Analysis of 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 prefer 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 7 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 treatment group were statistically significantly better than placebo at all assessment times from the 1 hour through 24.0 hours postdose.

The mean PID scores for the ibuprofen 400-mg group were statistically significant better than placebo from 1 hour through 24 hour 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 8 hours. At the 12 and 24 hour assessments the rofecoxib 50 mg treatment group had statistically significantly better PID scores.

Reanalyzing the data by using the baseline observation carried forward (BOCF) technique revealed the same results when comparing rofecoxib 50 mg to placebo. Ibuprofen was statistically superior to placebo from 1 hour through 8 hour postdose. rofecoxib 50 mg was statistically superior to ibuprofen at 8, 12 and 24-hour assessments.

Figure 2

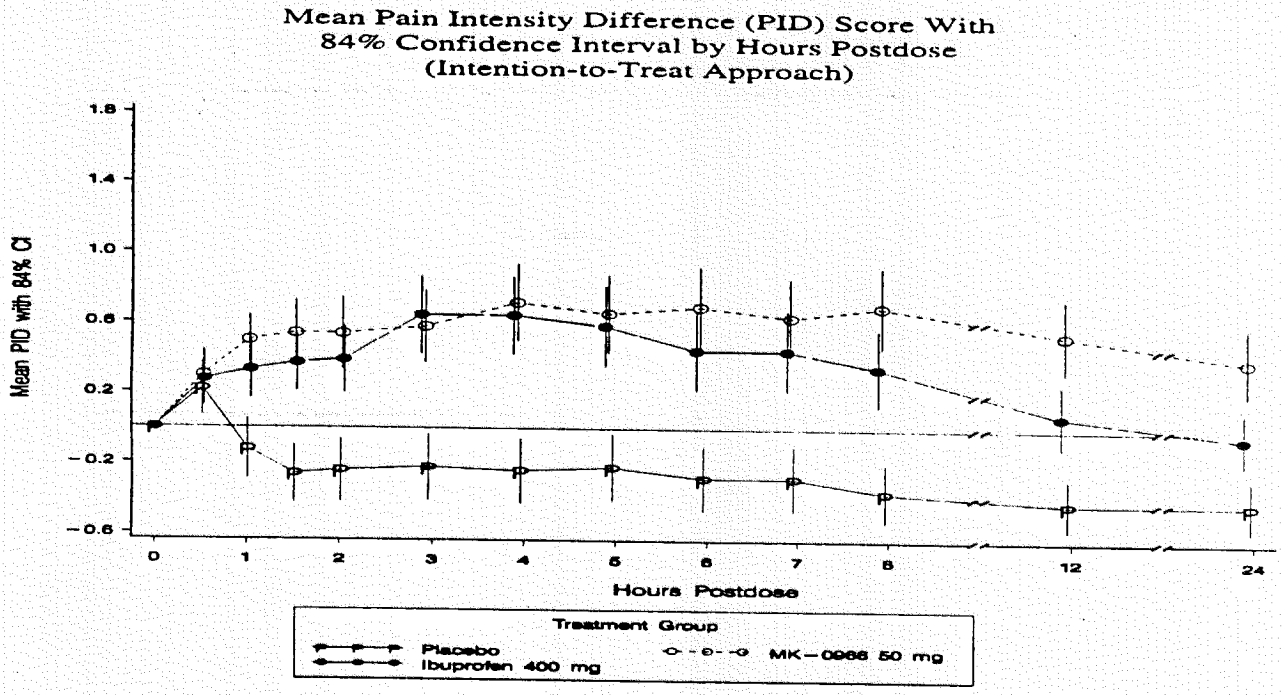


Table 7

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	24
Placebo	N (observed)	50	50	50	41	21	14	13	13	10	10	6	5
	MEAN	0.2 A†	-0.1B	-0.3 B	-0.2 B	-0.2 B	-0.2 B	-0.2 B	-0.3 B	-0.3 B	-0.4 B	-0.4 C	-0.4 B
	STD	0.8	0.8	0.8	0.9	0.9	0.9	1.0	0.9	0.9	0.8	0.7	0.7
rofecoxib 50 mg	N (observed)	50	50	50	45	36	33	30	28	27	26	25	23
	MEAN	0.3 A	0.5 A	0.5 A	0.5 A	0.6 A	0.7 A	0.7 A	0.7 A	0.6 A	0.7 A	0.5 A	0.4 A
	STD	0.7	0.7	0.9	1.0	1.0	1.1	1.1	1.1	1.1	1.1	1.1	1.0
ibuprofen 400 mg	N (observed)	51	51	51	45	65	32	31	29	23	21	18	11
	MEAN	0.3 A	0.3 A	0.4 A	0.4 A	0.6 A	0.6 A	0.6 A	0.5 A	0.5 A	0.4 A	0.1 B	-0.0 B
	STD	0.8	0.8	0.8	1.0	1.1	1.1	1.2	1.2	1.2	1.1	0.9	0.8
Pooled SD		0.7	0.8	0.8	0.9	1.0	1.0	1.1	1.1	1.0	1.0	0.9	0.8

†A, B, C — Letter A indicates the most effective dose(s), B indicates the next most effective, and so forth. Treatments sharing at least one letter were not significantly different from each other at the 5% significance level.

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	24
50 mg vs. Placebo	0.586	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Ibuprofen 400 mg vs. Placebo	0.791	0.007	<0.001	0.001	<0.001	<0.001	<0.001	0.001	0.001	<0.001	0.008	0.029
Ibuprofen 400 mg vs. 50 mg	0.779	0.240	0.261	0.336	0.816	0.647	0.643	0.185	0.290	0.077	0.008	0.005
Effect	p- Values by Time Point (Hours Postdose)											
Treatment	0.862	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
·:atum(Baseline PI)	0.045	0.023	0.012	0.002	0.066	0.052	0.022	0.005	0.004	0.077	0.061	0.005
.- by- Stratum Interaction	0.938	0.857	0.838	0.985	0.796	0.764	0.542	0.470	0.457	0.961	0.998	0.825

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

Figure 3 and table 8 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 treatment group were statistically significantly better than placebo at all assessment times from the 1 hour through 24.0 hours postdose.

The mean PR scores for the ibuprofen 400-mg group were statistically significant better than placebo from 1 hour through 8 hour postdose. At the 12 and 24 hour assessments the ibuprofen 400-mg treatment group was not statistically different from the placebo group in PR scores. The mean PR scores for the ibuprofen 400-mg group were not statistically different than those for the rofecoxib 50 mg group up to 8 hours. At the 12 and 24 hour assessments the rofecoxib 50 mg treatment group had statistically significantly better PR scores that the ibuprofen 400-mg group.

Reanalyzing the data by using the baseline observation carried forward (BOCF) technique revealed the same results when comparing rofecoxib 50 mg and ibuprofen to placebo. rofecoxib 50 mg was statistically superior to ibuprofen at 8, 12 and 24-hour assessments.

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

Figure 4 and table 9 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 treatment group were statistically significantly better than placebo at all assessment times from the 1 hour through 24.0 hours postdose.

The mean PRID scores for the ibuprofen 400-mg group were statistically significant better than placebo from 1 hour through 24 hour postdose. The mean PRID scores for the ibuprofen 400-mg group were not statistically different than those for the rofecoxib 50 mg group up to 8 hours. At the 12 and 24 hour assessments the rofecoxib 50 mg treatment group had statistically significantly better PRID scores that the ibuprofen 400-mg group.

Reanalyzing the data by using the baseline observation carried forward (BOCF) technique revealed the same results when comparing rofecoxib 50 mg to placebo. Ibuprofen was statistically superior to placebo from 1 hour through 8 hour postdose. rofecoxib 50 mg was statistically superior to ibuprofen at 8, 12 and 24-hour assessments.

Figure 3

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

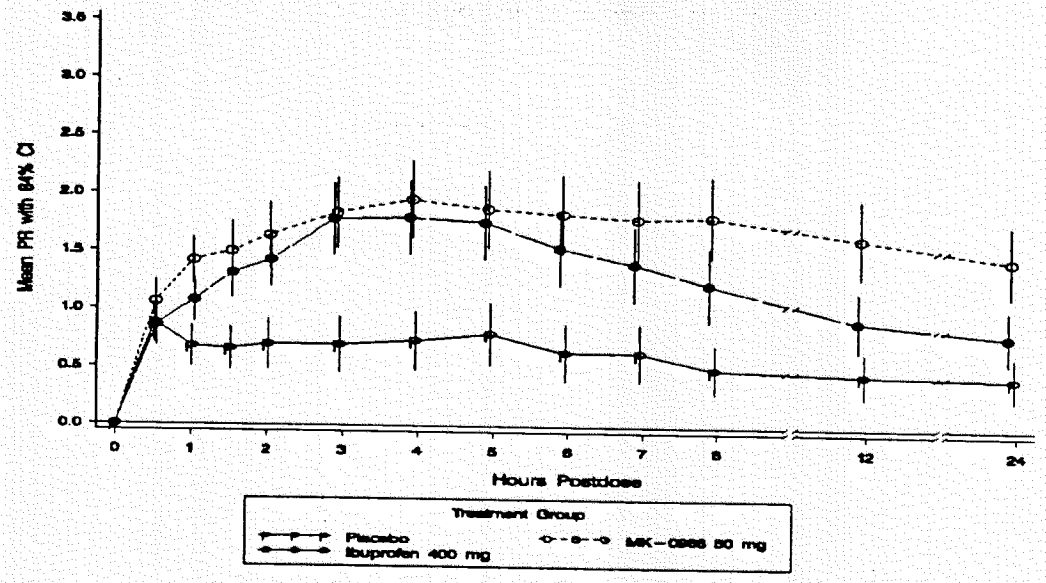


Table 8

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 (observed)	50	50	50	41	21	14	13	13	10	10	6	5
	MEAN	0.9 A†	0.7 B	0.7 B	0.7 B	0.7 B	0.7 B	0.8 B	0.6 B	0.6 B	0.5 B	0.5 B	0.4 B
	STD	0.8	0.9	0.9	1.1	1.2	1.3	1.4	1.2	1.2	1.1	1.0	1.0
rofecoxib 50 mg	N (observed)	50	50	50	45	36	33	30	28	27	26	25	23
	MEAN	1.1 A	1.4 A	1.5 A	1.6 A	1.8 A	2.0 A	1.9 A	1.8 A	1.8 A	1.8 A	1.6 A	1.5 A
	STD	0.9	1.0	1.3	1.4	1.5	1.7	1.7	1.7	1.7	1.7	1.7	1.5
Ibuprofen 400 mg	N (observed)	51	51	51	45	35	32	31	29	23	21	18	11
	MEAN	0.9 A	1.1 A	1.3 A	1.4 A	1.8 A	1.8 A	1.8 A	1.5 A	1.4 A	1.2 A	0.9 B	0.8 B
	STD	0.9	0.9	1.1	1.2	1.6	1.6	1.6	1.6	1.6	1.6	1.3	1.1
Pooled SD		0.9	0.9	1.1	1.2	1.4	1.5	1.5	1.5	1.5	1.5	1.4	1.2

†A, B, C — Letter A indicates the most effective dose(s), B indicates the next most effective, and so forth. Treatments sharing at least one letter were not significantly different from each other at the 5% significance level.

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	24
50 mg vs. Placebo	0.321	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Ibuprofen 400 mg vs. Placebo	0.949	0.032	0.003	0.003	<0.001	<0.001	0.002	0.004	0.015	0.014	0.083	0.149
Ibuprofen 400 mg vs. 50 mg	0.289	0.073	0.407	0.396	0.869	0.625	0.711	0.332	0.196	0.054	0.009	0.008
Effect	p- Values by Time Point (Hours Postdose)											
Treatment	0.494	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stratum(Baseline PI)	0.548	0.575	0.697	0.991	0.574	0.628	0.955	0.613	0.494	0.752	0.544	0.722
Rx- by- Stratum Interaction	0.634	0.854	0.895	0.710	0.806	0.861	0.696	0.638	0.563	0.979	0.811	0.673

Figure 4

84% Confidence Interval—Pain Relief + PID (PRID) Score by Hours Postdose
(Intention-to-Treat Approach)

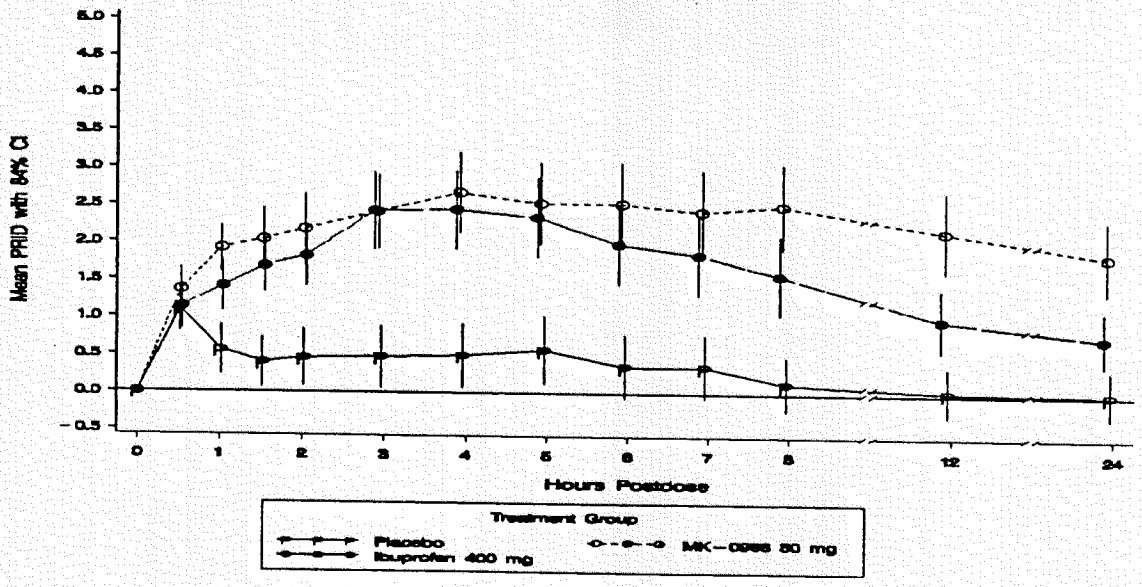


Table 9
Analysis of PRID by Time Point (Intention-to-Treat Approach)

		Summary Statistics by Time Point (Hours Postdose)											
reatment		0.5	1	1.5	2	3	4	5	6	7	8	12	24
lacebo	N (observed)	50	50	50	41	21	14	13	13	10	10	6	5
	MEAN	1.1 A	0.6 B	0.4 B	0.5 B	0.5 B	0.5 B	0.6 B	0.4 B	0.4 B	0.1 B	0.0 C	0.0 B
	STD	1.5	1.6	1.7	1.9	2.1	2.1	2.3	2.1	2.1	1.8	1.6	1.6
ofecoxib 50 mg	N (observed)	50	50	50	45	36	33	30	28	27	26	25	23
	MEAN	1.4 A	1.9 A	2.0 A	2.2 A	2.4 A	2.7 A	2.5 A	2.5 A	2.4 A	2.5 A	2.2 A	1.9 A
	STD	1.5	1.5	2.1	2.3	2.5	2.7	2.7	2.8	2.8	2.8	2.7	2.4
uprofen 400 mg	N (observed)	51	51	51	45	35	32	31	29	23	21	18	11
	MEAN	1.1 A	1.4 A	1.7 A	1.8 A	2.4 A	2.5 A	2.4 A	2.0 A	1.9 A	1.6 A	1.0 B	0.8 B
	STD	1.5	1.7	1.8	2.0	2.6	2.6	2.7	2.7	2.7	2.7	2.1	1.8
ooled SD		1.5	1.6	1.9	2.1	2.4	2.5	2.5	2.5	2.5	2.5	2.2	2.0
	p-Values From Between-Treatment Pairwise Comparisons by Time Point (Hours Postdose)												
airwise Comparison		0.5	1	1.5	2	3	4	5	6	7	8	12	24
0 mg vs. Placebo		0.389	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
uprofen 400 mg vs. Placebo		0.928	0.010	<0.001	0.002	<0.001	<0.001	<0.001	0.002	0.004	0.004	0.030	0.070
uprofen 400 mg vs. 50 mg		0.439	0.108	0.315	0.351	>0.999	0.625	0.676	0.255	0.221	0.057	0.007	0.005
ffect		p- Values by Time Point (Hours Postdose)											
reatment		0.638	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
tratum(Baseline PI)		0.534	0.424	0.354	0.158	0.653	0.606	0.355	0.141	0.107	0.584	0.688	0.159
x- by- Stratum Interaction		0.769	0.841	0.861	0.918	0.807	0.816	0.630	0.562	0.505	0.971	0.917	0.792

Total of Pain Relief Scores to 8 Hours (TOPAR8)

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

The least-squares mean (LSMean) TOPAR8 scores in patients who received placebo, 50 mg rofecoxib, and 400 mg ibuprofen were 5.4, 13.8, and 11.8 units, respectively. Over the 8 hours postdose, rofecoxib 50-mg dose produced significantly ($p<0.001$) greater LSMean TOPAR8 score compared with placebo (Table 10).

The LSMean TOPAR8 score in the 400-mg ibuprofen group was significantly ($p=0.001$) greater than that in the placebo group. The LSMean TOPAR8 in the rofecoxib 50-mg group was not statistically greater than that in the ibuprofen 400-mg group (Table 10).

Table 10
Analysis of Total Pain Relief Score Over 8 Hours (TOPAR8)
(Intention-to-Treat Approach)

Treatment	N	Mean	SD	LSMean	95% CI for LSMean
Placebo	50	5.5	8.2	5.4	(1.8, 8.9)
rofecoxib 50 mg	50	14.0	11.0	13.8	(10.2, 17.4)
Ibuprofen 400 mg	51	11.9	10.0	11.8	(8.3, 15.2)

Pairwise Comparison	Difference in LSMeans	95% CI for Difference	p- Value
rofecoxib 50 mg vs. Placebo	8.5	(4.6, 12.4)	<0.001
Ibuprofen 400 mg vs. Placebo	6.4	(2.5, 10.3)	0.001
Ibuprofen 400 mg vs. 50 mg	-2.0	(-5.9, 1.8)	0.299

Effect	p- Value	Pooled SD
Treatment	<0.001	9.9
Stratum (Baseline Pain Intensity)	0.919	
Treatment- by- Stratum Interaction	0.841	

Sum of Pain Intensity Difference to 8 Hours (SPID8)

Figure 2 shows the mean PID score plotted versus hours postdose. The SPID8 was an estimate of the area under the PID versus time curve during the 8 hours postdose.

The LSMean SPID8 scores in patients who received placebo, 50 mg rofecoxib, and 400 mg ibuprofen were 0.4, 7.1, and 5.8 units, respectively (Figure 2 and Table 11).

Over the 8 hours postdose, rofecoxib 50-mg dose produced significantly ($p<0.001$) greater LSMean SPID8 score compared with placebo (Table 11).
The LSMean SPID8 score in the 400-mg ibuprofen group was significantly ($p<0.001$) greater than that in the placebo group. The LSMean SPID8 score in the rofecoxib 50-mg group was not statistically significantly ($p=0.344$) greater than that in the ibuprofen group (Table 11).

Table 11
Analysis of Sum of Pain Intensity Difference to 8 Hours (SPID8)
(Intention-to-Treat Approach)

Treatment	N	Mean	SD	LSMean	95% CI for LSMean
Placebo	50	-1.8	6.5	0.4	(-2.2, 2.9)
rofecoxib 50 mg	50	4.9	7.3	7.1	(4.6, 9.6)
Ibuprofen 400 mg	51	3.8	7.4	5.8	(3.4, 8.2)

Pairwise Comparison	Difference in LSMeans	95% CI for Difference	p- Value
rofecoxib 50 mg vs. Placebo	6.7	(4.0, 9.5)	<0.001
Ibuprofen 400 mg vs. Placebo	5.4	(2.7, 8.2)	<0.001
Ibuprofen 400 mg vs. 50 mg	-1.3	(-4.0, 1.4)	0.344

Effect	p- Value	Pooled SD
Treatment	<0.001	6.9
Stratum (Baseline Pain Intensity)	0.009	
Treatment- by- Stratum Interaction	0.770	

Patient's Global Evaluation at 8 Hours
The LSMean Patient's Global Evaluation scores in the placebo, 50-mg rofecoxib, and 400-mg ibuprofen groups were 0.8, 2.0, and 1.8, respectively (Table 12).

Compared with placebo, the 50-mg dose of rofecoxib was associated with significantly ($p<0.001$) greater Patient's Global Evaluation scores at 8 hours (Table 12).

The LSMean Patient's Global Evaluation score at 8 hours was significantly ($p<0.001$) greater in the 400-mg ibuprofen group compared with that in the placebo group. The LSMean in the rofecoxib 50-mg group was not significantly greater than that in the ibuprofen group (Table 12).

Table 12
Analysis of Patient's Global Evaluation at 8 Hours
(Intention-to-Treat Approach)

Treatment	N	Mean	SD	LSMean	95% CI for LSMean
Placebo	50	0.9	1.1	0.8	(0.4, 1.3)
rofecoxib 50 mg	49	2.0	1.4	2.0	(1.5, 2.4)
Ibuprofen 400 mg	51	1.9	1.4	1.8	(1.4, 2.3)

Pairwise Comparison	Difference in LSMeans	95% CI for Difference	p- Value
rofecoxib 50 mg vs. Placebo	1.1	(0.6, 1.6)	<0.001
Ibuprofen 400 mg vs. Placebo	1.0	(0.5, 1.5)	<0.001
Ibuprofen 400 mg vs. 50 mg	-0.2	(-0.7, 0.4)	0.562

Effect	p- Value	Pooled SD
Treatment	<0.001	1.3
Stratum (Baseline Pain Intensity)	0.647	
Treatment- by- Stratum Interaction	0.975	

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

In the placebo, 50-mg rofecoxib, and 400-mg ibuprofen groups, 34.0, 64.0, and 62.7% of patients experienced Confirmed Perceptible Pain Relief, respectively.

The median Times to Confirmed Perceptible Pain Relief for patients in the 50-mg rofecoxib and 400-mg ibuprofen groups were 0.7 and 0.8 hours, respectively. The median time for the placebo group could not be estimated due to the low percentage (<50% for the 50th percentile) of patients who experienced Confirmed Perceptible Pain Relief (Figure 5).

The Confirmed Perceptible Pain Relief was significantly (p=0.009) more rapid in patients who received rofecoxib 50 mg compared with those who received placebo (Table 13).

The Time to Confirmed Perceptible Pain Relief for the 400-mg ibuprofen group was significantly (p=0.007) shorter compared with the time for the placebo group. However, the difference in the Time to Confirmed Perceptible Pain Relief was not significant between the 50-mg rofecoxib and 400-mg ibuprofen groups (Table 13).

Figure 5

Cumulative Proportions of Patients With Confirmed Perceptible Pain Relief by Hours Postdose
(Stopwatch Time to Perceptible Pain Relief, Confirmed by the Second Stopwatch)
(1—Kaplan-Meier Survival Distribution Function Estimates)
(Intention-to-Treat Approach)

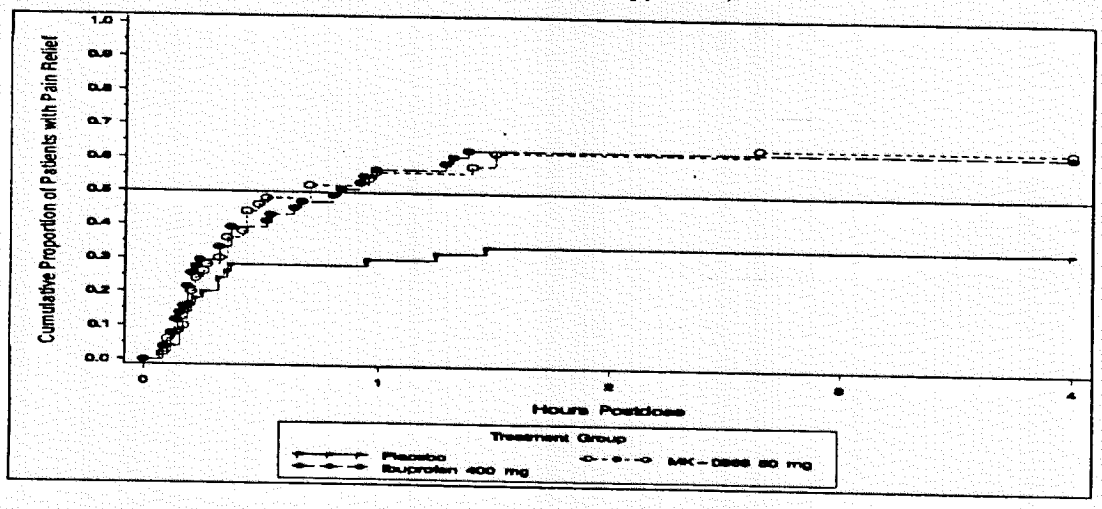


Table 13

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

Treatment	N	Number (% †) of Patients Confirmed Perceptible Pain Relief	Time (Hour) to Confirmed PerceptiblePain Relief by Percentile		
			25th	Median-50th (95% CI)	75th
Placebo	50	17 (34.0)	0.4	NE	NE
rofecoxib 50 mg	49	32 (64.0)	0.3	0.7 (0.4, 2.7)	NE
Ibuprofen 400 mg	51	32 (62.7)	0.2	0.8 (0.4, NE)	NE

Pairwise Comparison	Cox Proportional Hazards Regression (Primary Analysis)		Log-Rank Test ‡
	Risk Ratio (95% CI)	p- Value	p- Value
rofecoxib 50 mg vs. Placebo	2.20 (1.22, 3.96)	0.009	<0.007
Ibuprofen 400 mg vs. Placebo	2.24 (1.24, 4.05)	0.007	<0.007
Ibuprofen 400 mg vs. 50 mg	1.02 (0.62, 1.67)	0.935	0.993

Effect	p- Value	p-Value
Treatment	0.008	0.10
Stratum (Baseline Pain Intensity)	0.451	0.479
Treatment- by- Stratum Interaction	0.318	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.

Peak Analgesic Effect During 8 Hours Postdose

During the 8 hours postdose, rofecoxib 50-mg dose produced a significantly ($p<0.001$) greater peak analgesic effect, as measured by peak PID and peak Pain Relief, compared with placebo (Figures 6 and 7).

During the 8 hours postdose, rofecoxib 50-mg dose produced a significantly ($p<0.001$) greater peak analgesic effect, as measured by peak PID and peak Pain Relief, compared with placebo.

Ibuprofen 400-mg produced significantly ($p<0.001$) greater peak PID and Pain Relief scores compared with placebo. The peak analgesic effects in the rofecoxib 50-mg and ibuprofen 400-mg groups were not significantly different.

Figure 6

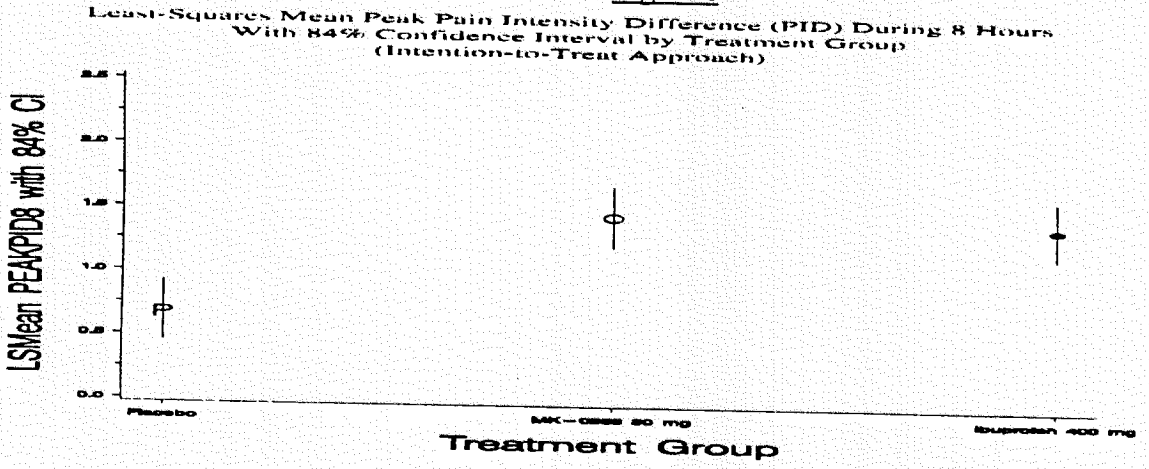
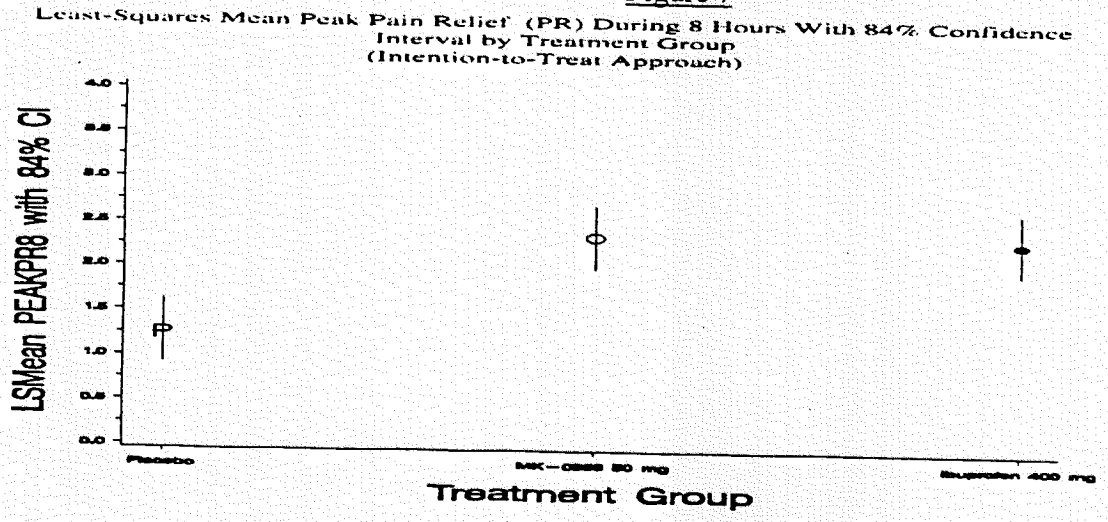


Figure 7



Duration of Analgesic Effect

1) Time to Rescue Medication

The median Times to Taking Rescue Medication (the time when 50% patients took rescue medication) for patients in the placebo, 50-mg rofecoxib, and 400-mg ibuprofen groups were 2.4, 9.5, and 6.1 hours, respectively (Table 14)

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

Patients who received 400 mg ibuprofen experienced significantly longer times to taking rescue medication compared with those who received placebo ($p=0.008$), but significantly ($p=0.039$) shorter times compared with those who received rofecoxib 50 mg.

Table 14
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	50	46 (92.0)	1.9	2.4 (2.2, 3.1)	5.7
rofecoxib 50 mg	49	28 (56.0)	2.4	9.5 (3.9, NE)	NE
Ibuprofen 400 mg	51	42 (82.4)	2.3	6.1 (3.3, 9.5)	16.0

	Cox Proportional Hazards Regression (Primary Analysis)		Log-Rank Test ‡
Pairwise Comparison	Risk Ratio (95% CI)	p- Value	p- Value
rofecoxib 50 mg vs. Placebo	0.34 (0.21, 0.55)	< 0.001	<0.001
Ibuprofen 400 mg vs. Placebo	0.56 (0.37, 0.86)	0.008	<0.005
Ibuprofen 400 mg vs. 50 mg	1.66 (1.03, 2.69)	0.039	0.030

Effect	p- Value	p-Value
Treatment	< 0.001	< 0.001
Stratum (Baseline Pain Intensity)	0.646	0.677
Treatment- by- Stratum Interaction	0.757	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 24 Hours

There were 92.0, 56.0, and 82.4% of patients who took rescue analgesia within 24 hours postdose in the placebo, 50-mg rofecoxib, and 400-mg ibuprofen groups, respectively. The Percent of Patients Who Took Rescue Medication within 24 hours of study drug administration was significantly ($p<0.001$) lower in the rofecoxib 50-mg group compared with the placebo group. The difference in percent of patients who took rescue medication between the placebo and 400-mg ibuprofen groups was not significant. There was a

significantly (p=0.005) lower percentage of patients who took rescue medication in the rofecoxib 50-mg group compared with that in the ibuprofen 400-mg group.

Safety Results

Clinical adverse experiences were reported by 36 (24%) of 151 randomized patients. Thirty-four, 12, and 26% of patients in the placebo, 50-mg rofecoxib, and ibuprofen groups, respectively, reported one or more adverse experiences (table 15).

Table 15
Clinical Adverse Experience Summary

	Placebo (N= 50)		rofecoxib50 mg (N= 50)		Ibuprofen 400 mg (N= 51)	
	n	(%)	n	(%)	n	(%)
Number of patients evaluated	50		50		51	
Number (%) of patients:						
with one or more adverse experiences	17	(34.0)	6	(12.0)*	13	(25.5)
with no adverse experience	33	(66.0)	44	(88.0)*	38	(74.5)
with drug- related adverse experiences †	12	(24.0)	2	(4.0)*	8	(15.7)

* $p < 0.05$ vs. placebo.
† 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 16. Most of the adverse events were GI related.

Table 16
Number (%) of Patients With Clinical Adverse Experiences by Body System

	Placebo (N= 50)		rofecoxib50 mg (N= 50)		Ibuprofen 400 mg (N= 51)	
	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	17	(34)	6	(12)	13	(25.5)
Patients with no adverse experience	33	(66)	44	(88)	38	(74.5)
Body as a whole/site unspecified	3	(6)	1	(2)	2	(3.9)
Digestive system	11	(22)	5	(10)	10	(19.6)
Ears, eyes, nose, and throat	1	(2)	1	920	0	(0)
Nervous and psychiatric	5	(10)	0	(0)	2	(3.9)
Psychiatric disorder	1	(2)	1	(2)	0	(0)
Urogenital system	1	(2)	0	(0)	0	(0)

No significant differences between treatment groups were observed.
Although a patients may have had two or more clinical adverse experiences, the patient was counted only once in a category. The same patient may appear in different categories.

There were no statistically significant associations between treatment and percent of patients with specific clinical adverse experiences. One patient in the ibuprofen 400-mg group experienced one episode of hematemesis about 1.5 hours postdose, observed by the nurse and described as bright red blood. A second episode of vomiting 30 minutes later was not described as hematemesis, i.e., there was no blood present. The patient's hemoglobin/hematocrit on the day of surgery was 13.6/38 and 5 days later at the poststudy visit it was 14.5/40.

The incidence of drug-related adverse experiences was 24, 4, and 16% for the placebo, rofecoxib 50-mg, and ibuprofen 400-mg groups, respectively. No specific adverse experience(s) accounted for this clinically insignificant difference.

No serious and/or drug related adverse events have been reported.

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

Adverse Experiences—Laboratory

All of the 151 randomized patients had at least one laboratory test postrandomization. Laboratory adverse experiences were recorded for 4 (3%) of these 151 randomized patients. The incidence of adverse experiences was not significantly greater in the rofecoxib treatment group compared with the placebo. Four, 2, and 2% of patients in the placebo, 50-mg rofecoxib, and ibuprofen 400-mg groups, respectively, were reported with one or more laboratory adverse experiences. There were no significant associations between treatment with rofecoxib and incidence of any specific laboratory adverse experiences.

No laboratory adverse experiences were considered serious.

No patient discontinued due to a laboratory adverse experience.

Discussion and Overall Conclusions for Study # 066

Rofecoxib at a dose of 50-mg dose demonstrated significantly greater analgesic effect compared with placebo in all measures of analgesic effect (i.e., the overall, onset, peak, and duration of analgesic effects) in the treatment of postoperative dental pain.

The analgesic effect of ibuprofen 400 mg was significantly greater than that of placebo in all measures of analgesic effect except that the Pain Relief score measured at 12 and 24 hours and the PRID score measured at 24 hours in the ibuprofen 400 group were not significantly greater than that in the placebo group. Therefore the study was validated.

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

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

Study Number: P071

Study Dates: 17 November 1997 – 24 February 1998

Title of Study: A Randomized, Placebo and Active-Comparator-Controlled Trial of the Effect of 50, 100, and 200 mg of rofecoxib as a [redacted] Formulation in the Treatment of Postoperative Dental Pain.

Investigator and Location: Donald R. Mehlisch, M.D., D.D.S.,

[redacted]

Austin, TX 78705

Objectives:

The primary objectives of this study were (as defied by the sponsor):

To determine the analgesic effect of a single oral dose of rofecoxib 50 mg compared with that of placebo in the treatment of postoperative dental pain.

The secondary objectives of this study were:

a) To determine the analgesic effect of a single oral dose of rofecoxib 50 mg compared with that of ibuprofen 400-mg in the treatment of postoperative dental pain.

b) To determine the peak, time to onset, and duration of analgesic effects of 50, 100, or 200 mg rofecoxib and 400 mg ibuprofen compared with those of placebo in the treatment of postoperative dental pain

c) To confirm the safety and tolerability of single 50-, 100-, or 200-mg doses of rofecoxib administered to patients with postoperative dental pain.

Study Description

This was a single-center, double-blind (with in-house blinding), parallel-group study comparing 50-, 100-, and 200-mg doses of rofecoxib with placebo and 400 mg ibuprofen administered once postoperatively to patients demonstrating moderate to severe dental pain. Patients came in for a total of 5 visits on 3 different days: the Prestudy Study Screening Visit occurred on Day A; the Presurgery Screening Visit, Postsurgery Screening Visit, and Treatment Visit occurred on Day B; and the Poststudy Visit occurred on Day C (Figure 1).