CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-042/S-007, S-008, S-010, S-012, S-013, S-014 and 21-052/S-004, S-005, S-006, S-007, S-008, S-009

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPTHALMIC DRUG PRODUCTS—HFD-550

sNDA #21042/s012

Submission date:	2/28/2001
Submission type:	NDA supplement
Review date:	12/15/2001
Drug name:	rofecoxib (Vioxx)
Applicant:	Merck
Pharmacologic category:	anti-inflammatory
Proposed indications:	signs and symptoms of RA
Dosage form and route:	oral tablets, 25mg, daily

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

The submitted application supports the demonstration of the efficacy of rofecoxib in the treatment of the signs and symptoms of rheumatoid arthritis. **Therefore, from a clinical perspective, rofecoxib 25 mg once daily is approvable for the following indication: for treatment of the signs and symptoms of rheumatoid arthritis. Labeling changes based on safety review of large long term studies including RA patients, should be incorporated at the time of labeling for this indication.**

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There are no phase IV studies required at this time

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The review that follows discusses the clinical program of orally administered rofecoxib, a non-steroidal anti-inflammatory drug with selectivity for the enzyme Cox-2 in the treatment of rheumatoid arthritis (RA). There are 2 pivotal 3 month placebo controlled trials in this submission, 096 and 097, as well as a phase II trial, 068 (parts I and II) that examine the efficacy of rofecoxib for the treatment of the signs and symptoms of RA. In part I, 1561 patients were treated with rofecoxib at any dose, 296 with naproxen, and 768 with placebo.

B. Efficacy

Results of the 2 pivotal trials 096 and 097 as well as supportive data from trial 068, demonstrate that rofecoxib is efficacious in the treatment of the signs and symptoms of RA. The trials included individuals on remittive agents, and in this regard the results are applicable to the general RA population. **However, concomitant aspirin was not allowed and patients on aspirin prophylaxis for cardiac disease were not represented in these studies. In addition, individuals with a recent history of cardiac disease or of stroke were excluded. In the**

general population of RA patients there will likely be individuals with cardiovascular disease. The safety of rofecoxib has not been specifically demonstrated in this population. Concerns remaining over safety relative to naproxen were noted in the VIGOR and ADVANTAGE trials. Such comparative data should be reflected in the label.

The major trial endpoints included tender and swollen joints as well as patient and physician global assessment . The sponsor demonstrated efficacy at each of these endpoints in the 2 pivotal trials. Furthermore the sponsor demonstrated efficacy using ACR 20 as an endpoint (the rheumatology community in general, and the Division of Analgesic and Anti-inflammatory Drug Products prefer this endpoint for clinical trials). For each endpoint the data were robust and statistically significant. 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 (extension studies were not provided for trials 096 and 097). However, the one year extension phase of study 068 did not have a placebo comparator. Rofecoxib was 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 have not shown 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 into 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 efficacy translate into clinically important long term effectiveness in terms of disability or joint damage? 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 studies presented here consistently demonstrate the superiority of rofecoxib over placebo in the treatment of the signs and symptoms of RA.

C. Safety

The safety evaluations for rofecoxib in the trials in this submission, as well as the safety data from the VIGOR trial of 8,00 patients (reviewed elsewhere), provide information on safety including absolute rates of serious adverse events (SAE), adverse events (AE), withdrawals due to AEs, as well as comparative safety in relation to naproxen. There is still concern for the question of cardiovascular (CV) thrombotic risks associated with the use of rofecoxib compared to naproxen or placebo, which cannot be definitively addressed by the studies to date.

The RA safety database contains approximately 2000 patients exposed to rofecoxib (12.5, 25 and 50 mg); 550 patients exposed to naproxen and 1000 patients exposed to placebo. The bulk of the exposure was to 3 and 6 months of treatment. Approximately 1500 patients were exposed to rofecoxib 25 mg (n= 797) and 50 mg (n= 677) in 3-month placebo controlled studies. Approximately 180, 140 and 80 patients were exposed to rofecoxib 25mg, rofecoxib 50mg and naproxen 1000 mg respectively, for one year or more. *The most relevant of the three datasets appears to be the one-year comparative data including naproxen.* However, since not all randomized patients actually completed the studies, for events of particular interest, it appears more appropriate to compare event rates based on true exposure.

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. .

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.

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 study evaluating ——————— with rofecoxib has recently been completed and is under review.

The number of patients who discontinued due to one or more AEs was slightly higher for rofecoxib 50 mg and naproxen groups (9 % and 8 %, respectively), compared to the placebo and rofecoxib 25 mg groups (4 % and 5 %, respectively). Of note, the body system with most discontinuations was the digestive, for all treatment groups, including placebo. The vast majority of the events leading to discontinuation were not considered serious by the investigator.

In the one year dataset, the number of patients discontinued due to AEs was 9.4%, 13.5%, and 12.5% in the rofecoxib 25 mg, rofecoxib 50 mg and naproxen, respectively. The most frequent events were in the body as a whole, cardiovascular and digestive systems.

In the extension studies dataset, the number of patients who discontinued due to AEs was 9.4%, 13.5 and 12.5% in the rofecoxib 25 mg group, rofecoxib 50 and naproxen groups respectively. The most frequent events leading to discontinuation were in the cardiovascular and digestive systems.

In the placebo controlled phase of the RA studies, 60 to 66% of patients had at least one adverse experience. In the one-year dataset, 81 to 85% of patients had at least one AE. In the extension studies, approximately 76 % of patients had at least one AE. The most frequent events were in the body as a whole system (22-26% of patients in the placebo controlled phase; 42-44% in the one year database and 31 to 37% in the extension studies) and in the digestive system (20.8%, 23.3 %, 30.6% and 39.5% in the placebo, rofecoxib 25 mg, rofecoxib 50 mg and naproxen groups, respectively in the placebo-controlled phase; 36% to 48 % in the one-year dataset and 24% to 30 % in the extension studies).

In summary, there were no substantial differences in the total number of serious adverse events, discontinuations due to adverse events and common adverse events between treatment groups in each of the three datasets, particularly the long term datasets. There appears to be a dose trend in the AEs described above.

The pattern of laboratory adverse events is consistent with those observed in prior databases with rofecoxib: the 50 mg dose is associated with higher number of renal-related laboratory AEs than naproxen 500 mg bid. Decrease in hematocrit with rofecoxib 50 mg is similar to naproxen and higher than with rofecoxib 25 mg. The incidence of liver-related laboratory AEs with rofecoxib appears to be similar to naproxen.

- Drug-drug interaction potential

There is no new information concerning drug-drug interactions provided in this sNDA. The interested reader is referred to the currently approved label for further discussion of this issue.

- Exposure in trials versus probable marketing exposure

The trials submitted enrolled RA patients that appear to be representative of the general population of RA patients that will be taking rofecoxib with the exception of the trial exclusions discussed below. The duration of exposure in these trials was at least one year and in some cases longer. The VIGOR study administered twice the recommended dose of rofecoxib for greater than 6 months. Furthermore, rofecoxib is already approved for the use in OA and acute pain and has been marketed for these indications for more than one year. Taken together there does not appear to be any new safety issues that have not been identified either in this submission or in post-marketing analyses. The reader is referred to the reviews of VIGOR and ADVANTAGE studies by Dr. Villalba.

- Effect of trial exclusions on safety profile versus expected marketed population

Patients at cardiovascular risk such as those with a recent history of myocardial infarction and stroke and those using prophylactic low dose aspirin were not included in these trials. This raises significant concern in view of the findings in VIGOR and ADVANTAGE, and the theoretical concern that rofecoxib may pro-thrombotic based on its COX-2 specificity. The existing published studies and databases reviewed are not conclusive. It is anticipated that individuals in the general population with CV risks will be placed on this drug, with or without aspirin prophylaxis. It is suggested that

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The sponsors submitted a meta-analysis to address this issue. Their conclusion is that this meta-analysis is supportive of the concept that naproxen is protective and reduces the risk of CV thrombotic events, and that rofecoxib is similar to placebo in terms of this risk. However, this analysis does not provide adequately robust data that a prospective randomized trial would provide to address this question. The size and

duration of submitted studies as well as the absence of meaningful comparisons to non-naproxen NSAIDs limits the conclusions from this meta-analysis.

- Relationship of safety to other drugs available for indication

The only active NSAID comparator used in the studies was naproxen. In these and other studies the overall incidence of adverse events with rofecoxib compared to naproxen is similar. However, the rate of PUBs is higher in naproxen treated individuals while the rate of CV thrombotic events is lower in naproxen users. The large GI outcome study VIGOR (reviewed elsewhere) has demonstrated that rofecoxib has a lower rate of PUBs than naproxen. Endoscopy studies do not provide additional relevant clinical outcomes data beyond that provided in the VIGOR trial.

- Unresolved safety issues

Analysis of the data from the RA application safety database demonstrates a trend consistent with the VIGOR (and ADVANTAGE) study: rofecoxib 50 mg/day has higher incidence of serious cardiovascular thrombotic events, edema-related, hypertension related and CHF related events than naproxen 1000 mg/day. Rofecoxib 25 mg dose behaves similarly to the 50 mg dose in this safety database. Therefore, the cardiovascular findings are consistent with those in the VIGOR and ADVANTAGE studies for rofecoxib as compared to naproxen, but do not provide information for the safety profile of rofecoxib in patients using low dose aspirin and in comparison to other NSAIDs. A major unresolved issue is whether the rate of CV thrombotic events is similar to placebo and naproxen is protective because of anti-platelet effects, or if rofecoxib is in fact pro-thrombotic.

A second area of concern is that there were more fractures in the rofecoxib 50 mg group as compared to naproxen in this data set, and this is consistent with the VIGOR study (also in a population of patients with RA) in which there were 41 (1%) and 29 (0.7%) fractures (all sites) in the rofecoxib and naproxen groups, respectively. The RA population is at high risk of osteoporosis because of the chronic use of steroids. The background fracture rate for this population is unknown. A recent study from Finland suggests that the risk of hip fracture is increased by three fold in patients with RA, as compared with that of non-RA patients. Since COX-2 is involved in regulation of bone metabolism, concerns have been raised regarding the long term bone effects of COX-2 inhibitors.

D. Dosing

Based on the studies in this sNDA, as well as the studies examining the use of rofecoxib 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. Clear evidence is provided that the 25 mg dose and the 50 mg dose are similar in efficacy and significantly better than either the —— or 12.5 mg dose. The dose escalation portion of the studies provides further support of this dose. Subjects moving from 25 mg in part I to 50 mg in part II demonstrated little improvement in clinical endpoints. Finally, the effective half life at steady state is approximately 17 hours. 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 (if any) 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 currently approved label. No additional information is provided in this submission in this regard.

E. Special Populations

A summary of age, race, and gender for the 25 and 50 mg doses only in trials 096, 097, and 068 is as follows: for 25 mg, a total of 177 males and 620 females were exposed to rofecoxib; for 50 mg, 380 females and 78 males; for 25 mg, 652 Caucasians, 42 Blacks, 42 Hispanics; for 50 mg, 366 Caucasians, 20 Blacks, and 27 Hispanics; for 25 mg and patients over 65, 136 and for 50 mg, 57 patients; in study 068, for 25 mg there were 62 subjects over 60, and for 50 mg there were 51.

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 and no definite conclusions can be drawn.

A single-dose pharmacokinetic study in mild (Child-Pugh score ≤6) hepatic insufficiency patients indicated that rofecoxib AUC was similar between these patients and healthy subjects. A pharmacokinetic study in patients with moderate (Child-Pugh score 7-9) hepatic insufficiency indicated that mean rofecoxib plasma concentrations were higher relative to healthy subjects. Patients with severe hepatic insufficiency have not been studied. Renal insufficiency does not appear to influence the pharmacokinetics of rofecoxib but it is not recommended in patients with advanced renal insufficiency.

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There are no studies in pregnant women. It is unlikely that the drug will be used to any significant extent in pregnant women. One pregnancy on rofecoxib resulted in a live birth with no known complications. One 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.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Rofecoxib (trade name: Vioxx) is a non-steroidal anti-inflammatory drug with the proposed indication as follows: for the treatment of the signs and symptoms of rheumatoid arthritis. The proposed dose is 25 mg orally on a daily basis. There are no pediatric studies submitted in this sNDA.

B. State of Armamentarium for Indication(s)

There are numerous non-selective NSAIDs available for the treatment of RA. These drugs work by inhibiting both the COX-1 and COX-2 enzymes. Celecoxib, a selective COX-2 inhibitor is also available for the treatment of RA. Rofecoxib appears to have advantages over naproxen in terms of GI safety as reflected in the VIGOR trial. Endoscopy studies have demonstrated fewer asymptomatic UGI ulcers associated with 3-6 months of rofecoxib 25 or 50 mg compared to naproxen. However, cardiovascular safety issues are of concern. The place for rofecoxib in the armamentarium for the treatment of RA is not clear at present, although it may be beneficial in a subpopulation of patients with a history of GI adverse events using traditional NSAIDs. On the other hand, the incidence of edema, CHF, and renal effects appears to favor naproxen.

C. Important Milestones in Product Development

During an end of phase II meeting on April 30, 1998, the Division recommended the use of the ACR 20 as the primary endpoint in RA clinical trials. However, agreement was reached that four primary endpoints were acceptable (number of tender joints, number of swollen joints, physician and patient global assessment), with success in 3 out of 4 endpoints adequate for success. In a teleconference on June 13, 2000 the Division stated that the proposal for controlling Type I error was acceptable since the sponsor had pre-specified which 3 of the 4 endpoints would be analyzed. The sponsor also agreed to include the ACR 20 as one of the secondary endpoints.

In identifying 3 out of 4 criteria for success of this these trials, the sponsor has referred to the FDA Guidance on Rheumatoid Arthritis which specifies either using the ACR 20 or 4 endpoints (tender and swollen joints, patient and physician global assessment) as satisfactory for documenting efficacy.

Rofecoxib has been reviewed and approved for use for acute analgesia and the treatment of the signs and symptoms of osteoarthritis.

There were no major issues that arose during the clinical trials in terms of design, safety, or ethical considerations.

D. Other Relevant Information

As of 01-Feb-2001, the marketing application for rofecoxib has not been rejected in any country. As of 01-Feb-2001, the marketing approval for rofecoxib has not been withdrawn in any country. As of 01-Feb-2001, the marketing approval for rofecoxib has not been suspended, revoked, or withdrawn by the Agency in any country.

E. Important Issues with Pharmacologically Related Agents

Rofecoxib is a member of the class of drugs known as COX-2 inhibitors. These drugs do not alter platelet function although they do appear to affect prostaglandin production by vascular smooth muscle cells. Therefore there are concerns about the possible thromboembolic complications arising from the use of rofecoxib. As of the present time, this issue has not been resolved. There are data from the safety study VIGOR (powered to examine GI events) that suggests that rofecoxib is associated with a higher incidence of thromboembolic complications as compared to naproxen. Two studies currently under review, the placebo controlled Alzheimers study and the ADVANTAGE study that appear to show a trend for MIs. Whether naproxen provides any cardioprotective effect is not known at this time. However, there does not appear to be a higher incidence of thromboembolic complications associated with the use of celecoxib, another COX-2 inhibitor.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There are no new clinically relevant findings from chemistry, toxicology, microbiology. Please see statistical review for a more detailed analysis of the data in the present submission.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

There are no new pharmacokinetic studies submitted in this sNDA. The reader is referred to the labeling of rofecoxib for details of PK properties etc.

B. Pharmacodynamics

There are no additional pharmacodynamic studies submitted in this sNDA. The reader is referred to the original NDA and the labeling of rofecoxib for details of PD studies etc.

IV. Description of Clinical Data and Sources

A. Overall Data

The sources of data used in this review are entirely from trials conducted by the sponsor.

B. Tables Listing the Clinical Trials

Table 1: Patient accounting for efficacy trials part I (randomized)

	placebo	Rofecoxib (mg)				naproxen	total
Trial #		—	12.5	25	50		
96 (12 weeks)	301		148	311		149	909
97 (12 weeks)	299			315	297	147	1058
68 (8 weeks)	168	158		171	161		658
total	768	158	148	797	458	296	2625

The total number of subjects treated with rofecoxib at any dose was 1561.

Table 2: Detailed patient accounting: study 096

Part I Patient Accounting

	Placebo	Rofecoxib 12.5 mg	Rofecoxib 25 mg	Naproxen 1000 mg	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
TOTAL PATIENTS ALLOCATED	301	148	311	149	909
CONTINUING at end of Part I	201 (66.8)	110 (74.3)	245 (78.8)	118 (79.2)	674† (74.1)
DISCONTINUED from Part I	100 (33.2)	38 (25.7)	66 (21.2)	31 (20.8)	235 (25.9)
Clinical Adverse Experiences	10 (3.3)	5 (3.4)	16 (5.1)	7 (4.7)	38 (4.2)
Laboratory Adverse Experiences	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Lack of efficacy	80 (26.6)	26 (17.6)	33 (10.6)	18 (12.1)	157 (17.3)
Lost to follow-up	1 (0.3)	2 (1.4)	0 (0.0)	0 (0.0)	3 (0.3)
Patient moved	1 (0.3)	2 (1.4)	1 (0.3)	2 (1.3)	6 (0.7)
Patient withdrew consent	3 (1.0)	0 (0.0)	4 (1.3)	2 (1.3)	9 (1.0)
Protocol deviation	5 (1.7)	3 (2.0)	7 (2.3)	2 (1.3)	17 (1.9)
Patient discontinued for other reasons	0 (0.0)	0 (0.0)	4 (1.3)	0 (0.0)	4 (0.4)

† One patient, AN 3213, was continuing at the end of Part I, and subsequently discontinued without having taken Part II drug. Hence, this patient did not count as formally having entered the Part II period.

Data Source: [4.1]

Table 3: Detailed patient accounting: study 097

Part I Patient Accounting

	Placebo		Rofecoxib 25 mg		Rofecoxib 50 mg		Naproxen 1000 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
RANDOMIZED	299		315		297		147		1058	
CONTINUING AT END OF PART I	237	(79.3)	281	(89.2)	250	(84.2)	126	(85.7)	894	(84.5)
DISCONTINUED FROM PART I	62	(20.7)	34	(10.8)	47	(15.8)	21	(14.3)	164	(15.5)
Clinical Adverse Experience	14	(4.7)	12	(3.8)	24	(8.1)	12	(8.2)	62	(5.9)
Laboratory Adverse Experience	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
Lack efficacy	39	(13.0)	16	(5.1)	13	(4.4)	5	(3.4)	73	(6.9)
Lost to follow-up	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)	2	(0.2)
Patient discontinued for other reasons	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Patient withdrew consent	3	(1.0)	4	(1.3)	3	(1.0)	2	(1.4)	12	(1.1)
Protocol deviation	5	(1.7)	2	(0.6)	4	(1.3)	2	(1.4)	13	(1.2)
TOTAL PATIENTS ALLOCATED	299		315		297		147		1058	

Data Source: [4.1]

As noted above, the primary analysis of integrated efficacy is based on 12-week data from the Phase III pivotal studies (Protocols 096 and 097) for the following treatment groups: placebo (n=600), rofecoxib 25 mg (n=626), and naproxen 1000 mg (n=296). Thus, the primary analysis of efficacy includes 1522 patients. The Phase III RA U.S. study (Protocol 096) also enrolled 148 patients who received 12.5 mg rofecoxib, and the Phase III RA multinational study (Protocol 097) enrolled 297 patients who received 50 mg rofecoxib daily.

Reviewers note: In trial 096 the following numbers of subjects were either lost to followup, moved, withdrew consent, discontinued or had a protocol deviation: placebo 10, rofecoxib 25 mg 16, and naproxen 6. In trial 097: placebo 9, rofecoxib 6, naproxen 4. Analysis of true ITT population for ACR20 (as will be seen later) should account for these differences.

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Protocol 068 is a phase II trial. For study 068 the following is patient accounting.

Table 4: Detailed patient accounting: study 068 (part I)

Patient Accounting

	Placebo	Rofecoxib — mg	Rofecoxib 25 mg	Rofecoxib 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]

Table 5: Detailed patient accounting study 097 (part II)

Part II Patient Accounting at Data Cutoff

	Rofecoxib 25 mg		Rofecoxib 50 mg		Naproxen 1000 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
COMPLETED THE PART II PERIOD	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
CONTINUING STUDY AT DATA CUTOFF (IN PART II)	236	(93.3)	363	(92.6)	237	(95.6)	836	(93.6)
DISCONTINUED STUDY (FROM PART II)	17	(6.7)	29	(7.4)	11	(4.4)	57	(6.4)
Clinical Adverse Experience	8	(3.2)	12	(3.1)	8	(3.2)	28	(3.1)
Laboratory Adverse Experience	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
Lack efficacy	5	(2.0)	9	(2.3)	1	(0.4)	15	(1.7)
Lost to follow-up	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
Patient discontinued for other reasons	2	(0.8)	1	(0.3)	0	(0.0)	3	(0.3)
Patient withdrew consent	2	(0.8)	5	(1.3)	1	(0.4)	8	(0.9)
Protocol deviation	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
TOTAL PATIENTS (ENTERED PART II)	253		392		248		893	

Data Source: [4.1]

Table 6: 068 part II

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]

Table 7: Detailed patient accounting study 096 (part II)

Part II Patient Accounting at Data Cutoff

	Rofecoxib		Naproxen	
	25 mg	50 mg	1000 mg	Total
	n (%)	n (%)	n (%)	n (%)
TOTAL PATIENTS (Entered Part II)	335	114	224	673
COMPLETED the Part II Period	12 (3.6)	6 (5.3)	6 (2.7)	24 (3.6)
CONTINUING STUDY at Data Cutoff (Part II)	257 (76.7)	88 (77.2)	182 (81.3)	527 (78.3)
DISCONTINUED STUDY (From Part II)	66 (19.7)	20 (17.5)	36 (16.1)	122 (18.1)
Clinical Adverse Experiences	16 (4.8)	6 (5.3)	12 (5.4)	34 (5.1)
Laboratory Adverse Experiences	4 (1.2)	2 (1.8)	1 (0.4)	7 (1.0)
Lack of efficacy	32 (9.6)	7 (6.1)	16 (7.1)	55 (8.2)
Lost to follow-up	3 (0.9)	0 (0.0)	1 (0.4)	4 (0.6)
Patient moved	0 (0.0)	1 (0.9)	1 (0.4)	2 (0.3)
Patient withdrew consent	3 (0.9)	3 (2.6)	2 (0.9)	8 (1.2)
Protocol deviation	4 (1.2)	0 (0.0)	2 (0.9)	6 (0.9)
Patient discontinued for other reasons	4 (1.2)	1 (0.9)	1 (0.4)	6 (0.9)

Data Source: [4.1]

Table 8: Summary of patient accounting part II efficacy trials

	Rofecoxib (mg)		naproxen	total
Trial #	25	50		
97 entered part II	253	392	248	836
discontinued	17 (6.7%)	29 (7.4%)	11 (4.4%)	57 (6.4%)
68 entered part II	235	223	86	544
discontinued	66 (28.1%)	78 (35%)	27 (31.4%)	171 (31.4%)
96 entered part II	335	114	224	673
discontinued	66 (19.7%)	20 (17.5%)	36 (16.1%)	122 (18.1%)

Table 9:Summary of clinical trials in the present submission

Rheumatoid Arthritis Supplemental Marketing Application
Phase IIb/III Clinical Studies

Protocol Number [Ref.]	Title	Location	Phase	Treatment Daily Doses (mg)
068 [P068P1; P068P2]	A 2-Part, Double-Blind, Randomized, Multicenter, Parallel-Group, 52-Week Study to Assess the Safety and Tolerability, and to Further Define the Clinically Effective Dose Range, of MK-0966 in Patients With Rheumatoid Arthritis.	U.S.	IIb	ROF 25, 50 PBO, NAP
068 [P068X]	First and Second Extensions of a 2-Part, Double-Blind, Randomized, Multicenter, Parallel-Group, 52-Week Study to Assess the Safety and Tolerability, and to Further Define the Clinically Effective Dose Range, of MK-0966 in Patients With Rheumatoid Arthritis.	U.S.	IIb	ROF 25, 50 NAP
096 [P096]	An Active-Comparator- and Placebo-Controlled, Parallel-Group, Double-Blind, 52-Week Study to Assess the Safety and Efficacy of MK-0966 in Rheumatoid Arthritis Patients.	U.S. and Multinational	III	ROF 12.5, 25 NAP, PBO
097 [P097]	An Active-Comparator- and Placebo-Controlled, Parallel-Group, Double-Blind, 52-Week Study to Assess the Safety and Efficacy of 25 mg and 50 mg MK-0966 Daily in Rheumatoid Arthritis Patients.	Multinational	III	ROF 25, 50 PBO NAP
098/103 [P098C]	A Multicenter, Randomized, Parallel-Group, Active- and Placebo-Controlled, Double-Blind Study, Conducted Under In-House Blinding Conditions, to Determine the Incidence of Gastroduodenal Ulcers in Patients With Rheumatoid Arthritis After 12 Weeks of Treatment With MK-0966, Naproxen, or Placebo.	U.S. and Multinational	III	ROF 50 PBO NAP

ROF = Rofecoxib.
NAP = Naproxen 500 mg twice daily.
PBO = Placebo.

Table 10: Dosages and comparators in present submission

Rofecoxib Studies in Adult Patients With Rheumatoid Arthritis

Phase/Short Title (Protocol) [Ref.]	Part I Treatments (mg)	Part II or Extension Treatments (mg)
Previously Filed		
[		]
Phase III GI Outcomes Study (Protocol 088/089) filed Jun-2000 [54]	ROF 50 NAP 1000	N/A
Filed in the Present Marketing Application		
Phase IIb RA Dose-Ranging Study and Extensions (Protocol 068) [P068P1; P068P2]	PBO, ROF — ROF 25 ROF 50	 ROF 25 ROF 50 NAP 1000
Phase III RA Pivotal Study—Primarily conducted within the U.S. (Protocol 096) [P096]	PBO, ROF 12.5 ROF 25 NAP 1000	 ROF 25 ROF 50 NAP 1000
Phase III RA Pivotal Study—Conducted outside the U.S. (Protocol 097) [P097]	PBO, ROF 25 ROF 50 NAP 1000	 ROF 25 ROF 50 NAP 1000
Phase III Gastrointestinal Endoscopy Study (Protocol 098/103) [P098C]	PBO, ROF 50 NAP 1000	N/A
PBO = Placebo; ROF = Rofecoxib; NAP = Naproxen; N/A = Not applicable.		

A total of 1522 patients, 761 patients from each study, were included in the integrated analysis of efficacy data from the 2 Phase III pivotal studies: 600, 626, and 296 in the placebo, 25-mg rofecoxib, and naproxen groups, respectively. Baseline demographics for the combined patient sample were summarized. Women comprised 79.2% of patients, 79.9% were Caucasian, and the mean age was 54.5 years (range 21 to 87 years). Weight ranged from 29.5 to 157.4 kg; mean weight was 73.1 kg. Height ranged from 130.8 to 195.6 cm; mean height was 163.4 cm. No important between-group differences were noted.

C. Postmarketing Experience

Please see safety review, which includes SUR.

D. Literature Review

Published clinical literature for rofecoxib was reviewed by the sponsor for consistency with the clinical study reports included in this marketing application. According to the sponsor, forty-nine abstracts and 23 manuscripts have been published as of 15-Dec-2000. These publications include data from clinical pharmacology studies and clinical trials in osteoarthritis, dysmenorrhea, rheumatoid arthritis, dental pain, and gastrointestinal safety. Of these publications, one

manuscript is from a study included in this marketing application, 19 manuscripts and 39 abstracts report the results of studies included in previous marketing applications or safety update reports, and 10 abstracts and 3 manuscripts report the results of studies that have not been included in marketing applications.

V. Clinical Review Methods

A. Describe How Review was Conducted

For the efficacy review, trials 068, a phase IIb trial, and pivotal trials 096 and 097, both phase III trials, were all reviewed in detail and results for each are included in this review.

B. Overview of Materials Consulted in Review

Electronically submitted materials were reviewed exclusively for this evaluation. **The safety review portion consists of safety data submitted with this sNDA in addition to the ADVANTAGE study and safety update reports.**

C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI previously audited the original submission of this NDA. There was no audit requested by the Division for this sNDA submission.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Trials appeared to be conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

There do not appear to be any financial disclosures that could cast doubt on the integrity of the findings. [redacted] according to the sponsor bias is minimized by trial design, i.e. double blind, randomized trial. Merck states they have not entered into any financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. For most, the number of sites utilized and the fact that no site entered a disproportionate number of subjects also minimizes any potential bias by each investigator.

VI. Integrated Review of Efficacy

A. Conclusions

Rofecoxib was demonstrated to be efficacious in the treatment of the signs and symptoms of RA in 2 pivotal trials. Supportive evidence of efficacy is provided by a third trial.

B. General Approach to Review of the Efficacy of the Drug

The efficacy database is comprised of 2 pivotal trials 096 and 097, and one supportive trial, 068. These studies are reviewed in detail in the efficacy portion of this review.

C. Detailed Review of Trials by Indication

Indication: for the treatment of the signs and symptoms of rheumatoid arthritis

Trial 096: An Active Comparator- and Placebo-Controlled, Parallel-Group, Double-Blind, 52-Week Study to Assess the Safety and Efficacy of rofecoxib in Rheumatoid Arthritis Patients (Part I was 12 weeks).

Objectives/rationale

1. To demonstrate superior clinical efficacy for rofecoxib 25 mg daily compared with placebo, in treatment of RA over a 12-week period.
2. To demonstrate safety and tolerability for rofecoxib 25 to 50 mg daily over a 1-year treatment period in RA patients.
3. To explore the efficacy of rofecoxib 12.5 mg daily for treatment of RA.
4. To explore the efficacy response to fixed-dose escalation from 25 to 50 mg and from 12.5 to 25 mg rofecoxib daily.
5. To assess the clinical efficacy of naproxen 500 mg twice daily over a 12-week period.
6. To assess the maintenance of therapeutic effects for rofecoxib 25 mg and 50 mg daily and naproxen 500 mg twice daily over a treatment period up to 1 year.

Design

This 2-part, double-blind, parallel-group, 52-week study enrolled patients with RA. Following a per-protocol discontinuation ("washout") of NSAID agent(s), patients were required to meet specific disease-activity criteria and have a worsening in signs and symptoms from the screening visit. Non-study antirheumatic therapy was permitted with anticipation that dose(s) would remain stable over the first 14 weeks of the study (through Visit 7.0). Patients were permitted to enroll taking low-dose oral corticosteroids (up to 10 mg prednisone daily) provided the dose had been stable for 1 month, and would remain stable for the first 14 weeks of study treatment (through Visit 7.0). Patients were allowed to take low-dose aspirin (defined as 81 mg daily or less) for cardioprotective or antiplatelet benefits. Solubilized Tumor Necrosis Factor (TNF)/TNF receptor antagonists were not permitted on entry but could be started after Visit 7.0 if clinically indicated. At Visit 2.0, patients who met all entry criteria following NSAID

washout were randomized to receive rofecoxib 12.5 mg (N=148) or 25 mg daily (N=311), naproxen 500 mg twice daily (N=149), or placebo (N=301) for 12 weeks. For the first 14 weeks of the study (up to Visit 7.0), acetaminophen was provided to patients as "rescue therapy" for breakthrough pain. Following completion of Part I, a 12-week, placebo-controlled period, patients entered Part II, a 40-week, active comparator-controlled period. Based on original randomization, some patients underwent reassignment of study treatment. Patients who received placebo in Part I were randomly reassigned, in approximately equal proportions, to 25 mg rofecoxib or naproxen 500 mg twice daily in Part II. At random, half of patients who received rofecoxib 25 mg in Part I received rofecoxib 50 mg in Part II; the other half continued on rofecoxib 25 mg. Patients who received 12.5 mg rofecoxib in Part I received 25 mg in Part II. Patients who received naproxen in Part I continued on the same treatment in Part II. Part II treatment assignment was determined by the patient's allocation at the time of entry into the study.

Protocol

Inclusion criteria:

1. Patient was >18 years of age and not considered "morbidly obese." For this protocol, "morbidly obese" was defined to mean the patient's weight interfered with the performance of usual and typical vocational/avocational activities and/or was a serious independent health risk, likely to result in medical complications within the year.
2. At prestudy, women of childbearing potential had a serum human beta HCG level consistent with a non-gravid state and agreed to use an acceptable form of contraception beginning at least 7 days prior to study treatment and continuing at least 14 days after Visit 12.0 or a discontinuation visit. Acceptable forms of contraception were specified in the protocol. Postmenopausal women, or women status posthysterectomy or tubal ligation, were exempt from this requirement .
3. Patient's diagnosis of RA satisfied at least 4 of 7 ARA 1987 revised criteria for the diagnosis of RA.
4. The diagnosis of RA was present at least 6 months prior to study start and no earlier than 16 years of age.
5. Patients were ARA functional Class I, II, or III.
6. Patient's global assessment of disease activity (100-mm Visual Analog Scale [VAS]) at the prestudy visit was less than 80 mm.
7. Patients had a history of a therapeutic benefit with NSAIDs.
8. Patients had taken an NSAID on a regular basis and at a therapeutic dose level for at least 30 days prior to study enrollment ("regular basis" was defined as greater than 25 of the previous 30 days).
9. Approved nonstudy antirheumatic therapy had been at stable dosing for the required time periods listed below and was not anticipated to undergo a change within the first 14 weeks on study treatment. Similarly, patients did not discontinue therapy within the given time frame immediately prior to entry. (Solubilized TNF/TNF receptor antagonists were not permitted on

entry but could be started after Visit 7.0 if such therapy was warranted. Patients must have been discontinued from a solubilized TNF/TNF receptor antagonist for at least 3 months prior to enrollment.)

Antimalarials 3 months
Azathioprine 6 months
Gold salts (oral or injectable) 6 months
Leflunomide 3 months
Methotrexate 3 months
D-penicillamine 6 months
Sulfasalazine 3 months
Oral corticosteroids 1 month

10. After a "washout" of prestudy NSAID, patients satisfied both activity and flare criteria. The minimum and maximum washout duration depended upon the particular prestudy NSAID .

Activity Criteria at Visit 2.0
Patient's global assessment of disease activity =40 mm,
Number of joints that were tender =9, and
Number of swollen joints =6.

Flare Criteria at Visit 2.0
An increase in patient's 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 that at Visit 2.0, patients were required to have at least 9 tender joints and an increase by =20% over the number recorded at 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 the first 14 weeks of the study (through Visit 7.0).
12. Excepting RA, patient was judged to be in otherwise 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 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 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 resulting 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 at rest or on minimal activity, and/or had a history of myocardial infarction, coronary angioplasty, or coronary arterial bypass grafting within the year prior to the study.
6. Patient had uncontrolled hypertension. (Note: Patients with medically controlled hypertension [diastolic blood pressure less than 95, systolic blood pressure less than 165] were permitted to participate.)
7. Patient had a history of stroke or transient ischemic attack within the 2 years prior to the study.
8. Patient had a history of hepatitis/hepatic disease that has been active within the previous 2 years.
9. Patient had a history of neoplastic disease and did not meet one of the specific exceptions listed immediately below. Patients with a history of leukemia, lymphoma, or myeloproliferative disease were ineligible for the study regardless of the time since treatment. Exceptions are listed immediately below.
Patients with adequately treated basal cell carcinoma or carcinoma in situ of the cervix.
Patients successfully treated for other malignancies greater than 10 years prior to screening, where in the judgment of both the investigator and treating physician, appropriate follow-up revealed no evidence of recurrence from the time of treatment through the time of screening.
Patients who, in the joint opinion of the Merck monitor and investigator, were highly unlikely to sustain a recurrence during the duration of the study.
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 confound the results of the study, posed additional risk to the patient, or contraindicated treatment with acetaminophen or an NSAID such as naproxen.

Previous or Concurrent Medication

12. Patients were excluded from participation if any of the following applied:
Oral corticosteroid therapy greater than the equivalent of 10 mg of daily prednisone and/or dose not stable for at least 1 month prior to screening.
Misoprostol or sucralfate use within the 1 month prior to screening.
Use of topical, oral, or systemic analgesic medications within 5 days of

study entry and through Visit 7.0. Acetaminophen use was permitted prior to entry, and acetaminophen for "rescue" analgesia was provided per protocol.
Concomitant use of a nonstudy NSAID.
Use of a COX-2-specific inhibitor as a concomitant nonstudy medication. (Patients with prior exposure to rofecoxib were not permitted into the study.)
Ongoing treatment with warfarin.
Ongoing ticlopidine, ———— or low-dose aspirin use, in excess of 81 mg/day.
Solubilized TNF/TNF receptor antagonists within 3 months of study entry and through Visit 7.0.
Intra-articular, intramuscular, or intravenous corticosteroids within 3 months of entry to the study. (Use of intra-articular corticosteroids were permitted after Visit 7.0.)
13. Patient's medical regimen had undergone changes in the month prior to the study (i.e., dosage adjustments, addition or discontinuation of medicines) or the investigator anticipated changes in concurrent medications during the first 14 weeks of the study (through Visit 7.0).

Laboratory Abnormalities
14. Patient had clinically significant abnormalities on prestudy clinical examination or laboratory safety tests. (Serum transaminases were >150% of the upper limit of normal.)

Miscellaneous
15. Patient used (including "recreational use") illicit drugs, or had a history (within the 5 years prior to the study) 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 4 weeks prior to the study. (Patients unwilling to refrain from donation of blood or blood products while participating in the protocol 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 were permitted to participate in this study. Identification of treatment allocation in prior rofecoxib studies had to be verified by the Merck monitor.)

Patients were randomized to treatment sequence (Part I/Part II) using a computer-generated allocation schedule. Patients were assigned an AN; allocation was stratified on the basis of concurrent oral corticosteroid usage. (Blocks of allocations were designated for either users or nonusers.)

A summary of the schedule of observations and laboratory tests is shown below.

Table 11: Schedule of observations

Schedule of Clinical Observations and Laboratory Measurements—Part I

	Prestudy	Flare	Treatment				
Clinic Visit #:	1.0	2.0	3.0	4.0	5.0	6.0	Discon-
Duration of Treatment:	Screening	Allocation	2 Weeks	4 Weeks	8 Weeks	12 Weeks	tinue
Review of entry criteria	X	X					
American Rheumatism Association functional class	X						
Informed consent	X						
Medical history	X						
Interim history and monitor for adverse experiences		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Physical examination	X					X	X
Hemoccult	X						
Electrocardiogram	X					X	X
Dispense study medication		X	X	X	X	X	
Study medication tablet count			X	X	X	X	X
Dispense acetaminophen	X	X	X	X	X	X	X
Acetaminophen tablet count		X	X	X	X	X	X
Patient global assessment of disease activity	X	X	X	X	X	X	X
Patient's global assessment of pain	X	X	X	X	X	X	X
Patient's global assessment of response to therapy			X	X	X	X	X
Health Assessment Questionnaire	X	X	X	X	X	X	X
Short Form-36 Health Survey	X	X		X		X	X
Duration of morning stiffness	X	X	X	X	X	X	X
Number of tender/number of swollen joints	X	X	X	X	X	X	X
Investigator's global assessment of disease activity	X	X	X	X	X	X	X
Investigator's global assessment of response to therapy			X	X	X	X	X
Complete blood count, serum chemistry, urinalysis	X	X	X	X	X	X	X
Plasma sample for archive		X	X	X†		X	X
Rheumatoid factor	X						
Serum beta-human chorionic gonadotropin (β-hCG)‡	X						
Urine β-hCG‡		X§	X	X	X	X	X
C-reactive protein	X	X	X	X	X	X	X

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

Data Source: [3.3]

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Schedule of Clinical Observations and Laboratory Measurements—Part II

	Treatment							
Clinic Visit #:	7.0	8.0	9.0	10.0	11.0	12.0	Discon-	13.0
Duration of Treatment:	14 Weeks	20 Weeks	26 Weeks	32 Weeks	40 Weeks	52 Weeks	tinue	Post
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	
Electrocardiogram						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 collection	X							X
Patient global assessment of disease activity	X	X	X	X	X	X	X	
Patient's global assessment of pain	X	X	X	X	X	X	X	
Patient's global assessment of response to therapy	X	X	X	X	X	X	X	
Health Assessment Questionnaire	X	X	X	X	X	X	X	
Short Form-36 Health Survey	X	X		X		X	X	
Duration of morning stiffness	X	X	X	X	X	X	X	
Number of tender/number of swollen joints	X	X	X	X	X	X	X	
Investigator's global assessment of disease activity	X	X	X	X	X	X	X	
Investigator's global assessment of response to therapy	X	X	X	X	X	X	X	
Complete blood count, serum chemistry, urinalysis	X	X	X	X	X	X	X	X
Plasma sample for archive		X	X†			X	X	
Urine beta-human chorionic gonadotropin (β-hCG)‡	X	X	X	X	X	X	X	X
C-reactive protein	X	X	X	X	X	X	X	

† Patients were instructed to not take their morning medication dose at Visit 9.0 until after the plasma archive sample had been obtained.
‡ Urine and serum β-hCG samples were obtained from women of childbearing potential only.

Data Source: [3.3]

Table 13: Endpoints

Efficacy Endpoints: Definition of Baseline and Direction of Improvement

Endpoint (Scales)	Definition of Baseline	Improvement
Primary		
Total 68 Tender Joint Count	Visit 2	Decreases
Total 66 Swollen Joint Count	Visit 2	Decreases
Patient's Global Assessment of Disease Activity (0- to 100-mm Visual Analog Scale)	Visit 2	Decreases
Investigator's Global Assessment of Disease Activity (0- to 4-Likert Scale)	Visit 2	Decreases
Key Secondary		
Arthritis Clinical Response Criteria 20% Responder Index	Visit 2	Increases
Patient Global Assessment of Pain (0- to 100-mm VAS)	Visit 2	Decreases
Stanford Health Assessment Questionnaire	Visit 2	Decreases
Other		
Patient's Global Assessment of Response to Therapy (0- to 4-Likert Scale)	No baseline value	Decreases†
Investigator's 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)	Visit 2	Decreases
Acetaminophen Use for Rescue (tablets/day)	Visit 2	Decreases
C-Reactive Protein (mg/dL)	Visit 2	Decreases
Short Form-36 Health Survey	Visit 2	Increases

† Graph and table results were reversed to show improvement with decreasing, rather than increasing, numbers.

Data Source: Not Applicable

Statistical analysis

No multiplicity adjustment of the alpha level for the statistical tests was made. The requirement that the primary efficacy hypothesis must be satisfied for the prespecified 3 of 4 primary endpoints (i.e., all except swollen joint count; equivalent to 3 out of 3) controls the alpha level for multiple endpoints. The use of the time-weighted average over the 12-week period as the primary efficacy response eliminates the need for any alpha adjustment for multiple time points.

Primary efficacy analyses were based on a modified intention-to-treat (ITT) approach, i.e., inclusion of all patients with a baseline and at least one on-treatment-period measurement. Dropouts were included in the analysis based on responses obtained up to and including those at the time of discontinuation. Analyses were performed on the time-weighted average response of observed data only, while the last-value-carried-forward method was used for longitudinal graphs. Since most

of the endpoints were analyzed as the time-weighted averages over the treatment period, no missing values were imputed (i.e., data points were not carried forward).

Additionally, the Division requested, and the sponsor carried out, efficacy analyses on all randomized subjects regardless of having any post-baseline data, and all randomized subjects who took at least one dose of drug regardless of any post-baseline data.

In the analysis of the proportion of patients completing and meeting the ACR20 criteria, dropouts were scored as "nonresponders." **An additional analysis performed by the Agency statistical reviewer imputed results for the placebo group with missing data as success and other groups as failures, a conservative approach to sensitivity analysis.**

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

Table 14: Endpoints

Listing of Endpoints and Their Statistical Analyses

Endpoint	Statistical Method	Analysis Approaches
Primary		
Tender Joint Count	ANCOVA	ITT and PP
Swollen Joint Count	ANCOVA	ITT and PP
Patient's Global Assessment of Disease Activity	ANCOVA	ITT and PP
Investigator's Global Assessment of Disease Activity	ANCOVA	ITT and PP
Secondary		
Arthritis Clinical Response Criteria 20% Responder Index	Cochran-Mantel-Haenszel test	ITT
Patient's Global Assessment of Pain	ANCOVA	ITT
Stanford Health Assessment Questionnaire	ANCOVA	ITT
Other		
Patient's Global Assessment of Response to Therapy	ANCOVA	ITT
Investigator's Global Assessment of Response to Therapy	ANCOVA	ITT
Discontinuation due to Lack of Efficacy	Fisher's exact test	ITT
Duration of Morning Stiffness	ANCOVA (on ranks)	ITT
Acetaminophen Use (for Rescue)	ANCOVA	ITT
C-Reactive Protein[†]	ANCOVA (log scale)	ITT
Short Form-36 Health Survey	ANCOVA	ITT

[†] When C-reactive protein was transformed to log scale, values less than 0.04 mg/dL were treated as 0.04 mg/dL because they became very small and may not be reliable.

Data Source: [3.3]

The original protocol was amended 3 times: 1) 096-01 (first amendment):
Cyclosporin A was removed as a prohibited concomitant medication.
Maximal recommended doses of H2-receptor antagonists and proton-pump inhibitors were removed as prohibited prior medications.
2) 096-02 (second amendment):
Allowed international study sites to participate in Protocol 096.
3) 096-03 (third amendment):
The study center was removed from the ANCOVA.
Forty-five-day and 1-year discontinued patient follow-up (for the occurrence of GI PUB events) was removed.

These amendments do not appear to significantly alter the study protocol.

Results

Patient disposition, comparability

There were no clinically meaningful differences between treatment groups for any characteristics including age, weight, concomitant use of DMARDs (including methotrexate) and corticosteroids, ARA functional class, and rheumatoid-factor positivity. The duration of RA was slightly longer in the naproxen group (8.3 years) versus the rofecoxib 25 mg groups (10.1 years) or placebo (10.4 years).Patients who were screened for the study but not randomized had baseline characteristics similar to randomized patients. There were no important differences between treatment groups in mean baseline values for any primary efficacy endpoint. Duration of morning stiffness was slightly shorter in the rofecoxib 25 mg group (195.68 minutes) versus placebo (216.89 minutes). There were no clinically meaningful differences between treatment groups in frequency or type of prior drug therapies. There were no clinically meaningful differences between treatment groups in frequency or type of concomitant drug therapies. More patients used aurothioglucose in the rofecoixb 25 mg group (3.5%) than in the placebo group (1.3%). More patients used azathioprine in the placebo group (2.7%) than in the rofecoxib 25 mg group (1.3%). See Table 2: Detailed patient accounting: study 096.

Comment: overall less patients discontinued from the rofecoxib 25 mg group compared to the placebo group (21 vs 33%; 10 vs 26% for lack of efficacy).

Efficacy endpoint outcomes/ dose response

This table (Table 15: Efficacy Summary) summarizes the results for each of the primary endpoints. Analyses of each endpoint in more detail will follow. Overall, 25 mg rofecoxib was superior to placebo at each endpoint and was similar but not superior to naproxen.

Table 15: Efficacy Summary

Efficacy Summary of Endpoints
Differences in Least-Squares Mean Changes Between Active Treatments and Placebo With 95% Confidence Intervals
Analysis of Time-Weighted Average Response (Weeks 2 to 12)
(Intention-to-Treat Approach)

Endpoint	Between-Treatment Difference in LS† Mean (95% CI‡ of the Difference)		
	12.5 mg versus Placebo	25 mg versus Placebo	Naproxen versus Placebo
Primary Endpoints			
Tender Joint Count (total 68)	-1.50 (-3.37, 0.36)	-2.73 (-4.23,-1.23)	-3.09 (-4.94,-1.24)
Swollen Joint Count (total 66)	-0.91 (-2.12, 0.30)	-1.22 (-2.19,-0.24)	-1.73 (-2.93,-0.53)
Patient's Global Assessment of Disease Activity (0 to 100 VAS)§	-5.33 (-9.34,-1.32)	-7.18 (-10.4,-3.95)	-10.4 (-14.4, -6.45)
Investigator's Global Assessment of Disease Activity (0 to 4 Likert scale)	-0.17 (-0.33,-0.01)	-0.32 (-0.45,-0.19)	-0.27 (-0.43,-0.11)

† CI = Confidence interval.
‡ LS = Least-squares.
§ Visual Analog Scale.

Data Source: [4.3]

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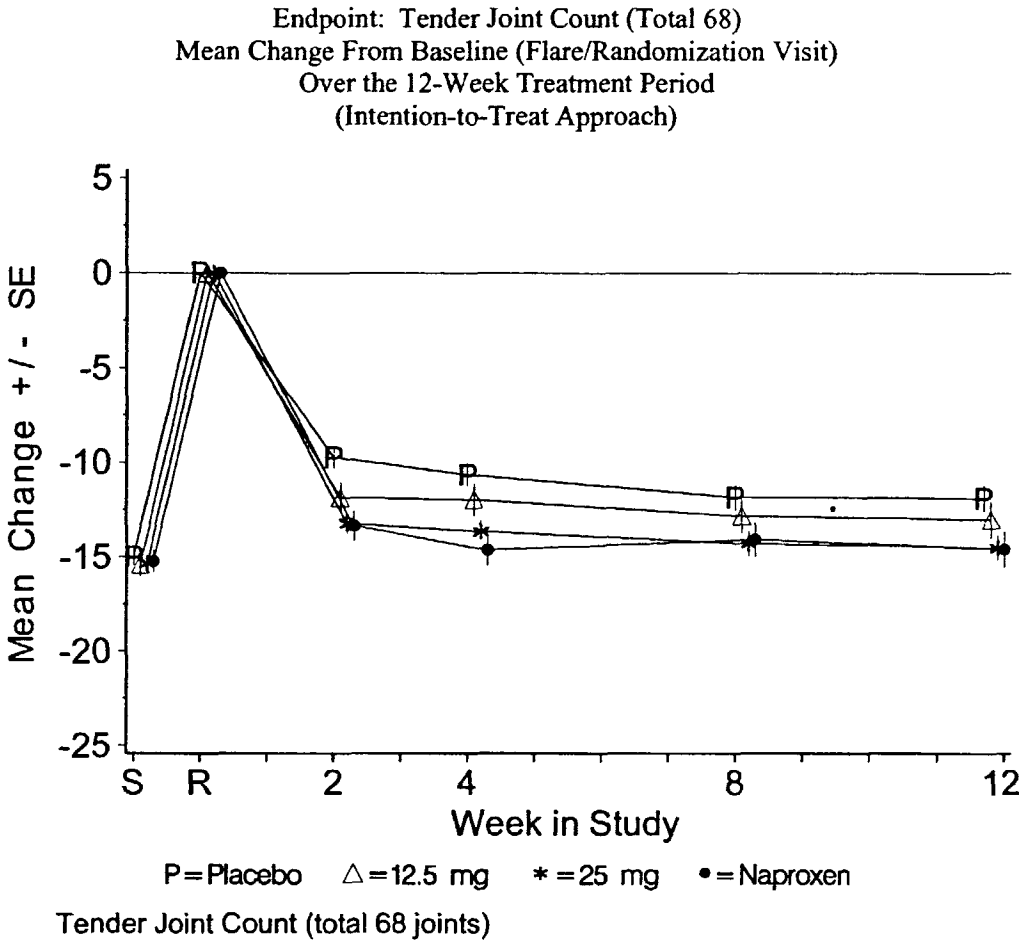
Figure 1: Tender joint count



SE = Standard error.
S = Screening.
R = Randomization (baseline).
Screening to Baseline = washout period for prior Rheumatoid Arthritis therapy.
Data points for each treatment group were shifted to maximize legibility at each time point.

(Please note: this is the sponsors defined ITT population, which is a modified ITT not the true ITT population)

This figure graphically illustrates the initial flare from screening to randomization with subsequent improvement. Of note even the placebo group improves within the first 2 weeks and continues to slowly improve over the remaining 10 weeks. Of additional note, the effect of rofecoxib is maintained at week 12 for this endpoint (as will be seen, for other endpoints the efficacy appears to diminish over time for the treatment groups). However, as will be seen in the next table, the improvement with rofecoxib 25 mg is

significantly better than placebo at week 12. Also of interest is that improvement in the treatment groups by week 12 does not improve beyond the joint count at screening.

Table 16: Tender joint count

Analysis of Endpoint: Tender Joint Count (Total 68 Joints)
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	29.85	18.05	-11.81	11.07	-11.52	(-12.59, -10.44)
12.5 mg	146	28.38	15.61	-12.77	11.67	-13.02	(-14.55, -11.49)
25 mg	309	29.26	14.94	-14.32	10.79	-14.25	(-15.30, -13.19)
Naproxen	149	29.48	14.67	-14.80	10.69	-14.61	(-16.13, -13.09)

Comparisons Between Treatment Groups	Difference in LS Mean‡	95% CI for Difference	p-Value
With Placebo			
25 mg versus Placebo	-2.73	(-4.23, -1.23)	<0.001
12.5 mg versus Placebo	-1.50	(-3.37, 0.36)	0.114
Naproxen versus Placebo	-3.09	(-4.94, -1.24)	0.001
Between Active Treatments			
25 mg versus 12.5 mg	-1.23	(-3.07, 0.62)	0.193
25 mg versus Naproxen	0.36	(-1.47, 2.20)	0.699
12.5 mg versus. Naproxen	1.59	(-0.55, 3.73)	0.146

Effect	p-Value	Pooled SD†
Baseline Covariate	<0.001	9.37
Low-Dose Corticosteroid Use	0.143	
Treatment	<0.001	

† Standard deviation.
‡ Least-squares mean.
§ Confidence interval.

Data Source: [4.3]

This table (Table 16: Tender joint count) illustrates that both naproxen and rofecoxib 25 mg but not 12.5 mg are superior to placebo at the end of 12 weeks(.001, < .001, and .114 respectively), and that there is no difference between naproxen and rofecoxib 25 mg. There is also no difference when subjects are analyzed by the covariate designated "low dose steroid use." **Of note, this analysis uses the sponsors defined ITT population (modified). The next table illustrates a re-analysis using the true ITT population as requested by the Division.**

Table 17: Tender joint count (ITT)

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	301	29.85	18.05	-11.53	11.09	-11.25	(-12.32, -10.18)
12.5 mg	148	28.38	15.61	-12.60	11.68	-12.85	(-14.38, -11.32)
25 mg	311	29.26	14.94	-14.23	10.81	-14.16	(-15.22, -13.10)
Naproxen	149	29.48	14.67	-14.80	10.69	-14.61	(-16.14, -13.09)

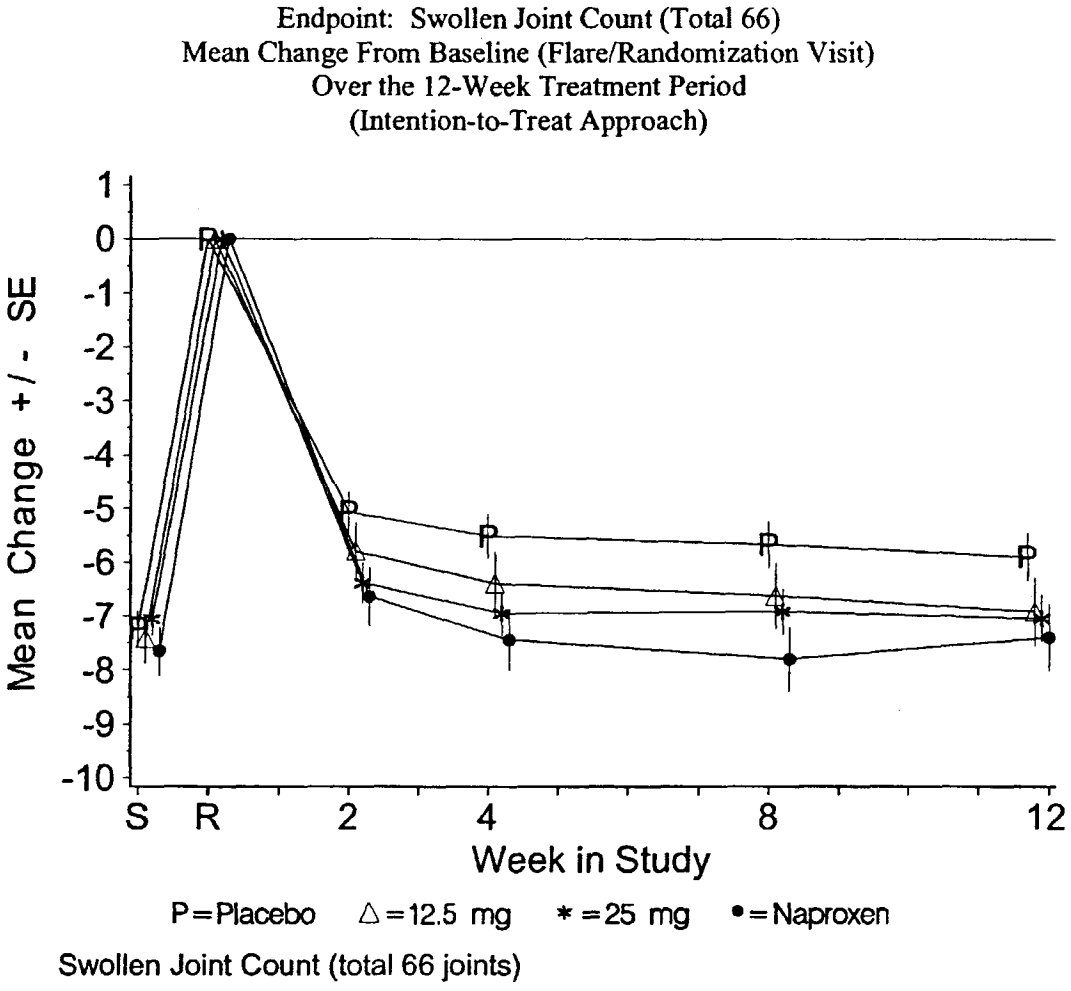
Comparisons Between Treatment Groups	Difference in LS Mean	95% CI for Diff.	p-Value
<u>With Placebo</u>			
25 mg vs. Placebo	-2.91	(-4.41, -1.42)	<0.001
12.5 mg vs. Placebo	-1.60	(-3.46, 0.25)	0.091
Naproxen vs. Placebo	-3.37	(-5.22, -1.51)	<0.001
<u>Between Active Treatments</u>			
25 mg vs. 12.5 mg	-1.31	(-3.16, 0.53)	0.164
25 mg vs. Naproxen	0.45	(-1.39, 2.29)	0.629
12.5 mg vs. Naproxen	1.76	(-0.38, 3.91)	0.107

Effect:	p-Value	Pooled SD
Baseline Covariate	<0.001	9.41
Low Dose Corticosteroid Use	0.153	
Treatment	<0.001	

† Least squares mean

This re-analysis of tender joint counts using all randomized subjects regardless of any post-baseline data confirms the previous analysis that rofecoxib 25 mg and naproxen are superior to placebo at 12 weeks. The p value for rofecoxib 12.5 mg improves slightly with this new analysis (.091) but remains greater than .05.

Figure 2: Swollen joint count



SE = Standard error.
S = Screening.
R = Randomization (baseline).
Screening to Baseline = washout period for prior Rheumatoid Arthritis therapy.
Data points for each treatment group were shifted to maximize legibility at each time point.

This figure graphically shows the changes in swollen joint count in the placebo and treatment groups. The next table provides the numerical changes at 12 weeks.

Table 18: Swollen joint count

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	18.78	12.85	-5.93	7.34	-5.82	(-6.52,-5.12)
12.5 mg	146	17.83	11.33	-6.50	7.64	-6.73	(-7.73,-5.73)
25 mg	309	18.29	11.32	-6.98	7.04	-7.04	(-7.73,-6.35)
Naproxen	149	19.21	11.38	-7.83	7.06	-7.55	(-8.54,-6.57)

Comparisons Between Treatment Groups	Difference in LS Mean‡	95% CI§ for Difference	p-Value
With Placebo			
25 mg versus Placebo	-1.22	(-2.19, -0.24)	0.014
12.5 mg versus Placebo	-0.91	(-2.12, 0.30)	0.142
Naproxen versus Placebo	-1.73	(-2.93, -0.53)	0.005
Between Active Treatments			
25 mg versus 12.5 mg	-0.31	(-1.51, 0.89)	0.610
25 mg versus Naproxen	0.51	(-0.68, 1.70)	0.400
12.5 mg versus Naproxen	0.82	(-0.57, 2.22)	0.246

Effect	p-Value	Pooled SD†
Baseline Covariate	<0.001	6.09
Low-Dose Corticosteroid Use	0.653	
Treatment	0.019	

† Standard deviation.
‡ Least-squares mean.
§ Confidence interval.

Data Source: [4.3]

At 12 weeks both rofecoxib 25 mg and naproxen are superior to placebo for swollen joints (p values of .014 and .005 respectively); however, rofecoxib 12.5 mg is not (p=.142). Again note, this analysis was performed on the sponsor defined ITT population.

Table 19: Swollen joint count (ITT)

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	301	18.78	12.85	-5.79	7.31	-5.69	(-6.38, -4.99)
12.5 mg	148	17.83	11.33	-6.41	7.62	-6.64	(-7.63, -5.65)
25 mg	311	18.29	11.32	-6.93	7.04	-7.00	(-7.68, -6.31)
Naproxen	149	19.21	11.38	-7.83	7.06	-7.55	(-8.54, -6.57)

Comparisons Between Treatment Groups	Difference in LS Mean	95% CI for Diff.	p-Value
With Placebo			
25 mg vs. Placebo	-1.31	(-2.28, -0.34)	0.008
12.5 mg vs. Placebo	-0.95	(-2.15, 0.25)	0.120
Naproxen vs. Placebo	-1.87	(-3.07, -0.67)	0.002
Between Active Treatments			
25 mg vs. 12.5 mg	-0.36	(-1.55, 0.84)	0.557
25 mg vs. Naproxen	0.56	(-0.64, 1.75)	0.360
12.5 mg vs. Naproxen	0.91	(-0.47, 2.30)	0.197

Effect:	p-Value	Pooled SD
Baseline Covariate	<0.001	6.09
Low Dose Corticosteroid Use	0.666	
Treatment	0.009	

† Least squares mean

A re-analysis of swollen joint count using the true ITT population as defined by all randomized patients regardless of any post-baseline data, demonstrates that rofecoxib 25 mg and naproxen are superior to placebo (p values .008 and .002 respectively).

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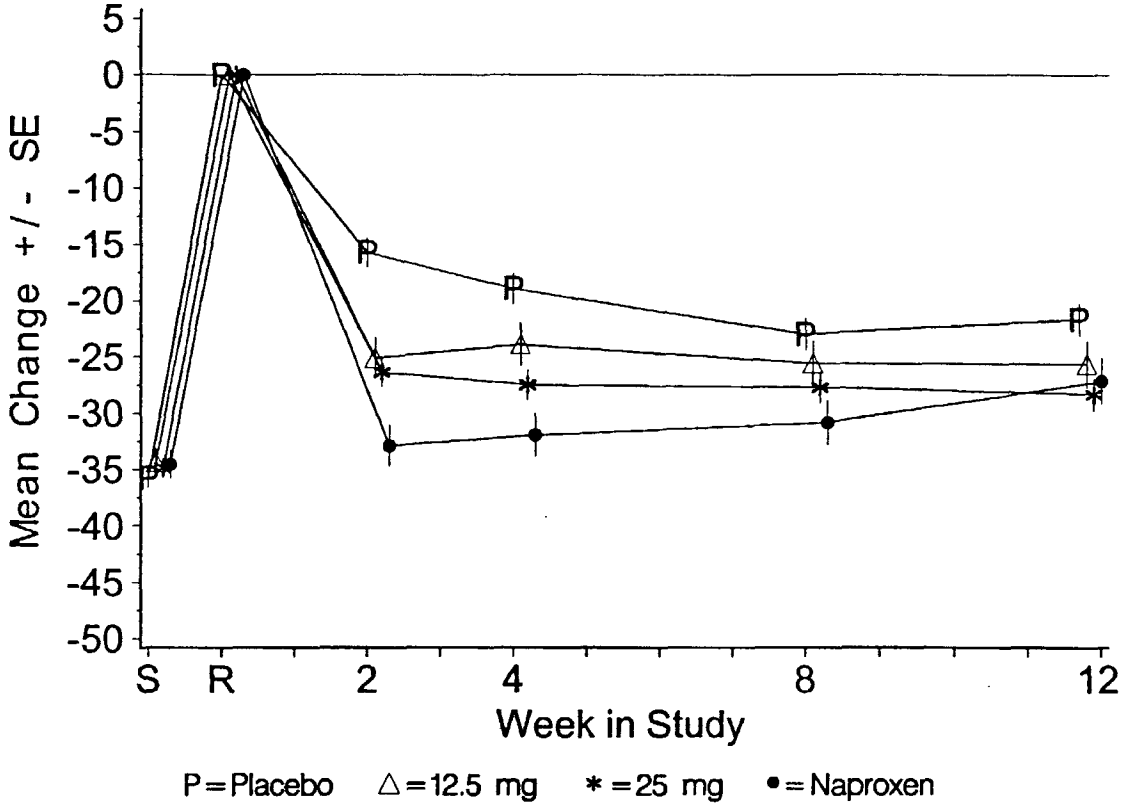
Figure 3: Patient Global Assessment

Endpoint: Patient's Global Assessment of Disease Activity (0 to 100-mm VAS)
Mean Change From Baseline (Flare/Randomization Visit)
Over the 12-Week Treatment Period
(Intention-to-Treat Approach)



Patient Global Assessment of Disease Activity (0 to 100 VAS scale)

SE = Standard error.
S = Screening.
R = Randomization (baseline).
VAS = Visual analog scale
Screening to Baseline = washout period for prior Rheumatoid Arthritis therapy.
Data points for each treatment group were shifted to maximize legibility at each time point.

This figure graphically illustrates the Patient Global Assessment. Of note naproxen shows a significantly greater change in the global assessment score then rofecoxib early in the course of treatment (weeks 2-4), but gradually loses some efficacy over time, while the effect of rofecoxib appears to be stable or slightly improved over the course of 12 weeks.

[ ]

Table 20: Patient 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	293	74.19	52.65	-21.55	20.86	-20.61	(-22.93, -18.30)
12.5 mg	144	73.81	46.85	-26.95	21.69	-25.94	(-29.25, -22.64)
25 mg	307	71.25	43.71	-27.54	21.02	-27.79	(-30.06, -25.51)
Naproxen	149	73.18	41.43	-31.75	21.87	-31.02	(-34.27, -27.77)

Comparisons Between Treatment Groups	Difference in LS Mean[§]	95% CI[‖] for Difference	p-Value
With Placebo			
25 mg versus Placebo	-7.18	(-10.40, -3.95)	<0.001
12.5 mg versus Placebo	-5.33	(-9.34, -1.32)	0.009
Naproxen versus Placebo	-10.41	(-14.37, -6.45)	<0.001
Between Active Treatments			
25 mg versus 12.5 mg	-1.84	(-5.82, 2.14)	0.364
25 mg versus Naproxen	3.24	(-0.70, 7.17)	0.107
12.5 mg versus Naproxen	5.08	(0.48, 9.68)	0.030

Effect	p-Value	Pooled SD[‡]
Baseline Covariate	<0.001	20.05
Low-Dose Corticosteroid Use	0.003	
Treatment	<0.001	

† Visual analog scale.
‡ Standard deviation.
§ Least-squares mean.
‖ Confidence interval.

Data Source: [4.3]

An analysis of Patients Global assessment of disease activity demonstrates that rofecoxib 12.5 mg, 25 mg and naproxen are all significantly superior to placebo (p= .009, <.001, <.001 respectively). No difference was demonstrated between rofecoxib 25 mg and naproxen. By ANCOVA there is a significant effect of steroid use on patient global assessment.

Table 21: Patient Global Assessment (ITT)

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	301	74.19	52.71	-20.97	20.87	-20.05	(-22.34, -17.76)
12.5 mg	148	73.81	46.73	-26.23	21.84	-25.22	(-28.50, -21.95)
25 mg	311	71.25	43.75	-27.19	21.11	-27.42	(-29.68, -25.15)
Naproxen	149	73.18	41.43	-31.75	21.87	-31.00	(-34.27, -27.74)

Comparisons Between Treatment Groups	Difference in LS Mean	95% CI for Diff.	p-Value
With Placebo			
25 mg vs. Placebo	-7.36	(-10.57, -4.16)	<0.001
12.5 mg vs. Placebo	-5.17	(-9.14, -1.20)	0.011
Naproxen vs. Placebo	-10.95	(-14.91, -6.99)	<0.001
Between Active Treatments			
25 mg vs. 12.5 mg	-2.19	(-6.14, 1.76)	0.276
25 mg vs. Naproxen	3.59	(-0.35, 7.53)	0.074
12.5 mg vs. Naproxen	5.78	(1.20, 10.36)	0.013

Effect:	p-Value	Pooled SD
Baseline Covariate	<0.001	20.12
Low Dose Corticosteroid Use	0.002	
Treatment	<0.001	

† Least squares mean

A re-analysis of patients global assessment of disease activity using the ITT population requested by the Division again demonstrates that rofecoxib (at both doses) and naproxen are superior to placebo and that there is no statistical difference between rofecoxib 25 mg and naproxen.

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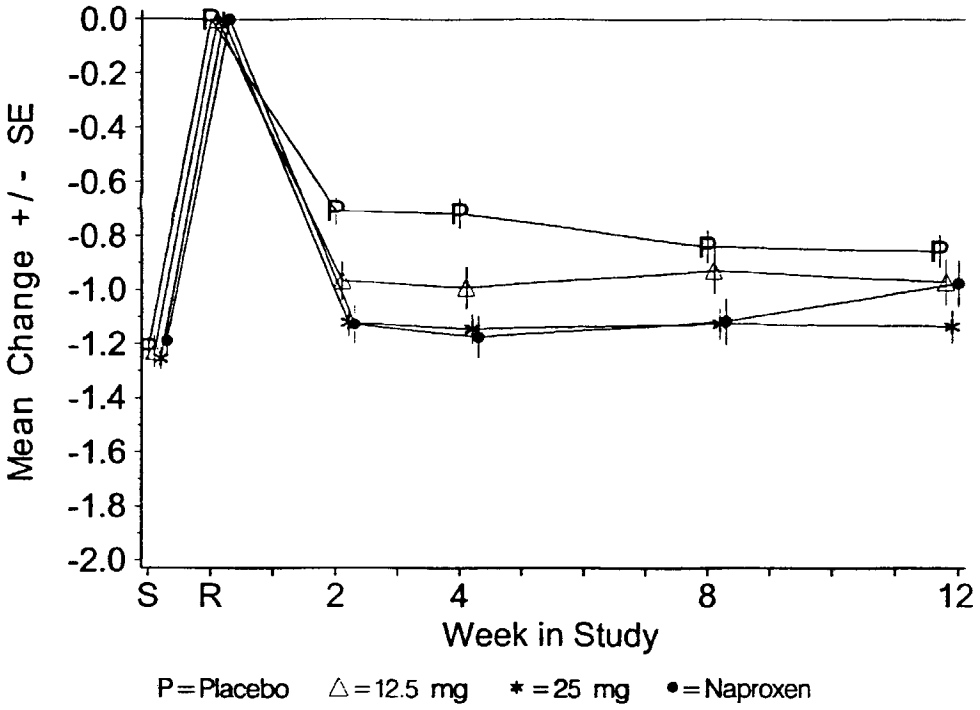
Figure 4: Investigators Global Assessment

Endpoint: Investigator's Global Assessment of Disease Activity (0- to 4-Likert Scale)
Mean Change From Baseline (Flare/Randomization Visit)
Over the 12-Week Treatment Period
(Intention-to-Treat Approach)



SE = Standard error.
S = Screening.
R = Randomization (baseline).
Screening to Baseline = washout period for prior Rheumatoid Arthritis therapy.
Data points for each treatment group were shifted to maximize legibility at each time point.

This figure (Figure 4: Investigators Global Assessment) graphically illustrates Investigator Global Assessment. **It is of interest that naproxen again appears to lose some efficacy at later time points (by week 12) compared to rofecoxib. Data from the long term extension studies would be of interest to identify if rofecoxib performs in the same fashion.**

Table 22: 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	294	2.65	1.79	-0.85	0.97	-0.84	(-0.93, -0.74)
12.5 mg	145	2.63	1.61	-1.02	0.93	-1.01	(-1.14, -0.87)
25 mg	308	2.67	1.48	-1.19	0.94	-1.15	(-1.25, -1.06)
Naproxen	145	2.58	1.49	-1.05	0.87	-1.10	(-1.24, -0.97)

Comparisons Between Treatment Groups	Difference in LS Mean‡	95% CI§ for Difference	p-Value
With Placebo			
25 mg versus Placebo	-0.32	(-0.45, -0.19)	<0.001
12.5 mg versus Placebo	-0.17	(-0.33, -0.01)	0.041
Naproxen versus Placebo	-0.27	(-0.43, -0.11)	0.001
Between Active Treatments			
25 mg versus 12.5 mg	-0.15	(-0.31, 0.01)	0.072
25 mg versus Naproxen	-0.05	(-0.21, 0.11)	0.543
12.5 mg versus Naproxen	0.10	(-0.09, 0.28)	0.302

Effect	p-Value	Pooled SD†
Baseline Covariate	<0.001	0.82
Low-Dose Corticosteroid Use	0.009	
Treatment	<0.001	

† Standard deviation.
‡ Least-squares mean.
§ Confidence interval.

Data Source: [4.3]

For Investigators assessment of disease activity(Table 22: Investigators Global Assessment), rofecoxib and naproxen are superior to placebo with p values of <.001 for 25 mg, .041 for 12.5 mg, and .001 for naproxen.

Table 23: Investigators Global Assessment (ITT)

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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	301	2.65	1.80	-0.83	0.96	-0.82	(-0.91, -0.72)
12.5 mg	148	2.63	1.61	-1.00	0.93	-0.99	(-1.12, -0.85)
25 mg	311	2.67	1.49	-1.18	0.94	-1.14	(-1.23, -1.05)
Naproxen	149	2.58	1.49	-1.09	0.87	-1.10	(-1.24, -0.97)

Comparisons Between Treatment Groups	Difference in LS Mean	95% CI for Diff.	p-Value
With Placebo			
25 mg vs. Placebo	-0.33	(-0.46, -0.20)	<0.001
12.5 mg vs. Placebo	-0.17	(-0.33, -0.01)	0.041
Naproxen vs. Placebo	-0.29	(-0.45, -0.13)	<0.001
Between Active Treatments			
25 mg vs. 12.5 mg	-0.16	(-0.32, 0.00)	0.055
25 mg vs. Naproxen	-0.04	(-0.20, 0.12)	0.640
12.5 mg vs. Naproxen	0.12	(-0.07, 0.31)	0.210

Effect:	p-Value	Pooled SD
Baseline Covariate	<0.001	0.82
Low Dose Corticosteroid Use	0.010	
Treatment	<0.001	

† Least squares mean

A re-analysis of investigator global assessment using the ITT population specified by the Division gives very similar results to the sponsors original analysis.

Table 24: Frequency of patients who met ACR 20

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

Treatment		Frequency‡ m/n (%)	
ACR20† Responder and Completers			
Placebo		90/297 (30.30)	
12.5 mg		62/146 (42.47)	
25 mg		160/311 (51.45)	
Naproxen		79/149 (53.02)	
Between-Group Comparisons	Difference in Percent	(95% CI§)	p-Value¶
25 mg versus Placebo	21.14	(13.52, 28.77)	<0.001
12.5 mg versus Placebo	12.16	(2.59, 21.73)	0.017
Naproxen versus Placebo	22.72	(13.15, 32.28)	<0.001
25 mg versus 12.5 mg	8.98	(-0.77, 18.74)	0.061
25 mg versus Naproxen	-1.57	(-11.32, 8.18)	0.771
12.5 mg versus Naproxen	-10.55	(-21.89, 0.78)	0.069
Treatment		Frequency‡ n/m (%)	
ACR20† Responder: Regardless of Completion Status			
Placebo		110/297 (37.04)	
12.5 mg		66/146 (45.21)	
25 mg		178/311 (57.23)	
Naproxen		88/149 (59.06)	
Between-Group Comparisons	Difference in Percent	(95% CI§)	p-Value¶
25 mg versus Placebo	20.20	(912.43, 27.970)	<0.001
12.5 mg versus Placebo	8.17	(-1.60, 17.930)	0.121
Naproxen versus Placebo	22.02	(12.41, 31.640)	<0.001
25 mg versus 12.5 mg	12.03	(2.26, 21.800)	0.014
25 mg versus Naproxen	-1.83	(-11.45, 7.800)	0.729
12.5 mg versus Naproxen	-13.85	(-25.15, -2.560)	0.017

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

Data Source: [4.3]

The ACR 20 is the endpoint preferred by the Agency for primary analysis (the sponsor included this as a secondary endpoint). An analysis of this endpoint demonstrates that for the groups of responders and completers, or subjects regardless of completion status, both rofecoxib 25 mg and naproxen are superior to placebo ($p = <.001$ for both). Pairwise comparison shows that rofecoxib is not statistically different than naproxen ($p=.729$).

Table 25: Proportion of patients who met ACR 20 (ITT)

Proportions of Patients Who Met ACR20 Responder Index Criteria

During 12 Weeks of Study

(All Randomized Subjects)

ACR20 Responder and Completers			
Treatment		Frequency † (%)	
Placebo		90/301 (29.90%)	
12.5 mg		62/148 (41.89%)	
25 mg		160/311 (51.45%)	
Naproxen		79/149 (53.02%)	
Between-Group Comparisons	Diff in Percent	(95% C.I.)	p-value §
25 mg vs. Placebo	21.55	(13.96, 29.14)	<0.001
12.5 mg vs. Placebo	11.99	(2.51, 21.47)	0.017
Naproxen vs. Placebo	23.12	(13.58, 32.66)	<0.001
25 mg vs. 12.5 mg	9.56	(-0.14, 19.25)	0.047
25 mg vs. Naproxen	-1.57	(-11.32, 8.18)	0.771
12.5 mg vs. Naproxen	-11.13	(-22.42, 0.16)	0.055
ACR20 Responder: regardless of completion status			
Treatment		Frequency † (%)	
Placebo		110/301 (36.54%)	
12.5 mg		66/148 (44.59%)	
25 mg		178/311 (57.23%)	
Naproxen		88/149 (59.06%)	
Between-Group Comparisons	Diff in Percent	(95% C.I.)	p-value §
25 mg vs. Placebo	20.69	(12.95, 28.42)	<0.001
12.5 mg vs. Placebo	8.05	(-1.63, 17.73)	0.121
Naproxen vs. Placebo	22.52	(12.93, 32.10)	<0.001
25 mg vs. 12.5 mg	12.64	(2.93, 22.35)	0.010
25 mg vs. Naproxen	-1.83	(-11.45, 7.80)	0.729
12.5 mg vs. Naproxen	-14.47	(-25.71, -3.22)	0.013

† 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 stratificaton factor.

A re-analysis of ACR20 using all randomized patients shows that rofecoxib 12.5 mg, 25 mg and naproxen are all superior to placebo. There is no difference between naproxen and rofecoxib 25 mg. There is a significant difference between rofecoxib 25 mg and 12.5 mg. This analysis

(performed by the sponsor) imputed missing values as no response. In protocol 096 there were 4, 2, 0 and 0 patients missing in the placebo, rofecoxib 12.5 mg, rofecoxib 25 mg, and naproxen groups respectively.