Table 19

Center #	% total patients	% total placebo ulcers	% total Vioxx ulcers	% total ibuprofen ulcers
001	3	0	7	7
018	2	0	0	7
020	4	0	10	9
021	6	33	6	9
033	4	0	6.5	7
035	3	0	3	7

Center 021 is a prominent center with 7% of the total number of patients. The 33% of total placebo ulcers represent 2 ulcers. The apparent imbalance in ascertainment is likely a result of the small total number of ulcers found.

2. Patient characteristics: Patients were equally distributed among groups based on age, race, gender, global assessment of disease activity, H. pylori status, prior NSAID use, and alcohol intake, tobacco use, prior history of gastrointestinal perforation, bleeding or symptomatic ulcer, history of cardiovascular disease and history of heartburn. The data on the number of gastroduodenal erosions appeared to be unequal on first glance. The large standard deviation and range suggest that the distribution is not dissimilar. The Vioxx 50-mg group had fewer patients with any erosions present compared to the other groups. The significance of this imbalance is not clear. The results are displayed in table 20.

Table 20

Baseline Patient Characteristics

	Placebo	MK-0966		Ibuprofen	Total
		25 mg	50 mg	2400 mg	
Number of Gastric and Duodenal Erosions					
N	194	195	193	193	775
Mean (SD)	0.38 (1.38)	0.52 (1.51)	0.31 (1.26)	0.57 (1.64)	0.44 (1.45)
Median	0.00	0.00	0.00	0.00	0.00
Range	0.00 to 10.00	0.00 to 9.00	0.00 to 10.00	0.00 to 11.00	0.00 to 11.00
Number of Gastric Erosions					
N	194	195	193	193	775
Mean (SD)	0.26 (0.98)	0.42 (1.29)	0.26 (1.19)	0.42 (1.24)	0.34 (1.18)
Median	0.00	0.00	0.00	0.00	0.00
Range	0.00 to 8.00	0.00 to 9.00	0.00 to 10.00	0.00 to 10.00	0.00 to 10.00
Number of Duodenal Erosions					
N	194	195	193	193	775
Mean (SD)	0.12 (0.75)	0.10 (0.75)	0.04 (0.42)	0.15 (1.02)	0.10 (0.76)
Median	0.00	0.00	0.00	0.00	0.00
Range	0.00 to 7.00	0.00 to 7.00	0.00 to 5.00	0.00 to 11.00	0.00 to 11.00
Gastric and Duodenal Erosions					
N	194	195	193	193	775
=0, n (%)	170 (87.63)	160 (82.05)	175 (90.67)	155 (80.31)	660 (85.16)
>0, n (%)	24 (12.37)	35 (17.95)	18 (9.33)	38 (19.69)	115 (14.84)

Patient accounting:
Table 21 lists withdrawal data. It is of note that 15 patients were withdrawn by investigators because of the development of gastroduodenal erosions. Table 22 reveals the list of patients and treatment group where patients went from a baseline endoscopy score of 0 erosions to a treatment endoscopy score of >10 gastroduodenal erosions at which point the individual investigators withdrew the patients from the protocol and treated them for the endoscopic findings. These withdrawals represent potentially informative data unavailable due to protocol violations by investigators. Over 10 erosions is considered by some investigators as comparable to an ulcer for purposes of measuring gastroduodenal injury. The likelihood of these patients going on to develop an ulcer if they had remained in the study is higher than with patients with lesser endoscopic

scores. This reviewer agrees with the sponsor's choice of endpoint, but notes the loss of potentially informative data on drug effect due to the early withdrawal of patients with informative data. A conservative approach to analysis of the ulcer data would consider these protocol violators due to the development of >10 gastroduodenal erosions to have reached "treatment failure" i.e. ulcer endpoint. Such an analysis would increase the ibuprofen ulcer rate the most and therefore the difference in ulcer rates for comparisons between Vioxx and ibuprofen. Such a reanalysis however increases the Vioxx ulcer rate to some extent and therefore increases the differences between Vioxx and placebo ulcer rates. This sensitivity analysis (that allocates patients removed by investigators as protocol violations due to the development of >10 erosions into the ulcer category) increases the difference in ulcer rates between the placebo Vioxx 25 mg and Vioxx 50 mg. The Vioxx 25mg ulcer rate at 12 weeks becomes slightly higher at 5.8% versus 5.1% for placebo. The Vioxx 50mg ulcer rate becomes 96% higher than the placebo rate (5.1 versus 10.0%).

Table 21

Patient Accounting

	Placebo	MK-0966		Ibuprofen	Total
		25 mg	50 mg	2400 mg	
ENTERED:	194	195	193	193	775
Female (age range)*	146 (49 to 83)	151 (49 to 85)	139 (49 to 81)	143 (49 to 88)	579 (49 to 88)
Male (age range)*	48 (50 to 81)	44 (49 to 82)	54 (49 to 81)	50 (50 to 79)	196 (49 to 82)
	n (%)	n (%)	n (%)	n (%)	n (%)
COMPLETED:	152 (78.4)	138 (70.8)	127 (65.8)	80 (41.5)	497 (64.1)
DISCONTINUED:	42 (21.7)	57 (29.2)	66 (34.2)	113 (58.6)	278 (35.9)
Clinical adverse experience	7 (3.6)	10[b] (5.1)	18 (9.3)	18 (9.3)	53 (6.8)
Laboratory adverse experience	0	1 (0.5)	3 (1.6)	1[b] (0.5)	5 (0.7)
Lack of efficacy	7 (3.6)	6 (3.1)	3 (1.6)	5 (2.6)	21 (2.7)
Lost to follow up	3 (1.6)	4 (2.1)	2 (1.0)	0	9 (1.2)
Patient moved	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	4 (0.5)
Patient withdrew consent	13 (6.7)	15 (7.7)	16 (8.3)	10 (5.2)	54 (7.0)
Deviation from protocol	6 (3.1)	5 (2.6)	4 (2.1)	5 (2.6)	20 (2.6)
Study endpoint†	5 (2.6)	15 (7.7)	19 (9.8)	73 (37.8)	112 (14.5)

Table 22

Investigator initiated withdrawals due to a change in endoscopy score from 0 erosions at baseline to over 10 erosions at follow-up endoscopy.(patient allocation number)

Ibuprofen		Vioxx 25 mg	Vioxx 50mg	placebo
1024	0722	1021	0581	none
0096	0773		1023	
0699	0825			
0701	0533			
0718	583			

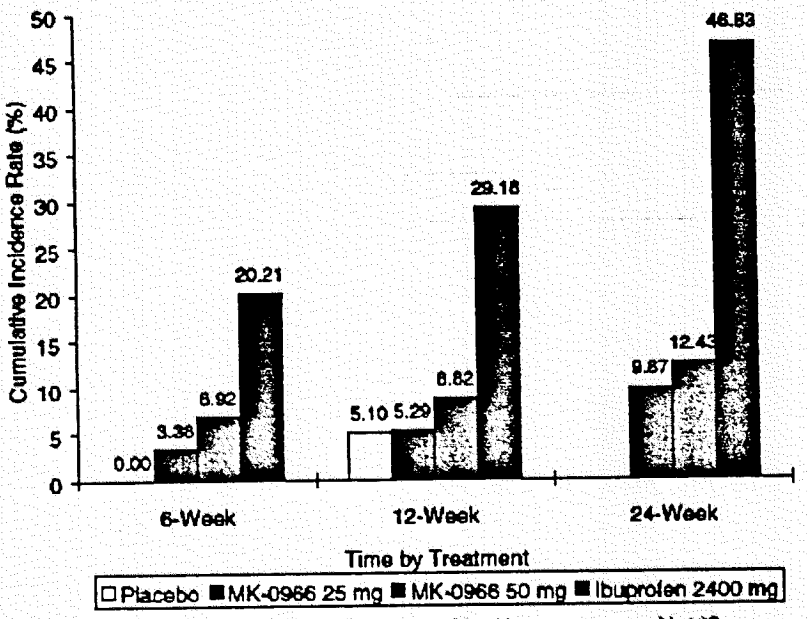
Endoscopy Results:

Figure 2 and table 23 display the endoscopic results. The important findings are:

1. Vioxx at either dose is clearly differentiated from ibuprofen in terms of ulcer rates at 6,12 and 24 weeks.
2. There is a relationship between dose and ulcer rate in the Vioxx groups that persists at all three intervals. This finding replicates the results in study 044.
3. The data on Vioxx and ibuprofen are similar to those from study 044.
4. Placebo ulcer rates at 6 and 12 weeks are not similar to study 044 data.
5. Placebo rate at 6 weeks is 0% compared to 3.38 and 6.92% in the Vioxx 25 and 50 mg groups respectively.
6. Placebo ulcer rate is "similar" to Vioxx 25-mg ulcer rates at one of the two interval points of comparison. It does not reach the 90% confidence interval for a comparability boundary of 4% set by the sponsor for study 044C.
7. Vioxx 50 mg dose results in an ulcer rate 70 % higher than placebo at 12 weeks.

Figure 2

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcer ≥3 mm
Intention-to-Treat



p<0.001 ibuprofen versus placebo, MK-0966 25 mg, MK-0966 50 mg at 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]

Table 23

Life-Table Analysis for 12-Week Cumulative Incidences of Gastroduodenal Ulcer ≥3 mm
Intention-to-Treat

Treatment	N	Number of Patients With Incidence	Rate[1] (%)	95% CI for Rate (%)
Placebo	182	5	5.10	(0.75, 9.46)
MK-0966 25 mg	187	9	5.29	(1.92, 8.66)
MK-0966 50 mg	182	15	8.82	(4.55, 13.09)
Ibuprofen 2400 mg	187	49	29.18	(22.15, 36.20)

Between-Treatment Comparison

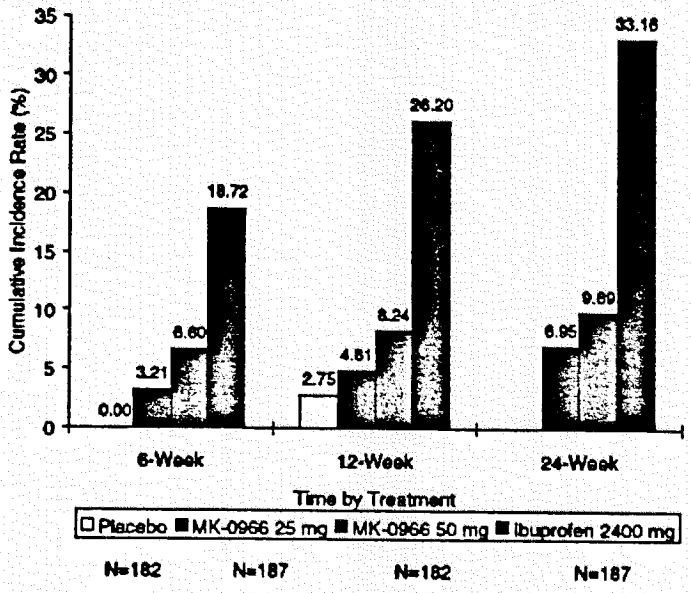
Treatment	Difference of Rates (%)	90% CI for Difference (%)	Ratio of Rates	90% CI for Ratio	p-Value[2]
MK-0966 25 mg vs. ibuprofen 2400 mg	-23.89	(-30.43, -17.35)	0.18	(0.10, 0.32)	<0.001
MK-0966 50 mg vs. ibuprofen 2400 mg	-20.35	(-27.25, -13.45)	0.30	(0.19, 0.48)	<0.001
Ibuprofen 2400 mg vs. placebo	24.07	(17.14, 31.01)	5.72	(2.72, 12.04)	<0.001
MK-0966 25 mg vs. placebo	0.19	(-4.44, 4.81)	1.04	(0.42, 2.53)	0.554
MK-0966 50 mg vs. placebo	3.72	(-1.40, 8.84)	1.73	(0.76, 3.94)	0.043
MK-0966 25 mg vs. MK-0966 50 mg	-3.54	(-8.10, 1.03)	0.60	(0.31, 1.17)	0.180

[1] Cumulative rate from the life-table analysis, it may not equal the number of events/N x 100.
[2] From the log-rank test.

Data Source: [4.10.1; 4.10.2]

Figure 3

Crude Cumulative Incidence Rate of Gastroduodenal Ulcers ≥3 mm
Intention-to-Treat



p<0.001 placebo, MK-0966 25 mg, MK-0966 50 mg versus ibuprofen at Week 12.
p<0.001 MK-0966 25 mg, MK-0966 50 mg versus ibuprofen at Week 24.

Data Source: [4.10.1; 4.10.2]

Table 24

Crude Rate Analysis for 12-Week Cumulative Incidences of Gastroduodenal Ulcer ≥3 mm
Intention-to-Treat

Treatment	N	Number of Patients With Ulcers	Rate† (%)	95% CI for Rate (%)
Placebo	182	5	2.75	(0.37, 5.12)
MK-0966 25 mg	187	9	4.81	(1.75, 7.88)
MK-0966 50 mg	182	15	8.24	(4.25, 12.24)
Ibuprofen 2400 mg	187	49	26.20	(19.90, 32.51)

Between-Treatment Comparison					
Treatment	Difference of Rates (%)	90% CI for Difference (%)	Ratio of Rates	90% CI for Ratio	p-Value‡
MK-0966 25 mg vs. Ibuprofen 2400 mg	-21.39	(-27.27, -15.51)	0.19	(0.11, 0.34)	<0.001
MK-0966 50 mg vs. Ibuprofen 2400 mg	-17.96	(-24.22, -11.70)	0.32	(0.21, 0.50)	<0.001
Ibuprofen 2400 mg vs. placebo	23.46	(17.80, 29.11)	8.76	(4.27, 17.98)	<0.001
MK-0966 25 mg vs. placebo	2.07	(-1.19, 5.32)	1.68	(0.71, 3.99)	0.415
MK-0966 50 mg vs. placebo	5.49	(1.59, 9.40)	2.82	(1.27, 6.26)	0.036
MK-0966 25 mg vs. MK-0966 50 mg	-3.43	(-7.66, 0.80)	0.60	(0.31, 1.15)	0.209

† Number of patients with the incidence /N x 100.
‡ From Fisher's exact test.

Data Source: [4.10.1; 4.10.2]

This study supports the conclusion of study 044 and medical literature regarding risk of ulcers over time. Table 25 displays data that show a decrease in the rate of new ulcer development over the 2nd 90-day interval of study. The decrease was significant for Vioxx 50 and ibuprofen but not for Vioxx 25. Pooled data from studies 044 and 045 are presented in study 044C, The only group with a statistically significant fall in ulcer rate during the second 90 day interval was the ibuprofen group. No firm conclusions can be drawn from this data about the change in ulcer risk over time with Vioxx versus ibuprofen. This was not a prespecified comparative endpoint and the results are not robust enough to make conclusions.

Table 25

Life-Table Within-Treatment Comparison of Incidences of Gastroduodenal Ulcer ≥3 mm
Relative Days 1 to 91 Versus Relative Days 92 to 182
Intention-to-Treat

Within-Treatment Between-Period Assessment							
		Rel Days 1 to 91		Rel Days 92 to 182			
Treatment	N	Number of Incidence	Rate (%)†	Number of Incidence‡	Rate (%)†	Difference (%)	95% CI (%) for Difference
Placebo	182	5	3.10	–	–	–	(–, –)
MK-0966 25 mg	187	9	5.29	4	4.58	-0.70	(-5.51, 4.10)
MK-0966 50 mg	182	15	8.82	3	3.61	-5.21	(-10.32, -0.11)
Ibuprofen 2400 mg	187	49	29.18	13	17.65	-11.52	(-21.63, -1.42)

Between-Treatment Comparison			
Treatment	Between-Treatment Difference of Within-Treatment Differences (%)	p-Value	90% CI for Between-Treatment Difference (%)
MK-0966 25 mg vs. ibuprofen 2400 mg	10.82	0.112	(-0.37, 22.01)
MK-0966 50 mg vs. ibuprofen 2400 mg	6.31	0.359	(-5.01, 17.63)
MK-0966 25 mg vs. MK-0966 50 mg	4.51	0.290	(-2.50, 11.52)

† Cumulative rate from the life-table analysis, it may not equal the number of events/N x 100.
‡ Ninety-five percent of the placebo treatment group discontinued per-protocol at Week 16; therefore, ulcer incidence was not analyzed for placebo beyond Day 91.

Data Source: [4.10.1; 4.10.2]

Breakdown by location of ulcer was typical of NSAID data in the medical literature. There was a predominance of gastric over duodenal ulceration. The gastric ulcer rates for the Vioxx groups were both differentiated from the ibuprofen group at 12 and 24 weeks. The duodenal ulcer rates however, were comparable between Vioxx 50mg and ibuprofen groups. (See tables 26 through 29).
Similar to study 044, the placebo gastric ulcer rate was higher than the placebo duodenal ulcer rate. This is not consistent with the medical literature regarding ulcer location for non-NSAID ulcers. This inconsistency possibly reflects:

1. That the study population is not typical of the general population
2. The recent NSAID use in many patients, concomitant drug usage, age and less likely underlying osteoarthritis differentiate this population from historical data on distribution of peptic ulcer disease.
3. Surreptitious NSAID or aspirin use by patients in the placebo group.

Table 26

Life-Table Analysis for 12-Week Cumulative Incidences of Gastric Ulcer ≥3 mm
Intention-to-Treat

Treatment	N	Number of Patients With Incidence	Rate† (%)	95% CI for Rate (%)
Placebo	158	9	7.63	(2.62, 12.63)
MK-0966 25 mg	186	5	2.98	(0.40, 5.56)
MK-0966 50 mg	178	10	6.17	(2.45, 9.88)
Ibuprofen 2400 mg	167	36	24.16	(17.14, 31.18)

Between-Treatment Comparison

Treatment	Difference of Rates (%)	90% CI for Difference (%)	Ratio of Rates	90% CI for Ratio	p-Value‡
MK-0966 25 mg vs. ibuprofen 2400 mg	-21.18	(-27.46, -14.90)	0.12	(0.06, 0.27)	<0.001
MK-0966 50 mg vs. ibuprofen 2400 mg	-18.00	(-24.66, -11.33)	0.26	(0.15, 0.45)	<0.001
Ibuprofen 2400 mg vs. placebo	16.53	(9.30, 23.77)	3.17	(1.73, 5.78)	<0.001
MK-0966 25 mg vs. placebo	-4.65	(-9.37, 0.07)	0.39	(0.16, 0.97)	0.129
MK-0966 50 mg vs. placebo	-1.46	(-6.69, 3.77)	0.81	(0.38, 1.71)	0.756
MK-0966 25 mg vs. MK-0966 50 mg	-3.19	(-6.98, 0.61)	0.48	(0.20, 1.17)	0.159

† Cumulative rate from the life-table analysis, it may not equal the number of events/N x 100.
‡ From the log-rank test.

Data Source: [4.10.1; 4.10.2]

Table 27

Life-Table Analysis for 24-Week Cumulative Incidences of Gastric Ulcer ≥3 mm
Intention-to-Treat

Treatment	N	Number of Patients With Incidence	Rate† (%)	95% CI for Rate (%)
MK-0966 25 mg	186	9	7.89	(2.46, 13.32)
MK-0966 50 mg	178	15	11.47	(5.51, 17.43)
Ibuprofen 2400 mg	167	46	41.66	(30.90, 52.42)

Between-Treatment Comparison

Treatment	Difference of Rates (%)	90% CI for Difference (%)	Ratio of Rates	90% CI for Ratio	p-Value‡
MK-0966 25 mg vs. ibuprofen 2400 mg	-33.77	(-43.88, -23.66)	0.19	(0.10, 0.35)	<0.001
MK-0966 50 mg vs. ibuprofen 2400 mg	-30.19	(-40.51, -19.87)	0.28	(0.17, 0.45)	<0.001
MK-0966 25 mg vs. MK-0966 50 mg	-3.58	(-10.34, 3.19)	0.69	(0.33, 1.42)	0.122

† Cumulative rate from the life-table analysis, it may not equal the number of events/N x 100.
‡ From the log-rank test.

Data Source: [4.10.1; 4.10.2]

Table 28

Life-Table Analysis for 12-Week Cumulative Incidences of Duodenal Ulcer ≥3 mm
Intention-to-Treat

Treatment	N	Number of Patients With Incidence	Rate[1] (%)	95% CI for Rate (%)
Placebo	158	3	3.11	(0.00, 6.71)
MK-0966 25 mg	186	2	1.15	(0.00, 2.74)
MK-0966 50 mg	178	3	1.92	(0.00, 4.08)
Ibuprofen 2400 mg	167	8	5.99	(1.92, 10.06)

Between-Treatment Comparison					
Treatment	Difference of Rates (%)	90% CI for Difference (%)	Ratio of Rates	90% CI for Ratio	p-Value[2]
MK-0966 25 mg vs. ibuprofen 2400 mg	-4.84	(-8.51, -1.17)	0.19	(0.05, 0.70)	0.023
MK-0966 50 mg vs. ibuprofen 2400 mg	-4.07	(-7.94, -0.21)	0.32	(0.11, 0.96)	0.069
Ibuprofen 2400 mg vs. placebo	2.88	(-1.68, 7.44)	1.92	(0.62, 5.92)	0.156
MK-0966 25 mg vs. placebo	-1.96	(-5.26, 1.34)	0.37	(0.08, 1.67)	0.331
MK-0966 50 mg vs. placebo	-1.20	(-4.71, 2.32)	0.62	(0.16, 2.38)	0.670
MK-0966 25 mg vs. MK-0966 50 mg	-0.76	(-3.01, 1.48)	0.60	(0.14, 2.68)	0.616

[1] Cumulative rate from the life-table analysis, it may not equal the number of events/N x 100.
[2] From the log-rank test.

Data Source: [4.10.1; 4.10.2]

Table 29

Life-Table Analysis for 24-Week Cumulative Incidences of Duodenal Ulcer ≥3 mm
Intention-to-Treat

Treatment	N	Number of Patients With Incidence	Rate[1] (%)	95% CI for Rate (%)
MK-0966 25 mg	186	3	1.86	(0.00, 3.95)
MK-0966 50 mg	178	6	4.26	(0.90, 7.63)
Ibuprofen 2400 mg	167	9	8.43	(2.26, 14.60)

Between-Treatment Comparison					
Treatment	Difference of Rates (%)	90% CI for Difference (%)	Ratio of Rates	90% CI for Ratio	p-Value[2]
MK-0966 25 mg vs. ibuprofen 2400 mg	-6.57	(-12.04, -1.11)	0.22	(0.07, 0.68)	0.024
MK-0966 50 mg vs. ibuprofen 2400 mg	-4.17	(-10.07, 1.73)	0.51	(0.20, 1.25)	0.213
MK-0966 25 mg vs. MK-0966 50 mg	-2.40	(-5.73, 0.92)	0.44	(0.14, 1.38)	0.270

[1] Cumulative rate from the life-table analysis, it may not equal the number of events/N x 100.
[2] From the log-rank test.

Data Source: [4.10.1; 4.10.2]

Subgroup analysis shown in table 30 revealed the same significant impact of prior GI history and baseline erosions that was seen in study 044. This impact was seen at both 12 and 24 weeks. The percent of patients with a prior GI history in study 044 was 80% higher than in the 045-study group. This significant difference in study population will

pose a problem when attempting to combine the results of studies 044 and 045 in study 044C in order to compare ulcer rates between placebo and Vioxx.

It is important to note the substantial impact of prior GI history on ulcer rates in all groups including Vioxx. Table 30B shows the results of this analysis at 12 weeks. Although the actual rates for placebo were very different between the two studies, there was a multifold rise in ulcer risk across the all groups at 12 weeks. There is overlap of the 95% CI for all 4 groups (see table30B) at 12 and 24 weeks.
Table 30 shows data from 24 weeks for active drugs from both studies 44 and 45. There was no placebo group at this time point. In patients with a prior GI history/PUB the cumulative gastroduodenal ulcer rate at 24 weeks in the Vioxx groups was approximately 20 % compared to 45% for ibuprofen. The 95% CI between Vioxx groups and ibuprofen did not overlap in this combined analysis of data from both endoscopy studies at 24 weeks. This combined analysis has a greater power to distinguish differences between groups. The subgroup analysis still points to an important attributable risk based on patient susceptibility in addition to the risk attributable to NSAID therapy.

Table 30 (from study 044C- combined analysis of studies 044 and 045)

Subgroup analysis based on prior GI history

Subgroup Analysis of 24-Week Cumulative Incidences of Gastroduodenal Ulcer ≥3 mm
Intention-to-Treat

Treatment	N	Number of Patients With Ulcers	Rate (%)†	95% CI for Rate (%)
Absent				
MK-0966 25 mg	309	13	4.21	(1.97, 6.45)
MK-0966 50 mg	307	27	8.79	(5.63, 11.96)
Ibuprofen	296	89	30.07	(24.84, 35.29)
Present				
MK-0966 25 mg	64	12	18.75	(9.19, 28.31)
MK-0966 50 mg	53	11	20.75	(9.84, 31.67)
Ibuprofen	58	26	44.83	(32.03, 57.63)

$p < 0.001$ for effect of prior GI history within treatment groups
$p = 0.117$ for treatment–by-subgroup interaction

There was a consistent lack of impact of H. pylori status across groups and time interval. This result is consistent with a growing body of medical literature that suggests the lack of an important relationship between H.pylori and NSAID related disease. The effects do not appear additive and some authors suggest even protective effects of H. pylori on the gastric injury associated with NSAIDs.

Table 30B

Subgroup Analysis of Incidences of Gastroduodenal Ulcer ≥3 mm at Week 12
Intention-to-Treat

Treatment	N	Number of Patients With Ulcers	Rate (%)	95% CI for Rate (%)
GI history (p=0.001)‡	P-value of treatment-by-subgroup interaction = 0.573.			
Absent				
Placebo	165	4	2.42	(0.08, 4.77)
MK-0966 25 mg	164	5	3.05	(0.42, 5.68)
MK-0966 50 mg	163	12	7.36	(3.35, 11.37)
Ibuprofen 2400 mg	162	39	24.07	(17.49, 30.66)
Present				
Placebo	17	1	5.88	(-5.30, 17.07)
MK-0966 25 mg	23	4	17.39	(1.90, 32.88)
MK-0966 50 mg	19	3	15.79	(-0.61, 32.19)
Ibuprofen 2400 mg	25	10	40.00	(20.80, 59.20)
H. pylori status§ (p=0.406)	P-value of treatment-by-subgroup interaction = 0.854.			
Absent				
Placebo	80	2	2.50	(-0.92, 5.92)
MK-0966 25 mg	80	4	5.00	(0.22, 9.78)
MK-0966 50 mg	75	6	8.00	(1.86, 14.14)
Ibuprofen 2400 mg	85	19	22.35	(13.50, 31.21)
Present				
Placebo	96	3	3.13	(-0.36, 6.61)
MK-0966 25 mg	105	5	4.76	(0.69, 8.84)
MK-0966 50 mg	100	7	7.00	(2.00, 12.00)
Ibuprofen 2400 mg	98	29	29.59	(20.55, 38.63)
Gastric and Duodenal Erosions (p=0.002)	P-value of treatment-by-subgroup interaction = 0.205.			
Baseline Number of Erosions =0				
Placebo	158	4	2.53	(0.08, 4.98)
MK-0966 25 mg	154	4	2.60	(0.09, 5.11)
MK-0966 50 mg	165	11	6.67	(2.86, 10.47)
Ibuprofen 2400 mg	150	36	24.00	(17.17, 30.83)
Baseline Number of Erosions >0				
Placebo	24	1	4.17	(-3.83, 12.16)
MK-0966 25 mg	33	5	15.15	(2.92, 27.38)
MK-0966 50 mg	17	4	23.53	(3.37, 43.69)
Ibuprofen 2400 mg	37	13	35.14	(19.75, 50.52)

The data on average ulcer size are felt to be imprecise. The accuracy of differentiating 1 or even 2 mm differences in ulcer size is questionable and no validation of accuracy is presented. This data will not be reviewed. The data on lesions ≥ 5mm are meaningful. Some authors believe this size represents potentially more significant ulcers and would

differentiate true ulcer from erosions more accurately. These data show the same differentiation between Vioxx and ibuprofen as well as the dose ulcer rate interaction in the Vioxx group seen in other data.

Table 31

Life-Table Analysis for 12-Week Cumulative Incidences of Gastroduodenal Ulcer ≥5 mm
Intention-to-Treat

Treatment	N	Number of Patients With Incidence	Rate[1] (%)	95% CI for Rate (%)
Placebo	182	5	5.10	(0.75, 9.46)
MK-0966 25 mg	187	6	3.46	(0.73, 6.18)
MK-0966 50 mg	182	13	7.71	(3.67, 11.75)
Ibuprofen 2400 mg	187	34	21.72	(15.16, 28.28)

Between-Treatment Comparison

Treatment	Difference of Rates (%)	90% CI for Difference (%)	Ratio of Rates	90% CI for Ratio	p-Value[2]
MK-0966 25 mg vs. ibuprofen 2400 mg	-18.27	(-24.23, -12.31)	0.16	(0.08, 0.32)	<0.001
MK-0966 50 mg vs. ibuprofen 2400 mg	-14.01	(-20.48, -7.55)	0.35	(0.21, 0.59)	0.001
Ibuprofen 2400 mg vs. placebo	16.62	(10.01, 23.23)	4.26	(1.99, 9.11)	<0.001
MK-0966 25 mg vs. placebo	-1.65	(-5.96, 2.67)	0.68	(0.26, 1.80)	0.910
MK-0966 50 mg vs. placebo	2.61	(-2.38, 7.59)	1.51	(0.65, 3.50)	0.100
MK-0966 25 mg vs. MK-0966 50 mg	-4.25	(-8.34, -0.17)	0.45	(0.20, 0.99)	0.087

[1] Cumulative rate from the life-table analysis, it may not equal the number of patients with incidence /N x 100.
[2] From the log-rank test.

Data Source: [4.10.1; 4.10.2]

Comparative gastroduodenal erosion rates were a secondary endpoint of study. Tables 32 and 33 show the results for both studies 044 and 045. Gastroduodenal erosion scores decreased over time in the placebo group.

The most informative aspect of the data displayed in table 32 is the striking difference between these results and the comparable data from study 044 shown in table 33.In study 044 the placebo baseline erosion rate was higher and increased rather than decreased over the course of the study. The difference between the placebo groups in the parameter of gastroduodenal erosions reinforces the difference between the study populations of studies 044 and 045. These type of data are not robust nor related to the primary hypotheses but do cause concern over the validity of combining results from 044 and 045.

Table 32

Analysis of Change From Baseline at Week 12 for Number of Gastroduodenal Erosions

Intention-to-Treat

Treatment	N*	Baseline Mean (SD)	Treatment Mean (SD)	Change Mean (SD)	Change Least Square Mean	95% CI for Least Square Mean
Placebo	182	0.41 (1.42)	0.37 (1.68)	-0.04 (1.64)	-0.12	(-0.65, 0.42)
MK-0966 25 mg	187	0.50 (1.49)	0.66 (1.96)	0.16 (2.18)	0.17	(-0.35, 0.68)
MK-0966 50 mg	182	0.27 (1.07)	0.80 (3.03)	0.53 (3.22)	0.41	(-0.12, 0.94)
Ibuprofen 2400 mg	186	0.53 (1.51)	3.66 (4.88)	3.12 (4.73)	3.15	(2.63, 3.66)

Between-Treatment Comparison

Treatments	Difference	90% CI for difference	p-Value
MK-0966 25 mg vs. Ibuprofen 2400 mg	-2.98	(-3.50,-2.46)	<0.001
MK-0966 50 mg vs. Ibuprofen 2400 mg	-2.74	(-3.26,-2.22)	<0.001
Ibuprofen 2400 mg vs. Placebo	3.26	(2.74, 3.79)	<0.001
MK-0966 25 mg vs. Placebo	0.28	(-0.24, 0.80)	0.370
MK-0966 50 mg vs. Placebo	0.52	(-0.00, 1.05)	0.101
MK-0966 25 mg vs. MK-0966 50 mg	-0.24	(-0.76, 0.28)	0.452

Effect	p-Value	Pooled SD
Treatment	<0.001	3.03
Baseline	<0.001	
GI history	0.613	
Site	0.001	
Treatment-by-Baseline-Covariate interaction	0.686	
Treatment-by-GI-history interaction	0.870	
Treatment-by-site interaction	0.001	

* Number of patients with available data at baseline and at a subsequent visit.

Data Source: [4.10.1]

Table 33 (study 044 table)

Analysis of Change From Baseline at Week 12 for Number of Gastroduodenal Erosions

Intention-to-Treat

Treatment	N*	Baseline Mean (SD)	Treatment Mean (SD)	Change Mean (SD)	Change Least Square Mean	95% CI for Least Square Mean
Placebo	158	0.57 (1.76)	0.74 (2.18)	0.17 (2.50)	0.28	(-0.15, 0.70)
MK-0966 25 mg	186	0.29 (1.14)	0.66 (2.09)	0.37 (2.25)	0.27	(-0.13, 0.66)
MK-0966 50 mg	178	0.49 (1.63)	0.71 (2.36)	0.22 (2.28)	0.26	(-0.15, 0.67)
Ibuprofen 2400 mg	167	0.41 (1.52)	2.37 (3.55)	1.95 (3.68)	1.94	(1.52, 2.36)

Between-Treatment Comparison

Treatments	Difference	90% CI for Difference	p-Value
MK-0966 25 mg vs. ibuprofen 2400 mg	-1.67	(-2.11,-1.23)	<0.001
MK-0966 50 mg vs. ibuprofen 2400 mg	-1.68	(-2.12,-1.24)	<0.001
Ibuprofen 2400 mg vs. placebo	1.66	(1.21, 2.12)	<0.001
MK-0966 25 mg vs. placebo	-0.01	(-0.46, 0.44)	0.971
MK-0966 50 mg vs. placebo	-0.01	(-0.46, 0.44)	0.957
MK-0966 25 mg vs. MK-0966 50 mg	0.00	(-0.43, 0.44)	0.985

Effect	p-Value	Pooled SD
Treatment	0.000	2.50
Baseline covariate	0.000	
GI history	0.815	
Site	0.002	
Treatment-by-baseline-covariate interaction	0.084	
Treatment-by-GI-history interaction	0.413	
Treatment-by-site interaction	0.774	

* Number of patients with available data at baseline and at a subsequent visit.

Data Source: [4.10.1]

Esophageal scores show trends similar to study 044 (See table 34). Protocol violations occurred such that the prevalence of esophageal scores ≥ 2 at baseline were 1.6, 1.6, 1.1 and 1.1% for the placebo, Vioxx 25mg, Vioxx 50 mg and ibuprofen groups respectively.

An analysis that would reveal the change in score rather than the cumulative incidence of esophageal score ≤ 2 may show a larger effect of the Vioxx 50 mg and ibuprofen groups. The trend at 12 weeks and 24 weeks in both studies 044 and 045 does suggest a true biological effect of Vioxx on the esophageal score. This is hypothesis-generating data and esophageal injury was not a specified endpoint. The presence of COX-2 within gastrointestinal tract raises the biological plausibility of the trend seen in esophageal injury.

Table 34

Life-Table Analysis for 12-Week Cumulative Incidence of Esophageal Score ≥2

Intention-to-Treat

Treatment	N[3]	Number of Patients With Incidence	Rate[1] (%)	95% CI for Rate(%)
Placebo	179	4	2.32	(0.07, 4.56)
MK-0966 25 mg	185	10	5.47	(1.98, 8.95)
MK-0966 50 mg	180	12	7.85	(3.57, 12.13)
Ibuprofen 2400 mg	185	18	12.67	(7.12, 18.21)

Between-Treatment Comparison

Treatment	Difference of Rates (%)	90% CI for Difference (%)	Ratio of Rates	90% CI for Ratio	p-Value[2]
MK-0966 25 mg vs. Ibuprofen 2400 mg	-7.20	(-12.70, -1.70)	0.43	(0.23, 0.83)	0.039
MK-0966 50 mg vs. Ibuprofen 2400 mg	-4.81	(-10.70, 1.07)	0.62	(0.34, 1.12)	0.143
Ibuprofen 2400 mg vs. Placebo	10.35	(5.32, 15.37)	5.46	(2.24, 13.33)	0.001
MK-0966 25 mg vs. Placebo	3.15	(-0.33, 6.62)	2.36	(0.89, 6.24)	0.200
MK-0966 50 mg vs. Placebo	5.53	(1.48, 9.59)	3.39	(1.33, 8.61)	0.074
MK-0966 25 mg vs. MK-0966 50 mg	-2.39	(-7.02, 2.24)	0.70	(0.34, 1.41)	0.561

[1] Cumulative rate from the life-table analysis, it may not equal the number of events/N x 100.
[2] From the log-rank test.
[3] Number of patients with available data at baseline and at a subsequent visit.

Data Source: [4.10.1]

The "catch-up" in incidence of esophageal injury (displayed in table 35) seen at 24 weeks between both doses of Vioxx and ibuprofen is of concern. As noted above, this is a finding of potential importance. It is not a statistically confirmed phenomenon at this point.

Table 35

Life-Table Analysis for 24-Week Cumulative Incidence of Esophageal Score≥2

Intention-to-Treat

Treatment	N[3]	Number of Patients With Incidence	Rate[1] (%)	95% CI for Rate(%)
MK-0966 25 mg	185	16	13.06	(6.55, 19.56)
MK-0966 50 mg	180	18	16.99	(9.05, 24.93)
Ibuprofen 2400 mg	185	18	12.67	(7.12, 18.21)

Between-Treatment Comparisons

Treatment	Difference of Rates (%)	90% CI for Difference (%)	Ratio of Rates	90% CI for Ratio	p-Value[2]
MK-0966 25 mg vs. Ibuprofen 2400 mg	0.39	(-6.78, 7.57)	1.03	(0.59, 1.80)	0.280
MK-0966 50 mg vs. Ibuprofen 2400 mg	4.32	(-3.80, 12.45)	1.34	(0.78, 2.30)	0.638
MK-0966 25 mg vs. MK-0966 50 mg	-3.93	(-12.35, 4.68)	0.77	(0.43, 1.36)	0.488

[1] Cumulative rate from the life-table analysis, it may not equal the number of events/N x 100.
[2] From the log-rank test.
[3] Number of patients with available data at baseline and at a subsequent visit.

Data Source: [4.10.1]

Escape Medication:
The reported compliance rate in this study was over 95% in all groups. The placebo and ibuprofen groups had slightly higher usage rates of acetaminophen. Gelusil usage was similar across groups. The least square mean ranged from .87 to 1.01 tablets a day.

Gastrointestinal adverse events:

Similar to study 044, the generic category of digestive symptoms and the specific symptoms of nausea, vomiting and heartburn all show numerical trends that differentiate Vioxx from placebo. This type of data are not confirmatory but are meaningful when defining placebo comparability.

Table 36

Number (%) of Patients With Clinical Adverse Experiences by Body System
Week 18

	Placebo (N=194)			MK-0966 25 mg (N=195)			MK-0966 50 mg (N=193)			Ibuprofen 2400 mg (N=193)		
	n	Life Table Rate† (%)	Crude Rate‡ (%)	n	Life Table Rate† (%)	Crude Rate‡ (%)	n	Life Table Rate† (%)	Crude Rate‡ (%)	n	Life Table Rate† (%)	Crude Rate‡ (%)
Patients with one or more adverse experiences	144	77.7	74.2	150	80.1	76.9	154	82.9	79.8	147	80.0	76.2
Patients with no adverse experience	50	22.3	25.8	45	19.9	23.1	39	17.1	20.2	46	20.0	23.8
Body as a whole	62	35.2	32.0	67	36.4	34.4	60	34.3	31.1	53	31.9	27.5
Cardiovascular	21	12.1	10.8	23	13.0	11.8	35	21.2*	18.1	17	10.3	8.8
Digestive	73	39.9	37.6	99	53.3*	50.8	105	57.3*	54.4	116	63.9*	60.1

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

	Placebo (N=194)			MK-0966 25 mg (N=195)			MK-0966 50 mg (N=193)			Ibuprofen 2400 mg (N=193)		
	n	Life Table Rate† (%)	Crude Rate‡ (%)	n	Life Table Rate† (%)	Crude Rate‡ (%)	n	Life Table Rate† (%)	Crude Rate‡ (%)	n	Life Table Rate† (%)	Crude Rate‡ (%)
Patients with one or more adverse experiences	144	--	74.2	160	87.6	82.1	161	88.3	83.4	150	82.4	77.7
Patients with no adverse experience	50	--	25.8	35	12.4	17.9	32	11.7	16.6	43	17.6	22.3
Body as a whole	62	--	32.0	79	47.4	40.5	66	41.1	34.2	61	40.3	31.6
Cardiovascular	21	--	10.8	27	16.8	13.8	40	26.7	20.7	20	13.5	10.4
Digestive	73	--	37.6	108	61.8	55.4	116	66.3	60.1	122	69.5	63.2

Table 37

Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence ≥2.0% in One or More Treatment Groups) by Body System
Week 18

	Placebo (N=194)			MK-0966 25 mg (N=195)			MK-0966 50 mg (N=193)			Ibuprofen 2400 mg (N=193)		
	n	Life Table Rate† (%)	Crude Rate‡ (%)	n	Life Table Rate† (%)	Crude Rate‡ (%)	n	Life Table Rate† (%)	Crude Rate‡ (%)	n	Life Table Rate† (%)	Crude Rate‡ (%)
Cardiovascular	**21**	**12.1**	**10.8**	**23**	**13.0**	**11.8**	**35**	**21.2***	**18.1**	**17**	**10.3**	**8.8**
Hypertension	7	3.9	3.6	11	6.2	5.6	23	14.3*	11.9	7	3.9	3.6
Petechia	1	0.6	0.5	3	1.8	1.5	4	2.4	2.1	3	2.0	1.6
Digestive	**73**	**39.9**	**37.6**	**99**	**53.3***	**50.8**	**105**	**57.3***	**54.4**	**116**	**63.9***	**60.1**
Acid reflux	4	2.3	2.1	2	1.1	1.0	2	1.1	1.0	6	4.1	3.1
Anorectal hemorrhage	0	0.0	0.0	1	0.5	0.5	4	2.4*	2.1	1	0.6	0.5
Constipation	3	1.8	1.5	6	3.3	3.1	5	3.1	2.6	3	1.6	1.6
Dental pain	4	2.5	2.1	0	0.0	0.0	0	0.0	0.0	2	1.6	1.0
Diarrhea	13	7.2	6.7	25	13.6*	12.8	19	10.8	9.8	19	12.6	9.8
Digestive gas symptoms	1	0.5	0.5	1	0.5	0.5	1	0.5	0.5	4	2.2	2.1
Duodenal disorder	1	0.6	0.5	4	2.2	2.1	2	1.1	1.0	1	0.6	0.5
Dysgeusia	1	0.5	0.5	2	1.1	1.0	4	2.1	2.1	1	0.5	0.5
Dyspepsia	10	5.5	5.2	11	5.9	5.6	10	6.2	5.2	13	7.7	6.7
Epigastric discomfort	21	11.6	10.8	26	14.4	13.3	24	13.7	12.4	45	24.7*	23.3
Esophageal erosion	1	0.6	0.5	3	1.8	1.5	3	1.9	1.6	5	3.5	2.6
Esophageal ulcer	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	4	2.3*	2.1
Digestive (Cont.)												
Esophagitis	2	1.1	1.0	4	2.3	2.1	7	4.3	3.6	7	4.5	3.6
Flatulence	5	2.7	2.6	10	5.5	5.1	7	3.9	3.6	5	2.9	2.6
Gastric Disorder	3	1.7	1.5	0	0.0	0.0	4	2.3	2.1	1	0.5	0.5
Gastritis	2	1.2	1.0	4	2.2	2.1	4	2.4	2.1	2	1.2	1.0
Gastrointestinal mucosal erythema	2	1.1	1.0	1	0.6	0.5	5	2.8	2.6	2	1.2	1.0
Heartburn	16	8.7	8.2	19	10.2	9.7	16	8.8	8.3	21	12.7	10.9
Nausea	8	4.5	4.1	19	10.2*	9.7	17	9.5	8.8	20	10.9*	10.4
Oral Ulcer	0	0.0	0.0	4	2.3*	2.1	7	3.9*	3.6	1	0.8	0.5
Vomiting	4	2.2	2.1	6	3.5	3.1	8	4.4	4.1	12	6.7*	6.2

The difference in the incidence of oral ulcers seen above is of interest as discussed previously related to esophageal injury. The data in study 044 do not support any pattern with only one oral ulcer in the entire study, which occurred in the ibuprofen group. Nausea and vomiting was consistently higher in both Vioxx groups compared to placebo.

The incidence of withdrawal due to adverse events was lowest in the placebo group. The higher dose Vioxx was associated with higher overall and specifically GI related adverse