Total of Pain Relief Scores to 8 Hours (TOPAR8)

Figure 3 shows a plot of the mean Pain Relief score versus hours postdose. The TOPAR8, was an estimate of the area under the Pain Relief versus time curve during the first 8 hours postdose.

The least-squares mean (LSMean) TOPAR8 scores in patients who received placebo, 50, 100, 200 mg rofecoxib, or 400 mg ibuprofen were 5.2, 15.2, 19.2, 20.3, and 12.4 units, respectively (Table 9).

Over the 8 hours postdose, all rofecoxib treatment groups produced significantly ($p \leq 0.001$) greater TOPAR8 values compared with the placebo group (Table 9).

TOPAR8 values increased with rising doses of rofecoxib. The 100- and 200-mg treatment groups produced mean TOPAR8 values significantly greater than those of the 50-mg group ($p \leq 0.05$). The difference in TOPAR8 between the 100- and the 200-mg groups was not significant ($p=0.527$) (Table 9).

The mean TOPAR8 score in the 400-mg ibuprofen group was significantly greater than that for the placebo group, but not significantly different from the rofecoxib 50-mg group. The rofecoxib 100- and 200-mg doses demonstrated significantly greater responses than ibuprofen ($p<0.001$) (Table 9).

Table 9
Analysis of Total Pain Relief Score Over 8 Hours (TOPAR8)
(Intention-to-Treat Approach)

Treatment	N	Mean	SD	LSMean	95% CI for LSMean
Placebo 50		5.2	6.2	5.2	(2.8, 7.7)
rofecoxib 50 mg	50	15.0	10.3	15.2	(12.7, 17.6)
rofecoxib 100 mg	52	19.1	8.3	19.2	(16.8, 21.6)
rofecoxib 200 mg	50	20.2	9.9	20.3	(17.8, 22.7)
Ibuprofen 400 mg	52	12.3	8.7	12.4	(10.0, 14.8)

Pairwise Comparison	Difference in LSMeans	95% CI for Difference	p- Value
rofecoxib vs. Placebo			
rofecoxib 50 mg vs. Placebo	9.9	(6.5, 13.4)	<0.001 †
rofecoxib 100 mg vs. Placebo	13.9	(10.5, 17.3)	<0.001 †
rofecoxib 200 mg vs. Placebo	15.0	(11.6, 18.5)	<0.001 †
Between rofecoxib Doses			
rofecoxib 100 mg vs. 50 mg	4.0	(0.6, 7.4)	0.035 ‡
rofecoxib 200 mg vs. 50 mg	5.1	(1.7, 8.6)	0.015 ‡
rofecoxib 200 mg vs. 100 mg	1.1	(- 2.3, 4.5)	0.527
With Ibuprofen 400 mg			
Ibuprofen 400 mg vs. Placebo	7.2	(3.7, 10.6)	<0.001
Ibuprofen 400 mg vs. 50 mg	-2.7	(- 6.2, 0.7)	0.114
Ibuprofen 400 mg vs. 100 mg	-6.8	(- 10.1, -3.4)	<0.001
Ibuprofen 400 mg vs. 200 mg	-7.9	(- 11.3 -4.4)	<0.001

† Step- down trend test procedure vs. placebo.
‡ Step- down trend test procedure vs. rofecoxib 50 mg.

Sum of Pain Intensity Difference to 8 Hours (SPID8)

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, 50, 100, and 200 mg rofecoxib, and 400 mg ibuprofen were 0.8, 7.6, 10.5, 11.6, and 6.5 units, respectively (Table 10).

Over the 8 hours postdose, all rofecoxib treatment groups had significantly ($p<0.001$) greater SPID8 values compared with the placebo group (Table 10).

The SPID8 scores of the 100- and 200-mg groups were significantly greater than the 50-mg group ($p\leq0.023$). The difference between the 100- and 200-mg groups was not significant (Table 10).

The mean SPID8 score in the 400-mg ibuprofen group was significantly ($p<0.001$) greater than that for the placebo group but not significantly different from the rofecoxib 50-mg group. However, the rofecoxib 100- and 200-mg doses demonstrated significantly greater responses than ibuprofen ($p<0.001$) (Table 10).

Table 10
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	50	0.7	5.8	0.8	(- 0.9, 2.5)
rofecoxib 50 mg	50	7.1	8.9	7.6	(5.9, 9.3)
rofecoxib 100 mg	52	10.1	6.5	10.5	(8.9, 12.2)
rofecoxib 200 mg	50	11.1	7.3	11.6	(9.9, 13.3)
Ibuprofen 400 mg	52	6.0	7.0	6.5	(4.8, 8.1)

Pairwise Comparison	Difference in LSMeans	95% CI for Difference	p- Value
rofecoxib vs. Placebo			
rofecoxib 50 mg vs. Placebo	6.8	(4.4, 9.2)	<0.001 †
rofecoxib 100 mg vs. Placebo	9.7	(7.3, 12.1)	<0.001 †
rofecoxib 200 mg vs. Placebo	10.7	(8.3, 13.1)	<0.001 †
Between rofecoxib Doses			
rofecoxib 100 mg vs. 50 mg	2.9	(0.6, 5.3)	0.023 ‡
rofecoxib 200 mg vs. 50 mg	4.0	(1.6, 6.4)	0.005 ‡
rofecoxib 200 mg vs. 100 mg	1.0	(- 1.4, 3.4)	0.399
With Ibuprofen 400 mg			
Ibuprofen 400 mg vs. Placebo	5.7	(3.3, 8.0)	<0.001
Ibuprofen 400 mg vs. 50 mg	-1.1	(- 3.5, 1.3)	0.360
Ibuprofen 400 mg vs. 100 mg	-4.1	(- 6.4, -1.7)	<0.001
Ibuprofen 400 mg vs. 200 mg	-5.1	(- 7.5, -2.7)	<0.001

† Step- down trend test procedure vs. placebo.
‡ Step- down trend test procedure vs. rofecoxib 50 mg.

Patient's Global Evaluation at 8 Hours

The LSMean scores for Patient's Global Evaluation at 8 hours in the placebo, rofecoxib 50-, 100-, 200-mg, and 400-mg ibuprofen groups were 0.4, 1.8, 2.7, 2.7, and 2.0, respectively (Table 11).

Over 8 hours postdose, all rofecoxib treatment groups had significantly ($p<0.001$) greater Patient's Global Evaluation scores compared with the placebo group (Table 11).

At 8 hours, the 100- and 200-mg treatment groups demonstrated significantly ($p\leq0.002$) greater Patient's Global Evaluation scores compared with the 50-mg group. The difference between the 100- and 200-mg groups did not reach significance (Table 11).

The mean Patient's Global Evaluation score at 8 hours in the 400-mg ibuprofen group was significantly ($p<0.001$) greater than that for the placebo group, but not significantly different from the rofecoxib 50-mg group. However, the rofecoxib 100- and 200-mg doses demonstrated significantly greater responses than ibuprofen ($p=0.003$) (Table 11).

Table 11
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	50	0.4	0.9	0.4	(0.1, 0.8)
rofecoxib 50 mg	50	1.8	1.4	1.8	(1.5, 2.1)
rofecoxib 100 mg	52	2.7	1.1	2.7	(2.4, 3.0)
rofecoxib 200 mg	50	2.7	1.3	2.7	(2.4, 3.0)
Ibuprofen 400 mg	52	2.0	1.3	2.0	(1.7, 2.3)

Pairwise Comparison	Difference in LSMeans	95% CI for Difference	p- Value
rofecoxib vs. Placebo			
rofecoxib 50 mg vs. Placebo	1.4	(0.9, 1.8)	<0.001 †
rofecoxib 100 mg vs. Placebo	2.3	(1.8, 2.7)	<0.001 †
rofecoxib 200 mg vs. Placebo	2.3	(1.8, 2.7)	<0.001 †
Between rofecoxib Doses			
rofecoxib 100 mg vs. 50 mg	0.9	(0.4, 1.4)	<0.001 ‡
rofecoxib 200 mg vs. 50 mg	0.9	(0.4, 1.4)	0.002 ‡
rofecoxib 200 mg vs. 100 mg	0.0	(- 0.5, 0.5)	0.973
With Ibuprofen 400 mg			
Ibuprofen 400 mg vs. Placebo	1.5	(1.1, 2.0)	<0.001
Ibuprofen 400 mg vs. 50 mg	0.2	(- 0.3, 0.6)	0.450
Ibuprofen 400 mg vs. 100 mg	-0.7	(- 1.2, -0.2)	0.003
Ibuprofen 400 mg vs. 200 mg	-0.7	(- 1.2, -0.3)	0.003

† Step- down trend test procedure vs. placebo.
‡ Step- down trend test procedure vs. rofecoxib 50 mg.

Time to Confirmed Perceptible Pain Relief (Stopwatch Time of Perceptible Pain Relief, Confirmed by the Second Stopwatch)

There were 24.0, 74.0, 86.5, 82.0, and 67.3% of patients who experienced onset of Confirmed Perceptible Pain Relief in the placebo, rofecoxib 50-, 100-, 200-mg, and ibuprofen 400-mg groups, respectively.

The median Times to Confirmed Perceptible Pain Relief (estimated time when 50% of patients experienced Confirmed Perceptible Pain Relief) for patients in the rofecoxib 50-, 100-, 200-mg and ibuprofen 400-mg groups were 0.7, 0.8, 0.5, and 0.7 hours, respectively. The median time for the placebo could not be estimated due to the low percentage (<50% for the 50th percentile) of patients who experienced Confirmed Perceptible Pain Relief.

Compared with the placebo group, the Confirmed Perceptible Pain Relief was significantly ($p<0.001$) more rapid in all rofecoxib treatment groups (Table 12).

The Time to Confirmed Perceptible Pain Relief was not significantly different among the rofecoxib doses. The difference between 50 and 200 mg approached significance ($p=0.063$) (Table 12).

The Time to Confirmed Perceptible Pain Relief for the ibuprofen group was significantly ($p<0.001$) shorter compared with the time for the placebo. However, the difference between ibuprofen and rofecoxib 50 or 100 mg was not significant. Only the difference between ibuprofen and rofecoxib 200 mg approached significance ($p=0.057$) (Table 12).

Table 12

Analysis of Time to Confirmed Perceptible Pain Relief (Stopwatch Time to Perceptible Pain Relief, Confirmed by the Second Stopwatch)
(Intention-to-Treat Approach)

Treatment	N	Number (% †) of Patients Confirmed Perceptible Pain Relief	Time (Hour) to Confirmed PerceptiblePain Relief by Percentile		
			25th	Median-50th (95% CI)	75th
Placebo	50	12 (24.0)	NE	NE	NE
rofecoxib 50 mg	50	37 (74.0)	0.5	0.7 (0.5, 1.0)	NE
rofecoxib 100 mg	52	45 (86.5)	0.4	0.8 (0.5, 0.9)	1.1
rofecoxib 200 mg	50	41 (82.0)	0.4	0.5 (0.4, 0.6)	1.0
Ibuprofen 400 mg	52	35 (67.3)	0.4	0.7 (0.5, 1.0)	NE

Pairwise Comparison	Cox Proportional Hazards Regression (Primary Analysis)		Log-Rank Test ‡
	Risk Ratio (95% CI)	p- Value	p- Value
rofecoxib vs. Placebo			
rofecoxib 50 mg vs. Placebo	4.13 (2.15, 7.93)	<0.001 §	<0.001
rofecoxib 100 mg vs. Placebo	5.25 (2.77, 9.97)	<0.001 §	<0.001
rofecoxib 200 mg vs. Placebo	6.31 (3.30, 12.05)	<0.001 §	<0.001
Between rofecoxib Doses			
rofecoxib 100 mg vs. 50 mg	1.27 (0.82, 1.97)	0.279 %	0.202
rofecoxib 200 mg vs. 50 mg	1.53 (0.98, 2.39)	0.063 %	0.089
rofecoxib 200 mg vs. 100 mg	1.20 (0.79, 1.84)	0.397	0.413
With Ibuprofen 400 mg			
Ibuprofen 400 mg vs. Placebo	4.06 (2.11, 7.84)	<0.001	<0.001
Ibuprofen 400 mg vs. 50 mg	0.98 (0.62, 1.56)	0.947	0.794
Ibuprofen 400 mg vs. 100 mg	0.77 (0.50, 1.21)	0.257	0.190
Ibuprofen 400 mg vs. 200 mg	0.64 (0.41, 1.01)	0.057	0.072

Effect	p- Value	p-Value
Treatment	<0.001	<0.001
Stratum (Baseline Pain Intensity)	0.058	0.053
Treatment- by- Stratum Interaction	0.865	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.
%Step-down test procedure vs. rofecoxib 50 mg.
NE: Not estimable. Percentile NE due to low percentage (x% for the x'th percentile).
NA: Not available from non-parametric log-rank test.

Peak Analgesic Effect During 8 Hours Postdose

During the 8 hours postdose, all rofecoxib treatment groups demonstrated a significantly ($p<0.001$) greater peak PID and peak Pain Relief compared with the placebo group (Figures 5 and 6).

The order of numerical responses for both peak PID and peak Pain Relief was increasing with rofecoxib dose. The difference between 50-mg and 100-mg doses of rofecoxib in both peak PID and peak Pain Relief approached significance ($p=0.068$ and $p=0.057$). The difference between the 50-mg and 200-mg doses was significant for peak PID ($p=0.036$) but only approached significance in peak Pain Relief ($p=0.084$). rofecoxib 100- and 200-mg groups were not significantly different from each other in both end points.

The numerical responses for the ibuprofen group and rofecoxib 50-mg group were similar for both end points. For both peak PID and Pain Relief scores, compared with placebo, ibuprofen demonstrated significantly greater response ($p<0.001$). The comparisons with rofecoxib doses were similar for both end points: the difference between ibuprofen and the 50 mg was not significant, that between ibuprofen and the rofecoxib 100-mg group approached significance ($p=0.055$) for peak PID and was significant ($p=0.042$) for peak Pain Relief, and that between ibuprofen and the rofecoxib 200-mg group was significant ($p<0.05$) for both end points

Figure 5

Least-Squares Mean Peak PID During 8 Hours With 84% Confidence Interval by Treatment Group (Intention-to-Treat Approach)

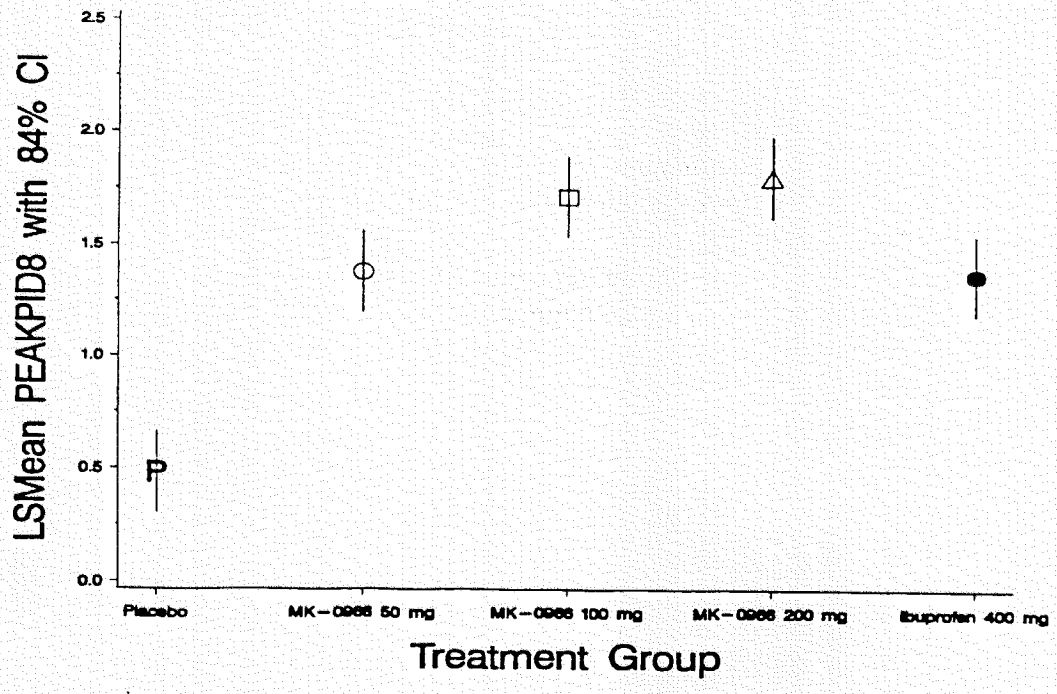
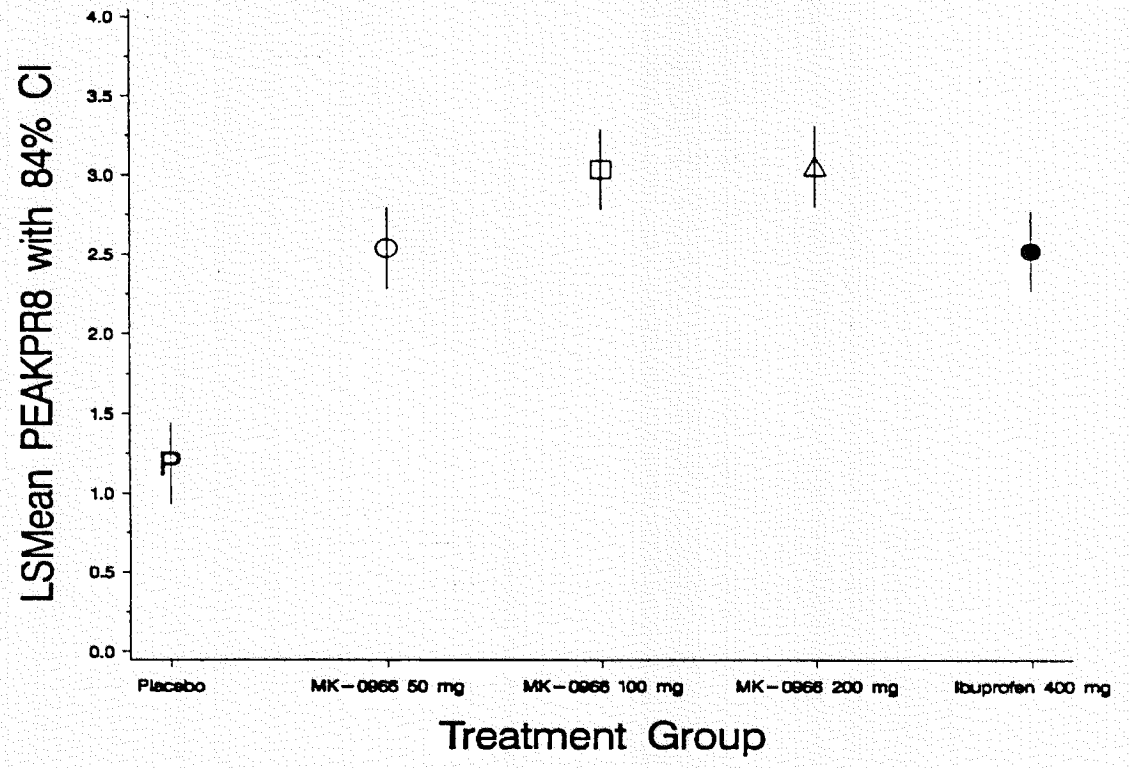


Figure 6

Least-Squares Mean Peak Pain Relief (PR) During 8 Hours With 84% Confidence Interval by Treatment Group (Intention-to-Treat Approach)



Duration of Analgesic Effect

1) Time to Rescue Medication

The median Times to Taking Rescue Medication were 1.6, 7.5, and 4.9 hours for placebo rofecoxib 50 mg and ibuprofen, respectively. The median times for rofecoxib 100 and 200 mg could not be estimated due to the low percentage (<50% for the 50th percentile) of patients who took rescue medication (Table 13).

Patients who received placebo took rescue medication significantly ($p<0.001$) earlier compared with those who received rofecoxib.

Patients who received the 50-mg dose took rescue medication significantly earlier compared with those who received 100 ($p=0.011$) or 200 mg ($p=0.015$). The difference between the 100- and 200-mg groups was not significant (Table 13).

Patients who received 400-mg ibuprofen experienced significantly longer times to taking rescue medication compared with those who received placebo ($p<0.001$). Patients in the ibuprofen group took rescue medication significantly ($p\leq 0.002$) earlier than those in each of the rofecoxib groups (Table 13).

Table 13
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 Treatment N		
			25th	Median-50th (95% CI)	75th
Placebo	50	49 (98.0)	1.5	1.6 (1.5, 2.0)	2.1
rofecoxib 50 mg	50	32 (64.0)	2.0	7.5 (4.1, 23.6)	NE
rofecoxib 100 mg	52	21 (40.4)	6.7	NE	NE
rofecoxib 200 mg	50	20 (40.0)	6.0	NE	NE
Ibuprofen 400 mg	52	48 (92.3)	2.0	4.9 (3.6, 6.1)	7.8

Pairwise Comparison	Cox Proportional Hazards Regression (Primary Analysis)		Log-Rank Test ‡
	Risk Ratio (95% CI)	p- Value	p- Value
rofecoxib vs. Placebo			
rofecoxib 50 mg vs. Placebo	0.22 (0.14, 0.36)	<0.001 §	<0.001
rofecoxib 100 mg vs. Placebo	0.11 (0.06, 0.19)	<0.001 §	<0.001
rofecoxib 200 mg vs. Placebo	0.11 (0.06, 0.19)	<0.001 §	<0.001
Between rofecoxib Doses			
rofecoxib 100 mg vs. 50 mg	0.49 (0.28, 0.85)	0.011 %	0.009
rofecoxib 200 mg vs. 50 mg	0.50 (0.29, 0.87)	0.015 %	0.015
rofecoxib 200 mg vs. 100 mg	1.02 (0.56, 1.89)	0.942	0.955
With Ibuprofen 400 mg			
Ibuprofen 400 mg vs. Placebo	0.44 (0.29, 0.66)	<0.001	<0.001
Ibuprofen 400 mg vs. 50 mg	1.97 (1.25, 3.10)	0.003	0.002
Ibuprofen 400 mg vs. 100 mg	4.04 (2.40, 6.81)	<0.001	<0.001
Ibuprofen 400 mg vs. 200 mg	3.95 (2.33, 6.72)	<0.001	<0.001

Effect	p- Value	p-Value
Treatment	<0.001	<0.001
Stratum (Baseline Pain Intensity)	0.652	0.727
Treatment- by- Stratum Interaction	0.471	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.
%Step-down test procedure vs. rofecoxib 50 mg.
NE: Not estimable. Percentile NE due to low percentage (x% for the x'th percentile).
NA: Not available from non-parametric log-rank test.

2) Percent of Patients Who Took Rescue Medication Within 24 Hours

Ninety-eight, 64.0, 40.4, 40.0, and 92.3% of patients took rescue medication within 24 hours of study drug in the placebo, 50-, 100-, 200-mg rofecoxib, and 400-mg ibuprofen groups, respectively.

The Percent of Patients Who Took Rescue Medication within 24 hours of study drug was significantly ($p \leq 0.002$) lower in the rofecoxib groups compared with the placebo group.

The Percent of Patients Who Took Rescue Medication in the 50-mg group was significantly higher than those in the 100- and 200-mg groups ($p \leq 0.018$). The difference between 100- and 200-mg doses was not significant.

The difference in Percent of Patients Who Took Rescue Medication between the placebo and ibuprofen was not significant. However, all rofecoxib groups had significantly lower percents taking rescue medication than the ibuprofen group ($p \leq 0.001$).

Safety Results

Clinical adverse experiences were reported by 102 (40%) of 254 randomized patients. The incidence of adverse experiences was generally similar across all treatment groups and was not significantly greater in rofecoxib groups compared with placebo. Fifty, 42, 40, 38, and 31% of patients in the placebo, 50-, 100-, and 200-mg rofecoxib, and ibuprofen groups, respectively, reported one or more adverse experiences. (Table 14).

Table 14
Clinical Adverse Experience Summary

		rofecoxib			
	Placebo (N= 50)	50 mg (N= 50)	100 mg (N=52)	200 mg (N=50)	Ibuprofen 400 mg (N= 51)
	n (%)	n (%)	n %	n %	n (%)
Number of patients evaluated	50	50	52	50	51
Number (%) of patients:					
with one or more adverse experiences	25 (50.0)	21 (42.0)	21 (40.4)	19 (38.0)	16 (30.8)
with no adverse experience	25 (50.0)	29 (58.0)	31 (59.6)	31 (62.0)	36 (69.2)
with drug- related adverse experiences †	12 (24.0)	8 (16.0)	13 (25.0)	7 (14.0)	9 (17.3)

No significant differences between treatment groups were observed.
† Determined by the investigator to be possibly, probably, or definitely drug related.
Although a patient may have had two or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

Clinical Adverse Experiences by Body System

The distribution of patients with clinical adverse experiences in each body system is in Table 15. Most of the adverse events were GI related.

Table 15

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

	Placebo (N= 50)		rofecoxib 50 mg (N= 50)		rofecoxib 100 mg (N= 52)		rofecoxib 200 mg (N= 50)		Ibuprofen 400 mg (N= 52)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	25	(50.0)	21	(42.0)	21	(40.4)	19	(38.0)	16	(30.8)
Patients with no adverse experience	25	(50.0)	29	(58.0)	31	(59.6)	31	(62.0)	36	(69.2)
Body as a whole/ site unspecified	8	(16.0)	4	(8.0)	4	(7.7)	3	(6.0)	4	(7.7)
Cardiovascular system	1	(2.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Digestive system	15	(30.0)	18	(36.0)	14	(26.9)	13	(26.0)	9	(17.3)
Eyes, ears, nose, and throat	3	(6.0)	3	(6.0)	1	(1.9)	1	(2.0)	0	(0.0)
Musculoskeletal system	0	(0.0)	1	(2.0)	1	(1.9)	0	(0.0)	0	(0.0)
Nervous and psychiatric	8	(16.0)	4	(8.0)	5	(9.6)	2	(4.0)	3	(5.8)
Psychiatric disorder	0	(0.0)	0	(0.0)	1	(1.9)	0	(0.0)	1	(1.9)
Skin and skin appendages	2	(4.0)	0	(0.0)	3	(5.8)	0	(0.0)	2	(3.8)
Urogenital system	0	(0.0)	1	(2.0)	1	(1.9)	0	(0.0)	0	(0.0)

No significant differences between treatment groups were observed.

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

The incidence of adverse experiences in each body system was not significantly greater in the rofecoxib treatment groups compared with the placebo group. The incidence of adverse experiences was generally similar across all treatment groups.

The incidence of drug-related adverse experiences was 24, 16, 25, 14, and 17% for the placebo, 50-, 100-, and 200-mg rofecoxib, and ibuprofen groups, respectively. The incidences of specific clinical adverse experiences were low and they were generally not dose related; the differences were not clinically meaningful.

No serious adverse events have been reported.

There were no patients who discontinued due to a clinical adverse experience.

Adverse Experiences—Laboratory

Of the 254 randomized patients, 248 had at least one laboratory test postrandomization. Laboratory adverse experiences were recorded for 6 (2%) of 248 randomized patients. The incidence of adverse experiences was not significantly greater in the rofecoxib treatment group compared with the placebo group. Two, 2, 4, 0, and 4% of patients in the placebo, 50-, 100-, and 200-mg rofecoxib, and ibuprofen groups, respectively, were reported with one or more laboratory adverse experiences with one or more laboratory adverse experiences.

There were no significant associations between treatment with rofecoxib and incidence of any specific laboratory adverse experiences.

No laboratory adverse experiences were considered serious.

No patient discontinued due to a laboratory adverse experience.

Discussion and Overall Conclusions for Study # 071

All doses of rofecoxib demonstrated significantly greater analgesic effect compared with placebo in all measures of analgesic effect (i.e., the overall, onset, peak, and duration of analgesic effects) in the treatment of postoperative dental pain.

The dose of 50 mg rofecoxib was significantly less effective on all end points of overall analgesic efficacy (PID, PR, PRID, TOPAR8, SPID8, and Patient's Global Evaluation) and on end points of duration of efficacy (Time to Rescue Medication) than the 100- and 200-mg rofecoxib doses. In addition, the peak analgesic effect of the 100- and 200-mg rofecoxib doses was nearly statistically significantly better than the dose of 50 mg. The onset of analgesia was generally similar amongst the 3 rofecoxib treatment groups. The 200-mg dose of rofecoxib was generally not distinguishable from the 100-mg dose of rofecoxib. Thus, in this study, the minimal dose of rofecoxib required to give maximal analgesic efficacy is 100 mg. This result contrasts to that of Protocol 027 in which doses of 7.5, 25, 50, and 100 mg of rofecoxib were compared. In that study, 50 mg rofecoxib was the minimal dose required to give maximal analgesic efficacy. This study and Protocol 027 were conducted by the same investigator at the same investigational site, but the formulations of rofecoxib used in the two studies were different. This study used the final Phase III, 12.5% formulation of rofecoxib, whereas Protocol 027 used the Phase II 25% formulation.

Ibuprofen 400 mg, an NSAID indicated for the relief of mild-to-moderate pain, was demonstrated to be superior to placebo for all analgesic end points and thus provided an active control that validated the study. The 50-mg dose of rofecoxib was generally similar to ibuprofen 400 mg in all measures of analgesic efficacy. The onset of analgesia for the rofecoxib 100- and 200-mg doses was generally similar to that of ibuprofen 400 mg. In contrast, the 100- and 200-mg doses of rofecoxib were superior to ibuprofen 400 mg on all measures of overall, peak, and duration of analgesic effect.

Rofecoxib 50 mg as well as 100 mg and 200 mg produced significantly longer duration of analgesic effect compared with ibuprofen 400 mg, as measured by the Time to Rescue Medication, the Percent of Patients Taking Rescue Medication, and the Pain Relief, PID, and PRID scores evaluated at later time points. However, in this study (like most dental pain studies) only small number of patients remained at these later time points to be evaluated.

Rofecoxib was generally well tolerated. The incidence of clinical and laboratory adverse experiences was generally similar across all treatment groups.

Study Number: P055

Study Dates: 27 August 1997 – 18 March 1998

Title of Study: A Randomized, Placebo- and Active-Comparator-Controlled Trial of the Effect of 50 mg of rofecoxib in the Treatment of Primary Dysmenorrhea.

Investigator and Location: Two centers, United States:

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   2121 North Robins Drive Layton,
   UT 84041
2. Woolsey, Carl T, M. D.
   [redacted]
   Salt Lake City, UT 84124

Objectives:

1) To confirm the efficacy of single oral doses of rofecoxib 50-mg tablets compared with that of naproxen sodium 550 mg and placebo in the treatment of pain due to primary dysmenorrhea.
2) To determine the peak, time to onset, and duration of analgesic effects of rofecoxib 50 mg and naproxen sodium 550 mg compared with those of placebo in the treatment of pain due to primary dysmenorrhea.
3) To characterize the efficacy of rofecoxib in the treatment of moderate-to-severe abdominal cramping pain due to primary dysmenorrhea when administered in repeated doses throughout a given menstrual cycle.

Eligibility:

1) Patients were female and ≥18 years of age. Patients demonstrated a serum β-HCG consistent with a nongravid state at the prestudy visit and agreed to remain abstinent or use double-barrier contraception (partner using condom and patient using diaphragm, contraceptive sponge, or spermicidal foam/jelly) throughout the study. Patients who were status posttubal ligation were exempt from this requirement.

2) Patients must have had, by their own report, moderate or severe primary dysmenorrhea with cramping abdominal pain during a minimum of 4 of the previous 6 menstrual cycles. Moderate: Over-the-counter analgesics provided significant relief in most cycles; discomfort interfered with usual activity. Severe: Over-the-counter analgesics not consistently effective or prescription analgesics required in at least some cycles; discomfort was incapacitating, causing an inability to work or perform usual activities.

3) Patient must have had a complete gynecological examination within 1 year prior to entering the study.

4) Patient was willing to avoid excess alcohol or unaccustomed strenuous physical activity (e.g., unaccustomed weight lifting, running, bicycling) for the duration of the study and follow-up period.

5) Patient was not morbidly obese.

6) Patient was judged to be in otherwise good health based on medical history, physical examination, and routine laboratory tests.

7) Patient understood the study procedures and agreed to participate in thestudy by giving written informed consent.

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 used concurrent therapy that could have interfered with the evaluation of efficacy, safety, or tolerability:

- Any analgesic, aspirin, acetaminophen, or ibuprofen (prescription or nonprescription) must be discontinued 24 hours prior to taking study medication.
- Other agents, including tricyclic antidepressants, narcotic analgesics, tranquilizers, hypnotics, sedatives, corticosteroids, or other therapy that, in the opinion of the investigator and agreed upon by the Merck monitor, may have confounded evaluation of patient safety or efficacy. Antihistamines, including terfenadine, loratadine, or diphenhydramine, must have been discontinued 48 hours prior to taking study drug; astemizole was excluded from use during the study.
- Oral contraceptives.
- Implantation of the NORPLANT™ (levonorgestrel implants, Wyeth-Ayerst Laboratories, PA U.S.A.) system within the preceding 3 months.

3) Patient had any of the following conditions or diseases:

- Evidence or suspicion of the presence of disease or abnormality of the reproductive organs.
- The use of an intrauterine device.
- Pregnancy, breast feeding, or was <6 weeks postpartum.

4) Patient had a history of a significant clinical or laboratory adverse experience that in the opinion of the investigator contraindicated single-dose therapy with an NSAID such as ibuprofen.

5) Patient had uncontrolled hypertension, uncontrolled diabetes mellitus, renal disease, stroke or neurological disorder, cardiovascular, hepatic or neoplastic disease (patients with adequately treated skin cancer or carcinoma in situ of the cervix were allowed to participate), or a history of any illness that, in the opinion of the investigator, might have confounded the results of the study or pose additional risk to the patient.

6) Patient had any personal or family history of an inherited bleeding disorder.

7) Patient had clinically significant abnormalities of prestudy clinical examination or laboratory safety tests. As a guide, the following values would generally be considered clinically significant: Hgb <11 g/dL, WBC <3500/cc, platelets <100,000/cc, AST >1.5x upper limit of normal (ULN), ALT >1.5 x ULN, bilirubin >1.5 x ULN, alkaline phosphatase >1.5 x ULN, creatinine >2.0 mg/dL.

8) Patient was allergic to naproxen sodium, aspirin, ibuprofen, indomethacin, or other NSAIDs or had a history of asthma in association with nasal polyps.

9) Patients with a recent history (within 5 years) of chronic analgesic or tranquilizer use or dependence.

10) Patient was, at the time of the study, a user (including "recreational use") of any illicit drugs or had a history (<5 years) of drug or alcohol abuse.

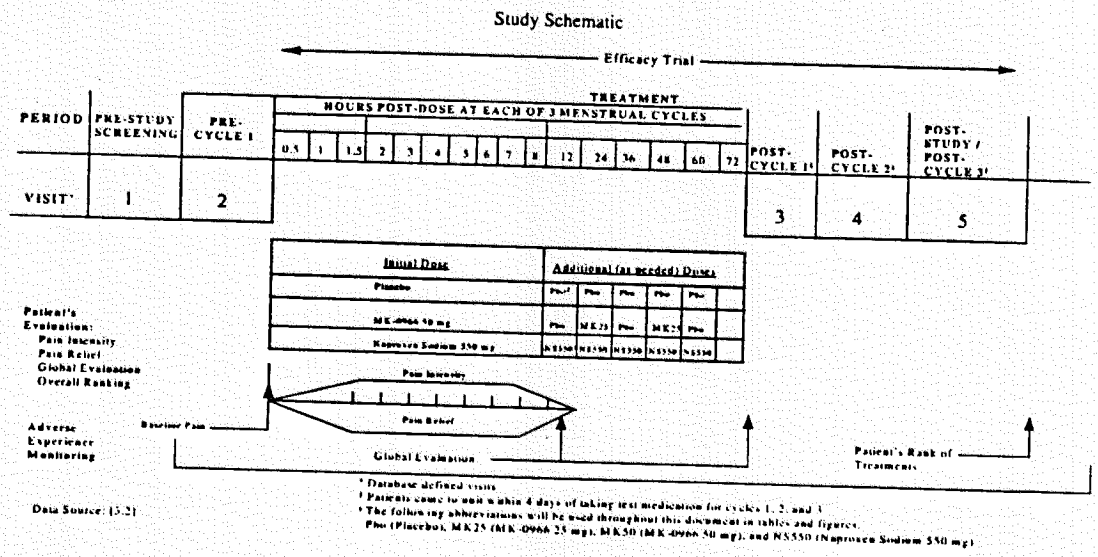
11) Patient had donated a unit of blood or plasma or participated in another clinical study within the last 4 weeks.

12) Patient had been in a previous study with rofecoxib.

Study Description

This was a multicenter, double-blind, randomized, 3-period, crossover, multiple-dose placebo- and active-comparator-controlled study comparing 50-mg doses of rofecoxib with placebo and with 550 mg naproxen sodium taken by patients at the onset of at least moderate, sustained abdominal cramping due to primary dysmenorrhea in each of three consecutive menstrual cycles (Figure 1). Patients were randomly assigned to balanced sequences of each of the following three test medication schedules: placebo followed by placebo every 12 hours as needed, naproxen sodium 550 mg followed by naproxen sodium 550 mg every 12 hours as needed, or rofecoxib 50 mg followed by rofecoxib 25 mg daily as needed.

Figure 1: Schedule of Observations and Procedures



Treatments Administered (Table 1):

Study Medication	Formulation No.
MK- 0966	
50 mg †	MR-3386
25 mg ‡	MR-3386
Placebo X §	MR-3416
Naproxen sodium	
550 mg	MR 3478
Placebo Y %	MR-3479

† The 50-mg dose consisted of two 25-mg tablets (Phase III [redacted] formulation).
‡ Patients who initially received rofecoxib 50-mg received subsequently 25-mg doses that could be taken daily as needed.
§ Placebo X was in the image of the 25-mg tablet.
% Placebo Y was in the image of the 550-mg naproxen sodium tablet.

Blinding

Patients received study medication in multiple bottles. The contents of the bottle for each group varied with the time of administration. Table 2 shows the bottle contents by treatment. The first dose of study medication contained 3 tablets, doses offered at 12, 36, and 60 hours after the first dose contained 1 tablet, and doses offered at 24 and 48 hours postdose contained 2 tablets.