Rescue Medication for Pain due to Primary Dysmenorrhea

For each of cycles 1 through 4, 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 date and time of consumption were recorded by the patient. 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 4 and provided an overall ranking of study drugs (if the patient detected any difference among the 3 treatments) at postcycle 4.

1) Ratings of Pain Intensity and Pain Relief

The following assessments were done 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 4 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>4)"

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 127 patients entered this study. Because of the complete block crossover design, each patient received up to four 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/ MK25/MK50/ NS550†,‡ (N= 31)	MK25/ NS550/PBO/ MK50†,‡ (N= 30)	MK50/ PBO/NS550/ MK25†,‡ (N= 33)	NS550/MK50/ MK25/ PBO†,‡ (N= 33)	Total (N= 127)
Daniels, Stephen	31	30	33	33	127

† PBO = placebo, MK25 = rofecoxib 25 mg, MK50 = rofecoxib 50 mg, NS550 = naproxen sodium 550 mg.

‡ Represents a treatment sequence in which patients received four different treatment regimens in the specified order. There were a total of 4 different treatment sequences used in the study.

Baseline demographic characteristics are presented in Table 5.
Of the 127 randomized patients, all were women, 79% were white, 12% were Hispanic-American, and 10% were of other origins. Patients' ages ranged from 18 to 44 years. The mean patient age was 31. Ninety-three percent of patients were older than 20 years of age; 58% of patients were older than 30 years of age.

Table 5
Baseline Patient Characteristics

	All Patients (N= 127)	
	n	(%)
Gender		
Female	127	(100.0)
Race		
Asian	1	(0.8)
Blach	11	(8.7)
Hispanic-American	15	(11.8)
White	100	(78.7)
Age		
≤20	9	(7.1)
21 to 30	44	(34.6)
31 to 40	63	(49.6)
41 to 50	11	(20.68.7)
Mean	31.4	
SD	6.73	
Median	32.0	
Range	18 to 44	

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 82 and 83%, 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	69.54	(7 to 99)
Menstrual	82.13	(14 to 99)
Intermenstrual	69.42	(18 to 99)
Water Retention		
Premenstrual	81.86	(4 to 99)
Menstrual	83.17	(4 to 99)
Intermenstrual	69.86	(16 to 99)
Autonomic Reactions		
Premenstrual	49.77	(27 to 99)
Menstrual	52.03	(24 to 99)
Intermenstrual	50.25	(34 to 99)
Negative Affect		
Premenstrual	61.90	(7 to 99)
Menstrual	62.23	(5 to 99)
Intermenstrual	54.58	(14 to 99)
Impaired Concentration		
Premenstrual	48.70	(18 to 99)
Menstrual	49.12	(14 to 99)
Inter menstrual	46.09	(27 to 99)
Behavioral Disturbance		
Premenstrual	56.55	(16 to 99)
Menstrual	58.82	(12 to 99)
Intermenstrual	52.89	(24 to 99)

Baseline Pain Intensity Score

Patients' pain intensity scores were measured predose during each of the 4 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 4 treatments.

Table 7
Baseline Pain Intensity

Period (Visit)	Treatment	Baseline Pain Intensity		Total
		Moderate	Severe	
1 (3)	Placebo	18 (58%)	13 (42%)	31
	MK- 0966 25 mg	24 (83%)	5 (17%)	29
	MK- 0966 50 mg	20 (61%)	13 (39%)	33
	Naproxen sodium 550 mg	25 (76%)	8 (24%)	33
	All	87 (69%)	39 (31%)	126
2 (4)	Placebo	22 (67%)	11 (33%)	33
	MK- 0966 25 mg	15 (54%)	13 (46%)	28
	MK- 0966 50 mg	22 (76%)	7 (24%)	29
	Naproxen sodium 550 mg	18 (62%)	11 (38%)	29
	All	77 (65%)	42 (35%)	119
3 (5)	Placebo	16 (57%)	12 (43%)	28
	MK- 0966 25 mg	20 (77%)	6 (23%)	26
	MK- 0966 50 mg	16 (57%)	12 (43%)	28
	Naproxen sodium 550 mg	18 (56%)	14 (44%)	32
	All	70 (61%)	44 (39%)	114
4 (6)	Placebo	15 (58%)	11 (42%)	26
	MK- 0966 25 mg	17 (53%)	15 (47%)	32
	MK- 0966 50 mg	18 (64%)	10 (36%)	28
	Naproxen sodium 550 mg	17 (61%)	11 (39%)	28
	All	67 (59%)	47 (41%)	114

Accounting for Patients in the Study

Of the 127 randomized patients, 114 completed the protocol as specified(Table 8). Two patients discontinued because they became pregnant during the study. One patient discontinued for usage of an NSAID and steroid injection, and 1 patient was participating in two studies simultaneously. Of the other patients who discontinued, 1 started a tricyclic antidepressant, 1 was due to start steroid injections, and 3 did not have four menses with at least moderate pain within the 5-month limit specified by the protocol.

Table 8
Patient Accounting

	Total
ENTERED: (age range)	127 (18 to 44)
COMPLETED	114
DISCONTINUED	13
Clinical adverse experience	2
Patient discontinued	3
Patient withdrew consent	3
Protocol deviation	4

Accounting for Patients in the Analysis

One hundred twenty-seven patients took initial dose of study medication, but 1 patient dropped out without providing any pain measurement during the first cycle. Therefore, 126 patients were included in the intention-to-treat approach to the efficacy analysis.

Each of the 126, 119, 114, and 114 patients included in the analysis of TOPAR8, the primary efficacy end point (as defined by the sponsor), for the four respective study periods 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		Naproxen Sodium	Total
		25/25	50/25 mg		
1 (3)	31	29	33	33	126
2 (4)	33	28	29	29	119
3 (5)	28	26	28	32	114
4 (6)	26	32	28	28	114
Total	118	115	118	122	473

There were 5 patients (2 in the placebo, 2 in the 25/25 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 patient was excluded 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 25 mg		MK- 0966 50 mg		Naproxen 550 mg	
	N	(%)	N	(%)	N	(%)	N	(%)
ENTERED †	127		127		127		127	
Included in the analysis	118	(93)	115	(91)	118	(93)	122	(96)
Did not take rescue medication	63	(50)	80	(63)	82	(65)	85	(67)
Took rescue medication prior to 2 hours	2	(2)	2	(2)	0		1	(1)
Took rescue medication at/ after 2 hours	53	(42)	33	(26)	36	(28)	36	(28)
Excluded from the analysis of TOPAR8 ‡	9	(7)	12	(9)	9	(7)	5	(4)

† 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 50/25 mg and 25/25 treatment groups were statistically significantly better than placebo at all assessment times from the 2 hours through 12 hours postdose. Within rofecoxib treatment groups, the mean PID scores were not statistically different between the two dose groups at any time.

The mean PID scores for the Naproxen Na 550 mg group were not statistically different than those for either of the rofecoxib dose groups at any time.

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

Figure 2

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

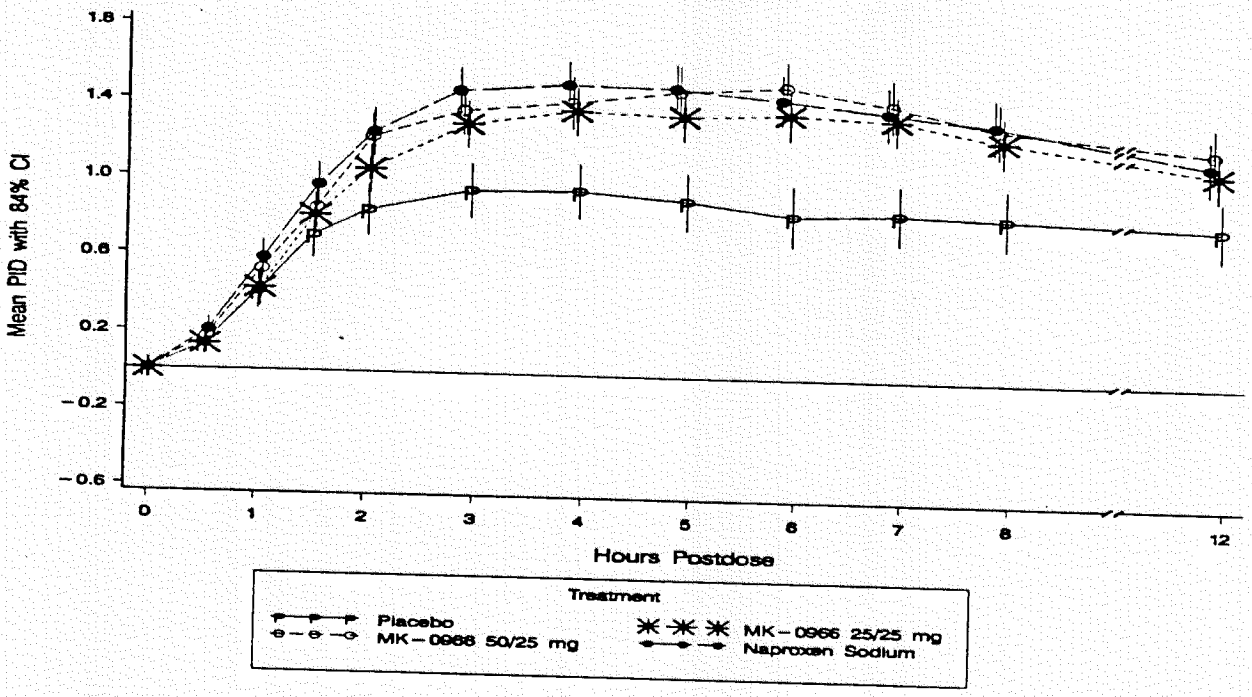

Table11

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	118	118	118	117	99	89	83	78	72	67	64
	MEAN	0.1A	0.4	0.7B	0.8B	0.9B	1.0B	0.9B	0.8B	0.9B	0.8B	0.8B
	STD	0.4	0.7	0.9	1.0	1.1	1.1	1.1	1.2	1.2	1.2	1.2
rofecoxib 25/25 mg	N	115	115	115	115	115	115	115	115	115	115	115
	MEAN	0.1A	0.4B	0.8B	1.1A	1.3A	1.4A	1.4A	1.4A	1.4A	1.3A	1.1A
	STD	0.4	0.7	0.8	0.9	0.9	1.0	1.0	1.0	1.0	1.0	1.0
rofecoxib 50/25 mg	N	117	118	118	118	118	118	118	118	118	118	118
	MEAN	0.2A	0.5B	0.8AB	1.2A	1.4A	1.4A	1.5A	1.5A	1.4A	1.3A	1.2A
	STD	0.4	0.7	0.8	0.9	1.0	1.0	1.0	1.0	1.1	1.1	1.1
Naproxen Na 550 mg	N	122	122	122	122	122	122	122	122	122	122	122
	MEAN	0.2A	0.6A	1.0A	1.2A	1.5A	1.5A	1.5A	1.5A	1.4A	1.3A	1.1A
	STD	0.5	0.7	0.9	1.0	0.9	1.0	1.0	1.0	1.1	1.1	1.1

†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
25/25 mg vs. Placebo	-	-	-	0.028	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.006
50/25 mg vs. Placebo	0.363	0.117	0.093	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
50/25 mg vs. 25/25 mg	0.501	0.297	0.746	0.148	0.544	0.687	0.283	0.241	0.501	0.606	0.357
Naproxen Na 550 mg vs. Placebo	0.110	0.020	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002
Naproxen Na 550 mg vs. 50/25 m	0.171	0.069	0.090	0.093	0.116	0.219	0.184	0.510	0.700	0.465	0.681
Naproxen Na 550 mg vs. 25/25 mg	0.485	0.433	0.166	0.816	0.329	0.404	0.798	0.603	0.772	0.829	0.606

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 50/25 mg treatment group were statistically significantly better than placebo at 1 hour, not better than placebo at 1.5 hour and then again better than placebo at all assessment times from the 2 hours through 12 hours postdose. The mean PR values for the rofecoxib 25/25 mg treatment group were statistically significantly better than placebo at all assessment times from the 2 hours through 12 hours postdose. Within rofecoxib treatment groups, the mean PR scores were not statistically different between the two dose groups at any time.

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 25/25 mg group at 1 and at 1.5 hours. The mean PR scores for the Naproxen Na 550 mg group were not statistically different than those for the rofecoxib 50/25 mg group at any time.

Reanalyzing the data by using the baseline observation carried forward (BOCF) technique revealed the same results with the exception for 1.5 hours postdose when Naproxen Na 550 mg was statistically better than both rofecoxib dose groups.

Figure 3

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

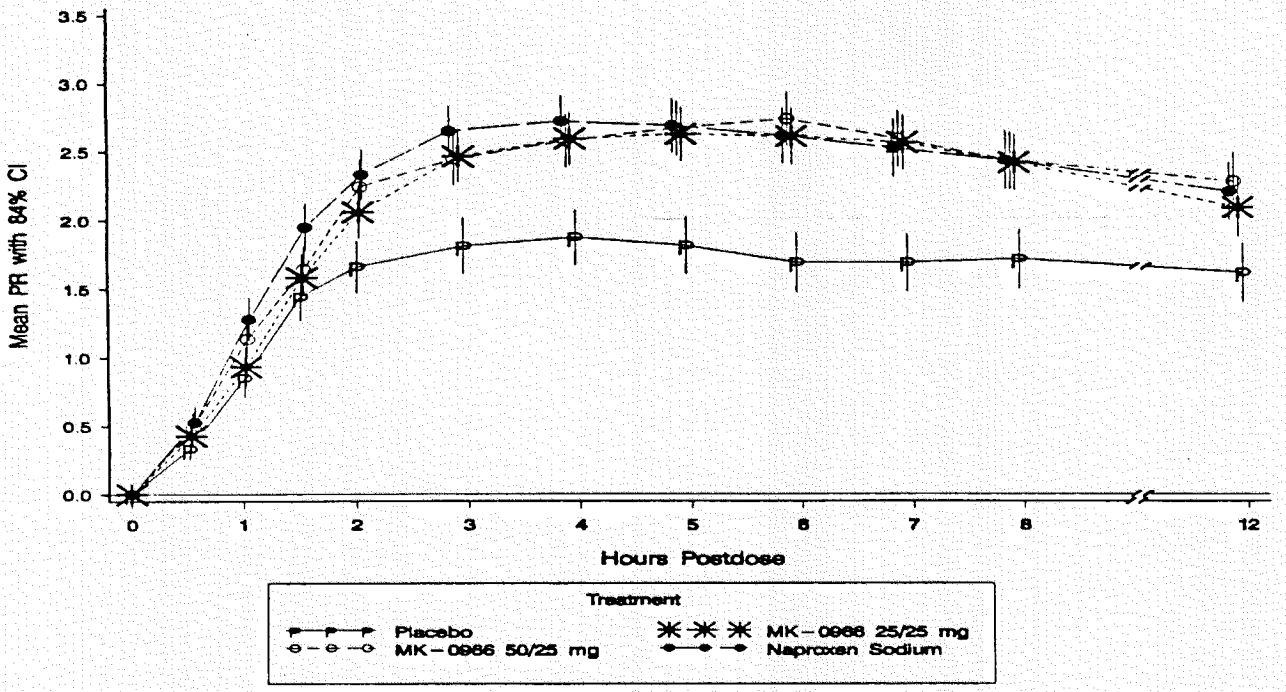

Table 12
Analysis of Pain Relief Score by Time Point (Intention-to-Treat Approach)

Treatment		Summary Statistics by Time Point (Hours Postdose)										
		0.5	1	1.5	2	3	4	5	6	7	8	12
Placebo	N	118	118	118	117	99	89	83	78	72	67	64
	MEAN	0.3A	0.8C	1.4B	1.7B	1.8B	1.9B	1.8B	1.7B	1.7B	1.7B	1.6B
	STD	0.6	1.1	1.4	1.5	1.6	1.6	1.6	1.7	1.7	1.7	1.7
rofecoxib 25/25 mg	N	115	115	115	115	115	115	115	115	115	115	115
	MEAN	0.4A	0.9C	1.6B	2.1A	2.5A	2.6A	2.6A	2.6A	2.6A	2.4A	2.1A
	STD	0.8	1.1	1.3	1.5	1.4	1.5	1.5	1.6	1.5	1.6	1.7
rofecoxib 50/25 mg	N	117	118	118	118	118	118	118	118	118	118	118
	MEAN	0.5A	1.1B	1.6AB	2.2A	2.4A	2.6A	2.7A	2.7A	2.6A	2.4A	2.3A
	STD	0.8	1.2	1.3	1.5	1.5	1.5	1.5	1.5	1.6	1.6	1.6
Naproxen Na 550 mg	N	122	122	122	122	122	122	122	122	122	122	122
	MEAN	0.5A	1.3A	2.0A	2.3A	2.7A	2.7A	2.7A	2.6A	2.5A	2.4A	2.2A
	STD	0.9	1.2	1.4	1.4	1.4	1.5	1.5	1.6	1.7	1.7	1.7
†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
25/25 mg vs. Placebo		-	0.473	-	0.020	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.010
50/25 mg vs. Placebo		0.109	0.025	0.185	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
50/25 mg vs. 25/25 mg		0.421	0.129	0.689	0.277	0.951	0.958	0.738	0.370	0.734	0.797	0.217
Naproxen Na 550 mg vs. Placebo		0.082	<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 m		0.345	0.009	0.014	0.105	0.247	0.378	0.615	0.894	0.922	0.840	0.428
Naproxen Na 550 mg vs. 25/25 mg		0.889	0.260	0.037	0.591	0.219	0.403	0.866	0.440	0.659	0.954	0.655

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 50/25 mg treatment group were statistically significantly better than placebo at 1 hour, not better than placebo at 1.5 hour and then again better than placebo at all assessment times from the 2 hours through 12 hours postdose. The mean PRID values for the rofecoxib 25/25 mg treatment group were statistically significantly better than placebo at all assessment times from the 2 hours through 12 hours postdose. Within rofecoxib treatment groups, the mean PRID scores were not statistically different between the two dose groups at any time.

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 25/25 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 50/25 mg group at any time.

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

Figure 4

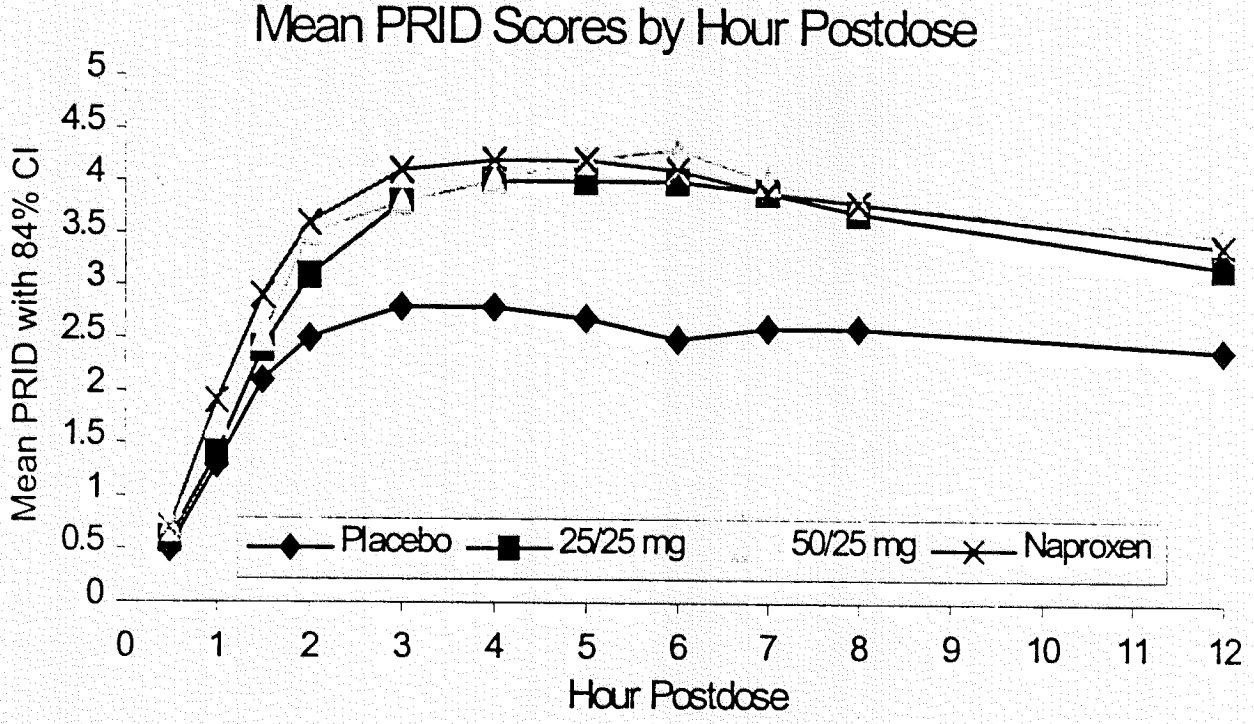

Table 13

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	118	118	118	117	99	89	83	78	72	67	64
	MEAN	0.5A	1.3C	2.1B	2.5B	2.8B	2.8B	2.7B	2.5B	2.6B	2.6B	2.4B
	STD	1.0	1.7	2.2	2.5	2.6	2.6	2.7	2.9	2.8	2.8	2.8
rofecoxib 25/25 mg	N	115	115	115	115	115	115	115	115	115	115	115
	MEAN	0.6A	1.4BC	2.4B	3.1A	3.8A	4.0A	4.0A	4.0A	3.9A	3.7A	3.2A
	STD	1.2	1.8	2.1	2.3	2.3	2.3	2.4	2.5	2.4	2.5	2.6
rofecoxib 50/25 mg	N	117	118	118	118	118	118	118	118	118	118	118
	MEAN	0.7A	1.7AB	2.5AB	3.5A	3.8A	4.0A	4.2A	4.3A	4.0A	3.8A	3.5A
	STD	1.2	1.8	2.1	2.4A	2.4	2.5	2.5	2.5	2.6	2.7	2.6
Naproxen Na 550 mg	N	122	122	122	122	122	122	122	122	122	122	122
	MEAN	0.7A	1.9A	2.9A	3.6A	4.1A	4.2A	4.2A	4.1A	3.9A	3.8A	3.4
	STD	1.3	1.9	2.2	2.3	2.3	2.3	2.4	2.5	2.7	2.7	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
25/25 mg vs. Placebo		-	0.473	-	0.020	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.010
50/25 mg vs. Placebo		0.109	0.025	0.185	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
50/25 mg vs. 25/25 mg		0.421	0.129	0.689	0.277	0.951	0.958	0.738	0.370	0.734	0.797	0.217
Naproxen Na 550 mg vs. Placebo		0.082	<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 m		0.345	0.009	0.014	0.105	0.247	0.378	0.615	0.894	0.922	0.840	0.428
Naproxen Na 550 mg vs. 25/25 mg		0.889	0.260	0.037	0.591	0.219	0.403	0.866	0.440	0.659	0.954	0.655

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, 25/25, 50/25 mg rofecoxib, or 550 mg naproxen sodium were 12.5, 17.4, 18.0, and 18.4 units, respectively (Table 14).

Over the 8 hours postdose, all rofecoxib doses had significantly ($p<0.001$) greater TOPAR8 values compared with placebo and the difference in TOPAR8 between the two rofecoxib doses was not significant (Table 14).

The mean TOPAR8 score for 550 mg naproxen sodium was significantly ($p<0.001$) greater than that for placebo but not significantly different from the mean scores in the rofecoxib doses (Table 14).

Table 14
Analysis of Total Pain Relief Score Over 8 Hours (TOPAR8)
(Intention-to-Treat Approach)

Treatment	N	Mean	SD	LSMean	95% CI for LSMean
Placebo	118	12.8	10.5	12.5	(10.9, 14.0)
MK- 0966 25/ 25 mg	115	17.8	9.4	17.4	(15.8, 19.0)
MK- 0966 50/ 25 mg	118	18.3	9.9	18.0	(16.4, 19.5)
Naproxen Sodium	122	18.7	9.5	18.4	(16.9, 19.9)

Pairwise Comparison	Difference in LSMeans	95% CI for Difference	p- Value
MK- 0966 25/ 25 mg vs. Placebo	4.9	(2.8, 7.1)	<0.001
MK- 0966 50/ 25 mg vs. Placebo	5.5	(3.4, 7.6)	<0.001
MK- 0966 50/ 25 mg vs. 25/25 mg	0.6	(-1.5, 2.7)	0.590
Naproxen Sodium vs. Placebo	6.0	3.8, 8.1)	<0.001
Naproxen Sodium vs. 25/ 25 mg	1.0	(-1.1, 3.1)	0.340
Naproxen Sodium vs. 50/ 25 mg	0.4	(-1.6, 2.5)	0.675

Effect	p- Value	Pooled Intra- Patient SD
Sequence	0.557	8.1
Patient (Sequence)	<0.001	
Period (Square)	0.033	
Treatment	<0.001	
Stratum (i. e., Baseline PI)	0.156	
Carryover (i. e., Residual)	0.194	
Treatment- by- Stratum Interaction	0.381	

Sum of Pain Intensity Difference to 8 Hours (SPID8)