

Table 4. Reasons for Study Termination : 6-Week Pivotal OA Studies 060 and 087

Study	Number of OA Patients by Treatment Group		
	Placebo	Celecoxib	
		100 mg BID	200 mg QD
Study 060	(N=232)(a)	(N=231)	(N=223)(a)
Total Completed	146 (63%)	194 (84%)	182 (82%)
Total Withdrawn	86 (37%)	37 (16%)	41 (18%)
Treatment Failure	56 (24%)	18 (8%)	21 (9%)
Adverse Event	20 (9%)	11 (5%)	9 (4%)
Other	10 (4%)	8 (3%)	11 (5%)
Study 087	(N=244)(b)	(N=243)^b	(N=231)
Total Completed	164 (67%)	194 (80%)	191 (83%)
Total Withdrawn	80 (33%)	49 (20%)	40 (17%)
Treatment Failure	55 (23%)	27 (11%)	24 (10%)
Adverse Event	12 (5%)	9 (4%)	6 (3%)
Other	13 (5%)	13 (5%)	10 (4%)

- a) One placebo patient and one celecoxib 200 mg QD patient were randomized but did not receive study medication.
 b) One placebo patient and two celecoxib 100 mg BID patients were randomized but did not receive study medication.

5.1.1.4 Patient Characteristics

Tables 5 and 6 show descriptive summaries of the pooled Baseline demographic characteristics and arthritis history for all patients enrolled in the 12- and 6-week pivotal OA trials, respectively. In these studies, age, race, gender, and arthritis history were similar across treatment groups. The demographic characteristics and arthritis history for each individual study were also consistent with the pooled summaries with no differences across treatment groups.

Table 5. Baseline Demographic Characteristics and Disease Status: Pooled 12-Week Pivotal OA Studies 020, 021, and 054

Baseline Demographic Characteristic	Placebo (N=664)(a)	Celecoxib			Naproxen 500 mg BID (N=631)
		50 mg BID (N=671)	100 mg BID (N=644)(a)	200 mg BID (N=648)	
Age (years)					
Mean (Std. Dev.)	62.3 (10.22)	61.6 (11.09)	61.9 (11.31)	61.9 (11.43)	62.7 (11.09)
Range	30-87	21-93	24-88	25-88	19-89
≥65 years - N (%)	303 (46%)	293 (44%)	286 (44%)	295 (46%)	297 (47%)
Race/Ethnic Origin					
Caucasian/ Hispanic - N (%)	599 (90%)	587 (87%)	576 (89%)	573 (88%)	564 (89%)
Black - N (%)	59 (9%)	80 (12%)	63 (10%)	71 (11%)	65 (10%)
Other - N (%)	6 (1%)	4 (1%)	5 (1%)	4 (1%)	2 (<1%)
Gender					
Female - N (%)	466 (70%)	444 (66%)	441 (68%)	451 (70%)	430 (68%)
Disease Duration - Years					
Mean (Std. Dev.)	9.0 (8.93)	8.4 (8.18)	8.6 (8.00)	8.5 (8.44)	8.8 (8.84)
Range	0.1-52.0	0.1-51.0	0.1-50.0	0.1-51.2	0.1-64.0
≥5 years - N (%)	407 (61%)	390 (58%)	389 (60%)	375 (58%)	367 (58%)

a) Total number of patients includes three patients (one in the placebo group [Study 020], one in the placebo group [Study 054], and one in the celecoxib 100 mg BID group [Study 021]) who were randomized into a study but did not receive study medication and are not included in the ITT cohort.

Table 6. Baseline Demographic Characteristics and Disease Status: Pooled 6-Week Pivotal OA Studies 060 and 087

Baseline Demographic Characteristic	Placebo (N=476) (a)	Celecoxib	
		100 mg BID (N=474)	200 mg QD (N=454)
Age (years)(b)			
Mean (Std. Dev.)	61.9 (11.49)	62.5 (11.16)	62.0 (11.59)
Range	18-89	27-89	29-88
≥65 years - N (%)	215 (45%)	220 (46%)	197 (43%)
Race/Ethnic Origin			
Caucasian/Hispanic - N (%)	425 (89%)	417 (88%)	398 (88%)
Black - N (%)	42 (9%)	50 (11%)	41 (9%)
Other - N (%)	8 (2%)	6 (1%)	15 (3%)
Gender			
Female - N (%)	333 (70%)	321 (68%)	306 (67%)
Disease Duration - Years			
Mean (Std. Dev.)	9.1 (8.47)	9.4 (8.79)	9.1 (7.92)
Range	0.1-59.0	0.1-50.0	0.1-60.0
≥5 years - N (%)	304 (64%)	316 (67%)	305 (67%)

a) Total number of patients includes five patients (one in the placebo group [Study 060], one in the placebo group [Study 087], one in the celecoxib 200 mg QD group [Study 060] and two in the celecoxib 100 mg BID group [Study 087]) who were randomized into a study but did not receive study medication and are not included in the ITT cohort.

b) n=475 for age.

5.1.1.5 Efficacy and Dose Response

5.1.1.5.1 Twelve-Week Pivotal Trials: Studies 020, 021 and 054

As shown by the Patient's Assessment of Arthritis Pain (VAS), Celecoxib 100 mg BID and 200 mg BID produced statistically significantly greater improvement compared to placebo by Week 2 and continuing through Week 12 in each of the 12-week pivotal OA

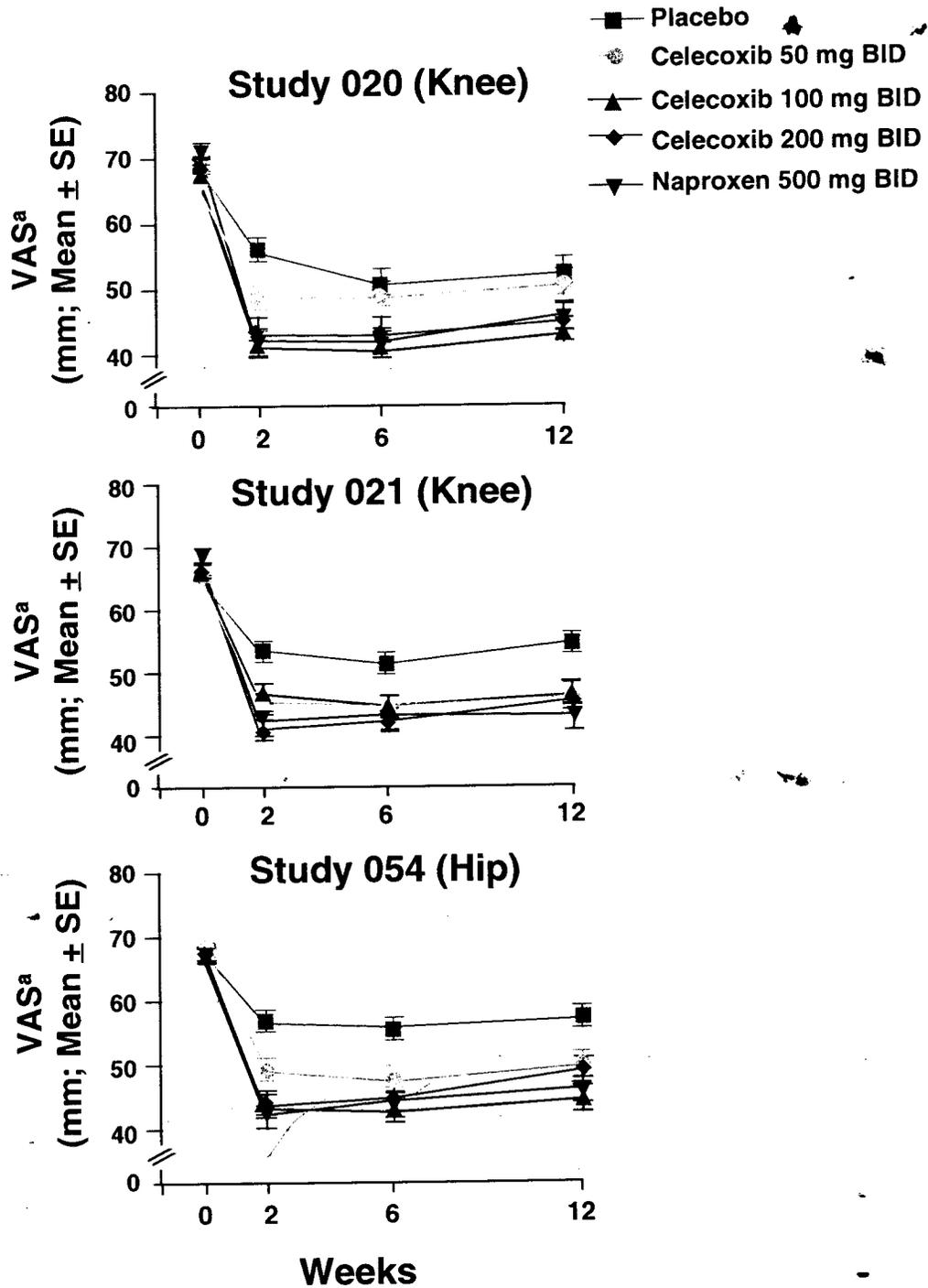
studies (Figure 10 and Table 7). Celecoxib 50 mg BID was also efficacious in two of these studies (Studies 021 and 054). In the other primary measures of efficacy, all doses of celecoxib were efficacious in each of the three pivotal 12-week studies (Figure 11 and Tables 8 and 9). Significant improvement was observed at Week 12 as well as earlier assessments with the exception of the Physician's Global Assessment for celecoxib 50 mg BID at Week 2 in Study 021.

For all primary measures of efficacy across the three pivotal 12 week studies, celecoxib doses of 100 and 200 mg BID produced a similar degree of improvement in OA patients (Tables 7, 8, and 9). No statistically significant differences between these doses were present at any assessment time for any measure of efficacy with one exception. A statistically significant difference occurred in Study 021 for the Patient's Assessment of Arthritis Pain (VAS) at Week 2 where the response was greater with celecoxib 200 mg BID compared to celecoxib 100 mg BID. The results indicate that celecoxib 100 mg BID is the full therapeutic dose for treating the signs and symptoms of OA and that increasing the dose to 200 mg BID provides no further benefit of improved efficacy.

The responses to celecoxib 100 mg BID and 200 mg BID were comparable to naproxen 500 mg BID for all primary measures of efficacy at all assessment times in all three 12-week pivotal studies with few exceptions (Tables 7, 8, and 9). In Study 020, the response to celecoxib 100 mg BID as determined by the WOMAC OA Index - Pain subscale was significantly greater than naproxen at Week 12 (Table 9). In Study 021, the response to naproxen was significantly greater than celecoxib 100 mg BID at Weeks 2 and 12 for Patient's Assessment of Arthritis Pain (VAS) (Table 7).

Although 50 mg BID provides efficacy in OA when compared to placebo, a consistent pattern emerges indicating that this dose is submaximally efficacious. The responses to celecoxib 50 mg BID were statistically significantly lower when compared to celecoxib doses of either 100 mg BID or 200 mg BID or naproxen 500 mg BID in Studies 020, 021, and 054 for many of the primary efficacy measures at one or more assessment times.

Figure 10. Patient's Assessment of Arthritis Pain: 12-Week Pivotal OA Studies 020, 021 and 054



a) Visual analog scale ranges from 0 (no pain) to 100 mm (most severe pain).

Table 7. Patient's Assessment of Arthritis Pain - VAS (Change in Least Square (LS) Mean Score from Baseline): 12-Week Pivotal OA Studies 020, 021 and 054

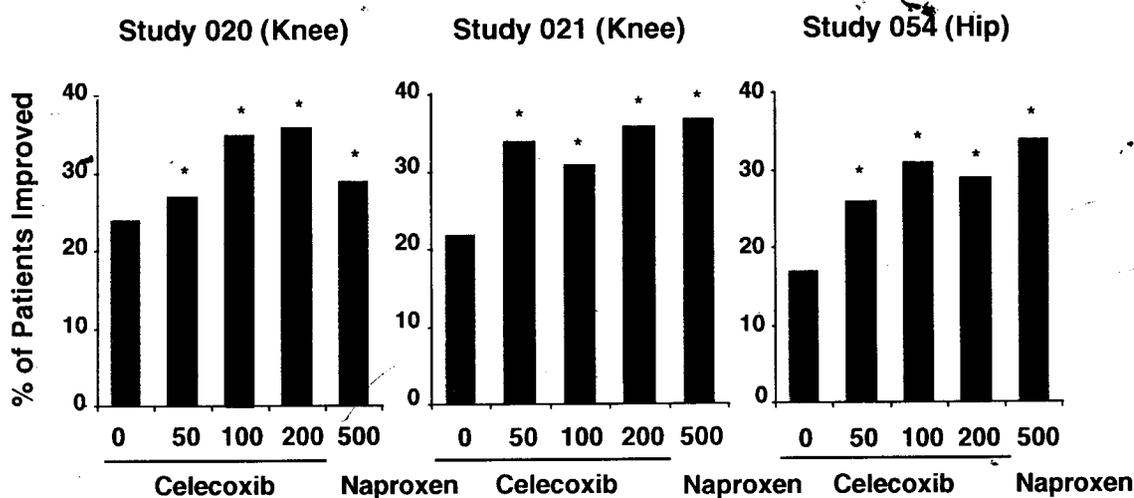
Treatment Group	N	Baseline LS Mean	LS Mean Change		
			Week 2	Week 4	Week 12
Study 020					
Placebo	201	69.5	-12.1	-16.6	-15.1
Celecoxib 50 mg BID	203	67.0	-18.4*	-17.9	-16.0
Celecoxib 100 mg BID	196	68.4	-26.1*†	-25.9*‡	-23.1*‡
Celecoxib 200 mg BID	201	69.1	-24.6*‡	-24.5*‡	-22.1*‡
Naproxen 500 mg BID	197	71.6	-27.3*‡	-27.0*‡	-22.7*‡
Study 021					
Placebo	242	65.9	-12.9	-14.6	-12.0
Celecoxib 50 mg BID	252	66.6	-21.5*	-21.7*	-20.3*
Celecoxib 100 mg BID	238	66.3	-20.3*†	-21.7*	-19.6*†
Celecoxib 200 mg BID	233	66.4	-26.4*‡	-24.1*	-21.0*
Naproxen 500 mg BID	226	68.5	-26.6*‡	-25.0*	-25.3*‡
Study 054					
Placebo	217	68.2	-11.8	-13.2	-11.1
Celecoxib 50 mg BID	216	68.4	19.7*	-21.5*	-19.0*
Celecoxib 100 mg BID	207	67.1	-24.4*‡	-25.1*	-23.3*
Celecoxib 200 mg BID	212	67.3	-24.4*‡	-23.9*	-19.3*
Naproxen 500 mg BID	207	67.3	-26.5*‡	-24.8*	-22.3*

* Significantly different from placebo; p<0.05.

† Significantly different from naproxen; p<0.05.

‡ Significantly different from celecoxib 50 mg BID; p<0.05.

Figure 11. Patient's Global Assessment at Week 12: 12-Week Pivotal OA Studies 020, 021 and 054



* Significantly different from placebo; p<0.05.

Doses are mg BID

Table 8. Percent of Patients Improved from Baseline for Primary (Categorical) OA Efficacy Variables: 12-Week Pivotal OA Studies 020, 021 and 054

Treatment Group	Study 020		Study 021		Study 054	
	N	% Improved(a) at Week 12	N	% Improved(a) at Week 12	N	% Improved(a) at Week 12
Patient's Global Assessment of Arthritic Condition (Categorical Change)						
Placebo	203	24	242	22	217	17
Celecoxib 50 mg BID	203	27*	252	34*	216	26*
Celecoxib 100 mg BID	197	35*	239	31*	207	31*
Celecoxib 200 mg BID	202	36*	233	36*	213	29*
Naproxen 500 mg BID	198	29*	226	37*	207	34*
Physician's Global Assessment of Arthritic Condition (Categorical Change)						
Placebo	203	21	242	21	217	18
Celecoxib 50 mg BID	203	30*	252	32*	216	27*
Celecoxib 100 mg BID	197	36*	239	31*	207	32*
Celecoxib 200 mg BID	202	32*	232	31*	213	30*
Naproxen 500 mg BID	198	33*	226	34*	207	32*

* Significantly different from placebo; p<0.05.

a) Improvement is defined as reduction of at least 2 grades from Baseline for grades 3-5 or a change in grade from 2 to 1.

Table 9. WOMAC Composite Score and Subscales: 12-Week Pivotal OA Studies 020, 021 and 054

Treatment (mg BID dose)	Study 020			Study 021			Study 054		
	N	Baseline	Change at Week 12	N	Baseline	Change at Week 12	N	Baseline	Change at Week 12
WOMAC OA Index: Composite Score (Change in LS Mean Score from Baseline)									
Placebo	182	51.6	-5.6	240	50.6	-5.4	217	51.2	-4.6
Celecoxib 50 mg	174	51.6	-9.6*	247	51.9	-12.9*	214	49.4	-8.0*
Celecoxib 100 mg	175	50.4	-13.6*‡	237	52.1	-12.0*	207	50.6	-10.3*
Celecoxib 200 mg	181	50.9	-12.1*	230	50.1	-11.5*	211	51.2	-11.0*‡
Naproxen 500 mg	177	52.6	-11.3*	225	52.6	-13.9*	205	50.4	-12.4*‡
WOMAC OA Index: Pain Subscale (Change in LS Mean Score from Baseline)									
Placebo	201	10.9	-1.2	242	10.6	-1.4	217	10.7	-1.0
Celecoxib 50 mg	197	10.7	-2.0*	248	10.8	-2.8*	215	10.5	-1.7*
Celecoxib 100 mg	196	10.5	-3.1*‡	237	10.8	-2.6*	207	10.7	-2.2*
Celecoxib 200 mg	201	10.7	-2.7*‡	232	10.4	-2.5*	211	10.9	-2.4*‡
Naproxen 500 mg	198	11.0	-2.4*	226	11.1	-3.0*	207	10.6	-2.7*‡
WOMAC OA Index: Joint Stiffness Subscale (Change in LS Mean Score from Baseline)									
Placebo	202	4.8	-0.5	242	4.8	-0.5	217	4.7	-0.4
Celecoxib 50 mg	197	4.8	-0.9*	248	4.8	-1.2*	216	4.7	-0.8*
Celecoxib 100 mg	196	4.6	-1.2*‡	237	4.8	-1.1*	207	4.7	-1.0*
Celecoxib 200 mg	201	4.9	-1.1*	232	4.8	-1.1*	211	4.7	-1.0*
Naproxen 500 mg	195	5.0	-1.1*	226	4.9	-1.3*	205	4.7	-1.1*‡
WOMAC OA Index: Physical Function Subscale (Change in LS Mean Score from Baseline)									
Placebo	184	36.0	-3.9	240	35.2	-3.6	217	35.9	-3.2
Celecoxib 50 mg	174	36.1	-6.8*	250	36.4	-8.9*	215	34.2	-5.5*
Celecoxib 100 mg	176	35.3	-9.5*‡	237	36.5	-8.3*	207	35.3	-7.0*
Celecoxib 200 mg	181	35.3	-8.1*	231	35.1	-7.9*	211	35.6	-7.5*‡
Naproxen 500 mg	180	36.5	-7.8*	225	36.7	-9.6*	207	35.1	-8.4*‡

* Significantly different from placebo; p<0.05.

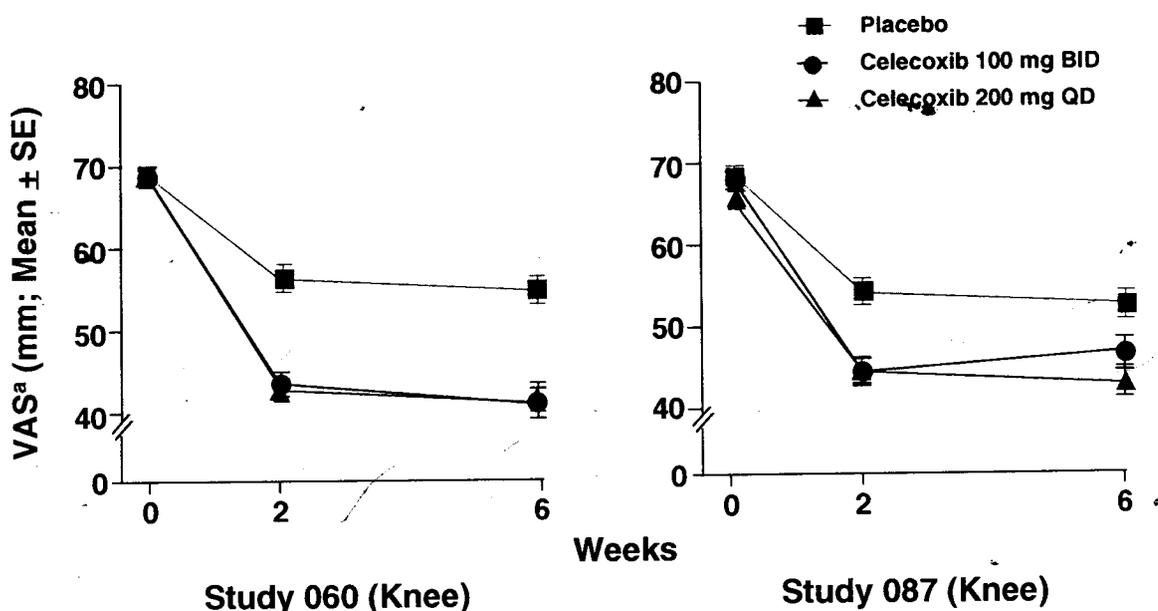
‡ Significantly different from celecoxib 50 mg BID; p<0.05.

5.1.1.5.2 Six-Week Pivotal Studies: Studies 060 and 087

Celecoxib doses of 100 mg BID and 200 mg QD were statistically significantly superior to placebo in the Patient's Assessment of Arthritis Pain (VAS) at Week 2 and Week 6 in both 6-Week pivotal OA studies (Figure 12 and Table 10). For all other primary measures of efficacy, the responses to celecoxib 100 mg BID and 200 mg QD were also significantly greater than placebo-treated patients at Week 6 (Figure 13, Tables 11 and 12) as well as the Week 2 assessment in both studies. The results obtained with 100 mg BID in Studies 060 and 087 were consistent with those demonstrated in the 12-Week pivotal OA studies (020, 021 and 054) for all primary measures of efficacy.

Celecoxib 100 mg BID and 200 mg QD provided comparable responses as determined by all measures of efficacy in both studies. No statistically significant differences between these two celecoxib dosing regimens were evident with the exception of a statistically significant difference in the Physician's Global Assessment favoring celecoxib 100 mg BID at the Week 2 assessment in Study 087.

Figure 12. Patient's Assessment of Arthritis Pain: 6-Week Pivotal OA Studies 060 and 087



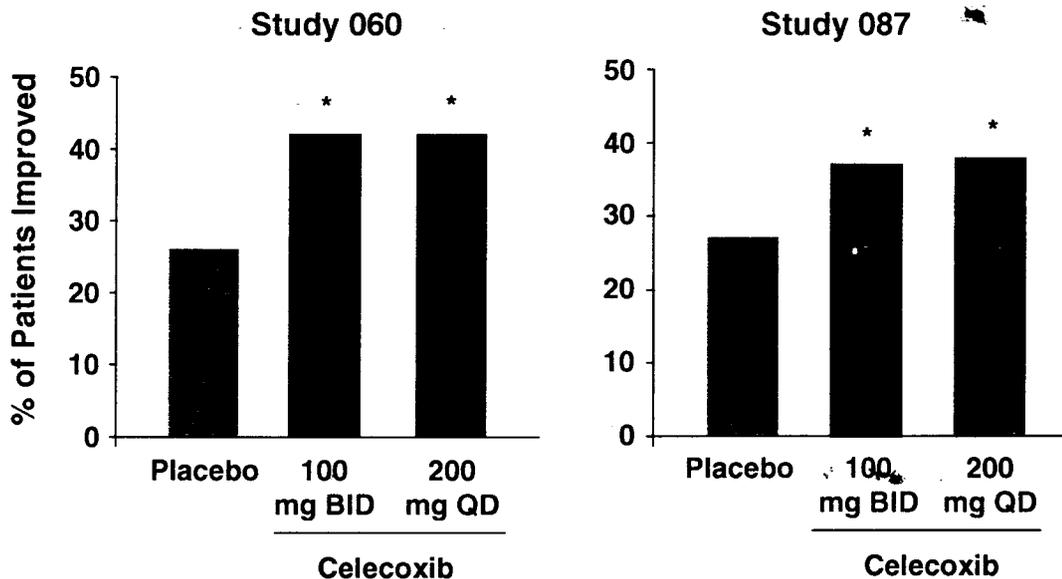
a) Visual analog scale ranges from 0 (no pain) to 100 mm (most severe pain).

Table 10. Patient's Assessment of Arthritis Pain: 6-Week Pivotal OA Studies 060 and 087

Treatment Group	Study 060			Study 087		
	N	Baseline	Change at Week 6	N	Baseline	Change at Week 6
Patient's Assessment of Arthritis Pain: VAS (LS Mean Score)						
Placebo	231	68.6	-14.8	243	68.5	-15.0
Celecoxib 100 mg BID	231	68.1	-28.5*	241	68.0	-21.2*
Celecoxib 200 mg QD	222	68.7	-27.7*	231	65.7	-23.5*

* Significantly different from placebo; p<0.05.

Figure 13. Patient's Global Assessment at Week 6: 6-Week Pivotal OA Studies 060 and 087



* Significantly different from placebo; p < 0.05

Table 11. Percent of Patients Improved from Baseline – Primary Categorical OA Efficacy Variables: 6-Week Pivotal OA Studies 060 and 087

Treatment Group	Study 060		Study 087	
	N	% Improved(a) at Week 6	N	% Improved(a) at Week 6
Patient's Global Assessment of Arthritic Condition (Categorical Change)				
Placebo	231	26	243	27
Celecoxib 100 mg BID	231	42*	241	37*
Celecoxib 200 mg QD	222	42*	231	38*
Physician's Global Assessment of Arthritic Condition (Categorical Change)				
Placebo	231	25	243	24
Celecoxib 100 mg BID	231	43*	241	35*
Celecoxib 200 mg QD	222	43*	231	35*

* Significantly different from placebo; p<0.05.

a) Improvement is defined as reduction of at least 2 grades from Baseline for grades 3-5 or a change in grade from 2 to 1.

Table 12. WOMAC Composite Score and Subscales: 6-Week Pivotal OA Studies 060 and 087

Treatment Group	Study 060			Study 087		
	N	Baseline	Change at Week 6	N	Baseline	Change at Week 6
WOMAC OA Index: Composite Score (LS Mean Score)						
Placebo	224	50.8	-6.6	243	53.0	-8.1
Celecoxib 100 mg BID	229	50.3	-14.1*	241	51.1	-13.3*
Celecoxib 200 mg QD	219	50.2	-12.8*	231	50.9	-13.9*
WOMAC OA Index: Pain Subscale (LS Mean Score)						
Placebo	231	10.5	-1.5	243	10.7	-1.6
Celecoxib 100 mg BID	230	10.5	-3.1*	241	10.1	-2.6*
Celecoxib 200 mg QD	220	10.5	-2.9*	231	10.2	-3.0*
WOMAC OA Index: Joint Stiffness Subscale (LS Mean Score)						
Placebo	230	4.6	-0.6	243	4.7	-0.8
Celecoxib 100 mg BID	230	4.7	-1.2*	241	4.5	-1.3*
Celecoxib 200 mg QD	220	4.6	-1.2*	231	4.7	-1.2*
WOMAC OA Index: Physical Function Subscale (LS Mean Score)						
Placebo	230	35.7	-4.5	243	37.6	-5.7
Celecoxib 100 mg BID	229	35.1	-9.7*	241	36.4	-9.4*
Celecoxib 200 mg QD	219	35.2	-8.8*	231	36.1	-9.7*

* Significantly different from placebo; p<0.05.

5.1.1.6 Health-related Quality of Life

The SF-36 Health Survey was administered at Baseline and at Weeks 2 and 12 of treatment in the 12-week pivotal OA studies (Studies 020, 021 and 054). The mean scores at Baseline together with mean changes from Baseline to Week 12 for the eight domains of the SF-36 Health Survey for each of these studies are shown in Table 13. Statistically significant improvements in Physical Functioning, Role-Physical, Bodily Pain, Vitality, and Social Functioning were observed with celecoxib 100 mg BID, celecoxib 200 mg BID and naproxen 500 mg BID when compared to placebo across all

three studies. Celecoxib 100 mg and 200 mg BID were also associated with significant improvements in mental health in all studies. A significant treatment effect with naproxen for the mental health domain was observed in two studies. The magnitude of improvement for celecoxib 100 mg BID and celecoxib 200 mg BID was consistent across the studies and similar to naproxen.

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Table 13. Baseline Mean Scores and Mean Changes from Baseline for SF-36 Quality-of-Life Domains: 12-Week Pivotal OA Trials 020, 021 and 054

SF-36 Domain(a) Treatment Group	Study 020		Study 021		Study 054	
	Baseline	Change at Week 12	Baseline	Change at Week 12	Baseline	Change at Week 12
Physical Functioning						
Placebo	34.2	3.9	36.3	3.1	34.4	0.9
Celecoxib 50 mg BID	34.3	6.1	34.9	8.3*	36.5	3.7
Celecoxib 100 mg BID	34.9	10.8*	34.7	6.4	35.7	8.1*
Celecoxib 200 mg BID	34.3	8.7*	36.4	7.7*	32.6	10.0*
Naproxen 500 mg BID	33.2	9.9*	33.0	9.9*	36.1	9.2*
Role Physical						
Placebo	24.5	8.5	24.3	5.6	20.2	4.3
Celecoxib 50 mg BID	27.4	9.5	19.4	21.4*	21.9	8.2
Celecoxib 100 mg BID	26.5	19.1*	24.2	13.7*	22.5	13.1*
Celecoxib 200 mg BID	26.2	17.0*	27.2	15.4*	20.5	14.1*
Naproxen 500 mg BID	25.8	18.6*	21.3	17.2*	25.5	14.3*
Bodily Pain						
Placebo	32.7	5.8	33.9	4.9	31.7	3.2
Celecoxib 50 mg BID	33.8	8.4	32.9	14.7*	33.4	8.0*
Celecoxib 100 mg BID	34.9	14.3*	31.6	13.5*	31.5	11.8*
Celecoxib 200 mg BID	33.4	12.6*	34.5	13.7*	31.7	12.1*
Naproxen 500 mg BID	32.6	14.6*	32.0	15.2*	34.0	12.7*
General Health						
Placebo	60.7	1.6	59.9	0.3	63.0	-1.3
Celecoxib 50 mg BID	61.8	1.4	58.8	3.9*	62.1	1.6*
Celecoxib 100 mg BID	64.3	2.9	59.4	2.7	59.9	1.6
Celecoxib 200 mg BID	60.6	2.6	62.6	1.6	59.7	2.4*
Naproxen 500 mg BID	60.6	4.5*	59.1	3.0	62.7	0.1
Vitality						
Placebo	41.1	1.6	41.8	0.1	39.5	0.2
Celecoxib 50 mg BID	42.9	4.8*	40.2	9.6*	41.6	5.7*
Celecoxib 100 mg BID	43.3	9.4*	40.4	6.7*	39.4	7.2*
Celecoxib 200 mg BID	42.7	5.8*	42.5	7.1*	39.7	4.7*
Naproxen 500 mg BID	40.3	8.0*	37.1	8.4*	41.8	7.2*
Social Functioning						
Placebo	64.4	0.0	64.3	-1.8	61.1	0.0
Celecoxib 50 mg BID	63.3	2.3	61.7	7.7*	63.4	2.6
Celecoxib 100 mg BID	64.4	7.9*	62.0	7.6*	60.4	5.3*
Celecoxib 200 mg BID	68.1	4.2*	64.8	7.2*	61.9	5.9*
Naproxen 500 mg BID	62.9	7.6*	59.8	9.5*	65.5	3.6*
Role Emotional						
Placebo	55.7	1.9	53.9	1.7	51.3	-1.9
Celecoxib 50 mg BID	55.3	3.2	49.7	10.2	50.5	6.4*
Celecoxib 100 mg BID	52.5	13.8*	52.4	9.2	53.2	5.5*
Celecoxib 200 mg BID	58.4	5.8	55.5	8.6*	52.5	4.5
Naproxen 500 mg BID	59.2	5.0	50.8	6.4	55.1	3.6
Mental Health						
Placebo	70.3	-0.6	68.7	0.0	70.9	-1.2
Celecoxib 50 mg BID	71.3	-1.2	69.7	3.6*	70.2	2.7*
Celecoxib 100 mg BID	71.2	3.4*	69.2	3.0*	71.3	2.4*
Celecoxib 200 mg BID	71.3	3.3*	70.6	3.5*	69.4	2.9*
Naproxen 500 mg BID	70.8	2.4*	67.4	3.6*	71.8	0.6

* Significantly different from placebo; p<0.05.

a) Scale ranged from 0 to 100 with lower score as worse for all domains.

5.1.2 Supportive OA Efficacy Studies

Data from the pivotal OA efficacy trials were supported by the results of five additional placebo- or active-controlled trials.

5.1.2.1 Placebo-Controlled Studies: Studies 013 and 047

Study 013 was a dose-ranging, randomized, double-blind, placebo-controlled, parallel-group, 2-week study to evaluate the safety and efficacy of celecoxib (40, 100, and 200 mg BID) in treating the signs and symptoms of OA of the knee. Patients were eligible if they had OA of the knee in a flare state, a Functional Capacity Classification of I-III, and had not received any NSAIDs or analgesics in the two days prior to receiving the first dose of study medication. Of the 293 ITT patients, 252 (86.0%) completed all two weeks of the study. For the analyses of primary efficacy endpoints, celecoxib 40 mg BID, 100 mg BID, and 200 mg BID were numerically superior to placebo at most visits and statistically superior at some visits.

Study 047 was a randomized, double-blind, placebo-controlled, parallel group, multicenter, four-week study designed to compare the efficacy of celecoxib 25 mg, 100 mg, and 400 mg BID versus placebo in treating the signs and symptoms of OA of the knee. The study also evaluated the efficacious dose range. Patients with OA of the knee in a flare state and who had not received any NSAIDs and analgesics within 48 hours before the Baseline Arthritis Assessments, were eligible for study participation. Overall, 301 (75.1%) of the 401 ITT patients completed all four weeks of the study. For each primary efficacy endpoint, celecoxib 100 mg BID and 400 mg BID were consistently numerically superior to placebo, and at some timepoints were statistically superior. The efficacy of celecoxib 25 mg BID was not superior to placebo.

5.1.2.2 Active-Controlled Studies: Studies 042, 062 and 071

Study 042 was an international, randomized, double-blind, multicenter, parallel group six-week study designed to evaluate the efficacy and safety of celecoxib 100 mg BID as compared to diclofenac 50 mg BID in treating the signs and symptoms of OA of the hip and/or knee. Patients with OA of the hip and/or knee (as defined by the ACR [American College of Rheumatology] criteria) that had been clinically evident for at least six months, who were anticipated to require continuous treatment with an anti-inflammatory analgesic to control arthritis symptoms for the duration of the study, and were

experiencing symptoms of OA at the time of admission to the study, were eligible for study participation. Overall, 617 (89.8%) of 687 ITT patients completed all six weeks of the study. Analysis of primary efficacy endpoints showed that both celecoxib 100 mg BID and diclofenac 50 mg BID provided clinically significant improvement in the signs and symptoms of OA compared to Baseline values.

Study 062 was a randomized, double-blind, parallel group, multicenter, 12-week study designed primarily to compare the cumulative incidence of gastroduodenal ulcers associated with celecoxib 200 mg BID to that of naproxen 500 mg BID in patients with OA or RA. Patients were eligible to participate in the study if they had a documented clinical diagnosis of OA or RA (not necessarily in flare) and required chronic NSAID treatment. Among those included in the ITT cohort, 388 were OA patients: 193 celecoxib 200 mg BID patients and 195 naproxen 500 mg BID patients. Overall, 359 (67.0%) of 536 ITT patients completed all 12 weeks of the study. There were no clinically significant differences between the celecoxib 200 mg BID and naproxen 500 mg BID treatment groups in the number of patients who showed improvement, no change, or worsening in arthritis condition at Weeks 4, 8, or 12.

Study 071 was a randomized, double-blind, parallel group, multicenter, 12-week study designed primarily to compare the cumulative incidence of gastroduodenal ulcers associated with celecoxib 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA. Patients were eligible to participate in the study if they had a documented clinical diagnosis of OA or RA (not necessarily in flare) and required chronic NSAID treatment. Among those included in the ITT cohort, 810 were OA patients: 271 celecoxib 200 mg BID patients, 285 diclofenac 75 mg BID patients, and 254 ibuprofen 800 mg TID patients. There were no clinically significant differences between celecoxib and the other treatment groups for Physician's Global Assessment or Patient's Global Assessment at Weeks 4, 8, or 12.

5.1.3 Conclusions

Based on the results of replicate pivotal trials in OA patients, it is concluded that:

- Celecoxib doses of 100 mg BID, 200 mg QD, and 200 mg BID were efficacious in treating the signs and symptoms of OA.

- Celecoxib doses of 100 mg BID and 200 mg QD demonstrated comparable efficacy.
- There was no therapeutic benefit in increasing the dose above a total daily dose of 200 mg.
- Celecoxib, at efficacious doses, had similar efficacy to full therapeutic doses of NSAIDs.
- Health-related quality of life improvements were observed with full therapeutic doses of celecoxib.

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5.2 Efficacy in Rheumatoid Arthritis

Seven studies, two pivotal and four supportive, and one open-label long-term safety study, were conducted in patients with RA to provide evidence for the efficacy of celecoxib for the treatment of signs and symptoms of RA (Table 14). The data presented in this section are primarily from the pivotal studies (022, 023), which were double-blind, placebo-controlled trials of 12 weeks duration with 200 or more patients per treatment. The four supportive controlled studies (012, 041, 062, and 071) are each summarized briefly.

Table 14. Summary of Celecoxib RA Studies

Study No. - Population	Duration	No. of Patients	Treatments
Pivotal Studies			
022 - RA flare	12 Weeks	1149	Celecoxib 100, 200, or 400 mg BID ; naproxen 500 mg BID; or placebo
023 - RA flare	12 Weeks	1103	Celecoxib 100, 200, or 400 mg BID ; naproxen 500 mg BID; or placebo
Supportive Controlled Studies			
012 - RA flare	4 weeks	330	Celecoxib 40, 200, or 400 mg BID or placebo
041 - Stable RA	24 weeks	655	Celecoxib 200 mg BID or diclofenac SR 75 mg BID
062 - OA or RA	12 weeks	537 (148 RA)	Celecoxib 200 mg or naproxen 500 mg BID
071 - OA or RA	12 weeks	1099 (287 RA)	Celecoxib 200 mg BID, diclofenac 75 mg BID, or ibuprofen 800 mg TID
Open-Label Study			
024 - OA or RA	1-2 years	4499 (1945 RA)	Celecoxib 200-400 mg BID for RA

5.2.1 Pivotal RA Efficacy Studies: Studies 022 and 023

5.2.1.1 Population and Design

The two pivotal studies (Studies 022 and 023) were randomized, multicenter, double-blind, active- and placebo-controlled comparison studies of the efficacy and safety of celecoxib 100 mg BID, 200 mg BID, and 400 mg BID and naproxen 500 mg BID in patients with RA.

Study patients were required to have RA in a flare state at Baseline subsequent to discontinuation of NSAID therapy. An RA flare was demonstrated if the Physician's Global Assessment of Arthritic Condition and the Patient's Global Assessment of Arthritic Condition were "fair," "poor," or "very poor" at the Baseline Visit and if a

comparison of the Screening arthritis assessments and the Baseline arthritis assessments met criteria 1 and 2 described below plus either criterion 3 or 4:

1. A minimum of six tender joints at the Baseline Arthritis Assessment AND an increase of at least two tender or painful joints (or 20% increase in the number of tender/painful joints, whichever was greater) at the Baseline Visit compared to the Screening Visit.
2. A minimum of three swollen joints at the Baseline Arthritis Assessment AND an increase of at least two swollen joints (or 20% increase in the number of swollen joints, whichever was greater) at the Baseline Visit compared to the Screening Visit.
3. A minimum of 45 minutes of morning stiffness at the Baseline Arthritis Assessment AND an increase in the duration of morning stiffness of at least 15 minutes at the Baseline Visit compared to the Screening Visit.
4. Patient's Assessment of Arthritis Pain measurement of at least 40 mm (on the VAS) at the Baseline Arthritis Assessment AND an increase of 10 mm (or 20% increase, whichever was greater) at the Baseline Visit compared to the Screening Visit.

Patients in these studies may have been on disease-modifying anti-rheumatic drug (DMARD) therapy but could not have begun taking any of the following medications within 12 weeks before receiving the first dose of study drug: gold salts (including oral gold), sulfasalazine (doses of up to 3 g/day were allowed), azathioprine, antimalarials, or penicillamine. Methotrexate was also allowed but could not have been begun or been altered within eight weeks prior to receiving the first dose of study medication for the pivotal studies. In the pivotal studies, patients could also have been on oral corticosteroids but could not have changed the dose regimen within four weeks before receiving the first dose of study medication (doses of up to 10 mg prednisone or equivalent/day were allowed), or had received intramuscular, intra-articular, or soft-tissue injections of corticosteroids within four weeks before receiving the first dose of study medication.

In supporting Study 012 patients could not have begun taking oral corticosteroids or methotrexate within 12 weeks or changed the dosage regimen within 8 weeks prior to their first dose of study medication. Intramuscular, intra-articular, or soft tissue

injections of corticosteroids were also disallowed within 12 weeks of treatment with study medication.

5.2.1.2 Scales Used for Measurement of RA Efficacy

For all studies, the analysis of celecoxib's efficacy in the treatment of the signs and symptoms of RA incorporated a large number of primary and secondary efficacy endpoints, some of which were the same as those used to analyze its effect in OA.

The primary RA efficacy endpoints included the following:

- Number of Swollen Joints (16)
- Number of Tender/Painful Joints (16)
- Patient's Global Assessment of Arthritic Condition (16)
- Physician's Global Assessment of Arthritic Condition (16)
- ACR-20 Responder Index (22)

The secondary RA efficacy endpoints included the following:

- Patient's Assessment of Arthritis Pain - VAS (15)
- Incidence of Withdrawal Due to Lack of Arthritis Efficacy
- Time to Withdrawal Due to Lack of Arthritis Efficacy
- ACR-50 Responder Index
- Tender/Painful Joints Score
- Swollen Joints Score
- Duration of Morning Stiffness
- Health Assessment Questionnaire (HAQ) Functional Disability Index (23)
- C-Reactive Protein

In addition, the ACR-70 Responder Index was performed as an exploratory analysis and quality-of-life was assessed using the SF-36 Health Assessment Questionnaire.

Efficacy evaluations were performed at Baseline, Week 2, Week 6, and Week 12 (or Early Termination) in each of the pivotal studies.

The primary population for analysis was the ITT cohort which was defined as all randomized patients who took at least one dose of the study drug. The LOCF method was used for imputing missing values.

In order to examine the overall effect of the study drug on the patient's condition, a categorical analysis was performed on all patients who met the ACR-20 criteria as improved compared to Baseline.

The ACR-20 criteria classifies a patient as "improved" if the patient experienced at least a 20% improvement from Baseline in the:

- Number of Tender/Painful Joints and
- Number of Swollen Joints;

as well as at least a 20% improvement from Baseline in three or more of the following five assessments:

- Physician's Global Assessment of Arthritic Condition,
- Patient's Global Assessment of Arthritic Condition,
- Patient's Assessment of Arthritis Pain - VAS,
- HAQ Functional Disability Index, and
- C-Reactive Protein.

Sixty-eight joints (right and left) were examined for Joint Tenderness/Pain. Artificial joints were not assessed. In response to pressure or motion, each joint was graded using the scale from 0 (none) to 3 (withdrawal by patient on examination).

Sixty-six joints were also graded for swelling using the scale from 0 (none) to 3 (bulging synovial proliferation with cystic characteristics). These joints were the same as those examined for tenderness except that the hip joints were not assessed.

Mean change analyses were performed for treatment comparisons for the above variables (with the exception of ACR-20 Responder Index) based on analysis of covariance models with center and treatment as factors and Baseline as a covariate. For ACR-20 Responder Index and other categorized variables, a categorical analysis based on the Cochran-Mantel-Haenszel test stratified by center was performed for treatment comparisons.

5.2.1.3 Patient Disposition

A total of 2250 patients with RA were entered into one of the two pivotal studies and randomized to receive one of five treatments for 12 weeks: celecoxib 100 mg BID, celecoxib 200 mg BID, celecoxib 400 mg BID, naproxen 500 mg BID, or placebo and were included in the ITT cohort. Table 15 presents a summary of all patients, by treatment group, who completed one of the 12-week pivotal studies. The reasons for study termination, grouped by treatment, for all randomized patients are also summarized in this table.

Table 15. Reasons for Study Termination: 12-Week Pivotal RA Studies 022 and 023

Study	Number of Rheumatoid Arthritis Patients by Treatment Group				
	Placebo	Celecoxib			Naproxen 500 mg BID
		100 mg BID	200 mg BID	400 mg BID	
Study 022	(N=231)	(N=240)	(N=235)	(N=218)(a)	(N=225)
Total Completed	101 (44%)	154 (64%)	158 (67%)	137 (63%)	138 (61%)
Total Withdrawn	130 (56%)	86 (36%)	77 (33%)	81 (37%)	87 (39%)
Treatment Failure	104 (45%)	67 (28%)	50 (21%)	59 (27%)	65 (29%)
Adverse Event	11 (5%)	13 (5%)	17 (7%)	12 (6%)	12 (5%)
Other	15 (5%)	6 (3%)	10 (4%)	10 (4%)	10 (4%)
Study 023	(N=221)	(N=228)	(N=219)(a)	(N=217)	(N=218)
Total Completed	78 (35%)	117 (51%)	124 (57%)	126 (58%)	133 (61%)
Total Withdrawn	143 (65%)	111 (49%)	95 (43%)	91 (42%)	85 (39%)
Treatment Failure	125 (57%)	92 (40%)	74 (34%)	69 (32%)	69 (32%)
Adverse Event	12 (5%)	12 (5%)	16 (7%)	16 (7%)	16 (7%)
Other	6 (3%)	7 (3%)	5 (2%)	6 (3%)	0 (0%)

a) Total number of patients includes two patients (one in the celecoxib 200 mg BID group [Study 023] and one in the celecoxib 400 mg BID group [Study 022]) who were randomized but did not receive study medication and are not included in the ITT cohort.

5.2.1.4 Patient Characteristics

Table 16 summarizes the pooled Baseline demographic characteristics and arthritis history for all patients enrolled in the two pivotal studies. In these studies, age, race, gender, arthritis history, and corticosteroid and DMARD use were comparable across treatment groups. The demographic characteristics, arthritis history and co-therapy for each individual study were consistent with the pooled results. Patients in the pivotal studies had long-standing arthritic disease as evidenced by an average RA duration in the pivotal trials of 10 years. In addition, approximately 75% of these patients were receiving DMARD co-therapy, and 40% were taking oral corticosteroids.

Table 16. Pooled Baseline Demographic Characteristics and Disease Status for RA Patients By Treatment Group: Pooled Pivotal RA Studies 022 and 023

Baseline Demographic Characteristic	Number of Patients by Treatment Group				
	Placebo (N=452)	Celecoxib			Naproxen 500 mg BID (N=443)
		100 mg BID (N=468)	200 mg BID (N=454)(a)	400 mg BID (N=435)(a)	
Age (years)					
Mean (Std. Dev.)	54.2 (12.42)	55.1 (11.99)	54.0 (12.09)	54.0 (12.10)	55.9 (12.09)
Range	23-84	22-85	20-90	21-85	21-82
≥65 years - N (%)	102 (23%)	104 (22%)	103 (23%)	91 (21%)	122 (28%)
Race/Ethnic Origin					
Caucasian/Hispanic - N (%)	414 (92%)	419 (89%)	412 (91%)	392 (90%)	405 (91%)
Black - N (%)	36 (8%)	42 (9%)	35 (8%)	35 (8%)	34 (8%)
Other - N (%)	2 (<1%)	7 (1%)	7 (2%)	8 (2%)	4 (1%)
Gender					
Female - N (%)	336 (74%)	346 (74%)	328 (72%)	314 (72%)	313 (71%)
Disease Duration - Years					
Mean (Std. Dev.)	10.3 (9.91)	10.7 (±9.01)	10.4 (9.32)	10.3 (8.77)	11.0 (9.80)
Range	0.3-60.0	0.3-53.0	0.3-53.0	0.3-58.0	0.3-55.0
≥5 years - N (%)	293 (65%)	333 (71%)	288 (63%)	285 (66%)	300 (68%)
Corticosteroid Use					
Yes - N (%)	175 (39%)	209 (45%)	172 (38%)	154 (35%)	167 (38%)
Methotrexate Use					
Yes - N (%)	192 (42%)	221 (47%)	205 (45%)	202 (46%)	200 (45%)
Other DMARD Use					
Yes - N (%)	148 (33%)	153 (33%)	139 (31%)	132 (30%)	149 (34%)

a) Total number of patients includes two patients (one in the celecoxib 200 mg BID group [Study 023] and one in the celecoxib 400 mg BID group [Study 022]) who were randomized into a study but did not receive study medication and were not included in the ITT cohort.

5.2.1.5 Efficacy and Dose Response

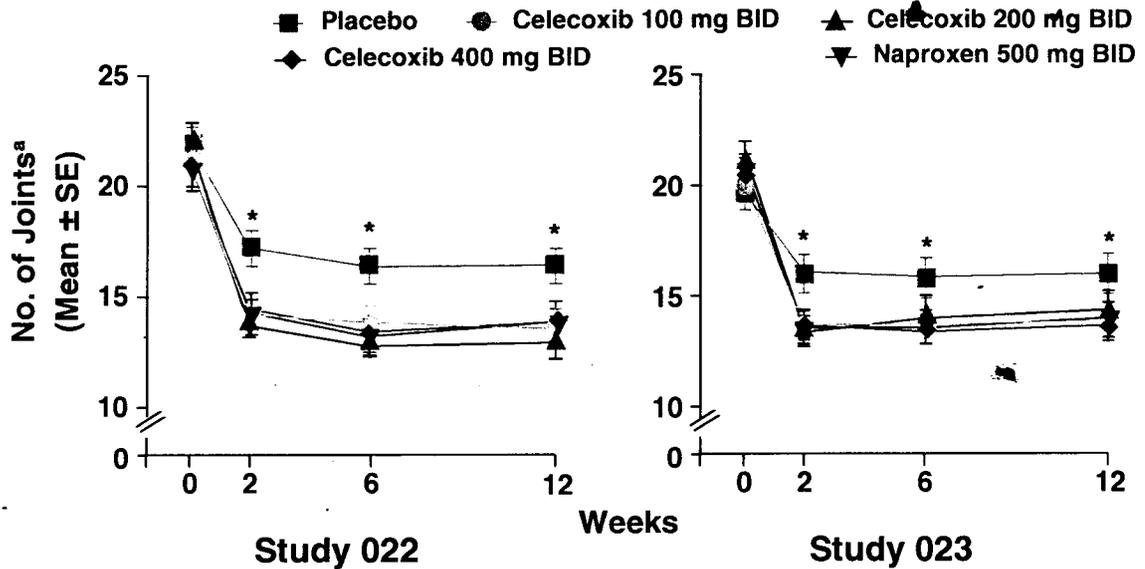
In two 12-Week pivotal studies, the Number of Swollen Joints in RA patients treated with celecoxib doses of 100 mg BID, 200 mg BID, and 400 mg BID were statistically significantly reduced when compared to placebo at the Week 2 assessment and this improvement was maintained through the Week 6 and Week 12 assessments (Figure 14, Table 17). Similarly, for the other primary measures of efficacy, all celecoxib doses showed statistically significantly greater improvement when compared to placebo treatment at Week 12 (Figure 15, Tables 18 and 19) as well as all earlier assessments in both studies with few exceptions. A significant treatment effect was not detected in the Physician's Global Assessment or the HAQ Functional Disability Index at Week 12 in Study 022 for the celecoxib 100 mg BID treatment group and in Study 023, the treatment effect observed with ACR-20 Responders Index at Week 12 for the celecoxib 100 mg BID dose did not separate statistically from placebo.

Celecoxib doses of 100 mg BID and 200 mg BID were efficacious and escalating the dose to 400 mg BID did not offer improved efficacy in either of the 12-Week pivotal RA studies. The responses to celecoxib 200 mg BID and 400 mg BID were not statistically significantly different in either study at any assessment time for any primary measure of efficacy. Only one statistically significant difference was detected between celecoxib doses of 200 mg BID and 400 mg BID. This difference was in favor of celecoxib 200 mg BID and occurred in Study 022 for ACR-20 Responders Index at Week 6. The responses to celecoxib 100 mg BID and 400 mg BID for all primary measures of efficacy at Weeks 2, 6, and 12 were also not significantly different.

The responses of celecoxib 100 mg BID were generally similar to 200 mg BID across all primary measures of efficacy in Study 023 with the exception of significantly lower response in the ACR-20 Responders Index at Week 12. In Study 022, the responses to celecoxib 200 mg BID tended to be greater than celecoxib 100 mg BID, but were also greater than celecoxib 400 mg BID. These results indicate that some RA patients may derive additional benefit from the 200 mg BID dose of celecoxib when compared to celecoxib 100 mg BID.

In both of the pivotal studies, comparable efficacy of celecoxib 100 mg BID and 200 mg BID to naproxen 500 mg BID was demonstrated. Celecoxib 100 mg BID, 200 mg BID and 400 mg BID were not statistically significantly different from naproxen 500 mg BID for all primary measures of efficacy at nearly all assessment times in both pivotal studies. The comparison to naproxen further suggests that celecoxib 100 mg BID and 200 mg BID are efficacious and the most appropriate doses for treating the signs and symptoms of RA. As is the case with the placebo comparisons, increasing the dose of celecoxib to 400 mg BID provided no further benefit of improved efficacy in RA patients when compared to naproxen 500 mg BID.

Figure 14. Number of Swollen Joints: 12-Week Pivotal RA Studies 022 and 023



* Significantly different from all active treatments; p<0.05.

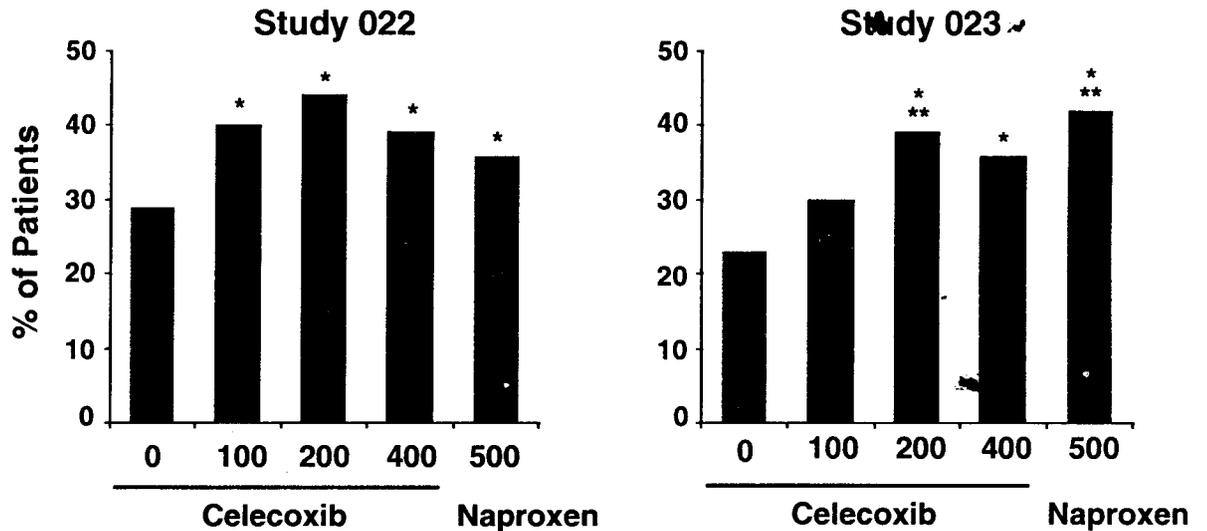
a) 66 joints examined

Table 17. Changes from Baseline for Number of Swollen Joints and Number of Tender/Painful Joints: 12-Week Pivotal RA Studies 022 and 023

Treatment Group	Study 022			Study 023		
	N	Baseline	Change at Week 12	N	Baseline	Change at Week 12
Swollen Joint Count (LS Mean Value)						
Placebo	231	22.2	-5.5	221	21.3	-3.7
Celecoxib 100 mg BID	240	21.0	-8.0*	228	21.4	-5.9*
Celecoxib 200 mg BID	235	22.1	-9.2*	218	22.6	-6.0*
Celecoxib 400 mg BID	217	20.8	-7.6*	217	22.3	-6.4*
Naproxen 500 mg BID	225	20.8	-7.6*	218	22.1	-6.1*
Tender/Painful Joint Count (LS Mean Value)						
Placebo	231	29.2	-8.2	221	30.1	-5.5
Celecoxib 100 mg BID	240	30.0	-12.0*	228	28.5	-10.0*
Celecoxib 200 mg BID	235	31.4	-12.3*	218	29.7	-10.2*
Celecoxib 400 mg BID	217	28.4	-12.4*	217	31.3	-11.1*
Naproxen 500 mg BID	225	28.9	-10.1	218	29.8	-11.2*

* Significantly different from placebo; p<0.05.

Figure 15. ACR-20 Responders Index - Percent of Patients Improved at Week 12: 12-Week Pivotal RA Studies 022 and 023



* Significantly different from placebo; $p < 0.05$.
 ** Significantly different from celecoxib 100 mg BID; $p < 0.05$.
 Doses are mg BID

Table 18. HAQ Functional Disability Index: Baseline Mean Score and LS Mean Change from Baseline: 12-Week Pivotal RA Studies 022 and 023

Treatment Group	Study 022		Study 023	
	Baseline(a)	Change at Week 12	Baseline	Change at Week 12
Placebo	1.45	-0.10	1.42	-0.07
Celecoxib 100 mg BID	1.43	-0.17	1.44	-0.14*
Celecoxib 200 mg BID	1.52	-0.30*	1.38	-0.25*
Celecoxib 400 mg BID	1.44	-0.29*	1.35	-0.25*
Naproxen 500 mg BID	1.51	-0.22*	1.43	-0.22*

* Significantly different from placebo; $p \leq 0.05$.
 a) Scale ranged from 0 to 3 with lower score as less disability.

Table 19. Percent of Patients Improved from Baseline: 12-Week Pivotal RA Studies 022 and 023

Treatment Group	Study 022		Study 023	
	N	% Improved(a) at Week 12	N	% Improved(a) at Week 12
Patient's Global Assessment of Arthritic Condition (Categorical Change)				
Placebo	231	16	221	13
Celecoxib 100 mg BID	240	22*	228	18*
Celecoxib 200 mg BID	235	30*†‡	218	23*
Celecoxib 400 mg BID	217	25*	217	19*
Naproxen 500 mg BID	225	19	218	26*‡
Physician's Global Assessment of Arthritic Condition (Categorical Change)				
Placebo	231	15	221	12
Celecoxib 100 mg BID	240	21	228	18*
Celecoxib 200 mg BID	235	30*†‡	218	22*
Celecoxib 400 mg BID	217	25*	217	20*
Naproxen 500 mg BID	224	20	218	25*
ACR-20 Responder Index (Categorical Change)				
Placebo	231	29	221	23
Celecoxib 100 mg BID	240	40*	228	30
Celecoxib 200 mg BID	235	44*	218	39*‡
Celecoxib 400 mg BID	217	39*	217	36*
Naproxen 500 mg BID	225	36*	218	42*‡

* Significantly different from placebo; p<0.05.

† Significantly different from naproxen; p<0.05.

‡ Significantly different from celecoxib 100 mg BID; p<0.05.

a) Improvement is defined as reduction of at least 2 grades from Baseline for grades 3-5 or a change in grade from 2 to 1

5.2.1.6 Health-related Quality of Life: Rheumatoid Arthritis

The SF-36 Health Survey was administered at Baseline and at Weeks 2 and 12 of treatment in the 12-week pivotal RA studies (Studies 022 and 023). The mean scores at Baseline together with mean changes from Baseline to Week 12 for the eight domains of the SF-36 Health Survey for each study are shown in Table 20. Statistically significant improvements in Physical Functioning, Role-Physical, Bodily Pain, Vitality and Mental Health were observed in both studies for celecoxib 200 mg BID and celecoxib 400 mg BID. Similarly, significant treatment-related effects in these same domains were observed with celecoxib 100 mg BID and naproxen 500 mg BID in one or both studies. General Health and Role Emotional were found to significantly improve in all active treatment groups when compared to placebo in Study 022. In contrast, none of the active treatments was associated with significant improvement in Study 023 for these two domains.

Table 20. Baseline Mean Scores and Mean Changes from Baseline for SF-36 Quality-of-Life Domains: 12-Week Pivotal RA Trials 022 and 023

SF-36 Domain(a) Treatment Group	Study 022		Study 023	
	Baseline	Change at Week 12	Baseline	Change at Week 12
Physical Functioning				
Placebo	38.1	0.8	37.8	0.5
Celecoxib 100 mg BID	39.2	3.4	40.0	4.1*
Celecoxib 200 mg BID	36.4	9.5*	38.6	9.3*
Celecoxib 400 mg BID	38.6	8.7*	38.5	7.7*
Naproxen 500 mg BID	36.9	5.6*	37.1	7.0*
Role Physical				
Placebo	18.9	6.8	23.5	0.2
Celecoxib 100 mg BID	21.8	11.7	23.6	10.6*
Celecoxib 200 mg BID	23.1	15.7*	25.1	13.5*
Celecoxib 400 mg BID	22.7	14.0*	19.4	17.4*
Naproxen 500 mg BID	23.4	9.7	21.7	17.2*
Bodily Pain				
Placebo	32.9	2.3	35.0	-1.0
Celecoxib 100 mg BID	34.9	6.6*	34.6	7.1*
Celecoxib 200 mg BID	32.4	12.1*	34.1	11.5*
Celecoxib 400 mg BID	33.9	9.2*	32.5	11.6*
Naproxen 500 mg BID	34.4	8.2*	34.3	10.7*
General Health				
Placebo	51.5	-1.1	53.5	0.4
Celecoxib 100 mg BID	52.6	1.9*	52.3	2.6
Celecoxib 200 mg BID	50.6	3.6*	52.9	2.5
Celecoxib 400 mg BID	52.0	4.3*	52.2	2.4
Naproxen 500 mg BID	52.5	2.4*	50.0	5.4*
Vitality				
Placebo	34.7	-0.4	34.0	0.5
Celecoxib 100 mg BID	34.4	5.1*	36.6	6.9*
Celecoxib 200 mg BID	34.7	9.1*	35.7	6.9*
Celecoxib 400 mg BID	34.0	8.4*	33.5	9.9*
Naproxen 500 mg BID	35.2	4.8*	35.3	8.5*
Social Functioning				
Placebo	57.3	-2.7	61.3	-5.4
Celecoxib 100 mg BID	62.0	2.8*	62.2	3.5*
Celecoxib 200 mg BID	55.4	10.8*	61.6	7.4*
Celecoxib 400 mg BID	60.0	6.4*	60.3	7.8*
Naproxen 500 mg BID	60.2	3.1*	62.1	6.4*
Role Emotional				
Placebo	48.1	1.5	51.8	2.5
Celecoxib 100 mg BID	51.3	6.9*	57.9	-1.2
Celecoxib 200 mg BID	44.2	13.3*	57.7	3.9
Celecoxib 400 mg BID	52.9	5.2*	56.7	3.6
Naproxen 500 mg BID	46.4	9.8*	53.0	9.5
Mental Health				
Placebo	69.5	-1.4	69.4	-3.0
Celecoxib 100 mg BID	69.4	1.2	68.9	2.8*
Celecoxib 200 mg BID	65.6	4.3*	70.5	0.6
Celecoxib 400 mg BID	69.1	2.0*	69.3	2.9*
Naproxen 500 mg BID	66.7	3.7*	67.5	4.3*

* Significantly different from placebo; p≤0.05.

a) Scale ranged from 0 to 100 with lower score as worse for all domains.

5.2.2 Supportive RA Efficacy Studies

5.2.2.1 Placebo-Controlled Study: Study 012

Study 012 was a dose-ranging, double-blind, placebo-controlled, parallel-group, 4-week study to evaluate the efficacy of celecoxib 40 mg, 200 mg and 400 mg BID in treating the signs and symptoms of RA. Patients were eligible if they had RA that was in a flare state and had not received any NSAIDs in the two days prior to the first dose of study medication. Of the 330 ITT patients, 265 (80.3%) completed all 4 weeks of the study. For all primary efficacy variables, celecoxib produced a reduction in the signs and symptoms of RA. This improvement was statistically significant for the 200 mg and 400 mg dose groups at Week 1, Week 2, and Week 4; the only exception to this was the Number of Swollen Joints at Week 2 which was not statistically significant for either the 200 or 400 mg dose groups. The 40 mg celecoxib dose group was statistically superior to placebo only at Week 1 and only for the Patient's Global Assessment of Arthritic Condition and the Patient's Assessment of Pain (VAS).

5.2.2.2 International Active-Controlled RA Study: Study 041

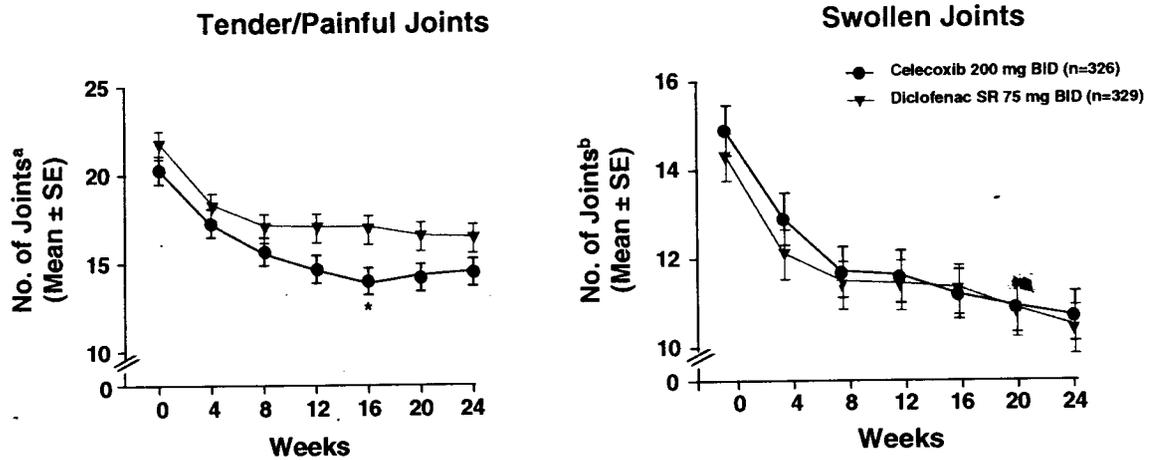
Study 041 was a randomized, double-blind, multicenter, parallel group trial designed to evaluate the efficacy and tolerability of celecoxib 200 mg BID as compared to diclofenac SR 75 mg BID in treating the signs and symptoms of RA.

To be enrolled, patients had to have met the ACR criteria for adult-onset RA that was clinically evident for at least six months prior to study enrollment. DMARD and oral corticosteroid co-therapy was allowed if it was stable for the 12 weeks prior to receiving the first dose of study medication. In addition, patients must have been anticipated to require continuous treatment with an anti-inflammatory drug to control arthritis symptoms for the duration of the study.

As illustrated in Tables 21 and 22, celecoxib provided clinically significant relief from the signs and symptoms of RA as measured by categorical change from Baseline in Patients and Physician's Global Assessments of Arthritic Condition. Similar results were observed for the Number of Tender/Painful Joints and the Number of Swollen Joints (Figure 16). For all primary efficacy analyses at all timepoints assessed, celecoxib and diclofenac SR 75 mg BID were similar. Among the primary measures of efficacy, there

was a statistically significant difference between the two treatments for only one assessment at one timepoint (Tender/Painful Joint Count at Week 16).

Figure 16. Numbers of Tender/Painful and Swollen Joints: Study 041



* Significantly different from diclofenac; p<0.05

a) 68 joints examined

b) 66 joints examined

Table 21. Tender/Painful and Swollen Joint Counts: Study 041

Treatment Group	N	Baseline	Change at Week 24*
Tender/Painful Joint Count (LS Mean Value)			
Celecoxib 200 mg BID	326	20.4	-5.8
Diclofenac SR 75 mg BID	329	21.7	-4.9
Swollen Joint Count (LS Mean Value)			
Celecoxib 200 mg BID	326	15.2	-3.9
Diclofenac SR 75 mg BID	329	14.6	-3.9

Table 22. Summary of Categorical Primary Efficacy Analyses: Study 041

Treatment Group	N	% Improved at Week 24*
Patient's Global Assessment Categorical Change(a)		
Celecoxib 200 mg BID	326	40
Diclofenac SR 75 mg BID	329	40
Physician's Global Assessment Categorical Change(a)		
Celecoxib 200 mg BID	326	43
Diclofenac SR 75 mg BID	329	43
ACR-20 Responder Index Categorical Change(b)		
Celecoxib 200 mg BID	326	25
Diclofenac SR 75 mg BID	329	22

a) Improved: reduction of at least 1 grade from baseline.

b) Improved: at least 20% improvement from baseline in the number of tender/painful joints and in the number of swollen joints as well as at least 20% improvement from Baseline in at least 3 of the following assessments: Physician's Global, Patient's Global, Patient's Assessment of Arthritis Pain, C-Reactive Protein, and HAQ Functional Disability Index. HAQ Functional Disability Index was only available at Baseline and Week 24.

* There were no statistically significant differences between celecoxib and diclofenac.

5.2.2.3 Active-Controlled Studies: Studies 062 and 071

Study 062 was a randomized, double-blind, parallel group, multicenter, 12-week study designed primarily to compare the cumulative incidence of gastroduodenal ulcers associated with celecoxib 200 mg BID to that of naproxen 500 mg BID in patients with OA or RA. The efficacy of celecoxib compared to naproxen in RA patients was assessed in this trial but there were many fewer RA patients than OA patients. Patients were eligible to participate in the study if they had a documented clinical diagnosis of OA or RA (not necessarily in flare) and required chronic NSAID treatment. Overall, 359 (67.0%) of 536 ITT patients completed all 12 weeks of the study. There were no clinically significant differences between the celecoxib 200 mg BID and naproxen 500 mg BID treatment groups in the number of RA patients who showed improvement, no change, or worsening in arthritis condition at Weeks 4, 8, or 12.

Study 071 was a randomized, double-blind, parallel group, multicenter, 12-week study was designed primarily to compare the cumulative incidence of gastroduodenal ulcers associated with celecoxib 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA. However, efficacy and overall safety were also assessed during the trial. The efficacy of celecoxib compared to ibuprofen and diclofenac in RA patients was assessed in this trial, but there were many fewer RA patients than OA patients. Patients were eligible to participate in the study if they had a documented clinical diagnosis of OA or RA (not necessarily in flare) and required chronic NSAID treatment. Of the 1097 patients in the ITT cohort, 806 (73%) completed

12 weeks of study participation. There were no clinically significant differences between the celecoxib 200 mg BID, diclofenac 75 mg BID, and ibuprofen 800 mg TID treatment groups in the number of RA patients who showed improvement, no change, or worsening in arthritis condition at Weeks 4, 8, or 12.

5.2.3 Conclusions

Based on the results of replicate pivotal studies in RA patients, it is concluded that:

- Celecoxib doses of 100 mg BID, 200 mg BID, and 400 mg BID were efficacious in treating the signs and symptoms of RA.
- Although 100 mg BID and 200 mg BID provided similar efficacy overall, some patients may derive additional benefit from the 200 mg BID dose.
- No additional efficacy was obtained by increasing the dose of celecoxib above 400 mg per day.
- Celecoxib, at efficacious doses, had similar efficacy to full therapeutic doses of NSAIDs.
- Health-related quality of life improvements were observed with full therapeutic doses of celecoxib.

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5.3 Pain Management

Analgesic efficacy was assessed in a variety of clinical settings which included postsurgical pain models (oral surgery, orthopedic surgery, and general surgery) and pain associated with arthritis (OA and RA). Seven randomized and placebo-controlled studies were conducted in patients with postsurgical pain; six of these studies were double-blind and designed to be pivotal studies (025, 027, 070, 028, 029, and 080) (Table 23).

Table 23. Summary of Celecoxib Pain Management Studies

Study Number - Population	Duration	No. of Patients	Treatments
Post-Oral Surgery Studies			
025 - extraction of third molar(s)	single dose	250	Celecoxib 25, 50, or 200 mg; ibuprofen 400 mg; or placebo
027 - extraction of third molar(s)	single dose	220	Celecoxib 100 or 200 mg, naproxen sodium 550 mg, or placebo
070 - extraction of third molar(s)	single dose	255	Celecoxib 50, 100, 200, or 400 mg; naproxen sodium 550 mg; or placebo
005 - extraction of third molar(s)	single dose	200	Celecoxib 100 or 400 mg, aspirin 650 mg, or placebo
Post-Orthopedic and Post-General Surgery Studies			
028 - orthopedic surgery	up to 5 days	255	Celecoxib 100 or 200 mg (PRN up to BID) or Darvocet N® 100 mg (PRN up to QID)
029 - general surgery	up to 5 days	167	Celecoxib 100 or 200 mg (PRN up to BID) or Darvocet N® 100 mg (PRN up to QID)
080 - orthopedic surgery	up to 5 days	1	Celecoxib 200 mg (PRN up to BID) or naproxen 500 mg (PRN up to BID)

5.3.1 Post-Oral Surgery Studies

5.3.1.1 Pivotal Studies: Studies 025, 027 and 070

5.3.1.1.1 Population and Design

Studies 025, 027 and 070 were double-blind, randomized, placebo-controlled, single-dose post-oral surgery studies that contained an active control. In order to be entered into these studies, patients must have undergone surgical extraction of one (Study 070) or two (Studies 025 and 027) or more impacted third molar(s) requiring bone removal, one of which must have been mandibular, experiencing moderate to severe postsurgical pain, and rated their Baseline pain intensity ≥ 50 mm on a Visual Analog Scale (VAS) of 100 mm.

The Treatment Period was the 24-hour period immediately following the administration of a single dose of study medication. Patients underwent the scheduled pain assessments

at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 hours postdose. Patients were allowed to take rescue medication at any time in the study, however, they were then dropped from the study.

In total across the three post-oral surgery studies (Studies 025, 027, 070), patients were randomized to receive one of eight treatments: celecoxib 25 mg SD, celecoxib 50 mg SD, celecoxib 100 mg SD, celecoxib 200 mg SD, celecoxib 400 mg SD, naproxen sodium 550 mg SD, ibuprofen 400 mg SD, or placebo.

5.3.1.1.2 Description of the Efficacy Scales Used

The primary measures of efficacy for the postsurgical pain studies were (24):

- Time-Specific Pain Intensity Difference (PID) (Categorical). Pain intensity assessed by patients on a 4 point scale from 0 (none) to 3 (severe);
- Time-Specific Pain Relief (PR), assessed by patients on a 5 point scale from 0 (none) to 4 (complete);
- Time-Specific Sum of PID on a categorical scale and PR (PRID) at the postdose timepoints, best possible score is 7 (complete pain relief [PR=4] and change from severe pain at Baseline to no pain [PID=3]. Worst possible score is -1 (no pain relief [PR=0] and change from moderate pain at Baseline to severe pain [PID=-1]) ;
- Time to Rescue Medication, the difference between the start time for the rescue medication and the time the first dose of study drug was taken; and
- Time to Onset of Perceptible Pain Relief, assessed by instructing the patient to stop a stopwatch at the time of perceptible pain relief.

The secondary measures of efficacy were:

- Time-Specific Pain Intensity Difference (PID) (VAS);
- Sum of PID scores (SPID);
- Total Pain Relief (TOTPAR), the sum of the PR scores;
- Sum of PRID Scores (SPRID);
- Time to First Experienced 50% Pain Relief;
- Proportion of Patients Experiencing at Least 50% Pain Relief; and
- Proportion of Patients Experiencing 100% Pain Relief.

The remaining measures of efficacy, considered supportive, were:

- Peak Pain Intensity Difference (PPID);
- Peak Pain Relief (PPR);
- Patient Global Evaluation of Study Medication;
- APS Pain Measure; and
- Time to Onset of Meaningful Pain Relief.

The primary population for analysis was the ITT cohort, defined as all randomized patients who took one dose of study drug and did not take rescue medication prior to the one-hour timepoint. In addition, patients were excluded from the cohort if that patient had two consecutive scheduled timepoints in the first two hours obtained by interpolation from the same two observed data points. The last observation carried forward was used for imputing missing values. The analyses of the post-oral surgery studies focus on the first eight hours after administration of the single dose of study medication. A secondary consideration was the period of 8-24 hours after the single dose.

5.3.1.1.3 Patient Disposition

A total of 725 patients with post-oral surgery pain were enrolled into clinical studies with celecoxib and were included in the ITT cohort. Table 24 presents a summary of all patients, by treatment group, who completed each study. The reasons for study termination, grouped by treatment, for all randomized patients are also summarized in this table.

Table 24. Reasons for Study Termination for Post-Oral Surgery Pain Patients: Studies 025, 027, 070

Study	Number of Postsurgical Patients by Treatment Group							
	Placebo	Celecoxib					Naproxen Sodium	Ibuprofen
		25 mg SD	50 mg SD	100 mg SD	200 mg SD	400 mg SD	550 mg SD	400 mg SD
Study 025								
Total Completed (a)	4 (8%)	4 (8%)	7 (14%)	---	13 (26%)	---	---	8 (16%)
Total Withdrawn	46 (92%)	46 (92%)	43 (86%)	---	37 (74%)	---	---	42 (84%)
Treatment Failure/ Rescue Medication	46 (92%)	46 (92%)	43 (86%)	---	37 (74%)	---	---	42 (84%)
Adverse Event	0 (0%)	0 (0%)	0 (0%)	---	0 (0%)	---	---	0 (0%)
Study 027								
Total Completed (a)	9 (16%)	---	---	17 (31%)	27 (48%)	---	28 (52%)	---
Total Withdrawn	46 (84%)	---	---	38 (69%)	29 (52%)	---	26 (48%) (b)	---
Treatment Failure/ Rescue Medication	46 (84%)	---	---	38 (69%)	29 (52%)	---	25 (46%)	---
Adverse Event	0 (0%)	---	---	0 (0%)	0 (0%)	---	0 (0%)	---
Study 070								
Total Completed (a)	2 (4%)	---	3 (9%)	10 (20%)	12 (24%)	13 (37%)	9 (26%)	---
Total Withdrawn	48 (96%)	---	32 (91%)	40 (80%)	38 (76%)	22 (63%)	26 (74%)	---
Treatment Failure/ Rescue Medication	48 (96%)	---	31 (89%)	40 (80%)	38 (76%)	22 (63%)	26 (74%)	---
Adverse Event	0 (0%)	---	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	---

a) Completed patient was defined as having completed evaluations through 24 hours (Studies 025, 027 and 070) without taking rescue medication.

b) One patient was discharged before the 24 hour assessment.

5.3.1.1.4 Patient Characteristics

Table 25 shows a descriptive summary of the pooled Baseline demographic characteristics for all patients enrolled in the 24-hour post-oral surgery studies (Studies 025, 027, 070).

Table 25. Pooled Baseline Demographic Characteristics for Post-Oral Surgery Pain Patients: Studies 025, 027, and 070

Baseline Demographic Characteristic	Number of Postsurgical Patients by Treatment Group							
	Placebo (N=155)	Celecoxib					Naproxen Sodium	Ibuprofen
		25 mg SD (N=50)	50 mg SD (N=85)	100 mg SD (N=105)	200 mg SD (N=156)	400 mg SD (N=35)	550 mg SD (N=89)	400 mg SD (N=50)
Age (years)								
Mean (Std Dev)	23.1 (4.43)	23.3 (5.72)	24.0 (5.50)	23.6 (5.61)	23.6 (5.28)	24.2 (5.97)	23.4 (5.64)	24.3 (5.48)
Range	18-43	18-46	18-45	18-50	18-47	18-41	18-52	18-50
Race/Ethnic Origin								
Caucasian/ Hispanic N (%)	137(88%)	46 (92%)	72 (85%)	93 (89%)	140 (90%)	31(89%)	82 (92%)	47 (94%)
Black N (%)	12 (8%)	3 (6%)	9 (11%)	9 (9%)	10 (6%)	3 (9%)	4 (4%)	1 (2%)
Other N (%)	6 (4%)	1 (2%)	4 (5%)	3 (3%)	6 (3%)	1 (3%)	3 (3%)	2 (4%)
Gender								
Female N (%)	89 (57%)	32 (64%)	53 (62%)	60 (57%)	93 (60%)	21 (60%)	51 (57%)	40 (80%)

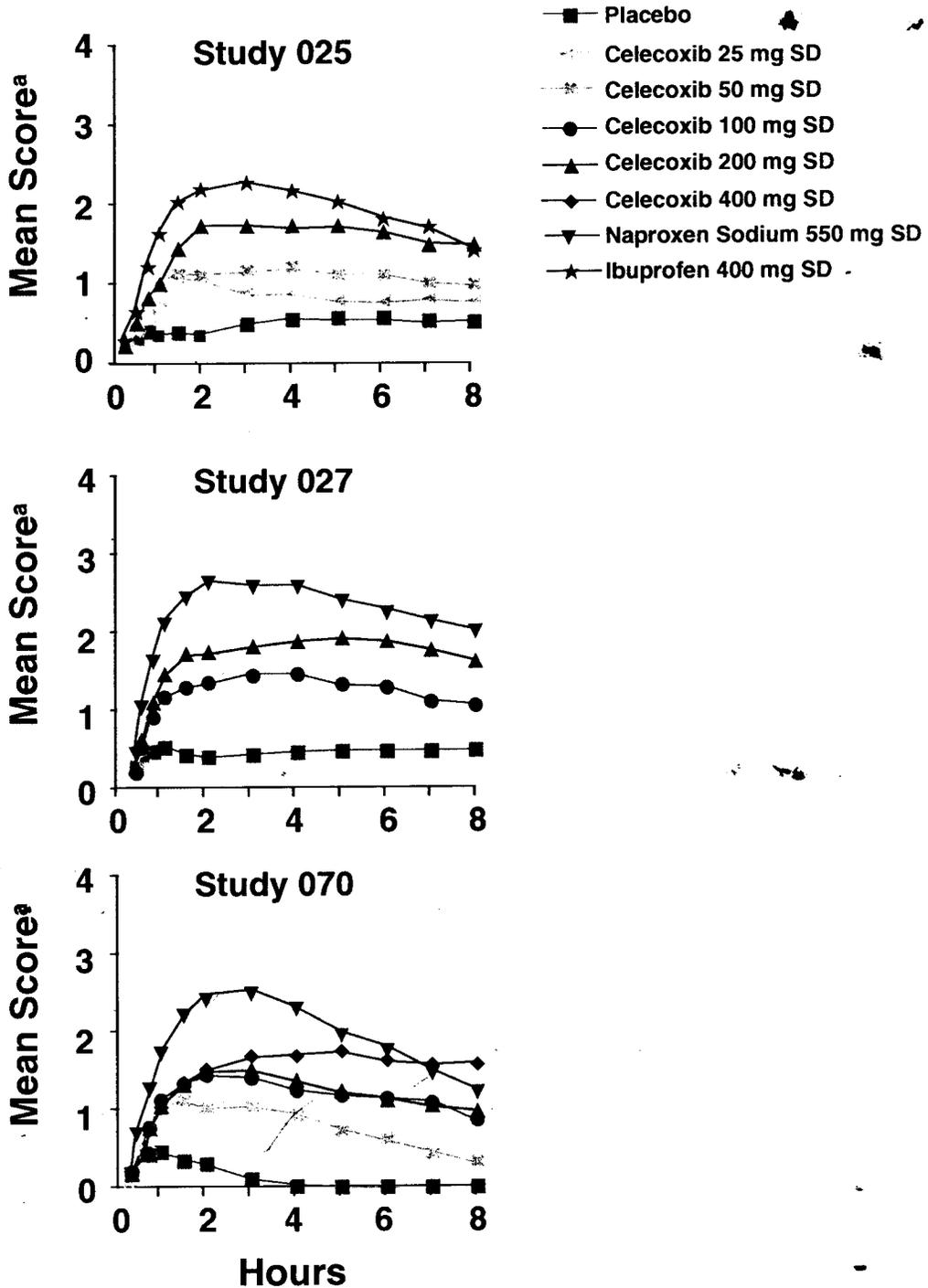
Within these studies, there were no clinically significant differences between any of the treatment groups with regard to age, race or gender with the exception of a higher proportion of females in the ibuprofen group (Study 025).

5.3.1.1.5 Efficacy and Dose Response

In replicate post-oral surgery studies, celecoxib doses of 100 mg (Studies 027 and 070) and 200 mg (Studies 025, 027, and 070) provided statistically significant Pain Relief (PR) compared to placebo beginning by one hour after dosing and continuing through eight hours (Figure 17, Table 26). Analogous results were observed in the PID and PRID (Table 26). Celecoxib doses below 100 mg were submaximally efficacious. A 400 mg dose of celecoxib was tested in Study 070. This dose did not provide statistically significantly greater analgesic efficacy when compared to the 100 mg and 200 mg doses of celecoxib over the entire eight hour post-dosing interval for the PID and PRID and for the first seven hours for the PR.

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Figure 17. Pain Relief: Pivotal Post-Oral Surgery Pain Studies 025, 027 and 070



a) Scale ranges from 0 (none) to 4 (complete).

Table 26. Categorical Primary Efficacy Variables: Studies 025, 027 and 070

Treatment Group	N	Time Postdose (Hours)				
		.75	1	2	6	8
Study 025 Pain Relief (PR) - Categorical Mean Score						
Placebo	50	0.42	0.38	0.38	0.58	0.52
Celecoxib 25 mg	50	0.58	0.78*	1.08*	0.78	0.80
Celecoxib 50 mg	50	0.72	0.98*	1.12*	1.12*	1.00
Celecoxib 200 mg	50	0.84*	1.02*	1.74*	1.66*	1.50*
Ibuprofen 400 mg	50	1.22*	1.64*	2.20*	1.82*	1.42*
Pain Intensity Difference (PID) - Categorical Mean Score						
Placebo	50	-0.08	-0.14	-0.14	-0.02	-0.06
Celecoxib 25 mg	50	0.08	0.14*	0.26*	0.12	0.12
Celecoxib 50 mg	50	0.24*	0.38*	0.42*	0.38*	0.34*
Celecoxib 200 mg	50	0.12	0.22*	0.56*	0.58*	0.52*
Ibuprofen 400 mg	50	0.52*	0.72*	1.02*	0.86*	0.66*
Pain Intensity Difference and Pain Relief (PRID) - Categorical Mean Score						
Placebo	50	0.34	0.24	0.24	0.56	0.46
Celecoxib 25 mg	50	0.66	0.92*	1.34*	0.90	0.92
Celecoxib 50 mg	50	0.96*	1.36*	1.54*	1.50*	1.34*
Celecoxib 200 mg	50	0.96*	1.24*	2.30*	2.24*	2.02*
Ibuprofen 400 mg	50	1.74*	2.36*	3.22*	2.68*	2.08*
Study 027 Pain Relief (PR) - Categorical Mean Score						
Placebo	55	0.55	0.60	0.51	0.60	0.62
Celecoxib 100 mg	55	0.98*	1.24*	1.45*	1.53	1.33*
Celecoxib 200 mg	56	1.18*	1.54*	1.88*	2.05*	1.80*
Naproxen Sodium 550 mg	54	1.70*	2.17*	2.72*	2.44*	2.24*
Pain Intensity Difference (PID) - Categorical Mean Score						
Placebo	55	-0.09	-0.15	-0.20	-0.15	-0.13
Celecoxib 100 mg	55	0.29*	0.36*	0.53*	0.56*	0.40*
Celecoxib 200 mg	56	0.39*	0.55*	0.77*	0.88*	0.77*
Naproxen Sodium 550 mg	54	0.69*	0.87*	1.26*	1.04*	0.93*
Pain Intensity Difference and Pain Relief (PRID) - Categorical Mean Score						
Placebo	55	0.45	0.45	0.31	0.45	0.49
Celecoxib 100 mg	55	1.27*	1.60*	1.98*	2.09*	1.73*
Celecoxib 200 mg	56	1.57*	2.09*	2.64*	2.93*	2.57*
Naproxen Sodium 550 mg	54	2.39*	3.04*	3.98*	3.48*	3.17*
Study 070 Pain Relief (PR) - Categorical Mean Score						
Placebo	50	0.50	0.54	0.48	0.32	0.48
Celecoxib 50 mg	35	0.86	1.06*	1.26*	0.91*	1.26*
Celecoxib 100 mg	50	0.84	1.20*	1.58*	1.42*	1.58*
Celecoxib 200 mg	50	0.84	1.14*	1.64*	1.36*	1.64*
Celecoxib 400 mg	35	0.83	1.11*	1.66*	1.89*	1.66*
Naproxen Sodium 550 mg	35	1.34*	1.80*	2.49*	1.89*	2.49*
Pain Intensity Difference (PID) - Categorical Mean Score						
Placebo	50	0.08	0.14	0.04	-0.08	-0.08
Celecoxib 50 mg	35	0.20	0.31	0.49*	0.29*	0.20
Celecoxib 100 mg	50	0.34	0.56*	0.78*	0.72*	0.56*
Celecoxib 200 mg	50	0.40	0.60*	0.84*	0.74*	0.70*
Celecoxib 400 mg	35	0.23	0.43	0.66*	0.77*	0.74*
Naproxen Sodium 550 mg	35	0.51*	0.77*	1.26*	0.91*	0.60*
Pain Intensity Difference and Pain Relief (PRID) - Categorical Mean Score						
Placebo	50	0.58	0.68	0.52	0.24	0.24
Celecoxib 50 mg	35	1.06	1.37	1.74*	1.20*	0.91
Celecoxib 100 mg	50	1.18	1.76*	2.36*	2.14*	1.76*
Celecoxib 200 mg	50	1.24	1.74*	2.48*	2.10*	1.98*
Celecoxib 400 mg	35	1.06	1.54*	2.31*	2.66*	2.60*
Naproxen Sodium 550 mg	35	1.86*	2.57*	3.74*	2.80*	2.03*

* Significantly different from placebo; p<0.05.

Celecoxib at doses of 100 and 200 mg was associated with a significantly longer duration of effect when compared to placebo in two or more of the post-oral surgery pain studies (Table 27). The median Time to Rescue Medication was longer with higher doses of celecoxib; however, no statistically significant differences were detected between the 100, 200, and 400 mg treatment groups or the distribution of time to rescue medication. The Median Times to Onset of Perceptible Pain Relief for Studies 025, 027, and 070 are also shown in Table 27. Statistically significant differences were observed for celecoxib 50 mg (Study 025), 100 mg (Study 027) and 200 mg (Studies 025 and 027).

Table 27. Temporal Primary Efficacy Variables: Studies 025, 027, and 070

Efficacy Assessment	Study 025		Study 027		Study 070	
	N	Median Time	N	Median Time	N	Median Time
Time to Rescue Medication						
Placebo	50	01:17	55	01:20	50	01:06
Celecoxib 25 mg	50	01:32	-	-	-	-
Celecoxib 50 mg	50	01:48*	-	-	35	01:41*
Celecoxib 100 mg	-	-	55	04:17*	50	02:36*
Celecoxib 200 mg	50	03:05*	56	10:02*	50	04:15*
Celecoxib 400 mg	-	-	-	-	35	08:13*
Ibuprofen 400 mg	50	07:00*	-	-	-	-
Naproxen Sodium 550 mg	-	-	54	>24:00*	35	07:00*
Time to Perceptible Pain Relief						
Placebo	50	>24:00	55	00:58	50	>24:00
Celecoxib 25 mg	50	00:53	-	-	-	-
Celecoxib 50 mg	50	01:05*	-	-	35	00:42
Celecoxib 100 mg	-	-	55	00:45	50	00:39
Celecoxib 200 mg	50	00:38*	56	00:30*	50	00:44
Celecoxib 400 mg	-	-	-	-	35	00:43
Ibuprofen 400 mg	50	00:33*	-	-	-	-
Naproxen Sodium 550 mg	-	-	54	00:24*	35	00:36

* Significantly different from placebo based on log rank test as in Fisher's Protected LSD; p<0.05.

5.3.1.2 Supportive Study: Study 005

Study 005 was a single-center, single-dose, randomized, placebo-controlled, single-blind, parallel group study designed to investigate the safety and analgesic efficacy of celecoxib in patients who had undergone surgical third molar extraction. Following dental surgery, patients experiencing moderate to severe pain received a single dose of celecoxib 100 mg, celecoxib 400 mg, aspirin 650 mg, or placebo.

A total of 50 patients per treatment group (200 total) were enrolled into the study all of whom received treatment and were included in the ITT cohort. For the three categorical primary measures of efficacy (PID, PR, and PRID) single oral doses of celecoxib at dose

levels of 100 and 400 mg provided statistically superior pain relief compared to placebo at all postdose assessment times after 0.5 hours. Similar responses were observed in aspirin-treated patients. Statistically significant differences were noted between aspirin and celecoxib at various timepoints, generally favoring aspirin up to 1 hour and favoring celecoxib between three and four hours after dosing. Median Time to Rescue was statistically significantly better for the celecoxib 100, and 400 mg treatment groups compared to placebo. Aspirin was also statistically superior to placebo for this temporal endpoint.

5.3.2 Post-Orthopedic Surgery Study: Study 028

5.3.2.1 Pivotal Study

5.3.2.1.1 Population and Design

Study 028 was a multicenter, multiple dose, double-blind, placebo-controlled, randomized, parallel group study designed to compare the analgesic efficacy of celecoxib 100 and 200 mg PRN up to BID to propoxyphene napsylate 100 mg with acetaminophen 650 mg (two Darvocet-N® 50) PRN up to QID, and placebo in post-orthopedic surgery patients with moderate to severe pain.

Patients were eligible to participate in the study if they had undergone orthopedic surgery involving a total or partial reconstruction procedure of the hip or knee or a major orthopedic procedure requiring open manipulation of bone with periosteal elevation.

The Treatment Period was defined as up to a five day period after the first dose of study medication. Patients received the second dose of study medication not less than four hours after the first dose of study medication. Subsequent doses of study medication were administered as needed, no closer than two hours apart, and could not exceed four doses in 24 hours. In the celecoxib groups, only the first two doses were active, doses three and four were matching placebo. In contrast, all four doses of Darvocet-N 50 (2 tablets) were active.

5.3.2.1.2 Description of Efficacy Scales Used

Primary measures of efficacy were (24):

- Time-Specific PID (Categorical)
- PR

- PRID
- Time to Rescue Medication or Remedication

Although the duration of treatment was up to five days and patients assessed pain at Baseline (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18 and 24 hours postdose (using self-rating scales), the primary analyses emphasized the first eight hours after the first dose was taken, in order to determine the efficacy response to a single dose. A secondary objective of this study was to compare the efficacy of celecoxib with placebo for the remainder of the first 24-hour period after dosing. The 24-hour analysis focused on multiple dose data.

5.3.2.1.3 Patient Disposition

A total of 246 patients were randomized and included in the ITT cohort. Three patients completed the 5-day study; the majority of patients were withdrawn for treatment failure.

5.3.2.1.4 Patient Characteristics

Baseline demographics for Study 028 are presented in Table 28. There were no meaningful differences across treatment groups in age, race, or gender.

Table 28. Baseline Demographic Characteristics for Post-Orthopedic Surgery Patients: Study 028

Baseline Demographic Characteristic	Number of Postsurgical Patients by Treatment Group(a)			
	Placebo (N=60)	Celecoxib		Darvocet-N
		100 mg BID PRN (N=68)	200 mg BID PRN (N=62)	100 mg QID PRN (N=65)
Age (years)				
Mean (Std Dev)	52.2 (16.52)	55.7 (16.35)	59.0 (16.10)	56.4 (15.73)
Range	23-87	19-82	21-86	27-84
Race/Ethnic Origin				
Caucasian/Hispanic N (%)	53 (88%)	63 (92%)	61 (98%)	57 (88%)
Black N (%)	7 (12%)	3 (4%)	1 (2%)	5 (8%)
Other N (%)	0 (0%)	2 (3%)	0 (0%)	3 (5%)
Gender				
Female N (%)	30 (50%)	31 (46%)	28 (45%)	29 (45%)

a) Table includes nine patients who were randomized but were excluded from the ITT cohort.

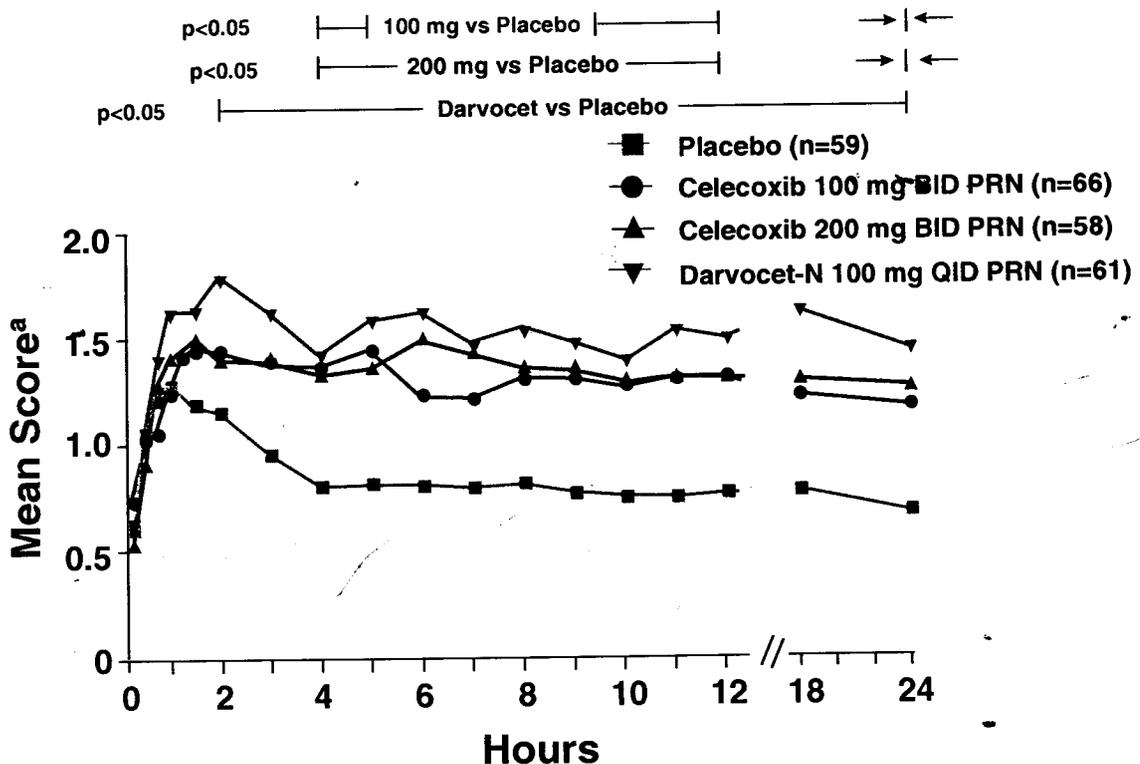
5.3.2.1.5 Efficacy and Dose Response

The results of the single-dose analyses demonstrate that, for all categorical primary measures of efficacy (PID, PR, PRID) over the first eight hours, celecoxib 100 mg and celecoxib 200 mg were numerically superior to placebo in providing relief from post-surgical pain at all timepoints after 0.5 hours (except 100 mg at 1 hour for PID) (data not

shown). There were isolated instances within some, but not all, measures in which celecoxib 100 or 200 mg was statistically significant when compared to placebo. The sensitivity to detect statistically significant differences in treatment effect from placebo was limited by the unexpectedly large placebo response at the early assessment times.

In the multiple dose analyses which continued up through the 24-hour timepoint, analgesic efficacy of multiple doses of celecoxib was indicated by the numerically greater mean PID (Categorical Scale), PR, and PRID scores for both the 100 and 200 mg BID PRN treatment groups, compared to placebo, at all timepoints from 0.75 hours to 24.0 hours (Figure 18 and Table 29). These differences were statistically significant at most assessment times from 4.0 hours through 24.0 hours for the celecoxib 200 mg BID PRN treatment group compared to placebo. Statistically significant differences favoring the celecoxib 100 mg BID PRN treatment group over placebo were also noted for mean PR after the 4.0 hour timepoint.

Figure 18. Pain Relief (Multiple Dose Analysis): Study 028



a) Scale ranges from 0 (none) to 4 (complete).

Table 29. Results of Categorical Primary Efficacy Analyses (Multiple Dose Analysis): Study 028

Efficacy Assessment	N	Time Postdose (Hours)						
		1	2	4	8	12	18	24
Pain Relief (PR) - Categorical Mean Score								
Placebo	59	1.25	1.10	0.77	0.78	0.73	0.74	0.64
Celecoxib 100 mg BID PRN	66	1.39	1.42	1.34*	1.26	1.28*	1.18	1.13*
Celecoxib 200 mg BID PRN	58	1.41	1.40	1.33*	1.36*	1.31*	1.30	1.26*
Darvocet-N 100 mg QID PRN	61	1.63	1.74*	1.40*	1.47*	1.44*	1.58*	1.34*
Pain Intensity Difference (PID) - Categorical Mean Score								
Placebo	59	0.50	0.44	0.19	0.19	0.15	0.17	0.12
Celecoxib 100 mg BID PRN	66	0.46	0.49	0.39	0.38	0.36	0.31	0.21
Celecoxib 200 mg BID PRN	58	0.66	0.63	0.50	0.57*	0.53*	0.57*	0.48*
Darvocet-N 100 mg QID PRN	60	0.80*	0.92*	0.69*	0.68*	0.65*	0.70*	0.55*
Pain Intensity Difference and Pain Relief (PRID) - Categorical Mean Score								
Placebo	59	1.75	1.54	0.96	0.97	0.88	0.91	0.76
Celecoxib 100 mg BID PRN	66	1.85	1.91	1.73	1.64	1.64	1.48	1.34
Celecoxib 200 mg BID PRN	58	2.07	2.03	1.83*	1.93*	1.85*	1.88*	1.74*
Darvocet-N 100 mg QID PRN	61	2.43	2.66*	2.09*	2.15*	2.09*	2.28*	1.89*

* Significantly different from placebo; p<0.05.

The Time to Rescue Medication or Remedication is displayed in Table 30. Median Time to Rescue Medication or Remedication after the first dose of study medication was longer in both celecoxib treatment groups compared to placebo but the difference was only statistically significant for the 100 mg BID group. Additional evidence of the analgesic efficacy of the celecoxib multiple dose regimen was provided by the proportion of patients who remained in the study 24 hours after the first dose. The proportion of patients remaining in the study at the 24-hour timepoint was similar for the three active treatment groups in contrast to the placebo group which had fewer patients than all active treatment groups at 24 hours (Table 30). These results indicate that celecoxib doses of 100 or 200 mg, administered as needed every 4-6 hours up to a maximum daily dose of 400 mg are efficacious in the management of pain.

Table 30. Variables Indicating Effect of Dose Regimen: Study 028

Time to Rescue Medication or Remedication (a)		
	N	Median Time (Hours : Minutes)
Placebo	59	03:33
Celecoxib 100 mg BID PRN	67	04:01*
Celecoxib 200 mg BID PRN	58	03:52
Darvocet-N 100 mg QID PRN	62	04:05*
Proportion of Patients Remaining in this Study at 24 Hours After the First Dose (b)		
	N	Patients
Placebo	59	4/59 (7%)
Celecoxib 100 mg BID PRN	67	16/67 (24%)*
Celecoxib 200 mg BID PRN	58	11/58 (19%)
Darvocet-N 100 mg QID PRN	62	17/62 (27%)*

* Significantly different from placebo; p<0.05.

a) Statistical significance calculated by Log Rank Test.

b) Statistical significance calculated by Fisher's Exact Test.

5.3.3 Post-General Surgery Study: Study 029

Study 029 was a multicenter, multiple dose, double-blind, placebo-controlled, randomized, parallel group study designed to compare the analgesic effect of celecoxib 100 mg BID PRN and celecoxib 200 mg BID PRN to propoxyphene napsylate 100 mg with acetaminophen 650 mg (two Darvocet-N® 50) QID PRN, and placebo in post-general (non-orthopedic) surgery patients with moderate to severe pain.

An interim analysis was performed on this study by an independent Data Monitoring Committee to evaluate the validity of the pain model. The analysis did not show differences between Darvocet-N 100 mg QID PRN or celecoxib at either dose and placebo sufficient to validate the model. Therefore, the Committee recommended cessation of the trial.

5.3.4 Analgesia Data from OA and RA Studies

5.3.4.1 Study Populations and Designs

Data from the pivotal arthritis trials, five in OA (Studies 020, 021, 054, 060, and 087) and two in RA (022 and 023) were analyzed in order to further assess celecoxib's efficacy in the management of pain. This analysis of pain management incorporated the results of primary and secondary efficacy endpoints specifically indicative of pain relief.

5.3.4.2 Description of the Efficacy Scales Used

Pain-specific primary and secondary efficacy endpoints from the OA and RA trials were combined for analysis to assess celecoxib's efficacy in an additional pain model.

For this summary, one measure of arthritis pain was selected for each type of trial. However, the measure selected was representative of the consistent analgesic response seen with all other pain measures that were used. The display of efficacy in OA pain is based on the APS Pain Measure, (20) and efficacy in RA pain is demonstrated based on the Patient's Assessment of Arthritis Pain - VAS. (15)

The APS Pain Measure consisted of five questions that assess the intensity and duration of pain experienced by patients (Table 31). The first question required a yes or no response. The remaining questions required rating the pain and its interference with daily activities on a scale of 0 (no pain) to 10 (worst pain possible). Patients completed the APS Pain Measure at Baseline and daily, thereafter, for the first seven days of dosing with study medication.

Table 31. APS Pain Scale

	Question	Scale
1	Have you experienced any pain in the past 24 hours?	yes/no
2	How much pain are you having right now?	0-10
3	Indicate the worst pain you have had in the past 24 hours.	0-10
4	Indicate the average level of pain you have had in the past 24 hours.	0-10
5	Indicate how pain has interfered with you in:	
	● General Activity	0-10
	● Mood	0-10
	● Walking Ability	0-10
	● Relations with other People	0-10
	● Sleep	0-10
	● Normal Work, Including Housework	0-10
	● Enjoyment of Life	0-10

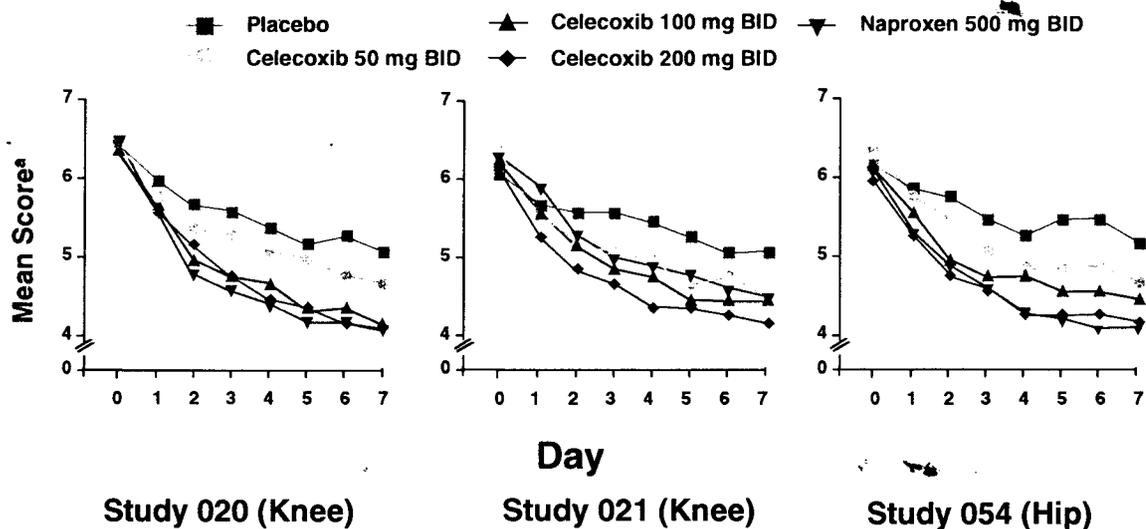
The Patient's Assessment of Arthritis Pain - VAS was performed for patient-identified "Index Joints." Patients assessed the amount of arthritis pain in the "Index Joint" on a 100 mm line VAS with the 0 mm point indicating no pain and 100 mm point indicating very severe pain.

5.3.4.3 Efficacy and Dose Response

5.3.4.3.1 Pain Analyses in Patients with OA: Studies 020, 021 and 054

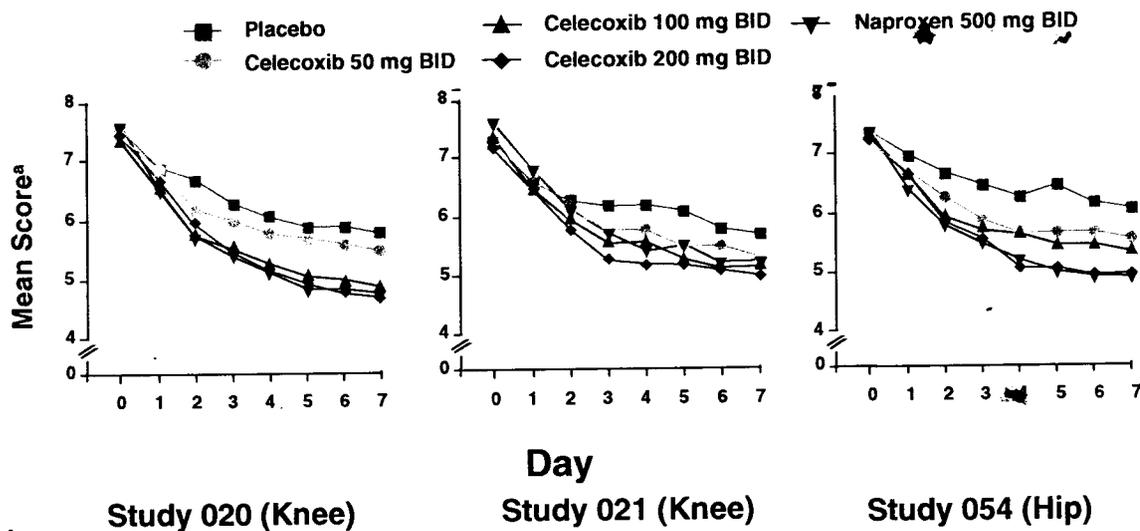
The APS Pain Measure was used to assess acute analgesic activity of celecoxib in patients with OA flare in Studies 020, 021, and 054. The results of this analysis as represented by the results of the questions “Indicate the average level of pain you have had in the past 24 hours” and “Indicate the worst pain you have had in the past 24 hours” are presented graphically, in Figures 19 and 20 and Tables 32 and 33.

**Figure 19. APS Pain Measure - Average Pain in Last 24 Hours:
 12-Week Pivotal OA Studies 020, 021 and 054**



a) Scale ranges from 0 (no pain) to 10 (worst pain possible)

**Figure 20. APS Pain Measure - Worst Pain in Last 24 Hours:
 12-Week OA Studies 020, 021 and 054**



a) Scale ranges from 0 (no pain) to 10 (worst pain possible)

The results of all five components of the APS Pain measure were similar. For four of the APS Pain Measure questions, celecoxib 100 and 200 mg BID were statistically significantly superior compared to placebo within 24 to 48 hours of the first dose of study medication and continuing through Day 7. For the question "Have you experienced any pain in the past 24 hours?", significantly more patients in the celecoxib 100 mg BID and 200 mg BID treatment groups answered "no" compared to the placebo group on some, but not all, of the days during the one-week assessment period in Studies 020 and 021 and only on Day 7 in Study 054.

Table 32. APS Pain Measure - Average Pain in the Past 24 Hours: 12-Week Pivotal OA Studies 020, 021 and 054

Treatment Group	N	Baseline Mean(a)	Observed Mean by Observation Day						
			1	2	3	4	5	6	7
Study 020									
Placebo	145	6.4	5.9	5.6	5.5	5.3	5.1	5.2	5.0
Celecoxib 50 mg BID	142	6.4	5.7	5.3*	5.2	5.0	4.9	4.7	4.6
Celecoxib 100 mg BID	143	6.3	5.6	4.9*	4.7*	4.6*	4.3*	4.3*	4.1*
Celecoxib 200 mg BID	141	6.4	5.5	5.1*	4.7*	4.4*	4.3*	4.1*	4.0*
Naproxen 500 mg BID	144	6.4	5.5	4.7*	4.5*	4.3*	4.1*	4.1*	4.0*
Study 021									
Placebo	169	6.0	5.6	5.5	5.5	5.4	5.2	5.0	5.0
Celecoxib 50 mg BID	170	6.3	5.5*	5.1*	5.0*	4.9*	4.6*	4.7*	4.4*
Celecoxib 100 mg BID	165	6.2	5.5*	5.1	4.8*	4.7*	4.4*	4.4*	4.4*
Celecoxib 200 mg BID	159	6.1	5.2*	4.8*	4.6*	4.3*	4.3*	4.2*	4.1*
Naproxen 500 mg BID	169	6.2	5.8	5.2*	4.9*	4.8*	4.7*	4.5*	4.4*
Study 054									
Placebo	211	6.1	5.8	5.7	5.4	5.2	5.4	5.4	5.1
Celecoxib 50 mg BID	210	6.3	5.7	5.4*	5.0*	4.8*	4.8*	4.8*	4.6*
Celecoxib 100 mg BID	205	6.1	5.5*	4.9*	4.7*	4.7*	4.5*	4.5*	4.4*
Celecoxib 200 mg BID	202	5.9	5.2*	4.7*	4.5*	4.2*	4.2*	4.2*	4.1*
Naproxen 500 mg BID	202	6.0	5.2*	4.8*	4.5*	4.2*	4.1*	4.0*	4.0*

* Significantly different from placebo; p<0.05.

a) Based on a scale of 0-10.

Table 33. APS Pain Measure - Worst Pain in the Past 24 Hours: 12-Week Pivotal OA Studies 020, 021 and 054

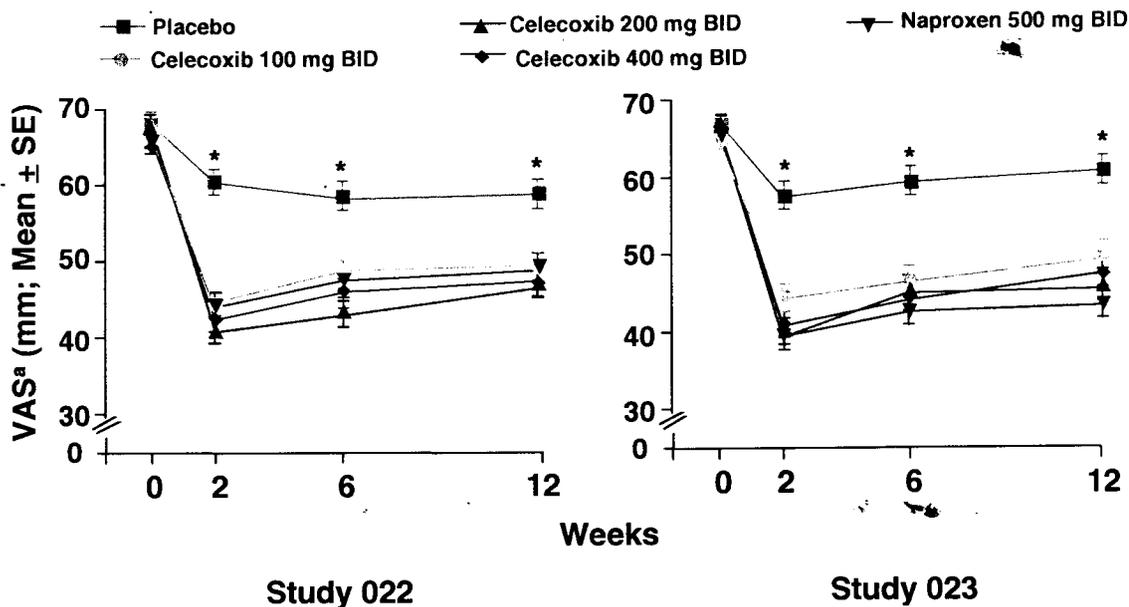
Treatment Group	N	Baseline Mean(a)	Observed Mean by Observation Day						
			1	2	3	4	5	6	7
Study 020									
Placebo	144	7.5	6.8	6.6	6.2	6.0	5.8	5.8	5.7
Celecoxib 50 mg BID	140	7.4	6.8	6.1	5.9	5.7	5.6	5.5	5.4
Celecoxib 100 mg BID	143	7.3	6.5	5.7*	5.5*	5.3*	5.0*	4.9*	4.8*
Celecoxib 200 mg BID	142	7.4	6.6	5.9*	5.4*	5.1*	5.0*	4.7*	4.6*
Naproxen 500 mg BID	144	7.5	6.4*	5.6*	5.3*	5.0*	4.7*	4.7*	4.6*
Study 021									
Placebo	170	7.2	6.5	6.2	6.1	6.1	6.0	5.7	5.6
Celecoxib 50 mg BID	172	7.5	6.7	6.0	5.7*	5.7*	5.4*	5.4*	5.2
Celecoxib 100 mg BID	165	7.3	6.4	5.9	5.5*	5.5*	5.2*	5.1*	5.1*
Celecoxib 200 mg BID	159	7.1	6.4	5.7	5.2*	5.1*	5.1*	5.0*	4.9*
Naproxen 500 mg BID	169	7.5	6.7	6.0	5.6*	5.3*	5.4*	5.1*	5.1*
Study 054									
Placebo	211	7.3	6.9	6.6	6.4	6.2	6.4	6.1	6.0
Celecoxib 50 mg BID	211	7.2	6.6	6.2*	5.8*	5.6*	5.6*	5.6*	5.5*
Celecoxib 100 mg BID	205	7.3	6.6*	5.9*	5.7*	5.6*	5.4*	5.4*	5.3*
Celecoxib 200 mg BID	206	7.2	6.6*	5.8*	5.5*	5.0*	5.0*	4.9*	4.9*
Naproxen 500 mg BID	202	7.3	6.3*	5.7*	5.4*	5.1*	4.9*	4.8*	4.8*

* Significantly different from placebo; p<0.05.

a) Based on a scale of 0-10.

5.3.4.3.2 *Pain Analyses in Patients with Rheumatoid Arthritis: Studies 022 and 023*
 Patient's Assessment of Pain (VAS) was used to assess the effects of celecoxib in patients with RA flare in Studies 022 and 023. As shown in Figure 21, all doses of celecoxib provided statistically significant reductions in pain compared to placebo by the Week 2 assessment and continuing through Week 12 in each of the 12-Week pivotal studies.

Figure 21. Patient's Assessment of Arthritis Pain - VAS: 12-Week Pivotal RA Studies 022 and 023



* Significantly different from all other treatments; p < 0.05
 a) Visual analog scale ranges from 0 (no pain) to 100 mm (most severe pain)

5.3.5 Conclusions

Based on the results of controlled trials in postsurgical pain, OA, and RA, it is concluded that:

- Evidence of the efficacy of celecoxib in alleviating pain was replicated in well-controlled clinical trials.
- For postsurgical pain:
 - Single doses of celecoxib of 100 mg, 200 mg, and 400 mg were efficacious.
 - Although 100 mg and 200 mg were similar in efficacy, some patients may derive additional benefit from the 200 mg dose.

- Celecoxib 100 mg or 200 mg administered as needed every 4-6 hours up to a maximum total daily dose of 400 mg was efficacious in the management of pain.
- Replicate well-controlled OA and RA trials confirmed the efficacy of celecoxib in the management of pain.

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6.0 CLINICAL SAFETY

6.1 Gastrointestinal Differentiation

6.1.1 Overview

As a specific inhibitor of COX-2, celecoxib was hypothesized to have anti-inflammatory and analgesic efficacy through COX-2 inhibition in the absence of deleterious GI effects resulting from COX-1 inhibition. To test this hypothesis, the effects of celecoxib on the GI tract were studied in prospective clinical trials. The focus was on two outcomes that are considered to be the most relevant in assessing GI mucosal toxicity: development of gastroduodenal ulcers, and occurrence of clinically significant upper gastrointestinal (UGI) events. The initiatives included 1) six clinical studies to determine the ulceration rate associated with celecoxib at therapeutic and suprathreshold doses in comparison to NSAIDs and placebo (Table 34), and 2) a rigorous monitoring program to identify clinically significant UGI events in studies of arthritis patients receiving both therapeutic and suprathreshold doses of celecoxib.

Table 34. Summary of Celecoxib GI Differentiation Studies

Study No. - Population	Duration	No. of Patients	Treatments
021 - Knee OA Flare	12 weeks	1215	Celecoxib 50, 100, or 200 mg BID; naproxen 500 mg BID; or placebo
022 - RA Flare	12 weeks	1149	Celecoxib 100, 200, or 400 mg BID; naproxen 500 mg BID; or placebo
041 - RA	24 weeks	655	Celecoxib 200 mg BID or diclofenac SR 75 mg BID
062 - OA or RA	12 weeks	537	Celecoxib 200 mg BID or naproxen 500 mg BID
071 - OA or RA	12 weeks	1099	Celecoxib 200 mg BID, diclofenac 75 mg BID, or ibuprofen 800 mg TID
014 - Healthy Subjects	7 days	128	Celecoxib 100 or 200 mg BID, naproxen 500 mg BID, or placebo

6.1.2 12-Week and 24-Week Endoscopy Studies

Five randomized, double-blind, endoscopy studies were performed with OA or RA patients receiving celecoxib or an NSAID. Two of the studies (Studies 021 and 022) also included a placebo group and served as pivotal efficacy trials.

- In four studies, a Baseline endoscopy was performed (Studies 021, 022, 062, and 071). In these studies, patients with a gastric or duodenal ulcer were excluded from study participation. In the fifth study (Study 041) Baseline endoscopy was not performed and only patients enrolled at preselected sites underwent endoscopy during treatment.

Selection of the sites that performed endoscopy was determined by the feasibility of performing endoscopies.

For all endoscopies, the gastric and duodenal mucosae were examined and graded separately. In the ulcer analyses, a patient was counted as having a gastroduodenal ulcer if either a gastric or duodenal ulcer (or both) was present. The studies employed varying endoscopy schedules. In Studies 021 and 022, endoscopy was performed at Baseline and at the end of 12 weeks of treatment. Studies 062 and 071 employed a multiple endoscopy design in which endoscopy was performed at Baseline and after four, eight, and 12 weeks of treatment. In Study 041, endoscopy was performed after 24 weeks of treatment. In addition to the scheduled endoscopies, patients withdrawing from any of these studies before completion were asked to undergo a final endoscopy at the time of withdrawal. Further, an endoscopy could have been performed at any time "for cause" (e.g., if a patient experienced GI symptoms). For calculating ulcer incidences, the denominator was the number of patients undergoing endoscopy at the scheduled time plus the number of patients who were found to have an ulcer at any endoscopy.

6.1.2.1 Studies with Baseline and 12-Week Endoscopy: Studies 021 and 022

The incidence of risk factors for gastroduodenal ulceration such as history of GI bleeding or ulceration, history of cardiovascular disease, positive *H. pylori* serology, or low dose aspirin use (≤ 325 mg/day) for patients enrolled in Studies 021 and 022 are shown in Table 35. Table 36 shows the baseline endoscopy scores. The distribution of scores was similar across treatment groups. More than 50% of the patients had normal gastric and duodenal mucosa and no patients had an ulcer.

Table 35. Demographics, Medical History, Baseline *H. pylori* Status, and Aspirin Use: Studies 021 and 022

Study 021	Placebo (N=247)	Celecoxib(BID Dose)				Naproxen 500 mg BID (N=233)
		50 mg (N=258)	100 mg (N=240)	200 mg (N=237)	400 mg	
Mean Age	61.1	60.8	61.8	61.2		62.5
% Female	69	65	68	70		68
History of GI Bleeding	9 (4%)	6 (2%)	9 (4%)	3 (1%)		3 (1%)
History of Gastroduodenal Ulcer	48 (19%)	40 (16%)	37 (15%)	36 (15%)	Dose not included in the study	42 (18%)
History of Cardiovascular Disease	161 (65%)	153 (59%)	137 (57%)	137 (58%)		147 (63%)
<i>H. pylori</i> Positive Serology	85 (35%)	103 (41%)	79 (33%)	87 (38%)		87 (39%)
Aspirin Use (≤325 mg/day)	35 (14%)	31 (12%)	32 (13%)	38 (16%)		39 (17%)
Study 022	(N=231)	-	(N=240)	(N=235)	(N=218)	(N=225)
Mean Age	54.1		54.4	54.7	54.1	54.6
% Female	73		74	73	72	72
History of GI Bleeding	6 (3%)		6 (3%)	4 (2%)	3 (1%)	4 (2%)
History of Gastroduodenal Ulcer	31 (13%)	Dose not included in the study	43 (18%)	38 (16%)	30 (14%)	33 (15%)
History of Cardiovascular Disease	105 (45%)		112 (47%)	104 (44%)	86 (39%)	95 (42%)
<i>H. pylori</i> Positive Serology	78 (34%)		77 (32%)	75 (32%)	50 (23%)	56 (25%)
Aspirin Use (≤325 mg/day)	19 (8%)		24 (10%)	26 (11%)	14 (7%)	19 (8%)

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Table 36. Baseline Endoscopy Scores(a): Studies 021 and 022

Endoscopy Score(b) Study 021	Placebo (N=247)	Celecoxib(BID Dose)				Naproxen 500 mg BID (N=233)
		50 mg (N=258)	100 mg (N=240)	200 mg (N=237)	400 mg -	
Gastric						
0 (no visible lesions)	130 (53%)	150 (58%)	145 (60%)	143 (60%)	Dose not included in the study	144 (61%)
1 (1-10 petechiae)	34 (14%)	24 (9%)	30 (13%)	21 (9%)		23 (10%)
2 (>10 petechiae)	5 (2%)	12 (5%)	4 (2%)	12 (5%)		4 (2%)
3 (1-5 erosions)	55 (22%)	58 (22%)	46 (19%)	41 (17%)		54 (23%)
4 (6-10 erosions)	21 (9%)	14 (5%)	15 (6%)	20 (8%)		11 (5%)
5 (11-25 erosions)	2 (<1%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)
Duodenal						
0 (no visible lesions)	208 (84%)	213 (83%)	212 (88%)	207 (87%)	Dose not included in the study	205 (88%)
1 (1-10 petechiae)	12 (5%)	17 (7%)	12 (5%)	19 (8%)		8 (3%)
2 (>10 petechiae)	2 (<1%)	7 (3%)	2 (<1%)	5 (2%)		4 (2%)
3 (1-5 erosions)	24 (10%)	20 (8%)	11 (5%)	6 (3%)		14 (6%)
4 (6-10 erosions)	1 (<1%)	1 (<1%)	3 (1%)	0 (0%)		2 (<1%)
5 (11-25 erosions)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)
Study 022	(N=231)	-	(N=240)	(N=235)	(N=218)	(N=225)
Gastric						
0 (no visible lesions)	134 (58%)	Dose not included in the study	144 (60%)	136 (58%)	117 (54%)	124 (55%)
1 (1-10 petechiae)	28 (12%)		21 (9%)	33 (14%)	30 (14%)	22 (10%)
2 (>10 petechiae)	2 (<1%)		2 (<1%)	6 (3%)	4 (2%)	7 (3%)
3 (1-5 erosions)	58 (25%)		59 (25%)	46 (20%)	48 (22%)	53 (24%)
4 (6-10 erosions)	9 (4%)		14 (6%)	13 (6%)	18 (8%)	19 (8%)
5 (11-25 erosions)	0 (0%)		0 (0%)	1 (<1%)	1 (<1%)	0 (0%)
Duodenal						
0 (no visible lesions)	199 (86%)	Dose not included in the study	215 (90%)	200 (85%)	187 (86%)	193 (86%)
1 (1-10 petechiae)	7 (3%)		11 (5%)	12 (5%)	15 (7%)	13 (6%)
2 (>10 petechiae)	3 (1%)		2 (<1%)	4 (2%)	2 (<1%)	2 (<1%)
3 (1-5 erosions)	21 (9%)		11 (5%)	16 (7%)	13 (6%)	13 (6%)
4 (6-10 erosions)	1 (<1%)		1 (<1%)	3 (1%)	1 (<1%)	4 (2%)
5 (11-25 erosions)	0 (0%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)

a) Number of patients (%)

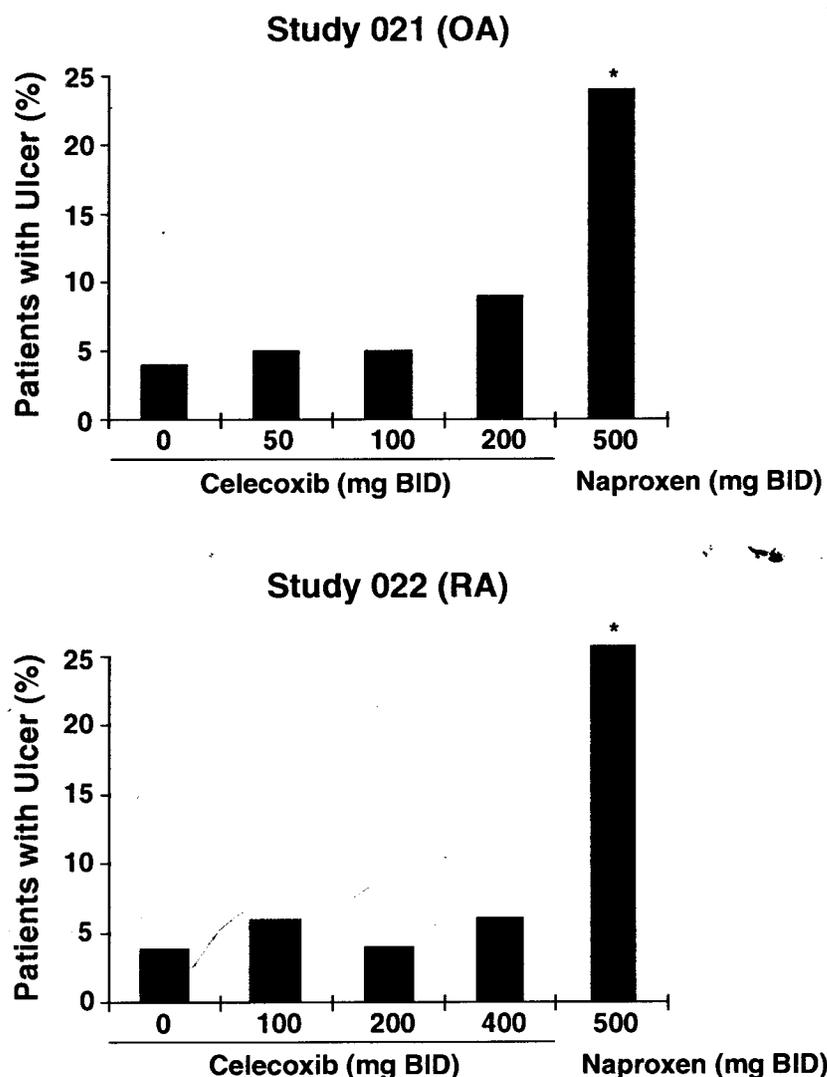
b) Endoscopy Scoring Scale ranged from 0 to 7. A score of 6 was >25 erosions and a score of 7 was an ulcer. An erosion was defined as any break in the mucosa without depth. An ulcer was defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth.

Figure 22 shows the gastroduodenal ulceration incidences in Studies 021 and 022. Table 37 summarizes the gastroduodenal results as well as showing the incidences of gastric and duodenal ulcer separately. Over the 12-week treatment period, gastroduodenal ulcer incidences for placebo were consistent between these two studies at 4%. Gastroduodenal ulcer incidences for celecoxib 50 mg BID through 400 mg BID were almost identical among dose groups and similar to placebo. In contrast, incidences of gastroduodenal ulcers over the 12 weeks of these studies for naproxen were markedly higher than those for celecoxib or placebo.

None of the differences in gastroduodenal ulcer incidence between placebo and celecoxib, at any dose, was statistically significant in these two studies, nor were there statistical differences among celecoxib doses. In contrast, all gastroduodenal ulcer

incidences were statistically significantly higher for naproxen than for placebo or celecoxib at all doses. Comparisons of the gastric and duodenal ulcer results separately yielded the same statistical results with the exception that the duodenal ulcer incidences were not statistically significantly different between celecoxib 100 mg (2%) and naproxen (6%) in Study 022.

Figure 22. Gastroduodenal Ulcer Incidences in 12-Week Studies with Baseline and 12-Week Endoscopy: Studies 021 and 022



* Significantly different from all other treatments; $p < 0.001$.

Table 37. Ulcer Incidences: Studies 021 and 022

Study	Placebo	Celecoxib				Naproxen 500 mg BID
		50 mg BID	100 mg BID	200 mg BID	400 mg BID	
Gastroduodenal						
021	4 (4/106)	5 (8/164)	5 (7/155)	9 (13/150)	-	23 (34/146)*
022	4 (4/99)	-	6 (9/148)	4 (6/145)	6 (8/130)	26 (36/137)*
Gastric						
021	4 (4/106)	5 (8/164)	5 (7/155)	7 (10/148)	-	18 (25/141)*
022	3 (3/99)	-	4 (6/147)	3 (4/144)	5 (7/130)	22 (29/134)*
Duodenal						
021	0 (0/104)	0 (0/158)	0 (0/151)	2 (3/148)	-	8 (11/140)*
022	1 (1/97)	-	2 (3/147)	1 (2/144)	<1 (1/129)	6 (8/128)**

* Significantly different from all other treatments; p<0.05.

** Significantly different from placebo and celecoxib 200 and 400 mg BID; p<0.05.

Entries are % of patients with ulcer (No. with ulcer/ No. with known result). Known endoscopy results include an ulcer detected at any time, or a finding of no ulcer at an endoscopy performed at 84 ±7 days.

6.1.2.2 24-Week Endoscopy Study: Study 041

In Study 041, patients with RA were treated with celecoxib 200 mg BID or diclofenac SR 75 mg BID for 24 weeks. Four hundred thirty patients (approximately 66% of the total enrolled) underwent UGI endoscopy at the final visit. Demographics, relevant medical history, and the incidence of positive *H. pylori* serology are shown in Table 38.

Table 38. Demographics, Medical History, and *H. pylori* Status(a): Study 041

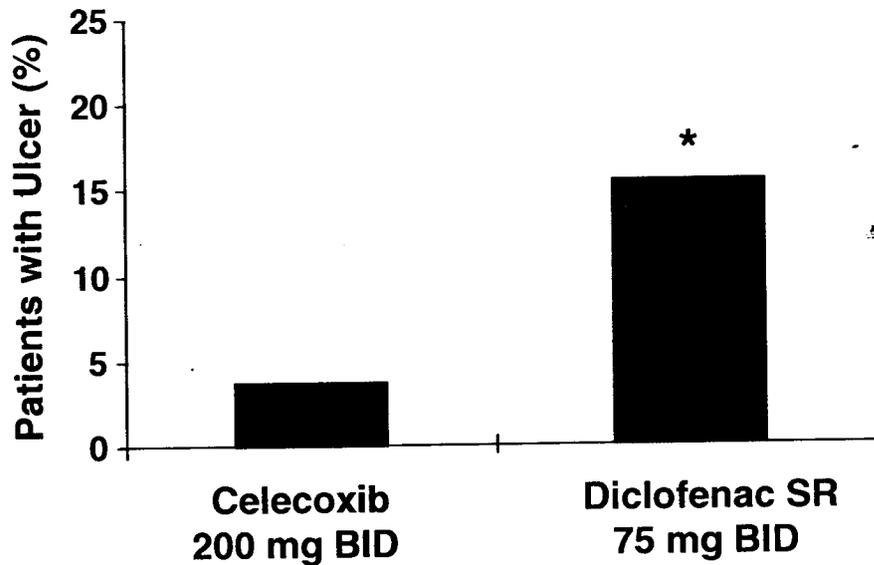
	Celecoxib 200 mg BID (N=326)	Diclofenac SR 75 mg BID (N=329)
Mean Age	55.9	54.5
% Female	76	71
History of GI Bleeding	4 (1%)	1 (<1%)
History of Gastroduodenal Ulcer	28 (9%)	27 (8%)
History of Cardiovascular Disease	83 (25%)	78 (24%)
<i>H. pylori</i> Positive Serology	122 (37%)	124 (38%)
Aspirin Use (≤325 mg/day)	5 (1.5%)	5 (1.5%)

a) Determined at time of endoscopy; N=212 for celecoxib and N=218 for diclofenac SR

Figure 23 shows the gastroduodenal ulceration incidences in this study, and Table 39 shows the gastroduodenal, gastric, and duodenal ulcer incidences. All ulcer incidences were statistically significantly lower for celecoxib than for diclofenac. The 4% gastroduodenal ulcer incidence for celecoxib 200 mg BID was similar to that observed for the same celecoxib dose in the 12-Week studies (Studies 021 and 022) and to the placebo incidence seen in those studies. The 15% incidence for diclofenac was consistent with results of previous endoscopy studies involving diclofenac. (2,25) The differences

in ulcer incidences between the two treatment groups were statistically significant in all three comparisons of gastroduodenal ulcers, gastric ulcers, and duodenal ulcers.

Figure 23. Gastroduodenal Ulcer Incidences in the 24-Week Endoscopy Study: Study 041



* Significantly different from celecoxib; p<0.001.

Table 39. Ulcer Incidences: Study 041

Endoscopy Result	Celecoxib 200 mg BID	Diclofenac SR 75 mg BID
Gastroduodenal	4 (8/212) *	15 (33/218)
Gastric	2 (5/212) *	11 (24/218)
Duodenal	2 (4/212) *	7 (15/217)

* Significantly different from diclofenac; p<0.05.

Entries are % of patients with ulcer (No. of patients with ulcer/total patients).

6.1.2.3 Serial Endoscopy Studies; Studies 062 and 071

Demographics, relevant medical history, and the incidence of positive *H. pylori* serology or low dose aspirin use for the serial endoscopy studies (Studies 062 and 071) are shown in Table 40. Table 41 shows the baseline endoscopy scores. The distribution of scores was similar across treatment groups. More than 50% of the patients had normal gastric and duodenal mucosa.

The gastroduodenal ulceration incidences within each interval (i.e., 0-4 weeks, 4-8 weeks, and 8-12 weeks) for the two 12-week serial endoscopy studies are shown in Figure 24. When an ulcer was detected, the patient was withdrawn from the study. Therefore, only patients who did not have an ulcer in a previous interval are included in the subsequent 4-week intervals in this analysis. As Figure 24 shows, in both of these studies, the highest incidence of ulceration occurred in the first four weeks of treatment. The ulcer incidences for celecoxib were 4% in the first month, and 2% in both of the remaining two 4 week intervals.

Table 40. Demographics, Medical History, Baseline *H. pylori* Status, and Aspirin Use: Studies 062 and 071

Study 062	Celecoxib 200 mg BID (N=270)(a)	Naproxen 500 mg BID (N=267)	Diclofenac 75 mg BID -	Ibuprofen 800 mg TID -
Mean Age	56.7	57.7		
% Female	67	67		
History of GI Bleeding	10 (4%)	14 (5%)	Treatment not included in the study	Treatment not included in the study
History of Gastroduodenal Ulcer	57 (21%)	53 (20%)		
History of Cardiovascular Disease	151 (56%)	133 (50%)		
<i>H. Pylori</i> Positive Serology	90 (33%)	88 (33%)		
Aspirin Use (≤325 mg/day)	38 (11%)	32 (12%)		
Study 071	(N=366)(a)	-	(N=387)	(N=346)(a)
Mean Age	57.2		57.2	57.6
% Female	70		67	66
History of GI Bleeding	7 (2%)	Treatment not included in the study	6 (2%)	5 (1%)
History of Gastroduodenal Ulcer	39 (11%)		48 (12%)	41 (12%)
History of Cardiovascular Disease	161 (44%)		153 (40%)	151 (44%)
<i>H. pylori</i> Positive Serology	119 (33%)		112 (29%)	110 (32%)
Aspirin Use (≤325 mg/day)	48 (13%)		44 (11%)	41 (12%)

a) Includes one patient who was randomized but did not receive study medication and was not included in the ITT cohort.

Table 41. Baseline Endoscopy Scores(a): Studies 062 and 071

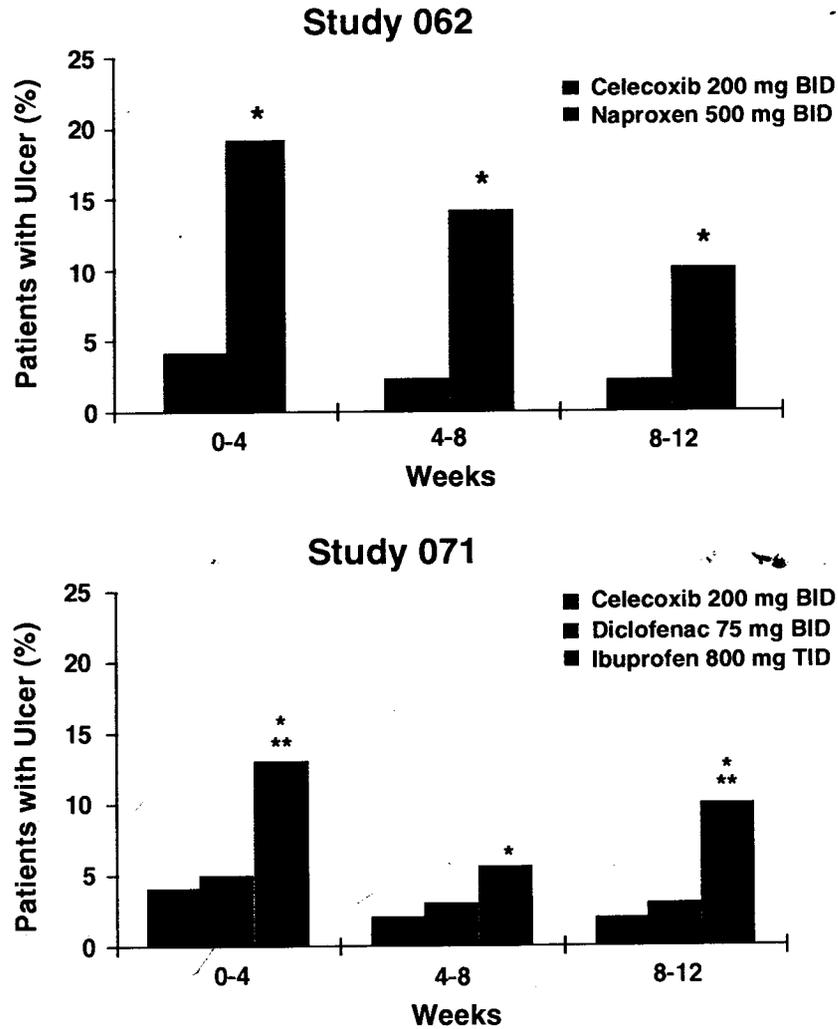
Endoscopy Score(b)	Celecoxib 200 mg BID (N=270)(c)	Naproxen 500 mg BID (N=267)	Diclofenac 75 mg BID -	Ibuprofen 800 mg TID -
Study 062				
Gastric				
0 (no visible lesions)	161 (60%)	159 (60%)	Treatment not included in the study	Treatment not included in the study
1 (1-10 petechiae)	29 (11%)	29 (11%)		
2 (>10 petechiae)	8 (3%)	5 (2%)		
3 (1-5 erosions)	52 (19%)	56 (21%)		
4 (6-10 erosions)	16 (6%)	11 (4%)		
5 (11-25 erosions)	3 (1%)	4 (1%)		
6 (>25 erosions)	1 (<1%)	2 (<1%)		
Ulcer	0 (0%)	1 (<1%)		
Duodenal				
0 (no visible lesions)	229 (85%)	235 (88%)	Treatment not included in the study	Treatment not included in the study
1 (1-10 petechiae)	19 (7%)	15 (6%)		
2 (>10 petechiae)	3 (1%)	4 (1%)		
3 (1-5 erosions)	17 (6%)	11 (4%)		
4 (6-10 erosions)	1 (<1%)	2 (<1%)		
5 (11-25 erosions)	1 (<1%)	0 (0%)		
Study 071				
Gastric				
0 (no visible lesions)	205 (56%)	Treatment not included in the study	240 (62%)	205 (59%)
1 (1-10 petechiae)	30 (8%)		41 (11%)	38 (11%)
2 (>10 petechiae)	11 (3%)		7 (2%)	9 (3%)
3 (1-5 erosions)	87 (24%)		71 (18%)	66 (19%)
4 (6-10 erosions)	19 (5%)		16 (4%)	16 (5%)
5 (11-25 erosions)	10 (3%)		9 (2%)	9 (3%)
6 (>25 erosions)	4 (1%)		3 (<1%)	2 (<1%)
Duodenal				
0 (no visible lesions)	297 (81%)	Treatment not included in the study	330 (85%)	292 (85%)
1 (1-10 petechiae)	30 (8%)		22 (6%)	20 (6%)
2 (>10 petechiae)	4 (1%)		5 (1%)	7 (2%)
3 (1-5 erosions)	30 (8%)		26 (7%)	23 (7%)
4 (6-10 erosions)	3 (<1%)		4 (1%)	2 (<1%)
5 (11-25 erosions)	2 (<1%)		0 (0%)	1 (<1%)

- a) No. of Patients (%)
b) Endoscopy Scoring Scale ranged from 0 to 7. A score of 7 was an ulcer. An erosion was defined as any break in the mucosa without depth. An ulcer was defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth.
c) Includes one patient who was randomized but did not receive study medication and was not included in the ITT cohort.

Table 40 summarizes the gastroduodenal, gastric and duodenal ulcer data. The incidences in the table are cumulative, meaning that an ulcer found at any endoscopy is counted for all subsequent assessments. Therefore, the incidences shown in the rows labeled "0-12 wk" in the table represent all ulcers identified at any time in the study. It is not unexpected that the ulcer incidences were higher than in the other endoscopy studies. Any given patient could have undergone three post-Baseline endoscopies, each of which contributed to the probability of finding an ulcer. The other studies (Studies 021, 022, and 041) only afforded one opportunity to identify an ulcer in a given patient.

In Studies 062 and 071, all differences in incidence of ulceration were statistically significant between celecoxib and both naproxen and ibuprofen at all time points for gastroduodenal, gastric, and duodenal ulcers. Differences between celecoxib and diclofenac did not achieve statistical significance except in the incidence of duodenal ulcers.

Figure 24. Gastroduodenal Ulcer Incidences in 12-Week Studies with Serial Endoscopies: Studies 062 and 071



* Significantly different from celecoxib; $p \leq 0.05$.

** Significantly different from diclofenac; $p < 0.002$.

Table 42. Cumulative Ulcer Incidences: Studies 062 and 071

Study	Celecoxib 200 mg BID	Naproxen 500 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Gastroduodenal				
062				
0-4 wk	4 (10/252) *	19 (47/247)	Treatment not included in the Study	Treatment not included in the Study
0-8 wk	6 (15/237) *	32 (73/229)		
0-12 wk	9 (18/211) *	41 (87/214)		
071				
0-4 wk	4 (13/337) †	Treatment not included in the Study	5 (18/350) †	13 (42/323)
0-8 wk	6 (20/309) †		9 (28/324) †	20 (57/283)
0-12 wk	9 (25/294) †		12 (36/306) †	28 (78/276)
Gastric				
062				
0-4 wk	3 (7/250) *	16 (39/245)	Treatment not included in the Study	Treatment not included in the Study
0-8 wk	4 (9/234) *	28 (61/221)		
0-12 wk	6 (12/205) *	37 (74/202)		
071				
0-4 wk	4 (12/337) †	Treatment not included in the Study	4 (14/350) †	9 (29/323)
0-8 wk	6 (18/308) †		7 (22/321) †	15 (40/270)
0-12 wk	8 (23/293) †		9 (27/301) †	23 (60/259)
Duodenal				
062				
0-4 wk	2 (4/251) *	5 (13/247)	Treatment not included in the Study	Treatment not included in the Study
0-8 wk	3 (7/231) *	9 (18/194)		
0-12 wk	4 (8/203) *	12 (19/158)		
071				
0-4 wk	<1 (1/337) ‡	Treatment not included in the Study	2 (8/350)	5 (16/321)
0-12 wk	<1 (2/296) ‡		3 (10/313) ‡	8 (20/256)
0-12 wk	1 (3/275) ‡		5 (14/287)	9 (22/238)

* Significantly different from naproxen; p<0.05.

† Significantly different from ibuprofen; p<0.05.

‡ Significantly different from diclofenac; p<0.05.

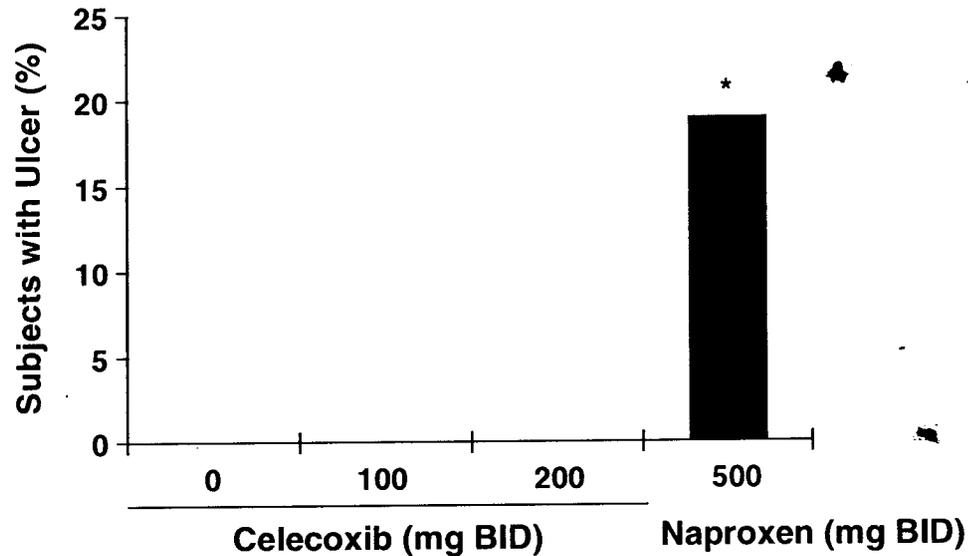
Entries are % of patients with ulcer (No. with ulcer/total no. with known result). Known endoscopy results include an ulcer detected at any time, or a finding of no ulcer at an endoscopy performed at the scheduled visit ±7 days.

6.1.3 7-Day Endoscopy Study

Study 014 was a randomized, double-blind study conducted in healthy volunteers with normal gastroduodenal mucosa at baseline endoscopy. Treatment groups included placebo, celecoxib 100 mg BID, celecoxib 200 mg BID, and naproxen 500 mg BID.

None of the 32 subjects receiving placebo, or the 64 subjects receiving celecoxib, developed an ulcer; in contrast, six of the 32 subjects receiving naproxen developed a gastric ulcer (Figure 25).

Figure 25. Ulcer Incidences at Day 7: Study 014



* Significantly different from other treatments; $p < 0.05$.

6.1.4 Clinically Significant UGI Events

An independent GI Consultants Committee consisting of three gastroenterologists was established to review, in a blinded fashion, case summaries of potential clinically significant UGI events that occurred during the conduct of clinical trials. This monitoring system included the 14 controlled arthritis trials (Studies 012, 013, 020, 021, 022, 023, 041, 042, 047, 054, 060, 062, 071, and 087) and the North American Long-term Open Label Arthritis Study (Study 024).

Investigators were instructed to report any event considered to represent a potentially clinically significant UGI event (e.g., UGI bleeding, perforation, or gastric outlet obstruction). Data pertaining to the event were summarized and distributed to each of the Committee members who reviewed each case and determined by consensus if the event was a clinically significant UGI event. Committee members were blinded to which treatment patients had received and in which study the patient was enrolled.

The definitions of clinically significant UGI events were based in large part on the design and results of a large prospective study on incidences of clinically significant UGI events caused by NSAIDs. (26)

The committee adjudicated all potentially clinically significant UGI events according to the following prospectively defined criteria:

1. UGI Bleeding

- a. hematemesis with a lesion* at endoscopy or x-ray,
- b. lesion at endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer),
- c. melena with a lesion at endoscopy or x-ray,
- d. hemoccult positive stools with a lesion at endoscopy or x-ray with evidence of serious bleeding, which included:
 - (1) fall in hematocrit over 5% (absolute change)
 - (2) signs of postural vital sign changes (increase of pulse rate of 30 bpm and a decrease in systolic blood pressure of 20 mm Hg and a diastolic blood pressure of 10 mm Hg)
 - (3) transfusion of more than two units of blood
 - (4) blood in the stomach

* A lesion is an ulcer or large erosion.

2. Perforation

This was defined as a perforated lesion that required surgery. It could involve a laparoscopic repair, but only if evidence of the perforation were unequivocal such as free air in the abdomen visible by x-ray, or peritoneal signs upon physical examination.

3. Gastric Outlet Obstruction

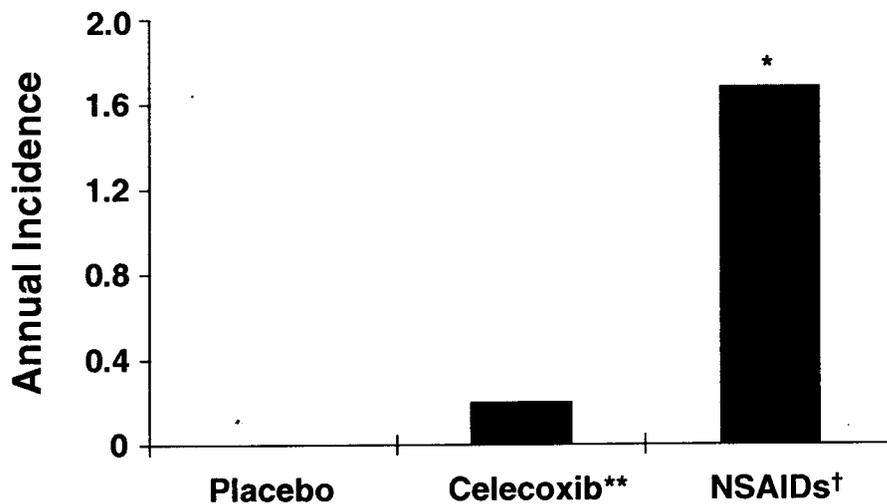
Gastric outlet obstruction was required to be diagnosed by the Investigator, and the diagnosis had to be supported by endoscopy (e.g., a tight edematous ulcer in the pyloric channel) or by x-ray results (e.g., a dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with ulcer in the channel or severe narrowing and edema).

When lower GI adverse events including small bowel or colonic obstruction, ulceration, bleeding, perforation, stricture, colitis were reported by investigators, the cases were reviewed by the committee.

6.1.4.1 Controlled Arthritis Trials

A total of 101 cases were referred to the Committee for adjudication. Eleven of these met the criteria for clinically significant UGI events. The annual incidence of clinically significant UGI events for placebo, celecoxib and NSAIDs are shown in Figure 26 and Table 43. The rate of development of these events per patient-year was approximately eight-fold lower for celecoxib (0.20%) than for NSAIDs (1.68%). The difference (1.48%) in the annual incidence of clinically significant UGI events between celecoxib and NSAIDs was statistically significant (95% confidence interval 0.35% to 2.62%).

Figure 26. Annual Incidence of Clinically Significant UGI Adverse Events: Controlled Arthritis Trials



* Significantly different from celecoxib; $P < 0.05$ (1.48%; 95% confidence interval 0.35% - 2.62%)

** Fourteen controlled arthritis trials: Celecoxib 25-400 mg BID

† Naproxen 500 mg BID; Diclofenac 50-75 mg BID; and Ibuprofen 800 mg TID

The nine clinically significant UGI events that occurred with NSAIDs included five events over 236 patient-years of exposure for naproxen (annual incidence 2.1%), three events over 237 patient-years of exposure for diclofenac (annual incidence 1.3%) and one event over 62 patient-years of exposure for ibuprofen (annual incidence 1.6%). Of these nine cases, seven were UGI bleeding episodes and two were gastric outlet obstructions (both occurring in patients receiving naproxen). The two clinically significant UGI events that were associated with 1020 patient-years of exposure with

celecoxib were UGI bleeding episodes. One of these events occurred in a patient taking celecoxib 100 mg BID and the other in a patient taking celecoxib 200 mg BID.

Table 43. Annual Incidence of Clinically Significant UGI Events: Controlled Arthritis Trials

	Placebo	Celecoxib	NSAIDs
No. of events	0	2	9
Patient-years of exposure	208	1020	535
Annual Incidence	0%	0.20%	1.68%*

* Significantly different from celecoxib; p<0.05

6.1.4.2 Long-Term Open-Label Arthritis Study

In the long-term open-label trial, 69 possibly clinically significant UGI events were referred to the Committee for evaluation. Seven cases met the criteria for clinically significant UGI events. The annual incidence of clinically significant UGI events of 0.26% with celecoxib in the long-term open-label arthritis study (Table 44) is consistent with an annual incidence of 0.20% seen in the controlled arthritis trials. Furthermore, as shown in Table 44, with increased patient exposure to celecoxib in this study, the annual incidence of clinically significant UGI events has fallen to 0.18%.

Table 44. Annual Incidence of Clinically Significant UGI Events: North American Long-Term Open-Label Arthritis Study

	Through 11/21/97(a)	Through 7/24/98(b)
No. of events	7	9
Patient-years of exposure	2672	5002
Annual Incidence	0.26%	0.18%

a) NDA Submission

b) 120-day Safety Update

6.1.5 Conclusions

Based on the results of replicate endoscopy trials and a monitoring program for clinically significant UGI events, it is concluded that:

- The incidences of gastroduodenal, gastric, and duodenal ulceration with celecoxib at therapeutic and supratherapeutic doses was statistically significantly lower than that of NSAIDs and similar to placebo.
- Celecoxib was associated with an eight-fold lower risk of clinically significant UGI events than NSAIDs, and the annual incidence with celecoxib was similar to that with placebo.

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6.2 Platelet Differentiation

Six clinical studies (Studies 009, 015, 026, 032, 065 and 079) were undertaken to compare the effects of celecoxib with those of placebo and NSAIDs on platelet aggregation, thromboxane production, and bleeding times. A principal feature of these studies was that celecoxib was evaluated at doses exceeding the recommended clinical dose range for anti-inflammatory and analgesic efficacy. Celecoxib doses as high as 800 mg single dose and 1200 mg BID (for up to 10 days) were evaluated (Table 45).

Table 45. Summary of Celecoxib Platelet Differentiation Studies

Study No. - Population	Duration	No. of Subjects	Treatments
032 - Healthy adults	8 days	24	Celecoxib 600 mg BID, naproxen 500 mg BID, or placebo
065 - Healthy adults	8 days	51	Celecoxib 600 mg BID, diclofenac 75 mg BID, ibuprofen 800 mg TID, or placebo
079 - Healthy adults	10 days	56	Celecoxib 800 or 1200 BID, naproxen 500 mg BID, or placebo
009 - Healthy adults	single dose	37	Celecoxib 100, 400, or 800 mg, ibuprofen 800 mg; or placebo
026 - Healthy adults	6 days	6	Celecoxib 400 mg BID + aspirin 650 mg (single dose)
015 - Healthy adults	10 days	48	Celecoxib 200 mg BID or placebo

6.2.1 Placebo-Controlled Multiple-Dose Studies versus NSAIDs: Studies 032, 065 and 079

Three placebo-controlled multiple-dose studies comparing the platelet effects of suprathreshold doses of celecoxib to therapeutic doses of NSAIDs were conducted. These studies were of similar design and examined the effects of celecoxib (600 mg, 800 mg or 1200 mg BID) on platelet aggregation induced by collagen and arachidonate, on bleeding time, and on serum thromboxane B₂ (TxB₂) levels.

In Study 032, healthy subjects received a single morning dose of celecoxib 600 mg (n=8), naproxen 500 mg (n=8), or placebo (n=8), followed 48 hours later by the same study medication administered BID for seven days and as a final morning dose on Day 10. Platelet aggregation, bleeding time, and serum TxB₂ were determined 30 minutes prior to and eight hours after the first dose of study medication on Day 1, and 30 minutes prior to and four, six, and eight hours after the final dose on Day 10.

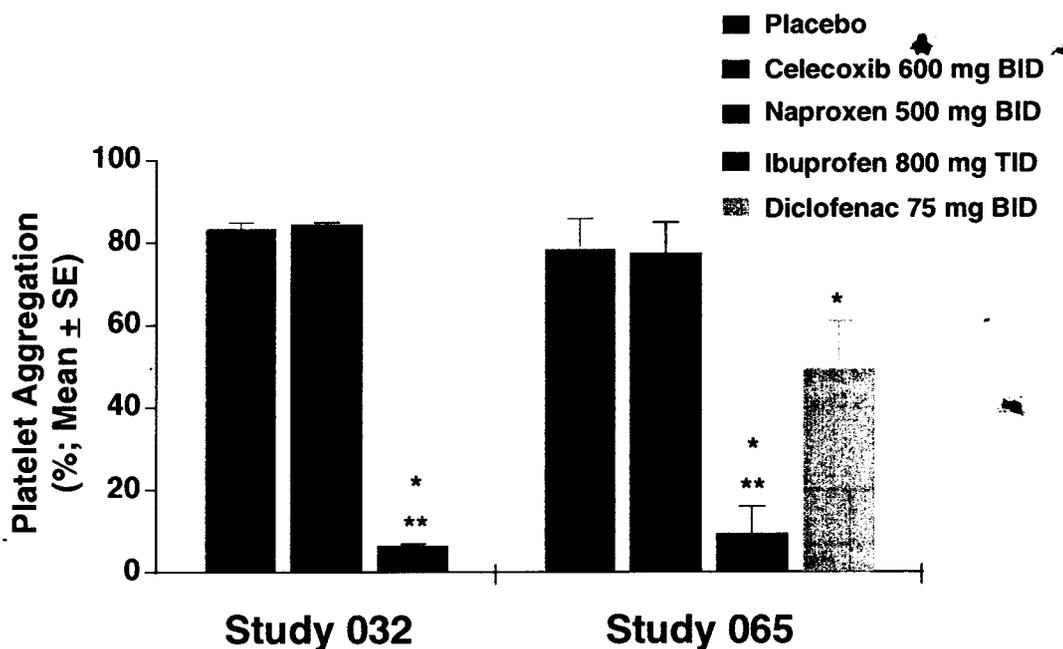
In Study 065, healthy subjects received one of the following treatments for seven days and as a single dose on the morning of Day 8: celecoxib 600 mg BID (N=12), diclofenac 75 mg BID (N=12), ibuprofen 800 mg TID (N=13) or placebo (N=14). Platelet aggregation, bleeding time, and serum TxB₂ levels were determined 30 minutes prior to and 2, 4, and 6 hours after the morning dose on Day 1 and Day 8.

In Study 079, healthy subjects received a single morning dose of celecoxib 800 mg (n=12), naproxen 500 mg (n=8), or placebo (n=8) followed 48 hours later by the same study medication administered BID for ten days. A second group of healthy subjects (n=28) was studied in an identical fashion except that subjects randomized to celecoxib treatment received a single dose of 1200 mg followed 48 hours later by 1200 mg BID for 10 days. Platelet aggregation, bleeding time and serum TxB₂ concentrations were determined 15 minutes prior to and three and six hours following the administration of the initial (single dose; Day 1), the first BID dose following the 48 hour washout (Day 3), and the last BID dose (Day 12). In addition, these same determinations were performed two weeks after the end of dosing (Day 26).

6.2.1.1 Arachidonate-Induced Aggregation

The effects of celecoxib, placebo and NSAIDs on arachidonate-induced platelet aggregation are presented in Figure 25 and Table 46. In both studies, celecoxib 600 mg BID was indistinguishable from placebo in arachidonate-induced platelet aggregation at all time points. Naproxen had a statistically significant and sustained effect throughout the entire dosing period, including predose trough levels on Day 10. The effect of ibuprofen on Days 1 and 8 was similar to that of naproxen. The differences were significant versus placebo at all times measured. The effect of diclofenac was less extreme but still significant. Statistically significant differences versus placebo were present on Day 1 at two and four hours, and on Day 8 at six hours post-dosing.

Figure 27. Platelet Aggregation to Arachidonate Following Multiple Doses: Studies 032 (Day 10, 8 hr) and 065 (Day 8, 6 hr)



* Significantly different from placebo; $p < 0.05$.
 ** Significantly different from celecoxib; $p < 0.05$.

Table 47 presents the effects of celecoxib 800 mg BID or 1200 mg BID, placebo and naproxen 500 mg BID on arachidonate-induced platelet aggregation. Celecoxib 800 mg BID and 1200 mg BID did not significantly inhibit platelet aggregation. Celecoxib 800 mg BID was not statistically significantly different from placebo across the study. At two assessment times (Day 1, 3 hrs and Day 3, 6 hrs postdose) a statistically significant difference was detected between placebo and celecoxib 1200 mg BID; however, this difference was the result of decreased platelet aggregation in the placebo group and increased platelet aggregation in the celecoxib 1200 mg BID group. Naproxen produced a statistically significant and sustained reduction of arachidonate-induced platelet aggregation, including predose trough levels on Day 12, when compared to placebo.

Table 46. Arachidonate-Induced Platelet Aggregation (%): Studies 032 and 065

Study 032								
	Baseline(a)	Day 1			Day 10			
		8 hr	-30 min	4 hr	6 hr	8 hr		
Placebo (n=8)	82.6	85.5	87.0	84.3	83.9	82.8		
Celecoxib 600 mg BID (n=8)	86.9	86.1	85.7	85.3	87.5	84.4		
Naproxen 500 mg BID (n=8)	82.9	4.8*	4.8*	5.8*	5.1*	5.6*		
Study 065								
	Baseline(b)	Day 1			Day 8			
		2 hr	4 hr	6 hr	-30 min	2 hr	4 hr	6 hr
Placebo (n=14)	85.2	80.2	84.8	81.5	89.3	86.1	84.8	78.3
Celecoxib 600 mg BID (n=12)	85.2	75.1	76.3	83.8	85.0	86.8	78.3	76.7
Ibuprofen 800 mg TID (n=12)	85.8	8.7*	2.5*	31.2*	76.6*	14.8*	7.4*	9.1*
Diclofenac 75 mg BID (n=13)	85.5	36.4*	56.7*	71.3	84.0	79.3	55.2	49.3*

* Statistically significant difference (p<0.05) from placebo in change from Baseline.

a) Baseline Value is an average of Day 0 and Day 1 Predose measurements.

b) Baseline value is Day 1 Predose (-30 minutes).

Table 47. Arachidonate-Induced Platelet Aggregation (%): Study 079

	Day 1			Day 3			Day 12			Day 26(b)
	Baseline(a)	3 hr	6 hr	-15 min	3 hr	6 hr	-15 min	3 hr	6 hr	
Placebo (n=16)	78.0	75.8	73.2	82.4	72.9	75.0	74.0	74.3	76.6	68.3
Celecoxib 800 mg BID (n=12)	73.6	68.2	61.2	69.3	67.4	74.0	74.7	77.6	70.1	70.2
Celecoxib 1200 mg BID (n=12)	70.8	80.6*	74.2	74.9	65.5	78.6*	68.4	67.4	65.5	72.7
Naproxen 500 mg BID (n=16)	73.4	2.6*	3.6*	75.8	4.2*	3.9*	3.4*	4.9*	4.6*	60.3

* Significantly different from placebo in change from Baseline; p<0.05.

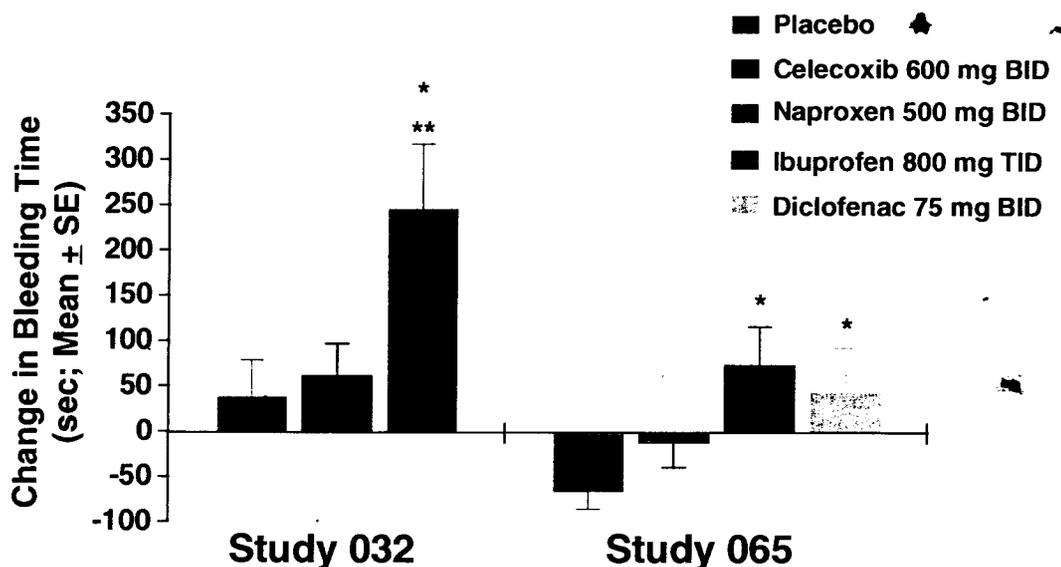
a) Baseline Value is Day 1 -15 min measurement.

b) Two weeks after last dose of study medication.

6.2.1.2 Bleeding Time

In both studies, celecoxib and placebo were not statistically different at any time during the study. In Study 032, naproxen caused a sustained significant increase versus placebo in bleeding time (Figure 28 and Table 48). In Study 065, diclofenac effects on bleeding time appeared to be reversible, with mean increases generally seen with the first post-Baseline dose which then returned toward Baseline, followed by an increase in bleeding time again after dosing on Day 8. The increases in bleeding time for diclofenac were significant compared to placebo on both Days 1 and 8. For ibuprofen an increase from the mean Baseline occurred after the first dose on Day 1 and was sustained on Day 8 without notable reversibility. Compared to placebo, both the Day 1 and Day 8 changes were significant.

**Figure 28. Mean Changes from Baseline in Bleeding Time:
Studies 032 (Day 10, 8 hr) and 065 (Day 8, 6 hr)**



* Significantly different from placebo; $p < 0.05$
** Significantly different from celecoxib; $p < 0.05$

**Table 48. Mean Changes from Baseline in Bleeding Time (Seconds):
Studies 032 and 065**

Study 032								
	Baseline(a) Mean Value	Mean Change from Baseline						
		Day 1		Day 10				
		8 hr	-30 min	4 hr	6 hr	8 hr		
Placebo (n=8)	290.3	114.0	45.5	33.3	76.5	38.1		
Celecoxib 600 mg BID (n=8)	264.0	100.8	44.6	91.9	53.0	60.5		
Naproxen 500 mg BID (n=8)	265.4	246.9	178.9*	271.8	299.2*	244.7*		
Study 065								
	Baseline(b) Mean Value	Mean Change from Baseline						
		Day 1			Day 8			
		2 hr	4 hr	6 hr	-30 min	2 hr	4 hr	6 hr
Placebo (n=14)	313.9	-53.6	-53.0	-50.2	-64.8	-32.8	-40.4	-63.0
Celecoxib 600 mg BID (n=12)	314.4	-31.8	-48.7	-51.3	63.8	0.2	5.7	-9.3
Ibuprofen 800 mg TID (n=12)	305.8	80.8*	68.1*	12.2	52.6*	50.6*	133.8*	72.5*
Diclofenac 75 mg BID (n=13)	325.1	116.8	20.6*	-24.4	-50.0	-35.1	78.1	43.0*

* Significantly different from placebo; $p \leq 0.05$.

a) Baseline Value is an average of Day 0 and Day 1 Predose measurements.

b) Baseline value is Day 1 Predose (-30 minutes).

In Study 079 bleeding times with celecoxib 1200 mg BID were not significantly different from placebo at any time during the study and celecoxib 800 mg BID was associated with significantly greater bleeding time only at the Day 12 post-dose assessments

(Table 49). In contrast, naproxen produced a sustained statistically significant increase in bleeding time versus placebo following dosing on Day 3 and Day 12.

Table 49. Mean Changes from Baseline in Bleeding Time (Seconds): Study 079

	Day 1			Day 3			Day 12			Day 26(b)
	Baseline(a) (Mean)	3 hr	6 hr	-15 min	3 hr	6 hr	-15 min	3 hr	6 hr	
Placebo (n=16)	289.4	24.9	59.1	43.7	21.1	54.4	29.0	23.6	-12.6	55.3
Celecoxib 800 mg BID (n=12)	283.3	85.6	55.0	113.7	119.9	54.9	28.7	197.5*	135.7*	55.6
Celecoxib 1200 mg BID (n=12)	300.2	2.5	8.1	124.5	78.7	126.1	38.7	37.6	73.2	34.3
Naproxen 500 mg BID (n=16)	327.9	140.7	235.3	75.0	226.9*	244.3*	159.3	250.9*	188.4*	121.9

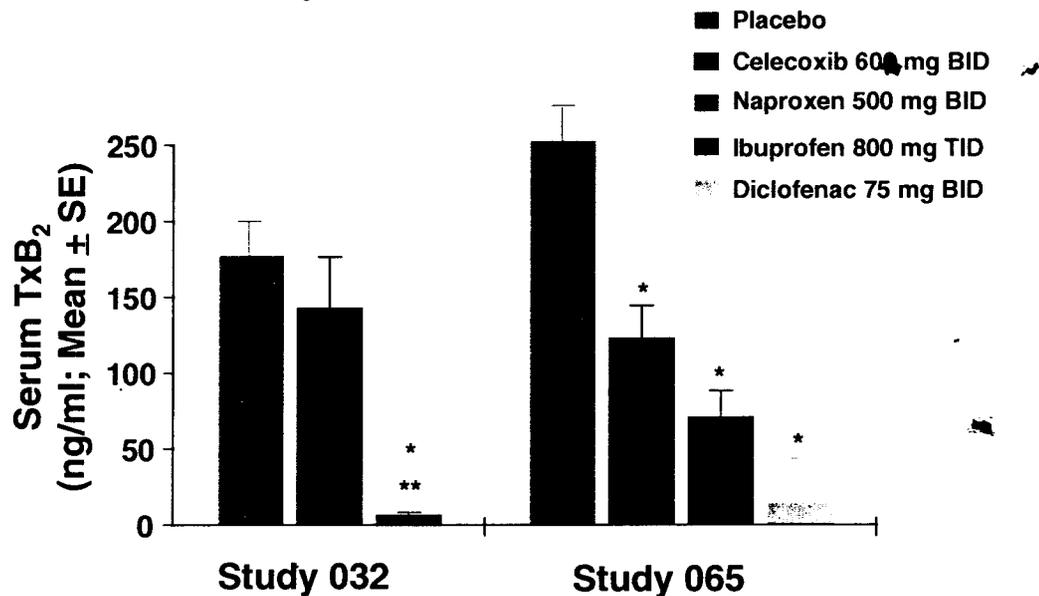
* Significantly different from placebo in change from Baseline; p≤0.05.
 a) Baseline Value is Day 1 -15 min measurement.
 b) Two weeks after last dose of study medication.

6.2.1.3 Serum TxB₂ Levels

Figure 29 shows the results of serum TxB₂ assays. For naproxen and ibuprofen, the mean decrease in serum TxB₂ levels exceeded 200 ng/mL at all post-Baseline measurements. Decreases for diclofenac were not as great as with naproxen but compared to placebo, diclofenac significantly reduced TxB₂ levels on both Day 1 and Day 8. Table 50 shows the statistical comparisons of the mean changes.

Celecoxib was associated with some decreases in serum TxB₂ levels but less than those seen with naproxen, ibuprofen and diclofenac. In Study 032, celecoxib was associated with minor decreases in serum TxB₂ levels, although none of the changes were significant versus placebo. In Study 065, celecoxib treatment was associated with decreases of approximately 85 ng/mL on Day 1, and slightly larger decreases on Day 8. This compares to a maximal placebo decrease of approximately 30 ng/mL in this study. The differences versus placebo were statistically significant at some time points.

Figure 29. Mean Serum TxB₂ Levels: Studies 032 (Day 10, 8 hr) and 065 (Day 8, 6 hr)



* Significantly different from placebo; p<0.05
** Significantly different from celecoxib; p<0.05

Table 50. Mean Serum TxB₂ Levels (ng/mL): Studies 032 and 065

Study 032								
	Baseline(a)	Day 1			Day 10			
		8 hr	-30 min	4 hr	6 hr	8 hr		
Placebo (n=8)	179.0	200.3	160.0	160.4	132.5	170.5		
Celecoxib 600 mg BID (n=8)	180.9	148.2	101.7	88.4	99.8	138.1		
Naproxen 500 mg BID (n=8)	220.2	9.3*	8.0*	2.3*	2.8*	4.5*		
Study 065								
	Baseline(a)	Day 1			Day 8			
		2 hr	4 hr	6 hr	-30 min	2 hr	4 hr	6 hr
Placebo (n=14)	237.4	245.3	220.5	259.4	231.8	218.3	260.3	250.3
Celecoxib 600 mg BID (n=12)	257.4	163.5*	178.8	176.6*	166.6	130.7	121.6*	128.0*
Diclofenac 75 mg BID (n=12)	251.3	87.0*	112.0*	130.2*	158.9	157.3	98.4*	75.4*
Ibuprofen 800 mg TID (n=13)	215.3	3.6*	6.6*	15.6*	64.5*	10.7*	8.1*	12.3*

* Significantly different from placebo in change from Baseline; p<0.05.

a) Baseline value is Day 1 Predose (-30 minutes).

The effect of treatment on serum TxB₂ levels in Study 079 are reported in Table 51. For naproxen 500 mg BID, serum TxB₂ levels decreased significantly when compared to placebo, similar to the findings observed in Study 032. The mean changes in serum TxB₂ levels with celecoxib 1200 mg BID were also statistically significantly reduced when compared to placebo at most assessments. The mean changes with celecoxib 800 mg BID were significantly different from placebo at fewer assessments. The mean

changes in serum TxB₂ levels with celecoxib 800 mg BID and 1200 mg BID in Study 079 were similar in magnitude to the changes seen with celecoxib 600 mg BID in Studies 032 and 065.

Table 51. Mean Serum TxB₂ Levels (ng/mL): Study 079

	Day 1			Day 3			Day 12			Day 26(b)
	Baseline(a)	3 hr	6 hr	-15 min	3 hr	6 hr	-15 min	3 hr	6 hr	
Placebo (n=16)	221.8	210.1	229.0	210.8	229.6	185.7	233.3	254.1	243.1	150.0
Celecoxib 800 mg BID (n=12)	187.9	125.7	134.9*	165.9	131.5*	131.1	143.2	142.2*	140.1*	148.2
Celecoxib 1200 mg BID (n=12)	221.5	152.3	122.5*	190.7*	121.4*	127.6*	123.0*	105.1*	-112.1*	155.7
Naproxen 500 mg BID (n=16)	205.0	8.8*	6.9*	75.1*	5.8*	5.8*	7.6*	3.4*	26.3*	131.6

* Significantly different from placebo in change from Baseline; p<0.05.

a) Baseline Value is Day 1 -15 min measurement.

b) Two weeks after last dose of study medication.

6.2.2 Single Dose Platelet Study: Study 009

In this double-blind study healthy subjects received a single dose of either celecoxib 100 mg, celecoxib 400 mg, celecoxib 800 mg, ibuprofen 800 mg or placebo. The effects of celecoxib 100, 400, and 800 mg on platelet aggregation induced by arachidonate were statistically indistinguishable from that of placebo (Table 52). In contrast, ibuprofen was associated with statistically significant inhibition of arachidonate-induced aggregation at three hours postdose.

Table 52. Mean Changes (± SE) from Baseline in Platelet Aggregation: Study 009

Agonist	Placebo (n=7)	Celecoxib 100 mg (n=7)	Celecoxib 400 mg (n=7)	Celecoxib 800 mg (n=7)	Ibuprofen 800 mg (n=7)
Arachidonate-induced aggregation					
3 hr postdose	1.3 ± 3.7	-2.1 ± 2.5	-10.1 ± 9.0	-9.1 ± 13.7	-66.6 ± 11.6*
8 hr postdose	-1.7 ± 5.4	-0.6 ± 5.9	-2.9 ± 3.7	-15.0 ± 12.0	-33.0 ± 14.7
24 hr postdose	5.6 ± 3.5	-0.6 ± 4.9	4.3 ± 4.6	-12.6 ± 12.0	-3.1 ± 3.4

* Significantly different from placebo; p<0.05.

Effects on bleeding time were highly variable; no significant effect was seen in any of the treatment groups. Serum TxB₂ levels were reduced 3-4 fold more in the ibuprofen group compared to celecoxib and placebo groups, and the difference from placebo was statistically significant at all time points. Celecoxib had no significant effects on serum TxB₂ levels when compared to placebo.

6.2.3 Open-Label Platelet Function Study: Study 026

Study 026 was an open-label, multiple-dose study of the effects of celecoxib on platelet function in six healthy male subjects who received celecoxib 400 mg BID for six days. After a seven-day washout period, all subjects had platelet aggregation and whole blood TxB₂ levels determined after receiving a single dose of aspirin 650 mg. The differences between celecoxib and aspirin were statistically significant at both two and four hours after dosing for changes from pretreatment in aggregation response to arachidonate (Table 53) and for TxB₂ levels. These study results provide additional data to indicate that celecoxib does not affect platelet function, and is significantly different from a nonselective COX-1 and COX-2 inhibitor, in this case aspirin.

Table 53. Mean Changes (± SE) from Baseline in Platelet Aggregation: Study 026

	Celecoxib 400 mg BID	Aspirin 650 mg SD
Arachidonate-induced aggregation, % change		
2 hr postdose	-0.5 ± 3.3 *	-44.2 ± 9.8
4 hr postdose	-0.5 ± 4.6 *	-39.7 ± 9.6

* Significantly different from aspirin; p<0.05.

6.2.4 Platelet Effects in Healthy Elderly Subjects: Study 015

Study 015 was a 14-day, randomized, double-blind, placebo-controlled study which compared the pharmacokinetic and pharmacodynamic profiles of celecoxib in 24 healthy elderly subjects to 24 non-elderly subjects. The placebo group consisted of four healthy elderly and four healthy non-elderly subjects. As part of this study, platelet aggregation responses to collagen and arachidonate were measured before dosing and at three and eight hours after dosing on Days 1 and 9. There were no statistically significant differences between the young and the elderly celecoxib-treated patients in platelet aggregation to collagen or arachidonate.

6.2.5 Conclusions

The results of replicate platelet function studies demonstrated that:

- Celecoxib did not affect platelet aggregation and bleeding times, even when given at doses up to 12-fold higher than the maximum recommended therapeutic dose.
- Supratherapeutic doses of celecoxib may result in reductions of serum TxB₂ levels, which are insufficient to affect bleeding time or platelet aggregation.
- NSAIDs at therapeutic doses were shown to reduce significantly both serum TxB₂ levels and platelet function.

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6.3 General Safety Profile

6.3.1 Extent of Exposure

A total of 13,072 unique individuals have received at least one dose of study medication in the celecoxib clinical trials. Table 54 summarizes the numbers of patients exposed to celecoxib, placebo, NSAIDs or other drugs, and combinations of celecoxib and other drugs.

Table 54. Summary of Unique Treated Subjects/Patients: Combined Studies

Treatment/Dose Level	No. of Unique Subjects/Patients Treated
Placebo	1354
Celecoxib	
5-1200 mg single dose	780
5-50 mg BID	948
100 mg BID	3261
200 mg QD	500
200 mg BID	3272
400 mg BID	665
600-1200 mg BID	20
Any Dose	9463
Celecoxib + Other Drug	17
NSAID Control or Other Drug	2255

5-50 mg = 5, 20, 25, 40, or 50 mg

600-1200 mg = 600, 800, 900, or 1200 mg

Unique = each individual is counted only once. Subjects/patients who participated in multiple periods of a crossover study or were treated in more than one study are only counted once. If a subject/patient received both placebo or a comparator and celecoxib, he/she is counted only as a celecoxib subject/patient.

The studies of greatest interest with respect to duration of exposure are the arthritis studies, since they represent all cases of chronic celecoxib administration. The intervals of exposure in these studies are summarized in Table 55. A total of 8,139 patients have received at least one dose of celecoxib in a controlled arthritis study or the North American Long-term, Open-label Arthritis Study.

Table 55. Duration of Exposure to Any Dose of Celecoxib: Controlled Arthritis Studies and North American Long-Term Open-Label Arthritis Study Combined

Time of Exposure	Cumulative No. of Patients (Any Dose and Regimen)
≥ 1 day	8139
≥ 2 weeks	7599
≥ 6 weeks	6123
≥ 13 weeks	3859
≥ 26 weeks	2429
≥ 39 weeks	1598
≥ 52 weeks	981
≥ 64 weeks	312

Table 56 summarizes the extent of exposure in the arthritis trials by patient-years of treatment at the various dose levels. Celecoxib has been administered for a total of over 3200 patient years at all doses combined. The majority of exposure to celecoxib in arthritis studies (over 2200 patient-years) has been at doses of 100 and 200 mg BID or 200 mg QD, the recommended doses for treating arthritis and pain.

Table 56. Patient-Years of Exposure to Celecoxib: All Arthritis Studies

Study Type	50 mg BID	100 mg BID	200 mg BID	200 mg QD	400 mg BID	Any Dose
Controlled arthritis	116.1	289.3	465.7	47.1	87.1	1020.3
Total (Including long-term open-label)	116.6	679.9	1567.0	47.1	499.4	3267.5

Frequently reported adverse events and withdrawals due to adverse events are presented for three distinct groups; the North American Controlled Arthritis Trials, the International Arthritis Trials and the North American Long-term Open Label Arthritis Study.

6.3.2 North American Controlled Arthritis Trials

The North American Controlled Arthritis Trials are a group of controlled studies performed in patients with OA and/or RA, in which patients were treated for two to 12 weeks with celecoxib (50-800 mg/day; BID or QD dosing), placebo, or an NSAID (naproxen, ibuprofen, or diclofenac).

In the North American Controlled Arthritis Trials, there were 9,666 treated patients: 5,704 celecoxib, 1,864 placebo, and 2,098 NSAIDs. In this patient population, the

overall mean age for patients receiving celecoxib was 59.5 years, compared with 60.0 years in placebo patients and 58.8 years in patients receiving NSAID control (naproxen, diclofenac, or ibuprofen). In all treatment groups, female patients predominated, with the proportion ranging from 66.2% to 72.7%. The patients in these studies were predominantly Caucasian (>82% in all treatment groups), followed by Black and then Hispanic patients. For female patients, mean weights across treatment groups ranged from 76.7 to 88.6 kg. Mean weights of male patients ranged from 88.0 to 97.0 kg.

6.3.3 International Arthritis Trials

Studies 042 and 041 were 6-week OA and 24-week RA efficacy studies, respectively, that were conducted at sites in Australia, Europe, Israel, New Zealand, and South Africa. Patients with symptomatic arthritis were eligible for the studies, but a symptomatic flare was not required for enrollment.

A total of 1,342 arthritis patients were enrolled in the International Arthritis Trials. All patients receiving celecoxib 100 mg BID (n=346) or diclofenac 50 mg BID (n=341) were enrolled in the six-week OA efficacy study (Study 042), while all patients receiving celecoxib 200 mg BID (n=326) or diclofenac SR 75 mg BID (n=329) were enrolled in the 24-week RA efficacy study (Study 041). In the celecoxib groups, the mean ages were 63.3 years for 100 mg BID and 55.9 years for 200 mg BID, compared to 64.1 and 54.5 years for diclofenac patients receiving 50 and 75 mg BID, respectively). The gender distribution was similar to that in the North American Arthritis Trials, with the proportion of female patients ranging from 71.1% to 75.8%. The patients in these studies were predominantly Caucasian. The mean weights for female patients were 76.2 kg for celecoxib 100 mg BID, 78.0 kg for diclofenac 50 mg BID, 67.1 kg for celecoxib 200 mg BID, and 66.3 kg for diclofenac SR 75 mg BID. For male patients, mean weights were 86.9 kg for celecoxib 100 mg BID, 85.2 kg for diclofenac 50 mg BID, 81.2 kg for celecoxib 200 mg BID, and 80.6 kg for diclofenac SR 75 mg BID.

6.3.4 North American Long-term Open-Label Arthritis Study: Study 024

The principal objective of Study 024 is to evaluate the safety of administering celecoxib for up to two years in patients with OA or RA. Patients were eligible to enter the open-label trial upon completing participation in one of nine controlled arthritis trials. All OA patients who entered the trial started with a 100 mg BID dose of celecoxib and had the

option to escalate their dose to 200 mg BID. All RA patients who entered the study started with a celecoxib dose of 200 mg BID and had the option to increase this dose to 300 mg BID or 400 mg BID. A total of 4499 patients (2554 OA patients and 1945 RA patients) have been enrolled. This study is ongoing. Table 57 summarizes the enrollment status as a function of the dose and duration for the study.

Table 57. Numbers of Patients at Various Exposures: North American Long-term Open Label Arthritis Study

	50 mg BID	100 mg BID	200 mg BID	300 mg BID	400 mg BID	Any Dose
> 3 mo.	7	637	1748	423	656	3517
> 6 mo.	0	236	941	222	410	2363
> 9 mo.	0	151	548	104	211	1573
> 12 mo.	0	62	234	30	56	965

Data from 4499 OA and RA patients enrolled into Study 024. Patients are counted once per dose column but may appear in several columns due to dose adjustment.

6.3.5 Frequently Reported Adverse Events

6.3.5.1 North American Controlled Arthritis Trials

Table 58 shows the most common events in any treatment group (excluding celecoxib 25 to 40 mg BID), sorted by descending incidence in the celecoxib 200 mg BID column for the North American Controlled Arthritis Trials. A total of 12 types of adverse event occurred in at least 3% of the patients in any treatment group. Six of the 12 types of adverse event were GI in nature and with the exception of diarrhea, GI adverse events were more common in patients receiving NSAIDs than in celecoxib patients. Headache was the most common adverse event, with the highest incidence among placebo patients. In general, the varying adverse event incidences among the celecoxib groups do not suggest a dose-response effect. (Note that the celecoxib 200 mg QD group includes only patients from six-week studies. All other columns include patients from at least two 12-week studies.)

Table 58. Adverse Events with Incidence $\geq 3\%$ in Any Treatment Group: North American Controlled Arthritis Trials

Adverse Event	Placebo	Celecoxib					NSAID
		50 mg BID	100 mg BID	200 mg QD	200 mg BID	400 mg BID	
No. treated	1864	690	1779	453	1914	615	2098
Any event	54.6	63.6	60.2	51.9	62.5	60.2	66.7
Headache	20.2	16.7	17.0	17.7	14.3	14.5	14.8
Dyspepsia	6.2	8.1	8.7	4.6	9.9	8.1	12.0
URTI	6.7	9.0	8.1	5.3	8.8	7.0	9.9
Diarrhea	3.8	5.4	5.0	3.5	6.6	6.5	6.1
Sinusitis	4.3	5.2	4.9	3.1	5.5	5.4	4.6
Abdominal pain	2.8	4.5	3.4	2.0	5.2	3.3	8.2
Nausea	4.2	3.8	3.6	2.4	3.7	3.6	5.6
Back pain	3.6	1.7	2.9	2.2	3.0	0.8	2.0
Accidental injury	2.3	2.6	3.0	2.4	2.9	2.4	2.9
Rash	2.1	2.5	2.2	1.1	2.5	3.4	1.8
Flatulence	1.0	2.3	2.1	2.2	2.3	2.0	3.7
Constipation	1.9	1.4	1.8	1.1	1.9	0.8	4.1

All numbers are percentages of patients unless otherwise specified.

Table 59 shows statistical analyses of adverse events among treatment groups. For the purpose of all such analyses, the celecoxib column includes all patients receiving full therapeutic doses of celecoxib (100 mg BID, 200 mg QD, or 200 mg BID). Further, when celecoxib is being compared with placebo, only patients in placebo-controlled studies are included in the celecoxib group; similarly, in comparisons of celecoxib incidences with those of NSAIDs, only patients from active-controlled studies are included in the celecoxib column. This accounts for the different numbers of patients between the two celecoxib columns in the analysis tables.

A statistically significant difference ($p \leq 0.05$) was found between celecoxib (all 100 mg and 200 mg doses combined) and either placebo or NSAIDs for nine of the 12 adverse events that occurred with an incidence $\geq 3\%$ (Table 59). The incidence of dyspepsia, abdominal pain, nausea, flatulence and constipation were significantly greater in patients receiving NSAIDs than those who were treated with celecoxib. Dyspepsia, upper respiratory tract infection (URTI), diarrhea, and flatulence were significantly higher in celecoxib-treated patients when compared to those receiving placebo.

Table 59. Analysis of Adverse Events between Celecoxib 100 mg BID, 200 mg QD and 200 mg BID and Placebo or NSAIDs

Adverse Event	Celecoxib*	Placebo	p Value	Celecoxib*	NSAID	p Value
No. treated	3512	1864	-	2890	2098	-
Any event	59.9	54.6	<0.001	63.9	66.7	0.044
Headache	16.8	20.2	0.002	16.0	14.8	-
Dyspepsia	8.4	6.2	0.004	9.9	12.0	0.021
URTI	8.4	6.7	0.029	9.4	9.9	-
Diarrhea	5.4	3.8	0.008	6.2	6.1	-
Sinusitis	4.8	4.3	-	5.6	4.6	-
Abdominal pain	3.5	2.8	-	4.9	8.2	<0.001
Nausea	3.6	4.2	-	3.8	5.6	0.002
Back pain	2.7	3.6	-	3.0	2.0	0.038
Accidental injury	2.8	2.3	-	3.1	3.0	-
Rash	2.4	2.1	-	2.6	1.8	-
Flatulence	2.1	1.0	0.003	2.2	3.7	0.003
Constipation	1.8	1.9	-	1.9	4.1	<0.001

Data are expressed in percentages of patients (except for p values).

*Column combines celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.

Table 60 shows an analysis similar to that above except that celecoxib 400 mg BID is compared with placebo and NSAIDs, since it represents the highest celecoxib dose studied in North American Controlled Arthritis Trials and twice the highest recommended dosage. Significantly higher incidences of dyspepsia and diarrhea for celecoxib 400 mg BID compared to placebo were observed. Constipation was significantly more common for NSAIDs than for celecoxib.

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Table 60. Analysis of Adverse Events between Celecoxib 400 mg BID and Placebo or NSAIDs

Adverse Event	Celecoxib 400 mg BID	Placebo	p Value	Celecoxib 400 mg BID	NSAID	p Value
No. treated	615	636	-	434	443	-
Any event	60.2	55.3	-	62.0	63.0	-
Headache	14.5	22.0	<0.001	15.2	14.0	-
Dyspepsia	8.1	4.9	0.021	8.8	12.4	-
URTI	7.0	7.7	-	8.3	12.2	-
Diarrhea	6.5	3.5	0.013	6.5	4.1	-
Sinusitis	5.4	4.9	-	4.8	3.8	-
Abdominal pain	3.3	2.7	-	3.5	5.9	-
Nausea	3.6	4.6	-	4.1	4.1	-
Back pain	0.8	3.6	<0.001	0.9	0.9	-
Accidental injury	2.4	2.4	-	3.0	1.8	-
Rash	3.4	2.0	-	3.2	1.8	-
Flatulence	2.0	0.8	-	1.8	1.8	-
Constipation	0.8	2.7	0.016	0.7	2.9	0.020

Data are expressed in percentages of patients (except for p values).

6.3.5.2 North American Controlled Arthritis Trials: OA and RA Populations

Two differences in patient characteristics between the OA and RA populations from the North American Controlled Arthritis Trials were evident when demographic data were compared. In general, mean ages in patients with OA were approximately seven years higher than in RA patients. Further, for both sexes, mean weights were approximately 10 kg higher for OA patients than for RA patients.

Table 61 separately lists adverse event incidences for OA and RA patients from the North American Controlled Arthritis Trials. Comparison of the adverse events between OA and RA patients demonstrates no clinically important differences between the populations, despite the differences in mean age, the systemic nature of RA, and the increased use of concomitant medications to treat RA compared with OA.

**Table 61. Comparison of Adverse Events between OA and RA Patients:
 North American Controlled Arthritis Trials**

Adverse Event	OA				RA			
	Placebo	100 mg BID	200 mg BID	NSAID	Placebo	100 mg BID	200 mg BID	NSAID
No. treated	1329	1311	1208	1388	535	468	706	710
Any event	54.3	59.3	63.8	68.1	55.5	62.6	60.3	63.9
Headache	19.3	17.1	14.1	14.7	22.6	16.7	14.6	15.1
Dyspepsia	6.5	8.2	10.7	12.0	5.6	10.0	8.5	12.1
URTI	6.3	7.2	8.6	9.4	7.7	10.5	9.1	10.8
Diarrhea	3.8	4.8	7.2	7.1	3.7	5.6	5.5	4.2
Abdominal pain	2.8	3.1	6.2	9.1	3.0	4.1	3.4	6.3
Sinusitis	4.1	4.7	5.0	4.3	4.7	5.8	6.2	5.1
Nausea	3.8	3.5	4.0	6.6	5.4	3.8	3.3	3.7
Back pain	3.6	3.0	3.6	2.7	3.6	2.6	1.8	0.8
Accidental injury	2.2	3.5	3.1	3.5	2.4	1.7	2.4	1.7
Peripheral edema	1.3	1.6	3.0	2.4	0.7	1.3	1.8	1.5
Insomnia	2.7	2.6	2.6	2.2	1.3	1.9	2.3	2.5
Flatulence	1.1	1.9	2.3	4.3	0.7	2.8	2.3	2.5
Constipation	1.5	1.9	2.2	4.9	2.8	1.5	1.4	2.4
Pharyngitis	1.1	2.2	2.2	1.9	0.9	2.6	3.0	1.5
Coughing	1.1	1.6	1.6	2.4	1.5	1.9	3.1	1.7
Rash	2.0	2.0	1.5	1.8	2.2	3.0	4.1	1.8

Includes any adverse event with incidence $\geq 3\%$ in either the celecoxib 100 mg BID or 200 mg BID group or a control group in either OA or RA.

6.3.5.3 International Arthritis Trials

Table 62 shows the most common events in any treatment group in the International Arthritis Studies. A total of 19 types of adverse event occurred in at least 3% of patients in any treatment group. Unlike the North American Controlled Arthritis Trials, in which headache was consistently the most common event, diarrhea was the most common event in the 6-week OA study, and diarrhea, dyspepsia, and abdominal pain were more common than headache in the 24-week RA study. For all adverse events in Table 62, the incidence was higher for celecoxib 200 mg BID than for celecoxib 100 mg BID. This difference likely results from the longer duration of the RA trial (24 weeks compared with six weeks for OA).

Table 62. Adverse Events with Incidence $\geq 3\%$ in Any Treatment Group: International Arthritis Trials

Adverse Event	6 Week OA (Study 042)		24 Week RA (Study 041)	
	Celecoxib 100 mg BID	Diclofenac 50 mg BID	Celecoxib 200 mg BID	Diclofenac SR 75 mg BID
No. treated	346	341	326	329
Any event	43.6	52.8	68.1	72.6
Diarrhea	6.4	7.6	12.0	14.0
Abdominal pain	4.9	6.7	11.0	20.7
Dyspepsia	3.2	6.7	9.8	12.8
Headache	4.3	7.3	9.2	5.8
URTI	2.0	2.3	5.8	9.1
Nausea	3.2	5.0	4.6	8.2
Back pain	1.7	0.3	4.3	2.1
Dizziness	1.7	2.1	3.7	4.0
Edema peripheral	2.0	2.3	3.4	4.5
Fatigue	1.2	0.9	3.4	4.9
Pharyngitis	0.9	0.3	3.4	2.7
Coughing	0.9	0.0	3.1	2.4
Influenza-like symptoms	1.7	1.8	3.1	4.0
Rash	2.3	0.3	2.5	4.0
Pruritus	1.7	2.1	2.1	3.6
Flatulence	1.4	1.5	2.1	4.3
Vomiting	1.2	0.9	1.8	5.2
Anemia	0.0	0.3	1.5	3.0
Stomatitis	0.3	0.6	0.9	3.6

All numbers are percentages of patients unless otherwise specified.

6.3.5.4 North American Long-term Open Label Arthritis Study

Adverse events occurring at an incidence of 3% or greater in the long-term open label arthritis study (Study 024) are shown in Table 63. These adverse events generally occurred at an incidence greater than that observed with the 200 mg BID dose of celecoxib in the North American Controlled Arthritis Trials (Table 58). However, when normalized for time of exposure, the incidence for all of the adverse events listed in Table 59, except for bronchitis, are lower in Study 024 when compared to celecoxib 200 mg BID in the North American Arthritis Trials. These data provide no evidence to suggest that there is an increasing incidence for frequently occurring adverse events ($\geq 3\%$) with increasing duration of exposure to celecoxib.

Table 63. Adverse Events with ≥3% Incidence: North American Long-term Open Label Arthritis Trial

Adverse Event	Long-term Open Label Arthritis Study (n=4499)		North American Controlled Arthritis Trials* (n=914)	
	Incidence (% of Patients)	Events Per 100 Patient-Years	Incidence (% of Patients)	Events Per 100 Patient-Years
Headache	16.0	26.9	14.3	58.6
URTI	14.1	23.8	8.8	36.1
Dyspepsia	10.1	17.0	9.9	40.6
Sinusitis	9.2	15.6	5.5	22.5
Diarrhea	7.7	13.0	6.6	27.1
Accidental injury	7.2	12.0	2.9	11.8
Abdominal pain	5.5	9.3	5.2	21.3
Nausea	5.4	9.0	3.7	15.2
Back pain	4.3	7.2	3.0	12.2
Rash	4.2	7.1	2.5	10.1
Bronchitis	4.2	7.0	1.0	4.1
Dizziness	4.1	6.9	2.1	8.8
Peripheral edema	3.8	6.4	2.6	10.5
Coughing	3.5	5.9	2.1	8.8
Insomnia	3.4	5.7	2.5	10.1
Rhinitis	3.1	5.3	1.9	7.9
Urinary tract infection	3.2	5.3	1.2	4.9

* This column shows the incidence of adverse events for the celecoxib 200 mg BID dose group.

6.3.6 Adverse Events Leading to Withdrawal

6.3.6.1 North American Controlled Arthritis Trials

Table 64 shows the most common adverse events leading to discontinuation of study treatment. Overall, the incidences of any adverse event causing withdrawal ranged from 3.3% to 7.8% in patients receiving celecoxib, and no dose response relationship was evident. The highest incidence occurred in patients receiving an NSAID (9.7%). Seven types of adverse event led to withdrawal in at least 0.5% of patients in any treatment group.

Table 64. Adverse Events Causing Withdrawal with an Incidence $\geq 0.5\%$ in Any Treatment Group: North American Controlled Arthritis Trials

Adverse Event	Placebo	Celecoxib					NSAID
		50 mg BID	100 mg BID	200 mg QD	200 mg BID	400 mg BID	
No. Treated	1864	690	1779	453	1914	615	2098
Any event	6.1	7.5	7.4	3.3	7.8	6.8	9.7
Abdominal pain	0.6	0.9	0.7	0.2	0.9	0.3	2.1
Dyspepsia	0.6	0.4	0.8	0.0	0.9	0.8	1.6
Rash	0.6	1.2	0.8	0.4	0.9	1.1	0.3
Diarrhea	0.3	0.7	0.4	0.2	0.3	0.3	0.4
Nausea	0.6	0.3	0.6	0.4	0.4	0.3	0.9
Pruritus	0.2	0.0	0.4	0.0	<0.1	0.5	0.0
Esophageal ulceration	0.0	0.0	0.0	0.0	0.2	0.0	0.6

All numbers are percentages of patients unless otherwise specified.

Statistically significant differences for four types of adverse event causing withdrawal at an incidence $\geq 0.5\%$ were evident between celecoxib and NSAIDs (Table 65). For rash and pruritus the incidences were higher for celecoxib; for abdominal pain and esophageal ulceration the difference represented higher incidences for NSAIDs. No statistically significant differences were apparent between celecoxib and placebo.

Table 65. Analysis of Adverse Events Causing Withdrawal between Celecoxib and Placebo or NSAIDs

Adverse Event	Celecoxib*	Placebo	p Value	Celecoxib*	NSAID	p Value
No. treated	3512	1864	-	2890	2098	-
Any event	7.3	6.1	-	8.5	9.7	-
Abdominal pain	0.7	0.6	-	0.9	2.1	<0.001
Dyspepsia	0.9	0.6	-	1.1	1.6	-
Rash	0.9	0.6	-	0.9	0.3	0.004
Diarrhea	0.4	0.3	-	0.3	0.4	-
Nausea	0.5	0.6	-	0.4	0.9	-
Pruritus	0.2	0.2	-	0.2	0.0	0.043
Esophageal ulceration	0.0	0.0	-	0.1	0.6	0.003

Data are expressed in percentages of patients (except for p values).

*Column combines celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.

6.3.6.2 International Arthritis Trials

Table 66 shows the most common adverse events causing withdrawal in the International Arthritis Trials. Overall, the incidences of adverse events causing withdrawal were similar to those in the North American Controlled Arthritis Trials. The incidence for celecoxib 200 mg BID was higher than for 100 mg BID, due to the longer duration of the RA trial. Nine events led to withdrawal in at least 0.5% of patients in any treatment

group. For most of these events, the incidence was higher for diclofenac-treated patients than for the corresponding celecoxib group.

Table 66. Adverse Events Causing Withdrawal with Incidence $\geq 0.5\%$ in Any Treatment Group: International Arthritis Trials

Adverse Event	6 Week OA (Study 042)		24 Week RA (Study 041)	
	Celecoxib 100 mg BID	Diclofenac 50 mg BID	Celecoxib 200 mg BID	Diclofenac SR 75 mg BID
No. treated	346	341	326	329
Any event	6.4	8.5	10.1	19.4
Abdominal pain	1.2	2.6	2.8	8.8
Diarrhea	0.6	1.5	1.8	3.0
Nausea	0.6	1.8	1.5	3.3
Rash	1.2	0.0	0.9	0.3
Dyspepsia	0.3	0.3	0.6	4.6
Vomiting	0.3	0.3	0.6	1.2
Dizziness	0.0	0.0	0.3	1.5
Rash erythematous	1.2	0.0	0.3	0.0
Flatulence	0.3	0.0	0.0	1.2

All numbers are percentages of patients unless otherwise specified.

The overall incidence of adverse events causing withdrawal was statistically significantly higher for diclofenac, and all three of the statistically significant differences in individual events (abdominal pain, nausea, and dyspepsia) represented higher incidences among diclofenac-treated patients than among those who received celecoxib.

6.3.6.3 North American Long-term Open Label Arthritis Study

A total of 6.6% of the patients discontinued Study 024 due to an adverse event. Fifty percent of these withdrawals took place during the first 90-day interval following initiation of treatment. The most common adverse events leading to withdrawal were abdominal pain (0.6%), rash (0.5%), dyspepsia (0.5%), diarrhea (0.4%), nausea (0.3%), and dizziness (0.3%).

6.3.7 Serious Adverse Events

None of the serious adverse events that occurred in patients receiving celecoxib were considered by a panel of external safety consultants to be related to study medication.

Serious adverse events were defined as:

- fatal,
- life-threatening,

- permanently disabling,
- requiring, or prolonging, inpatient hospitalization,
- a congenital anomaly,
- a cancer, or
- an overdose.

6.3.7.1 Controlled Arthritis Trials

Table 67 shows the overall incidences of serious adverse events that occurred in all of the controlled arthritis trials combined, summarized by treatment group. The incidence of serious adverse events across all celecoxib dose groups were similar and generally lower than that observed for either placebo or the NSAID treatment groups. The highest incidence of serious adverse events related to gastrointestinal or myocardial function. There were 26 patients with serious gastrointestinal adverse events; 10 were NSAID-treated patients (1.9 events per 100 patient-years), five were placebo-treated patients (2.4 events per 100 patient-years), five were patients receiving 200 mg BID celecoxib treatment groups (1.1 events per 100 patient-years) and three were patients receiving 100 mg BID celecoxib (1.0 events per 100 patient-years). The remaining three serious gastrointestinal adverse events occurred in patients receiving either 25-40 mg BID celecoxib or 50 mg BID celecoxib.

Table 67. Overall Incidences of Serious Adverse Events by Dose Regimen: Controlled Arthritis Trials

	Placebo (N=1864)	Celecoxib						NSAID Control (N=2768)
		25-40 mg BID (N=253)	50 mg BID (N=690)	100 mg BID (N=2125)	200 mg QD (N=453)	200 mg BID (N=2240)	400 mg BID (N=615)	
Patients with any serious adverse event	30	1	5	26	2	49	7	59
Patient-years of exposure	207.5	15.0	116.1	289.3	47.1	465.7	87.1	535.0
Serious adverse events per 100 patient-years	14.5	6.7	4.3	9.0	4.2	10.5	8.0	11.0

There were 28 patients with serious myocardial adverse events including 13 patients with myocardial infarction and nine patients with angina pectoris. Serious myocardial adverse events occurred in 10 patients taking celecoxib 200 mg BID (2.1 events per 100 patient-years), seven placebo-treated patients (3.3 events per 100 patient-years), five patients receiving celecoxib 100 mg BID (1.7 events per 100 patient-years) and four

patients receiving NSAIDs (0.7 events per 100 patient-years). The remaining two serious myocardial adverse events occurred in patients receiving either celecoxib 200 mg QD or celecoxib 400 mg BID.

6.3.7.2 North American Long-term Open Label Arthritis Study

Table 68 summarizes the overall rates of serious adverse events occurring in the North American Long-term Open Label Arthritis Study by dose regimen. The incidence of serious adverse events in the North American Long-term Open Label Arthritis Study is similar to that observed in the controlled arthritis trials when normalized for duration of patient exposure. There were 26 patients with serious gastrointestinal adverse events in the long-term open-label arthritis trial yielding an incidence of 1.0 events per 100 patient-years as compared to 1.1 events per 100 patient-years for patients receiving 200 mg BID celecoxib in the controlled arthritis trials. There were 36 patients with serious myocardial adverse events in the North American Long-term Open Label arthritis trial resulting in an incidence of 1.3 events per 100 patient-years. This closely agrees with the incidence of serious myocardial adverse events observed with celecoxib in the controlled arthritis trials (1.7 events per 100 patient-years).

Table 68. Overall Incidences of Serious Adverse Events by Dose Regimen and Length of Exposure: North American Long-term Open-Label Arthritis Study

	100 mg BID	200 mg BID	300 mg BID	400 mg BID	Any Dose
Patients with any serious adverse event	56	114	35	42	244
Patient-years of exposure	518.8	1271.0	340.1	465.2	2672.4
Serious adverse events per 100 patient-years	10.8	9.0	10.3	9.0	9.1

6.3.7.3 Analgesia Trials

One serious adverse event occurred in the post-oral surgery studies: a rectal carcinoma discovered in a patient who received a single dose of celecoxib 100 mg in Study 005.

Nine serious adverse events occurred in the post-orthopedic or post-general surgery pain trials: four in placebo patients (back pain, dysphagia, abscess, and impaired healing); one in a patient receiving celecoxib 100 mg (pneumothorax); two in patients receiving celecoxib 200 mg (ileus and infection); and two in patients receiving Darvocet-N 50 (cellulitis and infection).

6.3.8 Deaths

There were 26 deaths in patients who participated in the North American Controlled Arthritis Trials or the North American Long-term Open Label Arthritis Study of celecoxib and nine additional deaths in patients participating in other ongoing studies, for an overall total of 35 deaths. None were considered by an external panel of safety consultants to have been related to study medication.

6.3.8.1 Deaths in Completed Controlled Trials and the North American Long-term Open Label Arthritis Study

There were eight deaths during the controlled trials or within 28 days after the last dose of study medication. Of these, four patients had received celecoxib (200 mg QD, 100 mg BID or 200 mg BID) and four patients received NSAIDs. Five deaths were due to cardiovascular causes. Two of the cardiovascular-related deaths occurred in celecoxib-treated patients (2.0 cardiovascular deaths per 1000 patient-years) and three in patients receiving NSAIDs (5.6 cardiovascular deaths per 1000 patient-years).

Eighteen deaths occurred during the North American Long-term Open Label Arthritis Study or within 28 days after the last dose of study medication through May 1, 1998. Seven deaths occurred in patients who received 200 mg BID, two deaths in patients who received 300 mg BID and nine deaths in patients treated with celecoxib 400 mg BID. Fourteen deaths were related to cardiovascular causes yielding an incidence of 3.3 cardiovascular deaths per 1000 patient-years.

6.3.8.2 Deaths in Ongoing Studies

Nine deaths occurred in celecoxib studies that are ongoing. One death was in a post-surgical pain study (Study 082), one was in an open-label arthritis study (Study 058) (Investigational New Drug Application [IND] 48,395). Six deaths occurred in studies of Alzheimer's disease (IND 53,125), and one was in a chemoprevention study (IND 51,926 held by the NCI).

6.3.9 Clinical Laboratory Results

The studies used for this analysis are a subset of the 12-week North American Arthritis Trials that were used in the preceding analysis of adverse events. For analyses of all clinical laboratory results, the five pivotal 12-week arthritis trials that contained both a

placebo and active (naproxen) control group (Studies 020, 021, 022, 023, and 054) are used to facilitate a comparison of celecoxib versus placebo, celecoxib versus naproxen and naproxen versus placebo within the same group of studies. Mean changes in hematology and biochemistry and urinalysis laboratory results from baseline to the final treatment visit are shown for placebo, celecoxib and naproxen treatment groups in Tables 69-71. Due to the large total number of patients that were enrolled in these studies, many small changes in clinical laboratory values between treatment groups were statistically significant but not clinically meaningful. The incidence of clinically significant changes in laboratory results are discussed in the review of safety related to body systems. (Section 6.3.10).

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Table 69. Mean Changes in Hematology Laboratory Results: North American 12-Week Placebo- and Active-Controlled Arthritis Trials

Assessment (units)	Treatment	Number of Patients	Baseline Mean	Final Visit - Mean Change from Baseline
Hemoglobin (g/dL)	Celecoxib(a)	2183	13.64	0.00 * #
	Placebo	1075	13.69	0.06)
	Naproxen	1069	13.67	-0.18 *
Hematocrit	Celecoxib(a)	2183	0.414	0.002 #
	Placebo	1075	0.416	0.003
	Naproxen	1069	0.416	-0.003 *
RBC (x10 ¹² /L)	Celecoxib(a)	2183	4.52	0.01 * #
	Placebo	1075	4.53	0.03
	Naproxen	1069	4.55	-0.05 *
WBC (x10 ⁹ /L)	Celecoxib(a)	2183	7.136	-0.201 * #
	Placebo	1075	7.075	0.017
	Naproxen	1069	7.053	0.047
Platelet Count (x10 ⁹ /L)	Celecoxib(a)	2171	271.8	-6.1 * #
	Placebo	1071	268.6	3.2
	Naproxen	1059	263.2	2.5
Neutrophil Count (x10 ⁹ /L)	Celecoxib(a)	2182	4.665	-0.142 * #
	Placebo	1073	4.543	0.053
	Naproxen	1067	4.564	0.044
Lymphocyte Count (x10 ⁹ /L)	Celecoxib(a)	2182	1.826	-0.04 *
	Placebo	1073	1.874	-0.010
	Naproxen	1067	1.852	-0.023
Monocyte Count (x10 ⁹ /L)	Celecoxib(a)	2182	0.454	-0.014 #
	Placebo	1073	0.461	-0.010
	Naproxen	1067	0.450	0.002
Eosinophil Count (x10 ⁹ /L)	Celecoxib(a)	2182	0.138	0.001 * #
	Placebo	1073	0.144	-0.014
	Naproxen	1067	0.140	0.026 *
Basophil Count (x10 ⁹ /L)	Celecoxib(a)	2182	0.053	-0.003 #
	Placebo	1073	0.054	-0.002
	Naproxen	1067	0.052	0.000
Partial Thromboplastin Time (sec.)	Celecoxib(a)	2028	27.95	0.12
	Placebo	996	27.86	0.44
	Naproxen	992	27.96	-0.19 *
Prothrombin Time (sec.)	Celecoxib(a)	2042	12.70	-0.02
	Placebo	1004	12.69	0.07
	Naproxen	1000	12.69	0.08

* Significantly different from placebo in change from Baseline; $p \leq 0.05$.

Significantly different from naproxen in change from Baseline; $p \leq 0.05$.

a) Combines celecoxib 100 mg and 200 mg BID

Table 70. Mean Changes in Biochemistry Laboratory Results: North American 12-Week Placebo- and Active-Controlled Arthritis Trials

Assessment (units)	Treatment	Number of Patients	Baseline Mean	Final Visit - Mean Change from Baseline
Total Bilirubin (µmol/L)	Celecoxib(a)	2189	8.4	0.2 #
	Placebo	1080	8.3	0.1
	Naproxen	1072	8.2	-0.1 *
Alkaline Phosphatase (U/L)	Celecoxib(a)	2185	70.1	0.5 * #
	Placebo	1079	69.9	1.8
	Naproxen	1071	70.8	-0.4 *
AST (U/L)	Celecoxib(a)	2189	21.5	-0.2
	Placebo	1080	21.4	-0.3
	Naproxen	1972	21.5	-0.4
ALT (U/L)	Celecoxib(a)	2189	20.4	-0.7 #
	Placebo	1080	20.2	-0.3
	Naproxen	1072	20.7	-1.3 *
CPK (U/L)	Celecoxib(a)	2189	104.1	-3.9 #
	Placebo	1080	99.7	-7.2
	Naproxen	1072	102.6	3.5 *
Creatinine (µmol/L)	Celecoxib(a)	2190	69.0	-2.1 #
	Placebo	1080	70.0	-1.4
	Naproxen	1072	69.9	-0.8
BUN (mmol/L)	Celecoxib(a)	2190	5.67	0.09 * #
	Placebo	1080	5.71	-0.48
	Naproxen	1072	5.70	0.51 *
Uric Acid (µmol/L)	Celecoxib(a)	2190	300.3	4.0 *
	Placebo	1080	299.5	9.1
	Naproxen	1072	302.8	2.1 *
Glucose (mmol/L)	Celecoxib(a)	2188	5.735	0.239
	Placebo	1080	5.659	0.331
	Naproxen	1071	5.779	0.126 *
Protein (g/L)	Celecoxib(a)	2190	71.5	-0.9 * #
	Placebo	1080	71.3	0.0
	Naproxen	1072	71.2	-1.3 *
Albumin (g/L)	Celecoxib(a)	2189	39.9	-0.7 #
	Placebo	1080	39.8	-0.6
	Naproxen	1072	39.6	0.2 *
Sodium (mmol/L)	Celecoxib(a)	2189	139.6	0.5
	Placebo	1078	139.6	0.3
	Naproxen	1071	139.6	0.3
Potassium (mmol/L)	Celecoxib(a)	2183	4.24	0.00 *
	Placebo	1075	4.22	-0.04
	Naproxen	1069	4.23	0.01 *
Chloride (mmol/L)	Celecoxib(a)	2189	105.0	0.1 *
	Placebo	1078	105.1	-0.3
	Naproxen	1071	105.0	0.1 *
Calcium (mmol/L)	Celecoxib(a)	2190	2.308	-0.025 *
	Placebo	1080	2.299	-0.004
	Naproxen	1072	2.300	-0.020 *
Inorganic Phosphorous (mmol/L)	Celecoxib(a)	2184	1.133	0.000 #
	Placebo	1079	1.136	-0.001
	Naproxen	1070	1.124	-0.043 *

* Significantly different from placebo in change from Baseline; $p \leq 0.05$.

Significantly different from naproxen in change from Baseline; $p \leq 0.05$.

a) Combines celecoxib 100 mg and 200 mg BID

Table 71. Mean Changes in Urinalysis Laboratory Results: North American 12-Week Placebo- and Active-Controlled Arthritis Trials

Assessment (units)	Treatment	Number of Patients	Baseline Mean	Final Visit Mean Change from Baseline
Specific Gravity	Celecoxib(a)	2136	1.0183	0.0003* #
	Placebo	1034	1.0186	-0.0007
	Naproxen	1040	1.0178	0.0012 *
pH	Celecoxib(a)	2136	5.4	-0.0 #
	Placebo	1034	5.4	-0.0
	Naproxen	1040	5.3	0.1 *
Urine RBC (/HPF)	Celecoxib(a)	2136	1.8	-0.2
	Placebo	1034	2.1	-0.5
	Naproxen	1040	1.5	0.2
Urine WBC (/HPF)	Celecoxib(a)	2136	2.7	-0.1
	Placebo	1034	2.8	0.3
	Naproxen	1040	2.4	0.1

* Significantly different from placebo in change from Baseline; $p \leq 0.05$.

Significantly different from naproxen in change from Baseline; $p \leq 0.05$.

a) Combines celecoxib 100 mg and 200 mg BID

6.3.10 Grouped Safety Results

6.3.10.1 GI Effects

6.3.10.1.1 Adverse Events

Table 71 presents all GI adverse events with an incidence of 0.5% or more in any treatment group in the North American Controlled Arthritis Trials. The highest incidence of GI adverse events occurred in patients receiving NSAIDs and the incidences of individual GI adverse events were generally higher for patients receiving NSAIDs than for celecoxib for almost all doses. Little variation was evident among celecoxib doses and no increase in incidence with increasing doses was suggested.

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Table 72. GI Adverse Events with Incidence $\geq 0.5\%$ in Any Treatment Group: North American Controlled Arthritis Trials

Adverse Event	Placebo	Celecoxib					NSAID
		50 mg BID	100 mg BID	200 mg QD	200 mg BID	400 mg BID	
No. treated	1864	690	1779	453	1914	615	2098
Any GI event	18.5	24.1	23.8	15.5	27.8	23.3	35.4
Dyspepsia	6.2	8.1	8.7	4.6	9.9	8.1	12.0
Diarrhea	3.8	5.4	5.0	3.5	6.6	6.5	6.1
Abdominal pain	2.8	4.5	3.4	2.0	5.2	3.3	8.2
Nausea	4.2	3.8	3.6	2.4	3.7	3.6	5.6
Flatulence	1.0	2.3	2.1	2.2	2.3	2.0	3.7
Constipation	1.9	1.4	1.8	1.1	1.9	0.8	4.1
Tooth disorder	1.5	1.3	1.9	1.5	1.6	1.5	2.2
Vomiting	0.5	1.0	0.9	0.2	1.4	2.3	1.6
Hiatal hernia	<0.1	0.1	0.1	0.0	1.1	0.0	1.4
Gastroesophageal reflux	0.4	1.0	0.7	0.0	0.9	0.5	0.7
Gastroenteritis	0.7	1.2	0.8	0.4	0.8	0.8	1.0
Stomatitis	0.5	0.4	1.2	0.4	0.5	0.3	1.3
Esophageal ulceration	0.0	0.0	0.0	0.0	0.2	0.0	0.7
Gastric ulcer(a)	0.0	0.0	<0.0	0.0	0.1	0.0	0.5

All numbers are percentages of patients unless otherwise specified.

a) Symptomatic ulcers diagnosed by endoscopy or other means; ulcers found at scheduled visits in the UGI endoscopy studies were not recorded as adverse events.

Table 73 shows statistical analyses of the GI adverse events among treatment groups. In all eight GI adverse events for which the difference between celecoxib and NSAID was statistically significant, the incidence was higher for the NSAID. The incidence of dyspepsia, diarrhea and flatulence were significantly higher in celecoxib-treated patients when compared to placebo.

Table 73. Analysis of GI Adverse Events between Celecoxib and Placebo or NSAID: North American Controlled Arthritis Trials

Adverse Event	Celecoxib*	Placebo	p Value	Celecoxib*	NSAID	p Value
No. treated	3512	1864	-	2890	2098	-
Any GI event	23.5	18.5	<0.001	27.7	45.4	<0.001
Dyspepsia	8.4	6.2	0.004	9.9	12.0	0.021
Diarrhea	5.4	3.8	0.008	6.2	6.1	-
Abdominal pain	3.5	2.8	-	4.9	8.2	<0.001
Nausea	3.6	4.2	-	3.8	5.6	0.002
Flatulence	2.1	1.0	0.003	2.2	3.7	0.003
Constipation	1.8	1.9	-	1.9	4.1	<0.001
Tooth disorder	1.7	1.5	-	1.9	2.2	-
Vomiting	0.9	0.5	-	1.3	1.6	-
Hiatal hernia	<0.1	<0.1	-	0.8	1.4	0.024
GE Reflux	0.6	0.4	-	0.9	0.7	-
Gastroenteritis	0.7	0.7	-	0.9	1.0	-
Stomatitis	0.9	0.5	-	0.8	1.3	-
Esophageal ulceration	0.0	0.0	-	0.1	0.7	0.002
Gastric ulcer	<0.1	0.0	-	0.1	0.5	0.020

Data are expressed in percentages of patients (except for p values).

* Column combines celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.

The percentages of patients withdrawing due to a GI adverse event ranged from 0.7% to 3.2% in celecoxib groups, with no evidence of an escalation with increasing dose. This compares to withdrawal rates for GI adverse events of 6.3% NSAIDs and 2.0% for placebo. Only two individual GI adverse events led to withdrawal in more than 1.0% of patients in any treatment group: abdominal pain and dyspepsia. Both of these led to withdrawal more commonly in NSAID patients than in celecoxib patients. The difference between celecoxib and NSAIDs was statistically significant for abdominal pain (0.9% vs. 2.1%; p<0.001).

6.3.10.1.2 Summary and Conclusions

Celecoxib was superior to NSAIDs with respect to tolerability, as assessed by a lower incidence of GI adverse events, as well as withdrawals due to GI adverse events. Overall, GI adverse events with celecoxib were greater than placebo. However, the only GI adverse events that were frequent in occurrence ($\geq 1\%$) and associated with significantly greater incidence or withdrawal rates for celecoxib than placebo included dyspepsia, flatulence, and diarrhea.

6.3.10.2 Hepatic Effects

6.3.10.2.1 Adverse Events

All hepatic adverse events reported by $\geq 0.5\%$ of patients in any treatment group in the North American Controlled Arthritis Trials are listed in Table 74. Statistically significant differences between treatments are summarized in Table 75. The incidence of adverse events related to elevations in liver transaminases was significantly greater in patients treated with NSAIDs when compared to celecoxib-treated patients. No statistically significant differences were evident between celecoxib and placebo.

Table 74. Hepatic-Related Adverse Events as Reported by the Investigator with an Incidence $\geq 0.5\%$: North American Controlled Arthritis Studies

Adverse Event	Placebo (N=1864)	Celecoxib					NSAID (N=2098)
		50 mg BID (N=690)	100 mg BID (N=1779)	200 mg QD (N=453)	200 mg BID (N=1914)	400 mg BID (N=615)	
Any Hepatic Event	0.9	0.7	0.9	0.0	0.9	0.7	1.5
AST Elevated(a)	0.4	0.6	0.4	0.0	0.4	0.3	0.9
ALT Elevated(a)	0.5	0.4	0.6	0.0	0.5	0.3	1.0

Data are expressed as percent of patients.

a) Based on the Investigator's evaluation of clinical laboratory results and designation as an adverse event.

Table 75. Analysis of Hepatic Adverse Events Between Celecoxib and Placebo or NSAIDs

Adverse Event	Celecoxib(a) (N=3612)	Placebo (N=1864)	p-value	Celecoxib(a) (N=2890)	NSAID (N=2098)	p-value
Any Hepatic Event	0.8	0.9	-	0.8	1.5	0.026
AST Elevated(b)	0.4	0.4	-	0.3	0.9	0.008
ALT Elevated(b)	0.5	0.5	-	0.4	1.0	0.023

Data are expressed as percent of patients (except for p values).

a) Column combines celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.

b) Based on the Investigator's evaluation of clinical laboratory results and designation as an adverse event.

6.3.10.2.2 Adverse Events Causing Withdrawal

A total of 11 patients were withdrawn due to either a gall bladder disorder, abnormal hepatic function, or increased liver transaminases in the North American Controlled Arthritis Trials. There was one patient in the placebo group who withdrew ($<0.1\%$), two each in the celecoxib 100 mg and 200 mg BID dose groups (0.1%), and 6 in the NSAID treatment group (0.3%). Analyses of these findings revealed no statistically significant results.

6.3.10.2.3 Serious Adverse Events

There were four serious adverse events related to the hepatic and biliary system in the controlled arthritis trials. Two of the patients who received NSAIDs developed a gall bladder disorder, one patient receiving placebo developed cholecystitis, and one patient taking celecoxib 100 mg BID developed cholecystitis. There were six serious adverse events in the Long-term Open Label Arthritis Study related to the hepatic and biliary system. All six were cases of cholelithiasis.

6.3.10.2.4 Clinical Laboratory Results

The incidence of clinical laboratory changes related to hepatic function that occurred in the North American 12-Week Placebo- and Active-controlled Arthritis Trials (Studies 020, 021, 022, 023 and 054) are summarized in Table 76. No significant treatment-related effects were observed. A low percentage of patients with normal Baseline clinical laboratory results were found to have changes for any liver function test in all three treatment groups.

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