events requiring withdrawal. This dose phenomenon again suggests that the gastrointestinal impact of Vioxx is not comparable to placebo.

Table 38

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

	Placebo (N=194)		MK-0966 25 mg (N=195)		MK-0966 50 mg (N=193)		Ibuprofen 2400 mg (N=193)	
	n	(%)	n	(%)	n	(%)	n	(%)
Total[1]	7	3.6	9	4.6	18	9.3	18	9.3
Discontinuation due to: Gastrointestinal-type adverse experiences[2]	3	1.5	2	1.0	10	5.2	9	4.7

Specific data on "clinical relevant" UGI events will be reviewed more thoroughly in the section on study 069.

Discussion:

The hypotheses of this study were identical to study 044. The results of this study robustly support the hypotheses that the gastroduodenal ulcer rate at week 12 and 24 are lower with Vioxx 25 and 50 mg compared to ibuprofen. This was true for ulcers ≥3 mm as well as ≥5mm. The difference observed between the "gastroduodenal" ulcer rates in the Vioxx and ibuprofen groups is driven primarily by gastric ulcer data. This is not unexpected in a study of NSAID associated ulcer disease.

The other GI safety data were similar to the results seen in study 044. GI adverse events, withdrawal due to any adverse event as well as specifically GI adverse events showed a potentially meaningful difference between placebo and the Vioxx groups. Esophageal injury rates at 12 weeks (the last endoscopic placebo time point) reflected as the incidence of esophageal erosions and ulcers in the Vioxx 25 and 50mg groups were double and triple the placebo rates. At 18 weeks (the last time point with placebo adverse event data) nausea and vomiting was 50 to 100% higher than the placebo rate. Numeric heartburn rates were also lower in the placebo group. Esophageal injury scores, nausea, vomiting and heartburn data all suggest potential GI effects that are not measured by the primary endpoint of gastroduodenal ulceration. In addition, dose-related increases in many adverse events and ulcer data also suggest a GI safety profile for Vioxx different than placebo.

Study 044C: A combined analysis of two identically designed studies to determine the incidence of gastroduodenal ulceration after 12 weeks of treatment with MK-0966, ibuprofen or placebo with a 12 week continuation period (protocol 044/045)

This report is based on the merging of databases from studies 044 and 045. Such an approach has the potential to show statistically meaningful differences by increasing the population size and the number of events and hence the power of the study. Study populations must be comparable for such an analysis to be valid. This is discussed by the statistical reviewer as well as in the discussion of this review.
The study design of the actual trials is outlined on page 6 of this review.

"Primary Hypothesis
The incidence of gastric and/or duodenal ulcers ≥3 mm associated with MK-0966 25 mg once daily and placebo would be comparable during a 12-week treatment period using the combined database of two identically designed clinical trials, Protocols 044 and 045. For this assessment, a prespecified clinical comparability bound of 4% was established (the MK-0966 versus placebo between-treatment difference in 12-week cumulative ulcer rate must fall below 4 percentage points) ".

A 4% comparability bound was "considered to be reasonable" by the sponsor taking into account an assumed ulcer rate of 2.5% and 15% for the Vioxx and ibuprofen groups respectively.
The agency does not have standardized criteria on defining drug safety comparability to placebo. Can a drug be considered placebo-like in terms of safety related to one area of adverse events if the safety profile overall is not placebo-like? Can dose specific placebo comparability be claimed when other clinically used and approved dosage schedules are not comparable to placebo in safety for the same safety parameter. If these difficult questions are answered affirmatively then the question of allowable difference arises. Is the absolute risk of adverse event the only relevant point or is the relative risk compared to placebo equally or more important? Is the type/severity of the safety parameter important? Is the allowable difference the same for a highly morbid or minor adverse event? These questions exemplify the difficulty in assessing claims related to comparability to placebo.
The sponsor's choice of 4% for the comparability bound based on their assumed ulcer rates indicates that an ulcer rate over 6% associated with the use of Vioxx would be considered "comparable" to an ulcer rate of 2.5%. This choice may have been based on what could be statistically demonstrated with the population size available. The sponsor did not justify this choice in the study report based on public health statistics or any assumptions related to the clinical meaning of placebo effect.
This reviewer considers the comparability bounds to be excessive for use as marketing claims. It is not clear that a physician or patient consumer would consider a drug

associated with an ulcer rate of 2.5 times that of placebo to be comparable to placebo. In view of the difficulties noted above and the fact that the data ultimately deviated significantly from prospective estimates, the actual data should be analyzed without the constraints of the prespecified statistical plan.

Secondary objectives and exploratory evaluations and a post hoc analysis were included in the study as well.

"Secondary Objectives
To determine the comparative incidence of the endoscopic endpoints of gastric and/or duodenal ulcers (≥3 mm, ≥5 mm) and erosions following administration of MK-0966 25 mg once daily, MK-0966 50 mg once daily, ibuprofen 800 mg 3 times daily, and placebo over 12 weeks with a 12-week continuation period for MK-0966 25 mg, MK-0966 50 mg, and ibuprofen.
Exploratory Evaluations
Other exploratory evaluations included a combined comparison of the effect of treatment with MK-0966 25-mg once daily and MK-0966 50-mg once daily with respect to endoscopic endpoints of esophageal mucosal injury in comparison to ibuprofen 2400 mg and placebo."

A post hoc analysis was performed to compare the mean change from baseline for hematocrit (%) and hemoglobin (gm/dL) between patients who did and those who did not develop ulcers while on treatment. Other results in this submission indicate that fluid retention occurs with the use of Vioxx as it does with the use of NSAIDs. Minor change in hemoglobin or hematocrit may relate to hemodilution. Interpretation of such data must be made with caution. Fecal blood loss studies in combination with hematologic changes might offer more robust information.

Analyses based on a modified intention-to-treat (ITT) requiring at least one treatment phase measurement and per –protocol were performed. Sensitivity analyses were also performed and will be described in the results section.

Results:
Baseline patient characteristics:
Table 39 shows baseline comparative data. The sponsor noted the differences between the two study populations in terms of NSAID use prior to baseline visit and prior history of perforation, ulcer or bleed. These are very large differences in parameters that are well known to affect risk of ulcer disease. Tables 40 and 41 break down the data further and are taken from study 044 and 045 study reports. In view of the significant difference between placebo ulcer rates in studies 044 and 045 and the primary importance of placebo rates to the results of this study, these differences should be noted with concern regarding the validity of combining these two studies for placebo comparisons.

Table 39

Study Populations at Baseline

Category	Protocol 044 (US only)	Protocol 045 (International)	Combined Protocols 044/045
Randomized patients (N)	741‡	775	1516‡
Female (%)	67.3	74.7	71.0
Male (%)	32.7	25.3	29.0
Mean age (years)	62	61	62
Age range (years)†	47 to 87	49 to 88	47 to 88
Prior GI history§ (%)	19.4	11.1	15.2
H. pylori present (%)	26.7	54.7	41.0
Gastroduodenal erosions at baseline endoscopy (%)	13.0	14.8	13.9
NSAID use prior to baseline visit (%)	83.0	49.4	65.9

Table 40 (from study 044)

Baseline Patient Characteristics

	Placebo	MK-0966		Ibuprofen†	Total‡
		25 mg	50 mg	2400 mg	
Gender					
N	177	195	186	183	741
Male, n (%)	61 (34.46)	61 (31.28)	58 (31.18)	63 (34.43)	243 (32.79)
Female, n (%)	116 (65.54)	134 (68.72)	128 (68.82)	120 (65.57)	498 (67.21)
Race					
N	177	195	186	183	741
Asian, n (%)	1 (0.56)	1 (0.51)	0 (0.00)	2 (1.09)	4 (0.54)
black, n (%)	22 (12.43)	17 (8.72)	16 (8.60)	19 (10.38)	74 (9.99)
Eurasian, n (%)	0 (0.00)	1 (0.51)	0 (0.00)	0 (0.00)	1 (0.13)
Hispanic, n (%)	6 (3.39)	13 (6.67)	11 (5.91)	7 (3.83)	37 (4.99)
Indian, n (%)	2 (1.13)	0 (0.00)	0 (0.00)	1 (0.55)	3 (0.40)
Native Amer, n (%)	2 (1.13)	1 (0.51)	2 (1.08)	1 (0.55)	6 (0.81)
white , n (%)	144 (81.36)	162 (83.08)	157 (84.41)	153 (83.61)	616 (83.13)
GI History§					
N	177	195	186	183	741
absent , n (%)	145 (81.92)	152 (77.95)	152 (81.72)	148 (80.87)	597 (80.57)
present, n (%)	32 (18.08)	43 (22.05)	34 (18.28)	35 (19.13)	144 (19.43)
***H. pylori* Status¶**					
N	177	195	186	183	741
absent, n (%)	125 (70.62)	150 (76.92)	131 (70.43)	134 (73.22)	540 (72.87)
present, n (%)	49 (27.68)	45 (23.08)	55 (29.57)	49 (26.78)	198 (26.72)
unknown, n (%)	3 (1.69)	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.40)
Gastric and Duodenal Erosions					
N	177	195	186	183	741
=0, n (%)	150 (84.75)	176 (90.26)	157 (84.41)	162 (88.52)	645 (87.04)
>0, n (%)	27 (15.25)	19 (9.74)	29 (15.59)	21 (11.48)	96 (12.96)
Prior NSAID Use					
N	177	195	186	183	741
No , n (%)	32 (18.08)	33 (16.92)	33 (17.74)	27 (14.75)	125 (16.87)
Yes, n (%)	145 (81.92)	162 (83.08)	153 (82.26)	156 (85.25)	616 (83.13)

Table 41 (from study 045)

Baseline Patient Characteristics

	Placebo	MK-0966		Ibuprofen	Total
		25 mg	50 mg	2400 mg	
Gender					
N	194	195	193	193	775
Female, n (%)	146 (75.26)	151 (77.44)	139 (72.02)	143 (74.09)	579 (74.71)
Male, n (%)	48 (24.74)	44 (22.56)	54 (27.98)	50 (25.91)	196 (25.29)
Race					
N	194	195	193	193	775
Asian, n (%)	0 (0.00)	2 (1.03)	1 (0.52)	1 (0.52)	4 (0.52)
Black, n (%)	3 (1.55)	2 (1.03)	4 (2.07)	4 (2.07)	13 (1.68)
Europ, n (%)	0 (0.00)	1 (0.51)	1 (0.52)	0 (0.00)	2 (0.26)
Hispa, n (%)	54 (27.84)	53 (27.18)	56 (29.02)	53 (27.46)	216 (27.87)
Multi, n (%)	3 (1.55)	2 (1.03)	2 (1.04)	2 (1.04)	9 (1.16)
White, n (%)	134 (69.07)	135 (69.23)	129 (66.84)	133 (68.91)	531 (68.52)
Prior GI History‡					
N	194	195	193	193	775
absent, n (%)	176 (90.72)	171 (87.69)	174 (90.16)	168 (87.05)	689 (88.90)
present, n (%)	18 (9.28)	24 (12.31)	19 (9.84)	25 (12.95)	86 (11.10)
***H. pylori* Status§**					
N	194	195	193	193	775
absent, n (%)	84 (43.30)	83 (42.56)	77 (39.90)	88 (45.60)	332 (42.84)
present, n (%)	104 (53.61)	110 (56.41)	109 (56.48)	101 (52.33)	424 (54.71)
unknown, n (%)	6 (3.09)	2 (1.03)	7 (3.63)	4 (2.07)	19 (2.45)
Prior NSAID use					
N	194	195	193	193	775
No, n(%)	101 (52.06)	93 (47.69)	94 (48.70)	104 (53.89)	392 (50.58)
Yes, n(%)	93 (47.94)	102 (52.31)	99 (51.30)	89 (46.11)	383 (49.42)

A comparison of the two placebo populations in withdrawal data is also relevant. There are potentially meaningful differences in discontinuation rates (32 versus 22% for studies 044 and 045 respectively) tables 42 and 43 display these data.

Table 42

Patient Accounting

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

Table 43

Patient Accounting

	Placebo	MK-0966 25 mg	MK-0966 50 mg	Ibuprofen 2400 mg	Total
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[‡](5.1)	18 (9.3)	18 (9.3)	53 (6.8)
Laboratory adverse experience	0	1 (0.5)	3 (1.6)	1[‡](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)

Results :

Figures 4, 5, and 6 review the individual study results and then the combined analysis. The statistical analysis of the combined studies is shown in table 44. The 90% confidence interval for the difference between Vioxx 25-mg dose and placebo was well within the sponsor defined 4% confidence bounds. The placebo ulcer rates at both 12 and 24 weeks are in fact higher than the Vioxx 25mg rate.
The 90% confidence interval for the ulcer rate difference between the Vioxx 50mg dose and placebo was slightly over the prespecified bound of 4%. The upper bound of the 90% confidence interval was 4.88%. The trend is of note however.

Interestingly, there is a strong trend (p=0.066) suggesting a difference between the ulcer rate of the two dosages of Vioxx at 12 weeks (see table 44). At 24 weeks there is a statistically significant higher ulcer rate in the Vioxx -50mg compared to the 25-mg group (0=0.043). This dose related statistically significant difference between ulcer rates in the two Vioxx groups remains when considering larger of ulcers $\leq$ 5 mm as well (p=0.016). (See figure 7). These results heighten concerns over claims of comparability to placebo.

The results of data on changes in esophageal score over time also suggest a lack of placebo effect of Vioxx in a biologic parameter different than gastroduodenal injury. There is a trend suggesting a higher esophageal injury score in the Vioxx 25-mg group compared to placebo and a statistically significant difference between placebo and Vioxx 50-mg in this parameter. At 24 weeks ibuprofen and Vioxx maintain similarity in changes from baseline esophageal injury scores.

The data displayed in a categorical fashion in table 47 reveal that the majority (over 80%) of patients in all groups had no change in esophageal score. (See tables 45,46 and 47)

Subgroup analysis for study 044C revealed a statistically significant correlation between a history of PUBs and ulcer rate (p<0.001). The analysis of the effect of prior NSAID usage shows a strong trend with a p= 0.087. This statistical effect on the ulcer rates is particularly important in view of the differences in baseline rates of these two critical variables. This will be discussed later in the discussion of study 044C.

Two sensitivity analyses were done in this study. The first analysis imputed the observed placebo ulcer rate for the 4.2% of patients who withdrew from the studies due to GI adverse events. The ulcer rate for the patients withdrawn due to GI adverse events in the Vioxx groups was imputed to be equal to the observed ulcer rate for the ibuprofen group. The Vioxx 25-mg group remained within the sponsor's comparability bounds.

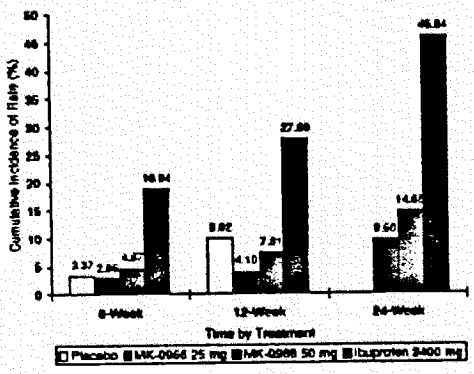
The second sensitivity analysis imputed the observed ulcer rate for each group for patients with missing data. The 90% confidence interval remained well below 4% (range –3.26 to 2.17) for the Vioxx 25 mg group compared to placebo.
These sensitivity analyses are of note. They are less relevant to assessing the results of this study than are the questions to be raised about the large differences in populations and associated placebo rates between studies 044 and 045. The appropriateness of combining data from two studies with different populations must first be considered before the meaning of results can be considered.

Table 4

Table 5

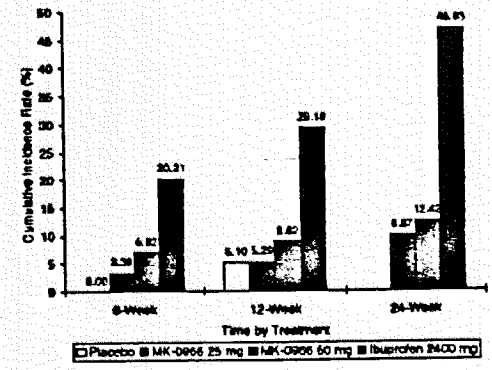
Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥3 mm
Intention-to-Treat

Protocol 044



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

Protocol 045

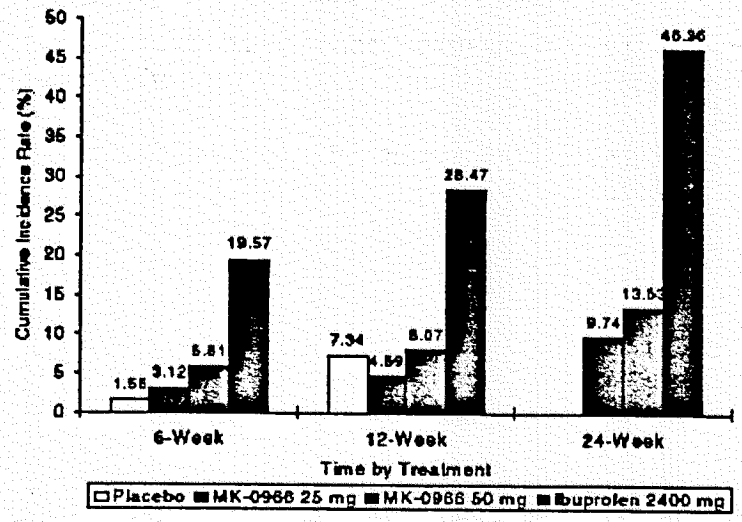


N=182 N=187 N=182 N=187

For both Protocols 044 and 045, p<0.001 for ibuprofen versus placebo, MK-0966 25 mg, and MK-0966 50 mg at Week 12 and for MK-0966 25 mg and MK-0966 50 mg at Week 24. Placebo was not included at Week 24 since 95% of the patients in the placebo group were discontinued at Week 16.
Data Source: [2.1.1; 2.1.2]

Figure 6

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



Combined: N=340 N=373 N=360 N=354

Data Source: [2.1.1; 2.1.2; 4.1.37]

Table 44

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

Treatment	N		Number of Patients With Incidences		Rate (%)†		Combined Rate (%)‡ and 95% CI
	Prot 044	Prot 045	Prot 044	Prot 045	Prot 044	Prot 045	
Placebo	158	182	11	5	9.92	5.10	7.54 (3.78, 10.91)
MK-0966 25 mg	186	187	7	9	4.10	5.29	4.69 (2.45, 6.94)
MK-0966 50 mg	178	182	12	15	7.31	8.82	8.07 (5.15, 11.00)
Ibuprofen	167	187	42	49	27.69	29.18	28.47 (23.43, 33.52)

		Between-Treatment Comparison				
		Difference of Rates (%)‡	90% CI for Difference (%)	Ratio of Rates‡	90% CI for Ratio	p-Value*
Primary Comparison:	MK-0966 25 mg vs. Placebo	-2.32	(-5.85, 1.21)	0.62	(0.34, 1.11)	0.419
Other Placebo Comparison:	MK-0966 50 mg vs. Placebo	1.01	(-2.87, 4.88)	1.04	(0.62, 1.74)	0.299
	Ibuprofen vs. Placebo	21.29	(16.10, 26.47)	3.57	(2.31, 5.52)	<0.001
Active Treatment Comparison:	MK-0966 25 mg vs. MK-0966 50 mg	-3.36	(-6.44, -0.27)	0.58	(0.35, 0.96)	0.066
	MK-0966 25 mg vs. Ibuprofen	-23.74	(-28.58, -19.10)	0.17	(0.11, 0.25)	<0.001
	MK-0966 50 mg vs. Ibuprofen	-20.37	(-25.26, -15.47)	0.28	(0.20, 0.40)	<0.001

† Cumulative rate from the life-table analysis, it may not equal the number of patients with the incidences/N x 100.

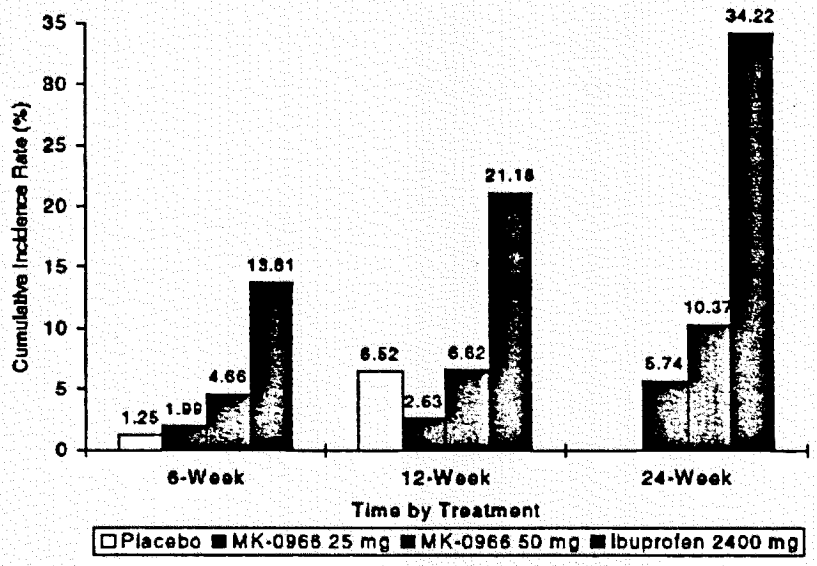
‡ Combined rate was calculated as a weighted combination of rates of the treatment from the individual studies (sample sizes were used as the weights), while the combined between-treatment difference was calculated as a weighted combination of the differences from the individual studies (inverses of the variances of the differences were used as the weights). The combined ratio of rates was calculated using the similar method as for combined difference (see the method section). Thus, the combined differences might not equal the differences of the combined rates, and the combined ratios might not equal the ratios of the combined rates.

* From the log-rank test adjusted for study.

Data Source: [2.1.1; 2.1.2]

Figure 7

Life-Table Cumulative Incidence Combined Rate† of Gastroduodenal Ulcer ≥5 mm
Intention-to-Treat



Combined: N=340 N=373 N=360 N=354

† Combined rate for a treatment was calculated as a weighted combination of rates of the treatment from the individual studies with sample sizes of the treatment from the individual studies as the weights.

Data Source: [2.1.1; 2.1.2; 4.1.38]

Table 45

Life-Table Analysis for 12-Week Cumulative Incidences of Esophageal Score ≥2
Intention-to-Treat, Adjusted for Study‡

Treatment	N		Number of Patients With Incidences		Rate (%)†		Combined Rate (%)‡ and 95% CI
	Prot 044	Prot 045	Prot 044	Prot 045	Prot 044	Prot 045	
Placebo	155	179	10	4	9.27	2.32	5.54 (2.63, 8.46)
MK-0966 25 mg	181	185	18	10	11.07	5.47	8.24 (5.27, 11.21)
MK-0966 50 mg	176	180	22	12	14.16	7.85	10.97 (7.49, 14.45)
Ibuprofen	164	185	15	18	11.87	12.67	12.29 (8.30, 16.28)

		Between-Treatment Comparison				
		Difference of Rates (%)‡	90% CI for Difference (%)	Ratio of Rates‡	90% CI for Ratio	p-Value§
Primary Comparison:	MK-0966 25 mg vs. Placebo	2.83	(-0.21, 5.88)	1.46	(0.86, 2.49)	0.198
Other Placebo Comparisons:	MK-0966 50 mg vs. Placebo	5.36	(1.89, 8.83)	1.94	(1.16, 3.24)	0.029
	Ibuprofen vs. Placebo	7.61	(3.57, 11.65)	2.14	(1.26, 3.63)	0.004
Active Treatment Comparisons:	MK-0966 25 mg vs. MK-0966 50 mg	-2.64	(-6.34, 1.06)	0.75	(0.50, 1.13)	0.322
	MK-0966 25 mg vs. Ibuprofen	-4.43	(-8.57, -0.29)	0.68	(0.45, 1.03)	0.135
	MK-0966 50 mg vs. Ibuprofen	-1.71	(-6.12, 2.71)	0.89	(0.61, 1.32)	0.578

† Cumulative rate from the life-table analysis, it may not equal the number of patients with the incidences/N x 100.
‡ Combined rate was calculated as a weighted combination of rates of the treatments from the individual studies (sample sizes were used as the weights), while the combined between-treatment difference was calculated as a weighted combination of the differences from the individual studies (inverses of the variances of the differences were used as the weights). The combined ratio of rates was calculated using the similar method as for combined difference (see the method section). Thus, the combined differences might not equal the differences of the combined rates, and the combined ratios might not equal the ratios of the combined rates.
§ From the log-rank test adjusted for study.

Data Source: [2.1.1; 2.1.2]

Table 46

Life-Table Analysis for 24-Week Cumulative Incidences of Esophageal Score≥2
Intention-to-Treat
Adjusted for Study@

Treatment	N		Number of Patients With Incidences		Rate(%)#		Combined Rate(%)@ and 95% CI
	Prot044	Prot045	Prot044	Prot045	Prot044	Prot045	
MK-0966 25 mg	181	185	23	16	14.78	13.06	13.91 (9.37, 18.45)
MK-0966 50 mg	176	180	26	18	19.00	16.99	17.99 (12.64, 23.33)
Ibuprofen	164	185	22	18	28.10	12.67	19.92 (13.63, 26.21)

Between-Treatment Comparison

		Difference of Rates(%)@	90% CI for Difference(%)	Ratio of Rates@	90% CI for Ratio	p-Value*
Active Treatment Comparisons:	MK-0966 25 mg vs MK-0966 50 mg	-4.09	(-9.95, 1.78)	0.77	(0.54, 1.12)	0.255
	MK-0966 25 mg vs Ibuprofen	-3.57	(-9.62, 2.48)	0.71	(0.49, 1.03)	0.096
	MK-0966 50 mg vs Ibuprofen	-0.10	(-6.75, 6.56)	0.91	(0.64, 1.30)	0.652

Cumulative rate from the life-table analysis. It may not equal the number of patients with the incidences/N x 100.

@ Combined rate was calculated as a weighted combination of rates of the treatment from the individual studies (sample sizes were used as the weights), while the combined between-treatment difference was calculated as a weighted combination of the differences from the individual studies (inverses of the variances of the differences were used as the weights). The combined ratio of rates was calculated using the similar method as for combined difference (see the method section). Thus, the combined differences might not equal the differences of the combined rates, and the combined ratios might not equal the ratios of the combined rates.

* From the log-rank test adjusted for study.

Table 47

Analysis of Change From Baseline at Week 24 for Esophageal Score
Intention-to-Treat

Treatment	N	Mean	Number (%) of Patients with Change from Baseline Score					
			Score -1	Score 0	Score 1	Score 2	Score 3	Score 4
MK-0966 25 mg	373	0.12	19 (5.09)	315 (84.45)	20 (5.36)	14 (3.75)	4 (1.07)	1 (0.27)
MK-0966 50 mg	360	0.14	19 (5.28)	304 (84.44)	12 (3.33)	19 (5.28)	3 (0.83)	3 (0.83)
Ibuprofen	354	0.16	16 (4.52)	298 (84.18)	13 (3.67)	21 (5.93)	5 (1.41)	1 (0.28)

Between-Treatment Comparison

Treatment	Mean Difference	Logistic Regression p-Value	ANOVA p-Value
MK-0966 25 mg vs MK-0966 50 mg	0.02	0.932	0.574
MK-0966 25 mg vs Ibuprofen	0.04	0.895	0.347
MK-0966 50 mg vs Ibuprofen	0.02	0.962	0.706

Effect	p-Value
Treatment (ANOVA):	0.638
GI History (ANOVA):	0.089
Protocol (ANOVA):	0.005
Site within Protocol (ANOVA):	0.001
Treatment-by-GI-history interaction (ANOVA):	0.867
Treatment-by-Protocol interaction (ANOVA):	0.622
Treatment-by-Site-within-Protocol interaction (ANOVA):	0.774
Proportional odds assumption:	0.313

Hematologic Effects:
The analysis of change in hematocrit revealed small drops in all three treatment groups compared to placebo. (See table 48). The sponsor then did a post hoc analysis separating out ulcer patients and nonulcer patients within each group. There was no statistical effect of the presence of ulcers on the change in hemoglobin in Vioxx groups. The ibuprofen group with ulcers did have a larger drop in hemoglobin and hematocrit than the nonulcer group. One hypothesis is that the changes in hematologic parameters seen in ibuprofen are to a significant extent related to ulcer bleeding, while the change in the Vioxx groups is due to hemodilution. This is conjectural and the data cannot be analyzed in a way to define the etiology of the changes in hemoglobin and hematocrit. Blood loss, hemodilution and primary hematologic impact are all possibilities.

Table 48

Table 1- Analysis of Endpoint: hematocrit (%)
Mean Change from Baseline (Randomization Visit)
Averaged on Rx
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean* Change	95% CI for LS Mean* Change
Placebo	344	41.84	41.81	-0.03	1.71	-0.01	(-0.22, 0.20)
25 mg	375	41.64	40.89	-0.76	2.00	-0.76	(-0.96, -0.55)
50 mg	360	41.51	40.37	-1.15	2.12	-1.14	(-1.35, -0.94)
Ibuprofen	350	41.89	40.40	-1.48	2.10	-1.48	(-1.68, -1.27)

Comparisons Between Treatment Groups	Diff. in LSmean	95% CI for Diff.	p-Value
With Active Comparator			
25 mg vs. Ibuprofen	0.72	(0.43, 1.01)	<0.001
50 mg vs. Ibuprofen	0.33	(0.04, 0.62)	0.026
Between MK-0966 Doses			
25 mg vs. 50 mg	0.39	(0.10, 0.68)	0.008
With Placebo			
25 mg vs. placebo	-0.74	(-1.04, -0.45)	<0.001
50 mg vs. placebo	-1.13	(-1.43, -0.84)	<0.001
Ibuprofen vs. Placebo	-1.47	(-1.76, -1.17)	<0.001

Effect:	p-Value	Pooled SD
Protocol	<0.001	1.98
Treatment	<0.001	

* adjusting for the protocol effect.

Table 49

Table 3. Analysis of Endpoint: hemoglobin (gm/dL)
Mean Change from Baseline (Randomization Visit)
Averaged on Rx
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean[1] Change	95% CI for LS Mean[1] Change
Placebo	344	13.85	13.88	0.02	0.53	0.03	(-0.03, 0.09)
25 mg	375	13.77	13.60	-0.18	0.61	-0.18	(-0.24, -0.12)
50 mg	360	13.75	13.45	-0.30	0.63	-0.30	(-0.36, -0.24)
Ibuprofen	350	13.80	13.45	-0.41	0.61	-0.40	(-0.47, -0.34)

Comparisons Between Treatment Groups	Diff. in LSmean	95% CI for Diff.	p-Value
With Active Comparator			
25 mg vs. Ibuprofen	0.23	(0.14, 0.31)	<0.001
50 mg vs. Ibuprofen	0.11	(0.02, 0.19)	0.018
Between MK-0966 Doses			
25 mg vs. 50 mg	0.12	(0.04, 0.21)	0.006
With Placebo			
25 mg vs. placebo	-0.20	(-0.29, -0.12)	<0.001
50 mg vs. placebo	-0.33	(-0.41, -0.24)	<0.001
Ibuprofen vs. Placebo	-0.43	(-0.52, -0.34)	<0.001

Effect:	p-Value	Pooled SD
Protocol	<0.001	0.59
Treatment	<0.001	

[1]adjusting for the protocol effect.

Discussion:

The sponsor's stated goal in this study was to compare Vioxx 25-mg to placebo at 12 weeks. The specific comparability bound chosen was 4%. The study succeeded at this limited endpoint. Other endpoints studied were not supportive of comparability to placebo claims.

1. There was a consistently higher ulcer rate in the Vioxx 50-mg versus the 25-mg group. This was true for both ulcer size endpoints of 3 and 5 mm. This difference in ulcer rates was statistically significant at 24 weeks. This dose –effect relationship is not suggestive of placebo like effect in the parameter of ulcer occurrence.
2. At 6-weeks there was a 60% higher ulcer rate in Vioxx 25mg and nearly threefold higher ulcer rate in the Vioxx 50mg group compared to placebo.
3. Hematologic parameters of hematocrit and hemoglobin both revealed small but statistically significant differences between placebo and Vioxx groups. It is not known whether these differences are due to GI blood loss or other causes.
4. Esophageal injury scores seen with Vioxx suggest ibuprofen-like effects rather than placebo-like effect. This parameter (esophageal injury) may not mechanistically relate to gastroduodenal injury. It was not part of any primary hypothesis. In terms of

morbidity, the parameter of gastroduodenal injury is felt to represent a more significant concern than esophageal injury. The adverse event rates for heartburn and discontinuation rates due to UGI symptoms do however suggest a potential for clinically meaningful impact of esophageal injury associated with the use of Vioxx.

This reviewer has serious concerns over the meaning and generalizability of the placebo data in study 044C. A Cox proportional hazard model was used by the sponsor to assess the homogeneity of treatment effect (treatment by study interaction) when looking at all groups at all time points. This analysis suggested no statistically significant differences between the studies and the sponsor concluded that the studies meet criteria for homogeneity. This reviewer is concerned as to whether such a statistical model and conclusions drawn are appropriate when the very direction of the results is different in the studies. The conclusions of comparability are also difficult to accept in view of the dose related rise in ulcer rates seen with Vioxx that reached statistical significance later in the study ($p=0.066$ at 12 weeks and $p=0.043$ at 24 weeks. This difference between the ulcer rates for the two dosages of Vioxx was also statistically significant at both 12 weeks ($p=0.014$ and 24 week ($p=0.016$) intervals when larger ulcers ($\geq$5mm in size) were analyzed; suggesting a true effect is present.

There were large differences between the two study populations in important baseline characteristics that were found to have strong statistical impact on the risk of developing ulcers. It is not certain whether the differences in these baseline characteristics fully account for the differences in placebo ulcer rates.
The high placebo ulcer rate of 9.9% in study 044 is quite different than the placebo rate of 5.1% at 12 weeks in study 045. A review of historical data may be somewhat informative. Such data on "placebo" ulcer rates must be interpreted with caution. Other published studies and data from other NDA submissions did not have protocol mandated 6-week ulcer data. Twelve-week ulcer data are therefore not fully comparable.
Recent data from the NDA submission on Celebrex can be used for comparison. The patient demographics in the Celebrex trials were similar in terms of underlying osteoarthritis diagnosis, age, prior GI history, prior cardiovascular history, H. pylori status, baseline disease activity and the number of patients with gastroduodenal erosions at baseline. In that study the life table 12-week ulcer incidence rate was 5.6%. In a similar study from the Celebrex NDA the placebo ulcer rate was 4.2% for patients with rheumatoid arthritis, a disease thought by some to have a higher incidence of underlying ulcer disease. The average age in that Celebrex study was 7 years younger than the osteoarthritis studies in the current submission. Celebrex studies did not have 6-week endoscopy data, which can be anticipated to increase the ulcer rate to some extent. Unlike interval scheduled endoscopies on active NSAID comparators, the impact of 6-week endoscopy data would not be anticipated to affect the placebo rate very much. The actual data from study 044supoprts this assumption, (6-week ulcer rate of 0%). A recent study by Fuller revealed a point prevalence ulcer rate of 5.2% in osteoarthritis patients off NSAIDs for a minimum of 7 days [10]. Studies in less well-controlled populations suggest