Table 26: Analysis of ACR20 with ITT population

Treatment	# of ACR20 response/# of subjects	p-value w.r.t Placebo
Placebo	94/301 (31.2%)	
12.5 mg	62/148 (41.9%)	0.037
25 mg	160/311 (51.4%)	< 0.001
Naproxen	79/149 (53.0%)	< 0.001

An additional re-analysis was performed by the Agency statistician. This analysis was based on imputing subjects in the placebo group with missing data as successes and other groups as failures, as a conservative approach. As can be seen from Table 26, rofecoxib 12.5, 25 mg and naproxen remain significantly superior to placebo for the ACR 20 endpoint.

Other endpoints in which 25 mg rofecoxib and naproxen treatments showed similar and significant improvements versus placebo were the duration of morning stiffness and Patient's and Investigator's Assessments of Response to treatment. Similar and significant reductions in rescue paracetamol usage were observed for all patients on active treatments, and all active groups showed similarly small but significant changes on the SF-36 physical component subscale. Discontinuations due to lack of efficacy were significantly less for all active treatments than for placebo: 17.6, 10.6, and 12.1% of patients in the 12.5-mg and 25-mg rofecoxib, and naproxen groups, respectively, versus 26.9% of patients on placebo, discontinued for lack of efficacy.

Therapeutic benefits were consistent for all active study treatments among patients who took concomitant corticosteroids, methotrexate, and DMARDs.

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Table 27: Summary changes from parts I to II

Summary of Changes From Parts I to II for Primary Endpoints
Mean Difference Between the Last 2 Assessments in Part I
and the First 2 Assessments in Part II

Treatment (Base/Extension)	N	Part I Mean†	Part II Mean‡	Mean Change§	SD‖ of Change	LS Mean¶ Change	95% CI# for LS Mean¶ Change
Tender Joint Count (Total 68)							
Placebo/25 mg	94	13.32	10.07	-3.24	5.19	-3.43	(-4.86, -2.00)
Placebo/Naproxen	104	15.19	12.13	-3.06	8.39	-2.83	(-4.19, -1.46)
25 mg/25 mg	130	11.99	11.41	-0.58	6.44	-0.75	(-2.02, 0.53)
25 mg/50 mg	114	13.22	12.12	-1.10	8.97	-0.96	(-2.32, 0.39)
12.5 mg/25 mg	110	12.51	11.28	-1.23	6.06	NA††	(-2.37, -0.10)††
Naproxen/Naproxen	118	12.66	10.69	-1.96	5.15	NA††	(-2.89, -1.03)††
Swollen Joint Count (Total 66)							
Placebo/25 mg	94	9.91	8.45	-1.46	4.25	-1.48	(-2.33, -0.64)
Placebo/Naproxen	104	10.40	8.91	-1.50	4.54	-1.42	(-2.23, -0.61)
25 mg/25 mg	130	9.60	9.81	0.20	4.27	0.11	(-0.60, 0.81)
25 mg/50 mg	114	11.07	10.44	-0.64	3.80	-0.59	(-1.34, 0.16)
12.5 mg/25 mg	110	9.77	9.53	-0.24	3.81	NA††	(-0.95, 0.47)††
Naproxen/Naproxen	118	10.04	9.29	-0.75	3.91	NA††	(-1.45, -0.04)††
Patient Global Assessment of Disease Activity (0 to 100 Visual Analog Scale)							
Placebo/25 mg	94	44.90	35.41	-9.49	15.76	-9.53	(-12.68, -6.38)
Placebo/Naproxen	104	45.44	35.86	-9.58	16.86	-9.47	(-12.48, -6.45)
25 mg/25 mg	130	38.28	37.53	-0.75	16.08	-0.55	(-3.11, 2.01)
25 mg/50 mg	114	37.49	34.10	-3.39	13.86	-3.38	(-6.09, -0.67)
12.5 mg/25 mg	110	38.18	36.05	-2.14	15.14	NA††	(-4.97, 0.69)††
Naproxen/Naproxen	118	38.04	37.26	-0.78	14.95	NA††	(-3.48, 1.92)††
Investigator Global Assessment of Disease Activity (0 to 4 Likert Scale)							
Placebo/25 mg	94	1.40	1.02	-0.38	0.72	-0.36	(-0.50, -0.22)
Placebo/Naproxen	103	1.35	1.01	-0.34	0.76	-0.34	(-0.47, -0.20)
25 mg/25 mg	130	1.25	1.32	0.08	0.75	0.05	(-0.07, 0.18)
25 mg/50 mg	114	1.30	1.24	-0.07	0.75	-0.07	(-0.20, 0.06)
12.5 mg/25 mg	110	1.28	1.23	-0.05	0.62	NA††	(-0.17, 0.07)††
Naproxen/Naproxen	118	1.29	1.21	-0.08	0.67	NA††	(-0.20, 0.04)††

† The average of last 2 assessments in Part I.
‡ The average of first 2 assessments in Part II.
§ Between Part I and Part II.
‖ Standard deviation.
¶ Least-square mean.
# Confidence interval.
†† There is no least-squares mean since this treatment sequence is not analyzed by the Analysis of Covariance model. The 95% CI is for raw mean change.

Data Source: [4.3]

As further evidence of efficacy, the sponsor analyzed the changes from part I to part II for the primary endpoints. Subjects with dose changes from placebo to either naproxen or rofecoxib 25 mg showed similar improvements in all primary endpoints. For example, the LS mean change for tender joints between part I and II was –3.43 for placebo/25 mg and –2.83 for placebo/naproxen.

Those individuals maintained on either 25 mg rofecoxib or naproxen through out both parts did not appear to worsen as evidenced by little change in primary endpoint scores (although this was only an additional 2 week period) . Subjects who received 12.5 mg in part I and 25 mg in part II showed marginal changes after dose escalation. Concomitant medications were maintained unchanged during the entire 14 week period.

In addition, the Division requested that the sponsor include an analysis from week 0-14 in patients who received 25 mg through the whole period. This analysis provided by the sponsor demonstrates that there was no statistical difference between the rofecoxib and naproxen groups in terms of tender, swollen joints, patient and investigator global assessment, or ACR 20 (regardless of completion status).

Reviewers comments/conclusions of study results

Rofecoxib 25 mg was demonstrated to be significantly better versus placebo at each of the four primary endpoints. On an absolute basis, both 25 mg rofecoxib and naproxen showed an approximately 3-joint reduction in the number of tender joints, a 1- to 2-joint reduction in the number of swollen joints, a 7- to 10-mm improvement in the patient global assessment (100-mm VAS), and an approximately 0.3-unit improvement in the investigator global assessment (0 to 4 Likert scale). Rofecoxib was significantly better than placebo for the secondary endpoint, the ACR 20. Furthermore, this was true when the modified ITT was examined (the sponsors originally defined group and analysis) as well as when all randomized subjects were examined, regardless of having any post-baseline data (the Divisions' requested analysis). Other endpoints in which 25 mg rofecoxib and naproxen treatments showed similar and significant improvements versus placebo were the duration of morning stiffness and Patient's and Investigator's Assessments of Response to treatment. Supportive of these conclusions are the data from the 2 week extension (part I to part II extension). Subjects maintained on 25 or 50 mg of rofecoxib continued to demonstrate improvement over baseline with little change over the additional 2 weeks. Subjects whose dose was increased from placebo to 25 mg rofecoxib or naproxen demonstrated improvement in primary endpoints over the 2 week extension and the changes with rofecoxib were comparable to those with naproxen . It is noted however that the efficacy of naproxen waned over time although this was likely not clinically relevant. However, it is important to examine the efficacy of rofecoxib over longer periods of time to assess whether efficacy is maintained.

In summary, this study demonstrates that rofecoxib 25 mg daily was superior to placebo in the treatment of the signs and symptoms of RA over the 12 weeks of this study. In terms of efficacy, rofecoxib 25 mg was not statistically different from the positive comparator naproxen, and was superior to 12.5 mg. Rofecoxib 12.5 mg once daily appears to be a less effective (subtherapeutic) dose for the treatment of RA (although based on ACR20 it appears to be effective).

Trial 097

The trial design of protocol 097 was identical to study 096 including inclusion/exclusion criteria and endpoints, except that the doses of rofecoxib studied were 25 and 50 mg and compared to placebo and naproxen.

Table 28: Tender joint count

Analysis of Endpoint: Tender Joint Count (Total 68)
Mean Change From Baseline (Flare/Randomization Visit)
Time-Weighted Average Over 12 Weeks
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean† Change	95% CI‡ for LS Mean† Change
Placebo	294	31.49	20.91	-10.58	12.56	-10.42	(-11.57, -9.27)
25 mg	315	30.70	17.42	-13.27	10.94	-13.38	(-14.49, -12.27)
50 mg	295	30.94	16.53	-14.41	10.70	-14.42	(-15.57, -13.27)
Naproxen	146	31.56	17.02	-14.54	9.90	-14.37	(-16.00, -12.74)

Comparisons Between Treatment Groups	Difference in LS Mean†	95% CI‡ for Difference	p-Value
With Placebo			
Rofecoxib§ versus Placebo	-3.48	(-4.88, -2.08)	<0.001
50 mg versus Placebo	-4.00	(-5.63, -2.38)	<0.001
25 mg versus Placebo	-2.96	(-4.56, -1.36)	<0.001
Naproxen versus Placebo	-3.95	(-5.95, -1.96)	<0.001
Between Active Treatments			
50 mg versus 25 mg	-1.04	(-2.64, 0.55)	0.200
50 mg versus Naproxen	-0.05	(-2.05, 1.94)	0.960
25 mg versus Naproxen	0.99	(-0.98, 2.97)	0.324

Effect	p-Value	Pooled SD‖
Baseline Covariate	<0.001	10.05
Low-Dose Corticosteroid Use	0.288	
Treatment	<0.001	

† LS = Least-squares mean.
‡ CI = Confidence interval.
§ Average of 25- and 50-mg doses.
‖ SD = Standard deviation.

Data Source: [4.3]

For tender joint count all treatments including rofecoxib at both 25 and 50 mg were significantly superior to placebo (p<.001). There was no difference between rofecoxib 25 and 50 mg, and both were comparable to naproxen. **Note: this was the sponsor's defined ITT population.**

Table 29: Tender joint count

Analysis of End Point: Tender Joint Count (total 68 joints)
Mean Change from Baseline (Flare/Randomization Visit)
Time-Weighted Average Over 12 Weeks
(All randomized subjects, regardless of having any post-baseline data)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean† Change	95% CI for LS Mean† Change
Placebo	299	31.49	20.91	-10.40	12.52	-10.24	(-11.38, -9.10)
25 mg	315	30.70	17.42	-13.27	10.94	-13.37	(-14.49, -12.26)
50 mg	297	30.94	16.53	-14.31	10.73	-14.32	(-15.47, -13.17)
Naproxen	147	31.56	17.02	-14.44	9.94	-14.27	(-15.90, -12.64)

Comparisons Between Treatment Groups	Difference in LS Mean	95% CI for Diff.	p-Value
With Placebo			
Rofecoxib‡ vs. Placebo	-3.61	(-5.00, -2.21)	<0.001
50 mg vs. Placebo	-4.08	(-5.70, -2.46)	<0.001
25 mg vs. Placebo	-3.13	(-4.73, -1.54)	<0.001
Naproxen vs. Placebo	-4.03	(-6.02, -2.04)	<0.001
Between Active Treatments			
50 mg vs. 25 mg	-0.95	(-2.54, 0.65)	0.245
50 mg vs. Naproxen	-0.05	(-2.04, 1.95)	0.964
25 mg vs. Naproxen	0.90	(-1.07, 2.87)	0.371

Effect:	p-Value	Pooled SD
Baseline Covariate	<0.001	10.06
Low Dose Corticosteroid Use	0.189	
Treatment	<0.001	

† Least squares mean
‡ Average 25 and 50 mg

A re-analysis of tender joint counts using the all randomized population (requested by the Division) demonstrated similar findings to the original analysis. All treatment groups were superior to placebo ($p<.001$)and were not significantly different from each other.

Table 30: Swollen joint count

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Analysis of Endpoint: Swollen Joint Count (Total 66)
Mean Change From Baseline (Flare/Randomization Visit)
Time-Weighted Average Over 12 Weeks
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean† Change	95% CI‡ for LS Mean† Change
Placebo	294	17.09	11.28	-5.81	7.65	-5.68	(-6.39, -4.97)
25 mg	315	16.39	9.61	-6.78	7.34	-6.93	(-7.61, -6.24)
50 mg	295	16.72	9.89	-6.83	6.91	-6.84	(-7.55, -6.13)
Naproxen	146	17.20	10.35	-6.84	6.78	-6.68	(-7.69, -5.67)

Comparisons Between Treatment Groups	Difference in LS Mean†	95% CI‡ for Difference	p-Value
With Placebo			
Rofecoxib§ versus Placebo	-1.20	(-2.07, -0.34)	0.006
50 mg versus Placebo	-1.16	(-2.16, -0.16)	0.023
25 mg versus Placebo	-1.24	(-2.23, -0.26)	0.014
Naproxen versus Placebo	-1.00	(-2.23, 0.24)	0.113
Between Active Treatments			
50 mg versus 25 mg	0.08	(-0.90, 1.07)	0.868
50 mg versus Naproxen	-0.16	(-1.40, 1.07)	0.794
25 mg versus Naproxen	-0.25	(-1.47, 0.97)	0.690

Effect	p-Value	Pooled SD‖
Baseline Covariate	<0.001	6.20
Low-Dose Corticosteroid Use	0.514	
Treatment	0.055	

† LS = Least-squares mean.
‡ CI = Confidence interval.
§ Average of 25- and 50-mg doses.
‖ Standard deviation.

Data Source: [4.3]

An analysis of swollen joints demonstrated that both 25 and 50 mg rofecoxib but not naproxen were superior to placebo (p=.014, .023, and .113 respectively). Furthermore, the 25 and 50 mg doses were not different from each other.

Table 31: Swollen joint count

Analysis of End Point: Swollen Joint Count (total 66 joints)
Mean Change from Baseline (Flare/Randomization Visit)
Time-Weighted Average Over 12 Weeks
(All randomized subjects, regardless of having any post-baseline data)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean† Change	95% CI for LS Mean† Change
Placebo	299	17.09	11.28	-5.72	7.63	-5.59	(-6.29, -4.88)
25 mg	315	16.39	9.61	-6.78	7.34	-6.92	(-7.61, -6.24)
50 mg	297	16.72	9.89	-6.78	6.91	-6.79	(-7.50, -6.09)
Naproxen	147	17.20	10.35	-6.80	6.78	-6.63	(-7.64, -5.63)

Comparisons Between Treatment Groups	Difference in LS Mean	95% CI for Diff.	p-Value
With Placebo			
Rofecoxib‡ vs. Placebo	-1.27	(-2.13, -0.41)	0.004
50 mg vs. Placebo	-1.21	(-2.20, -0.21)	0.018
25 mg vs. Placebo	-1.34	(-2.32, -0.35)	0.008
Naproxen vs. Placebo	-1.05	(-2.27, 0.18)	0.094
Between Active Treatments			
50 mg vs. 25 mg	0.13	(-0.85, 1.11)	0.796
50 mg vs. Naproxen	-0.16	(-1.39, 1.07)	0.797
25 mg vs. Naproxen	-0.29	(-1.51, 0.92)	0.639

Effect:	p-Value	Pooled SD
Baseline Covariate	<0.001	6.20
Low Dose Corticosteroid Use	0.390	
Treatment	0.034	

† Least squares mean
‡ Average 25 and 50 mg

A re-analysis of swollen joint using the all randomized patient group (requested by the Division) revealed similar results to the above analysis. Again, both 25 and 50 mg

rofecoxib were superior to placebo(p=.008 and .018 respectively), but naproxen was not (p=.094).

Table 32: Patients global assessment

Analysis of Endpoint: Patient's Global Assessment of Disease Activity (0 to 100 VAS[†])
Mean Change From Baseline (Flare/Randomization Visit)
Time-Weighted Average Over 12 Weeks
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean[‡] Change	95% CI[§] for LS Mean Change
Placebo	294	75.66	53.11	-22.55	21.97	-22.14	(-24.37, -19.90)
25 mg	314	73.93	45.29	-28.65	20.47	-29.09	(-31.25, -26.92)
50 mg	295	75.86	43.43	-32.44	20.60	-31.91	(-34.14, -29.68)
Naproxen	145	73.65	42.52	-31.12	19.60	-31.72	(-34.90, -28.54)

Comparisons Between Treatment Groups	Difference in LS Mean[‡]	95% CI[§] for Difference	p-Value
<u>With Placebo</u>			
Rofecoxib[‖] vs. Placebo	-8.36	(-11.08, -5.65)	<0.001
50 mg versus Placebo	-9.77	(-12.93, -6.62)	<0.001
25 mg versus Placebo	-6.95	(-10.06, -3.85)	<0.001
Naproxen versus Placebo	-9.59	(-13.47, -5.70)	<0.001
<u>Between Active Treatments</u>			
50 mg versus 25 mg	-2.82	(-5.93, 0.28)	0.075
50 mg versus Naproxen	-0.19	(-4.07, 3.70)	0.924
25 mg versus Naproxen	2.63	(-1.21, 6.47)	0.179

Effect	p-Value	Pooled SD[¶]
Baseline Covariate	<0.001	19.49
Low-Dose Corticosteroid Use	0.416	
Treatment	<0.001	

† VAS = Visual analogue scale.
‡ LS = Least-squares mean.
§ CI = Confidence interval.
‖ Average of 25- and 50-mg doses.
¶ SD = Standard deviations.

Data Source: [4.3]

Results for patients global assessment of disease activity demonstrated that all treatments were superior to placebo (p<.001).

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Table 33: Patients global assessment

Analysis of End Point: Patient Global Assessment of Disease Activity (0 to 100 VAS scale)
Mean Change from Baseline (Flare/Randomization Visit)
Time-Weighted Average Over 12 Weeks
(All randomized subjects, regardless of having any post-baseline data)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean† Change	95% CI for LS Mean† Change
Placebo	299	75.66	53.12	-22.17	21.98	-21.75	(-23.98, -19.53)
25 mg	315	73.93	45.27	-28.56	20.51	-28.98	(-31.15, -26.81)
50 mg	297	75.86	43.43	-32.22	20.70	-31.68	(-33.91, -29.44)
Naproxen	147	73.65	42.43	-30.70	19.80	-31.29	(-34.46, -28.12)

Comparisons Between Treatment Groups	Difference in LS Mean	95% CI for Diff.	p-Value
With Placebo			
Rofecoxib‡ vs. Placebo	-8.58	(-11.29, -5.87)	<0.001
50 mg vs. Placebo	-9.93	(-13.07, -6.78)	<0.001
25 mg vs. Placebo	-7.23	(-10.33, -4.12)	<0.001
Naproxen vs. Placebo	-9.54	(-13.41, -5.66)	<0.001
Between Active Treatments			
50 mg vs. 25 mg	-2.70	(-5.81, 0.41)	0.089
50 mg vs. Naproxen	-0.39	(-4.27, 3.49)	0.843
25 mg vs. Naproxen	2.31	(-1.53, 6.14)	0.238

Effect:	p-Value	Pooled SD
Baseline Covariate	<0.001	19.57
Low Dose Corticosteroid Use	0.261	
Treatment	<0.001	

† Least squares mean
‡ Average 25 and 50 mg

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Again, a re-analysis of this endpoint using all randomized patients demonstrated that all treatments were superior to placebo (p<.001) and that there was no statistical difference between the treatments.

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Table 34: Investigators global assessment

Analysis of Endpoint: Investigator's Global Assessment of Disease Activity
(0 to 4 Likert Scale) Mean Change From Baseline (Flare/Randomization Visit)
Time-Weighted Average Over 12 Weeks
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean† Change	95% CI‡ for LS Mean Change
Placebo	291	2.58	1.90	-0.68	0.98	-0.66	(-0.75, -0.57)
25 mg	314	2.54	1.55	-0.98	0.91	-0.99	(-1.07, -0.90)
50 mg	291	2.51	1.50	-1.00	0.85	-1.03	(-1.12, -0.94)
Naproxen	145	2.57	1.46	-1.11	0.87	-1.10	(-1.22, -0.97)

Comparisons Between Treatment Groups	Difference in LS Mean†	95% CI‡ for Difference	p-Value
With Placebo			
Rofecoxib§ versus Placebo	-0.35	(-0.45, -0.24)	<0.001
50 mg versus Placebo	-0.37	(-0.49, -0.24)	<0.001
25 mg versus Placebo	-0.33	(-0.45, -0.21)	<0.001
Naproxen versus Placebo	-0.43	(-0.59, -0.28)	<0.001
Between Active Treatments			
50 mg versus 25 mg	-0.04	(-0.16, 0.08)	0.540
50 mg versus Naproxen	0.07	(-0.08, 0.22)	0.379
25 mg versus Naproxen	0.11	(-0.04, 0.26)	0.166

Effect	p-Value	Pooled SD‖
Baseline Covariate	<0.001	0.76
Low-Dose Corticosteroid Use	0.877	
Treatment	<0.001	

† LS = Least-squares mean.
‡ CI = Confidence interval.
§ Average of 25- and 50-mg doses.
‖ SD = Standard deviation.

Data Source: [4.3]

An analysis of investigators global assessment of disease activity demonstrated that all treatments were superior to placebo ($p<.001$) and that there was no difference demonstrated between treatments.

Table 35: Investigators global assessment

Analysis of End Point: Investigator Global Assessment of Disease Activity (0 to 4 Likert scale)

Mean Change from Baseline (Flare/Randomization Visit)

Time-Weighted Average Over 12 Weeks

(All randomized subjects, regardless of having any post-baseline data)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean† Change	95% CI for LS Mean† Change
Placebo	299	2.58	1.90	-0.66	0.98	-0.64	(-0.73, -0.55)
25 mg	315	2.54	1.55	-0.98	0.91	-0.98	(-1.07, -0.90)
50 mg	297	2.51	1.51	-0.98	0.86	-1.00	(-1.09, -0.92)
Naproxen	147	2.57	1.45	-1.10	0.87	-1.08	(-1.20, -0.96)

Comparisons Between Treatment Groups	Difference in LS Mean	95% CI for Diff.	p-Value
With Placebo			
Rofecoxib‡ vs. Placebo	-0.35	(-0.46, -0.25)	<0.001
50 mg vs. Placebo	-0.36	(-0.49, -0.24)	<0.001
25 mg vs. Placebo	-0.34	(-0.46, -0.22)	<0.001
Naproxen vs. Placebo	-0.44	(-0.59, -0.29)	<0.001
Between Active Treatments			
50 mg vs. 25 mg	-0.02	(-0.14, 0.10)	0.743
50 mg vs. Naproxen	0.07	(-0.08, 0.23)	0.333
25 mg vs. Naproxen	0.10	(-0.06, 0.25)	0.214

Effect:	p-Value	Pooled SD
Baseline Covariate	<0.001	0.77
Low Dose Corticosteroid Use	0.842	
Treatment	<0.001	

† Least squares mean
‡ Average 25 and 50 mg

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A re-analysis of this endpoint using all randomized patients (requested by the Division) also demonstrated that all treatments were superior to placebo ($p<.001$) and that there was no difference between treatment groups.

Table 36: Frequency of patients who met ACR 20

Frequency (%) of Patients Who Met ACR20 Responder Index Criteria
During 12 Weeks of Study
(Intention-to-Treat Approach)

ACR20† Responders and Completers			
Treatment		Frequency‡ m/n (%)	
Placebo		119/295 (40.34)	
25 mg		157/315 (49.84)	
50 mg		155/295 (52.54)	
Naproxen		76/146 (52.05)	
Between-Group Comparisons	Difference in Percent	(95% CI§)	p-Value‖
Rofecoxib¶ versus Placebo	10.81	(3.95, 17.67)	0.002
50 mg versus Placebo	12.20	(4.22, 20.19)	0.003
25 mg versus Placebo	9.50	(1.64, 17.37)	0.018
Naproxen versus Placebo	11.72	(1.87, 21.57)	0.017
50 mg versus 25 mg	2.70	(-5.23, 10.64)	0.502
50 mg versus Naproxen	0.49	(-9.42, 10.39)	0.886
25 mg versus Naproxen	-2.21	(-12.02, 7.59)	0.661
ACR20† Responders: regardless of completion status			
Treatment		Frequency‡ m/n (%)	
Placebo		124/295 (42.03)	
25 mg		168/315 (53.33)	
50 mg		169/295 (57.29)	
Naproxen		83/146 (56.85)	
Between-Group Comparisons	Difference in Percent	(95% CI§)	p-Value‖
Rofecoxib¶ versus Placebo	13.21	(6.33, 20.09)	<0.001
50 mg versus Placebo	15.25	(7.28, 23.23)	<0.001
25 mg versus Placebo	11.30	(3.42, 19.18)	0.005
Naproxen versus Placebo	14.82	(5.00, 24.63)	0.003
50 mg versus 25 mg	3.95	(-3.93, 11.84)	0.326
50 mg versus Naproxen	0.44	(-9.38, 10.26)	0.895
25 mg versus Naproxen	-3.52	(-13.26, 6.23)	0.485

† ACR20 = American College of Rheumatology Rheumatoid Arthritis Clinical Response Criteria.
‡ m/n where m = number of patients with response and n = total number of patients evaluated.
§ CI = Confidence interval.
‖ From Cochran-Mantel-Haenszel test with stratum (corticosteroid use) as a stratification factor.
¶ Average of 25- and 50-mg doses.

Data Source: [4.3]

Table 37: Proportion of patients who met ACR 20

Proportions of Patients Who Met ACR20 Responder Index Criteria During 12 Weeks of Study (All Randomized Subjects)

ACR20 Responder and Completers			
Treatment		Frequency † (%)	
Placebo		119/299 (39.80%)	
25 mg		157/315 (49.84%)	
50 mg		155/297 (52.19%)	
Naproxen		76/147 (51.70%)	
Between-Group Comparisons	Diff in Percent	(95% C.I.)	p-value ‡
Rofecoxib‡ vs. Placebo	11.18	(4.36, 18.00)	0.002
50 mg vs. Placebo	12.39	(4.45, 20.33)	0.003
25 mg vs. Placebo	10.04	(2.21, 17.87)	0.012
Naproxen vs. Placebo	11.90	(2.10, 21.70)	0.015
50 mg vs. 25 mg	2.35	(-5.57, 10.27)	0.560
50 mg vs. Naproxen	0.49	(-9.39, 10.36)	0.891
25 mg vs. Naproxen	-1.86	(-11.64, 7.93)	0.712
ACR20 Responder: regardless of completion status			
Treatment		Frequency † (%)	
Placebo		124/299 (41.47%)	
25 mg		168/315 (53.33%)	
50 mg		169/297 (56.90%)	
Naproxen		83/147 (56.46%)	
Between-Group Comparisons	Diff in Percent	(95% C.I.)	p-value ‡
Rofecoxib‡ vs. Placebo	13.59	(6.76, 20.43)	<0.001
50 mg vs. Placebo	15.43	(7.50, 23.36)	<0.001
25 mg vs. Placebo	11.86	(4.02, 19.71)	0.003
Naproxen vs. Placebo	14.99	(5.22, 24.76)	0.002
50 mg vs. 25 mg	3.57	(-4.31, 11.45)	0.376
50 mg vs. Naproxen	0.44	(-9.36, 10.24)	0.900
25 mg vs. Naproxen	-3.13	(-12.86, 6.60)	0.533

† m/n where m=number of patients with response and n=total number of patients evaluated.

‡ Average 25 and 50 mg

‡ From Cochran-Mantel-Haenszel test with stratum (corticosteroid use) as a stratificaton factor.

The ACR 20 was the endpoint preferred by the Division although it was a secondary endpoint in these studies. For both ACR 20 responders regardless of completion status, and ACR 20 responders and completers, all treatments were superior to placebo and there was no difference between treatment groups (see Table 36: Frequency of patients who met ACR 20). A re-analysis of ACR20 using the all randomized population (requested by the Division; see Table 37) demonstrated that all treatments were superior to placebo for both the responders and responders and completers groups, and there was no significant differences between treatment groups.

In protocol 97 there were 4, 0, 2, and 1 patients missing from the original analysis in the placebo, rofecoxib 25 mg, rofecoxib 50 mg and naproxen groups respectively who were included in this additional analysis. This analysis (performed by the sponsor) imputed missing values as no response.

Table 38: Analysis of ACR20 using the true ITT population

Treatment	# of ACR20 response/# of subjects	p-value w.r.t Placebo
Placebo	123/299 (41.1%)	
25 mg	157/315 (49.8%)	0.030
50 mg	155/297 (52.2%)	0.007
Naproxen	76/147 (51.7%)	0.031

A further re-analysis of the ACR 20 was performed by the Agency statistician. This was based on imputing the subjects in the placebo group with missing data as successes and other groups as failures. Again, all treatment groups were superior to placebo(Table 38: Analysis of ACR20 using the true ITT population).

All active treatments showed significant and similar improvements versus placebo, on other key secondary measurements. These included patient pain assessment and the HAQ disability score. Other endpoints where all 3 active treatments showed similar and significant improvements versus placebo were the duration of morning stiffness, and patient and investigator assessments of response to treatment. Similar and significant reductions in rescue paracetamol usage were observed for all patients on active treatment, and all active groups showed similarly small but significant improvements on the SF-36 component subscales. Discontinuations due to lack of efficacy were significantly less for all active treatments than placebo: 5.0, 4.4 and 3.4% of patients in the 25 and 50 mg, and naproxen groups, respectively, versus 13% of patients on placebo, discontinued for lack of efficacy.

Table 39: Summary of changes from parts I to II

Summary of Changes From Part I to Part II for Primary Endpoints
Mean Difference Between the Average of the Last 2 Assessments in Part I
and the First 2 Assessments in Part II

Treatment (Base/Extension)	N	Part I Mean†	Part II Mean‡	Mean Change§	SD of Change	LS Mean‖ Change	95% CI¶ for LS Mean Change
Tender Joint Count (Total 68 Joints)							
Placebo/25 mg	114	16.51	12.13	-4.38	6.39	-4.59	(-5.75, -3.43)
Placebo/Naproxen	123	18.21	14.64	-3.57	7.53	-3.39	(-4.51, -2.28)
25 mg/25 mg	139	15.93	14.96	-0.97	7.23	-0.92	(-2.04, 0.19)
25 mg/50 mg	141	14.80	13.58	-1.22	6.33	-1.29	(-2.40, -0.18)
50 mg/50 mg	249	14.21	12.77	-1.44	6.34	NA#	(-2.23, -0.66)#
Naproxen/Naproxen	124	13.98	12.52	-1.46	6.29	NA#	(-2.57, -0.35)#
Swollen Joint Count (Total 66 Joints)							
Placebo/25 mg	114	8.83	7.85	-0.98	3.64	-1.01	(-1.65, -0.36)
Placebo/Naproxen	123	9.25	8.30	-0.96	3.65	-0.93	(-1.55, -0.30)
25 mg/25 mg	139	8.68	7.87	-0.81	3.75	-0.81	(-1.41, -0.21)
25 mg/50 mg	141	8.57	8.49	-0.09	3.59	-0.09	(-0.69, 0.51)
50 mg/50 mg	249	9.01	8.38	-0.63	4.24	NA#	(-1.16, -0.11)#
Naproxen/Naproxen	124	9.82	8.92	-0.90	4.40	NA#	(-1.68, -0.13)#
Patient's Global Assessment of Disease Activity (0 to 100 Visual Analog Scale)							
Placebo/25 mg	114	44.04	35.90	-8.14	15.70	-8.67	(-11.35, -5.99)
Placebo/Naproxen	123	47.43	38.01	-9.42	16.40	-8.84	(-11.43, -6.24)
25 mg/25 mg	139	42.13	39.30	-2.83	15.18	-2.72	(-5.02, -0.43)
25 mg/50 mg	140	41.08	38.81	-2.28	13.90	-2.41	(-4.70, -0.13)
50 mg/50 mg	250	40.42	40.14	-0.28	14.29	NA#	(-2.05, 1.50)#
Naproxen/Naproxen	124	37.69	36.89	-0.79	14.71	NA#	(-3.38, 1.79)#
Investigator's Global Assessment of Disease Activity (0 to 4 Likert Scale)							
Placebo/25 mg	114	1.58	1.18	-0.40	0.73	-0.42	(-0.54, -0.30)
Placebo/Naproxen	123	1.65	1.28	-0.37	0.73	-0.35	(-0.47, -0.24)
25 mg/25 mg	139	1.45	1.27	-0.18	0.56	-0.17	(-0.26, -0.07)
25 mg/50 mg	141	1.34	1.27	-0.08	0.67	-0.09	(-0.19, 0.00)
50 mg/50 mg	249	1.38	1.29	-0.09	0.69	NA#	(-0.17, -0.00)#
Naproxen/Naproxen	125	1.33	1.28	-0.05	0.64	NA#	(-0.16, 0.06)#

† The average of last 2 assessments in Part I.
‡ The average of first 2 assessments in Part II.
§ Between Part I and Part II.
‖ Least-square mean.
¶ CI = Confidence interval.
# There is no Least-square mean since this treatment sequence is not analyzed by the ANCOVA model. The 95% CI is for raw mean change.

Data Source: [4.3]

Those individuals treated with placebo in part I and rofecoxib 25 mg in part II, showed improvements in the scores of all primary endpoints. These improvements were comparable to the changes seen with going from placebo to naproxen. Individuals going from rofecoxib 25 mg in part I to 50 mg in part II showed modest improvements in all endpoints which, except for patient global assessment, were no better than the changes seen when patients remained on rofecoxib 50 mg for both parts I and II. Those subjects remaining on the same treatment in both parts maintained the improvements seen at the end of part I. In addition the Division requested

that the sponsor provide an analysis from weeks 0-14 in patients who received 25 and 50 mg through the whole period. This analysis was provided by the sponsor. There were no significant differences between the 25, 50, and naproxen groups for the endpoints of tender, swollen joints, patient and physician global assessment, and ACR 20.

Conclusions

In terms of efficacy, rofecoxib 25 and 50 mg was demonstrated to be significantly superior to placebo at each of the four primary endpoints over the 12 week study. On an absolute basis, all active treatments showed a 3- to 4-joint reduction in the number of tender joints, a one-joint reduction in the number of swollen joints, a 7- to 10-mm improvement in the patient global assessment (100-mm VAS), and a 0.3- to 0.4-unit improvement in the investigator global assessment (0 to 4 Likert scale). Rofecoxib was significantly superior to placebo for the secondary endpoint, the ACR 20. Furthermore, this was true when either the modified (sponsor) ITT population was examined (the sponsors originally defined group and analysis), or when all randomized subjects were examined (the Divisions' requested analysis. Individuals whose dose was increased between parts I and II showed improvement over the 2 week extension period. In transitioning from Part I to Part II treatment, no differences in response were seen for patients remaining on 25 mg, compared with those escalated from 25 to 50 mg rofecoxib. As a positive control, patients who switched from placebo to either 25 mg rofecoxib or naproxen showed significant, and similar improvements.

In study 097, although rofecoxib 50 mg was in general, numerically superior to 25 mg, this was not statistically different. In general naproxen was numerically but not statistically superior to rofecoxib 25 mg. Naproxen and rofecoxib 50 mg were essentially no different in terms of efficacy.

In summary, based on this study, rofecoxib 25 or 50 mg appear to be efficacious in the treatment of the signs and symptoms of RA over the 12 weeks of this study. The 25 mg dose and the 50 mg dose do not appear to be significantly different. Again, the 12.5 mg dose does not appear to be efficacious. *The fact that 50 mg provides no additional efficacy as compared to the 25 mg dose should be described in the revised label.*

Trial 068P1

Study 068P1 is a phase II eight week trial to investigate the use of rofecoxib in the treatment of the signs and symptoms of RA. A continuation of this trial P2 will be reviewed below. These trials are supportive of efficacy.

Objectives/rationale

Primary Objectives

Three primary objectives for the study were evaluated in Part I:

1. To demonstrate the clinical efficacy of rofecoxib in the treatment of RA during 8 weeks of treatment.
2. To further define the clinically active dose range of rofecoxib in the treatment of RA.
3. To investigate the safety and tolerability of continuous administration of rofecoxib for 52 weeks in patients with RA.

Secondary Objectives

1. To compare the safety and efficacy of rofecoxib in patients using concomitant methotrexate (MTX) versus patients not using MTX.
2. To compare the incidence of discontinuation due to lack of efficacy in the 3 rofecoxib and placebo treatment groups.
3. To monitor patient and investigator assessments of disease status and patient pain assessment with chronic administration of rofecoxib (52 weeks—Part II).
4. To explore the effects of rofecoxib on health-related quality of life as evaluated by the SF-36 (a standard short form 36-question survey used to evaluate health-related quality of life).

Design

This 2-part, double-blind, 52-week, parallel-group study was conducted in patients with RA. Part I consisted of an 8-week, double-blind, placebo-controlled treatment period, conducted under in-house blinding, to evaluate the safety and tolerability, and to define the clinically effective dose range of rofecoxib in RA patients. The primary analysis of efficacy focused on the average of clinical assessments recorded following 2, 4, and 8 weeks of study therapy.

Following completion of Part I, patients entered Part II, a double-blind continuation, to remain on study therapy for an additional 44 weeks. In Part I, patients who met all entry criteria (following discontinuation of prestudy NSAIDs) were randomized to rofecoxib 50 mg daily, rofecoxib 25 mg daily, rofecoxib – ng daily, or placebo for 8 weeks. Acetaminophen was provided to patients throughout Part I of the study as "rescue medication" for breakthrough pain. Acetaminophen use was recorded. Patients discontinued acetaminophen at least 24 hours prior to any assessments of clinical efficacy.

Inclusion Criteria

1. Patient was male or female and =18 years of age, not considered "morbidly obese" (i.e., at a weight that interfered with usual or typical vocational/avocational activities and/or was a serious independent health risk, likely to result in medical complications within the next year).
2. Female patients had a serum beta-hCG level consistent with a nongravid state at the prestudy visit and agreed to use an acceptable form of contraception beginning at least 7 days prior to treatment and continuing at least 14 days after Visit 5.0 or a discontinuation visit. Acceptable forms of contraception were:

abstinence, oral birth control pills, or double-barrier contraception (partner using condom and patient using diaphragm, contraceptive sponge, or IUD). Women who were postmenopausal (i.e., no menses for the previous year. If cessation of menses was within 18 months, follicle stimulating hormone [FSH] levels were documented as elevated into the postmenopausal range prestudy.) or had a hysterectomy or tubal ligation were exempt.
3. Patient satisfied at least 4 of 7 ARA 1987 revised criteria for the diagnosis of RA at the time of diagnosis.
4. The diagnosis of RA was present for at least 6 months prior to study start and no earlier than 16 years of age.
5. Patient was ARA functional Class I, II, or III.
6. Patient Global Assessment of Disease Activity (VAS of 100 mm) at the prestudy visit was less than 80 mm.
7. Patient reported a past history of positive therapeutic benefit with NSAIDs, and took an NSAID on a regular basis (>25 of the previous 30 days) at a therapeutic dose level for at least 30 days prior to study enrollment. Patients were permitted the following concurrent antirheumatic therapy: oral or intramuscular (IM) gold salts, azathioprine, hydroxychloroquine, chloroquine, or sulfasalazine provided that the dose had been stable for at least the previous 6 months. One-third of patients enrolled could take MTX at a dose =20 mg per week provided that the dose had been stable for 3 months.
8. At Visit 2.0, patients were assessed after a "washout" of prestudy NSAID and satisfied both activity and flare criteria before randomization. The minimum and maximum washout duration depended upon the particular prestudy NSAID and were prespecified.

9. Activity Criteria at Visit 2.0
Patient Global Assessment of Disease Activity =40 mm, and
Number of joints that were tender =9, and
Number of swollen joints =6.

10. Flare Criteria at Visit 2.0
An increase in Patient Global Assessment of Disease Activity by 15 mm over the value at Visit 1.0, and
An increase in number of tender joints by 20% over the number at Visit 1.0.
Note: At Visit 2.0, patients had at least 9 tender joints and an increase in the number of tender joints of =20% from Visit 1.0. (No minimum number of tender joints was required at Visit 1.0.)

11. Patient was willing to avoid excess alcohol for the duration of the study and unaccustomed physical activity (e.g., weight lifting, initiation of physical therapy) during Part I.
12. Excepting RA, patient was judged to be in general good health based on medical history, physical examination, and routine laboratory tests.
13. Patient was able to understand and complete study questionnaires, including questions requiring a visual analog scale (VAS) response.
14. Patient understood the study procedures and agreed to participate in the study by giving written informed consent.

Exclusion Criteria

1. Patient was mentally or legally incapacitated, had significant emotional problems at the time of the study, or had a history of psychosis.
2. Patient had a concurrent medical/arthropathic disease that could confound or interfere with evaluation of efficacy including, but not limited to: systemic lupus, spondyloarthropathy, polymyalgia rheumatica, gout, pseudogout, psoriatic arthritis, Paget's disease, and ochronosis.
3. Patient had a history of gastric, biliary, or small intestinal surgery that resulted in clinical malabsorption.
4. Patient's estimated creatinine clearance—Men: (140-age) x weight (kg)/(serum creatinine [mg/dL] x 72); Women: (0.85) (140-age) x weight (kg)/(serum creatinine [mg/dL] x 72)—was =30 mL/min or serum creatinine was greater than 2.0.
5. Patient had angina or congestive heart failure with symptoms that occurred at rest or with minimal activity.
Note: Patients with a history of myocardial infarction, coronary angioplasty, or coronary arterial bypass grafting over 1 year prior to study start were eligible.
6. Patient had uncontrolled hypertension.
Note: Patients with medically controlled hypertension (diastolic blood pressure less than 95, systolic blood pressure less than 165) were eligible.
7. Patient had a history of stroke or transient ischemic attack within the past 2 years.
8. Patient had a history of active hepatitis or hepatic disease within the previous 2 years.

9. Patient had a history of neoplastic disease. Patients with a history of leukemia, lymphoma, or myeloproliferative disease were ineligible for the study and no exceptions applied. Exceptions to the malignancy exclusion are given immediately below.
Patients with adequately treated basal cell carcinoma or carcinoma in situ of the cervix.
Patients successfully treated for malignancies =10 years prior to screening, if, in the judgment of the investigator and the treating physician, follow-up revealed no evidence of recurrence from the time of treatment through the time of screening.
Patients highly unlikely to sustain a recurrence during the duration of the study, in the joint opinion of the Merck monitor and investigator.

10. Patient had evidence of occult GI bleeding as documented by any 1 of 3 stool Hemoccult screens obtained and read prior to allocation.
11. Patient had a history of any illness that, in the opinion of the investigator, might have confounded the results of the study, posed an additional risk to the patient, or contraindicated treatment with an NSAID such as naproxen.

12. Patients were excluded from participation for:
Misoprostol or sucralfate use within the past 1 month.
Recent sustained use (for any period longer than 4 consecutive days during the month prior to study start) of H_2 blockers (cimetidine, ranitidine, famotidine, nizatidine), antacids, or a proton pump inhibitor (e.g., omeprazole, lansoprazole) at prescription doses, or doses indicated for treatment of active gastroduodenal ulcers. (Patients taking occasional

H2 blockers or antacids were permitted to continue this type of use during the study.) Patients not exceeding over-the-counter doses of ranitidine (75 mg twice daily), famotidine (10 mg twice daily), cimetidine (200 mg twice daily), and nizatidine (75 mg twice daily) were eligible for allocation and could continue therapy. Patients taking calcium-containing antacids solely for calcium supplementation were permitted in the study.
Use of topical, oral, or systemic analgesic medications within 5 days of study entry and for the duration of Part I. Acetaminophen use was permitted prior to entry. (Restrictions on the use of acetaminophen during the study were detailed.)
Ongoing treatment with warfarin.
Ongoing ticlopidine or low-dose aspirin (325 mg or less, daily or every other day) use. (Patients were not to stop taking ticlopidine or low-dose aspirin in order to participate in the study.)
MTX at a dose >20 mg per week.
Ongoing cyclosporin A treatment.
Intra-articular, intramuscular, or intravenous corticosteroids within 3 months prior to screening.
Concurrent use of both MTX and oral corticosteroids.
Note: One-third of the patients enrolled could take oral corticosteroids during Part I provided that the patient: had taken oral corticosteroids for the past 3 months; and had remained on a stable dose (no higher than the equivalent of 7.5 mg daily of oral prednisone) for the past month and the dose was anticipated to remain stable for the duration of Part I.
Patients were permitted the following concurrent antirheumatic therapies: oral or IM gold salts, azathioprine, hydroxychloroquine, chloroquine, or sulfasalazine; provided that the dose had been stable for at least the previous 6 months. One-third of patients enrolled could have been taking oral, subcutaneous, or IM MTX dose =20 mg per week provided that the dose had been stable for 3 months.

13. Patient's medical regimen had undergone changes in the past month (i.e., dosage adjustments, addition, or discontinuation of medicines) or the investigator anticipated that changes in concurrent medications would be made during Part I.
14. Patient had clinically significant abnormalities on prestudy clinical examination or laboratory safety tests (e.g., serum transaminases were =150% of the upper limit of normal).
15. Patient was currently a user (including "recreational use") of any illicit drugs or had a history (within the past 5 years) of drug or alcohol abuse.
16. Patient had donated a unit of blood or plasma or participated in another clinical study with an investigational agent within the last 4 weeks. (Patients unwilling to refrain from donating blood or blood products were excluded.)
17. Patient had previously been exposed to rofecoxib in a clinical study. (Patients previously enrolled in a rofecoxib study and allocated to placebo, as verified by the Merck monitor, could participate in this study.)

Table 40: Study flow chart

Study Flow Chart for Part I

Clinic Visit I.D. #:	1.0	2.0	3.0	4.0	5.0	If Discon-
Duration of Treatment:	Screening	Initiate	2 Weeks	4 Weeks	8 Weeks	tinued
Review of entry criteria	X	X				
ARA functional class	X					
Informed consent	X					
Medical history	X					
Interim history and monitor for adverse experiences		X	X	X	X	X
Vital signs	X	X	X	X	X	X
Weight	X	X	X	X	X	X
Physical examination	X				X	X
Hemoccult	X					
Rheumatoid factor	X					
CBC, chemistry, UA	X	X	X	X	X	X
Serum β-hCG†	X					
Urine β-hCG†		X§	X	X	X	X
C-reactive protein	X	X	X	X	X	X
ECG	X					X
Plasma sample for archive		X	X	X‡	X	X
Dispense study medication		X	X	X	X	
Study medication tablet count			X	X	X	X
Dispense acetaminophen	X	X	X	X		X
Acetaminophen tablet count		X	X	X	X	X
Patient Global Assessment of Pain	X	X	X	X	X	X
Patient Global Assessment of Disease Activity	X	X	X	X	X	X
Investigator Global Assessment§ of Disease Activity	X	X	X	X	X	X
Duration of AM stiffness	X	X	X	X	X	X
No. of tender/no. of swollen joints	X	X	X	X	X	X
Health Assessment Questionnaire (HAQ)	X	X	X	X	X	X
Patient Global Assessment of Response to Therapy			X	X	X	X
Investigator Global Assessment of Response to Therapy			X	X	X	X
SF-36	X	X			X	X

† Urine and serum β-hCG samples were obtained from women of childbearing potential only.
‡ Patients were instructed not to take morning dose until after the plasma archive sample was obtained at Visit 4.0.
§ Urine β-hCG was negative prior to dosing.

Data Source: [3.2]

Endpoints for this study were similar to those used in studies 096 and 097.

Table 41: Efficacy endpoints

Efficacy Endpoints: Definition of Baseline and Direction of Improvement

Endpoint (Scales)	Definition of Baseline	Improvement
Primary		
Total 68 Tender Joint Count	Visit 2.0	Decreases
Total 66 Swollen Joint Count	Visit 2.0	Decreases
Patient Global Assessment of Disease Activity (0- to 100-mm VAS)	Visit 2.0	Decreases
Investigator Global Assessment of Disease Activity (0 to 4 Likert)	Visit 2.0	Decreases
Key Secondary		
ACR20 Responder Index	Visit 2.0	Increases
Patient Global Assessment of Pain (0- to 100-mm VAS)	Visit 2.0	Decreases
Stanford Health Assessment Questionnaire (HAQ)	Visit 2.0	Decreases
Other		
Patient Global Assessment of Response to Therapy (0 to 4 Likert scale)	No baseline value	Decreases†
Investigator Global Assessment of Response to Therapy (0 to 4 Likert scale)	No baseline value	Decreases†
Discontinuation Due to Lack of Efficacy	No baseline value	None
Duration of Morning Stiffness (minutes)		
Acetaminophen Use (for rescue) (tablets/day)	Visit 2.0	Decreases
C-Reactive Protein (mg/dL)	Visit 2.0	Decreases
SF-36	Visit 2.0	Decreases
O'Brien Global Statistic	Visit 2.0	Decreases
† Numerical results were multiplied by -1 to show improvement with decreasing, rather than increasing numbers.		

Data Source: Not Applicable

Statistical considerations

No adjustment for multiplicity was made because only 1 primary hypothesis for efficacy and 1 for safety were specified. The sponsor used a step-down trend test to control the error rate for comparing multiple-dose groups with placebo. The sponsor used the average over time controls for serial assessments, and required significant results for 3 out of 4 primary endpoints to address multiplicity.

Primary efficacy analyses were based on the intention-to-treat principle, i.e., inclusion of all patients with a baseline and at least 1 post baseline measurement. Analyses were performed on the average change from baseline of observed data only, while the last-value-carry-forward method was used for longitudinal graphs. Since the primary and most secondary endpoints were analyzed as the averages over the treatment period, no missing values were imputed (e.g., data points were not carried forward). A corroborative per-protocol analysis was also performed for

the primary endpoints. The per-protocol (PP) analysis population excluded patients and/or data points with clinically important protocol deviations based on prespecified criteria.

Table 42: Listing of endpoints

Listing of Endpoints and Their Statistical Analyses

Endpoints	Statistical Method	Analysis Approaches
Primary		
Tender Joint Count	ANCOVA	ITT and PP
Swollen Joint Count	ANCOVA	ITT and PP
Patient Global Assessment of Disease Activity	ANCOVA	ITT and PP
Investigator Global Assessment of Disease Activity	ANCOVA	ITT and PP
Key Secondary		
ACR20 Responder Index	Fisher's exact test	ITT
Patient Global Assessment of Pain	ANCOVA	ITT
Stanford Health Assessment Questionnaire (HAQ)	ANCOVA	ITT
Secondary		
Patient Global Assessment of Response to Therapy	ANCOVA	ITT
Investigator Global Assessment of Response to Therapy	ANCOVA	ITT
Discontinuation Due to Lack of Efficacy	Fisher's exact test	ITT
Duration of Morning Stiffness	ANCOVA	ITT
Acetaminophen Use (for Rescue)	ANCOVA	ITT
C-Reactive Protein	ANCOVA	ITT
SF-36	ANCOVA	ITT
O'Brien's Global Statistic	ANCOVA	ITT
ITT = Intention-to-treat; PP = per-protocol.		

Data Source: [3.2]

The primary, key secondary, and other endpoints (excluding Discontinuation Due to Lack of Efficacy) were evaluated as the average (change from baseline, if measured at baseline) of all measurements obtained during the 8-week treatment period. The primary endpoints were also evaluated as time-weighted (where the weights were the time increments since the last observation) averages of all measurements obtained during the 8-week treatment period, and at last observed time point up to Week 8 (Visit 5). Baseline was defined as the values at the flare/randomization visit. The LS mean (with standard error [SE]) change from baseline was stratified by treatment group and plotted over the 8-week treatment period for each efficacy endpoint. For intention-to-treat approach, missing values were imputed through the last-value-carried-forward approach.

Results

Table 43: Number of patients excluded

Number of Patients Excluded in Primary Endpoints

Endpoint	Treatment	Randomized	Included in Intention-To-Treat	
			Total Included (Excluded From ITT)	Included in PP (Excluded From PP)
Total 68 Tender Joint Count				
	Placebo	168	163 (5)	146 (17)
	Rofecoxib – mg	158	156 (2)	142 (14)
	Rofecoxib 25 mg	171	163 (8)	147 (16)
	Rofecoxib 50 mg	161	161 (0)	139 (22)
Total 66 Swollen Joint Count				
	Placebo	168	163 (5)	146 (17)
	Rofecoxib – mg	158	156 (2)	142 (14)
	Rofecoxib 25 mg	171	163 (8)	147 (16)
	Rofecoxib 50 mg	161	161 (0)	139 (22)
Patient Assessment of Disease Activity (VAS)				
	Placebo	168	167 (1)	148 (19)
	Rofecoxib – ng	158	158 (0)	144 (14)
	Rofecoxib 25 mg	171	169 (2)	153 (16)
	Rofecoxib 50 mg	161	161 (0)	139 (22)
Investigator Assessment of Disease Activity (Likert)				
	Placebo	168	165 (3)	146 (19)
	Rofecoxib –mg	158	158 (0)	144 (14)
	Rofecoxib 25 mg	171	167 (4)	152 (15)
	Rofecoxib 50 mg	161	160 (1)	138 (22)
All 4 Primary Endpoints				
	Placebo	168	168 (0)	148 (20)
	Rofecoxib – ng	158	158 (0)	144 (14)
	Rofecoxib 25 mg	171	171 (0)	153 (18)
	Rofecoxib 50 mg	161	161 (0)	139 (22)

Data Source: [4.1]

The numbers of patients excluded from various analyses is shown in the table. Similar numbers of patients were excluded from the placebo and rofecoxib 25 mg groups.

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Table 44: Patient accounting

Patient Accounting

	Placebo	Rofecoxib — mg	25 mg	50 mg	Total
ENTERED Part I	168	158	171	161	658
Male (age range)	47 (24 to 86)	38 (30 to 76)	36 (33 to 81)	31 (37 to 75)	152 (24 to 86)
Female (age range)	121 (26 to 80)	120 (26 to 80)	135 (26 to 80)	130 (27 to 76)	506 (26 to 80)
Total Patients	168	158	171	161	658
COMPLETED Part I (Visits 1 to 5)	131 (78.0)	134 (84.2)	145 (84.8)	135 (83.9)	545 (82.9)
DISCONTINUED during Part I	37 (22.0)	24 (15.2)	26 (15.2)	26 (16.1)	113 (17.2)
Clinical adverse experience	5 (3.0)	5 (3.2)	8 (4.7)	10 (6.2)	28 (4.3)
Laboratory adverse experience	0 (0.0)	2 (1.3)	1 (0.6)	2 (1.2)	4 (0.6)
Lack efficacy	24 (14.3)	16 (10.1)	11 (6.4)	11 (6.8)	62 (9.4)
Lost to follow-up	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	2 (0.3)
Patient discontinued	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	2 (0.3)
Patient moved	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Patient withdrew consent	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.3)
Protocol deviation	5 (3.0)	0 (0.0)	4 (2.3)	3 (1.8)	12 (1.8)

Data Source: [4.34; 4.33; 4.16]

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Eight, 10, and 5 subjects in the rofecoxib 25 and 50 mg and placebo doses respectively, discontinued due to clinical adverse events. Four, 3 and 5 subjects respectively discontinued for a protocol deviation.

There were no clinically meaningful differences between the treatment groups for characteristics, including height, weight, duration of disease, concomitant use of DMARDs (including MTX) and corticosteroids, and rheumatoid-factor positivity. There were no important differences between treatment groups in mean baseline values (Visit 2.0) for any primary efficacy endpoint (duration of morning stiffness was slightly longer in the placebo group-230 minutes- versus the rofecoxib 25 mg group-202minutes). There were slightly more patients diagnosed with depression in the placebo group (16.1%) versus the 25 mg rofecoxib group (10.5%). There were no clinically meaningful differences between treatment groups in frequency or type of concomitant drug therapies.
More patients discontinued due to lack of efficacy in the placebo group compared to the treatment groups.

Efficacy endpoint outcomes

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Table 45: Summary of LS mean differences

Summary of LS Mean Difference Between Rofecoxib and Placebo
Mean Change From Baseline in Primary Endpoints
Averaged Over 8-Week Treatment Period
(Intention-to-Treat Approach)

Endpoint	LS Mean Difference Between Rofecoxib and Placebo (95% CI)		
	Rofecoxib		
	— mg	25 mg	50 mg
Total 68 Tender Joint Count	1.42 (-0.75, 3.59)	-2.62 (-4.76, -0.48)	-1.68 (-3.83, 0.47)
Total 66 Swollen Joint Count	1.07 (-0.31, 2.45)	0.20 (-1.17, 1.57)	-0.27 (-1.65, 1.10)
Investigator Global Assessment of Disease Activity (0 to 4 Likert)	0.01 (-0.16, 0.18)	-0.35 (-0.52, -0.18)	-0.29 (-0.47, -0.12)
Patient Global Assessment of Disease Activity (0- to 100-mm VAS)	-1.66 (-6.06, 2.74)	-10.4 (-14.71, -6.08)	-10.0 (-14.41, -5.66)

Data Source: [4.34; 4.9]

For rofecoxib 25 mg, the confidence interval for the swollen joint endpoint includes 0; for 50 mg the CI includes 0 for tender and swollen joint counts; for — ng the CI includes 0 for all endpoints. *It is not clear why 25 mg is slightly more efficacious than 50 mg for the tender joint and global assessment endpoints. This was not seen in the pivotal trial 097. However, this supports the fact that 50 mg was not more efficacious than 25 mg.*
Note: there is no positive comparator in these studies although this is a dose ranging study.

Table 46: Tender joint count

Analysis of Endpoint: Tender Joint Count (Total 68)
Mean Change From Baseline (Flare/Randomization Visit)
Averaged Over 8 Weeks
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean† Change	95% CI for LS Mean† Change
Placebo	163	31.14	19.12	-12.02	12.44	-13.28	(-15.29, -11.27)
—ng	156	31.72	20.86	-10.85	11.56	-11.86	(-13.88, -9.84)
25 mg	163	31.52	16.65	-14.87	11.37	-15.90	(-17.90, -13.89)
50 mg	161	31.26	17.36	-13.90	10.40	-14.96	(-16.98, -12.94)

Comparisons Between Treatment Groups	Diff. in LS Mean	95% CI for Diff.	p-Value
With Placebo			
—ng vs. Placebo	1.42	(-0.75, 3.59)	0.199
25 mg vs. Placebo	-2.62	(-4.76, -0.48)	0.017
50 mg vs. Placebo	-1.68	(-3.83, 0.47)	0.009
Between Rofecoxib Doses			
—mg vs. 25 mg	4.04	(1.87, 6.21)	<0.001
—mg vs. 50 mg	3.10	(0.92, 5.27)	0.005
25 mg vs. 50 mg	-0.94	(-3.09, 1.21)	0.392

Effect:	p-Value	Pooled SD
MTX Use	0.008	9.84
Study Center	<0.001	
Baseline Covariate	<0.001	
Treatment	0.001	

† Least-squares mean.

Data Source: [4.34]

For tender joint counts rofecoxib 25 and 50 mg but not —mg was superior to placebo (p=.017, .009, and .199 respectively). There was a significance difference between the — mg dose and the 25 or 50 mg dose (p=<.001 and .005 respectively), but no difference between the 25 and 50 mg dose (p=.392).

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Table 47: Swollen joint count

Analysis of Endpoint: Swollen Joint Count (Total 66)
Mean Change From Baseline (Flare/Randomization Visit)
Averaged Over 8 Weeks
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean† Change	95% CI for LS Mean† Change
Placebo	163	20.17	13.24	-6.92	6.87	-7.09	(-8.37, -5.80)
—mg	156	20.98	14.81	-6.17	8.08	-6.02	(-7.31, -4.73)
25 mg	163	21.53	14.29	-7.24	7.60	-6.89	(-8.17, -5.61)
50 mg	161	21.10	13.49	-7.61	7.37	-7.36	(-8.65, -6.07)

Comparisons Between Treatment Groups	Diff. in LS Mean	95% CI for Diff.	p-Value
With Placebo			
— mg vs. Placebo	1.07	(-0.31, 2.45)	0.130
25 mg vs. Placebo	0.20	(-1.17, 1.57)	0.777
50 mg vs. Placebo	-0.27	(-1.65, 1.10)	0.443
Between Rofecoxib Doses			
—mg vs. 25 mg	0.87	(-0.51, 2.26)	0.217
— mg vs. 50 mg	1.34	(-0.04, 2.73)	0.058
25 mg vs. 50 mg	0.47	(-0.90, 1.84)	0.499

Effect:	p-Value	Pooled SD
MTX Use	0.391	6.28
Study Center	0.001	
Baseline Covariate	<0.001	
Treatment	0.259	

† Least-squares mean.

Data Source: [4.34]

For swollen joints, none of the doses was demonstrated to be superior to placebo. For this endpoint there was an effect of study center on the outcome (the significance of this is unclear).

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Table 48: Patient global assessment

Analysis of Endpoint: Patient Global Assessment of Disease Activity (0- to 100-mm VAS) Mean Change From Baseline (Flare/Randomization Visit) Averaged Over 8 Weeks (Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean† Change	95% CI for LS Mean† Change
Placebo	167	72.76	55.70	-17.06	21.52	-18.84	(-22.91, -14.77)
—ng	158	73.42	54.41	-19.02	21.53	-20.50	(-24.62, -16.38)
25 mg	169	72.21	44.96	-27.25	23.39	-29.24	(-33.30, -25.18)
50 mg	161	72.12	45.21	-26.91	21.50	-28.88	(-33.00, -24.75)

Comparisons Between Treatment Groups	Diff. in LS Mean	95% CI for Diff.	p-Value
With Placebo			
— ng vs. Placebo	-1.66	(-6.06, 2.74)	0.459
25 mg vs. Placebo	-10.40	(-14.71, -6.08)	<0.001
50 mg vs. Placebo	-10.04	(-14.41, -5.66)	<0.001
Between Rofecoxib Doses			
—mg vs. 25 mg	8.74	(4.35, 13.13)	<0.001
—mg vs. 50 mg	8.38	(3.94, 12.81)	<0.001
25 mg vs. 50 mg	-0.36	(-4.72, 4.00)	0.871

Effect:	p-Value	Pooled SD
MTX Use	0.062	20.14
Study Center	0.091	
Baseline Covariate	<0.001	
Treatment	<0.001	

† Least-squares mean.

Data Source: [4.34]

For patient global assessment both the 25 and 50 mg doses were superior to placebo ($p<.001$), but the —mg dose was not ($p=.459$). There was no statistical difference between the 25 and 50 mg dose.

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Table 49: Investigator global assessment

Analysis of Endpoint: Investigator Global Assessment of Disease Activity
(0 to 4 Likert Scale)
Mean Change From Baseline (Flare/Randomization Visit)
Averaged Over 8 Weeks
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean† Change	95% CI for LS Mean† Change
Placebo	165	2.73	1.90	-0.83	0.84	-0.90	(-1.06, -0.74)
—mg	158	2.79	1.94	-0.85	0.89	-0.89	(-1.05, -0.73)
25 mg	167	2.78	1.56	-1.22	0.91	-1.25	(-1.41, -1.09)
50 mg	160	2.66	1.57	-1.09	0.92	-1.20	(-1.36, -1.04)

Comparisons Between Treatment Groups	Diff. in LS Mean	95% CI for Diff.	p-Value
With Placebo			
—mg vs. Placebo	0.01	(-0.16, 0.18)	0.911
25 mg vs. Placebo	-0.35	(-0.52, -0.18)	<0.001
50 mg vs. Placebo	-0.29	(-0.47, -0.12)	<0.001
Between Rofecoxib Doses			
— mg vs. 25 mg	0.36	(0.19, 0.53)	<0.001
— mg vs. 50 mg	0.30	(0.13, 0.48)	<0.001
25 mg vs. 50 mg	-0.06	(-0.23, 0.12)	0.529

Effect:	p-Value	Pooled SD
MTX Use	0.009	0.79
Study Center	0.273	
Baseline Covariate	<0.001	
Treatment	<0.001	

† Least-squares mean.

Data Source: [4.34]

For the investigator global assessment the 25 and 50 mg doses were superior to placebo ($p<.001$) but the —mg dose was not ($p=.911$). There was no difference between 25 and 50 mg ($p=.529$).

Table 50: Proportion of patients who met ACR 20

Proportions of Patients Who Met ACR20 Responder Index Criteria
During 8 Weeks of Study

ACR20 Responder and Completers			
Treatment		Frequency (%)	
Placebo		53/167 (31.74%)	
[illegible] mg		53/158 (33.54%)	
25 mg		74/169 (43.79%)	
50 mg		80/161 (49.69%)	
Between-Group Comparisons	Diff. in Percent	(95% CI)	p-Value
[illegible] mg vs. Placebo	1.81	(-8.39, 12.01)	0.813
25 mg vs. Placebo	12.05	(1.77, 22.34)	0.025
50 mg vs. Placebo	17.95	(7.49, 28.42)	0.001
[illegible] mg vs. 25 mg	-10.24	(-20.74, 0.25)	0.069
[illegible] ng vs. 50 mg	-16.15	(-26.82, -5.48)	0.004
25 mg vs. 50 mg	-5.90	(-16.65, 4.85)	0.321

ACR20 Responder: Regardless of Completion Status			
Treatment		Frequency (%)	
Placebo		58/167 (34.73%)	
[illegible] ng		56/158 (35.44%)	
25 mg		82/169 (48.52%)	
50 mg		86/161 (53.42%)	
Between-Group Comparisons	Diff. in Percent	(95% CI)	p-Value
[illegible] mg vs. Placebo	0.71	(-9.67, 11.09)	0.908
25 mg vs. Placebo	13.79	(3.35, 24.23)	0.011
50 mg vs. Placebo	18.69	(8.13, 29.25)	<0.001
[illegible] mg vs. 25 mg	-13.08	(-23.68, -2.48)	0.019
[illegible] ng vs. 50 mg	-17.97	(-28.70, -7.25)	0.002
25 mg vs. 50 mg	-4.90	(-15.67, 5.88)	0.381

Data Source: [4.34]

For the ACR 20, both the 25 and 50 mg dose was superior to placebo for either ACR 20 responders and completers or regardless of completion status. The — ng dose did not differ from placebo. There was no difference between the 25 and 50 mg dose.

Summary

See summary of efficacy after review of trial 068P2 below.

Trial 068P2

Trial 068P2 is a continuation of trial 068P1.

Objectives/rationale

Note: Primary objectives 1 and 2 were addressed in Part I. Primary objective 3 is addressed in Part II.
1. To demonstrate the clinical efficacy of rofecoxib in the treatment of RA during 8 weeks of treatment.
2. To further define the clinically active dose range of rofecoxib in the treatment of RA.
3. To investigate the safety and tolerability of continuous administration of rofecoxib for 52 weeks in patients with RA.

Design

Following completion of Part I, patients entered Part II of the study. Study therapy for Part II was assigned in a double-blind fashion at the randomization Visit 2.0. Patients who received placebo or rofecoxib —mg daily in Part I were reassigned to rofecoxib 25 mg daily (approximately one-third), rofecoxib 50 mg daily (approximately one-third), or naproxen 500 mg 2 times daily (approximately one-third). Patients who received rofecoxib 25 or 50 mg daily in Part I continued on the same therapy during Part II. No patient received placebo in this part.

Table 51: Study flow chart

Study Flow Chart for Part II

	Treatment							
Clinic Visit ID #:	6.0	7.0	8.0	9.0	10.0	11.0	Discon-	Post-study
Duration of Treatment:	12 wks	20 wks	28 wks	36 wks	44 wks	52 wks	tinued	12.0
Interim history and monitor for adverse experiences	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X
Physical examination						X	X	
CBC, chemistry, UA	X	X	X	X	X	X	X	X
Urine β-hCG‡	X	X	X	X	X	X	X	X
C-reactive protein	X	X	X	X	X	X	X	
ECG						X	X	
Plasma sample for archive†			X			X	X	
Dispense study medication	X	X	X	X	X			
Study medication tablet count	X	X	X	X	X	X	X	
Dispense acetaminophen						X	X	
Acetaminophen tablet count							X	X
Patient global assessment of pain	X	X	X	X	X	X	X	
Patient global assessment of disease activity	X	X	X	X	X	X	X	
Investigator global assessment of disease activity	X	X	X	X	X	X	X	
HAQ			X			X	X	

† Patients were instructed not to take morning dose until after the plasma archive sample was obtained.
‡ Urine β-hCG samples were obtained from women of childbearing potential only.

Data Source: [3.2]

Protocol

Table 52: Definition of baseline and direction of improvement

Efficacy Endpoints: Definition of Baseline and Direction of Improvement

Endpoint (Scales)	Visit Which Established Baseline Value	Improvement
Patient Global Assessment of Disease Activity (0 to 100-mm VAS)	Visit 2	Decreases
Investigator Global Assessment of Disease Activity (0 to 4 Likert)	Visit 2	Decreases
Patient Assessment of Pain (0- to 100-mm VAS)	Visit 2	Decreases
Stanford Health Assessment Questionnaire (HAQ)	Visit 2	Decreases
Discontinuation Due to Lack of Efficacy	No baseline value	None

Data Source: Not Applicable

Since the study was exploratory for long-term effects, no multiplicity adjustments were made. To assess the effects of switching treatment from placebo or [redacted] mg rofecoxib in Part I to active treatments in Part II, plots of the difference between the average of the first 2 assessments in Part II and the average of the last 2 assessments in Part I for each treatment sequence were examined for Patient Global Assessment of Disease Activity, Investigator Global Assessment of Disease Activity, and Patient Global Assessment of Pain. Results were plotted by treatment assignment in Part I.

Results

Patient disposition, comparability

In the intention-to-treat approach, patients were included in the analysis for a particular endpoint if both baseline and 1 or more Part II measurements were captured. In the longitudinal plots, the last-value-carried-forward method was used to impute missing data for individual time points; however, no data were carried forward from Part I to Part II

Table 53: Patient accounting

Patient Accounting by Assigned Treatment—Part II

	Rofecoxib		Naproxen	
	25 mg	50 mg	1000 mg	Total
	n (%)	n (%)	n (%)	n (%)
ENTERED PART II:	235	223	86	
Male (age range)	57 (33 to 81)	47 (24 to 86)	28 (30 to 75)	
Female (age range)	178 (26 to 80)	176 (26 to 79)	58 (26 to 77)	
TOTAL PATIENTS	235	223	86	544
COMPLETED (Visits 6 to 12) did not enter subsequent extension	26 (11.1)	17 (7.6)	10 (11.6)	53 (9.7)
COMPLETED (Visits 6 to 12) and entered subsequent extension	143 (60.9)	128 (57.4)	49 (57.0)	320 (58.8)
DISCONTINUED during Part II	66 (28.1)	78 (35.0)	27 (31.4)	171 (31.4)
Clinical adverse experience	14 (6.0)	20 (9.0)	9 (10.5)	42 (7.7)
Laboratory adverse experience	1 (0.4)	2 (0.9)	0 (0.0)	4 (0.7)
Lack efficacy	29 (12.3)	45 (20.2)	10 (11.6)	84 (15.4)
Lost to follow-up	4 (1.7)	0 (0.0)	1 (1.2)	5 (0.9)
Patient moved	3 (1.3)	2 (0.9)	1 (1.2)	6 (1.1)
Patient withdrew consent	6 (2.6)	3 (1.3)	1 (1.2)	10 (1.8)
Protocol deviation	4 (1.7)	5 (2.2)	3 (3.5)	12 (2.2)
Other	5 (2.1)	1 (0.4)	2 (2.3)	8 (1.5)

Data Source: [4.22; 4.9; 4.5; 4.13; 4.14; 4.21; 2.1.17]

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It is unclear why almost twice as many subjects discontinued for lack of efficacy in the 50 mg group than either the 25 mg or naproxen groups.

There were no important differences between assigned Part II treatment groups in mean baseline values for any evaluated efficacy endpoint. There were no clinically meaningful differences between assigned Part II treatment groups in frequency or type of prior drug therapies. There were no clinically meaningful differences between assigned Part II treatment groups in frequency or type of concomitant drug therapies.

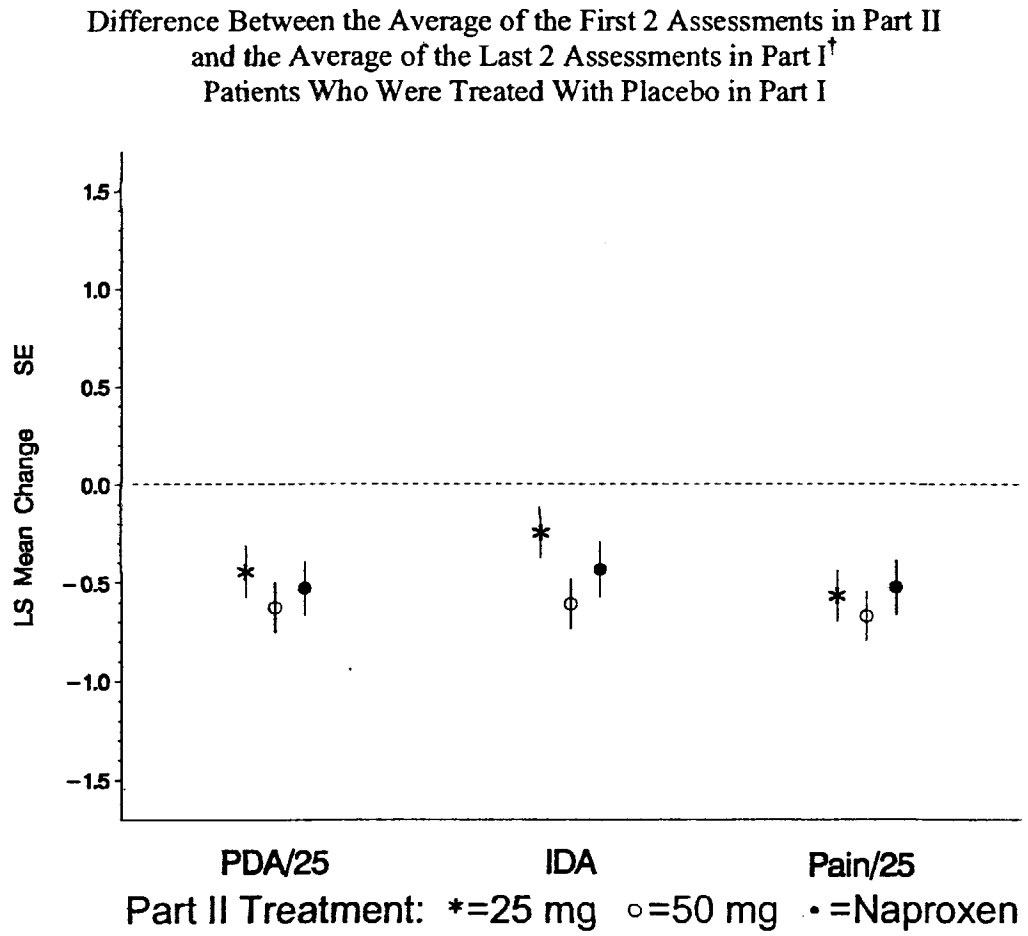
Efficacy endpoint outcomes

All analyses were based on intention-to-treat approach. Visual inspection by the sponsor, of plots of mean change from baseline over Part II, by specific treatment sequence (i.e., Placebo/25 mg, — mg/25 mg, 25 mg/25 mg, Placebo /50 mg, — ng/50 mg, 50 mg/50 mg, Placebo/Naproxen, and — mg/Naproxen), revealed that responses for Part II treatment groups were similar regardless of

Part I treatment assignment. Therefore, data for these patients were combined by the sponsor based on Part II assigned treatment.

The transition from part I to part II involved a dose escalation, for example from placebo to either rofecoxib 25 or 50 mg, or naproxen. This figure (Figure 5: Difference between assessments) indicates that there was improvement in patient and investigator global assessments as well as pain assessment by VAS. Furthermore, the improvement with 50 mg was greater than with 25 mg rofecoxib. In general the improvement with 50 mg rofecoxib was comparable to the improvement with naproxen. Although the changes for rofecoxib and naproxen are similar the clinical significance of the absolute change is unclear. There is no placebo group for comparison in part II.

Figure 5: Difference between assessments



PDA/25=Patient Global Assessment of Disease Activity (VAS) score divided by 25.
IDA=Investigator Global Assessment of Disease Activity.
Pain/25=Patient Global Assessment of Pain (VAS) score divided by 25.
† Negative value represents improvement.

Subjects taking rofecoxib—mg in part I were switched to rofecoxib at higher doses or naproxen. Again, improvements in PDA, IDA, and pain were seen in all 3 groups. *However, it is not clear why those in the 25 mg group improved to a greater extent than those in the 50 mg group.*

Figure 6: Differences between assessments

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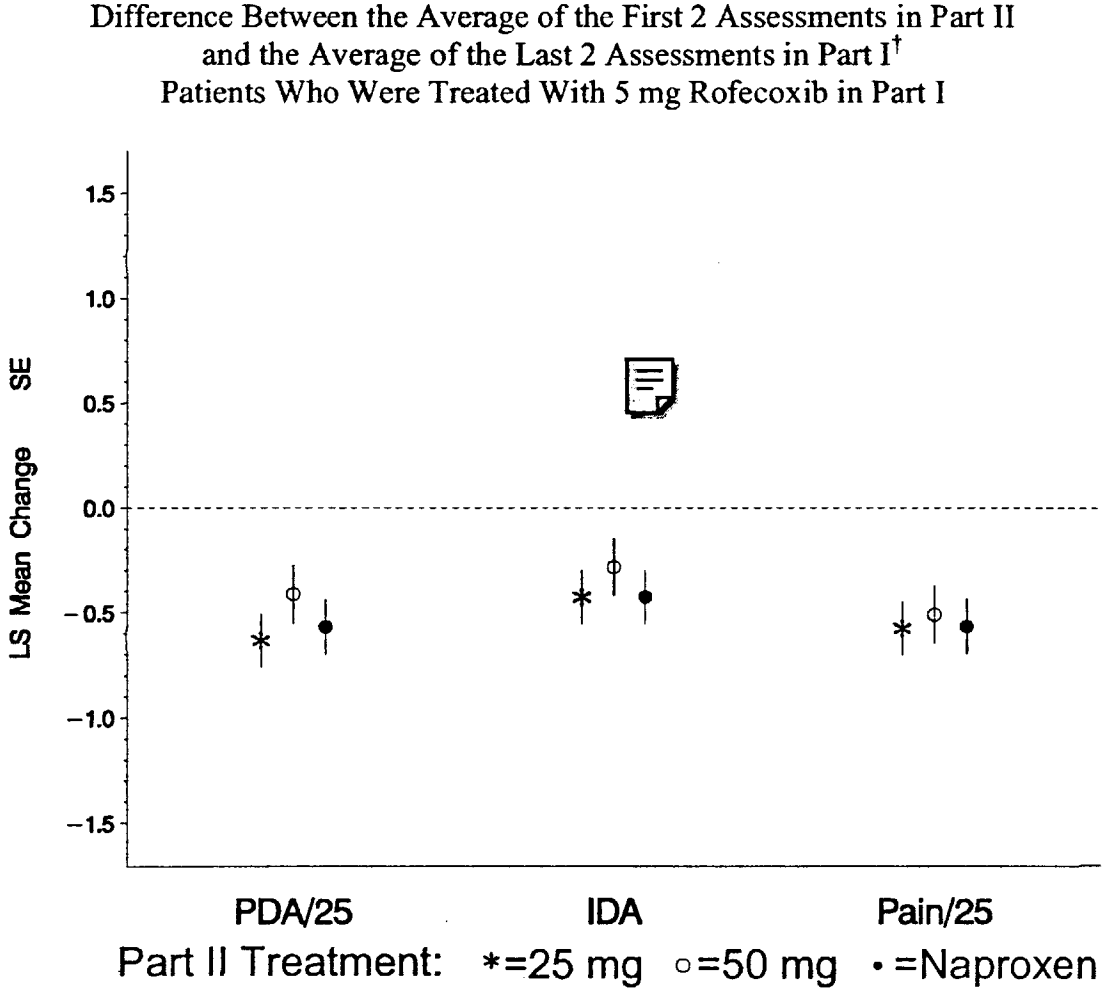

PDA/25=Patient Global Assessment of Disease Activity (VAS) score divided by 25.
IDA=Investigator Global Assessment of Disease Activity.
Pain/25=Patient Global Assessment of Pain (VAS) score divided by 25.
† Negative value represents improvement.

An analysis of patient global assessment indicates that improvement over baseline on rofecoxib or naproxen was maintained over the course of this study from 12 to 52 weeks and was similar in all three groups (Figure 7: Patient global assessment).

Note: concomitant medications were not held constant during this time.

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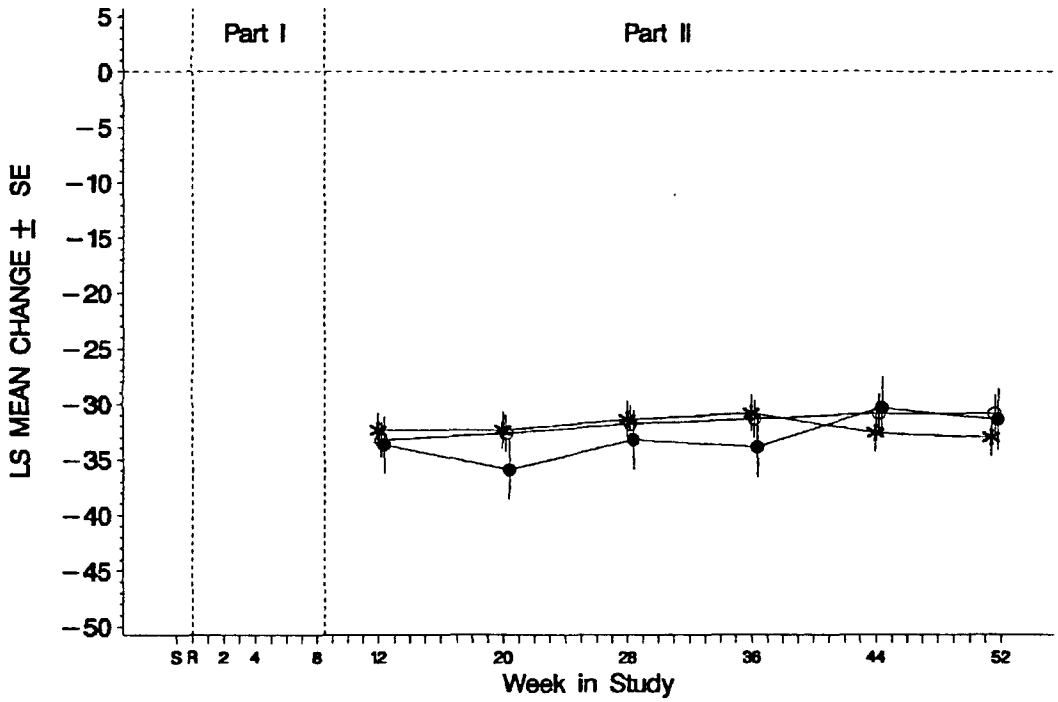
Figure 7: Patient global assessment

Endpoint: Patient Global Assessment of Disease Activity
Mean Change From Baseline (Flare/Randomization Visit)
(Intention-to-Treat Approach)



Part II Treatment: *=25 mg ○=50 mg • =Naproxen

Patient Global Assessment of Disease Activity (0−100 mm VAS)

S=Screening; R=Randomization (Baseline).

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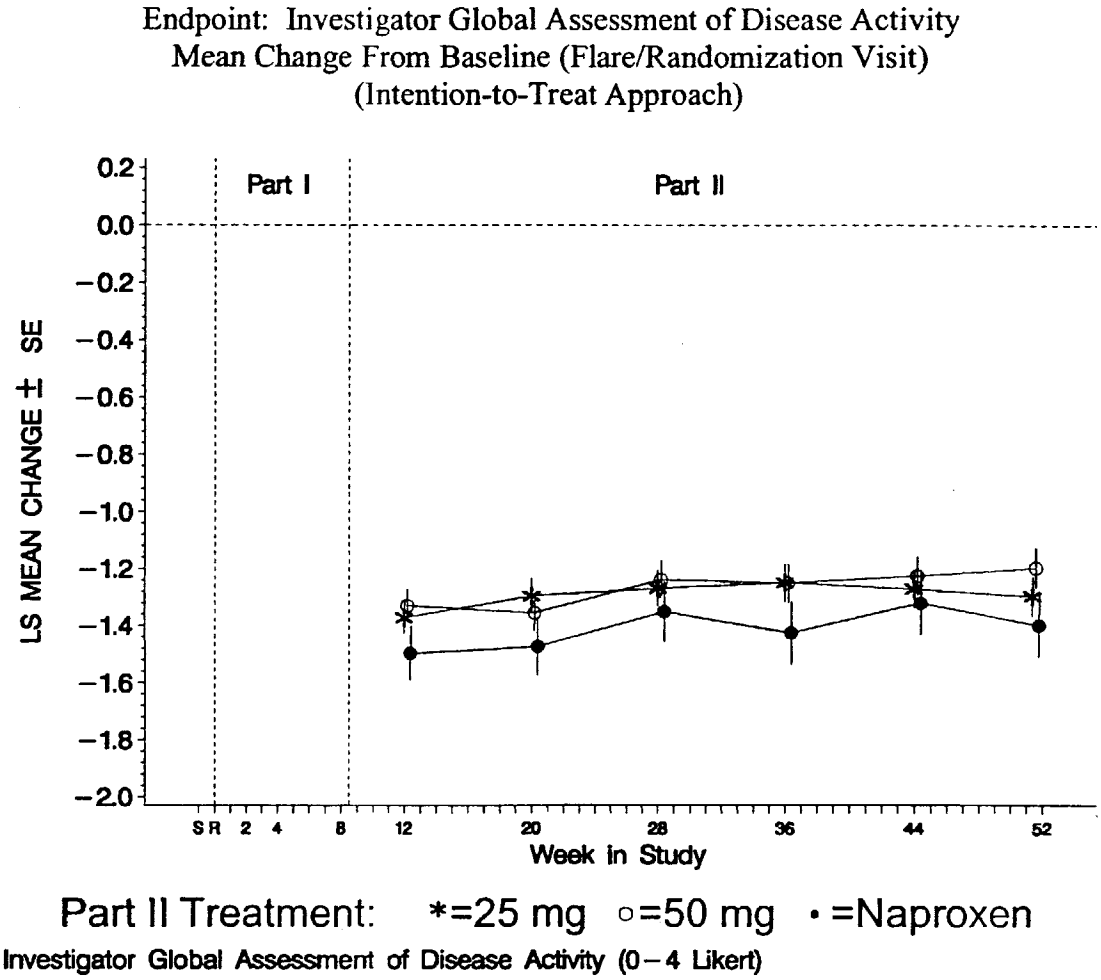
Figure 8: Investigator global assessment



S=Screening; R=Randomization (Baseline).

Likewise, for investigator global assessment improvement over baseline was maintained over the 12 to 52 week period.

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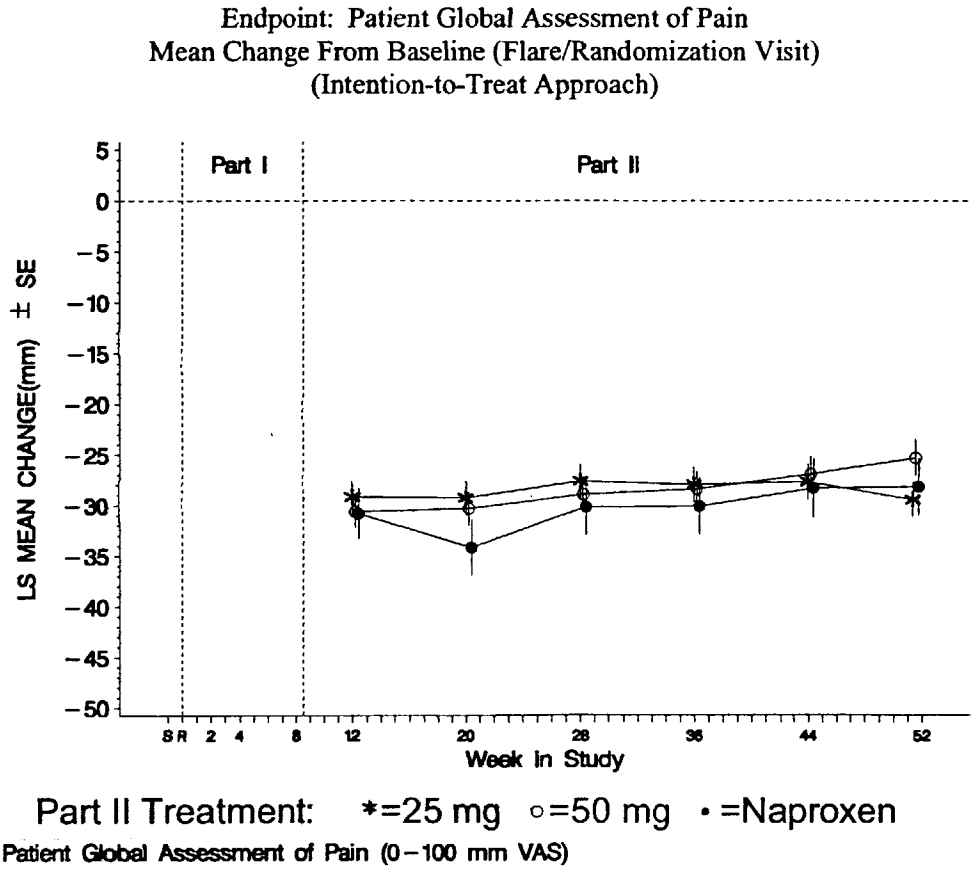
Figure 9: Patient global assessment



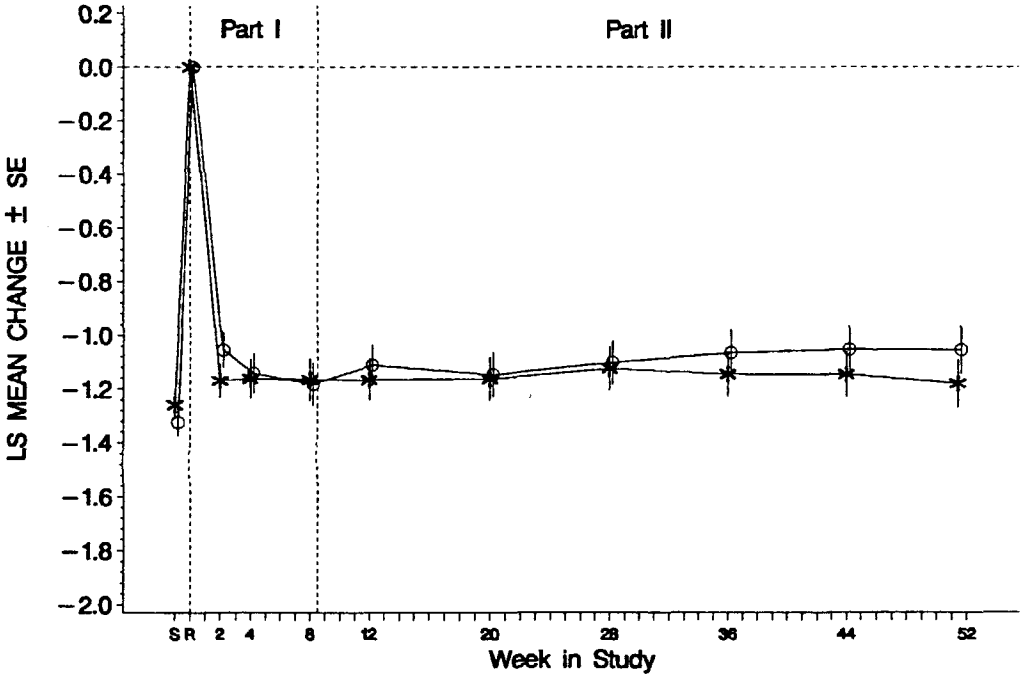
S=Screening; R=Randomization (Baseline).

Improvement in patient global assessment of pain was also maintained over the 12 to 52 week period, although there is a suggestion that efficacy may be waning towards the end of the time period.

For subjects who remained on 25 or 50 mg of rofecoxib throughout the study, improvement in investigator global assessment was maintained out to 52 weeks with a slight worsening in the 50 mg group (Figure 10: Investigator global assessment). Whether this loss of efficacy will continue to worsen beyond 52 weeks is not known at this time.

Figure 10: Investigator global assessment

Endpoint: Investigator Global Assessment of Disease Activity
Mean Change From Baseline (Flare/Randomization Visit)
Patients Who Were Treated With 25 or 50 mg Rofecoxib Daily in Part I
(Intention-to-Treat Approach)



Part I Treatment/Part II Treatment: *=25 mg/25 mg o=50 mg/50 mg
Investigator Global Assessment of Disease Activity (0 – 4 Likert)

S=Screening; R=Randomization (Baseline); Screening (S) to Baseline (R) = Washout period for prior RA NSAID therapy.

Similarly, patient global assessment of pain was also maintained out to week 52. Again, there appears to be a slight loss of efficacy towards the end of the trial in the 50 mg group.

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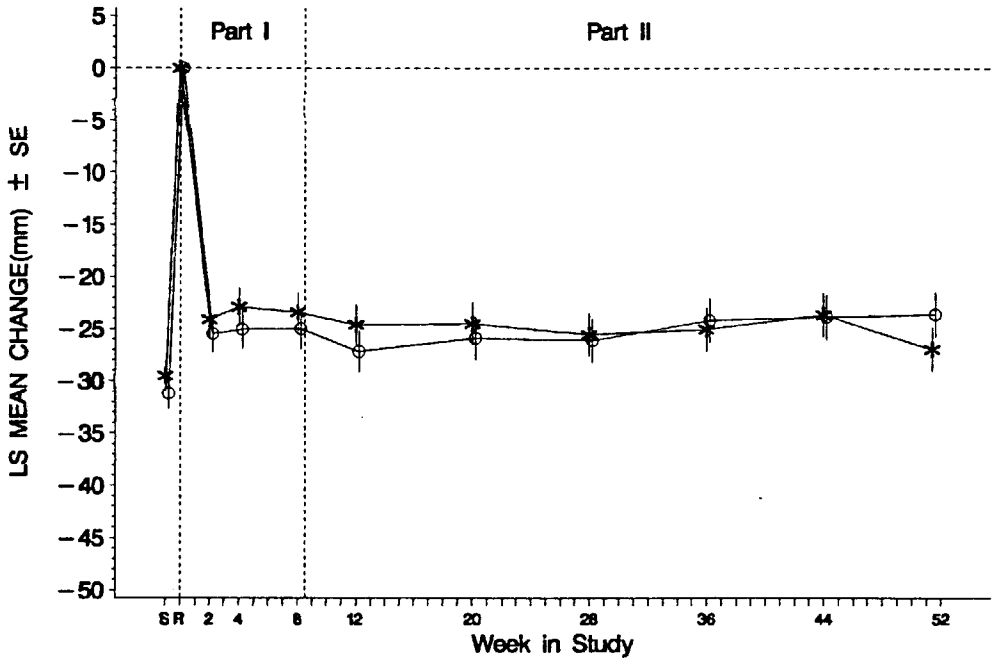
Figure 11: Patient global assessment

Endpoint: Patient Global Assessment of Pain
Mean Change From Baseline (Flare/Randomization Visit)
Patients Who Were Treated With 25 or 50 mg Rofecoxib Daily in Part I
(Intention-to-Treat Approach)



Part I Treatment/Part II Treatment: *=25 mg/25 mg ○=50 mg/50 mg
Patient Global Assessment of Pain (0−100 mm VAS)

S=Screening; R=Randomization (Baseline); Screening (S) to Baseline (R) = Washout period for prior RA NSAID therapy.

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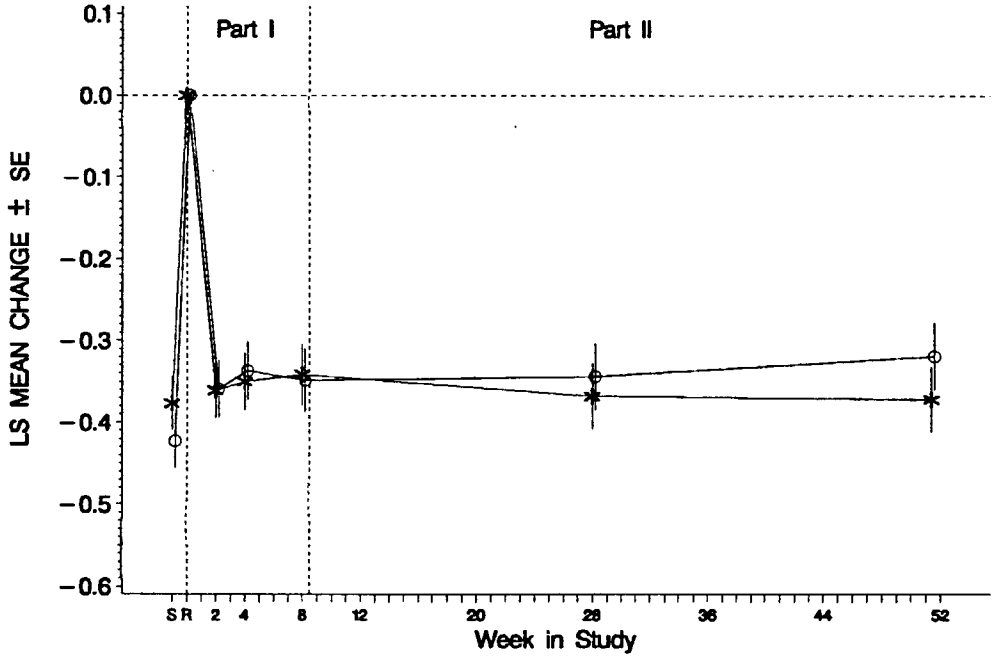
Finally, improvement in the Stanford HAQ showed only a slight deterioration over the last half of part II that occurred in the 50 mg treated group.

Figure 12: Stanford health assessment

Endpoint: Stanford Health Assessment Questionnaire (0 to 3 Likert)
Mean Change From Baseline (Flare/Randomization Visit)
Patients Who Were Treated With 25 or 50 mg Rofecoxib Daily in Part I
(Intention-to-Treat Approach)



Part I Treatment/Part II Treatment: *=25 mg/25 mg o=50 mg/50 mg
HAQ Disability (0−3 Likert)

S=Screening; R=Randomization (Baseline); Screening (S) to Baseline (R) = Washout period for prior RA NSAID therapy.

Reviewers comments/conclusions of study results

In summary, parts I and II support the efficacy of rofecoixb in the treatment of the signs and symptoms of RA. Part I , an eight week trial demonstrated that for two doses of rofecoxib 25 and 50 mg but not for the —ıg dose, there was a significant improvement over placebo, in 3 primary endpoints for the 25 and 50 mg doses, as well as ACR 20. Although part I only lasted for 8 weeks, it is supportive of and consistent with the data provided in studies, 096 and 097, which lasted for 12 weeks. It is not clear why rofecoxib 50 mg was found to be slightly less efficacious than 25 mg for some of the endpoints studied. This was not the case in trial 097. The part II extension demonstrates that this improvement is maintained over the following 44 weeks (for a total of 52 weeks) for those subjects on 25 or 50 mg rofecoxib, and there was an improvement in multiple endpoints for those subjects who were transitioned from placebo or — ıg rofecoxib to either 25, 50 mg rofecoxib or naproxen. *It is difficult to explain the slight but consistent loss of efficacy towards the end of the trial in the rofecoxib 50 mg group compared to the 25 mg group. In addition, interpretation of the efficacy over 52 weeks is made difficult by the fact that after the initial treatment period concomitant medications were allowed to change depending on the clinical situation. Therefore, it is not entirely clear if maintenance of efficacy is due to rofecoxib or other concomitant medications.*

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D. Efficacy Conclusions

Based on results of the 2 pivotal trials 096 and 097 as well as supportive data from trial 068, rofecoxib appears efficacious in the treatment of the signs and symptoms of RA. The major trial endpoints include tender and swollen joints as well as patient and physician global assessment . The sponsor demonstrates efficacy at each of these endpoints in the 2 pivotal trials. Furthermore the sponsor demonstrates efficacy using ACR 20 as an endpoint (the Division of Analgesic and Anti-inflammatory Drug Products prefers this endpoint for clinical trials). For each endpoint the data is robust and p values are less than the .05 level. These results are supported by data from trial 068, except that in this trial, for the primary endpoint of swollen joints, rofecoxib was not demonstrated to be significantly different from placebo. However, multiple secondary endpoints were found to be significantly improved with the use of rofecoxib. The efficacy appeared to be maintained out to one year in trial 068 — . However, the one year extension phase of study 068 did not have a placebo comparator. Rofecoxib is also shown to be comparable to naproxen based on the degree of improvement of each endpoint. However, no other NSAIDs were used as comparators in these studies, and the studies were not designed to demonstrate equivalence to the comparator drug. Studies of rofecoxib do not show any unique efficacy advantage over existing therapies.

In terms of the relationship of studied endpoints to patient benefit, the endpoints included in these trials are felt to be sensitive in demonstrating clinical improvement. Using improvement in ACR 20 provides some insight as to the size of the treatment effect. In studies 096 and 097,

ACR 20 improved by 25-50%. However, it may be difficult to translate changes in ACR 20 with clinically (rather than statistically) meaningful improvement.. Does improvement in tender joints of 20% (e.g. a patient moves from 15 tender joints to 12 tender joints) translate into improvement a patient or physician feels is clinically important? Additionally, does a 20% response in ACR20 translate into clinically important long term effectiveness in terms of disability or joint damage? In a sense these are surrogate markers since it is presumed that improvements in ACR 20 will translate into improved long term outcomes. While the ACR 20 appears to be superior to other indices in separating placebo from treated subjects, will the ACR 50 or 70 represent a more clinically relevant and important endpoint?

Nevertheless the ACR 20 is a validated measure of improvement in RA patients and the results of these studies consistently demonstrate the superiority of rofecoxib over placebo in the treatment of the signs and symptoms of RA.

VII. Integrated Review of Safety

For a complete safety review the reader is referred to the review by Dr. Lourdes Villalba found in Appendix II..

Summary of Safety findings in RA database

1. Overall safety in the RA application database

There were a total of eight deaths: five on rofecoxib, two on naproxen and one on placebo. There were two, one and one cardiovascular deaths in the rofecoxib 50 mg, rofecoxib 25 mg and naproxen groups, respectively. The pattern of adverse events, discontinuations due to adverse events, laboratory AE's and vital signs was consistent with data submitted in the original NDA submission. .

2. Cardiovascular safety in the RA application database.

There were 6 MI 's (one fatal) in the rofecoxib 25 mg group, 5 MI's (one fatal) and 1 sudden death in the rofecoxib 50 mg group and one fatal MI in the naproxen group. Although the number of events is small, the higher incidence of MI's on rofecoxib as compared to naproxen is consistent with findings in VIGOR and ADVANTAGE. Consistent with VIGOR but different from ADVANTAGE, there was no excess of strokes in the naproxen group in the RA database.

Hypertension related events were observed two to three times more often in each of the rofecoxib arms, as compared to the naproxen arm or placebo. A higher percentage of patients presented important increase of blood pressure and required concomitant antihypertensive medication and/or discontinued from each of the rofecoxib arms compared to the naproxen arm. The numbers of patients with edema-related events were higher in the rofecoxib 25 and 50 mg groups as compared to naproxen. These findings were consistent in the placebo-controlled treatment phase and in the long-term exposure databases.

Three CHF related events occurred during one year studies - all in the rofecoxib 50 mg group -. Two additional cases occurred in the extension period, one in rofecoxib 25 mg and one in rofecoxib 50 mg. The number of CHF events is small to draw definitive conclusions but is consistent with VIGOR in which rofecoxib 50 mg was associated with higher risk of developing CHF related events than naproxen.

3. Signal of increased risk of fractures with rofecoxib as compared to naproxen.

More fractures occurred in the rofecoxib arms (9 and 3 for rofecoxib 50mg and 25 mg respectively) as compared to the naproxen arm (no fractures). This trend was consistent with the VIGOR study. However, in a larger safety database of approximately 3000 patients exposed to either rofecoxib 25 mg or placebo for one year there was no differences in the numbers of fractures.

A. Brief Statement of Conclusions

Analysis of the data from the RA application safety database showed a trend consistent with VIGOR and ADVANTAGE: rofecoxib 25 mg and 50 mg had higher incidence of myocardial infarction, edema-related and hypertension related events than naproxen 1000 mg/day. In regards to GI safety, there were more symptomatic ulcers in the naproxen group as compared to rofecoxib and placebo. There were no complicated ulcers in this database.

For a more complete review of safety data the reader is referred to the safety review by Dr. Lourdes Villalba found in the Appendix II.

B. Description of Patient Exposure (i.e., number of patients at given duration, dose, demographic, distribution, country)

See appendix.

C. Methods and Specific Findings of Safety Review

See appendix.

D. Adequacy of Safety Testing

The safety evaluation of rofecoxib in this application appears adequate. Limitations of the data are discussed in the following section (E).

E. Summarize Critical Safety Findings and Limitations of Data

Analysis of the data from the RA application safety database showed a trend consistent with VIGOR and ADVANTAGE: rofecoxib 25 mg and 50 mg had higher incidence of myocardial infarction, edema-related and hypertension related events than naproxen 1000 mg/day. In regards to GI safety, there were more symptomatic ulcers in the naproxen group as compared to rofecoxib and placebo. There were no complicated ulcers in this database.

The major limitations of this database are:

1. Patients at cardiovascular risk such as those with recent history of myocardial infarction and stroke and those using prophylactic low dose aspirin were not included.

2. The only active NSAID comparator used in the studies was naproxen.

3. This is a relatively small database to assess clinically meaningful outcomes.

In summary, GI and cardiovascular findings including cardiovascular thrombotic events, HTN and edema-related events are consistent with those in VIGOR and ADVANTAGE for rofecoxib compared to naproxen but do not provide comparative safety to other NSAIDs or safety information in patients using concomitant low dose ASA. The reason for the excess of MIs in the rofecoxib groups as compared to naproxen is still unclear.

VIII. Dosing, Regimen, and Administration Issues

Based on the studies in this sNDA, as well as the studies examining the use of rofecoixb in the treatment of OA, the level of confidence in the dose and dosing regimen of rofecoxib for the treatment of RA is high. Previous studies have demonstrated that rofecoxib daily is effective for OA. The present studies have robustly demonstrated the efficacy of daily rofecoxib for RA. Dose ranging supports the 25 mg dose as the lowest dose that is most efficacious. Evidence is provided that the 25 mg dose and the 50 mg dose are similar in efficacy and significantly better than either the —mg or 12.5 mg dose. Further support of this dose is provided by the dose escalation portion of the studies. Furthermore, the effective half life at steady state is approximately 17 hours. In summary, based on these studies in RA and those in OA previously submitted, and based on PK data, the daily regimen appears appropriate. Taken together, the data supports the use of rofecoxib for RA at the 25 mg daily dose level. **It is important to have practitioners understand that little efficacy is gained by dose escalation ("dose creep"), while the risk for additional toxicity is increased with higher doses. Thus there is little room for dose**

escalation if the desire on the practitioner's part is for increased efficacy. The use of rofecoxib in individuals with advanced renal or hepatic disease is not recommended according to the label. No additional information is provided in this submission in this regard. For additional information concerning drug interaction, relation to meals and how to handle dose modifications the reader is referred to the product label.

IX. Use in Special Populations

A. Sponsor's Gender Effects Analyses and Adequacy of Investigation.

There were no significant treatment differences from placebo across various subgroups including gender and age. The pharmacokinetics of rofecoxib are comparable in men and women. Treatment differences from placebo were consistent across subgroups defined by gender and age. With few exceptions, p-values for all interaction tests were >0.100. Exceptions included a significant treatment-by-ethnic group interaction observed for Swollen Joint Count (p=0.044) and Investigator's Global Assessment of Disease Activity (p=0.046). Small treatment effects in Hispanic patients, in the 25-mg rofecoxib treatment group for both endpoints, and in "other" race patients in the naproxen treatment group for Swollen Joint Count, were the cause of the interactions. However, the sample sizes for Hispanic and "other" race patients were relatively small.

B. Pediatric Program

There was no evaluation of pediatric subjects in this sNDA submission. The sponsor has received a Pediatric Written Request dated 5/01.

C. Other Populations

The single pregnancy on rofecoxib resulted in a live birth with no known complications. The pregnancy on naproxen resulted in a spontaneous abortion. No patient became pregnant on Long-Term Continuous Therapy. In the Part II Continuation and Extension Periods, one patient on 25 mg rofecoxib became pregnant, and this ended in a spontaneous abortion. No conclusions are possible.

There was no specific data provided in this submission in regards to the use of rofecoxib in renal or hepatic compromised patients. Information and recommendations can be found in the present labeling for rofecoxib.

X. Conclusions and Recommendations

A. Conclusions

A large-scale GI outcomes study (VIGOR), demonstrated a substantially reduced risk of PUBs in RA patients treated with 50 mg rofecoxib (twice the recommended 25-mg dose) versus naproxen 500 mg twice daily. Thus, in RA patients, rofecoxib has a GI safety advantage over the nonselective NSAID naproxen, but has similar therapeutic effects on the signs and symptoms of RA. Reviews of the ADVANTAGE study and potential cardiovascular issues are still ongoing. However, based on the available data and the fact that rofecoxib is approved for OA and acute pain, the risk/benefit ratio appears to be acceptable to allow approval of rofecoxib for the treatment of the signs and symptoms of RA.

B. Recommendations

Rofecoxib is approvable for the following indication: for the treatment of the signs and symptoms of rheumatoid arthritis. There are two pivotal trials provided, 096 and 097, both of which clearly demonstrate statistically significant differences of rofecoixb 25 mg over placebo for all the primary endpoints and the secondary endpoint ACR 20 (which is the Divisions preferred endpoint). Supportive evidence is provided by study 068 which was an 8 week study of efficacy. Furthermore, this study was continued for one year and demonstrated that rofecoxib maintained its efficacy for at least 52 weeks. In terms of safety, the data presented in this submission is consistent with the original database and VIGOR and did not raise any major new safety concerns. The label should address the fact that 50 mg was no more efficacious than 25 mg and dose titration is not recommended. Furthermore, the label should address the fact that rofecoxib was associated with a higher incidence of hypertension and edema as compared to naproxen and/or placebo.

Recommendations for regulatory action:

It is recommended that the approved dose be 25 mg daily.
The label should state that doses higher than 25 mg have not been shown to provide greater efficacy and are not recommended.

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XI. Appendix I

A. Additional response to reviewers request for analysis of ACR 50 and 70

The following tables present data for ACR 50 and 70. Although none of the comparisons reach statistical significance, in each case rofecoxib and naproxen are numerically greater than placebo. These results utilize the sponsors modified intention to treat population.

Results for Study 096

Proportions of Patients Who Met ACR 50 Responder Index Criteria

During 12 Weeks of Study

(Modified Intention-to-Treat Approach)

ACR 50 Responder and Completers			
Treatment		Frequency † (%)	
Placebo		20/297 (6.73%)	
12.5 mg		18/146 (12.33%)	
25 mg		31/311 (9.97%)	
Naproxen		20/149 (13.42%)	
Between-Group Comparisons	Diff in Percent	(95% C.I.)	p-value §
25 mg vs. Placebo	3.23	(-1.15, 7.62)	0.156
12.5 mg vs. Placebo	5.59	(-0.45, 11.64)	0.056
Naproxen vs. Placebo	6.69	(0.52, 12.86)	0.023
25 mg vs. 12.5 mg	-2.36	(-8.65, 3.93)	0.473
25 mg vs. Naproxen	-3.45	(-9.86, 2.95)	0.288
12.5 mg vs. Naproxen	-1.09	(-8.74, 6.55)	0.779
ACR 50 Responder: regardless of completion status			
Treatment		Frequency † (%)	
Placebo		24/297 (8.08%)	
12.5 mg		20/146 (13.70%)	
25 mg		34/311 (10.93%)	
Naproxen		21/149 (14.09%)	
Between-Group Comparisons	Diff in Percent	(95% C.I.)	p-value §
25 mg vs. Placebo	2.85	(-1.80, 7.50)	0.241
12.5 mg vs. Placebo	5.62	(-0.76, 12.00)	0.073
Naproxen vs. Placebo	6.01	(-0.38, 12.40)	0.055
25 mg vs. 12.5 mg	-2.77	(-9.33, 3.80)	0.416
25 mg vs. Naproxen	-3.16	(-9.74, 3.41)	0.351
12.5 mg vs. Naproxen	-0.40	(-8.29, 7.50)	0.922

† m/n where m=number of patients with response and n=total number of patients evaluated.

§ From Cochran-Mantel-Haenszel test with stratum (corticosteroid use) as a stratification factor.