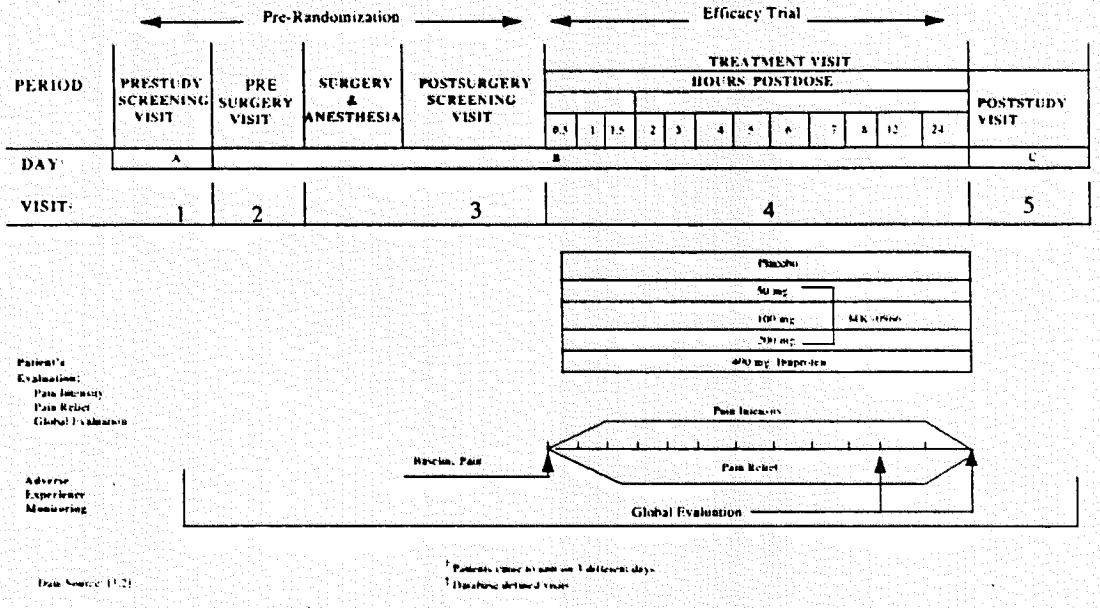
Schedule of Observations and Procedures

Figure 1

Study Schematic



Eligibility:

1) Patient was a male or female and ≥16 years of age. Female patients demonstrated a serum β-HCG consistent with a nongravid state at the prestudy visit and agreed to remain abstinent, use oral contraceptives, or use double-barrier contraception (partner using condom and patient using diaphragm, contraceptive sponge, intrauterine device [IUD], or spermicidal foam/jelly) from the prestudy visit until 24 hours postsurgery. Women who were postmenopausal or status posthysterectomy or tubal ligation were exempt from this requirement.

2) All patients selected had been scheduled to have two or more third molars removed, at least one of which was partially embedded in bone and was a mandibular impaction. Patient may not have had a previous molar extraction within the past 45 days.

3) Patients must have been experiencing moderate to severe pain following the procedure.

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

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

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

Exclusions:

1) Patient was mentally or legally incapacitated, had significant emotional problems at the time of the study, or had a history of psychiatric disorders.

2) Patients had prior therapy that could interfere with the evaluation of efficacy, safety, or tolerability:

- Any analgesic, aspirin, acetaminophen, or ibuprofen must have been discontinued 24 hours prior to taking study medication. Naproxen (NAPROSYN ™ [Syntex Puerto Rico, Inc., Puerto Rico, U. S. A.]) or naproxen sodium (ANAPROX ™ [Syntex Puerto Rico, Inc., Puerto Rico, U. S. A.], ALEVE ™ [Proctor and Gamble, Ohio, U. S. A.]) must have been discontinued 48 hours prior to taking study medication; NAPRELAN ™ (naproxen sodium, Elan Pharma, Ltd., Thlone, County Westmeath, Ireland) must have been discontinued 72 hours prior to taking study medication.

- Any analgesics or other agents, during the 6 hours preceding surgery, that could have confounded the analgesic responses. Specifically excluded were tricyclic antidepressants, narcotic analgesics, antihistamines, tranquilizers, hypnotics, sedatives, or corticosteroids. Presurgical medications such as nitrous oxide, xylocaine with epinephrine, VALIUM ™ (diazepam, Hoffman- La Roche, Inc., NJ, U. S. A.), VERSED ™ (midazolam hydrochloride, Hoffman- La Roche, Inc., NJ, U. S. A.), BREVITAL ™ (methohexital sodium, Eli Lilly and Company, IN, U. S. A.) atropine, or fentanyl were exempt from this exclusion.

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

4) 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 may have participated), or a history of any illness that, in the opinion of the investigator, might have confounded the results of the study or posed additional risk to the patient.

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

6) Patient had clinically significant abnormalities of prestudy clinical examination or laboratory safety tests. As a guide, the following values were generally considered clinically significant: Hgb <11 g/ dL, WBC <3500/ cc, platelets <100,000/ cc, AST >1.5 x 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.

7) Patient was allergic or intolerant to naproxen sodium, aspirin, ibuprofen, indomethacin, or other NSAIDs or had a history of asthma in association with nasal polyps. Patient was allergic or intolerant to VICODIN ™ (acetaminophen plus hydrocodone bitartrate, Knoll Pharmaceutical Company, NJ, U. S. A.), hydrocodone bitartrate, or acetaminophen.

8) Patient had morbid obesity and demonstrated significant health problems stemming from their obesity.

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

10) Patient was, at the ti me 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.

Treatments Administered (Table 1):

Study Medication	Formulation No.
rofecoxib	
50 mg	MR-3360
100 mg ‡	MR-3370
200 mg §	MR-3370
Placebo X ¢	MR-3361
Placebo Y¶	MR-3361
Ibuprofen# 400-mg	MR- 3557
Placebo Z††	MR-3382

The 50-mg dose consisted of two 25-mg tablets.
‡ The 100-mg dose consisted of two 50-mg tablets.
§ The 200-mg dose consisted of four 50-mg tablets.
¢ Placebo X was in the image of the 25-mg rofecoxib tablet.
¶ Placebo Y was in the image of the 50-mg rofecoxib tablet.
# MOTRIN™, McNeil Consumer Products Co., PA, U.S.A.
†† Placebo Z was in the image of the ibuprofen 400-mg tablet.

Blinding

Patients received study medication in a single bottle. Each patient received 7 tablets. All bottles were labeled with double-blind, three-part, tear-off labels.
Table 2 shows the bottle contents by treatment.

Table 2
Bottle Contents by Treatment Group

Treatment Group	rofecoxib 25- mg Tablet	Placebo of rofecoxib 25- mg Tablet	rofecoxib 50-mg Tablet	Placebo of rofecoxib 50- mg Tablet	Ibuprofen 400-mg tablet	Placebo Image of Ibuprofen 400- mg Tablet
rofecoxib 50 mg	2	0	0	4	0	1
100 mg	0	2	2	2	0	1
200mg	0	2	4	0	0	1
Ibuprofen 400 mg	0	2	0	4	1	0
Placebo	0	2	0	4	0	1

Rescue Medication for Dental Pain

During the 8- hour postdose period, a combination analgesic medication consisting of acetaminophen plus hydrocodone bitartrate was administered as "rescue analgesia" (at a dose determined by the investigator) if the patient experienced inadequate pain relief with study medication. Patients were asked to avoid using rescue analgesia during the first 90 minutes postdose to allow the study drug to exhibit an effect. The time the rescue analgesia was used during the 24-hour study was recorded. In the event "rescued" patients continued to experience inadequate pain relief, they received additional doses of acetaminophen plus hydrocodone bitartrate as needed.

Efficacy Assessment:

The patient recorded specific assessments of Pain Relief, Pain Intensity, and Global (overall) Evaluation of the study drug.
Patients were required to fast from all food and drink except water for a minimum of 2 hours prior to obtaining the serum chemistry panel during the pre- and poststudy evaluations and from midnight on the evening prior to surgery. Patients continued to fast, except for beverages, following surgery, and until dosing. Two hours postdose, the patient's diet was advanced as determined by the investigator. The patients remained in the study unit for the ensuing 8 hours and then completed additional assessments as outpatients.

1) Ratings of Pain Intensity and Pain Relief
The following assessments at 0.50, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours postdose:

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

2) Time to Confirmed Perceptible Pain Relief (Stopwatch)
Two stopwatches were initiated at the time of dosing. The coordinator instructed the patient to click "off" one stopwatch at the time the patient experienced perceptible pain relief and to click "off" the other stopwatch at the time the patient experienced meaningful pain relief (double-click stopwatch technique). The coordinator recorded the elapsed times on the patient's case report form.

3) Time to Taking Rescue Medication
Patients were instructed to ask the study coordinator for additional medication, as needed, while in the study center. The date and time of this request was recorded by the patient in their diary. If additional medication was taken after the patient left the study center, the date and time of rescue medication was recorded by the patient in their diary.

4) Patient's Global Evaluation
At 8 and 24 hours postdose, or at the time the patient took rescue medication, the patient answered the following question in the diary:
"How would you rate the study medication you received for pain?"
"POOR," "FAIR," "GOOD," "VERY GOOD," or "EXCELLENT."

Statistical Analysis

There were no missing pain scores for any other reasons than taking a rescue medication. No patient was excluded due to a protocol violation. Therefore, the per-protocol analysis was not performed. 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	
Overall Analgesic Effect	
TOPAR8 (primary), SPID8 (secondary), Patient's Global Evaluation at 8 (secondary) and at 24 hours	Analysis of variance (ANOVA) model †, Tukey step-down trend test procedure for comparison between rofecoxib doses and placebo, and comparisons between each pair of rofecoxib doses, plot of LSMean with 84% confidence interval (CI) for TOPAR8 by treatment, plot and summary table of percent of patients in each category of the Global Evaluation Score by treatment group, analysis of covariance
Onset of Analgesic Effect	
Time to Confirmed Pain Relief (Stopwatch Time of Perceptible Pain Relief, confirmed by the second stopwatch), Time to PID^{3}1	Cox proportional hazards regression model †, Kaplan-Meier estimates of 25, 50, and 75th percentiles and 95% CI for the 50th percentile, plot of cumulative proportion of patients with meaningful Pain Relief or PID^{3}1 over time (1-Kaplan-Meier estimates of survival function), bar chart of incidence rates, logistic regression † on the proportions of patients who experienced onset of analgesia
Peak Analgesic Effect	
Peak Pain Relief and Peak PID	ANOVA †, Tukey step-down trend test procedure for comparisons between MK-066 doses and placebo, and comparisons between each pair of rofecoxib doses, plot of LSMean with 84% CI by treatment group
Duration of Analgesic Effect	
Time to Rescue Medication Use	Cox proportional hazards regression model †, Kaplan-Meier estimates of 25, 50, and 75th percentiles and 95% CI for the median, plot of cumulative proportion of patients taking rescue medication over time (1-Kaplan-Meier estimates of survival function), bar chart of incidence rates
Percent of Patients Who Took Rescue Medication	Logistic regression model †, bar chart of proportion of patients taking rescue medication by treatment group
Pain Relief, PID, PRID at 12 and 24 hours	ANOVA †, Tukey step-down trend test procedure for comparisons between rofecoxib doses and placebo, and comparisons of plot of LSMean with 84% CI by treatment between each pair of rofecoxib doses
Pain Assessment at Each Time Point	
Pain Relief, PID, PRID, APAR, APID	ANOVA †, Tukey step-down trend test procedure for assessment of dose response, plot of mean with 84% CI over time
TOPAR, SPID	ANOVA †, Tukey step-down trend test procedure for assessment of dose response, plot of mean with 84% CI over time

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

Safety	
Vital Signs and Laboratory Safety Parameters	
Percent of patients with pre-defined changes in vital signs and laboratory parameters	The step-down trend test procedure (Cochran-Armitage) for assessing dose response, the step-down Fisher's exact test for comparisons vs. ibuprofen (if the difference between rofecoxib 200 mg and ibuprofen is not significant then the p-value for the difference between 100 mg and ibuprofen will not be provided, and so forth)
Observed or log (observed value) for some laboratory parameters	Summary statistics, plot of observed mean and mean change from baseline with 84% confidence limits over time
End Point	Statistical Analysis
Adverse Experience Counts	
Number (%) of patients with adverse experiences (including by category)	The step-down trend test procedure (Cochran-Armitage) for assessing dose response, the step-down Fisher's exact test for comparisons vs. ibuprofen (If the difference between rofecoxib 200 mg and ibuprofen is not significant then the p-value for the difference between 100 mg and ibuprofen will not be provided, and so forth)
† Model included treatment and baseline Pain Intensity as factors. The treatment-by-baseline Pain Intensity was tested and removed from the model, if it was found not significant at the 5% level.	

RESULTS:

Disposition of Patients

Two hundred and fifty four (254) patients were enrolled in this study and were randomized to receive one of five treatments: 50 patients received rofecoxib 50 mg, 52 patients received rofecoxib 100 mg, 50 patients received rofecoxib 200 mg, 52 patients received ibuprofen 400 mg, and 50 patients received placebo.
Baseline demographic characteristics are presented in table 4.
The treatment groups were comparable for age, race and gender. For all patients, the age range was 15 to 42 years. Across treatment groups, 23% of the patients were male and 65% were white.

Table 4
Baseline Patient Characteristics by Treatment Group

	Placebo		rofecoxib						Ibuprofen		Total	
	(N= 50)		50 mg (N= 50)		100 mg (N= 52)		200 mg (N= 50)		400 mg (N= 52)		(N= 254)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gender												
Female	40	(80.0)	39	(78.0)	43	(82.7)	36	(72.0)	38	(73.1)	196	(77.2)
Male	10	(20.0)	11	(22.0)	9	(17.3)	14	(28.0)	14	(26.9)	58	(22.8)
Race												
Asian	4	(8.0)	0	(0.0)	1	(1.9)	0	(0.0)	3	(5.8)	8	(3.1)
Black	5	(10.0)	2	(4.0)	5	(9.6)	8	(16.0)	7	(13.5)	27	(10.6)
European	0	(0.0)	1	(2.0)	1	(1.9)	0	(0.0)	0	(0.0)	2	(0.8)
Hispanic American	17	(34.0)	5	(10.0)	12	(23.1)	6	(12.0)	13	(25.0)	53	(20.9)
White	24	(48.0)	42	(84.0)	33	(63.5)	36	(72.0)	29	(55.8)	164	(64.6)
Age												
≤ 20	22	(44.0)	18	(36.0)	18	(34.6)	22	(44.0)	22	(42.3)	102	(40.2)
21 to 30	23	(46.0)	29	(58.0)	28	(53.8)	27	(54.0)	27	(51.9)	134	(52.8)
31 to 40	5	(10.0)	2	(4.0)	6	(11.5)	1	(2.0)	3	(5.8)	17	(6.7)
41 to 50	0	(0.0)	1	(2.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Mean	22.1		23.2		23.2		21.6		22.3		22.5	
SD	4.72		5.77		5.20		3.97		4.95		4.96	
Median	21.5		22.0		22.0		21.5		21.0		21.5	
Range	16 to 33		16 to 42		16 to 38		15 to 34		15 to 37		15 to 42	

Summary of Dental Surgery

The baseline pain intensity, duration of surgery, degree of impaction, and number of molars extracted and were comparable across all treatment groups (table 5).

Table 5
Additional Patient Characteristics by Treatment Group

	Placebo	rofecoxib			Ibuprofen 400 mg	Total
		50 mg	100 mg	200 mg		
Baseline Pain Intensity: n (%) Patients						
Moderate	26 (52.00)	28 (56.00)	29 (55.77)	28 (56.00)	29 (55.77)	140 (55.12)
Severe	24 (48.00)	22 (44.00)	23 (44.23)	22 (44.00)	23 (44.23)	114 (44.88)
Duration of Surgery (Minutes)						
Mean	16.16	16.64	14.07	15.68	16.78	15.86
SD	8.45	8.62	6.56	6.61	7.83	7.66
Median	15.00	15.00	12.00	15.00	15.00	15.00
Range	5 to 55	5 to 51	5 to 35	5 to 30	4 to 42	4 to 55
Number of Teeth Removed						
Mean	2.08	2.16	2.06	2.18	2.15	2.13
SD	0.34	0.51	0.31	0.52	0.46	0.44
Median	2.00	2.00	2.00	2.00	2.00	2.00
Range	2 to 4	2 to 4	2 to 4	2 to 4	2 to 4	2 to 4
Impaction Score (1 to 4 Scale)						
Mean	3.43	3.46	3.45	3.34	3.35	3.41
SD	0.41	0.43	0.40	0.49	0.49	0.45
Median	3.50	3.50	3.50	3.50	3.50	3.50
Range	2.5 to 4	2.5 to 4	2.3 to 4	2.3 to 4	2.3 to 4	2.3 to 4

Accounting for Patients in the Analysis

Of the 254 randomized patients, 249 completed the protocol as specified. Five patients were lost to follow-up and were therefore discontinued (1 placebo, 1 rofecoxib 50 mg, 1 rofecoxib 100 mg, 2 rofecoxib 200 mg).

Of the 254 patients included in the intention-to-treat approach to the efficacy analysis, each had a valid baseline pain intensity score and at least one valid postdose pain evaluation. No patient took rescue medication prior to 90 minutes. There were 98, 64, 40, 40, and 92% of the patients in the placebo, 50-, 100-, 200-mg rofecoxib, and 400-mg ibuprofen groups, respectively, who used rescue medication 1.5 to 24 hours postdose. There were no missing pain scores for any other reasons. No patient was excluded due to a protocol violation. Therefore, the per-protocol analysis was not performed. All 254 randomized patients were included in the safety analysis.

Analysis of Primary Efficacy Measures

Pain Intensity score, Pain Relief score, Patient's Global Evaluation, Time to Perceptible and Meaningful Pain Relief (stopwatch), 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 Global Evaluation Score at 24 Hours as the measures for overall analgesic effect.
The reviewer preferred the Division's approach and analyzed first the Mean Pain Intensity Difference Scores Over Time (PID) and the Mean Pain Relief Scores Over Time (PR) as measures for overall analgesic effect.

Mean Pain Intensity Difference Scores Over Time (PID, LOCF and BOCF)
Figure 2 and table 6 present the mean PID scores (categorical scale) at all assessment times during the 24 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 and 100-mg treatment groups were statistically significantly better than placebo at all assessment times from the 1 hour through 24.0 hours postdose. The mean PID values for the rofecoxib 200-mg treatment group were statistically significantly better than placebo at all assessment times from the 0.5 hour through 24.0 hours postdose.

Within rofecoxib treatment groups, the mean PID scores for the rofecoxib 200-mg group were statistically better than mean scores for the rofecoxib 50-mg treatment group at the 0.5 through 24.0-hour assessment times and statistically better than mean scores for the rofecoxib 100-mg treatment group at the 0.5 and 1.5-hour assessment time only. The mean PID scores for the rofecoxib 100-mg treatment group were statistically better than mean scores for the rofecoxib 50-mg group at the 3 through 8-hour assessment times and at the 24.0-hour assessment time.

The mean PID scores for the ibuprofen 400-mg group were statistically significant better than placebo from 1 hour through 24 hours postdose. The mean PID scores for the ibuprofen 400-mg group were not statistically different than those for the rofecoxib 50-mg group up to 6 hours. At 7 through 24-hour assessments the rofecoxib 50-mg treatment group had statistically significantly better PID scores. The rofecoxib 200-mg treatment group was statistically superior to the ibuprofen group at 1.5 through 24 hour assessment times. The rofecoxib 100-mg treatment group was statistically superior to the ibuprofen group at 3 through 24-hour assessment times.

Reanalyzing the data by using the baseline observation carried forward (BOCF) technique revealed the same statistically significant superiority for all rofecoxib treatment groups over the placebo in the mean PID values at all assessment times from the 1 hour through 24.0 hours postdose.

Within rofecoxib treatment groups, the BOCF analysis revealed the same superiority of the 200-mg group over the 50 and 100-mg groups. The rofecoxib 100-mg treatment group was statistically better than the rofecoxib 50-mg group in mean PID scores at the 3 through 5-hour assessment times only (instead of 3 through 8 and at 24).

Ibuprofen was statistically superior to placebo from 1 hour only through 8 hours postdose (instead of 24 hours). The mean PID scores for the ibuprofen 400-mg group were not statistically different than those for the rofecoxib 50-mg group up to 5 hours. At 6 through 24-hour assessments the rofecoxib 50-mg treatment group had statistically significantly better PID scores. The superiority of the rofecoxib 200-mg (at 1.5 through 24 hours) and 100-mg (at 3 through 24 hours) over the ibuprofen group remained the same.

Figure 2

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

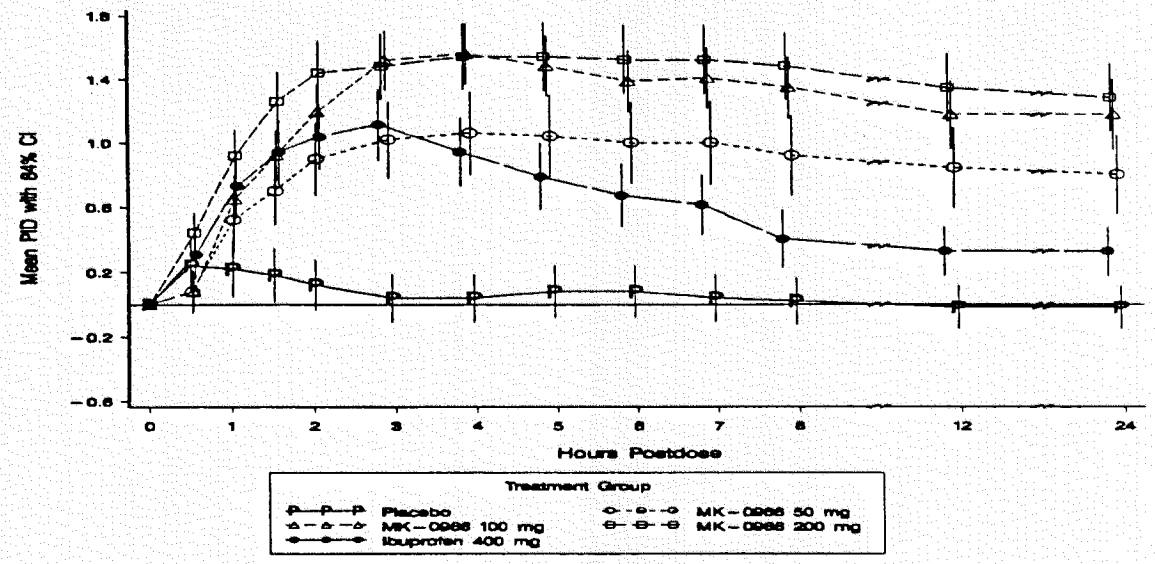


Table 6

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

		Summary Statistics by Time Point (Hours Postdose)											
Treatment		0.5	1	1.5	2	3	4	5	6	7	8	12	24
acebo	N	50	50	50	24	12	5	4	4	4	4	2	1
	MEAN	0.2 AB	0.2 C	0.2 C	0.1 C	0.0 C	0.0 C	0.1 C	0.1 C	0.0 D	0.0 D	0.0 D	-0.0 D
	STD	0.7	0.9	0.8	0.8	0.7	0.7	0.8	0.8	0.7	0.4	0.7	0.7
rofecoxib 50 mg	N	50	50	50	38	34	32	30	28	26	25	23	20
	MEAN	0.1 B	0.5 B	0.7 B	0.9 B	1.0 B	1.1 B	1.1 B	1.0 B	1.0 B	0.9 B	0.8 B	0.8 B
	STD	0.7	1.0	1.0	1.1	1.2	1.3	1.3	1.3	1.3	1.2	1.2	1.2
rofecoxib 100 mg	N	51	51	52	46	45	45	44	44	39	38	36	31
	MEAN	0.1 B	0.9 AB	0.9 B	1.2 AB	1.5 A	1.6 A	1.5 A	1.4 A	1.4 A	1.3 A	1.2 AB	1.2 A
	STD	0.6	0.8	0.8	0.9	0.9	1.0	1.0	1.0	1.0	1.0	1.1	1.1
rofecoxib 200 mg	N	50	50	50	44	42	39	38	38	37	36	34	31
	MEAN	0.4 A	0.7 A	1.3 A	1.4 A	1.5 A	1.5 A	1.5 A	1.5 A	1.5 A	1.5 A	1.3 A	1.3 A
	STD	0.6	1.0	0.9	1.0	1.0	1.0	1.1	1.1	1.1	1.0	1.1	1.1
Ibuprofen 400 mg	N	52	52	52	42	38	33	27	21	19	15	6	4
	MEAN	0.3 AB	1.6 AB	0.9 B	1.0 B	1.1 B	0.9 B	0.8 B	0.7 B	0.6 C	0.4 C	0.3 C	0.3 C
	STD	0.8	1.2	1.0	1.0	1.1	1.1	1.1	1.0	0.9	0.9	0.9	0.8
p- Values from Between- Treatment Pairwise Comparisons by Time Point (Hours Postdose) Pairwise Comparison													
rofecoxib vs Placebo:													
rofecoxib 50 mg vs Placebo a		-	0.027	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
rofecoxib 100 mg vs Placebo a		-	0.003	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
rofecoxib 200 mg vs Placebo a		0.066	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Between rofecoxib Doses													
rofecoxib 100 mg vs 50 mg b		0.946	0.439	0.165	0.087	0.005	0.006	0.016	0.034	0.024	0.015	0.059	0.036
rofecoxib 200 mg vs 50 mg b		0.003	0.009	<0.001	0.002	0.011	0.009	0.007	0.005	0.004	0.002	0.005	0.007
rofecoxib 200 mg vs 100 mg		0.003	0.062	0.034	0.140	0.834	0.932	0.735	0.444	0.504	0.435	0.335	0.538
With Ibuprofen 400 mg													
Ibuprofen 400 mg vs Placebo		0.452	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.017	0.031	0.033
Ibuprofen 400 mg vs rofecoxib 50 mg		0.061	0.166	0.131	0.420	0.599	0.506	0.163	0.068	0.030	0.003	0.004	0.008
Ibuprofen 400 mg vs rofecoxib 100 mg		0.051	0.540	0.903	0.358	0.022	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Ibuprofen 400 mg vs rofecoxib 200 mg		0.267	0.204	0.045	0.017	0.039	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

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

Figure 3 and table 7 present the mean PR scores (categorical scale) at all assessment times during the 24 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, 100-mg and 200-mg treatment groups were statistically significantly better than placebo at all assessment times from the 1 hour through 24.0 hours postdose.

Within rofecoxib treatment groups, the mean PR scores for the rofecoxib 200-mg group were statistically better than mean scores for the rofecoxib 50-mg treatment group at the 1 through 24.0-hour assessment times and statistically comparable to the mean scores for the rofecoxib 100-mg treatment group. The mean PR scores for the rofecoxib 100-mg treatment group were statistically better than mean scores for the rofecoxib 50-mg group at the 3 through 24-hour assessment times.

The mean PR scores for the ibuprofen 400-mg group were statistically significant better than placebo from 1 hour through 7 hours postdose. The mean PR scores for the ibuprofen 400-mg group were not statistically different than those for the rofecoxib 50-mg group up 4 hours. At 5 through 24-hour assessments the rofecoxib 50-mg treatment group had statistically significantly better PR scores. The rofecoxib 200-mg treatment group was statistically superior to the ibuprofen group at 2 through 24-hour assessment times. The rofecoxib 100-mg treatment group was statistically superior to the ibuprofen group at 3 through 24-hour assessment times.

Reanalyzing the data by using the baseline observation carried forward (BOCF) technique revealed the same statistically significant superiority for all rofecoxib treatment groups over the placebo in the mean PR values at all assessment times from the 1 hour through 24.0 hours postdose.

Within rofecoxib treatment groups, the BOCF analysis revealed the same results as the LOCF one (superiority of the 200-mg group over the 50-mg at 1 through 24 hours and comparability to the 100-mg group and superiority of the 100-mg group over the 50-mg group at 3 through 24 hours).

The mean PR scores for the ibuprofen 400-mg group were statistically significant better than placebo from 1 hour through 7 hours postdose (same as the LOCF analysis). The mean PR scores for the ibuprofen 400-mg group were not statistically different than those for the rofecoxib 50-mg group up 5 (instead of 4) hours postdose. At 6 through 24-hour assessments the rofecoxib 50-mg treatment group had statistically significantly better PR scores. The rofecoxib 200-mg treatment group was statistically superior to the ibuprofen group at 3 (instead of 2) through 24-hour assessment times. The rofecoxib 100-mg treatment group was statistically superior to the ibuprofen group at 3 (same as the LOCF analysis) through 24-hour assessment times.

Figure 3

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

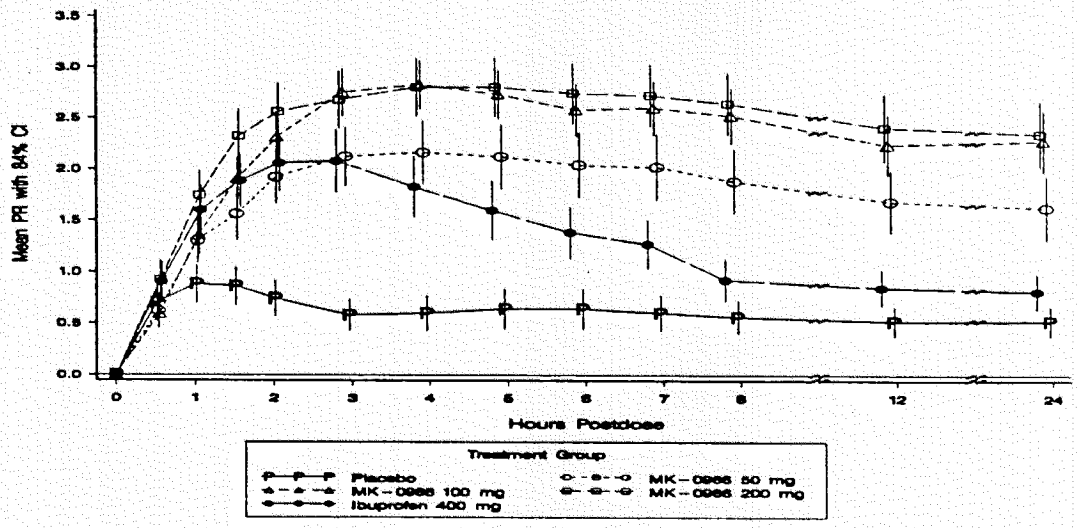


Table 7

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

		Summary Statistics by Time Point (Hours Postdose)											
Treatment		0.5	1	1.5	2	3	4	5	6	7	8	12	24
Placebo	N	50	50	50	24	12	5	4	4	4	4	2	1
	MEAN	0.7 A	0.9 C	0.9 C	0.7 C	0.6 C	0.6 C	0.6 D	0.6 D	0.6 D	0.6 C	0.5 C	0.5 C
	STD	0.9	0.9	0.9	0.9	0.8	0.9	1.0	1.0	0.9	0.8	0.7	0.7
rofecoxib 50 mg	N	50	50	50	38	34	32	30	28	26	25	23	20
	MEAN	0.6 A	1.3 B	1.6 B	1.9 B	2.1 B	2.2 B	2.1 B	2.0 B	2.0 B	1.9 B	1.7 B	1.6 B
	STD	0.8	1.1	1.3	1.3	1.4	1.5	1.6	1.6	1.6	1.6	1.5	1.6
rofecoxib 100 mg	N	51	51	52	46	45	45	44	44	39	38	36	31
	MEAN	0.6 A	1.4 AB	1.9 AB	2.3 AB	2.8 A	2.8 A	2.7 A	2.6 A	2.6 A	2.5 A	2.2 A	2.3 A
	STD	0.7	0.9	1.0	1.1	1.2	1.2	1.2	1.3	1.3	1.4	1.5	1.5
rofecoxib 200 mg	N	50	50	50	44	42	39	38	38	37	36	34	31
	MEAN	0.9 A	1.7 A	2.3 A	2.6 A	2.7 A	2.8 A	2.8 A	2.7 A	2.7 A	2.6 A	2.4 A	2.3 A
	STD	0.9	1.2	1.3	1.4	1.4	1.4	1.4	1.5	1.5	1.5	1.6	1.6
Ibuprofen 400 mg	N	52	52	52	42	38	33	27		19	15	6	4
	MEAN	0.9 A	1.6 AB	1.9 AB	2.1 B	2.1 B	1.8 B	1.6 C	1.4 C	1.3 C	0.9 C	0.8 C	0.8 C
	STD	1.0	1.2	1.3	1.4	1.6	1.5	1.4	1.3	1.2	1.0	0.9	0.9
p- Values from Between- Treatment Pairwise Comparisons by Time Point (Hours Postdose)													
rofecoxib vs Placebo:													
rofecoxib 50 mg vs Placebo a	-	0.045	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
rofecoxib 100 mg vs Placebo a	-	0.025	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
rofecoxib 200 mg vs Placebo a	0.185	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
Between rofecoxib Doses													
rofecoxib 100 mg vs 50 mg b	-	0.816	0.138	0.115	0.015	0.012	0.022	0.044	0.029	0.014	0.034	0.013	
rofecoxib 200 mg vs 50 mg b	0.082	0.041	0.001	0.010	0.032	0.017	0.012	0.010	0.009	0.004	0.006	0.006	
rofecoxib 200 mg vs 100 mg	0.052	0.068	0.072	0.302	0.787	0.921	0.793	0.538	0.636	0.639	0.513	0.785	
With Ibuprofen 400 mg													
Ibuprofen 400 mg vs Placebo	0.215	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.005	0.010	0.154	0.202	0.263	
Ibuprofen 400 mg vs rofecoxib 50 mg	0.097	0.165	0.162	0.576	0.865	0.208	0.049	0.014	0.005	<0.001	0.001	0.002	
buprofen 400 mg vs rofecoxib 100 mg	0.062	0.246	0.933	0.303	0.009	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
Ibuprofen 400 mg vs rofecoxib 200 mg	0.922	0.497	0.060	0.041	0.020	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	

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

Figure 4 and table 8 present the mean PRID scores (categorical scale) at all assessment times during the 24 hour Treatment Period. Imputing PRID data has been done using last observation carried forward (LOCF) method.

The mean PRID values for the rofecoxib 50-mg, 100-mg and 200-mg treatment groups were statistically significantly better than placebo at all assessment times from the 1 hour through 24.0 hours postdose.

Within rofecoxib treatment groups, the mean PRID scores for the rofecoxib 200-mg group were statistically better than mean scores for the rofecoxib 50-mg treatment group at the 0.5 through 24.0-hour assessment times and statistically comparable to the mean scores for the rofecoxib 100-mg treatment group (except for superiority at 0.5 and 1.5 hours). The mean PR scores for the rofecoxib 100-mg treatment group were statistically better than mean scores for the rofecoxib 50-mg group at the 3 through 24-hour assessment times.

The mean PRID scores for the ibuprofen 400-mg group were statistically significant better than placebo from 1 hour through 7 hours postdose. The mean PRID scores for the ibuprofen 400-mg group were not statistically different than those for the rofecoxib 50-mg group up 5 hours. At 6 through 24-hour assessments the rofecoxib 50-mg treatment group had statistically significantly better PR scores. The rofecoxib 200-mg treatment group was statistically superior to the ibuprofen group at 1.5 through 24-hour assessment times. The rofecoxib 100-mg treatment group was statistically superior to the ibuprofen group at 3 through 24-hour assessment times.

Reanalyzing the data by using the baseline observation carried forward (BOCF) technique revealed the same statistically significant superiority for all rofecoxib treatment groups over the placebo in the mean PRID values at all assessment times from the 1 hour through 24.0 hours postdose.

Within rofecoxib treatment groups, the BOCF analysis revealed the same results as the LOCF one (superiority of the 200-mg group over the 50-mg at 0.5 through 24 hours and over the 100-mg group at 0.5 through 1.5 hours, and superiority of the 100-mg group over the 50-mg group at 3 through 24 hours).

The mean PRID scores for the ibuprofen 400-mg group were statistically significant better than placebo from 1 hour through 7 hours postdose (same as the LOCF analysis). The mean PR scores for the ibuprofen 400-mg group were not statistically different than those for the rofecoxib 50-mg group up 5 hours postdose (same as the LOCF analysis). At 6 through 24-hour assessments the rofecoxib 50-mg treatment group had statistically significantly better PR scores. The rofecoxib 200-mg treatment group was statistically superior to the ibuprofen group at 1.5 (same as the LOCF analysis) through 24-hour assessment times. The rofecoxib 100-mg treatment group was statistically superior to the ibuprofen group at 3 (same as the LOCF analysis) through 24-hour assessment times.

Figure 4

4.1.8: Plot of Mean Pain Relief + Pain Intensity Difference Score (PRID) With 84% Confidence Interval by Hours Postdose (Intention-to-Treat Approach)

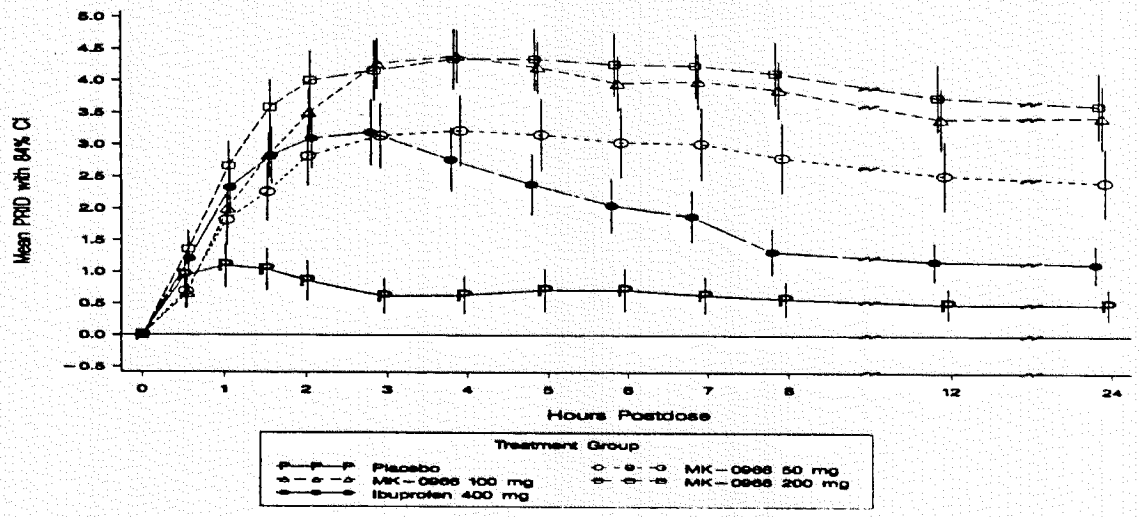


Table 8

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

		Summary Statistics by Time Point (Hours Postdose)											
Treatment		0.5	1	1.5	2	3	4	5	6	7	8	12	24
Placebo	N †	50	50	50	24	12	5	4	4	4	4	2	1
	MEAN	0.9ABC	1.1 C	1.0 C	0.9 C	0.6 C	0.6 C	0.7 C	0.7 D	0.6 D	0.6 C	0.5 C	0.5 C
	STD	1.5	1.7	1.7	1.5	1.4	1.5	1.7	1.7	1.5	1.4	1.2	1.2
rofecoxib 50 mg	N †	50	50	50	38	34	32	30	28	26	25	23	20
	MEAN	0.7 BC	1.8 B	2.3 B	2.8 B	3.1 B	3.2 B	3.2 B	3.0 B	3.0 B	2.8 B	2.5 B	2.4 B
	STD	1.4	2.0	2.3	2.3	2.5	2.8	2.8	2.8	2.8	2.7	2.7	2.7
rofecoxib 100 mg	N †	51	51	52	46	45	45	44	44	39	38	36	31
	MEAN	0.7 C	2.0 AB	2.8 B	3.5 AB	4.3 A	4.4 A	4.2 A	4.0 A	4.0 A	3.9 A	3.4 A	3.4 A
	STD	1.2	1.6	1.7	1.9	2.0	2.1	2.1	2.2	2.2	2.3	2.5	2.5
rofecoxib 200 mg	N †	50	50	50	44	42	39	38	38	37	36	34	31
	MEAN	1.4 A	2.7 A	3.6 A	4.0 A	4.2 A	4.3 A	4.3 A	4.3 A	4.2 A	4.1 A	3.7 A	3.6 A
	STD	1.5	1.9	2.2	2.4	2.3	2.4	2.4	2.5	2.5	2.5	2.6	2.6
Ibuprofen 400 mg	N †	52	52	52	42	38	33	27	21	19	15	6	4
	MEAN	1.2 AB	2.3 AB	2.8 B	3.1 B	3.2 B	2.8 B	2.4 B	2.1 C	1.9 C	1.3 C	1.2 C	1.1 C
	STD	1.6	2.2	2.3	2.4	2.6	2.5	2.4	2.2	2.1	1.9	1.6	1.5
p- Values from Between- Treatment Pairwise Comparisons by Time Point (Hours Postdose)													
rofecoxib vs Placebo:													
rofecoxib 50 mg vs Placebo a		-	0.031	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
rofecoxib 100 mg vs Placebo a		-	0.009	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
rofecoxib 200 mg vs Placebo a		0.106	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Between rofecoxib Doses													
rofecoxib 100 mg vs 50 mg b		0.879	0.638	0.140	0.096	0.009	0.008	0.018	0.037	0.025	0.013	0.039	0.018
rofecoxib 200 mg vs 50 mg b		0.019	0.019	<0.001	0.004	0.019	0.012	0.008	0.006	0.006	0.002	0.005	0.006
rofecoxib 200 mg vs 100 mg		0.012	0.058	0.048	0.216	0.803	0.924	0.765	0.492	0.575	0.545	0.427	0.674
With Ibuprofen 400 mg													
Ibuprofen 400 mg vs Placebo		0.276	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002	0.003	0.065	0.096	0.118
Ibuprofen 400 mg vs rofecoxib 50 mg		0.067	0.153	0.140	0.500	0.908	0.301	0.078	0.025	0.009	<0.001	0.002	0.003
Ibuprofen 400 mg vs rofecoxib 100 mg		0.046	0.336	>0.999	0.315	0.011	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Ibuprofen 400 mg vs rofecoxib 200 mg		0.587	0.341	0.048	0.026	0.024	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001