Table 7

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

Treatment	N	Number of Patients with Incidence	Rate† (%)	95% CI for Rate (%)
Placebo	158	11	9.92	(4.12, 15.73)
MK-0966 25 mg	186	7	4.10	(1.12, 7.07)
MK-0966 50 mg	178	12	7.31	(3.31, 11.30)
Ibuprofen 2400 mg	167	42	27.69	(20.43, 34.95)

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	-23.59	(-30.17, -17.01)	0.15	(0.08, 0.28)	<0.001
MK-0966 50 mg vs. ibuprofen 2400 mg	-20.38	(-27.33, -13.43)	0.26	(0.16, 0.44)	<0.001
Ibuprofen 2400 mg vs. placebo	17.76	(9.97, 25.56)	2.79	(1.63, 4.78)	<0.001
MK-0966 25 mg vs. placebo	-5.83	(-11.30, -0.35)	0.41	(0.19, 0.90)	0.111
MK-0966 50 mg vs. placebo	-2.62	(-8.53, 3.30)	0.74	(0.38, 1.44)	0.642
MK-0966 25 mg vs. MK-0966 50 mg	-3.21	(-7.39, 0.97)	0.56	(0.26, 1.20)	0.203

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

Data Source: [4.10.1; 4.10.2]

It is of note that analysis by the sponsor revealed no change in the rate of ulcer development when comparing the first three-month rate with the second three-month rate. This is consistent with literature on the subject of NSAID ulcer risk over time (excluding the first month of therapy for which there are substantial data suggesting higher rates during this period when adaptive changes take place in the gastric mucosa).

Table 8

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(%)
***H. pylori* Status§ (p=0.983)**		**p-value of treatment-by-subgroup interaction =0.325**		
Absent				
Placebo	111	10	9.01	(3.68, 14.34)
MK-0966 25 mg	145	5	3.45	(0.48, 6.42)
MK-0966 50 mg	126	7	5.56	(1.56, 9.56)
Ibuprofen 2400 mg	123	31	25.20	(17.53, 32.88)
Present				
Placebo	44	1	2.27	(-2.13, 6.68)
MK-0966 25 mg	41	2	4.88	(-1.72, 11.47)
MK-0966 50 mg	52	5	9.62	(1.60, 17.63)
Ibuprofen 2400 mg	44	11	25.00	(12.21, 37.79)

Table 9

Analysis at 24 week

***H. pylori* status§ (p=0.102)**		**p-value of treatment-by-subgroup interaction =0.270**		
Absent				
MK-0966 25 mg	145	8	5.52	(1.80, 9.23)
MK-0966 50 mg	126	10	7.94	(3.22, 12.66)
Ibuprofen 2400 mg	123	38	30.89	(22.73, 39.06)
Present				
MK-0966 25 mg	41	4	9.76	(0.67, 18.84)
MK-0966 50 mg	52	10	19.23	(8.52, 29.94)
Ibuprofen 2400 mg	44	15	34.09	(20.08, 48.10)

Subgroup analysis based on potential risk factors showed a statistically significant correlation between increasing age and ulcer rate at 12 weeks but not at 24 weeks. The statistically significant correlation between history of clinical ulcer disease (PUB) and ulcer rate was consistent at 12 and 24 weeks. Although this effect was seen across all groups, it was more pronounced in the Vioxx and placebo group than in the ibuprofen group. In the subanalysis of patients with a history of "PUB" the ulcer rate at 12 and 24 weeks for the Vioxx 50 mg group fell with the 95% CI for the ulcer rate in the ibuprofen group. At 24 weeks, the ulcer rate for both dosages of Vioxx fell within the 95% CI for the ibuprofen group.

Although the subgroup analysis is not a study endpoint, it does have vital importance to the group of patients at highest risk of NSAID complications who are likely to be the patients with most to potentially gain from the use of a less ulcerogenic NSAID. Race, gender, alcohol and tobacco use did not correlate with ulcer rate at either interval. Interestingly, H.pylori status in the placebo group (defined as either urease or histopathology results) showed a trend towards a higher rate in H.pylori negative compared to positive patients at 12 weeks (9% 10/111 versus 2% 1/44) suggesting a protective effect of H.pylori in this group. This trend was not seen at all in the Vioxx or ibuprofen groups. In fact there was a slight but consistent trend towards a positive interaction between H. pylori and ulcer incidence in the ibuprofen and Vioxx groups at both time intervals. It is unclear if these trends represent any meaningful biologic interaction. The data from this submission and the Celebrex NDA 20-998 do not suggest a meaningful interaction between NSAIDs and H.pylori as risk factors for gastroduodenal ulcers. These data are displayed in tables 8 and 9.

Subgroup analysis for baseline gastroduodenal erosions revealed a significant relationship between baseline erosions and the ulcer rate. See table 10. This effect was seen at both intervals and crosses all treatment groups.

Table 10

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(%)
Gastric and Duodenal Erosions (p<0.001)		**p-value of treatment-by-subgroup interaction =0.463**		
Baseline Number of Erosions =0				
Placebo	134	5	3.73	(0.52, 6.94)
MK-0966 25 mg	168	4	2.38	(0.08, 4.69)
MK-0966 50 mg	150	8	5.33	(1.74, 8.93)
Ibuprofen 2400 mg	146	33	22.60	(15.82, 29.39)
Baseline Number of Erosions >0				
Placebo	24	6	25.00	(7.68, 42.32)
MK-0966 25 mg	18	3	16.67	(-0.55, 33.88)
MK-0966 50 mg	28	4	14.29	(1.32, 27.25)
Ibuprofen 2400 mg	21	9	42.86	(21.69, 64.02)

The sponsor presented data on ulcer rate per 100 patient-months. Given the similarity in exposure across the groups, these data add little to the report and are not reviewed here. The sponsor also reports data on ulcer size (only for ulcers over 3mm. in size). The method of measurement relies on visual estimate of mm differences compared to a reference sized biopsy forceps. This method is of questionable accuracy and no validation on reproducibility is given. These data are not reviewed here. The sponsor analyzed rates of ulcers $\geq$ 5mm in size. This measurement also involves inherent inaccuracy. The ascertainment is binary and less imprecise than the measurement of average ulcer size referred to above. The results were not meaningfully different. There is some suggestion in the medical literature that 5mm is a more reliable size compared to 3mm for ascertainment purposes in endoscopy studies[6]. This is intuitively true due to the subjective nature of endoscopic measurement and limits of the human visual judgement needed to compare the size of a subcentimeter lesion compared to a fixed size subcentimeter biopsy forceps. The analysis of ulcer size $\geq$ 5mm does add robustness to the ulcer results.

Additional statistical analysis

The sponsor presents a sensitivity analysis assuming that all withdrawals due to GI adverse events in the Vioxx groups and none of the withdrawals due to adverse events in the ibuprofen group were due to ulcers. Using this approach, the difference in ulcer rates remained significant at the $p<0.001$ level at both 12 and 24 weeks.
A second sensitivity analysis for missing data was performed. The ulcer rate was assumed to be 25% for the patients with missing data from the Vioxx groups and 0% for the placebo and ibuprofen groups. The difference between both Vioxx groups and ibuprofen maintained statistical significance.

The sponsor performed a crude ulcer analysis using the number of patients with at least one treatment phase endoscopy as the denominator. The results were similar to the life table analysis at both 12 and 24-week intervals.

The analysis of ulcer data by interval time and location is displayed in tables 11, 12 and 13. The data are consistent with the medical literature on NSAID ulcers. NSAID ulcers are more common in the stomach than the duodenum. On the other hand, in the medical literature "non-NSAID" related ulcers are more common in the duodenum. In this study the placebo rate of ulcers in the duodenum was 3% at 12 weeks and 8% in the stomach. The reason for the high placebo rate in this study may relate to this unexpected ratio of 3% : 8%. It suggests that the overall high placebo rate is not totally explained by highly sensitive observation or overinterpretation of endoscopic findings. These explanations would not cause a reversal in the ratio of the distribution of ulcers. This finding may indicate:

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 11

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 12

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 13

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

Treatment	N	Number of Patients With Incidence	Rate† (%)	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‡
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

† 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 13 (continued)

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

Treatment	N	Number of Patients With Incidence	Rate† (%)	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‡
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

† 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]

Analysis of change in the mean number of gastroduodenal erosions from baseline is of note in that all groups including placebo showed a rise in number of erosions.(See table 33) This is consistent with frank ulceration data in trend. Just as one may ask why the placebo group ulcer incidence should rise over time, one may ask why erosion score

should rise. Given the high percent of patients on NSAIDs prior to enrollment (80%) one would expect, if anything a fall in erosion score fall in the placebo group. Possible explanations include 1) withdrawal from prior anti-ulcer/antacid therapy (approximately 20 % of enrollees used these medications prior to enrollment). Rebound effects of anti-ulcer medication withdrawal on acid production may exacerbate withdrawal effect. 2) surreptitious NSAID or aspirin use 3) bias in endoscopic interpretation of all subjects , including placebo treated patients, while on "treatment".

Esophageal scores were analyzed and appear in table 14. Week 12 and week 24 data show a dose-related rate for Vioxx. It is of note that the ibuprofen group had a much higher rise in esophageal score ≥ 2 (erosion or ulcer) rate between 12 and 24 weeks than Vioxx. The 12-week data on placebo show a numerically lower rate that in the ibuprofen group but no conclusions can be drawn from these data. The dose dependent rise in incidence of esophageal scores ≥ 2 in the Vioxx groups over the subsequent 3 months is of concern and suggest a biologic phenomenon.

The 9% incidence rate of the development of esophageal erosion/ulcer over 12 weeks in the placebo group, however, suggests that at least part of the rates overall are not due to NSAID effect. The same considerations as discussed above related to gastroduodenal erosions need to be considered. The prior therapy data listed in the patient characteristics section reveal that 20, 23, 23 and 15% of the patients in the placebo, Vioxx 25 mg, Vioxx 50 mg and ibuprofen 2400 mg respectively had been on antacid or anti-ulcer medication prior to entering the study. Discontinuation of these medications may play a role in the interpretation of the esophageal injury data. Review of the concomitant therapy data however, reveal that 14, 14, 17 and 29% of the patients in the same respective groups in the study used this same group of antacid and anti-ulcer drugs. Use of Gelusil was comparable among the groups. Invoking anti-ulcer/reflux therapy withdrawal does not appear to explain the findings well. Review of the baseline data among groups related to secondary diagnosis is important to the interpretation of the endoscopic findings. There was no consistent imbalance between the groups in baseline history of heartburn or gastroesophageal reflux disease (GERD). The heartburn rates were 14.7, 10.8, 7.5 and 8.7% in the placebo, Vioxx 25mg, Vioxx 50 mg and ibuprofen groups respectively. The respective GERD rates were 6.2, 7.2, 4.3 and 4.3%. The adverse experience data related to heartburn, nausea and vomiting in table 17 add plausibility to the concerns over esophageal injury due to Vioxx.
The data in table 17 reveal a consistent pattern of heartburn rates higher in treatment groups compared to placebo at 18 weeks. The rate of heartburn compared to placebo was numerically higher in the Vioxx 25-mg group and statistically significantly higher in the Vioxx 50-mg group at 18 weeks. The rates were numerically higher in both Vioxx groups compared to ibuprofen. The Vioxx 50-mg group had an 80% higher rate of heartburn and 67% higher erosive esophagitis rate compared to the ibuprofen group at 18 weeks. The higher rate of heartburn in the Vioxx 50-mg group persisted at 24 weeks, although the ibuprofen group had a higher rate of erosive esophagitis than the Vioxx group at 24 weeks. Definite conclusions, however, cannot be drawn from such data. The data do not differentiate Vioxx as safer than ibuprofen in regards to esophageal injury. They do

suggest that Vioxx has a worse safety profile related to esophageal injury compared to placebo. This is hypothesis-generating data. Comparison with study 045 may be of value.

Table 14

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

Treatment	N‖	Number of Patients With Incidence	Rate† (%)	95% CI for Rate (%)
Placebo	155	10	9.27	(3.54, 15.00)
MK-0966 25 mg	181	18	11.07	(6.23, 15.91)
MK-0966 50 mg	176	22	14.16	(8.65, 19.67)
Ibuprofen 2400 mg	164	15	11.87	(6.13, 17.60)

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	-0.80	(-7.09, 5.50)	0.93	(0.54, 1.61)	0.887
MK-0966 50 mg vs. ibuprofen 2400 mg	2.29	(-4.38, 8.97)	1.19	(0.71, 2.01)	0.570
Ibuprofen 2400 mg vs. placebo	2.60	(-4.20, 9.40)	1.28	(0.66, 2.47)	0.349
MK-0966 25 mg vs. placebo	1.80	(-4.49, 8.10)	1.19	(0.63, 2.25)	0.501
MK-0966 50 mg vs. placebo	4.89	(-1.78, 11.57)	1.53	(0.83, 2.82)	0.157
MK-0966 25 mg vs. MK-0966 50 mg	-3.09	(-9.25, 3.07)	0.78	(0.48, 1.28)	0.421

† Cumulative rate from the life-table analysis, it may not equal the number of patients with the incidence/N x 100.
‡ From the log-rank test.
‖ Number of patients with available data at baseline and at a subsequent visit.

Data Source: [4.10.1]

Table 14

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

Treatment	N‖	Number of Patients With Incidence	Rate† (%)	95% CI for Rate (%)
MK-0966 25 mg	181	23	14.78	(8.46, 21.11)
MK-0966 50 mg	176	26	19.00	(11.85, 26.15)
Ibuprofen 2400 mg	164	22	28.10	(16.28, 39.93)

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	-13.32	(-24.57, -2.06)	0.53	(0.32, 0.87)	0.202
MK-0966 50 mg vs. ibuprofen 2400 mg	-9.10	(-20.70, 2.50)	0.68	(0.42, 1.09)	0.848
MK-0966 25 mg vs. MK-0966 50 mg	-4.22	(-12.23, 3.79)	0.78	(0.48, 1.25)	0.363

† Cumulative rate from the life-table analysis, it may not equal the number of patients with the incidence/N x 100.
‡ From the log-rank test.
‖ Number of patients with available data at baseline and at a subsequent visit.

Escape medication:

The use of escape medication in the form of acetaminophen was highest in the placebo group and lowest in the Vioxx 50mg group. The data were presented as the least square s

mean number of tablets per day. The rates for placebo, Vioxx 25 mg, Vioxx 50mg and ibuprofen groups were 2.7, 2.3, 1.9 and 2.1 respectively. These do not appear to be meaningful differences
Gelusil use was not different among the groups at 12 or 24 weeks.

Gastrointestinal Adverse events

The safety data are viewed as valuable information regarding trends. The multiplicity of endpoints and relatively vague terminology of some symptomatic adverse events must be kept in mind when reviewing such safety data. As the sponsor's report notes:

"In general, statistical hypothesis testing for safety parameters must be interpreted cautiously, due to the multiplicity of endpoints being assessed. The usual hypothesis testing paradigm and the resulting p-values are appropriate for a limited number of prespecified hypotheses for which there is reasonable power to detect clinically important effects. However, the analysis of safety data is in essence a screening process, with both the number of and the specific hypotheses tested being a data-driven exercise. These statistical tests function as indices to help identify outcomes that may require further clinical assessment. Therefore, even if p-values indicate significant differences between treatments, assessment of the clinical relevance of the magnitude of the observed difference and relationship to other safety variables must be considered."

Given that important hypotheses being tested in this submission relate to gastrointestinal safety, abdominal pain, nausea and vomiting are important symptomatic parameters. These are more concretely understood terms than are other symptoms such as dyspepsia, epigastric discomfort and digestive gas symptoms that appear in tables 16 and 17. If abdominal pain, nausea and vomiting all trend in the same direction in reported adverse events at weeks 18 and 24 as well as in discontinuation data one might expect that this nonstatistican data reflects a real phenomenon. Likewise, dose trends would also suggest a biologic phenomenon rather than random results. Data on placebo are limited to 18 weeks due to the design of the protocol. Meaningful comparisons involving placebo data extend only to 18 weeks. It would be misleading and introduce bias against the active NSAID comparators to compare 18-week data for placebo with 24-week data for Vioxx and ibuprofen.
The sponsor presents both life table and crude data.

Table 15

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

	Placebo (N=177)			MK-0966 25 mg (N=195)			MK-0966 50 mg (N=186)			Ibuprofen 2400 mg (N=184)		
	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 experience	118	72.1	66.7	148	78.3	75.9	138	77.5	74.2	129	74.7	70.1
Patients with no adverse experience	59	27.9	33.3	47	21.7	24.1	48	22.5	25.8	55	25.3	29.9
Body As A Whole	**51**	**33.3**	**28.8**	**69**	**37.8**	**35.4**	**71**	**40.9**	**38.2**	**58**	**37.9**	**31.5**
Abdominal pain	10	6.5	5.6	16	8.3	8.2	16	9.5	8.6	13	7.6	7.1

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

	Placebo (N=177)			MK-0966 25 mg (N=195)			MK-0966 50 mg (N=186)			Ibuprofen 2400 mg (N=184)		
	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 experience	120	--	67.8	157	85.7	80.5	147	84.4	79.0	143	89.9	77.7
Patients with no adverse experience	57	--	32.2	38	14.3	19.5	39	15.6	21.0	41	10.1	22.3
Body As A Whole	**54**	**--**	**30.5**	**87**	**54.8**	**44.6**	**86**	**56.6**	**46.2**	**74**	**58.9**	**40.2**
Abdominal pain	10	--	5.6	19	10.5	9.7	16	9.5	8.6	14	8.8	7.6

When abdominal pain per se was analyzed the life table rates were 6.5, 8.3,9.5 and 7.6% respectively for placebo, Vioxx 25 mg, Vioxx 50 mg and ibuprofen 2400 mg at 18 weeks. For the entire study the rates for the Vioxx 25mg, Vioxx 50 mg and ibuprofen 2400 mg groups were 10.5, 9.5 and 8.8% respectively. (See table 15)

Table 16 reports the gastrointestinal adverse events more specifically. Such data must be interpreted with caution. The rates of erosive esophagitis, heartburn, nausea and vomiting appear numerically or statistically significantly higher in the Vioxx group compared to the placebo group at 18 weeks. The data comparing the Vioxx and ibuprofen groups for the entire study show similar rates for nausea and vomiting with erosive esophagitis higher in the ibuprofen group and heartburn higher in the Vioxx groups. The lack of meaningful differentiation between Vioxx groups and ibuprofen is the most relevant information to be drawn from this data.

Withdrawal due to adverse events data are presented in table18. These data trend in the same direction as adverse events. Withdrawal data represents more significant events than the simple reporting of symptoms. Vioxx trends much closer to ibuprofen than placebo. The data from the Vioxx and ibuprofen groups include 24 weeks exposure

compared to the 18-week placebo exposure. (On review of the listing of patients discontinued due to clinical adverse events, there were no Vioxx withdrawals and only 2 ibuprofen group withdrawals for GI adverse events after the 18th week. Thus week-18 rates for ibuprofen would be even lower than 6.5%. These data highlight the comparability of Vioxx and ibuprofen in overall GI adverse events and distinguishes both from placebo.)

The adverse event data are distinctly different than the ulcer data in cross group comparisons. Vioxx groups trend closer to placebo and much lower than the ibuprofen group when examining the gastroduodenoscopy data. Esophagoscopy data as well as symptoms of abdominal pain, nausea, vomiting, and withdrawal due to GI adverse events all suggest more similarity between Vioxx and ibuprofen than between Vioxx and placebo. One partial explanation for this apparent lack of consistency between ulcer and adverse event data is the previously quoted medical literature that documents the asymptomatic nature of up to 70% of endoscopic NSAID related ulcers. Even a 30% rate of symptomatic ulcers would be expected to give a higher rate of abdominal pain and UGI symptoms in the ibuprofen group compared to Vioxx in view of the 400% higher rate of ulcers in the ibuprofen group. The ulcer data are convincing in differentiating Vioxx from ibuprofen. There may be a biologic phenomenon unrelated to gastroduodenal damage to explain the adverse event findings noted. These data remain unexpected and unexplained in the context of the hypothesis being tested regarding the safety of Vioxx compared to ibuprofen and placebo. Comparison to study 045 and review of study 069 may shed some light on this issue.

Table 16

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

	Placebo (N=177)			MK-0966 25 mg (N=195)			MK-0966 50 mg (N=186)			Ibuprofen 2400 mg (N=184)		
	n	Life Table Rate† (%)	Crude Rate‡ (%)	n	Life Table Rate† (%)	Crude Rate‡ (%)	n	Life Table Rate† (%)	Crude Rate‡ (%)	n	Life Table Rate† (%)	Crude Rate‡ (%)
Digestive	**58**	**36.7**	**32.8**	**77**	**41.7**	**39.5**	**79**	**45.0**	**42.5**	**68**	**40.5**	**37.0**
Constipation	4	2.5	2.3	5	2.8	2.6	6	3.4	3.2	9	5.6	4.9
Dental disorder	0	0.0	0.0	1	0.6	0.5	3	2.0	1.6	0	0.0	0.0
Dental pain	2	1.5	1.1	5	2.1	2.6	1	0.6	0.5	0	0.0	0.0
Diarrhea	16	9.9	9.0	16	8.7	8.2	16	9.3	8.6	16	10.5	8.7
Digestive gas symptoms	2	1.2	1.1	6	3.1	3.1	6	3.5	3.2	6	3.7	3.3
Dry mouth	4	2.4	2.3	1	0.5	0.5	1	0.6	0.5	2	1.2	1.1
Dyspepsia	5	3.2	2.8	5	2.7	2.6	5	3.0	2.7	7	4.4	3.8
Epigastric discomfort	1	0.6	0.6	1	0.5	0.5	2	1.2	1.1	6	3.4	3.3
Erosive esophagitis	3	2.1	1.7	9	5.2	4.6	14	8.6*	7.5	7	5.1	3.8
Esophageal ulcer	2	1.4	1.1	2	1.2	1.0	1	0.6	0.5	3	2.2	1.6
Esophagitis	3	2.1	1.7	4	2.5	2.1	2	1.2	1.1	2	1.5	1.1
Flatulence	5	2.9	2.8	4	2.1	2.1	5	3.1	2.7	3	1.8	1.6
Gastritis	2	1.5	1.1	5	2.9	2.6	0	0.0	0.0	6	4.2	3.3
Heartburn	6	4.1	3.4	14	7.5	7.2	19	11.2*	10.2	10	6.1	5.4
Infectious gastroenteritis	4	2.6	2.3	2	1.1	1.0	2	1.3	1.1	1	0.6	0.5
Nausea	7	4.0	4.0	16	8.9	8.2	12	6.7	6.5	15	9.1	8.2
Vomiting	2	1.1	1.1	7	4.1	3.6	6	3.4	3.2	8	4.8	4.3

Table 17

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

	Placebo (N=177)			MK-0966 25 mg (N=195)			MK-0966 50 mg (N=186)			Ibuprofen 2400 mg (N=184)		
	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	**6**	--	**3.4**	**20**	**13.2**	**10.3**	**20**	**14.5**	**10.8**	**14**	**12.0**	**7.6**
Hypertension	1	--	0.6	11	6.8	5.6	14	9.8	7.5	9	8.2	4.9
Digestive	**58**	--	**32.8**	**83**	**48.7**	**42.6**	**93**	**57.2**	**50.0**	**77**	**56.9**	**41.8**
Constipation	4	--	2.3	5	2.8	2.6	8	6.8	4.3	9	5.6	4.9
Dental disorder	0	--	0.0	2	2.2	1.0	5	3.7	2.7	0	0.0	0.0
Dental pain	2	--	1.1	5	2.1	2.6	1	0.6	0.5	0	0.0	0.0
Diarrhea	16	--	9.0	17	9.4	8.7	19	11.8	10.2	16	10.5	8.7
Digestive gas symptoms	2	--	1.1	6	3.1	3.1	6	3.5	3.2	7	4.9	3.8
Dry mouth	4	--	2.3	1	0.5	0.5	1	0.6	0.5	2	1.2	1.1
Dyspepsia	5	--	2.8	6	4.3	3.1	5	3.0	2.7	9	9.4	4.9
Epigastric discomfort	1	--	0.6	1	0.5	0.5	3	2.0	1.6	6	3.4	3.3
Erosive esophagitis	3	--	1.7	11	8.2	5.6	16	11.1	8.6	12	17.3	6.5
Esophageal ulcer	2	--	1.1	2	1.2	1.0	1	0.6	0.5	5	7.3	2.7
Esophagitis	3	--	1.7	5	4.0	2.6	3	2.9	1.6	2	1.5	1.1
Flatulence	5	--	2.8	5	2.8	2.6	5	3.1	2.7	3	1.8	1.6
Gastritis	2	--	1.1	5	2.9	2.6	2	2.6	1.1	7	5.6	3.8
Heartburn	6	--	3.4	15	8.2	7.7	23	14.4	12.4	11	7.4	6.0
Infectious gastroenteritis	4	--	2.3	3	1.8	1.5	2	1.3	1.1	1	0.6	0.5
Nausea	7	--	4.0	18	11.2	9.2	16	9.9	8.6	15	9.1	8.2
Vomiting	2	--	1.1	10	7.2	5.1	8	5.0	4.3	8	4.8	4.3

Table 18

Number (%) of Patients Discontinued Due to Clinical Adverse Experiences by Category

	Placebo (N=177)		MK-0966 25 mg (N=195)		MK-0966 50 mg (N=186)		Ibuprofen 2400 mg (N=184)	
	n	(%)	n	(%)	n	(%)	n	(%)
Total*	12	6.8	20	10.3	22	11.8	21	11.4
Discontinuation due to:								
Gastrointestinal-type adverse experiences§	5	2.8	12	6.2	9	4.8	12	6.5
Cardiovascular adverse experiences	1	0.6	3	1.5	3	1.6	4	2.2
Nervous system adverse experiences	1	0.6	2	1.0	2	1.1	0	0.0
Musculoskeletal-type adverse experiences	1	0.6	0	0.0	2	1.1	0	0.0
Body as a whole adverse experiences	2	1.2	0	0.0	2	1.1	2	1.1
Edema-type adverse experiences	0	0.0	3	1.5	2	1.1	1	0.5
Skin (Rash) adverse experiences	0	0.0	0	0.0	0	0.0	1	0.5
All other adverse experiences‡	2	1.1	0	0.0	2	1.1	1	0.5

* Data in table represents the entire study. Twenty (10.9% crude rate) patients in the ibuprofen treatment group discontinued for a clinical adverse experience by Week 18; only 1 patient (ibuprofen treatment group) discontinued after Week 18.
‡ Adverse experiences not covered by listed categories; single occurrences only.
Patients are counted only once within a category. The number and percentage of patients appear as the crude rates.
§ Gastrointestinal-type adverse experiences include Digestive System adverse experiences and abdominal pain adverse experiences.

Data Source: [4.12.1]

Discussion:

The primary hypothesis of this study was that, compared to ibuprofen 800 mg 3 times daily, the percentage of osteoarthritis patients who develop gastric and/or duodenal ulcers (≥3 mm) after 12 weeks of treatment would be lower with Vioxx 25 mg once daily. The results robustly support this conclusion. The supporting hypotheses related to ulcer rates at 24 weeks and rates for Vioxx 50mg compared to ibuprofen are also robustly supported by the results of this study. The data are not as robust when duodenal ulcers are examined separately. There was no statistically significant difference in duodenal ulcer rate between Vioxx 50 mg and ibuprofen at 12 and 24 weeks. As noted previously, the majority of NSAID damage occurs in the stomach. The results on duodenal ulcer when examined separate from gastric ulcers may reflect the small number of events or the difference in the biologic patterns of gastric and duodenal injury related to NSAIDs.

It is interesting to note that the ulcer data depart significantly from the anticipated rates for all study groups:

"With at least 150 evaluable patients completing the study in each treatment group, there would be 95% power to detect a difference in the cumulative incidence rate between MK-0966 25 or 50 mg once daily or placebo and ibuprofen 800 mg 3 times daily if the true incidence rates were 2.5, 2.5,

2.5 and 15% for the MK-0966 25 mg once daily, MK-0966 50 mg once daily, placebo, and ibuprofen treatment groups, respectively. This power calculation was based on a two-sided test with α=0.05."

The sponsor's assumptions were most likely based on historical data related to placebo and ibuprofen related ulcer incidence and their limited prior experience with Vioxx. The actual results meaningfully differed from the anticipated results. Although this deviation is easily understandable for a new molecular entity, the major departure from the anticipated placebo rate is not well understood. This issue will be further discussed in relation to study 044C.

Despite the unexpected rates, the results did differentiate gastroduodenal injury associated with both Vioxx 25 and 50 mg from ibuprofen 2400mg per day. The data on larger ulcers (≥5 mm) and the results of the sensitivity analyses were confirmatory. The more difficult question will come when comparing Vioxx and placebo in terms of GI toxicity. Esophageal score data and adverse event data qualitatively suggest more similarity between Vioxx and Ibuprofen that between Vioxx and placebo. The issue of placebo comparability will be addressed when discussing studies 045, 044C, 041,050 and 069.

It is of concern that in the population at highest risk for ulcer complications, (those with a history of PUBs) the data is significantly less robust in terms of relative ulcer rates between Vioxx and ibuprofen. This lack of robust differentiation applies to the placebo group as well. The trend remains in favor of lower ulcer rates in the Vioxx and placebo groups compared to the ibuprofen group. The relatively high incidence rate of ulcers in all the groups in the patients with a history of PUBs suggests individual susceptibility plays a strong role in the overall risk associated with the use of NSAIDs. The ulcer risk associated with each group is not solely due to the risk attributable to the study drugs.

Study 045

Study 045 was identical to 044 except for the international predominance of study centers and the use of different escape medicine. The neutralizing capacities of Kompensan and Gelusil are not meaningfully different.

Results

Baseline patient characteristics

1. Center Allocation

None of the 37 centers accounted for more than 7% of the study population. The centers with relative imbalance in ascertainment are listed in table 19.