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, rofecoxib 50 mg, or naproxen sodium 550 mg were 12.1, 17.5, and 19.5 units, respectively (Table 14).

Over the 8 hours postdose, rofecoxib 50 mg had significantly (p=0.002) greater TOPAR8 value compared with placebo. (Table 14).

The LSMean TOPAR8 score for naproxen sodium 550 mg was significantly (p<0.001) greater than that for placebo, but not significantly different from the LSMean score for rofecoxib 50 mg (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	60	11.4	8.9	12.1	(9.7, 14.4)
MK- 0966 50/ 25 mg	60	18.4	9.8	17.5	(15.2, 19.8)
Naproxen Sodium	59	20.3	8.7	19.5	(17.0, 22.0)

Pairwise Comparison	Difference in LSMeans	95% CI for Difference	p- Value
MK- 0966 50/ 25 mg vs. Placebo	5.4	(2.0, 8.8)	0.002
Naproxen Sodium vs. Placebo	7.4	(4.0, 10.8)	<0.001
Naproxen Sodium vs. 50/ 25 mg	2.0	(- 1.4, 5.4)	0.239

Effect	p- Value	Pooled Intra- Patient SD
Sequence	0.728	8.1
Patient (Sequence)	0.017	
Period (Square)	0.066	
Treatment	<0.001	
Stratum (i. e., Baseline PI)	0.939	
Carryover (i. e., Residual)	0.025*	
Treatment- by- Stratum Interaction	0.205	

* Carryover effect included in the model to estimate LSMeans.

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, rofecoxib 50 mg, and naproxen sodium 550 mg were 6.8, 10.2, 11.2 units, respectively (Table 15). Over the 8 hours postdose, rofecoxib 50 mg had significantly (p=0.003) greater SPID8 score compared with placebo (Table 15).

The LSMean SPID8 score for naproxen sodium 550 mg was significantly (p<0.001) greater than that for placebo but not significantly different from the score in rofecoxib 50 mg. (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	60	5.5	6.6	6.8	(5.2, 8.3)
MK- 0966 50/ 25 mg	60	10.3	6.8	10.2	(8.6, 11.7)
Naproxen Sodium	59	10.8	6.3	11.2	(9.5, 12.9)

Pairwise Comparison	Difference in LSMeans	95% CI for Difference	p- Value
MK- 0966 50/ 25 mg vs. Placebo	3.4	(1.2, 5.7)	0.003
Naproxen Sodium vs. Placebo	4.4	(2.2, 6.7)	<0.001
Naproxen Sodium vs. 50/ 25 mg	1.0	(- 1.2, 3.3)	0.355

Effect	p- Value	Pooled Intra- Patient SD
Sequence	0.867	5.4
Patient (Sequence)	0.001	
Period (Square)	0.038	
Treatment	<0.001	
Stratum (i. e., Baseline PI)	<0.001	
Carryover (i. e., Residual)	0.018*	
Treatment- by- Stratum Interaction	0.082	

* Carryover effect included in the model to estimate LSMeans.

Patient's Global Evaluation at 8 Hours

The LSMean scores for placebo, rofecoxib 50 mg, and naproxen sodium 550 mg were 1.3, 1.7, and 2.1, respectively (Table 16).

Compared with placebo, the 50-mg dose of rofecoxib was associated with a borderline significantly ($p=0.060$) greater Patient's Global Evaluation score at 8 hours (Table 16).

Patient's Global Evaluation score at 8 hours for naproxen sodium 550 mg was significantly ($p<0.001$) greater than that for placebo. The difference between naproxen sodium 550 mg and rofecoxib 50 mg 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	57	0.9	1.1	1.3	(0.9, 1.6)
MK- 0966 50/ 25 mg	56	1.9	1.4	1.7	(1.4, 2.1)
Naproxen Sodium	58	2.3	1.3	2.1	(1.8, 2.5)

Pairwise Comparison	Difference in LSMeans	95% CI for Difference	p- Value
MK- 0966 50/ 25 mg vs. Placebo	0.5	(0.0, 1.0)	0.060
Naproxen Sodium vs. Placebo	0.9	(0.4, 1.4)	<0.001
Naproxen Sodium vs. 50/ 25 mg	0.4	(- 0.1, 0.9)	0.113

Effect	p- Value	Pooled Intra- Patient SD
Sequence	0.526	5.4
Patient (Sequence)	0.043	
Period (Square)	0.112	
Treatment	0.003	
Stratum (i. e., Baseline PI)	0.485	
Carryover (i. e., Residual)	<0.001*	
Treatment- by- Stratum Interaction	0.615	

* Carryover effect included in the model to estimate LSMeans.

Patient's Rank of Treatment Preference

Compared with those taking placebo, 67.2% of patients ranked rofecoxib 50 mg higher and 73.7% ranked naproxen sodium 550 mg higher (Table 17).

Table 17
Summary of Patient's Rank of Treatment Preference

Treatment	Total	Best	Second Best	Worst
		N (%)	N (%)	N (%)
Placebo	59	8 (13.6)	21 (35.6)	30 (50.8)
MK- 0966 50/ 25 mg	59	26 (44.1)	17 (28.8)	16 (27.1)
Naproxen sodium	58	26 (44.8)	22 (37.9)	10 (17.2)

Patients ranked the analgesic effect of rofecoxib 50 mg significantly higher (p=0.009) than placebo (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 rofecoxib 50 mg 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 50/ 25 mg vs. Placebo	58	39 (67.2)	0.009
Comparison With Naproxen Sodium			
Naproxen Sodium vs. Placebo	57	42 (73.7)	0.001
Naproxen Sodium vs. 50/ 25 mg	57	30 (52.6)	0.691

Peak Analgesic Effect During 8 Hours Postdose

The LSMean Peak PID scores for placebo, rofecoxib 50 mg, and naproxen sodium 550 mg were 1.4, 1.9, 2.0, respectively (Figure 5). The LSMean Peak Pain Relief scores for placebo, rofecoxib 50 mg, and naproxen sodium 550 mg were 2.4, 3.1, 3.3, respectively (Figure 6).

During the 8 hours postdose, rofecoxib 50 mg demonstrated a significantly greater (p=0.001) Peak PID and (p=0.003) Peak Pain Relief compared with placebo.

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 mg.

Figure 5

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

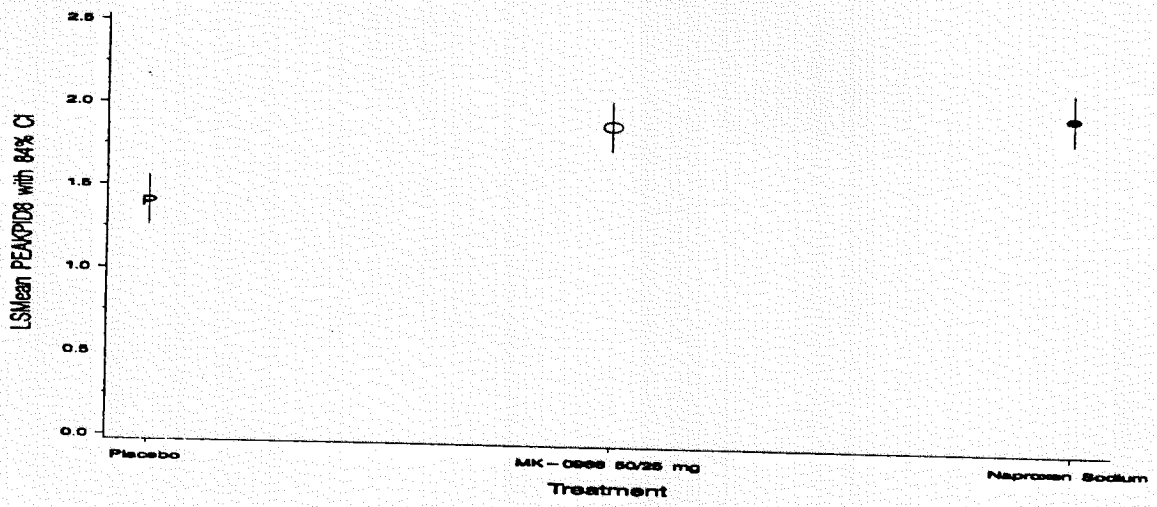
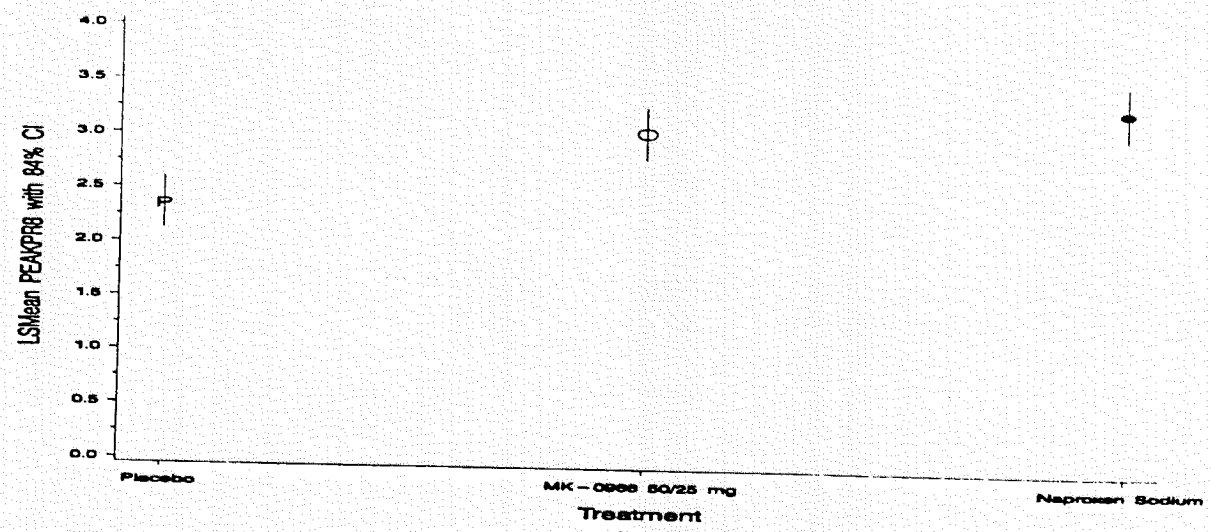


Figure 6

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



Duration of Analgesic Effect

1) Time to Rescue Medication

The median Times to Rescue Medication could not be estimated for rofecoxib 50 mg and naproxen sodium because less than 50% of patients took rescue medication after each treatment. The median time to rescue medication for placebo was 11.8 hours (Table 19).

Patients who received placebo took rescue medication significantly (p=0.001) earlier compared with those who received rofecoxib 50 mg.

Patients who received naproxen sodium 550 mg experienced significantly (p=0.010) longer times to rescue medication compared with those who received placebo. The difference between naproxen sodium 550 mg and rofecoxib 50 mg was not significant (Table 18).

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	60	30 (51.3)	4.7	11.8 (8.5 , NE)	NE
MK- 0966 50/ 25 mg	60	12 (20.4)	NE	NE	NE
Naproxen Sodium	59	16 (27.6)	9.5	NE	NE

Pairwise Comparison	Cox Proportional Hazards Regression (Primary Analysis)		Log-Rank Test ‡
	Risk Ratio (95% CI)	p- Value	p- Value
MK- 0966 50/ 25 mg vs. Placebo	0.33 (0.17, 0.65)	0.001	<0.001
Naproxen Sodium vs. Placebo	0.45 (0.24, 0.82)	0.010	0.007
Naproxen Sodium vs. 50/ 25 mg	1.34 (0.63, 2.83)	0.445	0.427

Effect	p- Value	p-Value
Treatment	0.002	<0.001
Stratum (Baseline Pain Intensity)	0.418	0.427
Treatment- by- Stratum Interaction	0.252	NA

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

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

Of the patients receiving placebo, rofecoxib 50 mg, and naproxen sodium 550 mg, 50.0, 20.0, and 27.1% of patients took rescue medication 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 50-mg treatment compared with placebo.

The difference in Percent of Patients Who Took Rescue Medication between placebo and naproxen sodium 550 mg was significant ($p=0.006$). The difference between rofecoxib 50 mg and naproxen sodium 550 mg 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.

Percent of Patients Who Took Additional Dose of Study Medication

Twenty-three, 37, and 36 patients who did not take rescue medication in the placebo, rofecoxib 50-mg, and naproxen sodium 550-mg treatment. These differences were not statistically significant. Among these patients, there were 47.8, 29.7, and 25.0% of patients who took additional dose of study medication within 12 to 72 hours postdose with placebo, rofecoxib 50 mg, and naproxen sodium 550 mg, respectively.

Patient's Global Evaluation of Treatments at 72 Hours

Patient's Global Evaluations of Treatments at 72 were not statistically different among the different treatment groups.

Safety Results

The incidence of adverse experiences was generally similar across all treatment groups and was not significantly greater in rofecoxib groups compared with placebo. Thirty-three, 27, and 41% of patients in the placebo, rofecoxib 50-mg, and naproxen sodium 550-mg treatments, respectively, reported one or more adverse experiences (Table 19).

Table 19
Clinical Adverse Experience Summary

	Placebo (N= 60)		Rofecoxib 50 mg (N= 60)		Naproxen 550 mg (N=59)	
	n	(%)	n	(%)	n	(%)
Number of patients evaluated	60		60		59	
Number (%) of patients:						
with one or more adverse experiences	20	(33.3)	16	(26.7)	24	(40.7)
with no adverse experience	40	(66.7)	44	(73.3)	35	(59.3)
with drug- related adverse experiences	9	(15.0)	7	(11.7)	12	(20.3)
with serious adverse experiences †	0	(0.0)	0	(0.0)	1	(1.7)
with serious drug- related adverse experiences †	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	0	(0.0)	0	(0.0)	1	(1.7)
Discontinued due to drug-related adverse experiences †	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)	1	(1.7)
discontinued due to serious drug- related adverse experiences †	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.
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 20. Most of the adverse events were GI related. The incidence of adverse experiences was generally similar across all treatments.

Table 20

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

	Placebo (N= 60)		MK- 0966 50 mg (N= 60)		Naproxen Sodium 550 mg (N= 59)	
	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	20	(33.3)	16	(26.7)	24	(40.7)
Patients with no adverse experience	40	(66.7)	44	(73.3)	35	(59.3)
Body as a whole/ site unspecified	6	(10.0)	7	(11.7)	11	(18.6)
Cardiovascular system	1	(1.7)	0	(0.0)	1	(1.7)
Digestive system	8	(13.3)	4	(6.7)	9	(15.3)
Ears, eyes, nose, and throat	4	(6.7)	2	(3.3)	5	(8.5)
Musculoskeletal system	1	(1.7)	2	(3.3)	4	(6.8)
Nervous and psychiatric system	5	(8.3)	3	(5.0)	2	(3.4)
Psychiatric disorder	1	(1.7)	2	(3.3)	0	(0.0)
Respiratory system	1	(1.7)	0	(0.0)	1	(1.7)
Skin- skin appendages	1	(1.7)	0	(0.0)	1	(1.7)
Urogenital system	0	(0.0)	0	(0.0)	4	(6.8)

No significant differences between treatments 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 15, 12, and 20% for placebo, rofecoxib 50 mg, and naproxen sodium 550 mg, respectively. The incidence of drug-related adverse experiences was not significantly greater with rofecoxib 50 mg compared with placebo.

A pregnancy occurred in 1 of 63 patients in who was assigned to naproxen sodium 550 mg. There were no other serious adverse experiences in any of the treatments. This was the only patient who discontinued due to a clinical adverse experience.

Adverse Experiences—Laboratory

Of the 63 randomized patients, 62 (98%) had at least one laboratory test postrandomization (postbaseline). Laboratory adverse experiences were recorded for 2 of these 62 randomized patients, both of them in the placebo group.

No laboratory adverse experiences were considered serious.

No patient discontinued due to a laboratory adverse experience.

Discussion and Overall Conclusions for Study # 055

Rofecoxib at a dose of 50-mg dose demonstrated a significantly greater analgesic effect compared to placebo and a comparable analgesic effect compared to naproxen 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 between 1 to 1.5 hours post dose and it seems that efficacy has been sustained for 12 hours. 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 acceptable. The single dose administration of rofecoxib provided results of efficacy and was validated by naproxen in this study model.

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

Study Number: P056

Study Dates: 6 July 1997 – 13 February 1998

Title of Study: A Randomized, Placebo- and Active Comparator-Controlled Trial Comparing 25 mg to 50 mg of rofecoxib in the Treatment of Primary Dysmenorrhea.

Investigator and Location: Steven E. Daniels, D.O.

[redacted]

Austin, Texas 78705

Objectives:

a) To determine the analgesic effects of a single oral dose of rofecoxib 50 mg and compare with that of naproxen sodium 550 mg and placebo in the treatment of pain due to primary dysmenorrhea.
b) To determine the dose response of analgesic effects of a single oral dose of rofecoxib 25 or 50 mg and compare with that of naproxen sodium 550 mg and placebo in the treatment of pain due to primary dysmenorrhea.
c) To determine the peak, time to onset, and duration of analgesic effects of rofecoxib 25 and 50 mg and naproxen sodium 550 mg compared with those of placebo in the treatment of pain due to primary dysmenorrhea.
d) To characterize the efficacy of rofecoxib when administered in repeated doses throughout a given menstrual cycle in the treatment of moderate-to-severe abdominal cramping pain due to primary dysmenorrhea.

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 the study 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) that was not 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.

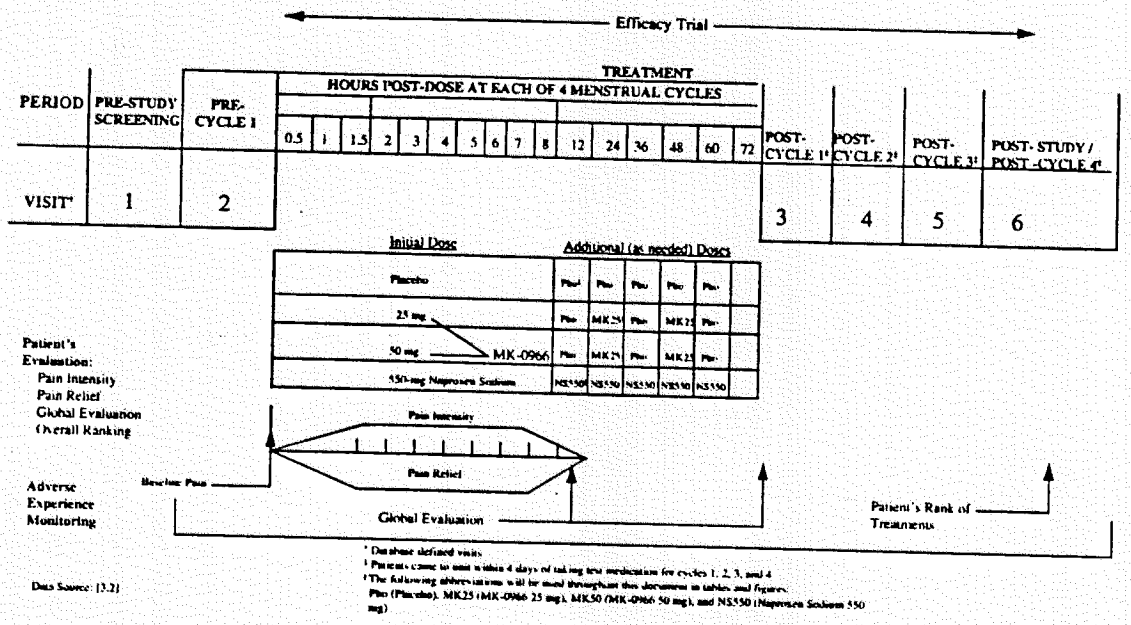
11) Patient had donated a unit of blood or plasma or participated in another clinical study within the last 4 weeks.

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

Study Description

This was a single-center, double-blind, randomized, balanced, 4-period, complete block, crossover study comparing 25- and 50-mg doses of rofecoxib with placebo and 550 mg naproxen sodium administered to patients experiencing moderate-to-severe pain due to primary dysmenorrhea in each of four consecutive menstrual cycles (Figure 1). Patients were randomly assigned to balanced sequences of each of the following four 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, rofecoxib 50 mg followed by rofecoxib 25 mg daily as needed, or rofecoxib 25 mg followed by rofecoxib 25 mg daily as needed.

Figure 1: Schedule of Observations and Procedures



[1] Database defined visits

[2] Patients came to unit within 4 days of taking test medication for cycles 1, 2, 3, and 4

[3] The following abbreviations will be used throughout this document in tables and figures: Plac (Placebo), MK25 (MK-0966 25 mg), MK50 (MK-0966 50 mg), and NS550 (Naproxen Sodium 550 mg)

Treatments Administered (Tables 1&2):

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]

‡ 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.

Table 2
Sample Allocation Schedule

Sequence of Sequence of Treatment	Treatment Period			
	1	2	3	4
1	A	B	C	D
2	B	D	A	C
3	Celecoxib	A	D	B
4	D	C	B	A

Treatment:
A = Placebo/placebo.
B = Rofecoxib 25 mg/25 mg.
C = Rofecoxib 50 mg/25 mg.
D = Naproxen sodium 550 mg/550 mg.

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, 2, and 3 Visits (Visits 3, 4, and 5)
Each patient returned to the clinical research center for evaluation within 4 days after having taken test medication for cycles 1, 2, and 3. Test drug and a new patient diary for menstrual cycle 2, 3 or 4 were given to the patient at this time.

Postcycles 4 Visit (Visit 6)
Upon completion of the fourth 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 4 treatments in order of overall efficacy. Patients received a final telephone contact 2 weeks after the last dose for safety evaluation.