a statistical meaning to the results. The sponsor's results however are problematic in view of

1. The small number of cases
2. Weakness of some endpoint definitions
3. Merging of multiple studies with different designs, duration, dose and NSAID comparator

The analysis of study 069 is primarily exploratory and hypothesis generating. Hypotheses related to drug dose are at least as important as hypotheses related to how the combined groups compare.

Table 59 represents the dose and NSAID specific rates of confirmed PUBs using the sponsor defined events. The small number of events (36) spread over a multiple treatment groups limits the conclusions possible from this data. At the 12-week to 24-week interval there were 5 events in the Vioxx 50-mg group. There were only 94 patients taking Vioxx 50 mg surviving in the clinical trials at 6 months and 63 patients at 12 months. Therefore the cumulative rate of confirmed PUBs at 6 and 12 months for this group (2.52 and 5.31% respectively) does not appear in the table below. The most relevant point about the PUB data for Vioxx 50 mg at 6 and 12 months is that there is an insufficient database to establish a rate. The trend in rate over time is of note but cannot be interpreted given the limited available database. This same problem is present when analyzing the NSAID specific data which suggests a lower PUB rate for diclofenac compared to ibuprofen and Vioxx 50-mg. This represents a major weakness in the safety database when comparing Vioxx to NSAIDs.

Table 59: Confirmed PUBs % cumulative rates
(# of cumulative events)

Treatment	Initial N	*6 weeks	*12 weeks	*24 weeks	*52 weeks
Placebo	514	0.22 (1)	0.88 (3)	-	-
Vioxx 12.5 mg	1209	0.00 (0)	0.51 (3)	0.70 (4)	0.98 (5)
Vioxx 25 mg	1603	0.00 (0)	0.00 (0)	0.39 (3)	0.87 (5)
Vioxx 50 mg	545	0.76 (4)	1.22 (6)	-	-
Ibuprofen	590	1.25 (10)	2.06 (12)	-	-
Diclofenac	847	0.00 (0)	0.19 (1)	0.64 (3)	1.15 (5)
Nabumetone	127	-	-	-	-

- *rates for treatment groups only with $\geq$ 200 patients at end of interval

Confidence intervals are extremely wide in the cells within table 59 due to the small number of events. Statistical comparisons cannot be made with adequate power to draw valid conclusions. The data suggest that Vioxx dose specific and NSAID specific rates

need to be considered before accepting an analysis of combined groups as presented by the sponsor's original analysis.

Reviewer's recalculation of results:

The sponsor has robustly demonstrated in studies 044 and 045 that Vioxx is associated with statistically significantly lower incidence of endoscopic ulcers than ibuprofen. As noted previously, the purpose of study 069 was to support claims that Vioxx is associated with fewer clinically relevant UGI adverse events. The protocol did not define rigorously how clinically silent ulcers would be excluded from the protocol. This reviewer's recalculation is based on the exclusion of clinically silent ulcers. Silent giant ulcers as noted by the sponsor do represent a uniquely high-risk ulcer and are therefore clinically relevant. These are therefore not excluded from the reanalysis. This analysis is felt to be true to the meaning and spirit of the claim made by the sponsor.

Table 60 A: Cumulative Confirmed PUB rate-reanalysis excluding asymptomatic ulcers that were not giant ulcers (cumulative # of events)

Comparator	Number of patients at baseline	*6-weeks	*12-week	*6 months	*1 year
Placebo	514	0.22 (1)	0.22	-	-
Vioxx 12.5 mg	1209	0.00 (0)	0.35 (2)	0.54 (3)	0.81 (4)
Vioxx 25 mg	1603	0.00 (0)	0.00 (0)	0.39 (3)	0.87(5)
Vioxx 50 mg	545	0.76 (4)	1.22 (6)	-	-
Ibuprofen	847	1.12 (9)	1.12 (9)	-	-
Diclofenac	590	0.00 (0)	0.19 (1)	0.64 (3)	0.91 (4)
Nabumetone	127	-	-	-	-

*Minimum of 200 patients at end of study interval

Table 60B Cumulative Confirmed Complicated PUB rate-reanalysis excluding asymptomatic ulcers that were not giant ulcers

(cumulative # of events)

Comparator	Number of patients at baseline	*6-weeks	*12-week	*6 months	*1 year
Placebo	514	0.00 (0)	0.00 (0)	-	-

Vioxx 12.5 mg	1209	0.00 (0)	0.17 (1)	0.36 (2)	0.64 (3)
Vioxx 25 mg	1603	0.00 (0)	0.00 (0)	0.13 (1)	0.13 (0)
Vioxx 50 mg	545	0.19 (1)	0.19 (1)	-	-
Ibuprofen	847	0.25 (2)	0.25 (2)	-	-
Diclofenac	590	0.00 (0)	0.19 (1)	0.41 (2)	0.41
Nabumetone	127	-	-	-	-

*Minimum of 200 patients at end of study interval

The reanalysis shown in table 60A is most important in showing the small amount of data available to assess comparative rates of clinically relevant ulcers (PUBs). Caution is advised in interpreting these data. It represents with fidelity the type of events described in the objectives section of study 069 but cannot represent event rates with any statistical meaning. One hypothesis suggested by the data in table 60A is that the PUB rates for the 12.5 and 25 mg doses of Vioxx are different than the rates associated with the higher dose of 50mg. This is not a novel concept for NSAIDs. The dose-event rate relationship warrants further clarification before claims about comparative PUB rates can be made. Again, this is particularly true until the most common dosage levels to be used in clinical practice are established.

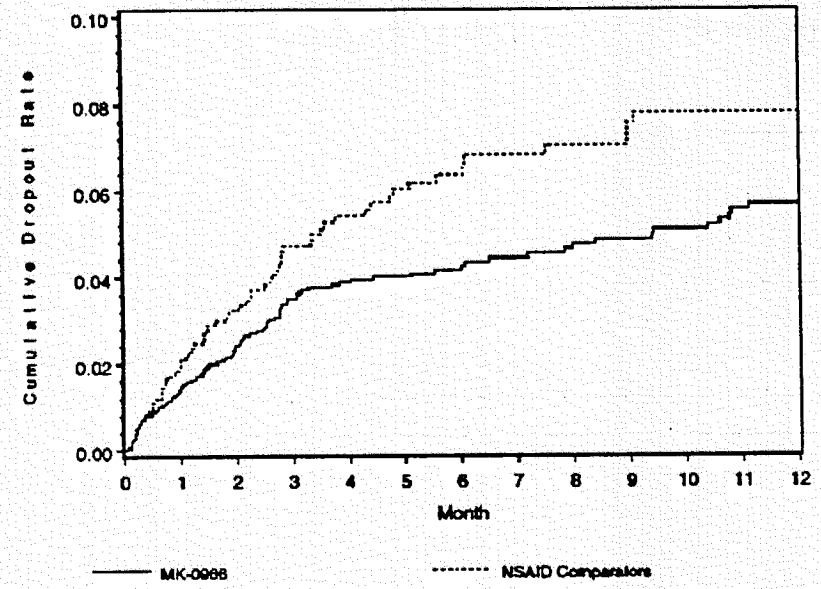
A second hypothesis is that NSAIDs are not all comparable in the risk of PUBs. This is also not a novel concept. Although attempts to define a "toxicity index " or scale for NSAIDs in terms of GI adverse events have been made; the database has not been adequate from available literature to accurately order NSAIDs, standardizing for dose and duration. A review of the medical literature would not have predicted the differences seen in this database between diclofenac and ibuprofen. The recent NDA submission for Celebrex used diclofenac as a comparator in two of the endoscopic studies submitted. In only one of these studies was a statistical difference seen between Celebrex and diclofenac. The possibility of a significant difference in GI safety profile between ibuprofen and diclofenac does warrant consideration when interpreting data as displayed in tables 59 and 60A. It may not be appropriate to define an "NSAID PUB rate" from the current submission, compare it to Vioxx and then extrapolate to the universe of NSAIDs used in clinical practice. The exposure and event rate in the NSAID group in study 069 are very heavily influenced by 1 NSAID, ibuprofen. Class comparisons may not be appropriate based on such a database.

Discontinuation due to GI Adverse Events:

Figure 10 and table 61 shows the results on discontinuation due to GI adverse experiences presented by the sponsor.

Figure 10

Cumulative Rate of Discontinuation Due to GI Adverse Experiences



Data Source: [2.1.1 to 2.1.3; 2.1.5 to 2.1.12]

Table 61

Survival Analysis for Discontinuation Due to GI Adverse Experiences
Intention-to-Treat

Time Point	Number of Discontinued Patients: Placebo (N=514)	MK-0966 (N=3357)	NSAIDs (N=1564)	Rate Per 100 Patient-Years: Placebo	MK-0966	NSAIDs	Cumulative Rate* (%) at Each Time Point: Placebo	MK-0966	NSAIDs
6 weeks	5	62	42	8.79	16.25	23.88	1.05	1.95	2.90
4 months	8	99	62	7.16	12.99	18.55	2.08	3.89	5.42
6 months	n/a	104	68	n/a	10.42	15.84	n/a	4.25	6.37
12 months	n/a	117	74	n/a	8.20	12.03	n/a	5.67	7.81

Overall Summary Statistics for Between-Treatment Comparison

		Cumulative Incidence Difference (%)	95% CI for Cumulative Incidence Diff. (%)	Relative Risk‡	95% CI for Relative Risk	p-Value• for the Primary Analysis
Primary Results:	MK-0966 vs. NSAIDs (across first 12 months)	-2.14	(-4.36, 0.09)	0.70	(0.52, 0.94)	0.016
Other Results:	MK-0966 vs. NSAIDs (across first 6 weeks)	-0.94	(-1.94, 0.05)	0.68	(0.46, 1.01)	0.054
	MK-0966 vs. NSAIDs (across first 4 months)	-1.52	(-3.11, 0.06)	0.71	(0.52, 0.98)	0.036
	MK-0966 vs. NSAIDs (across first 6 months)	-2.13	(-3.91, -0.35)	0.68	(0.50, 0.92)	0.012
Placebo Results:	NSAIDs vs. placebo (across first 4 months)	3.34	(1.32, 5.36)	2.63	(1.26, 5.50)	0.007
	MK-0966 vs. placebo (across first 4 months)	1.82	(0.15, 3.48)	1.88	(0.92, 3.87)	0.080

* Cumulative rate from the survival analysis, it may not equal (number of discontinued patients/N) x 100.
‡ From the Cox Proportional Hazards Model.
• From the log rank test for the comparison of the cumulative discontinuation curves.

Data Source: [2.1.1 to 2.1.3; 2.1.5 to 2.1.12]

There is a clear difference between the discontinuation rate due to GI adverse events at 12 months for Vioxx (combined doses) and NSAID comparators as shown above. (5.67 verses 7.81%) The relative risk of Vioxx compared to NSAID groups was 0.7. The discontinuation rate for GI adverse experiences at 4 months for the Vioxx group was nearly double the rate for placebo; 3.89% verses 2.08 % respectively. The relative risk was 1.88. Despite the much smaller sample size of the placebo group the p=0.08 suggests a strong trend. The numeric differences (cumulative incidence differences) at 4 months are almost identical between placebo and Vioxx and between Vioxx and NSAID. This does not suggest placebo –like effect of Vioxx in terms of the meaningful endpoint of withdrawal due to GI adverse events.

A breakdown based on dose of Vioxx and specific comparator is shown below in table 62.

Table 62
Discontinuation due to GI adverse events (%)

Comparator	Initial number of patients exposed	*6 weeks	*12 weeks	*6 months	*1 year
Placebo	514	1.05	1.38	-	-
Vioxx 12.5 mg	1209	1.5	3.02	3.82	5.03
Vioxx 25 mg	1603	2.00	3.03	3.90	4.84
Vioxx 50 mg	545	2.30	4.85	-	-
Ibuprofen	847	3.42	5.71	-	-
Diclofenac	590	1.55	2.89	5.04	6.27
Nabumetone	-	-	-	-	-

*Minimum of 200 patients exposed to end of timepoint

Caution must be taken in the interpretation of the above data due to the shrinking population at risk over time. The Vioxx data above suggest a possible dose related rising rate for GI adverse events that are significant enough to require discontinuation of therapy. The data are limited and involve post hoc stratification. There are sound reasons to perform this type of analysis. Dose related event rates underlie valid safety data in the field of NSAID toxicity as in other fields of drug related adverse events. This reviewer would have considered such an analysis appropriate for inclusion as a prespecified endpoint of study. However limited, the data does suggest a higher event rate with Vioxx 50 mg than Diclofenac at 6 and 12 weeks and Vioxx 25 mg compared to Diclofenac at 6 weeks. No statistical significance is implied to these trends. It is meaningful to note the absence of trend towards lower rates for Vioxx 50 mg at any time interval compared to the diclofenac group. The trends related to ibuprofen are noted. The statistically

significant differences noted by the sponsor between Vioxx and NSAID groups are driven by the ibuprofen and Vioxx 12.5 and 25 mg data. Generalizations cannot be made about all NSAIDs based on this data.

Discontinuation due to NSAID-type GI adverse events

Figure 10 and table 63 show the data on discontinuation specifically due to NSAID-type GI adverse events as defined by the sponsor.

Figure 10

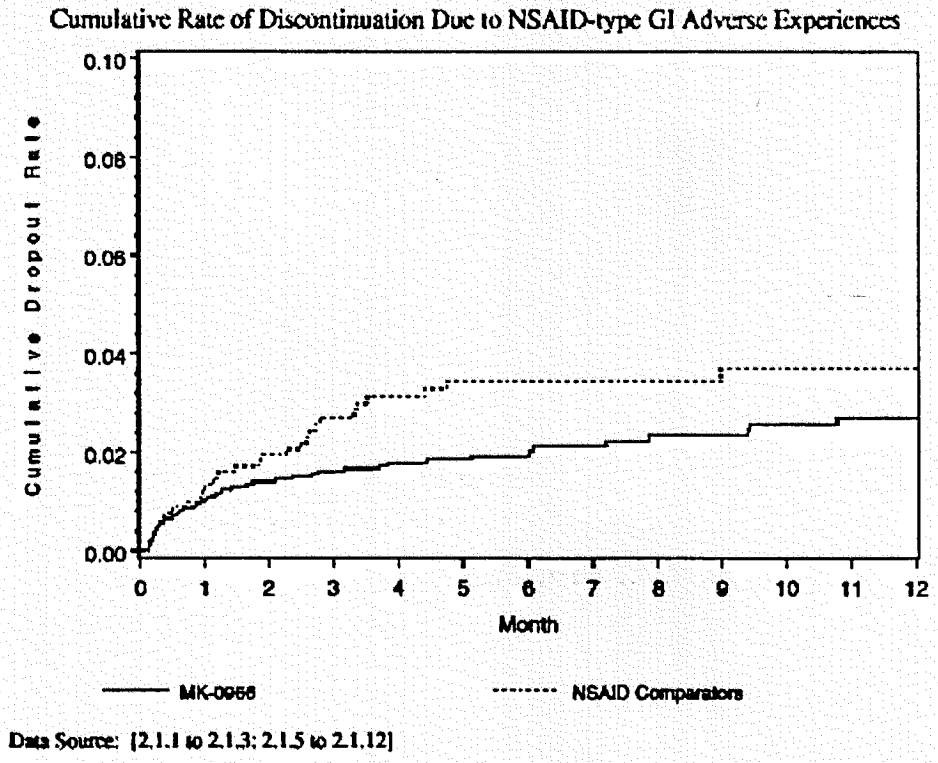


Table 63

Survival Analysis for Discontinuation Due to NSAID-type GI Adverse Experiences
Intention-to-Treat

Time Point	Number of Discontinued Patients			Rate Per 100 Patient-Years			Cumulative Rate† (%) at Each Time Point		
	Placebo (N=514)	MK-0966 (N=3357)	NSAIDs (N=1564)	Placebo	MK-0966	NSAIDs	Placebo	MK-0966	NSAIDs
6 weeks	4	42	25	7.03	11.01	14.21	0.81	1.30	1.71
4 months	4	51	36	3.58	6.69	10.77	0.81	1.79	3.13
6 months	n/a	54	38	n/a	5.41	8.85	n/a	2.02	3.44
12 months	n/a	60	39	n/a	4.20	6.34	n/a	2.68	3.70

Overall Summary Statistics for Between-Treatment Comparison

		Cumulative Incidence Difference (%)	95% CI for Cumulative Incidence Diff. (%)	Relative Risk‡	95% CI for Relative Risk	p-Value* for the Primary Analysis
Primary Results:	MK-0966 vs. NSAIDs (across first 12 months)	-1.01	(-2.48, 0.45)	0.69	(0.46, 1.03)	0.069
Other Results:	MK-0966 vs. NSAIDs (across first 6 weeks)	-0.41	(-1.18, 0.37)	0.78	(0.47, 1.27)	0.317
	MK-0966 vs. NSAIDs (across first 4 months)	-1.33	(-2.51, -0.16)	0.64	(0.42, 0.98)	0.039
	MK-0966 vs. NSAIDs (across first 6 months)	-1.42	(-2.70, -0.14)	0.64	(0.42, 0.97)	0.033
Placebo Results:	NSAIDs vs. placebo (across first 4 months)	2.31	(0.99, 3.64)	3.07	(1.09, 8.63)	0.025
	MK-0966 vs. placebo (across first 4 months)	0.98	(0.04, 1.92)	1.89	(0.68, 5.24)	0.211

† Cumulative rate from the survival analysis, it may not equal (number of discontinued patients/N) x 100.
‡ From the Cox Proportional Hazards Model.
* From the log rank test for the comparison of the cumulative discontinuation curves.

Data Source: [2.1.1 to 2.1.3; 2.1.5 to 2.1.12]

There was no statistical difference at one year between the discontinuation rate due to NSAID type GI adverse events between Vioxx and the NSAID comparator group, relative risk .71 and p=0.069. This was the prespecified endpoint. As table 63 above indicates there was a statistical difference at earlier endpoints although multiplicity correction is required. The trend is certainly of note. The NSAID specific rates shown in table 64 suggest that the diminishing difference between groups over time may relate to the loss of ibuprofen after 6 months as an NSAID comparator.

Once again, a dose comparison would be helpful in ascertaining the potential magnitude of adverse events at a dose that patients may well be exposed to in clinical practice. Dose related data on discontinuation due to NSAID-type GI adverse events is shown in table 64.

Table 64

Dose related Discontinuation due to NSAID-type adverse events

Comparator	Number of patients at baseline	*6-weeks	*12-week	*24 week	*52 week
Placebo	514	0.81	0.81	-	-
Vioxx 12.5 mg	1209	0.96	1.28	1.92	2.63
Vioxx 25 mg	1603	1.48	1.71	1.95	2.45
Vioxx 50 mg	545	1.53	2.01	-	-
Ibuprofen	847	2.00	2.44	-	-
Diclofenac	590	0.87	1.83	2.69	2.95
Nabumetone	127	-	-	-	-

*Minimum of 200 patients at end of study interval

This analysis shows a numeric rate of events for Vioxx 50 mg that falls between the 2 NSAID comparators at the evaluable intervals of 6 and 12 weeks.

NSAID-type GI symptoms:

An evaluation of the composite of nausea, vomiting, dyspepsia, heartburn, epigastric tenderness and acid regurgitation revealed no difference between Vioxx and NSAID comparator groups. The data are displayed in figure 11 and table 65. Early small differences in rates converge at the prespecified 12-month endpoint. The difference in NSAID-type GI adverse event rate was a mere .41% (29.87% for the Vioxx group verses 29.46% for the NSAID group).
Dose related data are displayed in table 66. The results of dose related NSAID-type adverse experience analysis does not change the overall impression of a lack of difference between Vioxx and NSAIDs groups in NSAID –type symptom experience. The dose related rise in events between Vioxx 25 and 50 mg groups is consistent with other parameters studied. The clinical significance of this rise is unknown. The limited

placebo rates are not significantly different than the active comparators. The high placebo rates suggest that this endpoint may not be meaningful in differentiating the active drugs.

Figure 11

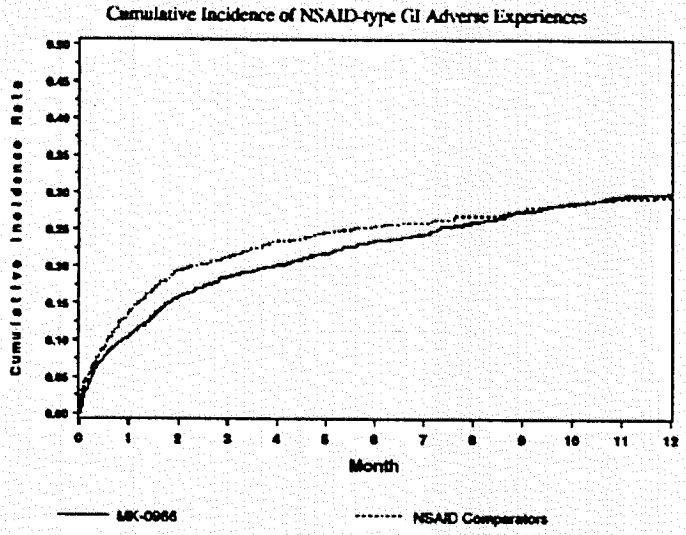


Table 65

Survival Analysis for Incidence of NSAID-type GI Adverse Experiences

Time Point	Number of Patients With Events: Placebo (N=514)	MK-0966 (N=3357)	NSAIDs (N=1564)	Rate Per 100 Patient-Years: Placebo	MK-0966	NSAIDs	Cumulative Incidence† (%) at Each Time Point: Placebo	MK-0966	NSAIDs
6 weeks	61	422	251	115.33	119.20	156.76	12.90	13.22	16.90
4 months	79	555	304	79.76	81.75	103.55	22.91	20.13	23.40
6 months	n/a	605	317	n/a	69.29	85.20	n/a	23.50	25.49
12 months	n/a	667	334	n/a	54.51	63.56	n/a	29.87	29.46

Overall Summary Statistics for Between-Treatment Comparison

		Cumulative Incidence Difference (%)	95% CI for Cumulative Incidence Diff. (%)	Relative Risk‡	95% CI for Relative Risk	p-Value* for the Primary Analysis
Primary Results:	MK-0966 vs. NSAIDs (across first 12 months)	0.41	(-3.40, 4.22)	0.88	(0.78, 1.01)	0.065
Other Results:	MK-0966 vs. NSAIDs (across first 6 weeks)	-3.68	(-5.93, -1.43)	0.77	(0.66, 0.90)	0.001
	MK-0966 vs. NSAIDs (across first 4 months)	-3.27	(-6.18, -0.36)	0.81	(0.71, 0.94)	0.004
	MK-0966 vs. NSAIDs (across first 6 months)	-1.99	(-5.15, 1.17)	0.85	(0.74, 0.97)	0.015

† Cumulative incidence from the survival analysis, it may not equal (number of patients with events/N) x 100.
‡ From the Cox Proportional Hazards Model.
* From the log rank test for the comparison of the cumulative incidence curves.

Data Source: [2.1.1 to 2.1.3; 2.1.5 to 2.1.12; 4.6.1]

Table 66

Dose related NSAID- type GI adverse experiences(%)

Comparator	Number of patients at baseline	*6-weeks	*12-week	*24 week	*52 week
Placebo	514	11.1	15.7	-	-
Vioxx 12.5 mg	1209	10.2	14.0	18.9	23.3
Vioxx 25 mg	1603	13.4	16.8	21.8	29.3
Vioxx 50 mg	545	12.6	21.1	-	-
Ibuprofen	847	18.6	-	-	-
Diclofenac	590	13.7	16.3	20.7	24.8
Nabumetone	127	-	-	-	-
NSAIDs combined	1564	16.9	23.4 (at 16 weeks)	25.49	29.45

*Minimum of 200 patients at end of study interval

As noted the analysis in table 66 does not add meaningfully to the sponsor's analysis. Using the composite endpoint as defined by the sponsor, there was little difference between groups in rate of withdrawal due to NSIAD-type adverse events.

The sponsor did an exploratory post hoc analyses of diarrhea and of all reported abdominal pain for their prespecified combined Vioxx groups and NSAID groups. The analysis of abdominal pain did show a relative risk of 0.71 for the Vioxx group compared to the NSAID comparators. The analysis of diarrhea showed a relative risk of 0.89 suggesting little if any difference between groups. Dose related analysis was not provided.

The review of studies 044 and 045 suggested similar rates of certain UGI symptomatic adverse events and endoscopic injury scores in Vioxx groups compared to the ibuprofen group. For this reason an analysis of heartburn, nausea and vomiting of the larger database of 069 was performed by the sponsor at the agency's request.

Table 67
Heartburn incidence (%)

Comparator	Number of patients at baseline	*6-weeks	*12-week	*6 months	*1year
Placebo	514	3.17	4.63	-	-
Vioxx 12.5 mg	1209	2.85	3.86	5.08	7.35
Vioxx 25 mg	1603	3.34	4.52	6.03	9.03
Vioxx 50 mg	545	4.85	7.00	-	-
Ibuprofen	847	3.87	5.18	-	-
Diclofenac	590	2.94	3.86	4.50	5.83
Nabumetone	127	-	-	-	-

*Minimum of 200 patients at end of study interval

Table 68
Incidence of nausea/vomiting (%)

Comparator	Number of patients at baseline	*6-weeks	*12-week	*6 months	*1 year
Placebo	514	3.72	4.96	-	-
Vioxx 12.5 mg	1209	3.44	5.21	6.55	8.03
Vioxx 25 mg	1603	5.50	6.81	9.50	12.3
Vioxx 50 mg	545	5.19	8.71	-	-
Ibuprofen	847	7.31	8.11	-	-
Diclofenac	590	5.66	6.60	7.89	10.2
Nabumetone	127	-	-	-	-

*Minimum of 200 patients at end of study interval

Discussion

The lack of clinically important differentiation between proposed dosages of Vioxx and NSAIDs using symptoms requiring withdrawal as endpoints is distinctly different that the data from endoscopic studies. This finding is consistent with the medical literature, which suggests a disconnection between ulcers, and symptoms related to NSAIDs. Given the claims of distinction between Vioxx as a Cox-2 selective agent and NSAIDs this

continued disconnection between symptoms and ulcers is an interesting finding. The trends noted above reinforce the fact that we do not currently know what accounts for most of the symptoms associated with the use of NSAIDs. Whatever the etiology, Vioxx as a COX-2 selective inhibitor does not appear to spare these symptoms.
The results from study 069 highlight the limitation of using endoscopic ulcers as the only parameter or even the most relevant parameter when studying the overall safety of cyclooxygenase inhibitors. The difference in endoscopic ulcer rates between ibuprofen and Vioxx is greater than three fold even at the highest dose of Vioxx tested. The limited PUB data and the adverse event data suggest a much less significant difference in safety between Vioxx and the limited universe of NSAID comparators tested. The clinical safety profile of a drug cannot ignore endpoints that impact on the patient's well being. Tolerance to medication as evidenced in the adverse event analysis is significantly better in the Vioxx compared to the NSAID groups only in a limited number of parameters tested and to a lesser degree than would be assumed based on endoscopic ulcer data. In addition, the different rates for the NSAIDs tested and different dosages of Vioxx tested make it difficult to make generalizations about the adverse event profile of Vioxx compared to NSAIDs as a group.
The conclusion to be drawn from study 069 is that Vioxx should be studied at the dosages likely to be used by a substantial percentage of consumers for the meaningful safety endpoints of tolerance and morbidity in comparison to NSAIDs before an accurate comparative assessment can be made. The validity of class comparisons will continue to be a difficult issue to resolve within the limits of even a well designed and extensive drug development program. In view of the different event rate patterns seen among different dosages of Vioxx and different NSAIDs, the small number of clinically significant PUB events prohibits any firm conclusions about comparative PUB rates.

Study 041: A double Blind placebo controlled Four Period Crossover Study in Healthy Volunteers to determine the Effects of treatment with MK-0966 and indomethacin for seven days on small intestinal permeability

The gastroduodenal adverse effects of NSAIDs are considered to be the most clinically relevant ones. It has become well established however that small and large bowel are affected by NSAIDs as well. Small bowel damage has been identified in 60-70% of asymptomatic on NSAIDs for over 6 months.[16] This landmark study by Bjarnason was not a controlled study of a single agent. The most prominent agent studied in the short term is indomethacin. There are no good comparative safety profiles of the many NSAIDs available related to small and large bowel damage that control for exposure time and dose. Studies have suggested that enterohepatic circulation of NSAIDs may play a role in the enteropathy. Misoprostol partially ablates the toxicity of indomethacin.[17] This fact suggests that prostaglandins play some role in indomethacin- related enteropathy. Other theories suggest that intraluminal bacterial effects are also relevant to this process.

The short term versus long term effect of NSAID is not well characterized nor is the mechanism of damage or relative effects of the various NSAIDs. Once small bowel damage has occurred as measured by permeability changes and radiolabelled neutrophil studies it has been shown to persist for months to over a year despite cessation of NSAID. Short-term study of small bowel permeability changes with documented reversal of effect may be a precursor of chronic enteropathy. This is not certain however. Therefore short-term study with one active comparator are meaningful but not conclusive regarding long term sequelae of NSAID effects on the bowel. Comparisons to placebo are of also important.
The methodology used to conduct this study has been used extensively to study small bowel permeability in various situations including inflammatory bowel disease, celiac sprue, chemotherapy induced intestinal changes and NSAID induced changes. The differential urinary excretion of two separate substances is felt to provide a specific index of permeability less affected by pre and post mucosal variables.[18]
The sponsor studied Vioxx 25 mg and 50 mg daily compared to indomethacin 50-mg tid and placebo. Details of the study are described below.

"Hypotheses
Primary Hypotheses
Compared to placebo, the ratio of ^{51}Cr EDTA/L-rhamnose in urine collected for 5 hours following oral administration of ^{51}Cr EDTA and L-rhamnose would not be greater in healthy volunteers treated with MK-0966 25 mg once daily for 7 days. Expressed as a geometric mean ratio vs. placebo, excretion of ^{51}Cr EDTA/L-rhamnose following MK-0966 25 mg once daily would not exceed 1.37 (i.e., the upper 95% confidence interval for the MK-0966/placebo ratios of ^{51}Cr EDTA/L-rhamnose would fall below 1.37. With sample size equal to 24, and log-scaled SD=0.3, the maximum observed ratio that would satisfy this criteria is 1.17.) In a previous study, the observed geometric mean ratio of ^{51}Cr EDTA/L-rhamnose for nabumetone 50 mg three times daily vs. placebo was 1.15 with an upper bound of the 95% confidence interval of 1.46. Also, compared to indomethacin 50 mg three times daily the ratio of ^{51}Cr EDTA/L-rhamnose in urine collected for 5 hours following oral administration of ^{51}Cr EDTA and L-rhamnose will be lower after 7 days of treatment with MK-0966 25 mg once daily in a population of healthy volunteers. (In a previous comparison of indomethacin vs. a baseline control period, the geometric mean ratio [indomethacin: control] of ^{51}Cr EDTA/L-rhamnose was 1.79 with geometric means of 0.068 for indomethacin 50 mg three times daily and 0.038 for the baseline control period.)

Secondary Hypotheses
Compared to indomethacin 50 mg three times daily, the ratio of ^{51}Cr EDTA/L-rhamnose in urine collected for 5 hours following oral administration of ^{51}Cr EDTA and L-rhamnose would be lower after 7 days of treatment with placebo in a population of healthy volunteers.
Compared to placebo, the ratio of ^{51}Cr EDTA/L-rhamnose in urine collected

for 5 hours following oral administration of ^{51}Cr EDTA and L-rhamnose would not be greater in healthy volunteers treated with MK-0966 50 mg once daily for 7 days.
Compared to indomethacin 50 mg three times daily, the ratio of ^{51}Cr EDTA/L-rhamnose in urine collected for 5 hours following oral administration of ^{51}Cr EDTA and L-rhamnose would be lower after 7 days of treatment with MK-0966 50 mg once daily in a population of healthy volunteers. (In a previous comparison of indomethacin vs. a baseline control period, the geometric mean ratio [indomethacin: control] of ^{51}Cr EDTA/L-rhamnose was 1.79 with geometric means of 0.068 for indomethacin 50 mg three times daily and 0.038 for the baseline control period.)

Inclusion Criteria

a. Subject was a healthy male or female volunteer (age, 18 to 55 years). Female subjects of childbearing potential were allowed to be enrolled, but a pregnancy test (serum β-HCG) was used to screen any females who had not undergone a hysterectomy (i.e., recently postmenopausal or status posttubal ligation).
b. Subject was within 20% of ideal body weight based on the Metropolitan Life Height and Weight Tables [3.2]. Men had to weigh between 130 and 200 pounds; women, between 100 and 170 pounds.
c. In the opinion of the study nurse/coordinator and the investigator, subjects had to be able to comply with the protocol and to complete a daily diary form.
d. Subject had to demonstrate a willingness to participate in the study as indicated by written informed consent.

Exclusion Criteria

a. Subject was under the age of legal consent, was mentally or legally incapacitated, had significant emotional problems at the time of the study, or had a history of psychiatric disorders.
b. Subject had participated in an investigational drug study within 4 months of entering this study.
c. Subject had any of the following conditions or diseases:
1) Positive result for the fecal occult blood screening test.
2) History of peptic ulcers, gastroesophageal reflux disease (GERD), inflammatory bowel disease, irritable bowel syndrome, pancreatic or biliary disorder, or other significant gastrointestinal disease.

3) History of significant gastrointestinal surgery (i.e., other than appendectomy or inguinal hernia repair).
4) Known significant medical conditions (e.g., heart disease, blood dyscrasia or coagulopathy, neurologic disease, hepatic or renal dysfunction, active malignant disease, hypertension, or uncontrolled diabetes).
5) Allergy or intolerance (including dyspepsia) to diclofenac, indomethacin,

ibuprofen, aspirin, or other nonselective inhibitors of cyclooxygenase, or a history of asthma, nasal polyps, angioedema, or bronchospastic reactivity to another nonselective inhibitor of cyclooxygenase (e.g., aspirin).
6) Drug or alcohol dependence.
7) Any thoracic or abdominal surgery (except for inguinal hernia repair or appendectomy) in the 4 weeks prior to the study.
8) History of psychiatric disorders.
d. Subject habitually consumed greater than four 8-oz cups of caffeinated beverages per day.
e. Subject was in a situation or had any condition which, in the opinion of the investigator, may have interfered with optimal participation in the study.
f. Subject had a history of frequent use (>2 times/month) of either antacids, H_2-receptor antagonists (e.g., cimetidine, famotidine, nizatidine, or ranitidine), proton pump inhibitors (i.e., omeprazole or lansoprazole), or misoprostol.
g. Subject was pregnant or breast-feeding an infant.
h. Subject had used or anticipated the need for any of the following drugs during the study:
Within Four Weeks of the Baseline Visit
1) Antacids (frequent use: >2 times/month) for symptoms of dyspepsia; H_2-receptor antagonists (e.g., cimetidine, famotidine, nizatidine, or ranitidine), a proton pump inhibitor (i.e., omeprazole or lansoprazole), or misoprostol.
2) Analgesic or tranquilizer (chronic use: >2 times per week).
Within Two Weeks of the Baseline Visit
1) Any prescription or nonprescription (including over-the-counter) preparation containing aspirin, ibuprofen, naproxen, or any other nonselective inhibitor of cyclooxygenase, or products such as pain relievers or cold or sinus remedies that contain nonselective inhibitors of cyclooxygenase.
2) Acetaminophen at a dose higher than 1000 mg daily.
Within One Week of the Baseline Visit
Drugs other than acetaminophen (up to 1000 mg daily).
i. Subject was a smoker or had smoked during the year prior to study start.
j. Subjects could not abstain from smoking and alcoholic beverages for the duration of this study.
k. Subject had any pretreatment laboratory values outside the normal range, except minor deviations not considered clinically significant by the investigator.
l. Subject had any condition which, in the opinion of the investigator, could confound the evaluations required in this study.
m. Subject was previously enrolled in this study.
n. Subject had received radiolabeled substances or had been exposed to radiation sources over the year prior to study start such that participation in this study would increase their total exposure beyond the recommended levels