Table 4

Effect of Rofecoxib on SPID8 and Patient's Global Evaluation of Study Medication in Phase III Post-Dental Surgery Pain Studies
(Protocols 066 and 071)

Parameter	Protocol 066		Protocol 071	
	Placebo N= 50	Rofecoxib 50 mg N= 50	Placebo N= 50	Rofecoxib 50 mg N= 50
Baseline Pain Intensity— n (%)				
Moderate	46 (92.0)	46 (92.0)	26 (52.0)	28 (56.0)
Severe	4 (8.0)	4 (8.0)	24 (48.0)	22 (44.0)
Overall Analgesic Efficacy				
SPID8 (-8 to 24 scale)	LS Mean (95% CI)			
	0.4 (- 2.2, 2.9)	7.1 (4.6, 9.6)	0.8 (- 0.9, 2.5)	7.6 (5.9, 9.3)
Difference in SPID8 from Placebo	NA	6.7* (4.0, 9.5)	NA	6.8* (4.4, 9.2)
Patient's Global Evaluation at 8 hours (0 to 4 scale)	0.8 (0.4, 1.3)	2.0 (1.5, 2.4)	0.4 (0.1, 0.8)	1.8 (1.5, 2.1)
Difference in Patient's Global Evaluation from Placebo	NA	1.1* (0.6,1.6)	NA	1.4* (0.9,1.8)

* p< 0.001 for difference from placebo.
NA= Not applicable.

Onset of Analgesic Effect

The onset of analgesic effect was assessed using the end points of Time to Confirmed Perceptible Pain Relief (Stopwatch). The values for this end point are in Table 5. In both studies, the results demonstrated that 50 mg rofecoxib had a significantly ($p \leq 0.032$) faster onset of analgesia compared with placebo. The values for Time to Confirmed Perceptible Relief (Stopwatch) were consistent between the studies.

Table 5

Effect of Rofecoxib on Time to Confirmed Perceptible Pain Relief (Stopwatch) in Phase III Post- Dental Surgery Pain Studies
(Protocols 066 and 071)

Parameter	Protocol 066		Protocol 071	
	Placebo N= 50	Rofecoxib 50 mg N= 50	Placebo N= 50	Rofecoxib 50 mg N= 50
Onset of Analgesic Effect				
Time (hours) to 50% of Patients With Confirmed Perceptible Pain Relief (Stopwatch) †	Hours (95% CI)			
	NE	0.7* (0.4, 2.7)	NE	0.7* (0.5, 1.0)

* p≤0.032 versus placebo.
† The 50th percentile of the respective end points.
NE=Not estimable because <50% of patients attained end point.

Peak Analgesic Effect

The peak analgesic effect was assessed using the clinical end points of Peak Pain Relief and Peak PID. The LS mean scores for these end points are in Table 6. In both studies, the results from both end points demonstrated that during the 8 hours postdose, 50 mg rofecoxib produced a significantly ($p<0.001$) greater peak analgesic effect compared with placebo. The magnitude of the difference between the rofecoxib group and placebo was generally similar between the studies.

Table 6

Effect of Rofecoxib on Peak Pain Relief and Peak PID in Phase III Post-Dental Surgery Pain Studies
(Protocols 066 and 071)

	Protocol 066		Protocol 071	
Parameter	Placebo N= 50	Rofecoxib 50 mg N= 50	Placebo N= 50	Rofecoxib 50 mg N= 50
Peak Analgesic Effect				
	LS Mean (95% CI)			
Peak PID During 8 Hours Postdose (-1 to 3 scale)	0.7 (0.4, 1.0)	1.4 (1.1, 1.8)	0.5 (0.2, 0.7)	1.4 (1.1, 1.6)
Difference in Peak PID from Placebo	NA	0.8* (0.4, 1.1)	NA	0.9* (0.5, 1.3)
Peak Pain Relief (During 8 Hours Postdose (0 to 4 scale)	1.3 (0.8, 1.8)	2.4 (1.9, 2.9)	1.2 (0.8, 1.5)	2.5 (2.2, 2.9)
Difference in Peak Pain Relief from Placebo	NA	1.1* (0.5, 1.6)	NA	1.4* (0.8, 1.9)
*p<0.001 for difference from placebo. NA=Not applicable.				

Duration of Analgesia

Analyzing the time to taking rescue medication and the percent of patients who took rescue medication within 24 hours postdose assessed the duration of analgesic effect. Figure 5 shows a plot of the cumulative percent of patients taking rescue medication over time and analyses of these end points are in Table 7. In both studies, the results demonstrated that during the 24 hours postdose, patients receiving 50 mg rofecoxib were less likely to take rescue analgesia compared with patients receiving placebo, and the time to take rescue medication was longer with 50 mg rofecoxib compared with placebo.

Figure 5

Cumulative Proportions of Patients Requiring Rescue Medication by Hours Postdose
(1 - Kaplan-Meier Survival Distribution Function Estimates)
Phase III Post-Dental Surgery Pain Studies

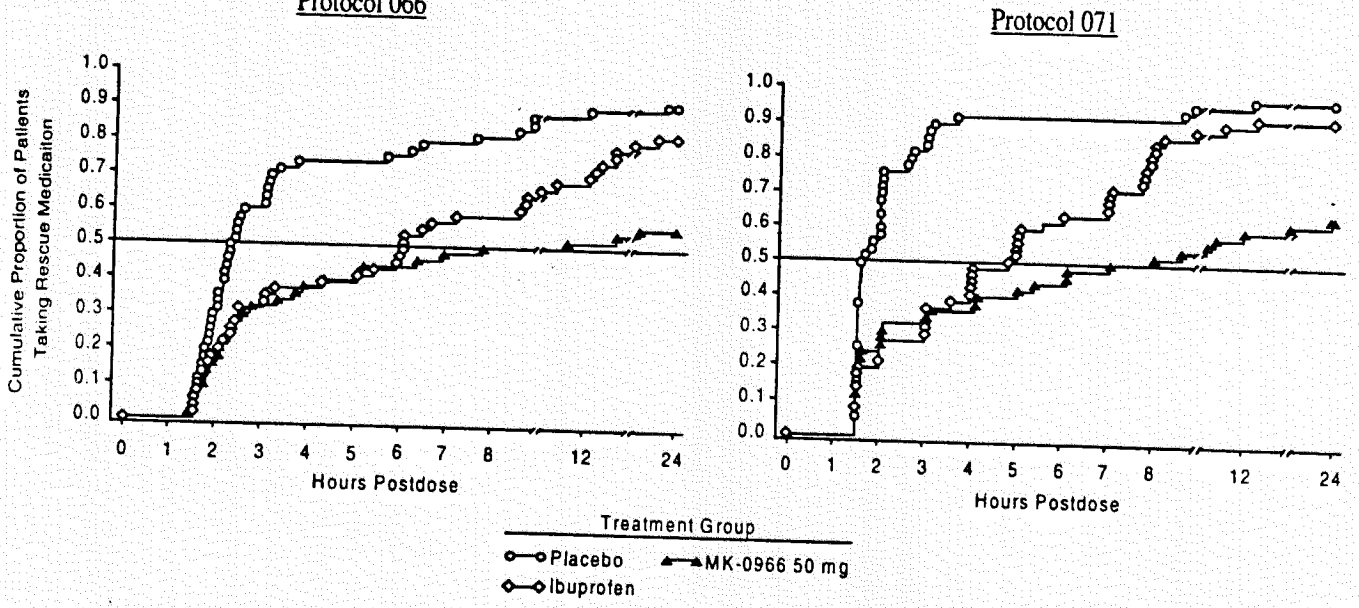


Table 7

Effect of Rofecoxib on End Points Assessing Duration of Analgesic Effect in Phase III Post-Dental Surgery Pain Studies
(Protocols 066 and 071)

Parameter	Protocol 066		Protocol 071	
	Placebo N= 50	Rofecoxib 50 mg N= 50	Placebo N= 50	Rofecoxib 50 mg N= 50
Duration of Analgesic Effect				
	Number (%)			
Number (%) of Patients Who Took Rescue Medication Within 24 Hours	46 (92.0)	28 (56.0)*	49 (98.0)	32 (64.0)*
	Hours (95% CI)			
Time (hours) to 50% of Patients Took Rescue Medication †, ‡	2.4 (2.2, 3.1)	9.5* (3.9, ∞)	1.6 (1.5, 2.0)	7.5* (4.1, 23.6)
	LS Mean (95% CI)			
PRID at 24 hour Time Point (-1 to 7 scale)	0.3 (0.0, 1.1)	2.2 (1.5, 2.9)	0.5 (-0.1, 1.1)	2.5 (1.9, 3.1)
Difference in PRID at 24 Hours from Placebo	NA	1.8* (1.1, 2.6)	NA	2.0* (1.1, 2.8)

* p≤0.002 versus placebo.
† The 50th percentile of the respective end point.
‡ Results are not presented as difference from placebo for this time-to-event end point.
NA=Not applicable.

Relation to Baseline Pain and Patient Characteristics

Both in Study 066 and Study 071, there was no significant ($p>0.05$) treatment-by-baseline pain intensity interaction in the efficacy measures.

The ANOVA for TOPAR8 by subgroup comparing placebo, rofecoxib, and ibuprofen was performed for the combined data from Protocols 066 and 071. Only data for the treatments in common to both protocols were assessed: placebo, rofecoxib 50 mg, and ibuprofen.

The subgroups considered were:

- Gender (male, female)
- Age group: tertiles of youngest (15 to 17 years), intermediate (18 to 20 years), and oldest (21 to 42 years)
- Race (White, Black, and other [Asian, European, Hispanic-American, Polynesian])

No significant interaction was observed between treatment and any of the subgroups. The overall ordering of treatment group results was generally consistent across all subgroups.

Additional Data From Phase III Studies: Study 071

In study 071, both 100 and 200 mg rofecoxib were also studied to establish the dose required to provide maximal efficacy using the final Phase III 12.5% formulation (formulation C). The results of study 071 are summarized in Table 8. Significant differences from placebo and significant differences from 50 mg rofecoxib (the recommended initial dose for analgesia) are noted in Table 8 by one and two asterisks, respectively. Study 071 confirmed the efficacy of 50 mg rofecoxib compared with placebo. However, it was observed in study 071 that the doses of 100 and 200 mg rofecoxib were significantly more effective on all end points of overall analgesic efficacy (TOPAR8, SPID8, and Patient's Global Evaluation) and on end points of duration of efficacy (Time to Rescue Medication) than the 50-mg rofecoxib dose (Table 8). Also, time specific pain relief and pain intensity scores were significantly better for the 100- and 200-mg doses. The mean pain relief (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. 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 (Figure 6). The mean pain intensity difference (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. 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 (Figure 7). In addition, the peak analgesic effect of the 100- and 200-mg rofecoxib doses was numerically, and nearly statistically significantly, better than the dose of 50 mg (Table 8). The 200-mg dose of rofecoxib was generally not distinguishable from the 100-mg dose of rofecoxib. The onset of analgesia was generally similar among the 3 rofecoxib treatment groups.

These results contrast with those of study 027 in which 50 and 100 mg rofecoxib were generally comparable in all parameters of analgesic efficacy, however, in study 027 a different formulation of rofecoxib was used (formulation B) which is different than the final formulation (formulation C) used in study 071.

Table 8

Effect of 50, 100, and 200 mg Rofecoxib on All End Points in Phase III Post-Dental Surgery Pain Study
(Protocol 071)

End Points	Placebo N= 50	Rofecoxib 50 mg N= 50	Rofecoxib 100 mg N= 52	Rofecoxib 200 mg N= 50
Overall Analgesic Effect				
	LS Mean (95% CI)			
TOPAR8 (0 to 32 scale)	5.2** (2.8, 7.7)	15.2* (12.7, 17.6)	19.2*, ** (16.8, 21.6)	20.3*, ** (17.8, 22.7)
SPID8 (-8 to 24 scale)	0.8** (- 0.9, 2.5)	7.6* (5.9, 9.3)	10.5*, ** (8.9, 12.2)	11.6*, ** (9.9, 13.3)
Patient's Global Evaluation at 8 Hours (0 to 4 Scale)	0.4** (0.1, 0.8)	1.8* (1.5, 2.1)	2.7* **, (2.4,3.0)	2.7* **, (2.4, 3.0)
Onset of Analgesic Effect				
	Hours (95% CI)			
Time (hours) to 50% of Patients With Confirmed Perceptible Pain Relief (Stopwatch) †	NE**	0.7* (0.5, 1.0)	0.8* (0.5, 0.9)	0.5* (0.4, 0.6)
Peak Analgesic Effect				
	LS Mean (95% CI)			
Peak PID (During 8 Hours Postdose; -1 to 3 Scale)	0.5** (0.2, 0.7)	1.4* (1.1, 1.6)	1.7* (1.5, 2.0)	1.8*, ** (1.5, 2.1)
Peak Pain Relief (During 8 Hours Postdose; 0 to 4 Scale)	1.2** (0.8, 1.5)	2.5* (2.2, 2.9)	3.0* (2.7, 3.4)	3.1* (2.7, 3.4)
Duration of Analgesic Effect				
Number (%) of Patients Who Took Rescue Medication (Within 24 Hours)	49 (98.0)**	32 (64.0)*	21 (40.4) *, **	20 (40.0) *, **
	Hours (95% CI)			
Time (hours) to 50% of Patients Who Took Rescue Medication †	1.6** (1.5, 2.0)	7.5* (4.1, 23.6)	NE*, **	NE*, ** (1.1, 2.8)

* p<0.05 versus placebo.
** p<0.05 versus 50 mg rofecoxib.
† The 50th percentile of the respective end points.
NE=Not estimable because <50% of patients attained end point.

Figure 6

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

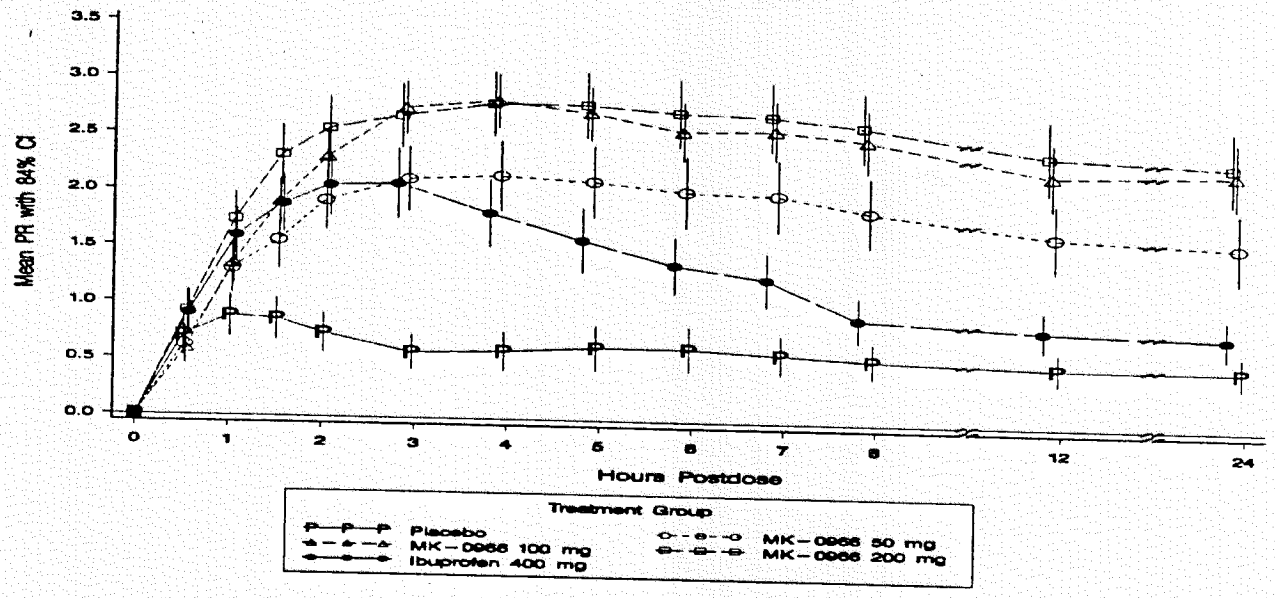
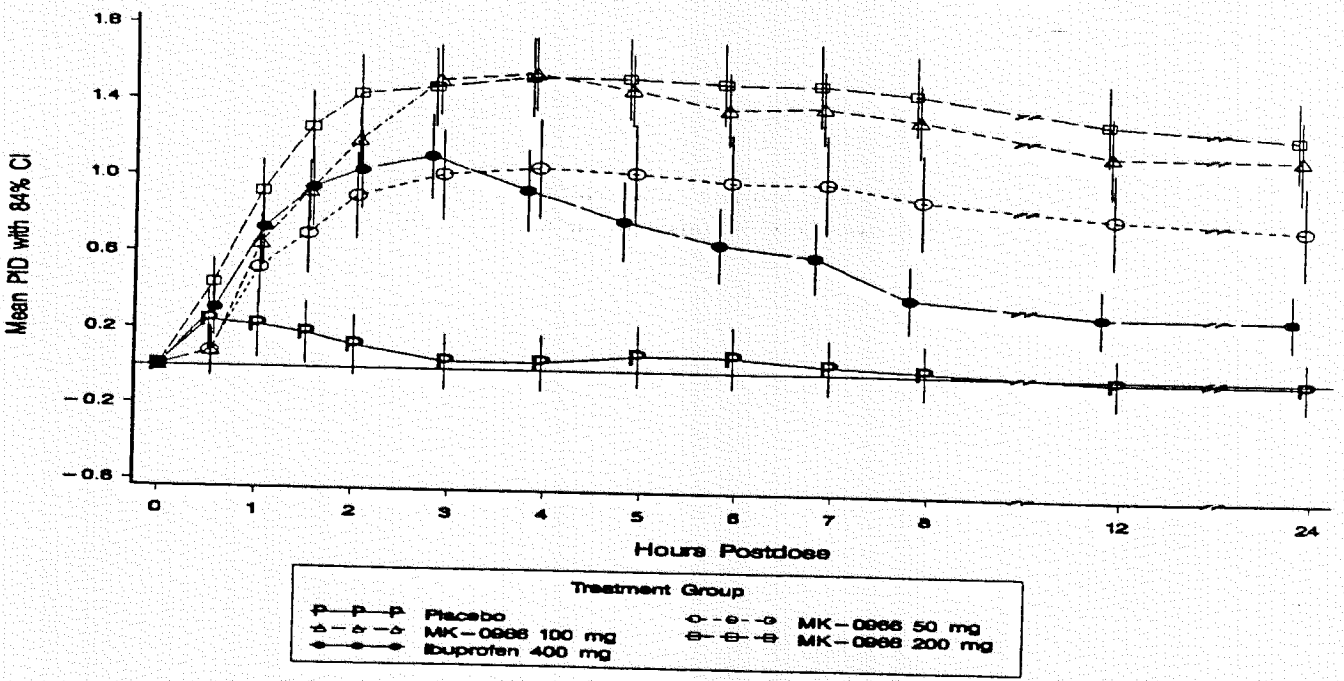


Figure 7

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



Efficacy of Rofecoxib Versus Naproxen Sodium and Ibuprofen in Post-Dental Surgery Pain

The Phase II studies used 550 mg naproxen sodium as the comparator and the Phase III studies used 400 mg ibuprofen as the comparator. Formal comparability criteria were not prespecified for comparing rofecoxib versus the comparator NSAID; the statistical comparisons made between rofecoxib and the comparator are therefore primarily provided to assess large between-treatment differences and not to conclude that true comparability exists.

Naproxen Sodium

In both studies 027 and 051, naproxen sodium 550 mg was significantly better than placebo for almost all end points examined, including those characterizing overall effect (TOPAR8, SPID8, Patient's Global Evaluation of Study Medication at 8 hours), onset of analgesia (Stopwatch Time to Meaningful Pain Relief, Time to PID ≥1), peak effect (Peak Pain Relief, Peak PID), and duration of analgesia (Time to Rescue Medication, PRID at 24-hour time point, but not for Percent of Patients Taking Rescue Medication within 24 hours). The efficacy of 50 mg rofecoxib was generally similar in magnitude to the effect of 550 mg naproxen sodium for all end points analyzed.

Ibuprofen

In both studies 066 and 071, ibuprofen 400 mg was significantly better than placebo for almost all end points examined, including those characterizing overall effect (TOPAR8, SPID8, Patient's Global Evaluation of Study Medication at 8 hours), onset of analgesia (Stopwatch Time to Confirmed Perceptible Pain Relief, Time to PID ≥1), and peak effect (Peak Pain Relief, Peak PID). For measures of duration of effect, ibuprofen was significantly better than placebo for the end point of Time to Rescue Medication. The analgesic efficacy of 50 mg rofecoxib was generally similar in magnitude to the effect of 400 mg ibuprofen in both Phase III protocols. The duration of analgesic effect was, however, longer with 50 mg rofecoxib than with ibuprofen. This was seen in both Time to Take Rescue Medication and Percent of Patients Taking Rescue Medication within 24 hours.

Summary of Post-Dental Surgery Pain Studies

The results of the Phase II Dose-Ranging studies showed that 50 mg was the minimal dose required to give analgesic efficacy and that the efficacy of 50 mg rofecoxib was generally similar to 550 mg of naproxen sodium. Both the 100 mg and the 200 mg doses provided analgesic efficacy significantly greater than the 50 mg rofecoxib dose in study 071. Phase III studies confirmed the efficacy of 50 mg rofecoxib compared with placebo for all analgesic end points. The results of the Phase III studies also demonstrated that the analgesic effect of 50 mg rofecoxib was generally similar to the analgesic effect of the analgesic dose of ibuprofen (400 mg). The 50 mg rofecoxib had a longer duration of action than 400 mg ibuprofen but it is unclear if this is clinically significant in the dental pain model which is not a good long term (more than several hours) pain model.

Analgesia Efficacy Studies—Dysmenorrhea

Single-Dose Study in Dysmenorrhea
(Study 038)

Doses used in this study were 7.5, 25, and 50 mg. The results of study 038 (Figure 8, Table 9) demonstrated that in the treatment of primary dysmenorrhea, rofecoxib administered as a single dose of 7.5, 25, or 50 mg: (1) was more effective than placebo only at the 50-mg dose (neither the 7.5- nor the 25-mg dose of rofecoxib provided clinically or statistically significant improvements in any primary or secondary end point compared with placebo, indicating that they were both clinically ineffective doses for the treatment of primary dysmenorrhea in this study) and (2) exhibited efficacy (including onset, peak, and duration of analgesia) similar to 400 mg ibuprofen at the 50-mg dose.

Figure 8

Mean Pain Relief (PR) Score† With 84% Confidence Interval by Hours Postdose (Intention-to-Treat Approach) Phase II Primary Dysmenorrhea Dose-Ranging Study (Protocol 038)

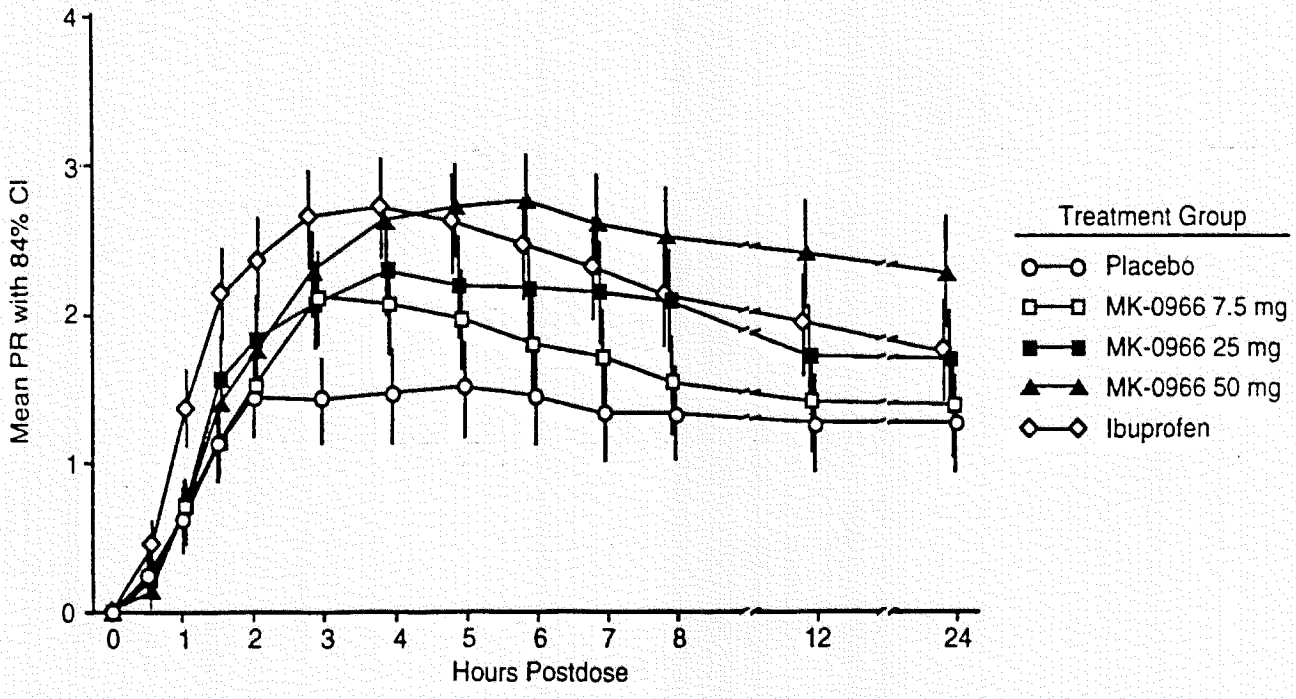


Table 9

Effect of Rofecoxib on All End Points in Phase II Primary Dysmenorrhea Dose-Ranging Study
(Protocol 038)

	Placebo	Rofecoxib			Ibuprofen
	N= 17	7.5 mg N= 16	25 mg N= 16	50 mg N= 17	400 mg N= 16
Baseline Pain Intensity (First Cycle)— n (%)					
Moderate	14 (82%)	15 (94%)	10 (62%)	15 (88%)	15 (94%)
Severe	3 (18%)	1 (6%)	6 (38%)	2 (12%)	1 (6%)
End Points					
Overall Analgesic Effect	LS Mean (95% CI)				
TOPAR8 (0 to 32 scale)	10.9 (8.1, 13.6)	12.6 (9.9, 15.4)	14.2 (11.5, 16.9)	17.7* (15.1, 20.4)	17.3* (14.6, 20.1)
SPID8 (- 8 to 24 scale)	7.2 (5.5, 8.9)	7.5 (5.8, 9.2)	8.1 (6.5, 9.8)	10.1* (8.5, 11.7)	10.7* (9.1, 12.4)
Patient's Global Evaluation at 8 Hours (0 to 4 Scale)	1.3 (0.9, 1.7)	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)	1.7 (1.4, 2.1)	2.3* (1.9, 2.7)
Peak Analgesic Effect	LS Mean (95% CI)				
Peak PID During 8 Hours Postdose (-1 to 3 Scale)	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)	1.6 (1.3, 1.8)	1.9* (1.6, 2.1)	1.9* (1.6, 2.2)
Peak Pain Relief During 8 Hours Postdose (0 to 4 Scale)	2.1 (1.6, 2.6)	2.2 (1.7, 2.6)	2.6 (2.2, 3.1)	3.2* (2.8, 3.7)	3.0* (2.5, 3.4)
Duration of Analgesic Effect					
Number (%) of Patients Who Took Rescue Medication Within 24 Hours	29 (61.7)	30 (63.8)	26 (53.1)	18 (37.5)*	21 (42.9)*
	Hours (95% CI)				
Time (hours) to 50% of Patients Took Rescue Medication †	6.8 (4.3, ∞)	8.5 (6.3,13.0)	14.6 (6.8, ∞)	NE*	NE*

* p< 0.05 versus placebo.
† The 50th percentile of the respective end points.
NE = Not estimable because <50% of patients attained end point.

Phase III Studies in Dysmenorrhea
(studies 055 and 056)

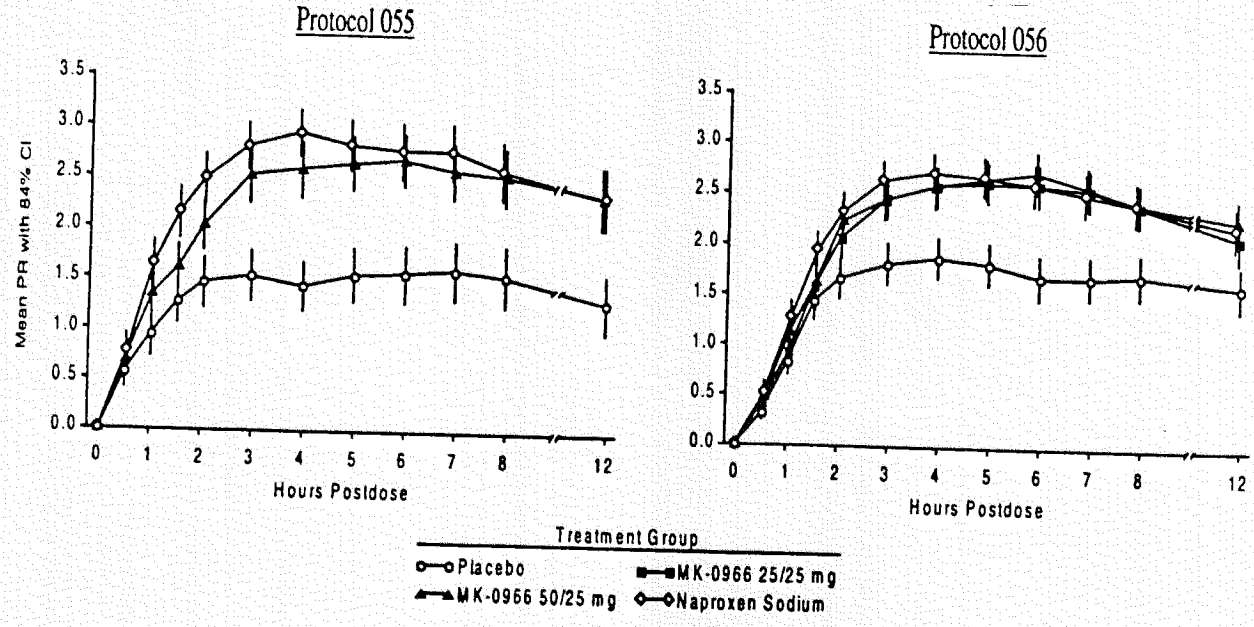
Two pivotal Phase III studies (studies 055 and 056) were performed to confirm the efficacy of 50 mg rofecoxib in the primary dysmenorrhea model. The 2 studies were similar in design. Both studies included an initial dose of 50 mg rofecoxib followed by subsequent, as-needed doses of 25 mg rofecoxib. Study 056 also included a treatment group of 25 mg rofecoxib followed by subsequent, as-needed doses of 25 mg rofecoxib. The findings of the 2 studies were consistent with one another and demonstrated that 50 mg rofecoxib has analgesic efficacy greater than placebo on all measures of overall analgesic effect, peak analgesic effect, and duration of analgesia following administration of the first dose.

Figure 9 shows a plot of the mean Pain Relief score versus hours postdose in the two studies.

Figure 9

D-28

Mean Pain Relief (PR) Score[†] With 84% Confidence Interval by Hours Postdose (Intention-to-Treat Approach)
Phase III Primary Dysmenorrhea Studies



Overall Analgesic Effect

In both studies over the 8 hours postdose, 50 mg rofecoxib produced significantly ($p \leq 0.002$) greater LS mean TOPAR8 scores compared with placebo. The magnitude of the difference between the 50-mg rofecoxib group and placebo was generally similar between the studies (Table 10).

Table 10

Effect of Rofecoxib on TOPAR8 in Phase III Primary Dysmenorrhea Studies (Protocols 055 and 056)

Parameter	Protocol 055		Protocol 056		
	Placebo N= 60	Rofecoxib 50 mg/ 25 mg † N= 60	Placebo N= 118	Rofecoxib 25 mg/ 25 mg † N= 115	Rofecoxib 50 mg/ 25 mg † N= 118
Baseline Pain Intensity— n (%)					
Moderate	38 (63)	37 (62)	71 (60)	76 (66)	76 (64)
Severe	22 (37)	23 (38)	47 (40)	39 (34)	42 (36)
	LS Mean (95% CI)				
TOPAR8 (0 to 32 scale)	12.1 (9.7, 14.4)	17.5 (15.2, 19.8)	12.5 (10.9, 14.0)	17.4 (15.8, 19.0)	18.0 (16.4, 19.5)
Difference in TOPAR8 From Placebo	NA	5.4* (2.0, 8.8)	NA	4.9* (2.8, 7.1)	5.5* (3.4, 7.6)

* $p \leq 0.002$ for difference from placebo.
† 50 mg/25 mg indicates an initial dose of 50 mg followed by optional subsequent doses of 25 mg; 25 mg/25 mg indicates an initial dose of 25 mg followed by optional subsequent doses of 25 mg.
NA=Not applicable.

In both studies, the results from the SPID8 end point demonstrated that rofecoxib 50 mg produced significantly ($p \leq 0.003$) greater overall analgesic effects compared with placebo. The magnitude of the difference between the 50-mg rofecoxib group and placebo was generally similar between the studies. In study 056, the results from the Patient's Global Evaluation end point demonstrated that rofecoxib 50 mg produced significantly ($p \leq 0.003$) greater overall analgesic effects compared with placebo. In Protocol 055, this value was ($p=0.060$) (Table 11).

Table 11

Effect of Rofecoxib on SPID8 and Patient's Global Evaluation of Study Medication in Phase III Primary Dysmenorrhea Studies
(Protocols 055 and 056)

Parameter	Protocol 055		Protocol 056		
	Placebo N= 60	Rofecoxib 50 mg/ 25 mg † N= 60	Placebo N= 118	Rofecoxib 25 mg/ 25 mg † N= 115	Rofecoxib 50 mg/ 25 mg † N= 118
Baseline Pain Intensity— n (%)					
Moderate	38 (63)	37 (62)	71 (60)	76 (66)	76 (64)
Severe	22 (37)	23 (38)	47 (40)	39 (34)	42 (36)
SPID8 (- 8 to 24 Scale)	LS Mean (95% CI)				
	6.8 (5.2, 8.3)	10.2 (8.6, 11.7)	6.7 (5.7, 7.7)	9.8 (8.7, 10.8)	10.4 (9.4, 11.4)
Difference in SPID8 From Placebo	NA	3.4* (1.2, 5.7)	NA	3.0* (1.6, 4.4)	3.7* (2.3, 5.1)
Patient's Global Evaluation at 8 Hours (0 to 4 Scale)	1.3 (0.9, 1.6)	1.7 (1.4, 2.1)	1.2 (1.0, 1.5)	1.8 (1.6, 2.0)	2.0 (1.8, 2.2)
Difference in Patient's Global Evaluation From Placebo	NA	0.5** (0.0, 1.0)	NA	0.6* (0.3, 0.9)	0.8* (0.5, 1.1)

* p≤0.003 for difference from placebo.
** p=0.060 for difference from placebo.
† 50 mg/25 mg indicates an initial dose of 50 mg followed by optional subsequent doses of 25 mg; 25 mg/25 mg indicates an initial dose of 25 mg followed by optional subsequent doses of 25 mg.
NA=Not applicable.

Peak Analgesic Effect

The LS mean scores for Peak Pain Relief and Peak PID are in Table 12. The findings of the 2 studies are consistent with one another and demonstrated that during the 8 hours postdose, 50 mg rofecoxib produced a significantly (p≤0.003) greater peak analgesic effect compared with placebo. The magnitude of the difference between the rofecoxib group and placebo was generally similar between the studies.

Table 12

Effect of Rofecoxib on Peak Pain Relief and Peak PID in Phase III Primary Dysmenorrhea Studies
(Protocols 055 and 056)

Parameter	Protocol 055		Protocol 056		
	Placebo N= 60	Rofecoxib 50 mg/ 25 mg † N= 60	Placebo N= 118	Rofecoxib 25 mg/ 25 mg † N= 115	Rofecoxib 50 mg/ 25 mg † N= 118
Peak Analgesic Effect	LS Mean (95% CI)				
Peak PID During 8 Hours Postdose (Scale-1 to 3)	1.4 (1.2, 1.6)	1.9 (1.7, 2.1)	1.4 (1.3, 1.5)	1.8 (1.6, 1.9)	1.7 (1.6, 1.9)
Difference in Peak PID From Placebo	NA	0.5* (0.2, 0.8)	NA	0.4* (0.2, 0.6)	0.4* (0.2, 0.6)
Peak Pain Relief During 8 Hours Postdose (Scale 0 to 4)	2.4 (2.0, 2.7)	3.1 (2.7, 3.4)	2.3 (2.1, 2.5)	3.0 (2.8, 3.2)	2.9 (2.7, 3.2)
Difference in Peak Pain Relief From Placebo	NA	0.7* (0.2, 1.2)	NA	0.7* (0.4, 1.0)	0.6* (0.3, 0.9)

* p≤0.003 for difference from placebo.
† 50 mg/25 mg indicates an initial dose of 50 mg followed by optional subsequent doses of 25 mg; 25 mg/25 mg indicates an initial dose of 25 mg followed by optional subsequent doses of 25 mg.
NA=Not applicable.

Duration of Analgesia

The duration of rofecoxib was assessed using the Percent of Patients Taking Rescue Medication within 12 hours and the Time to Rescue Medication (Table 13). The findings of the 2 studies were consistent with one another and demonstrated that the percent of patients who took rescue medication within 12 hours postdose was significantly (p≤0.005) lower in the 50-mg rofecoxib group compared with the placebo group. The findings of the 2 studies also consistently indicated that patients who received placebo took rescue medication significantly (p≤0.005) earlier compared with those who received 50 mg rofecoxib.

Table 13

Effect of Rofecoxib on Percent of Patients Taking Rescue Medication Within 12 Hours and the Time to Rescue Medication in Phase III Primary Dysmenorrhea Studies
(Protocols 055 and 056)

Parameter	Protocol 055		Protocol 056		
	Placebo N= 60	Rofecoxib 50 mg/ 25 mg † N= 60	Placebo N= 118	Rofecoxib 25 mg/ 25 mg † N= 115	Rofecoxib 50 mg/ 25 mg † N= 118
Duration of Analgesic Effect					
Number (%) of Patients Who Took Rescue Medication Within 12 Hours	30 (50.0)	12 (20.0)*	53 (44.9)	31 (27.0)*	32 (27.1)*
	Time (95% CI)				
Time (Hours) to 50% of Patients Took Rescue Medication ‡	11.8 (8.5, ∞)	NE*	NE	NE*	NE*

† 50 mg/25 mg indicates an initial dose of 50 mg followed by optional subsequent doses of 25 mg; 25 mg/25 mg indicates an initial dose of 25 mg followed by optional subsequent doses of 25 mg.
‡ The 50th percentile of the respective end point.
NE = Not estimable because less than 50% of patients took rescue medication.
* p≤0.005 for difference from placebo.

End Points of Multiple Dose Administration

In both Phase III Primary Dysmenorrhea Studies, patients were allowed to take additional doses of rofecoxib 25 mg as needed for continued menstrual cramping pain (patients who took rescue medication were excluded from this portion of the study). The results show that the majority of patients in all treatment groups did not take additional doses of study medication (Table 14). This may be due to a limited duration of pain in these analgesic trials.

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. In both studies there were no differences in any of these endpoints between neither rofecoxib nor naproxen sodium 550-mg and placebo except for study 056 in which the Patient's Global Evaluation at 72 hours for naproxen sodium 550 mg was significantly ($p<0.001$) greater than placebo but not that rofecoxib.

Table 14

Effect of Rofecoxib on Percent of Patients Taking Additional As-Needed Doses of Study Medication in Phase III Primary Dysmenorrhea Studies
(Protocols 055 and 056)

Parameter	Protocol 055		Protocol 056		
	Placebo N= 60	Rofecoxib 50 mg/ 25 mg † N= 60	Placebo N= 118	Rofecoxib 25 mg/ 25 mg † N= 115	Rofecoxib 50 mg/ 25 mg † N= 118
Multiple- Dose Efficacy					
Number (%) of Patients Who Took Additional Doses of Study Medication ‡	11 (18.3)	11 (18.3)	28 (23.7)	31 (27.0)	33 (27.9)

† 50 mg/25 mg indicates an initial dose of 50 mg followed by optional subsequent doses of 25 mg; 25 mg/25 mg indicates an initial dose of 25 mg followed by optional subsequent doses of 25 mg.
‡ Patients who took rescue medication were not eligible to take additional as-needed doses.

Efficacy of Rofecoxib Versus Ibuprofen and Naproxen Sodium in Dysmenorrhea

The Phase II Primary Dysmenorrhea Dose-Ranging Study (Study 038) used 400 mg ibuprofen as the comparator and the two Phase III studies used 550 mg naproxen sodium as the comparator. Formal comparability criteria were not prespecified for comparing rofecoxib versus the comparator NSAID; the statistical comparisons made between rofecoxib and the comparator are therefore primarily provided to assess large between-treatment differences and not to conclude that true comparability exists.

Ibuprofen

Ibuprofen 400 mg was significantly better than placebo for all end points examined including those characterizing overall effect (TOPAR8, SPID8, Patient's Global Evaluation of Study Medication at 8 hours), peak effect (Peak Pain Relief, Peak PID), and duration of analgesia (Time to Rescue Medication, Percent of Patients Taking Rescue Medication), thus validating the study.

The efficacy of 50 mg rofecoxib was generally similar in magnitude to the effect of 400 mg ibuprofen for all end points analyzed (Table 15). The only end point in which there was a statistically significant difference between 50 mg rofecoxib and ibuprofen was the Patient's Global Evaluation at 8 hours (p=0.025), in which greater efficacy was seen with ibuprofen compared with rofecoxib 50 mg.

Table 15

Effect of Rofecoxib and 400 mg Ibuprofen on All End Points in Phase II Primary Dysmenorrhea Dose-Ranging Study
(Protocol 038)

	Placebo N= 17	Rofecoxib 50 mg N= 17	Ibuprofen 400 mg N= 16
Baseline Pain Intensity (First Cycle)— n (%)			
Moderate	14 (82%)	15 (88%)	15 (94%)
Severe	3 (18%)	2 (12%)	1 (6%)
Overall Analgesic Effect	LS Mean (95% CI)		
TOPAR8 (0 to 32 scale)	10.9 (8.1, 13.6)	17.7* (15.1, 20.4)	17.3* (14.6, 20.1)
SPID8 (- 8 to 24 Scale)	7.2 (5.5, 8.9)	10.1* (8.5, 11.7)	10.7* (9.1, 12.4)
Patient's Global Evaluation at 8 Hours (0 to 4 Scale)	1.3 (0.9, 1.7)	1.7 (1.4, 2.1)	2.3* (1.9, 2.7)
Peak Analgesic Effect	LS Mean (95% CI)		
Peak PID During 8 HoursPostdose (-1 to 3 Scale)	1.3 (1.1, 1.6)	1.9* (1.6, 2.1)	1.9* (1.6, 2.2)
Peak Pain Relief During8 Hours Postdose (0 to 4 Scale)	2.1 (1.6, 2.6)	3.2* (2.8, 3.7)	3.0* (2.5, 3.4)
Duration of Analgesic Effect			
Number (%) of Patients Who Took Rescue Medication Within 24 Hours	29 (61.7)	18 (37.5)*	21 (42.9)*
Time (Hours) to 50% of Patients Took Rescue Medication †	6.8 (4.3, ∞)	NE*	NE*

* p<0.05 versus placebo.
† The 50th percentile of the respective end points.
NE = Not estimable because <50% of patients attained end point.

Naproxen Sodium

In both Protocols 055 and 056, 550 mg naproxen sodium was significantly better than placebo for all end points examined, including those characterizing overall effect (TOPAR8, SPID8, Patient's Global Evaluation of Study Medication at 8 hours), peak effect (Peak Pain Relief, Peak PID), and duration of analgesia (Time to Rescue Medication, Percent of Patients Taking Rescue Medication) (Table 16).

In study 055 the naproxen sodium demonstrated statistically significant better pain relief and pain intensity scores at 1 and 1.5 hours postdose compared with rofecoxib 50 mg. The overall efficacy of 50 mg rofecoxib, as assessed by the end points of TOPAR8, SPID8 and Patient's Global Evaluation, was generally similar in magnitude to the effect of 550 mg naproxen sodium in both Phase III studies.

The duration of analgesia of 50 mg rofecoxib, as assessed by Percent of Patients Taking Rescue Medication and the Time to Taking Rescue Medication, was generally similar in magnitude to the effect of 550 mg naproxen sodium in both Phase III studies.

Table 16

Effect of 50 mg Rofecoxib and 550 mg Naproxen Sodium on All End Points Phase III in Primary Dysmenorrhea Studies
(Protocols 055 and 056)

	Study 055			Study 056			
	Placebo N= 60	Rofecoxib 50/25 mg N= 60	Naproxen Sodium 550 mg N= 59	Placebo N= 118	Rofecoxib 25/25 mg N= 115	Rofecoxib 50/25 mg N= 118	Naproxen Sodium 550 mg N= 122
Baseline Pain Intensity (First Cycle)— n (%)							
Moderate	38 (63)	37 (62)	39 (66)	71 (60)	76 (66)	76 (64)	78 (64)
Severe	22 (37)	23 (38)	20 (34)	47 (40)	39 (34)	42 (36)	44 (36)
Overall Analgesic Effect	LS Mean (95% CI)						
TOPAR8 (0 to 32 scale)	12.1 (9.7, 14.4)	17.5* (15.2, 19.8)	19.5* (17.0, 22.0)	12.5 (10.9, 14.0)	17.4* (15.8, 19.0)	18.0* (16.4, 19.5)	18.4* (16.9, 19.9)
SPID8 (- 8 to 24 Scale)	6.8 (5.2, 8.3)	10.2* (8.6, 11.7)	11.2* (9.5, 12.9)	6.7 (5.7, 7.7)	9.8* (8.7, 10.8)	10.4* (9.4, 11.4)	10.7* (9.7, 11.7)
Patient's Global Evaluation at 8 Hours (0 to 4 Scale)	1.3 (0.9, 1.6)	1.7** (1.4, 2.1)	2.1* (1.8, 2.5)	1.2 (1.0, 1.5)	1.8* (1.6, 2.0)	2.0* (1.8, 2.2)	1.9* (1.7, 2.2)
Peak Analgesic Effect	LS Mean (95% CI)						
Peak PID During 8 Hours Postdose (-1 to 3 Scale)	1.4 (1.2, 1.6)	1.9* (1.7, 2.1)	2.0* (1.8, 2.2)	1.4 (1.3, 1.5)	1.8* (1.6, 1.9)	1.7* (1.6, 1.9)	1.8* (1.7, 2.0)
Peak Pain Relief During8 Hours Postdose (0 to 4 Scale)	2.4 (2.0, 2.7)	3.1* (2.7, 3.4)	3.3* (3.0, 3.7)	2.3 (2.1, 2.5)	3.0* (2.8, 3.2)	2.9* (2.7, 3.2)	3.1* (2.9, 3.3)
Duration of Analgesic Effect							
Number (%) of Patients Who Took Rescue Medication Within 12 Hours	30 (50.0)	12 (20.0)*	16 (27.1)*	53 (44.9)	31 (27.0)*	32 (27.1)*	36 (29.5)*
Time (Hours) to 50% of Patients Took Rescue Medication †	11.8 (8.5 , ∞)	NE*	NE*	NE	NE*	NE*	NE*

* p< 0.05 versus placebo.
** p= 0.06 versus placebo.†50 mg/ 25 mg indicates an initial dose of 50 mg followed by optional subsequent doses of 25 mg; 25 mg/ 25 mg indicates an initial dose of 25 mg followed by optional subsequent doses of 25 mg.
‡ The 50th percentile of the respective end points.
NE = Not estimable.