Figure 2 shows the mean PID score plotted versus hours postdose. The SPID8 was an estimate of the area under the PID versus time curve during the 8 hours postdose.

The LSMean SPID8 scores in patients who received placebo, 25/25, 50/25 mg rofecoxib, and 550 mg naproxen sodium were 6.7, 9.8, 10.4, 10.7 units, respectively (Table 15).

Over the 8 hours postdose, the rofecoxib doses had significantly ($p<0.001$) greater SPID8 scores compared with placebo and the difference in SPID8 between the two rofecoxib doses was not significant (Table 15).

The mean SPID8 score for 550 mg naproxen sodium was significantly ($p<0.001$) greater than that for placebo but not significantly different from the scores in the rofecoxib doses (Table 15).

Table 15
Analysis of Sum of Pain Intensity Difference to 8 Hours (SPID8)
(Intention-to-Treat Approach)

Treatment	N	Mean	SD	LSMean	95% CI for LSMean
Placebo	118	6.4	7.5	6.7	(5.7, 7.7)
MK- 0966 25/ 25 mg	115	9.2	6.0	9.8	(8.7, 10.8)
MK- 0966 50/ 25 mg	118	9.9	6.7	10.4	(9.4, 11.4)
Naproxen Sodium	122	10.2	6.3	10.7	(9.7, 11.7)

Pairwise Comparison	Difference in LSMeans	95% CI for Difference	p- Value
MK- 0966 25/ 25 mg vs. Placebo	3.0	(1.6, 4.4)	<0.001
MK- 0966 50/ 25 mg vs. Placebo	3.7	(2.3, 5.1)	<0.001
MK- 0966 50/ 25 mg vs. 25/25 mg	0.7	(-0.7, 2.0)	0.346
Naproxen Sodium vs. Placebo	4.0	2.6, 5.3)	<0.001
Naproxen Sodium vs. 25/ 25 mg	1.0	(-0.4, 2.3)	0.175
Naproxen Sodium vs. 50/ 25 mg	0.3	(-1.1, 1.7)	0.677

Effect	p- Value	Pooled Intra- Patient SD
Sequence	0.771	5.3
Patient (Sequence)	<0.001	
Period (Square)	0.054	
Treatment	<0.001	
Stratum (i. e., Baseline PI)	<0.001	
Carryover (i. e., Residual)	0.165	
Treatment- by- Stratum Interaction	0.355	

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Patient's Global Evaluation at 8 Hours

The LSMean scores for placebo, 25/25, 50/25 mg rofecoxib, and 550 mg naproxen sodium were 1.2, 1.8, 2.0, 1.9, respectively (Table 16).

Compared with placebo, the 25/25- and 50/25-mg doses of rofecoxib were associated with significantly ($p<0.001$) greater Patient's Global Evaluation scores at 8 hours. There was no significant difference in the Patient's Global Evaluation scores between the two doses of rofecoxib (Table 16).

Patient's Global Evaluation score at 8 hours for 550 mg naproxen sodium was significantly ($p<0.001$) greater than that for placebo. However, the difference between 550 mg naproxen sodium and each of the rofecoxib doses was not significant. (Table 16).

Table 16
Analysis of Sum of Patient's Global Evaluation at 8 Hours
(Intention-to-Treat Approach)

Treatment	N	Mean	SD	LSMean	95% CI for LSMean
Placebo	116	1.3	1.3	1.2	(1.0, 1.5)
MK- 0966 25/ 25 mg	113	1.9	1.3	1.8	(1.6, 2.0)
MK- 0966 50/ 25 mg	117	2.0	1.3	2.0	(1.8, 2.2)
Naproxen Sodium	122	2.0	1.3	1.9	(1.7, 2.2)

Pairwise Comparison	Difference in LSMeans	95% CI for Difference	p- Value
MK- 0966 25/ 25 mg vs. Placebo	0.6	(0.3, 0.9)	<0.001
MK- 0966 50/ 25 mg vs. Placebo	0.8	(0.5, 1.1)	<0.001
MK- 0966 50/ 25 mg vs. 25/25 mg	0.2	(-0.1, 0.5)	0.220
Naproxen Sodium vs. Placebo	0.7	(0.4, 1.0)	<0.001
Naproxen Sodium vs. 25/ 25 mg	0.1	(-0.2, 0.4)	0.373
Naproxen Sodium vs. 50/ 25 mg	-0.1	(-0.4, 0.3)	0.732

Effect	p- Value	Pooled Intra- Patient SD
Sequence	0.759	1.2
Patient (Sequence)	<0.001	
Period (Square)	0.339	
Treatment	<0.001	
Stratum (i. e., Baseline PI)	0.013	
Carryover (i. e., Residual)	0.187	
Treatment- by- Stratum Interaction	0.053	

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Patient's Rank of Treatment Preference

Compared with those taking placebo, the percent of patients who ranked 25/25 mg, 50/25 mg rofecoxib, and naproxen sodium higher, were 65.5, 69.3, and 69.9% respectively (Table 17).

Table 17
Summary of Patient's Rank of Treatment Preference

Treatment	Total	Best	Second Best	Third Best	Worst
		N (%)	N (%)	N (%)	N (%)
Placebo	114	16 (14.0)	20 (17.5)	22 (19.3)	56 (49.1)
MK- 0966 25/ 25 mg	114	31 (27.2)	34 (29.8)	29 (25.4)	20 (17.5)
MK- 0966 50/ 25 mg	117	37 (31.6)	24 (20.5)	37 (31.6)	19 (16.2)
Naproxen sodium	117	34 (29.1)	40 (34.2)	25 (21.4)	18 (15.4)

Patients ranked the analgesic effect of each of the rofecoxib 50 doses significantly higher (p=0.001) than placebo and there was no significant difference in the patient's rank of the analgesic effect between the doses of rofecoxib. (Table 18).

The analgesic effect of naproxen sodium was ranked significantly (p=0.001) higher than that of placebo. The rank of the analgesic effect between naproxen sodium and each of the rofecoxib doses was not significant. (Table 18).

Table 18
Analysis of Patient's Rank of Treatment Preference

Pairwise Comparison	N	Number (%) of Patients Favoring A vs. B	p- Value †
MK- 0966 vs. Placebo			
MK- 0966 25/ 25 mg vs. Placebo	113	74 (65.5)	0.001
MK- 0966 50/ 25 mg vs. Placebo	114	79 (69.3)	0.001
Comparison Between rofecoxib Doses			
rofecoxib 50/25 mg vs. 25/25 mg	113	55 (48.7)	0.778
Comparison With Naproxen Sodium			
Naproxen Sodium vs. Placebo	113	79 (69.9)	0.001
Naproxen Sodium vs. 25/ 25 mg	114	58 (50.9)	0.851
Naproxen Sodium vs. 50/ 25 mg	116	62 (53.5)	0.458

Peak Analgesic Effect During 8 Hours Postdose

The LSMean Peak PID scores for placebo, 25/25, 50/25 mg rofecoxib, and 550 mg naproxen sodium were 1.4, 1.8, 1.7, 1.8, respectively (Figure 5). The LSMean Peak Pain Relief scores for placebo, 25/25, 50/25 mg rofecoxib and 550 mg naproxen sodium were 2.3, 3.0, 2.9, 3.1, respectively (Figure 6).

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During the 8 hours postdose, rofecoxib doses demonstrated a significantly greater ($p<0.001$) Peak PID and Peak Pain Relief compared with placebo. The peak analgesic effects between the rofecoxib doses were not significantly different.

The Peak PID and Peak Pain Relief scores for naproxen sodium 550 mg were significantly ($p<0.001$) greater than placebo. The Peak PID and Peak Pain Relief scores for naproxen sodium 550 mg were not significantly different from rofecoxib 50 doses.

Figure 5

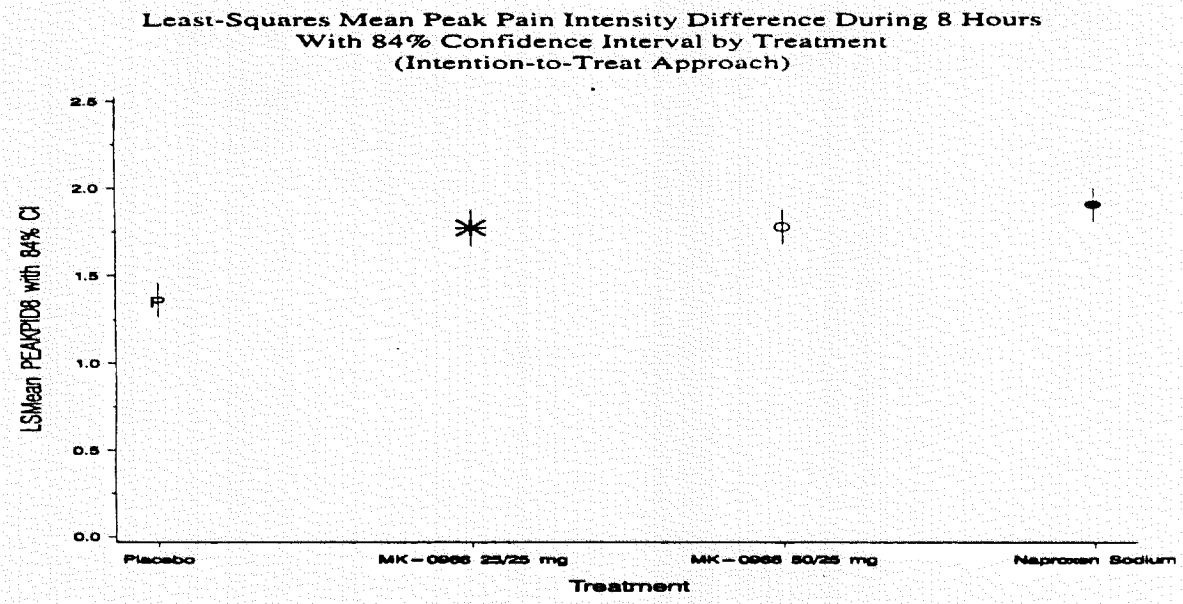
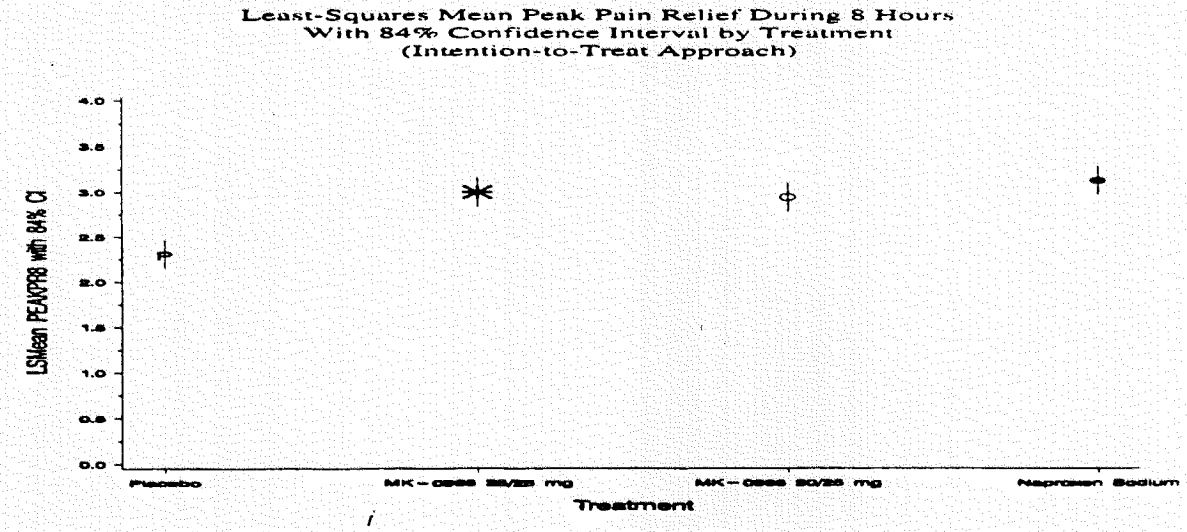


Figure 6



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Duration of Analgesic Effect

1) Time to Rescue Medication

The median Times to Rescue Medication (the time when 50% of the patients took rescue medication) could not be estimated for any of the treatments because less than 50% of patients took rescue medication after each treatment. The estimated 25th percentiles of the Time to Rescue Medication for placebo, 25/25, 50/25 mg rofecoxib, and naproxen sodium were 3.7, 8.2, 8.3, and 8.1 hours (Table 19).

Patients who received placebo took rescue medication significantly ($p \leq 0.005$) earlier compared with those who received rofecoxib. The difference between the rofecoxib doses was not significant. Patients who received naproxen sodium experienced significantly ($p=0.009$) longer times to rescue medication compared with those who received placebo. The difference between naproxen sodium and each of the doses of rofecoxib was not significant.

Table 19
Analysis of Time to Taking Rescue Medication
(Intention-to-Treat Approach)

Treatment	N	Number (% †) of Patients Taking Rescue Medication	Time (Hour) to Rescue Medication by Percentile		
			25th	Median-50th (95% CI)	75th
Placebo	118	53 (45.3)	3.7	NE	NE
MK- 0966 25/ 25 mg	115	31 (27.0)	8.2	NE	NE
MK- 0966 50/ 25 mg	118	32 (27.1)	8.3	NE	NE
Naproxen Sodium	122	36 (29.5)	8.1	NE	NE

	Cox Proportional Hazards Regression (Primary Analysis)		Log-Rank Test ‡
Pairwise Comparison	Risk Ratio (95% CI)	p- Value	p- Value
MK- 0966 25/ 25 mg vs. Placebo	0.53 (0.34, 0.82)	0.005 §	0.003
MK- 0966 50/ 25 mg vs. Placebo	0.52 (0.34, 0.81)	0.004 §	0.003
MK- 0966 50/ 25 mg vs. MK- 0966 25/ 25 mg	0.99 (0.61, 1.63)	0.977	0.997
Naproxen Sodium vs. Placebo	0.57 (0.37, 0.87)	0.009	0.006
Naproxen Sodium vs. 25/ 25 mg	1.08 (0.67, 1.74)	0.766	0.739
Naproxen Sodium vs. 50/ 25 mg	1.08 (0.67, 1.75)	0.741	0.760

Effect	p- Value	p-Value
Treatment	0.007	0.002
Stratum (Baseline Pain Intensity)	0.029	0.028
Treatment- by- Stratum Interaction	0.816	NA

† Kaplan-Meier estimate of incidence rate (This may be different from the crude rate).
‡ Secondary supportive results from non-parametric test.
§ Step-down test procedure vs. placebo.
NE: Not estimable. Percentile NE due to low percentage (<= x% for the x'th percentile).
NA: Not available from non-parametric log-rank.

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2) Percent of Patients Who Took Rescue Medication Within 12 Hours

Of the patients in the placebo, 25/25-, 50/25-mg rofecoxib, and 550-mg naproxen sodium treatments, 44.9, 27.0, 27.1, and 29.5% took rescue analgesia within 12 hours postdose, respectively. The Percent of Patients Who Took Rescue Medication Within 12 hours postdose was significantly ($p<0.001$) lower in the rofecoxib doses compared with placebo. The Percent of Patients Who Took Rescue Medication was not significantly different between the rofecoxib doses.

The difference in Percent of Patients Who Took Rescue Medication between placebo and 550 mg naproxen sodium was significant ($p=0.006$). The difference between each of the rofecoxib doses and naproxen sodium was not significant.

Analgesic Effect of Multiple Doses of Rofecoxib

No pain measurements have been carried out beyond 12 hours postdose. The analgesic effect of multiple doses of rofecoxib was assessed by the Percent of Patients Who Took Additional Dose of Study Medication, Patient's Total Additional Dose of Study Medication from 12 to 72 Hours Postdose and Patient's Global Evaluation at 72 hours. These assessments were restricted to only patients who did not take any rescue medication during each of the study periods.

1) Percent of Patients Who Took Additional Dose of Study Medication

There were 63, 80, 82, and 85 patients who did not take any rescue medication in the placebo, 25/25, 50/25 mg rofecoxib, and the naproxen sodium treatments. Among these patients, 44.4, 38.8, 40.2, and 41.2% took an additional dose of study medication within 12 to 72 hours postdose in the placebo, 25/25, 50/25 mg rofecoxib, and naproxen sodium treatments, respectively. There were no significant differences between the rofecoxib doses and placebo in the Percent of Patients Who Took Additional Dose of Study Medication. There was no significant difference between placebo and naproxen sodium and between each of the rofecoxib doses and naproxen sodium in the Percent of Patients Who Took Additional Dose of Study Medication.

Patient's Global Evaluation of Treatments at 72 Hours

Patient's Global Evaluations of Treatments at 72 hours were statistically better among the two rofecoxib doses compared to the placebo treatment group. Within rofecoxib treatment groups, the Patient's Global Evaluation at 72 hours was not statistically different between the two dose groups at any time. The Patient's Global Evaluation at 72 hours for naproxen sodium 550 mg was significantly ($p<0.001$) greater than placebo. The Patient's Global Evaluation at 72 hours for naproxen sodium 550 mg was not significantly different from rofecoxib 50 doses (Tables 20&21).

Table 20

Summary of Patient Global Evaluation Score at 72 Hours PostdosePatients Taking

Treatment	Total	Poor	Fair	Good	Very Good	Excellent
		N (%)	N (%)	N (%)	N (%)	N (%)
Placebo	65	12 (18.5)	15 (23.1)	12 (18.5)	20 (30.8)	6 (9.2)
MK- 0966 25/ 25 mg	83	7 (8.4)	14 (16.9)	21 (25.3)	28 (33.7)	13 (15.7)
MK- 0966 50/ 25 mg	85	4 (4.7)	13 (15.3)	23 (27.1)	33 (38.8)	12 (14.1)
Naproxen Sodium	85	4 (4.7)	11 (12.9)	23 (27.1)	34 (40.0)	13 (15.3)

Table 21

Analysis of Patients Global Evaluation at 72 Hours
(Intention-to-Treat Approach)

Treatment	N	Mean	SD	LSMean	95% CI for LSMean
Placebo	65	1.9	1.3	1.8	(1.6, 2.1)
MK- 0966 25/ 25 mg	83	2.3	1.2	2.3	(2.0, 2.5)
MK- 0966 50/ 25 mg	85	2.4	1.1	2.4	(2.2, 2.7)
Naproxen Sodium	85	2.5	1.1	2.4	(2.2, 2.7)

Pairwise Comparison	Difference in LSMeans	95% CI for Difference	p- Value
MK- 0966 25/ 25 mg vs. Placebo	0.5	(0.1, 0.8)	0.012
MK- 0966 50/ 25 mg vs. Placebo	0.6	(0.3, 1.0)	<0.001
MK- 0966 50/ 25 mg vs. 25/25 mg	0.2	(-0.2, 0.5)	0.308
Naproxen Sodium vs. Placebo	0.6	(0.3, 1.0)	<0.001
Naproxen Sodium vs. 25/ 25 mg	0.2	(-0.2, 0.5)	0.305
Naproxen Sodium vs. 50/ 25 mg	0.0	(-0.3, 0.3)	0.982

Effect	p- Value	Pooled Intra- Patient SD
Sequence	0.592	5.3
Patient (Sequence)	<0.001	
Period (Square)	0.516	
Treatment	<0.002	
Stratum (i. e., Baseline PI)	<0.121	
Carryover (i. e., Residual)	0.828	
Treatment- by- Stratum Interaction	0.272	

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Safety Results

The incidence of adverse experiences was generally similar across all treatments and was not significantly greater with rofecoxib 25 mg and 50 mg compared with placebo. Eleven, 13, 22, and 17% of patients in the placebo, rofecoxib 25 mg, rofecoxib 50 mg, and naproxen sodium 550-mg treatments, respectively, reported one or more adverse experiences.

Table 19
Clinical Adverse Experience Summary

	Placebo (N= 118)		Rofecoxib				Naproxen 550 mg (N=122)	
			25 mg (N=116)		50 mg (N= 119)			
	n	(%)	N	(%)	n	(%)	n	(%)
Number of patients evaluated	118		116		119		122	
Number (%) of patients:								
with one or more adverse experiences	13	(11.0)	15	(12.9)	26	(21.8)	21	(17.2)
with no adverse experience	105	(89.0)	101	(87.1)	93	(78.2)	101	(82.8)
with drug- related adverse experiences	4	(3.4)	7	(6.0)	13	(10.9)*	11	(9.0)
with serious adverse experiences †	2	(1.7)	0	(0.0)	0	(0.0)	1	(0.8)
with serious drug- related adverse experiences †	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	1	(0.8)	0	(0.0)	0	(0.0)	1	(0.8)
Discontinued due to drug-related adverse experiences †	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious adverse experiences	1	(0.8)	0	(0.0)	0	(0.0)	1	(0.8)
discontinued due to serious drug- related adverse experiences †	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

No significant differences between treatments were observed.
† Determined by the investigator to be possibly, probably, or definitely drug related.

Clinical Adverse Experiences by Body System

The incidence of adverse experiences in the digestive system was significantly greater ($p=0.012$) for rofecoxib 50 mg compared with both placebo and rofecoxib 25 mg, most of them were GI related. The incidence of adverse experiences in the other body systems was not significantly greater on rofecoxib compared with placebo and was generally similar across all treatments (Table 22).

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Table 22

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

	Placebo (N= 118)		Rofecoxib				Naproxen 550 mg (N=122)	
			25 mg (N=116)		50 mg (N= 119)			
	n	(%)	N	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	13	(11.0)	15	(12.9)	26	(21.8)	21	(17.2)
Patients with no adverse experience	105	(89.0)	101	(87.1)	93	(78.2)	101	(82.8)
Body as a whole/ site unspecified	1	(0.8)	4	(3.4)	6	(5.0)	7	(5.7)
Cardiovascular system	1	(0.8)	2	(1.7)	2	(1.7)	1	(0.8)
Digestive system	4	(3.4)	4	(3.4)	16	(13.4)*	8	(6.6)
Eyes, ears, nose, and throat	2	(1.7)	0	(0.0)	1	(0.8)	0	(0.0)
Endocrine system	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)
Metabolites and nutrition	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)
Musculoskeletal system	1	(0.8)	1	(0.9)	0	(0.0)	1	(0.8)
Nervous and psychiatric	0	(0.0)	3	(2.6)	2	(1.7)	4	(3.3)
Psychiatric disorder	1	(0.8)	2	(1.7)	2	(1.7)	4	(3.3)
Respiratory system	1	(0.8)	0	(0.0)	0	(0.0)	2	(1.6)
Skin and skin appendages	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.8)
Urogenital system	4	(3.4)	3	(2.6)	4	(3.4)	4	(3.3)

* p<0.05 vs. placebo.

The incidence of drug-related adverse experiences was 3, 6, 11, and 9% for placebo, rofecoxib 25 mg, rofecoxib 50 mg, and naproxen sodium 550 mg, respectively. The incidence of drug-related adverse experiences was significantly greater (p=0.049) for rofecoxib 50 mg compared with placebo. This was primarily due to a borderline significant (p=0.092) increased incidence of drug-related adverse experiences seen the in the digestive system with rofecoxib 50 mg to include: diarrhea, digestive gas symptoms, dyspepsia, gastric disorder, nausea, and rectal disorder (Table 23). The 12 drug-related digestive system adverse events in 50 mg rofecoxib occurred in 10 different patients; 1 patient (AN 1070) had both nausea and dyspepsia and a second patient (AN 1120) had both dyspepsia and rectal disorder (rectal cramping). No patient had reported a history of a similar adverse experience at the screening visit. The incidence of drug-related adverse experiences in the other body systems was not significantly greater in the rofecoxib treatments compared with placebo and was generally similar across all treatments.

Pregnancies occurred in 3 (2.4%) of 127 patients. Two of the pregnancies occurred in patients assigned to placebo and one occurred in a patient assigned to naproxen sodium 550 mg. All three pregnancies were electively terminated.

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Table 23
Number (%) of Patients With Clinical Adverse Experiences
(Incidence ≥2.0% in One or More Treatments)
Digestive System

	Placebo (N= 118)		MK- 0966 25 mg (N= 116)		MK- 0966 50 mg (N= 119)		Naproxen Sodium 550 mg (N= 122)	
	n	(%)	n	(%)	n	(%)	n	(%)
Digestive System	4	(3.4)	4	(3.4)	16	(13.4)*	8	(6.6)
Dental caries	0	(0.0)	0	(0.0)	3	(2.5)	0	(0.0)
Diarrhea	2	(1.7)	0	(0.0)	3	(2.5)	0	(0.0)
Dry mouth	2	(1.7)	1	(0.9)	0	(0.0)	3	(2.5)
Dyspepsia	0	(0.0)	0	(0.0)	3	(2.5)	0	(0.0)
Nausea	1	(0.8)	0	(0.0)	4	(3.4)	5	(4.1)

* $p<0.05$ vs. placebo.

Adverse Experiences—Laboratory

There were no serious laboratory adverse experiences.

Discussion and Overall Conclusions for Study # 055

For this study, the initial dose of rofecoxib was either 25 or 50 mg. Rofecoxib at both doses demonstrated a significantly greater analgesic effect compared to placebo in most measures of analgesic effect derived from pain intensity and pain relief scores following the first dose administration and up to 12 hours. Onset of analgesia was observed at 2 hours post dose and it seems that efficacy has been sustained for 12 hours. The active comparator Naproxin Sodium 550 mg showed onset of analgesia at 1 hour (statistically significant compare to placebo) and numerically (but not statistically significantly) better analgesia at 1 and 1.5 hours postdose compared to rofecoxib.

Unfortunately, no pain measurements have been done beyond 12 hours. Not well-validated surrogate markers such as percent of patients who took additional dose of study medication were used resulting in not establishing any statistical differentiation from placebo for the multiple-dose administration of the drug (as well as the naproxen) over several days. Therefor, the sponsor's statement that "Additional studies of more prolonged pain will be necessary to further evaluate repeated dosing with rofecoxib" is definitely correct.

Rofecoxib 50 mg as the initial dose followed by 25 mg daily as needed was associated with greater incidences, which were statistically significant, of overall drug-related adverse experiences and adverse experiences in the digestive system. These adverse experiences included nausea, and dyspepsia. These adverse experiences were mild to moderate in severity and self-limited and therefore no safety conclusions can be drawn from this short-term acute pain model. More safety data should be available after reviewing the longer-term OA studies included in this submission.

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Study Number: P072

Study Dates: 12 November 1997 – 23 April 1998

Title of Study: A Phase III, Randomized, Active-Comparator (naproxen) and Placebo-Controlled Trial of the Efficacy of 50 mg of rofecoxib in the Treatment of Post Orthopedic Surgery Pain.

Investigator and Location: Nine clinical centers in the United States.

Objectives:

- To determine the analgesic effect of a single oral dose of 50 mg rofecoxib compared with that of naproxen sodium 550 mg in the treatment of postorthopedic surgical pain.

- To characterize the efficacy of 2 multiple-dose regimens of rofecoxib in the treatment of postorthopedic surgical pain: (a) a 50-mg initial dose followed by 25 mg each day and (b) a 50-mg initial dose followed by 50 mg each day.

Eligibility:

1) Patient was male or female and ≥18 years of age. Female patients demonstrated a serum β-hCG consistent with a nongravid state at the prestudy visit and agreed to remain abstinent, use oral contraceptives, or use double-barrier contraception (partner using condom and patient using diaphragm, contraceptive sponge, intrauterine device [IUD], or spermicidal foam/jelly) from the prestudy visit until 14 days after the last dose of study therapy. Women who were postmenopausal or status posthysterectomy or tubal ligation were exempt from this requirement.
2) Patient was scheduled to have major orthopedic surgery defined as either a total hip replacement, a total knee replacement, or a fracture repair with open reduction and internal fixation.
3) Patient was judged to be in otherwise good health based on medical history, physical examination, and routine laboratory tests. Patients with chronic health conditions must have been stable.
4) Patient understood the study procedures and agreed to participate in the study by giving written informed consent.
5) Patient was experiencing moderate to severe pain following the discontinuation of the patient-controlled intravenous analgesia (PCA) pump or epidural used to control postoperative pain and required treatment with an analgesic agent.
6) Patient was able to tolerate food and oral medication. Patients must have taken liquids and/or solids without vomiting at least 1 hour prior to dosing.
7) Patient completed surgery within 72 hours of study drug administration.

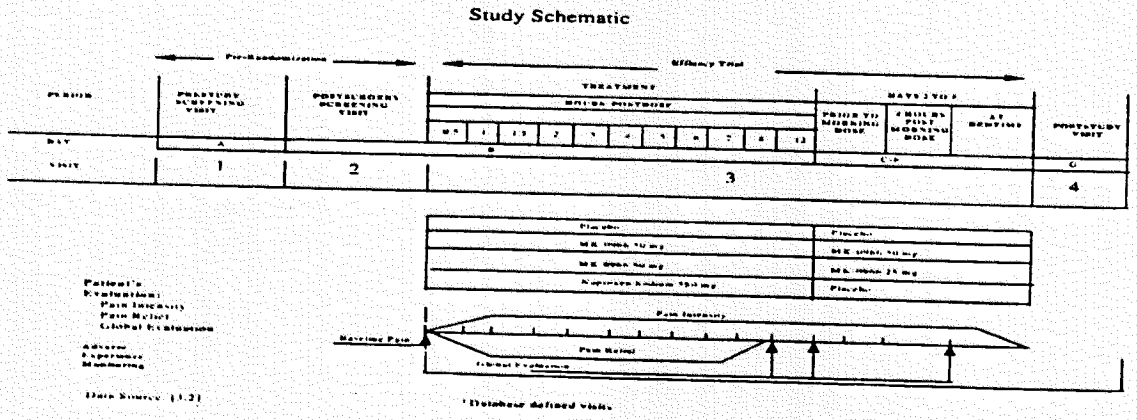
Exclusions:

1) Patient was under the age of legal consent, was mentally or legally incapacitated, had significant emotional problems at the time of the study, or had a history of psychiatric disorders.
2) Patient was allergic to naproxen sodium, aspirin, ibuprofen, indomethacin, or other NSAIDs or had a history of asthma in association with nasal polyps. Patient was intolerant to naproxen sodium. Patient was allergic or intolerant to hydrocodone bitartrate, or acetaminophen.
3) Patient had morbid obesity and demonstrated significant health problems stemming from their obesity.
4) Patient had a history of a significant clinical or laboratory adverse event that, in the opinion of the investigator, contraindicated multiple-dose therapy with an NSAID such as naproxen sodium.
5) Patient had clinically significant abnormalities of prestudy clinical examination or laboratory safety tests.
6) Patient had a recent history (within 5 years) of chronic analgesic, narcotic, or tranquilizer abuse or dependence.
7) Patient had donated a unit of blood or plasma or participated in another investigational drug study within the last 4 weeks.

Study Description

This was a multicenter, Phase III, double-blind, parallel-group study to evaluate the efficacy, safety, and tolerability of rofecoxib in the treatment of patients experiencing moderate to severe postorthopedic surgical pain. Patients were allocated to one of the following groups: rofecoxib 50 mg followed by 50 mg daily for 4 additional days, rofecoxib 50 mg followed by 25 mg daily for 4 additional days, naproxen sodium 550 mg followed by placebo for 4 additional days, or placebo followed by placebo for 4 additional days (Figure 1).

Figure 1: Schedule of Observations and Procedures



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Treatments Administered (Tables 1):

Study Medication	Formulation No.
MK- 0966	
50 mg †	MR- 3415
25 mg ‡	MR- 3415
Placebo X §	MR- 3416
Naproxen sodium	
550 mg	MR- 3478
Placebo Y %	MR- 3479

† The 50-mg dose consisted of two 25-mg tablets.
§ Placebo X was in the image of the 25-mg tablet.
% Placebo Y was in the image of the 550-mg naproxen sodium tablet.

Study Design:

Prestudy (Screening) Visit (Visit 1)
Patients were required to satisfy inclusion/exclusion criteria at the prestudy screening visit (Visit 1).

Postsurgery Screening Visit (Visit 2)
At Visit 2, patients who satisfied inclusion/exclusion criteria were randomized. Allocation was done by a computer-generated schedule. Specific allocation ranges existed for hip versus knee/fracture. Within a given allocation range, patients with moderate pain were assigned to the lowest remaining allocation number in the allocation schedule while patients with severe pain were assigned to the highest remaining allocation number.

Patients were administered a single dose of randomly assigned study drug (50 mg rofecoxib, 550 mg naproxen sodium, or placebo). The patients remained in the study unit for at least the ensuing 8 hours. Patients continued to take study drug once daily for the next 4 days. (Patients who received 50 mg rofecoxib on Day 1 received either 25 or 50 mg rofecoxib on Days 2 to 5). After the 5-day study period, patients returned to the study center within 14 days of the final dose of study medication for postsurgical and safety evaluations.

Rescue Medication for Pain:

During the 8-hour postdose period, LORTAB 7.5™ was administered as "rescue analgesia" (1 tablet every 4 to 6 hours as needed), if the patient experienced inadequate pain relief with study medication. Patients were asked to avoid using rescue analgesia during the first 60 minutes postdose. The time the rescue analgesia was used during the 8-hour post-first dose study period was recorded. In the event patients experienced inadequate pain relief during the remainder of the 5-day study period, they received additional doses of LORTAB 7.5™ as needed. The time at which additional doses of LORTAB 7.5™ were taken was recorded.

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Efficacy Assessment:

The patient recorded specific assessments of Pain Relief, Pain Intensity, and overall Global Evaluation of the study drug.

1) Ratings of Pain Intensity and Pain Relief
The following assessments were done at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, and 12 hours postdose as well as at prior to morning dose, 4 hours post morning dose and at bedtime of days 2 to 5 post initial dosing:

1. Pain Intensity (none = 0, severe = 3)
2. Pain Relief (none = 0, complete = 4)

2) Time to Confirmed Perceptible Pain Relief (Stopwatch)
The two-stopwatch technique was used to record time to perceptible and time to meaningful pain relief.

3) Time of Rescue Medication or Additional Doses of Study Medication
Patients were instructed to ask the study coordinator for additional medication, as needed, while in the study center. The date and time that rescue medication was taken was recorded by the patient in their diary. If additional medication was taken, the date and time of the supplemental rescue medication was recorded by the patient in their diary.

4) Patient's Global Evaluation
At 8 and 12 hours post first dose and every evening (at bedtime) on Days 2 to 5, or at the time the patient took rescue medication, the patient answered the following question in the diary:
"How would you rate the study medication you received for pain?"
"POOR," "FAIR," "GOOD," "VERY GOOD," or "EXCELLENT."

Statistical Analysis

All patients who took study medication, recorded a baseline pain intensity score of moderate or severe, and recorded at least one pain evaluation postdose were included in the efficacy analysis. An intention-to-treat analysis was performed based on this patient population and considered the primary analysis.

The missing pain assessment values after rescue medication were replaced with the last postdose datum available prior to the time point of interest (LOCF) as directed by the protocol and the statistical DAP, however, in response to the reviewer's request the sponsor also analyzed the data using the baseline observation carried forward (BOCF) technique.

A listing of statistical analyses performed on efficacy (primary and other end points as defined by the sponsor) and safety end points is in Table 2.