA/L-rhamnose Urinary Excretion (Per-Protocol Analysis)

| Treatment | N | Baseline LS Geometric Mean | Day 7 LS Geometric Mean | Day 7/Baseline LS Geometric Mean Ratio | 95% CI for Day 7/Baseline Ratio |
|---|---|---|---|---|---|
| Placebo | 29 | 0.036 | 0.035 | 0.97 | (0.82, 1.16) |
| MK-0966 25 mg | 29 | 0.036 | 0.029 | 0.80 | (0.68, 0.95) |
| MK-0966 50 mg | 27 | 0.035 | 0.035 | 0.98 | (0.82, 1.17) |
| Indomethacin 150 mg | 26 | 0.038 | 0.055 | 1.53 | (1.27, 1.85) |

| Between-Treatment Comparison | Between-treatment Ratio of Day 7/Baseline LS Geometric Mean Ratios | 95% CI for Between-treatment Ratio | p-Value |
|---|---|---|---|
| MK-0966 25 mg vs. Placebo | 0.82 | (0.65, 1.05) | 0.115 |
| MK-0966 50 mg vs. Placebo | 1.01 | (0.79, 1.29) | 0.940 |
| Indomethacin 150 mg vs. Placebo | 1.58 | (1.22, 2.04) | 0.001 |
| MK-0966 50 mg vs. MK-0966 25 mg | 1.22 | (0.96, 1.57) | 0.108 |
| Indomethacin 150 mg vs. MK-0966 25 mg | 1.91 | (1.47, 2.48) | <0.001 |
| Indomethacin 150 mg vs. MK-0966 50 mg | 1.56 | (1.21, 2.01) | 0.001 |

| Effect | p-Value |
|---|---|
| Treatment | <0.001 |
| Baseline covariate | <0.001 |
| Period | 0.977 |
| Carryover | 0.087 |
| Pooled SD for log Percent of Baseline | 0.433 |

Data Source: [4.9.2]

The sponsor stated that the intention to treat analysis was similar to the per protocol analysis. In view of the small size of the study and selective censoring of data, this sensitivity analysis is important. Analysis of the intention to treat data reveals a day7/baseline ratio of LS mean of 1.08,0.83,1.21 and 1.87 for the placebo, Vioxx 25mg, Vioxx 50mg and indomethacin groups respectively. In this analysis there is a statistically significant difference between Vioxx 25 mg and Vioxx 50 mg despite the lack of difference between placebo and Vioxx 25mg. This analysis maintains the robust differences seen in the per protocol analysis between Vioxx and indomethacin. The sponsor evaluated the potential for crossover effects from one phase of the study to another and a small effect was identified. This effect was reported to not affect the significance of the results.

**Discussion:**

The results of this study are supportive of the claim that the type of acute toxicity seen with indomethacin is not seen with Vioxx 25 mg. In view of the intention to treat data, comparisons between Vioxx and placebo are difficult to interpret. If Vioxx 50 mg in a short term study is statistically significantly worse than Vioxx 25mg based on the chosen

endpoint in an intention to treat analysis, it is difficult to convincingly compare the drug to placebo. This study corroborates past studies that show that the acute effects of indomethacin and other NSAIDs are rapidly reversible. This reversibility is not typical of the type of enteropathy that results from chronic (greater than 6 months) exposure. This study does not answer questions about long term exposure. The data must be interpreted in the context of short-term exposure.
Landmark data on small bowel inflammation associated with NSAIDs revealed that the inflammation may not be evident in patients receiving less than 6 months of therapy and continued to reveal inflammation for as long as 18 months after discontinuation of the NSAID [23]. These two facts limit the value of short-term studies of intestinal damage. The patients in this study did have near total resolution of their small bowel abnormalities during a brief washout period suggesting that the phenomenon seen in this study may not be an adequate endpoint to evaluate NSAID enteropathy.

The choice of indomethacin as the only active comparator does not allow relative safety comparisons with the most commonly used NSAIDs.
This study does support the claim that Vioxx at the doses tested has a significantly diminished short term effect over 7 days on the permeability of the small bowel compared to indomethacin. The comparisons to placebo are worth noting. In view of the intention to treat data revealing a statistical difference between the two doses of Vioxx, true comparability to placebo is difficult to support. The statistical conundrum is similar to the endoscopic studies where dose related effects were seen despite prespecified comparability to placebo at one dose and one time interval. While the differences between both therapeutic doses of Vioxx and indomethacin in short term effects on small bowel are conclusive, the relevance of this finding over the long term is unclear. Also unclear is comparisons to other NSAIDs.
Long-term studies would be important to clarify the long-term effects of selective cyclooxygenase-2 inhibition on the bowel.

## Study 050: A Randomized, double blind, active and placebo controlled study with MK-0966, ibuprofen and placebo to evaluate the gastrointestinal blood loss in normal healthy volunteers during a four week treatment period

This study was intended to analyze the gastrointestinal safety profile of Vioxx based on fecal blood loss. This parameter has been used since 1959 with little change in the basic technique[19]. The persistence of radioactive chromium RBC binding in vivo and potential for biliary excretion to account of some of the radioactive label in fecal collection has been questioned[20]. Overall it is a widely accepted technique and these concerns have not impacted on the usage of the technique. Similar data have been submitted to the FDA in the past in support of safety claims made by other sponsor's and accepted.

**"Hypotheses**
Primary Hypothesis
Compared to ibuprofen 800 mg three times daily, $^{51}$Cr red blood cell loss will be lower with MK-0966 25 mg once daily for 4 weeks in a population of healthy volunteers (the ibuprofen/MK-0966 ratio of fecal $^{51}$Cr red blood cell loss is expected to be >2.0).

Secondary Hypotheses
Compared to placebo, $^{51}$Cr fecal red blood cell loss will not be greater in healthy volunteers treated with MK-0966 25 mg once daily for 4 weeks (the MK-0966/placebo ratios of fecal $^{51}$Cr red blood cell loss will fall below 1.7).

Compared to placebo, treatment with ibuprofen 800 mg three times daily for 4 weeks will be associated with an increase in $^{51}$Cr fecal red blood cell loss in a population of healthy volunteers.

Compared to placebo, $^{51}$Cr fecal red blood cell loss will not be greater in healthy volunteers treated with MK-0966 50 mg once daily for 4 weeks.

Compared to ibuprofen 800 mg three times daily for 4 weeks, $^{51}$Cr fecal red blood cell loss will be lower in a population of healthy volunteers treated with MK-0966 50 mg once daily for 4 weeks. "

The intention to treat population was the basis for the primary analysis.

The study design minimized confounding sources of fecal blood such as hemorrhoids, oral/periodontal disease or vaginal bleeding in women. Potential subjects with baseline occult positive stool or daily fecal blood loss over 2 ml in a single baseline day or greater than 1.5ml average loss over the baseline one week period were excluded based on prespecified criteria.
Subjects were continuously boarded as inpatients in a study center to ensure full compliance and stool collection.
The results were analyzed as the least square geometric mean daily blood loss in ml/day over the entire 4-week interval as well as week by week."

The 1.7 ratio for Vioxx/placebo fecal blood loss to claim comparability to placebo was based on a similar study between nabumetone, placebo and aspirin that was presented by SmithKline Beecham in support of labeling that was accepted by the agency.[25] In this study the ratio of Relafen to placebo was 1.8 This study was accepted as showing "no difference" between placebo and Relafen ™.

**Results:**
The discontinuation rate was very low. (See table71)

# Table 71

Subject Accounting

| | Placebo | MK-0966 | | Ibuprofen | Total |
|---|---|---|---|---|---|
| | | 25 mg | 50 mg | 2400 mg | |
| ENTERED: Total | 17 | 18 | 19 | 13 | 67 |
| Male (age range) | 17 (19 to 25) | 18 (20 to 37) | 19 (19 to 24) | 13 (21 to 27) | 67 (19 to 37) |
| Female (age range) | 0 | 0 | 0 | 0 | 0 |
| COMPLETED: | 17 | 17 | 18 | 13 | 65 |
| DISCONTINUED: | 0 | 1 | 1 | 0 | 2 |
| Total | | | | | |
| Other (Fecal Blood Loss >2.0 mL in a single day during pretreatment baseline week) | 0 | 1 | 1 | 0 | 2 |

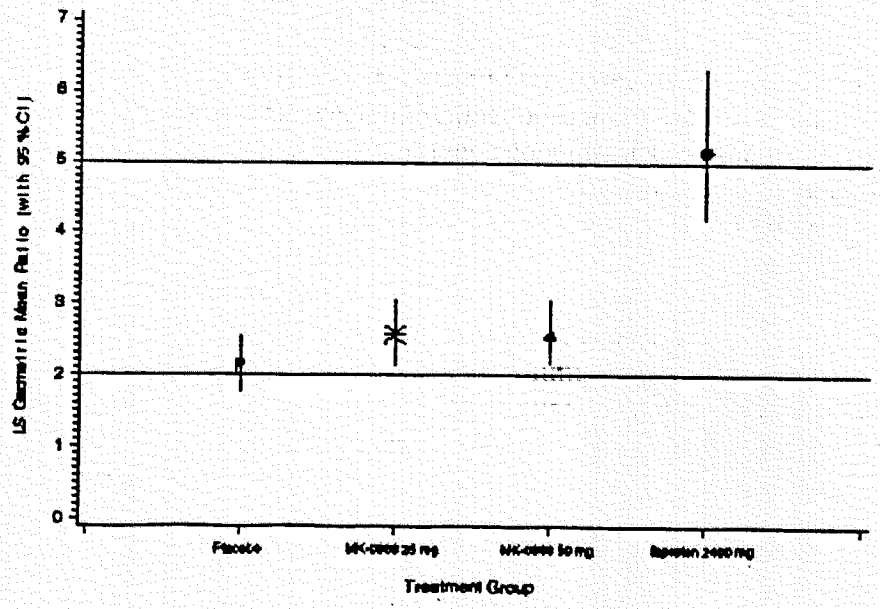
Data Source: [4.1; 4.8; 4.10.5]



# Table 72

Weeks 2 to 4/Baseline LS Geometric Mean Ratio for Daily Fecal Blood Loss

(Intention-to-Treat)




Data Source: [4.10.5]

# Table 73

Intention-to-Treat Analysis of Weeks 2 to 4 Daily Fecal Blood Loss (mL/day)

| Treatment | N | Baseline Geometric Mean | Weeks 2 to 4 Geometric Mean | Weeks 2 to 4/Baseline LS Geometric Mean Ratio | 95% CI for Weeks 2 to 4/ Baseline Ratio |
|---|---|---|---|---|---|
| Placebo | 17 | 0.32 | 0.69 | 2.13 | (1.79, 2.54) |
| MK-0966 25 mg | 17 | 0.33 | 0.84 | 2.57 | (2.15, 3.06) |
| MK-0966 50 mg | 18 | 0.31 | 0.81 | 2.57 | (2.16, 3.04) |
| Ibuprofen 2400 mg | 13 | 0.36 | 1.78 | 5.16 | (4.21, 6.32) |

| Between-Treatment Comparison | Between-Treatment Ratio of Weeks 2 to 4/Baseline Ratios | 90% CI for Between-Treatment Ratio | p-Value |
|---|---|---|---|
| MK-0966 25 mg vs. Placebo | 1.20 | (0.98, 1.48) | 0.140 |
| MK-0966 50 mg vs. Placebo | 1.20 | (0.98, 1.48) | 0.135 |
| Ibuprofen 2400 mg vs. Placebo | 2.42 | (1.93, 3.03) | <0.001 |
| MK-0966 50 mg vs. MK-0966 25 mg | 1.00 | (0.82, 1.23) | 0.998 |
| Ibuprofen 2400 mg vs. MK-0966 25 mg | 2.01 | (1.61, 2.51) | <0.001 |
| Ibuprofen 2400 mg vs. MK-0966 50 mg | 2.01 | (1.61, 2.51) | <0.001 |

| Effect | p-Value |
|---|---|
| Treatment | <0.001 |
| Baseline | 0.002 |
| Baseline by Treatment Interaction | 0.261 |
| Pooled SD for log Percent of Baseline | 0.361 |

Data Source: [4.10.5]



The sponsor reports similar statistical findings when the data are looked at week by week. Table 74 reveals that for all four periods the pattern of daily fecal blood loss was the same. Placebo had the lowest rate followed by Vioxx 50 mg, Vioxx 25 mg and ibuprofen. When the extreme measures are reviewed the Vioxx 50 mg dose was associated with higher minimum and higher maximum blood loss per day than any individual in the placebo group.

# Table 74

Intention-to-Treat Summary Statistics for Daily Fecal Blood Loss (mL/day)

| Period | Treatment | N | Geometric Mean (SD‡) | 84% CI | Minimum | Maximum |
|---|---|---|---|---|---|---|
| Baseline† | Placebo | 17 | 0.32 (0.29) | (0.29, 0.35) | 0.18 | 0.59 |
| | MK-0966 25 mg | 17 | 0.33 (0.31) | (0.29, 0.36) | 0.20 | 0.62 |
| | MK-0966 50 mg | 18 | 0.31 (0.33) | (0.27, 0.35) | 0.17 | 0.75 |
| | Ibuprofen 2400 mg | 13 | 0.36 (0.35) | (0.31, 0.42) | 0.26 | 0.85 |
| Week 1 | Placebo | 17 | 0.42 (0.38) | (0.37, 0.48) | 0.27 | 1.41 |
| | MK-0966 25 mg | 17 | 0.48 (0.27) | (0.43, 0.52) | 0.26 | 0.68 |
| | MK-0966 50 mg | 18 | 0.46 (0.44) | (0.39, 0.53) | 0.29 | 2.02 |
| | Ibuprofen 2400 mg | 13 | 1.14 (0.38) | (0.97, 1.33) | 0.49 | 2.43 |
| Week 2 | Placebo | 17 | 0.49 (0.28) | (0.44, 0.54) | 0.27 | 0.88 |
| | MK-0966 25 mg | 17 | 0.62 (0.26) | (0.56, 0.68) | 0.34 | 1.03 |
| | MK-0966 50 mg | 18 | 0.58 (0.47) | (0.50, 0.69) | 0.33 | 2.99 |
| | Ibuprofen 2400 mg | 13 | 1.61 (0.52) | (1.29, 2.00) | 0.71 | 4.68 |
| Week 3 | Placebo | 17 | 0.70 (0.37) | (0.62, 0.80) | 0.43 | 1.91 |
| | MK-0966 25 mg | 17 | 0.89 (0.31) | (0.79, 0.99) | 0.50 | 1.98 |
| | MK-0966 50 mg | 18 | 0.81 (0.42) | (0.71, 0.94) | 0.48 | 2.48 |
| | Ibuprofen 2400 mg | 13 | 1.78 (0.50) | (1.44, 2.19) | 0.87 | 4.23 |
| Week 4 | Placebo | 17 | 0.84 (0.31) | (0.75, 0.94) | 0.42 | 1.45 |
| | MK-0966 25 mg | 17 | 1.00 (0.25) | (0.92, 1.09) | 0.57 | 1.56 |
| | MK-0966 50 mg | 18 | 0.99 (0.52) | (0.83, 1.19) | 0.55 | 4.32 |
| | Ibuprofen 2400 mg | 13 | 1.81 (0.62) | (1.40, 2.34) | 0.94 | 10.39 |

† For only those who were enrolled into the treatment period.
‡ Log scaled SD.

Data Source: [4.10.5]



## Discussion

The data presented in the 050 study report support the conclusion that Vioxx at 25 and 50 mg dosages are associated with significantly less occult GI blood loss over a 4 week period compared to ibuprofen. The results from the entire period as well as the week by week analysis reveal a small but consistently higher blood loss in the Vioxx groups compared to the placebo group. The clinical significance of this difference is unclear. As noted in an earlier section of this review, hemoglobin and hematocrit levels fell in the Vioxx groups over time. The reason for these small changes is not clear. Given the short-term nature of this study and the known adaptation of the gastric mucosa when exposed to NSAIDs; long term differences between placebo, Vioxx and ibuprofen are not fully addressed by this study. Historical data do suggest that adaptation does not fully reverse GI blood loss associated with NSAIDs.

This study does support the conclusion that Vioxx is associated with significantly less occult GI blood over the course of 4 weeks compared to ibuprofen. The clinical relevance of the small differences seen compared to placebo is unknown.

## Conclusions from GI Studies in NDA 21-042:

The goal and execution of studies by the sponsor in support of NDA 21-042 aimed at evaluating a broad set of GI safety variables for Vioxx compared to ibuprofen, diclofenac and placebo. Preclinical studies were followed by clinical studies using surrogate endpoint that follow accepted physiologic and clinically applied methodologies. Endpoints reflecting GI safety included endoscopic findings occult fecal blood loss, intestinal permeability, GI symptoms and withdrawal due to GI symptoms and finally clinically relevant gastroduodenal ulcers (PUBs).

1. **Endoscopic ulcers:**

a) **Endoscopic comparisons to ibuprofen:** This endpoint was defined by protocol mandated endoscopies to assess gastroduodenal mucosal injury over time in studies 044 and 045. Endoscopic ulcers represent an important endpoint in testing the hypothesized safety of COX-2 selective agents. The large differences seen in gastroduodenal ulcer rates between Vioxx at both proposed dosages and ibuprofen suggested a substantial difference in safety profile.

The decision to compare Vioxx to only one active drug comparator represents a limitation of the data. It is not possible to make class claims based on such limited data. This limitation is particularly true in view of the PUB and symptomatic endpoint results which were not suggestive of class distinctions when comparing ibuprofen and diclofenac and Vioxx study endpoint rates in study 069.

**Endoscopic comparisons to placebo:** Although large differences between Vioxx and placebo in endoscopic ulcer rates were not seen in study 044C; it is not possible to conclude that the rates for Vioxx and placebo are comparable. Issues in the analysis of study 044C include:

i. Statistical comparability of Vioxx to placebo in ulcer rate was only claimed for one of two proposed dosages studied, at one of two time intervals studied.
ii. The results were based on merging data from two studies with different baseline patient characteristics in the critical areas of recent NSAID use and history of clinical ulcer disease. There were significant differences in placebo ulcer rates between the two studies. The lack of internal placebo rate validation in these two identically designed studies is problematic.
iii. Comparability to placebo bounds was set at 4%. This amounts to an allowable

twofold higher ulcer rate for Vioxx if placebo ulcer rate is 4% or 67% higher Vioxx ulcer rate for a 6% placebo ulcer rate. These bounds are high for event rates at this level.

iv. Gastrointestinal adverse event data are not consistent with placebo-like effects and do not follow the dramatic differentiation between Vioxx and ibuprofen seen in gastroduodenal ulcer rates.

**c. Esophageal effects**

Esophageal injury was scored in studies 044 and 045 as well. A finding of note was the effect on esophageal injury seen in the Vioxx as well as the ibuprofen groups. It is unclear if this represents a COX related phenomenon, local effect of the pill or other unknown effects of Vioxx. The differences compared to placebo in both studies and the dose related rise in event rate suggest that the esophageal score data represents a biologic phenomenon.

2. **Small bowel permeability**

The sponsor evaluated potential effects of Vioxx on small bowel using studies on intestinal permeability changes over a one-week period in study 041. These studies showed a statistically significant increase in intestinal permeability during 1-week intervals of exposure to indomethacin compared to placebo or Vioxx 25 or 50 mg. Per protocol analysis showed no difference compared to placebo. Intention to treat analysis revealed statistically significantly higher permeability results for Vioxx 50mg compared to 25 mg .

3. **Occult fecal blood loss**

The sponsor studied occult GI blood loss over a 4-week period in study 050. This short-term study did show a statistically significantly lower blood loss rate associated with Vioxx 25 and 50 mg compared to ibuprofen. There was a small but consistently higher rate of blood loss with both dosages of Vioxx at every weekly interval compared to placebo.

4. **GI symptomatic adverse events**

Study 069 represented a combined analysis of several controlled studies comparing clinically significant GI adverse events in patients receiving Vioxx, diclofenac, ibuprofen, nabumetone and placebo. Clinically significant endpoints chosen by the sponsor for analysis in this study included 1) discontinuation due to GI adverse events, 2) discontinuation due to NSAID- type GI adverse events (dyspepsia, epigastric discomfort, acid reflux, heartburn, nausea and vomiting) and 3) total reporting of NSAID- type GI adverse events.

The sponsor's analysis revealed a statistically significantly lower rate of discontinuation due to GI adverse events for all doses of Vioxx combined compared to NSAIDs (5.67 versus 7.81%). Analysis by dose of Vioxx and specific NSAID

revealed an event rate for Vioxx 50mg between the rates for ibuprofen and diclofenac for time intervals with over 200 surviving patients for each group.

Discontinuation rates due to NSAID-type adverse events were not statistically significantly different between Vioxx and NSAID combined groups. There was a trend in favor of the Vioxx group with a relative risk of 0.69 (2.68 versus 3.70% at 12 months). By dose and NSAID, Vioxx 25 and 50 mg had numerically higher rates than diclofenac and lower than ibuprofen. Both doses of Vioxx had rates over twice the placebo rate at 12 weeks.

Total rates of NSAID-type adverse events were similar between Vioxx and NSAID groups at 12 months (29.87 versus 29.46% respectively). At 4 months rates were similar in all three groups including placebo. Breakdown by dose and specific NSAID did not add meaningfully to the analysis.

Additional post hoc analyses of heartburn, nausea and vomiting revealed little differentiation between Vioxx 25 and 50 mg and the NSAIDs.

Overall symptomatic adverse event GI safety parameters did not differentiate proposed dosage forms of Vioxx from NSAIDs as a class.



5. **PUBs**

The sponsor chose symptomatic and complicated ulcer rates as clinically relevant endpoints in study 069. The results of this study are difficult to interpret for many reasons. See the statistician's review for further insights.

a) Data are taken from multiple studies with different endpoints and study design.

b) It is important to examine dose related adverse event rate for analysis. This is particularly important given the dose related event rates in other parameters tested. The many empty cells in tables 69, 74, 76 and 78 due to small exposure rates highlight the limited exposure to the Vioxx 50 mg dose associated with this submission.

c) It is difficult to define an adequately large comparator universe of NSAIDs to make any generalizations. Under 200 patients remained on ibuprofen for 6 months. The rates for this group were different than for the larger diclofenac group that had over 200 patients under study for a year. There were only 127 patients studied on nabumetone. Less than 50 remained beyond 12 weeks. The relatively small number and limited exposure to NSAID comparator groups compared to Vioxx creates difficulties in interpreting results meaningfully.

d) As discussed earlier in this review, the chosen endpoint definitions are subject to

interpretation and were reanalyzed using more rigorous criteria for inclusion of events.

Results:

When merging all dosages of Vioxx and all 3 NSAID comparators there was a statistically significantly lower PUB rate for Vioxx compared to NSAIDs at 12 months (1.58 versus 2.68% respectively). Complicated ulcer rates revealed no statistical differences with low total event rates of.45 versus .55% respectively at 12 months.

When stratifying for Vioxx dose and individual NSAID, the very limited data available suggest 1) A dose related rise in PUB rate from Vioxx 12.5 and 25 mg to 50 mg and 2) A Vioxx 50 mg PUB rate lower than ibuprofen but higher than diclofenac.

A sensitivity analysis was conducted excluding patients whom had silent ulcers without high-risk stigmata based on ulcer size. This analysis was intended to assess clinically relevant ulcers without inclusion of asymptomatic protocol derived ulcers. The basis for this reanalysis is found in the review of study 069. The results revealed the same pattern seen in the sponsor's less rigorous evaluation. There was a statistically significantly lower ulcer rate in the combined Vioxx groups compared to the combined NSAID group at all 4 timepoints examined. The relative risk was 0.51 at 12 months. The rates and relative risk of complicated PUBs remained identical to the sponsor's initial analysis.
When analyzed based on dosage of Vioxx and individual NSAID the rate relationship between groups for confirmed PUBs continued to show the highest rate for ibuprofen followed by Vioxx 50 mg, diclofenac and Vioxx 12.5 mg. (See table 60A).

To summarize the results of study 069; both total GI adverse events, GI adverse events resulting in withdrawal and PUB data show a trend towards lesser incidence of GI adverse events for Vioxx 12.5 and 25 mg (compared to the NSAID comparators).The wide confidence intervals when individual dose and NSAID are analyzed represent significant restraints when trying to reach conclusions. Furthermore, this study does not give results of similar dimension compared to the endoscopic ulcer data. The degree of differentiation between other NSAIDs and Vioxx in terms of clinically relevant endpoints cannot be well quantitated based on the data available from the GI studies in this submission. A large simple trial with clinical endpoints comparing Vioxx and NSAID comparators is needed to answer this question better than is currently possible. Class claims will remain difficult to make when a limited number of NSAID comparators are studied. Efficacy data and practice trends in use of analgesics in general suggest that patients may move from 25 to 50mg Vioxx doses. Therefore safety comparisons should be considered most relevant at the higher dose.

## Additional reviewer comments:

**High risk populations:** Studies 044 and 045 demonstrated a substantially increased risk of ulcer formation in patients with a prior history of clinically relevant ulcers. This is consistent with reports in the medical literature. This increased risk was maintained in all groups (placebo, Vioxx and ibuprofen). The use of Vioxx did not appear to decrease the biologic impact of this factor on ulcer risk. Ulcer rates were several fold higher in patients with a history of clinically relevant ulcers compared to patients without such a history in the placebo and Vioxx groups. The ulcer rate in the ibuprofen group differed by only 50%. The higher incidence of ulcers associated with the use of ibuprofen in the lower risk, unselected population may account for the less significant rise in the high risk group. Ulcer rates remained lower in the Vioxx groups compared to the ibuprofen group even in the high-risk patients. The data on PUBs are less convincing. PUB rates overlap significantly among groups. This may reflect either the small number of total events or a real phenomenon pointing to the importance of non-attributable risk of NSAID ulcers in patients with a history of PUBs.

**Aspirin**

The drug development plan excluded aspirin use (including low dose- $\leq$ 325-mg aspirin) in all but one small 6-week efficacy study in the elderly (058). This approach is considered scientifically valid because of the potential confounding effects of aspirin. The true biologic effects of Vioxx cannot be fully evaluated when nonselective cyclooxygenase inhibition with aspirin in present. On the other hand, concomitant use of the 2 agents is likely in practice and the effects of combining the two drugs may not be purely additive. Does low dose aspirin negate any potential safety advantage conferred by the use of Vioxx over ibuprofen? This is an important question.
In study 058 only 118 patients over 80 years of age were on Vioxx 12.5 mg and 56 were on Vioxx 25 mg. Approximately 30% of the patients in this study took concomitant low dose aspirin. Thus, approximately 50 patients in the entire controlled clinical study population were exposed to aspirin and Vioxx concomitantly. This exposure was limited to 6 weeks. Even fewer patients were exposed during extensions of this one study. The elderly do represent an enriched population of patients likely to be exposed to these two drugs concomitantly. A broader experience over a longer duration would be important for safety assessment.

**Colitis**
Concerns over the effects of Cox-2 selective agents on the colon have been raised by some. Potential exacerbations of preexisting colitis and de novo development of colitis are theoretical concerns in view of experience with NSAIDs. The database was examined

and only one case of colitis that could reasonably be associated with the use of Vioxx was found. It must be cautioned that patients with diarrhea were not specifically evaluated for cause of diarrhea in these studies unless clinically indicated by treating physicians. Self limited rectal bleeding and patients withdrawn due to diarrhea were not necessarily evaluated for colitis and therefore cases could have been missed. Post-marketing experience will be required to assess this concern.

**Esophageal injury**

Exploratory analyses from this submission contain well controlled data supporting clinical impressions and some historical literature that suggest that NSAIDs are associated with esophageal injury in the form of erosive esophagitis and ulcers. While appearing to be associated with significantly less morbidity than gastroduodenal injury, esophageal injury may correlate with UGI symptoms such as heartburn, nausea epigastric pain or discomfort and be associated with a low incidence of clinically serious adverse events. Odynophagia and dysphagia were not included in the Merck dictionary of adverse events and these symptoms cannot be evaluated in the studies presented. The data in this submission are not adequate to meaningfully compare Vioxx with other comparator NSAIDs. Post marketing experience will be required to ascertain whether there is any clinical significance of the esophageal findings in this submission.



## Safety Update

The additional data available from the safety update are small, less than 25% of that presented in the original NDA. There were no endoscopic or other surrogate endpoint studies with extensions. Adverse events were the only type of GI endpoints with updated information.

The 6-month osteoarthritis studies were completed with the original submission and no new safety update information is available.

The long-term exposure studies with extensions (029-20/30/40, 034, and 035) did not show any meaningful increases in GI adverse events or withdrawals due to GI adverse events.

The elderly osteoarthritis study (058) is worth reviewing. It must be kept in mind that these patients are likely to be at a higher risk of GI adverse events based on high rates of

concomitant medications, higher baseline risk for GI tract disease compared to younger populations and the allowance for low dose aspirin use in this study. Furthermore, the group included in the extension of study 058 was a selected group of patients, not a randomly assigned population. Tables 75 and 76 reveal that there were substantially higher rates of GI system adverse events as well as withdrawals due to GI adverse events in the Vioxx and nabumetone groups compared to placebo in the primary study. The safety update did not however reveal any new patterns.

## Table 75



Number (%) of Patients With Clinical Adverse Experiences by Body System
Base Study

| | Placebo (N=52) | | MK-0966 12.5 mg (N=118) | | MK-0966 25 mg (N=56) | | Nabumetone 1500 mg (N=115) | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Patients with one or more adverse experiences | 26 | (50.0) | 68 | (57.6) | 33 | (58.9) | 67 | (58.3) |
| Patients with no adverse experience | 26 | (50.0) | 50 | (42.4) | 23 | (41.1) | 48 | (41.7) |
| Body as a whole/site unspecified | 14 | (26.9) | 31 | (26.3) | 13 | (23.2) | 26 | (22.6) |
| Cardiovascular system | 3 | (5.8) | 11 | (9.3) | 3 | (5.4) | 8 | (7.0) |
| Digestive system | 4 | (7.7) | 24 | (20.3)* | 12 | (21.4) | 23 | (20.0) |
| Eyes, ears, nose and throat | 0 | (0.0) | 8 | (6.8) | 2 | (3.6) | 7 | (6.1) |
| Endocrine system | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.9) |
| Hemic and lymphatic | 0 | (0.0) | 0 | (0.0) | 1 | (1.8) | 0 | (0.0) |
| Immune system | 0 | (0.0) | 2 | (1.7) | 1 | (1.8) | 0 | (0.0) |
| Metabolic and nutrition | 1 | (1.9) | 2 | (1.7) | 1 | (1.8) | 1 | (0.9) |
| Musculoskeletal system | 3 | (5.8) | 11 | (9.3) | 4 | (7.1) | 11 | (9.6) |
| Nervous psychiatric | 4 | (7.7) | 9 | (7.6) | 5 | (8.9) | 12 | (10.4) |
| Psychiatric disorder | 1 | (1.9) | 2 | (1.7) | 0 | (0.0) | 1 | (0.9) |
| Respiratory system | 0 | (0.0) | 8 | (6.8) | 4 | (7.1) | 8 | (7.0) |
| Skin-skin appendages | 3 | (5.8) | 5 | (4.2) | 6 | (10.7) | 7 | (6.1) |
| Urogenital system | 0 | (0.0) | 11 | (9.3)* | 5 | (8.9) | 8 | (7.0) |

* p<0.05 vs. placebo.

## Table 76

Patients Discontinued Due to a Clinical Adverse Experience by Category
Base Study

| | Placebo (N=52) | | MK-0966 12.5 mg (N=118) | | MK-0966 25 mg (N=56) | | Nabumetone 1500 mg (N=115) | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| **Total** | **1** | **(1.9)** | **8** | **(6.8)** | **4** | **(7.1)** | **8** | **(7.0)** |
| Discontinuation due to: | | | | | | | | |
| Gastrointestinal-type adverse experiences | 0 | (0.0) | 2 | (1.7) | 4 | (7.1) | 2 | (1.7) |
| Cardiovascular adverse experiences | 0 | (0.0) | 1 | (0.8) | 0 | (0.0) | 1 | (0.9) |
| Edema adverse experiences | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Skin adverse experiences | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (1.7) |
| All other adverse experiences† | 1 | (1.9) | 5 | (4.2) | 0 | (0.0) | 3 | (2.6) |

† Patients appear in this category if not in any of the above categories.
No statistically significant between-group differences were observed.