Summary of Primary Dysmenorrhea Studies

The results of the Phase II dose-ranging study (Study 038) 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 400 mg of ibuprofen.

Phase III studies confirmed the efficacy of 50 mg rofecoxib following a single dose administration compared with placebo and also demonstrated that the analgesic effect of 50 mg rofecoxib was generally similar to the analgesic effect of 550 mg naproxen sodium. Study 056 also demonstrated that 25 mg was both more effective than placebo and similar to 50 mg in the treatment of primary dysmenorrhea however, these results are inconsistent with the results of all the other analgesia studies including those of the other dysmenorrhea study (055).

Although one of the primary purposes of the dysmenorrhea studies was to demonstrate the multiple-dose efficacy of rofecoxib, no pain measurements have been carried out beyond 12 hours postdose in neither study. No analgesic effect of multiple doses of rofecoxib has been demonstrated by the surrogate end points of 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.

Analgesia Efficacy Studies—Post-Orthopedic Surgery Pain
(Study 072)

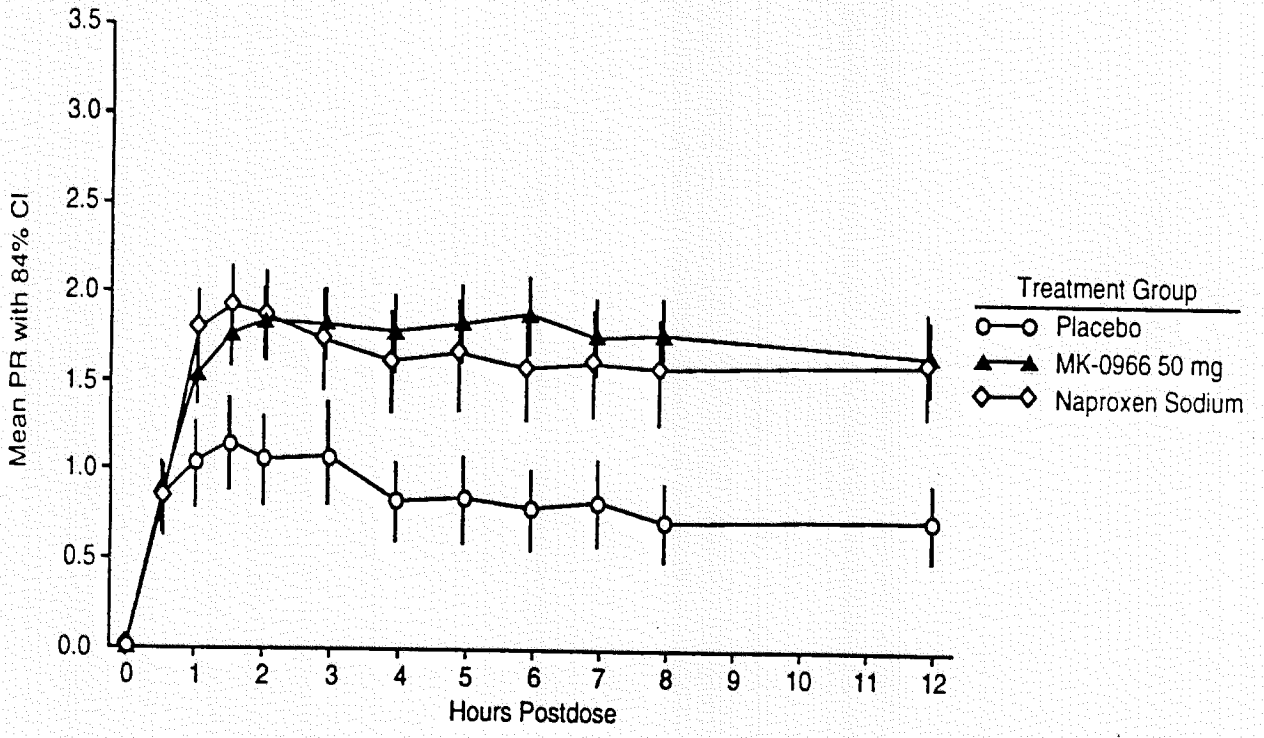
Single-Dose Analgesic Efficacy in the Post-Orthopedic Surgery Pain Study

The results of the analysis of the single-dose analgesic end points from study 072 demonstrated that in the treatment of post-orthopedic surgery pain, 50 mg rofecoxib was more effective than placebo for end points assessing analgesic effects, pain relief, pain intensity, onset of analgesic effect, peak analgesic effect, and duration of analgesia (Figure 10, Table 17).

Naproxen sodium 550 mg was significantly better than placebo for most end points examined, thus validating the study. As seen in The single-dose analgesic efficacy of 50 mg rofecoxib was generally similar in magnitude to the effect of 550 mg naproxen sodium for all end points analyzed.

Figure 10

Figure D-29 Mean Pain Relief (PR) Score† With 84% Confidence Interval by Hours Postdose (Intention-to-Treat Approach) Phase III Post-Orthopedic Surgery Pain Study (Protocol 072)



† Pain Relief was rated on a 0 to 4 scale as 0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete.

Table 17

Effect of Rofecoxib on Single-Dose Analgesic End Points in Phase III Post-Orthopedic Surgery Pain Study
(Protocol 072)

	Placebo/ Placebo N= 53	Rofecoxib 50/25 mg N= 56	Rofecoxib 50/50 mg N= 54	Naproxen Sodium 550 mg/ Placebo N= 55
Baseline Pain Intensity (First Cycle)— n (%)				
Moderate	43 (81.1)	45 (80.4)	44 (81.5)	46 (83.6)
Severe	10 (18.9)	11 (19.6)	10 (18.5)	9 (16.4)
End Points				
	Placebo N= 53	Rofecoxib 50 mg ‡ N= 110		Naproxen Sodium 550 mg N= 55
Overall Analgesic Effect	LS Mean (95% CI)			
TOPAR8 (0 to 32 scale)	5.8 (2.9, 8.7)	12.3* (10.2, 14.5)		11.7* (8.8, 14.5)
SPID8 (- 8 to 24 scale)	1.8 (- 0.1, 3.8)	6.2* (4.8, 7.6)		5.5* (3.6, 7.3)
Patient's Global Evaluation at 8 Hours (0 to 4 Scale)	1.0 (0.6, 1.5)	1.8* (1.5, 2.1)		1.7* (1.3, 2.2)
Peak Analgesic Effect	LS Mean (95% CI)			
Peak PID During 8 Hours Postdose (-1 to 3 Scale)	0.8 (0.5, 1.0)	1.3* (1.1, 1.5)		1.2* (1.0, 1.5)
Peak Pain Relief During 8 Hours Postdose (0 to 4 Scale)	1.5 (1.1, 1.9)	2.2* (1.9, 2.5)		2.3* (1.9, 2.7)
Duration of Analgesic Effect				
Number (%) of Patients Who Took Rescue Medication Within 24 Hours	51 (96.2)	72 (65.5)*		(72.7)*
	Hours (95% CI)			
Time (hours) to 50% of Patients Took Rescue Medication †	2.8 (1.8, 3.8)	5.3* (4.0, 8.1)		5.3* (3.3, 7.5)

* $p < 0.05$ versus placebo.

† 50 mg/25 mg indicates an initial dose of 50 mg followed by 25 mg daily; 50 mg/50 mg indicates an initial dose of 50 mg followed by 50 mg daily.

‡ Both groups took 50 mg as the initial dose and are therefore combined for the single-dose efficacy analysis.

§ The 50th percentile of the respective end points.

NE = Not estimable because <50% of patients attained end point.

Multiple-Dose Analgesic Efficacy in the Post-Orthopedic Surgery Pain Study
Rofecoxib was dosed as either 25 or 50 mg daily for Days 2 to 5. No active comparator was used in this portion of the study; patients who received naproxen sodium as their initial dose then received placebo for all subsequent doses. The analgesic effect on Days 2 to 5 was established using the end points of Average Supplemental Rescue Medication Use Over Days 2 to 5, Patient's Global Evaluation Scores averaged over Days 2 to 5, and Pain Intensity Score averaged over Days 2 to 5.

Average Supplemental Rescue Medication Use Over Days 2 to 5
Most patients in all treatment arms required at least 1 dose of supplemental rescue medication on Days 2 to 5. Hydrocodone 7.5 mg/acetaminophen 500 mg (LORTAB 7.5™) was used as the rescue medication.

The LS mean number of Tablets of Rescue Medication taken per day in the 50-mg/50-mg group but not in the 50-mg/25-mg group was significantly lower than that in the placebo group (Table 18). This statistical difference between rofecoxib and placebo was of one LORTAB 7.5™ tablet daily on average.

Table 18

Effect of Rofecoxib on Average Supplemental Rescue Medication Use Days 2 to 5 in Phase III Post-Orthopedic Surgery Pain Study
(Protocol 072)

Parameter	Placebo/ Placebo N= 38	Rofecoxib 50 mg/ 25 mg † N= 47	Rofecoxib 50 mg/ 50 mg † N= 46
Overall Analgesic Effect Days 2 to 5			
Average Supplemental Rescue Medication Use (Tablets/ Day)	LS Mean (95% CI)		
	2.6 (2.0, 3.1)	2.1 (1.6, 2.6)	1.6 (1.2, 2.1)
Difference in Rescue Medication Use From Placebo	NA	-0.5 (- 1.1, 0.1)	-0.9* (- 1.6, -0.3)

* p = 0.005 for difference from placebo.
† 50 mg/25 mg indicates an initial dose of 50 mg followed by 25 mg daily; 50 mg/50 mg indicates an initial dose of 50 mg followed by 50 mg daily.
NA=Not applicable.

Pain Intensity Score Averaged Over Days 2 to 5
Pain intensity was measured at prior to morning dose, 4 hours post morning dose and at bedtime of days 2 to 5 post initial dosing. The LSMean Pain Intensity scores averaged over Days 2 to 5 in the rofecoxib 50-mg/25-mg and rofecoxib 50-mg/50-mg groups were not significantly different from that in the placebo group (Table 19). It is to note that the mean scores for all treatment groups were relatively low both prior to and after dosing with study medication, reflecting overall mild pain in the patient population on Days 2 to 5. Patients who used rescue medication prior to a pain intensity evaluation were included

in the analysis (there were no restrictions on the use of rescue medication in relation to pain intensity evaluations) and likely contributed to the overall low scores.

Table 19

Effect of Rofecoxib on Pain Intensity Score Averaged Over Days 2 to 5 in Phase III Post-Orthopedic Surgery Pain Study
(Protocol 072)

Parameter	Placebo/ Placebo N= 42	Rofecoxib 50 mg/ 25 mg † N= 48	Rofecoxib 50 mg/ 50 mg † N= 48
Pain Intensity Score Averaged over Days 2 to 5			
	LS Mean (95% CI)		
Pain Intensity Score Averaged Over Days 2 to 5 (0 to 3 Scale)	1.3 (1.1, 1.5)	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)
Difference in Pain Intensity Score Averaged Over Days 2 to 5 From Placebo	NA	-0.1 (-0.3, 0.1)	-0.2 (-0.4, 0.1)

No significant differences between treatment groups were detected.
† 50 mg/25 mg indicates an initial dose of 50 mg followed by 25 mg daily; 50 mg/50 mg indicates an initial dose of 50 mg followed by 50 mg daily.
NA=Not applicable.

Patient's Global Evaluation Score Averaged Over Days 2 to 5

The LS mean Patient's Global Evaluation scores averaged over Days 2 to 5 in the 50-mg/50-mg group but not in the 50-mg/25-mg group was significantly greater than that in the placebo group (Table 20).

Table 20

Effect of Rofecoxib on Patient's Global Evaluation Score Averaged Over Days 2 to 5 In Phase III Post-Orthopedic Surgery Pain Study
(Protocol 072)

Parameter	Placebo/ Placebo N= 41	Rofecoxib 50 mg/ 25 mg † N= 48	Rofecoxib 50 mg/ 50 mg † N= 48
Patient's Global Evaluation Score Averaged Over Days 2 to 5			
	LS Mean (95% CI)		
Patient's Global Evaluation Score Averaged Over Days 2 to 5 (0 to 4 Scale)	1.8 (1.4, 2.2)	2.0 (1.7, 2.4)	2.3 (1.9, 2.7)
Difference in Patient's Global Evaluation Score From Placebo	NA	0.3 (-0.2, 0.8)	0.5* (0.0, 1.0)

* p=0.041 for difference from placebo.
† 50 mg/25 mg indicates an initial dose of 50 mg followed by 25 mg daily; 50 mg/50 mg indicates an initial dose of 50 mg followed by 50 mg daily.
NA=Not applicable.

Summary of Post-Orthopedic Surgery Pain Study

The purpose of the Post-Orthopedic Surgery Pain Study was to demonstrate both single- and multiple-dose analgesic efficacy of rofecoxib, a specific COX-2 inhibitor, in a third analgesic model. The results of the single-dose portion of this study further support the efficacy of 50 mg rofecoxib as a single dose for the treatment of acute pain.
The results of multiple-dose portion of this study (Days 2 to 5) however, are less obvious to interpret. The results of this portion demonstrated that rofecoxib 50 mg (but not 25 mg) once daily is more effective than placebo in patient's global evaluation scores averaged over Days 2 to 5. Superiority of rofecoxib 50 mg over placebo was also demonstrated in the number of tablets of rescue medication taken per day however, this statistical difference between rofecoxib and placebo was of one LORTAB 7.5™ tablet daily on average and therefore of unclear clinical significance. Moreover, the Pain Intensity scores averaged over Days 2 to 5 in the two rofecoxib treatment groups were not significantly different from that in the placebo group.

Safety in Analgesia Studies

One thousand two patients were treated with rofecoxib in the analgesia studies: 631 in the Post-Dental Surgery Pain Studies, 261 in the Primary Dysmenorrhea Studies, and 110 in the Post-Orthopedic Surgery Pain Study. All patients in the Post-Dental Surgery Pain Studies received only a single dose of study medication. Patients in the Primary Dysmenorrhea Studies may have taken up to 3 doses of rofecoxib and those in the Post-Orthopedic Surgery Pain Study were prescribed 5 doses of rofecoxib (Table 21).

Table 21

Number of Patients on Rofecoxib in the Analgesia Population by Dose and Exposure

Dose of Rofecoxib	Number of Patients Treated
Any Dose	1002
Single- Dose Exposure	
7.5 mg	87
12.5 mg	72
25 mg	257
50 mg	447
100 mg	91
200 mg	50
250 mg	8
500 mg	20
>1 to ≤ 5 Doses	
25 mg	17
50/ 25 mg †	84
50 mg	48

† 50 mg as an initial dose followed by 25 mg daily 1 or more times.
Although some patients may have taken two or more different dosages, they have been counted only one time each, on the "Any dose" row.

Post-Dental Surgery Pain and Primary Dysmenorrhea Studies

The clinical adverse experience profile for the combined Post-Dental Surgery Pain and Primary Dysmenorrhea Studies (relatively young and otherwise healthy) demonstrated that in this group, 521 patients (26.6%) reported at least one clinical adverse experience. One hundred nine (24.4%), 301 (29.4%), 39 (22.7%), and 72 (26.8%) patients in the placebo, rofecoxib, ibuprofen, and naproxen sodium groups, respectively, reported one or more adverse experiences. The incidence of adverse experiences was generally similar across all treatments (Table 22).

Serious adverse experiences were uncommon and none were considered to be drug related. Discontinuation due to an adverse experience was also uncommon. No deaths were reported in this study group.

Table 22

Clinical Adverse Experience Summary in Combined Post- Dental Surgery Pain and Primary Dysmenorrhea Studies

	Placebo N=446		Rofecoxib ≤ 12.5 mg N=159		Rofecoxib 25 mg N=274		Rofecoxib 50 mg N=291		Rofecoxib 50/25 mg N=179		Rofecoxib 100 mg N=91		Rofecoxib ≥200 mg N=78		Ibuprofen 400 mg N=172		Naproxen 550 mg N=269	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of patients evaluated:																		
Number (%) of patients:																		
with one or more adverse experiences	109	(24.4)	47	(29.6)	64	(23.4)	89	(30.6)	42	(23.5)	33	(36.3)	26	(33.3)	39	(22.7)	72	(26.8)
with no adverse experience	337	(75.6)	112	(70.4)	210	(76.6)	202	(69.4)	137	(76.5)	58	(63.7)	52	(66.7)	133	(77.3)	197	(73.2)
with drug- related adverse experiences †	41	(9.2)	2	(1.3)	10	(3.6)	14	(4.8)	20	(11.2)	17	(18.7)	10	(12.8)	20	(11.6)	26	(9.7)
with serious adverse experiences	2	(0.4)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.7)
with serious drug- related Adverse experiences †	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to an adverse experience	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.7)
Discontinued due to a drug related adverse experience †	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to a serious Adverse experience	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.7)
Discontinued due to a serious, drug-related adverse experience †	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely drug related.
‡ This group includes patients from only the Primary Dysmenorrhea Studies (Protocols 055 and 056).
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

A dose-related trend across doses of rofecoxib was noted for the incidence of adverse experiences in the body as a whole/site unspecified body system; however, the incidences were not generally distinguishable from the placebo incidence. No specific adverse experience within the body as a whole/site unspecified body system accounted for this trend; no individual adverse experience showed an increasing incidence with an increasing dose of rofecoxib and the incidence for specific adverse experiences within the body as a whole/site unspecified system was generally indistinguishable from the corresponding placebo incidence.

The incidence of adverse experiences in the other body systems was not greater on rofecoxib compared with placebo and was generally similar across all treatments (Table 23).

Table 23

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥ 1.0% in One or More Treatment Groups) by Body System in Combined Post- Dental Surgery Pain and Primary Dysmenorrhea Studies

	Placebo N=446		Rofecoxib ≤ 12.5 mg N=159		Rofecoxib 25 mg N=274		Rofecoxib 50 mg N=291		Rofecoxib 50/25 mg N=179		Rofecoxib 100 mg N=91		Rofecoxib ≥200 mg N=78		Ibuprofen 400 mg N=172		Naproxen 550 mg N=269	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	N	(%)	n	(%)
Patients with one or more adverse experiences	109	(24.4)	47	(29.6)	64	(23.4)	89	(30.6)	42	(23.5)	33	(36.3)	26	(33.3)	39	(22.7)	72	(26.8)
Patients with no adverse experience	337	(75.6)	112	(70.4)	210	(76.6)	202	(69.4)	137	(76.5)	58	(63.7)	52	(66.7)	133	(77.3)	197	(73.2)
Body as a Whole/ Site Unspecified	**24**	**(5.4)**	**7**	**(4.4)**	**13**	**(4.7)**	**15**	**(5.2)**	**13**	**(7.3)**	**7**	**(7.7)**	**6**	**(7.7)**	**10**	**(5.8)**	**21**	**(7.8)**
Abdominal pain	1	(0.2)	0	(0.0)	2	(0.7)	3	(1.0)	1	(0.6)	0	(0.0)	3	(3.8)	0	(0.0)	3	(1.1)
Asthenia/ fatigue	5	(1.1)	0	(0.0)	1	(0.4)	1	(0.3)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Chest pain	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.1)
Contusion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Dizziness	7	(1.6)	2	(1.3)	3	(1.1)	3	(1.0)	4	(2.2)	5	(5.5)	2	(2.6)	6	(3.5)	5	(1.9)
Fever	1	(0.2)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	1	(1.1)	1	(1.3)	0	(0.0)	0	(0.0)
Influenza- like disease	2	(0.4)	1	(0.6)	2	(0.7)	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
Upper respiratory infection	5	(1.1)	1	(0.6)	3	(1.1)	4	(1.4)	3	(1.7)	0	(0.0)	0	(0.0)	3	(1.7)	8	(3.0)
Cardiovascular System	3	(0.7)	0	(0.0)	2	(0.7)	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.7)
Digestive System	**61**	**(13.7)**	**37**	**(23.3)**	**37**	**(13.5)**	**64**	**(22.0)**	**20**	**(11.2)**	**22**	**(24.2)**	**14**	**(17.9)**	**20**	**(11.6)**	**39**	**(14.5)**
Constipation	1	(0.2)	0	(0.0)	2	(0.7)	1	(0.3)	0	(0.0)	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Dental caries	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhea	6	(1.3)	0	(0.0)	1	(0.4)	2	(0.7)	3	(1.7)	1	(1.1)	2	(2.6)	1	(0.6)	3	(1.1)
Digestive gas symptoms	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.6)	0	(0.0)	1	(1.3)	1	(0.6)	0	(0.0)
Dry mouth	3	(0.7)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.1)
Dyspepsia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	3	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastric disorder	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.1)	1	(1.1)	0	(0.0)	0	(0.0)	2	(0.7)
Nausea	30	(6.7)	5	(3.1)	5	(1.8)	18	(6.2)	6	(3.4)	8	(8.8)	2	(2.6)	12	(7.0)	15	(5.6)
Oral hemorrhage	4	(0.9)	3	(1.9)	1	(0.4)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.2)	0	(0.0)
Oral infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)
Oral ulcer	1	(0.2)	2	(1.3)	1	(0.4)	1	(0.3)	0	(0.0)	1	(1.1)	0	(0.0)	1	(0.6)	0	(0.0)

	Placebo	Rofecoxib							Ibuprofen	Naproxen
	N=446	≤12.5 mg N=159	25 mg N=274	50 mg N=291	50/25 mg N=179	100 mg N=91	≥200 mg N=78		400 mg N=172	550 mg N=269
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		N (%)	n (%)
Postextraction alveolitis †	19 (4.3)	28 (17.6)	27 (9.9)	43 (14.8)	0 (0.0)	16 (17.6)	9 (11.5)		6 (3.5)	16 (5.9)
Vomiting	15 (3.4)	2 (1.3)	5 (1.8)	10 (3.4)	0 (0.0)	3 (3.3)	2 (2.6)		7 (4.1)	2 (0.7)
Eyes, Ears, Nose, and Throat	13 (2.9)	3 (1.9)	4 (1.5)	9 (3.1)	3 (1.7)	3 (3.3)	2 (2.6)		1 (0.6)	5 (1.9)
External otic obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)		0 (0.0)	0 (0.0)
Otic pain	3 (0.7)	0 (0.0)	2 (0.7)	3 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)		0 (0.0)	1 (0.4)
Pharyngitis	4 (0.9)	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.6)	0 (0.0)	2 (2.6)		0 (0.0)	0 (0.0)
Tinnitus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)		0 (0.0)	0 (0.0)
Tonsillar disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)		0 (0.0)	0 (0.0)
Musculoskeletal System	3 (0.7)	0 (0.0)	4 (1.5)	2 (0.7)	2 (1.1)	1 (1.1)	1 (1.3)		0 (0.0)	6 (2.2)
Muscular weakness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)		0 (0.0)	0 (0.0)
Rhabdomyolysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 ‡ (1.3)		0 (0.0)	0 (0.0)
Nervous System	23 (5.2)	3 (1.9)	13 (4.7)	14 (4.8)	5 (2.8)	8 (8.8)	6 (7.7)		8 (4.7)	9 (3.3)
Headache	18 (4.0)	1 (0.6)	6 (2.2)	7 (2.4)	2 (1.1)	7 (7.7)	3 (3.8)		8 (4.7)	2 (0.7)
Paresthesia	0 (0.0)	0 (0.0)	3 (1.1)	1 (0.3)	1 (0.6)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Somnolence	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	1 (1.1)	1 (1.3)		0 (0.0)	6 (2.2)
Tremor	1 (0.2)	0 (0.0)	1 (0.4)	2 (0.7)	0 (0.0)	0 (0.0)	1 (1.3)		0 (0.0)	0 (0.0)
Trismus	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.7)	0 (0.0)	0 (0.0)	1 (1.3)		0 (0.0)	0 (0.0)
Psychiatric Disorder	3 (0.7)	0 (0.0)	3 (1.1)	3 (1.0)	4 (2.2)	1 (1.1)	0 (0.0)		1 (0.6)	4 (1.5)
Anxiety	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)		0 (0.0)	1 (0.4)
Irritability	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Respiratory System	4 (0.9)	0 (0.0)	1 (0.4)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	3 (1.1)
Skin and Skin Appendages	5 (1.1)	5 (3.1)	0 (0.0)	4 (1.4)	1 (0.6)	5 (5.5)	0 (0.0)		2 (1.2)	3 (1.1)
Pruritus	1 (0.2)	3 (1.9)	0 (0.0)	2 (0.7)	0 (0.0)	4 (4.4)	0 (0.0)		2 (1.2)	1 (0.4)
Rash	2 (0.4)	1 (0.6)	0 (0.0)	2 (0.7)	1 (0.6)	1 (1.1)	0 (0.0)		2 (1.2)	0 (0.0)
Urogenital System	5 (1.1)	0 (0.0)	3 (1.1)	1 (0.3)	4 (2.2)	1 (1.1)	0 (0.0)		0 (0.0)	8 (3.0)
Menstrual disorder	2 (0.4)	0 (0.0)	2 (0.7)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)		0 (0.0)	2 (0.7)
Urinary tract infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)		0 (0.0)	2 (0.7)
Urine abnormality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 ‡ (1.1)	0 (0.0)		0 (0.0)	1 (0.4)

† This adverse experience is unique to the Post-Dental Surgery Pain Studies, although Ns may include patients who were not in the Post-Dental Surgery Pain Studies.
‡ No clinical manifestations. Determined by the investigator to be due to strenuous physical exercise and definitely not due to study medication [P004].
Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Clinical Adverse Experiences Considered Drug Related

Drug-related adverse experiences (those determined by the investigator to be possibly, probably, or definitely related to study medication) in the recommended dose for analgesia of 50 mg, were generally similar to placebo. However, drug-related adverse experiences do appear to increase with dose escalation beyond the dose of 50 mg, mainly in the "Body as a Whole/Site Unspecified" and in the digestive (mainly nausea) body systems (Table 24).

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ON ORIGINAL

Table 24

Number (%) of Patients With Drug Related † Clinical Adverse Experiences by Body System in Combined Post- Dental Surgery Pain and Primary Dysmenorrhea Studies

	Placebo N=446		Rofecoxib ≤ 12.5 mg N=159		Rofecoxib 25 mg N=274		Rofecoxib 50 mg N=291		Rofecoxib 50/25 mg N=179		Rofecoxib 100 mg N=91		Rofecoxib ≥200 mg N=78		Ibuprofen 400 mg N=172		Naproxen 550 mg N=269	
	n	(%)	n	(%)	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)	N	(%)	n	(%)
Patients with one or more adverse experiences	41	(9.2)	2	(1.3)	10	(3.6)	14	(4.8)	20	(11.2)	17	(18.7)	10	(12.8)	20	(11.6)	26	(9.7)
Patients with no adverse experience	405	(90.8)	157	(98.7)	264	(96.4)	277	(95.2)	159	(88.8)	74	(81.3)	68	(87.2)	152	(88.4)	243	(90.3)
Body as a Whole/ Site Unspecified	5	(1.1)	1	(0.6)	2	(0.7)	5	(1.7)	5	(2.8)	5	(5.5)	3	(3.8)	3	(1.7)	9	(3.3)
Abdominal pain	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.6)	0	(0.0)	2	(2.6)	0	(0.0)	3	(1.1)
Abdominal tenderness	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Asthenia/ fatigue	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Body ache	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Chest pain	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Dehydration	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Digestive gas symptoms	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dizziness	2	(0.4)	0	(0.0)	1	(0.4)	1	(0.3)	3	(1.7)	4	(4.4)	1	(1.3)	3	(1.7)	5	(1.9)
Dry mucous membranes	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Edema	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Fever	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Presyncope	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Syncope	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiovascular System	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.6)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.4)**
Palpitation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Vasodilatation	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Digestive System	**29**	**(6.5)**	**1**	**(0.6)**	**3**	**(1.1)**	**9**	**(3.1)**	**13**	**(7.3)**	**9**	**(9.9)**	**4**	**(5.1)**	**9**	**(5.2)**	**15**	**(5.6)**
Constipation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhea	4	(0.9)	0	(0.0)	0	(0.0)	2	(0.7)	3	(1.7)	0	(0.0)	1	(1.3)	1	(0.6)	1	(0.4)
Digestive gas symptoms	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	1	(1.3)	1	(0.6)	0	(0.0)
Dry mouth	3	(0.7)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.1)
Dyspepsia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Epigastric discomfort	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.7)
Gastric disorder	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.1)	1	(1.1)	0	(0.0)	0	(0.0)	2	(0.7)
Gastrointestinal bleeding	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
Heartburn	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Nausea	22	(4.9)	1	(0.6)	1	(0.4)	7	(2.4)	4	(2.2)	7	(7.7)	2	(2.6)	7	(4.1)	9	(3.3)

	Placebo N=446		Rofecoxib ≤ 12.5 mg N=159		Rofecoxib 25 mg N=274		Rofecoxib 50 mg N=291		Rofecoxib 50/25 mg N=179		Rofecoxib 100 mg N=91		Rofecoxib ≥200 mg N=78		Ibuprofen 400 mg N=172		Naproxen 550 mg N=269	
	n	(%)	n	(%)	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)	N	(%)	n	(%)
Oral hemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
Rectal disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Taste loss	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	10	(2.2)	0	(0.0)	1	(0.4)	4	(1.4)	0	(0.0)	2	(2.2)	1	(1.3)	4	(2.3)	1	(0.4)
Eyes, Ears, Nose, and Throat	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.4)**
Ophthalmic disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Pharyngitis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tinnitus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Metabolism and Nutrition	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.6)**	**1**	**(0.4)**
Anorexia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
Thirst increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Nervous System	**8**	**(1.8)**	**0**	**(0.0)**	**2**	**(0.7)**	**3**	**(1.0)**	**3**	**(1.7)**	**5**	**(5.5)**	**3**	**(3.8)**	**6**	**(3.5)**	**4**	**(1.5)**
Headache	7	(1.6)	0	(0.0)	0	(0.0)	3	(1.0)	1	(0.6)	4	(4.4)	1	(1.3)	6	(3.5)	0	(0.0)
Insomnia	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Paresthesia	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Somnolence	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	1	(1.1)	1	(1.3)	0	(0.0)	0	(0.0)
Tremor	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)	0	(0.0)	4	(1.5)
Psychiatric Disorder	**1**	**(0.2)**	**0**	**(0.0)**	**2**	**(0.7)**	**1**	**(0.3)**	**3**	**(1.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.6)**	**2**	**(0.7)**
Agitation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Anxiety	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Euphoria	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Irritability	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Mental acuity decreased	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nervousness	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Respiratory System	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Respiratory pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin and Skin Appendages	**0**	**(0.0)**	**1**	**(0.6)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(4.4)**	**0**	**(0.0)**	**1**	**(0.6)**	**0**	**(0.0)**
Pruritus	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	3	(3.3)	0	(0.0)	1	(0.6)	0	(0.0)
Rash	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)	1	(0.6)	0	(0.0)
Urogenital System	**1**	**(0.2)**	**0**	**(0.0)**	**2**	**(0.7)**	**0**	**(0.0)**	**1**	**(0.6)**	**1**	**(1.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.4)**
Menstrual disorder	1	(0.2)	0	(0.0)	2	(0.7)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Urine abnormality	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely drug related.
‡ This group includes patients from the Primary Dysmenorrhea Studies only (Protocols 055 and 056).

Serious Clinical Adverse Experiences and Discontinuations Due to Clinical Adverse Experiences

All the nonfatal serious clinical adverse experiences were pregnancies. No deaths were reported in these studies.

Patients in the combined Post-Dental Surgery Pain and Primary Dysmenorrhea Studies who discontinued, did so due to pregnancies.

Adverse Experiences in Post-Orthopedic Surgery Pain Study

Clinical adverse experiences were reported by 152 (70%) of 218 randomized patients in the Post-Orthopedic Surgery Pain Study (Protocol 072). The incidence of adverse experiences was generally similar across all treatment groups and was not significantly greater in the rofecoxib groups compared with placebo. The incidence of adverse experiences in each body system was not significantly greater in the rofecoxib treatment groups compared with the placebo group.

The most commonly reported adverse experiences were constipation (28.3, 10.7, 20.4, and 21.8%), fever (20.8, 5.4, 9.3, and 5.5%), and nausea (11.3, 10.7, 20.4, and 16.4%) in the placebo/placebo, rofecoxib 50/25-mg, rofecoxib 50/50-mg, and naproxen sodium/placebo groups, respectively.

Clinical Adverse Experiences Considered Drug Related

The incidence of drug-related adverse experiences (as determined by the investigator to be possibly, probably, or definitely related to study medication) was 13.2, 14.3, 13.0, and 14.5% for placebo/placebo, rofecoxib 50/25-mg, rofecoxib 50/50-mg, and naproxen sodium/placebo groups, respectively. The incidence of drug-related adverse experiences was not significantly greater with rofecoxib compared with placebo. There were no statistically significant differences in drug-related adverse experiences by body system or specific adverse experience between treatment groups.

Serious Clinical Adverse Experiences

Serious adverse experiences occurred in 10 (4.6%) of the 218 patients. Four, 3, 1, and 2 patients in the placebo/placebo, rofecoxib 50/25-mg, rofecoxib 50/50-mg, and naproxen sodium/placebo groups, respectively, had one or more adverse experiences. None were considered by the investigator to be drug related (Table 25).