Table 2
Bottle Contents by Treatment Group

Group	Placebo of MK- 0966 25 mg	MK- 0966 25- mg Tablet	Placebo of Naproxen Sodium	Naproxen Sodium 550- mg Tablet
Placebo Regimen				
Placebo (initial dose)	2	0	1	0
Placebo (12-, 36-, or 60- hour dose)	0	0	1	0
Placebo (24- or 48- hour dose)	1	0	1	0
MK- 0966 50- mg/ 25- mg Regimen				
MK- 0966 50/ 25 mg (initial dose)	0	2	1	0
MK- 0966 50/ 25 mg (12-, 36-, or 60- hour dose)	0	0	1	0
MK- 0966 50/ 25 mg (24- or 48- hour dose)	0	1	1	0
Naproxen Sodium Regimen				
Naproxen Sodium 550 mg	2	0	0	1
Naproxen Sodium (12, 36, or 60- hour dose)	0	0	0	1
Naproxen Sodium (24- or 48- hour dose)	1	0	0	1

Study Design:

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

Randomization and Allocation (Pre-Cycle 1, Visit 2)
At Visit 2, patients who satisfied inclusion/exclusion criteria were randomized and given a beeper. Allocation was done by a computer-generated schedule

Patients were given 6 bottles of study medication (rofecoxib 25 or 50 mg, naproxen sodium 550 mg, or placebo), based on their randomly assigned treatment regimen, for each of cycles 1, 2, and 3. The patient was instructed that when abdominal cramping pain consistent with menstruation began, she was to test her urine for β-HCG and call the coordinator. After the coordinator confirmed that the patient's urine was negative for β-HCG and that she had moderate-to-severe pain, the patient was to ingest the contents of bottle study medication and record the severity of abdominal cramping pain, as well as the time the medication was taken. The study coordinator used a beeper to alert the patient to complete the diary at specified times thereafter.

Postcycles 1 and 2 Visits (Visits 3 and 4)
Each patient returned to the clinical research center for evaluation within 4 days after having taken test medication for cycles 1 and 2. Test drug and a new patient diary for menstrual cycle 2 or 3 were given to the patient at this time.

Postcycle 3 Visit (Visit 5)
Upon completion of the third treatment, the patient returned to the clinical research center for a final safety evaluation, again within 4 days of taking study medication. In addition, if the patient detected any difference among the four treatments, she was asked to rank the 3 treatments in order of overall efficacy. Patients received a final telephone contact 2 weeks after the last dose for safety evaluation.

Rescue Medication for Pain due to Primary Dysmenorrhea

For each of cycles 1 through 3, if a patient required an analgesic (after having waited at least 2 hours after the initial dose of study drug), she was instructed to take either (1) a rescue analgesic (specific drug and dose was determined by the investigator) if less than 12 hours had elapsed since taking study drug, or (2) a second dose of study medication if more than 12 hours had elapsed since taking study drug. Additional doses of study drug could be taken every 12 (±1) hours as needed. If additional doses were taken, the patient recorded the date and time of consumption. The patient was to take rescue medication if, at any time, she needed additional analgesic relief and it had not been at least 11 hours since her last dose of study medication. Patients were asked to avoid using rescue analgesia during the first 2 hours postdose, in order to allow the study drug to exhibit an effect. The date, identity, and time rescue analgesia was used during each cycle were recorded if necessary. Once a patient had been medicated with the rescue analgesic, she was told not to record any additional pain intensity/relief information in her diary and was told not to take any additional doses of study medication.

Efficacy Assessment:

The patient recorded specific assessments of Pain Relief, Pain Intensity, and overall Global Evaluation of the study drug at each of cycles 1 through 3 and provided an overall ranking of study drugs (if the patient detected any difference among the 3 treatments) at postcycle 3.

1) Ratings of Pain Intensity and Pain Relief
The following assessments at 0.50, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, and 12 hours postdose:

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

2) Time of Rescue Medication or Additional Doses of Study Medication
Patients were instructed to take additional doses of study medication or rescue medication as needed. The date and time that rescue medication or additional doses of study medication were taken and its identity were recorded by the patient in a diary.

3) Patient's Global Evaluation

Eight hours after having taken the first dose of study medication in each period, or at the time of remedication if less than 8 hours postdose, the patient answered the following question in the diary. The patient also answered this question at 72 hours postdose or at completion of menstrual cycle, whichever came first:

"How would you rate the study medication you received for pain?"

"POOR," "FAIR," "GOOD," "VERY GOOD," or "EXCELLENT."

4) Overall Ranking of Study Drugs

Upon completion of all 3 treatment cycles, the patient was asked to rank the 3 treatments by answering the following questions:

"Did you detect any difference among the 3 treatment groups?"

"If so, please list the treatments in order of overall efficacy from best to worst (e.g., 1>2>3)."

5) Analgesic Effect of Multiple Doses of Rofecoxib

It is important to point out that no pain measurements were taken beyond 12 hours post first dose. The sponsor used the following surrogate measurements to assess the analgesic effect of multiple doses: percent of patients who took additional dose(s) of study medication, which was defined as the percent of patients, who took additional doses of study medication 12 to 72 hours postdose and total additional dose(s) of study medication which was defined as the total dose of additional study medication taken by the patient during 12 to 72 hours postdose.

Statistical Analysis

All patients who took study medication (including those who took rescue medication), recorded a baseline pain intensity score of moderate or severe, and recorded at least one pain evaluation during the first hour 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 3.

Table 3
Listing of End Points and Their Statistical Analyses

End Point	Statistical Analysis
Efficacy	
Pain Assessment at Each Time Point	
Pain Relief, PID, PRID, APAR, APID	ANOVA †, plot of mean with 84% CI over time.
TOPAR, SPID	ANOVA †, plot of mean with 84% CI over time.
Overall Analgesic Effect	
TOPAR8 (primary), SPID8, patient's global evaluation at 8 and at 72 hours	Analysis of Variance Model (ANOVA) †, plot of LSMean with 84% confidence interval (CI) at 8 hours for TOPAR8, plot and summary table of percent of patients in each category of the global evaluation score by treatment at 8 and 72 hours postdose.
Duration of Analgesic Effect	
Time to Rescue Medication Use	Cox proportional hazards regression model ‡ and Kaplan-Meier estimates of 25, 50, and 75th percentiles and 95% CI for the 50% percentile, plot of cumulative proportion of patients requiring rescue medication over time (1-Kaplan Meier estimates of survival function).
Percent of Patients Who Took Rescue Medication	GEE regression model ‡, bar chart of percent of patients who took rescue medication for each treatment.
Pain Relief, PID, PRID at 12 hours	ANOVA †, plot of LSMean with 84% CI for each treatment.
Peak Analgesic Effect	
Peak PID and peak pain relief within 8 hours	ANOVA †, plot of LSMean with 84% CI by treatment.
Analgesic Effect of Multiple Doses of Rofecoxib	
Percent of patients who took additional dose of study medication 12 to 72 hours postdose.	GEE regression model ‡, bar chart of percent of patients taking additional dose of study medication.
Patient's total additional dose of study medication during 12 to 72 hours postdose	ANOVA †

† Model included factors for sequence, patient nested within sequence, period within square, treatment, baseline Pain Intensity, and carryover (i.e., residual) effects. The carryover effect was removed from the model when it was determined not significant at 5% level.

‡ Model included factors for treatment and baseline Pain Intensity effects. The treatment-by-baseline Pain Intensity was tested and removed from the model if it was found not significant at 5% level.

Table 3 (Cont.)
Listing of End Points and Their Statistical Analyses

End Point	Statistical Analysis
Safety	
Vital Signs and Laboratory Safety Parameters	
Percent of patients with predefined limits of changes in vital signs and laboratory parameters	Summary statistics.
Observed or log (observed value) for vital signs and laboratory parameters	Summary statistics of observed and change from baseline.
Adverse Experience Counts	
Number (%) of patients with adverse experiences (including by category)	Pairwise McNemar's Test.

RESULTS:

Disposition of Patients

A total of 63 patients were entered into this study from two centers. Because of the complete block crossover design, each patient received up to 3 possible treatment regimens. The number of patients in each treatment sequence is in Table 4.

Table 4
Number of Patients Entered by Investigator

Investigator	PBO/ MK50/ NS550 †,‡ (N= 10)	PBO/ NS550/ MK50 †,‡ (N= 11)	MK50/ PBO/ NS550 †,‡ (N= 11)	MK50/ NS550/ PBO †,‡ (N= 10)	NS550/ MK50/ PBO†,‡ (N= 11)	NS550/ PBO/ MK50 †,‡ (N= 10)	Total (N= 63)
Bitner, Mark	5	5	5	5	5	5	30
Woolsey, Carl	5	6	6	5	6	5	33

† PBO = placebo, MK50 = MK- 0966 50 mg, NS550 = naproxen sodium 550 mg.

‡ Represents a treatment sequence in which patients received 3 different treatment regimens in the specified order. There were a total of 6 different treatment sequences used in the study.

Baseline demographic characteristics are presented in Table 5.
Of the 63 randomized patients, 94% were white, and 6% were of other origins. Patients' ages ranged from 17 to 47 years in the database. The mean patient age was 30. Sixty-eight percent of patients were older than 20 years of age; 49% of patients were older than 30 years of age. There were no clinically meaningful differences between the sequence groups for any of these characteristics.

Table 5
Baseline Patient Characteristics

	All Patients (N= 63)	
	n	(%)
Gender		
Female	63	(100.0)
Race		
Asian	1	(1.6)
Eurasian	1	(1.6)
Multi- Racial	1	(1.6)
Native American	1	(1.6)
White	59	(93.7)
Age		
≤20	20	(31.7)
21 to 30	12	(19.0)
31 to 40	18	(28.6)
41 to 50	13	(20.6)
Mean		29.5
SD		10.00
Median		29.0
Range		17 to 47

Baseline Menstrual Distress Questionnaire

At Visit 2, each patient completed Form C of the MDQ to provide descriptive information concerning the symptoms experienced during their usual menstrual cycles. (Table 6). The mean menstrual pain scale percent score and the mean menstrual water retention score were 84 and 77%, respectively. These are greater than the mean scores for a general population (50%), indicating that the women in the study had greater than average menstrual pain and water retention, while other menstrual symptoms were approximately average.

Table 6
Menstrual Distress Questionnaire

	Mean (Range)	
Pain		
Premenstrual	74.11	(7 to 99)
Menstrual	83.52	(3 to 99)
Intermenstrual	68.49	(18 to 99)
Water Retention		
Premenstrual	72.56	(4 to 99)
Menstrual	77.29	(4 to 99)
Intermenstrual	58.71	(16 to 99)
Autonomic Reactions		
Premenstrual	53.62	(27 to 99)
Menstrual	65.65	(24 to 99)
Intermenstrual	53.97	(34 to 99)
Negative Affect		
Premenstrual	64.49	(7 to 99)
Menstrual	66.22	(5 to 99)
Intermenstrual	52.16	(14 to 99)
Impaired Concentration		
Premenstrual	56.29	(18 to 99)
Menstrual	58.17	(14 to 99)
Inter menstrual	55.87	(27 to 99)
Arousal		
Premenstrual	55.63	(7 to 99)
Menstrual	50.65	(7 to 99)
Intermenstrual	58.56	(7 to 99)
Control		
Premenstrual	50.54	(27 to 99)
Menstrual	54.78	(27 to 99)
Intermenstrual	46.25	(0 to 99)
Behavioral Disturbance		
Premenstrual	53.59	(16 to 99)
Menstrual	65.32	(12 to 99)
Intermenstrual	45.86	(24 to 99)

Baseline Pain Intensity Score

Patients' pain intensity scores were measured predose during each of the 3 study periods (Table 7). There was no apparent treatment-related difference in the percent of patients with moderate or severe baseline pain intensity before each of the 3 treatments.

Table 7
Baseline Pain Intensity

Period (Visit)	Treatment	Baseline Pain Intensity		Total
		Moderate	Severe	
1 (3)	Placebo	14 (67%)	7 (33%)	21
	MK- 0966 50 mg	13 (62%)	8 (38%)	21
	Naproxen sodium 550 mg	14 (67%)	7 (33%)	21
	All	41	22	63
2 (4)	Placebo	10 (53%)	9 (47%)	19
	MK- 0966 50 mg	15 (75%)	5 (25%)	20
	Naproxen sodium 550 mg	15 (71%)	6 (29%)	21
	All	40	20	60
3 (5)	Placebo	14 (70%)	6 (30%)	20
	MK- 0966 50 mg	9 (47%)	10 (53%)	19
	Naproxen sodium 550 mg	10 (59%)	7 (41%)	17
	All	33	23	56

Accounting for Patients in the Study

Of the 63 randomized patients, 56 completed the protocol as specified (Table 8). Of the patients who discontinued, 1 patient became pregnant during the study, 1 moved and could not come to the clinic for study visits, and 5 did not have moderate to severe pain within the 5-month limit specified by the protocol. Of the 5 patients who did not have moderate-to-severe pain within the specified time limit, 2 were classified as patients who discontinued and 3 were classified as protocol deviations.

Table 8
Patient Accounting

	Total
ENTERED: (age range)	63 (17 to 47)
COMPLETED	56
DISCONTINUED	7
Clinical adverse experience	1
Other §	6

§ Of these 6 patients, 5 discontinued because they did not have moderate to severe pain for 3 cycles within the 5- month limit specified by the protocol and 1 moved.

Accounting for Patients in the Analysis

Three patients dropped out after the first period and 4 after the second period. Each of the 63, 60, and 56 patients included in the analysis of TOPAR8, the primary efficacy end point (as defined by the sponsor), for the three respective study periods (Visits 3 to 5) had a valid baseline pain intensity score and at least one valid postdose pain evaluation during the first hour (Table 9). Patients who used rescue analgesia prior to 2 hours were also included in all the efficacy analyses.

Table 9
Number of Patients Included in the Analysis of TOPAR8 by Treatment and Period

Period (Visit)	Placebo	MK- 0966 50 mg	Naproxen Sodium	Total
1 (3)	21	21	21	63
2 (4)	19	20	21	60
3 (5)	20	19	17	56
Total	60	60	59	179

There were 5 patients (2 in the placebo, 2 in the rofecoxib 50-mg and 1 in the naproxen sodium treatments) who took rescue medication prior to 2 hours postdose (Table 10). No patients were excluded from the analysis of TOPAR8 due to missing Pain Relief score during the first hour postdose. There were no missing pain scores due to any other reasons. No patients were excluded from the analysis due to a protocol violation. Therefore, the per-protocol analysis was not performed. All randomized patients, including the 5 patients who used rescue medication prior to 2 hours postdose during the specific study periods, were included in the safety analysis.

Table 10
Accounting for Patients in the Analysis

Study Status	Placebo		MK- 0966 50 mg		Naproxen Sodium 550 mg	
	N	(%)	N	(%)	N	(%)
ENTERED †	63		63		63	
Included in the analysis	60	(95)	60	(95)	59	(94)
Did not take rescue medication	23	(36)	37	(59)	36	(57)
Took rescue medication prior to 2 hours	2	(3)	2	(3)	1	(2)
Took rescue medication at/ after 2 hours	35	(56)	21	(33)	22	(35)
Excluded from the analysis of TOPAR8 ‡	3	(5)	3	(5)	4	(6)

† Patients who entered study and expected to complete study.
‡ Discontinued.

Analysis of Primary Efficacy Measures

Pain Intensity score, Pain Relief score, Patient's Global Evaluation, and Time to Rescue Medication were all recorded. The sponsor chose Total of Pain Relief Scores Over 8 Hours (TOPAR8), Sum of Pain Intensity Differences Over 8 Hours (SPID8), Patient's Global Evaluation Score at 8 Hours, and Patient's Rank of Treatment Preference as the measures for overall analgesic effect.
The reviewer preferred the Division's approach and analyzed first the time specific Mean Pain Intensity Difference Scores (PID) and the Mean Pain Relief Scores (PR) as primary measures of analgesic efficacy.

Mean Pain Intensity Difference Scores Over Time (PID, LOCF and BOCF)

Figure 2 and table 11 present the mean PID scores at all assessment times during the first 12 hour Treatment Period. The PID scores were calculated by subtracting the pain intensity at a specific assessment time from the baseline pain intensity. Imputing pain intensity data has been done using last observation carried forward (LOCF) method.

The mean PID values for the rofecoxib 50 mg treatment group were statistically significantly better than placebo at all assessment times from the 1.5 hours through 12 hours postdose.

The mean PID scores for the Naproxen Na 550 mg group were statistically significant better than placebo from 1 hour through 12 hours postdose. The mean PID scores for the Naproxen Na 550 mg group were statistically better than those for the rofecoxib 50 mg group from 1.5 through 2 hours. The mean PID scores for the Naproxen Na 550 mg group were not statistically different than those for the rofecoxib 50 mg group from 3 through 12 hours.

Reanalyzing the data by using the baseline observation carried forward (BOCF) technique revealed the same results.

Figure 2

Mean PID Score With 84% Confidence Interval
by Hours Postdose
(Intention-to-Treat Approach)

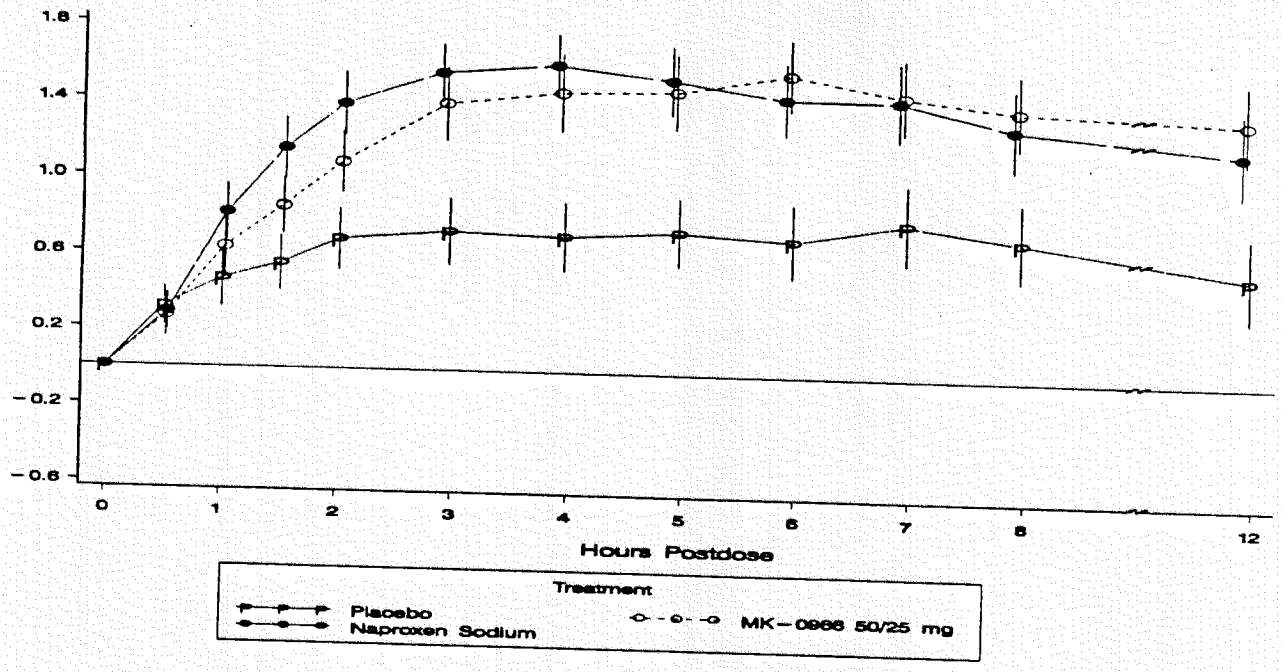

Table 11
Analysis of Pain Intensity Difference by Time Point (Intention-to-Treat Approach)

Treatment		Summary Statistics by Time Point (Hours Postdose)										
		0.5	1	1.5	2	3	4	5	6	7	8	12
Placebo	N	60	60	60	60	60	60	60	60	60	60	60
	MEAN	0.3A†	0.5B	0.6C	0.7C	0.7B	0.7B	0.8B	0.7B	0.8B	0.7B	0.6B
	STD	0.6	0.9	0.8	0.9	1.0	1.0	1.0	1.1	1.1	1.1	1.2
rofecoxib 50 mg	N	60	60	60	60	60	60	60	60	60	60	60
	MEAN	0.3A	0.6AB	0.9B	1.1B	1.4A	1.5A	1.5A	1.6A	1.5A	1.4A	1.4A
	STD	0.6	0.8	0.8	0.9	1.1	1.1	1.1	1.0	1.1	1.1	1.2
Naproxen Na 550 mg	N	59	59	59	59	59	59	59	59	59	59	59
	MEAN	0.3A	0.8A	1.2A	1.4A	1.6A	1.6A	1.5A	1.5A	1.5A	1.3A	1.2A
	STD	0.5	0.8	0.9	0.9	0.8	0.9	1.0	1.0	1.1	1.2	1.2

†A, B, C — Letter A indicates the most effective dose(s), B indicates the next most effective, and so forth.

p- Values From Between- Treatment Pairwise Comparisons by Time Point (Hours Postdose)											
Pairwise Comparison	0.5	1	1.5	2	3	4	5	6	7	8	12
50/25 mg vs. Placebo	0.571	0.185	0.041	0.015	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Naproxen Na 550 mg vs. Placebo	0.818	0.003	<0.001	0.001	<0.001	<0.001	<0.001	0.001	0.001	<0.001	<0.001
Naproxen Na 550 mg vs. 50/25 mg	0.740	0.096	0.0010	0.017	0.206	0.235	0.445	0.651	0.873	0.738	0.413

Mean Pain Relief Scores Over Time (PR, LOCF and BOCF)

Figure 3 and table 12 present the mean PR scores at all assessment times during the first 12 hour Treatment Period. Imputing pain relief data has been done using last observation carried forward (LOCF) method.

The mean PR values for the rofecoxib 50 mg treatment group were statistically significantly better than placebo at 1 hour and at all assessment times from the 2 hours through 12 hours postdose.

The mean PR scores for the Naproxen Na 550 mg group were statistically significant better than placebo from 1 hour through 12 hours postdose. The mean PR scores for the Naproxen Na 550 mg group were statistically better than those for the rofecoxib 50 mg group at 1.5 and at 2 hours. The mean PR scores for the Naproxen Na 550 mg group were not statistically different than those for the rofecoxib 50 mg group at 1 hour and at all assessment times from the 3 hours through 12 hours postdose.

Reanalyzing the data by using the baseline observation carried forward (BOCF) technique revealed the same results.

Figure 3

Mean Pain Relief Score With 84% Confidence Interval by Hours Postdose
(Intention-to-Treat Approach)

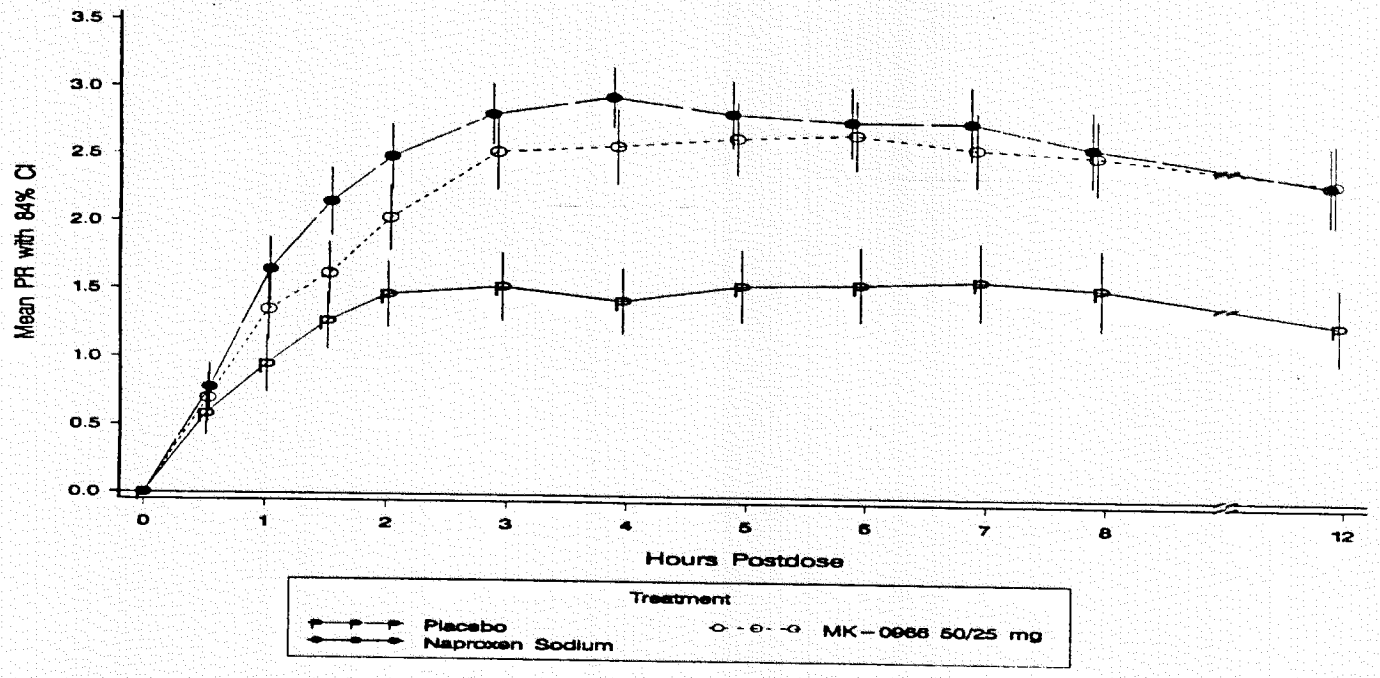

Table 12
Analysis of Pain Relief Score by Time Point (Intention-to-Treat Approach)

Treatment		Summary Statistics by Time Point (Hours Postdose)										
		0.5	1	1.5	2	3	4	5	6	7	8	12
Placebo	N	60	60	60	60	60	60	60	60	60	60	60
	MEAN	0.6A†	1.0B	1.3B	1.5C	1.5B	1.4B	1.6B	1.6B	1.6B	1.6B	1.3B
	STD	0.9	1.1	1.1	1.3	1.3	1.3	1.5	1.5	1.6	1.6	1.5
rofecoxib 50 mg	N	60	60	60	60	60	60	60	60	60	60	60
	MEAN	0.7A	1.4A	1.6B	2.0B	2.5A	2.6A	2.7A	2.7A	2.6A	2.5A	2.4A
	STD	1.0	1.2	1.2	1.3	1.5	1.5	1.5	1.4	1.5	1.5	1.7
Naproxen Na 550 mg	N	59	59	59	59	59	59	59	59	59	59	59
	MEAN	0.8A	1.6A	2.2A	1.3A	1.2A	1.2A	1.4A	1.4A	1.5A	1.4A	1.3A
	STD	0.8	1.1	1.2	1.2	1.3	1.3	1.3	1.3	1.4	1.4	1.3
†A, B, C — Letter A indicates the most effective dose(s), B indicates the next most effective, and so forth.												
p- Values From Between- Treatment Pairwise Comparisons by Time Point (Hours Postdose)												
Pairwise Comparison		0.5	1	1.5	2	3	4	5	6	7	8	12
50/25 mg vs. Placebo		0.327	0.039	0.104	0.015	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Naproxen Na 550 mg vs. Placebo		0.199	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	0.001	0.001	<0.001	<0.001
Naproxen Na 550 mg vs. 50/25 mg		0.752	0.161	0.014	0.50	0.294	0.136	0.430	0.737	0.492	0.862	0.862

Mean Pain Intensity Difference and Pain Relief (PRID, LOCF and BOCF)

Table 13 and figure 4 present the mean PRID scores at all assessment times during the first 12 hour Treatment Period. Imputing pain intensity data has been done using last observation carried forward (LOCF) method.

The mean PRID values for the rofecoxib 50 mg treatment group were statistically significantly better than placebo at all assessment times from the 2 hours through 12 hours postdose.

The mean PRID scores for the Naproxen Na 550 mg group were statistically significant better than placebo from 1 hour through 12 hours postdose. The mean PID scores for the Naproxen Na 550 mg group were statistically better than those for the rofecoxib 50 mg group from 1.5 through 2 hours. The mean PRID scores for the Naproxen Na 550 mg group were not statistically different than those for the rofecoxib 50 mg group from 3 through 12 hours.

Reanalyzing the data by using the baseline observation carried forward (BOCF) technique revealed the same results.

Figure 4
Mean PRID Scores by Hour Postdose

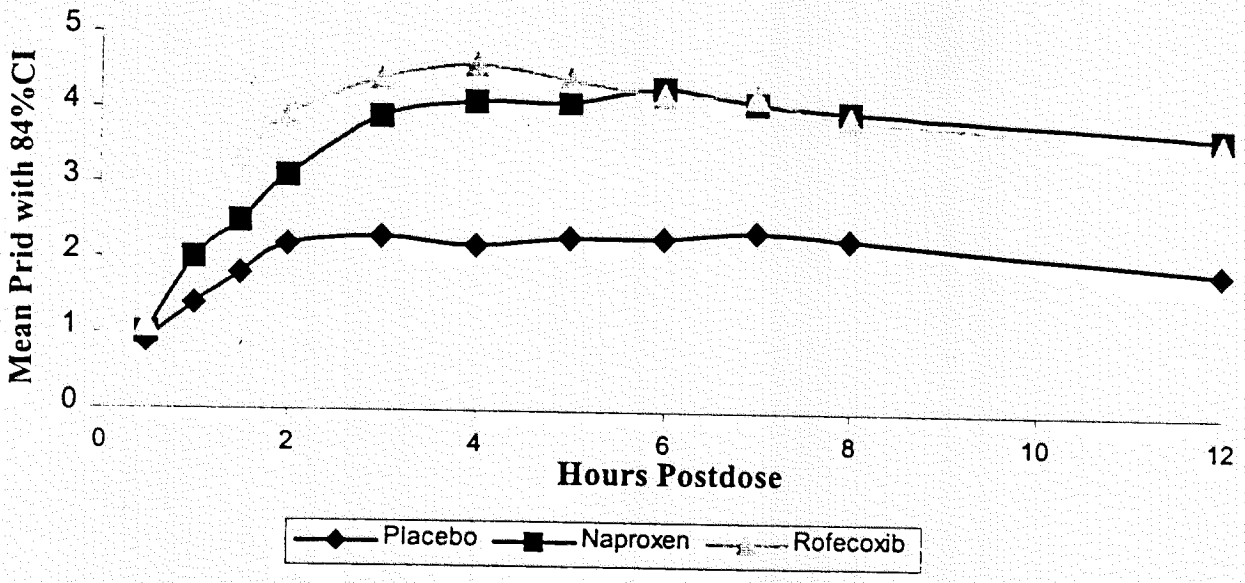

Table 13
Analysis of PRID by Time Point (Intention-to-Treat Approach)

Treatment		Summary Statistics by Time Point (Hours Postdose)										
		0.5	1	1.5	2	3	4	5	6	7	8	12
Placebo	N	60	60	60	60	60	60	60	60	60	60	60
	MEAN	0.9A†	1.4B	1.8B	2.2C	2.3B	2.2B	2.3B	2.3B	2.4B	2.3B	1.9B
	STD	1.4	1.9	1.8	2.2	2.2	2.2	2.4	2.5	2.6	2.7	2.6
rofecoxib 50 mg	N	60	60	60	60	60	60	60	60	60	60	60
	MEAN	1.0A	2.0A	2.5B	3.1B	3.9A	4.1A	4.1A	4.3A	4.1A	4.0A	3.7A
	STD	1.5	2.0	1.9	2.1	2.5	2.5	2.4	2.3	2.4	2.5	2.7
Naproxen Na 550 mg	N	59	59	59	59	59	59	59	59	59	59	59
	MEAN	1.1A	2.5A	3.3A	3.9A	4.4A	4.6A	4.4A	4.2A	4.2A	3.9A	3.6A
	STD	1.3	2.0	2.1	2.1	1.9	2.0	2.2	2.3	2.5	2.6	2.7

†A, B, C — Letter A indicates the most effective dose(s), B indicates the next most effective, and so forth.

p- Values From Between- Treatment Pairwise Comparisons by Time Point (Hours Postdose)											
Pairwise Comparison	0.5	1	1.5	2	3	4	5	6	7	8	12
50/25 mg vs. Placebo	0.674	0.062	0.063	0.012	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Naproxen Na 550 mg vs. Placebo	0.441	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	0.001	0.001	<0.001	<0.001
Naproxen Na 550 mg vs. 50/25 mg	0.723	0.116	0.009	0.028	0.243	0.160	0.425	0.982	0.629	0.975	0.657