have a history of PUB. The relative risk of using naproxen in a patient with a prior history of a PUB is over 15 fold. This finding would argue strongly against the use of naproxen in patients with a history of a PUB. This is generally accepted in clinical practice. However, the absolute UGI safety of V for patients with a history of PUB appears to be less than that of naproxen in the general population. While affording a GI safety advantage in this high-risk group compared to naproxen, caution should be advised to the use of V in this population based on absolute risk rates for GI events.

3. Patients over the age of 65 experienced a 2.5-fold higher risk than younger patients. The relative risk associated with the use of V compared to naproxen is maintained in this subpopulation (0.41). The absolute risk however in the V group **over** the age of 65 was nearly the same as the rate in the naproxen group that was **under** the age of 65.

4. The use of steroids did not appear to be a risk factor associated with the use of V in this study. The strength of this finding in a post-hoc analysis is unclear.

5. A history of ASCVD had little effect on the relative risk associated with the use of naproxen. A history of ASCVD appeared to have a "protective" effect for subjects in the V group. Active cardiovascular disease was an exclusion criterion that prevents any generalizability of this finding. A biologically plausible reason for this is finding is not apparent. The meaning of this finding is unclear.

The subanalysis based on "aspirin use-FDA Rules" that appears in table 12.3.9 is of unclear value. The protocol itself spoke to the issue of aspirin indicated subjects. The investigators were to use their judgement in excluding subjects that had an indication for prophylactic aspirin use. In addition, subjects with a history of significant active angina, history of MI or coronary artery bypass graft surgery within the prior year or recent stroke or TIA were explicitly excluded. It would appear that clinical decision making by investigators as to the candidacy of an individual for prophylactic aspirin would have greater validity than a post hoc chart-review based assessment.

Table 12.3-1

Confirmed PUBs
Analysis of Treatment by Prior History of PUBs Interaction
All-Patients-Randomized

	No Prior History of PUBs		Prior History of PUBs	
	Rofecoxib	Naproxen	Rofecoxib	Naproxen
N	3733	3713	314	316
Patients with events	43	92	13	29
Patient-years at risk	2504	2505	194	189
Rate†	1.72	3.67	6.72	15.33
Relative Risk‡				
Estimate	0.47		0.44	
95% CI	(0.33, 0.67)		(0.23, 0.85)	
Model Effects: Prior History vs. No Prior History (Combined Treatments)§				
Estimate	4.05			
95% CI	(2.87, 5.73)			
Model Effects: Treatment by Subgroup Interaction‡				
p-Value	0.874			

† Per 100 patient-years at risk.
‡ Cox model includes treatment, subgroup, and treatment by subgroup interaction.
§ Cox model includes treatment and subgroup main effect.

Data Source: [4.15]

Table 12.3-2

Confirmed PUBs
Analysis of Treatment by Study Region Interaction
All-Patients-Randomized

	U.S.		Non-U.S.	
	Rofecoxib	Naproxen	Rofecoxib	Naproxen
N	1748	1750	2299	2279
Patients with events	18	42	38	79
Patient-years at risk	1096	1093	1601	1601
Rate†	1.64	3.84	2.37	4.93
Relative Risk‡				
Estimate	0.43		0.48	
95% CI	(0.25, 0.74)		(0.33, 0.71)	
Model Effects: Non-U.S. vs. U.S. (Combined Treatments)§				
Estimate	1.35			
95% CI	(0.98, 1.84)			
Model Effects: Treatment by Subgroup Interaction‡				
p-Value	0.731			

† Per 100 patient-years at risk.
‡ Cox model includes treatment, subgroup, and treatment by subgroup interaction.
§ Cox model includes treatment and subgroup main effect.

Data Source: [4.6; 4.15]

Table 12.3-3

Confirmed PUBs
Analysis of Treatment by Age Group Interaction
All-Patients-Randomized

	Non-Elderly (<65 Years)		Elderly (≥65 Years)	
	Rofecoxib	Naproxen	Rofecoxib	Naproxen
N	3050	2959	997	1070
Patients with events	34	64	22	57
Patient-years at risk	2076	2034	622	660
Rate†	1.64	3.15	3.54	8.63
Relative Risk‡				
Estimate	0.52		0.41	
95% CI	(0.34, 0.79)		(0.25, 0.67)	
Model Effects: Elderly vs. Non-Elderly (Combined Treatments)§				
Estimate	2.53			
95% CI	(1.88, 3.40)			
Model Effects: Treatment by Subgroup Interaction‡				
p-Value	0.466			

† Per 100 patient-years at risk.
‡ Cox model includes treatment, subgroup, and treatment by subgroup interaction.
§ Cox model includes treatment and subgroup main effect.

Data Source: [4.6; 4.15]

Table 12.3-5

Confirmed PUBs
Analysis of Treatment by Gender Interaction
All-Patients-Randomized

	Female		Male	
	Rofecoxib	Naproxen	Rofecoxib	Naproxen
N	3223	3215	824	814
Patients with events	45	98	11	23
Patient-years at risk	2149	2139	549	555
Rate†	2.09	4.58	2.01	4.14
Relative Risk‡				
Estimate	0.46		0.48	
95% CI	(0.32, 0.65)		(0.24, 0.99)	
Model Effects: Male vs. Female (Combined Treatments)§				
Estimate	0.92			
95% CI	(0.63, 1.34)			
Model Effects: Treatment by Subgroup Interaction‡				
p-Value	0.892			

† Per 100 patient-years at risk.
‡ Cox model includes treatment, subgroup, and treatment by subgroup interaction.
§ Cox model includes treatment and subgroup main effect.

Data Source: [4.6; 4.15]

Table 12.3-6

Confirmed PUBs
Analysis of Treatment by Baseline Steroid Use Interaction
All-Patients-Randomized

	No Baseline Steroid Use		Baseline Steroid Use	
	Rofecoxib	Naproxen	Rofecoxib	Naproxen
N	1803	1776	2244	2253
Patients with events	24	35	32	86
Patient-years at risk	1184	1178	1513	1516
Rate†	2.03	2.97	2.11	5.67
Relative Risk‡				
Estimate	0.68		0.37	
95% CI	(0.41, 1.15)		(0.25, 0.56)	
Model Effects: Baseline Steroid Use vs. No Baseline Steroid Use (Combined Treatments)§				
Estimate	1.56			
95% CI	(1.14, 2.14)			
Model Effects: Treatment by Subgroup Interaction‡				
p-Value	0.073			

† Per 100 patient-years at risk.
‡ Cox model includes treatment, subgroup, and treatment by subgroup interaction.
§ Cox model includes treatment and subgroup main effect.

Data Source: [4.5; 4.15]

Table 12.3-7

Confirmed PUBs
Analysis of Treatment by H. Pylori‖ Interaction
All-Patients-Randomized

	Negative H. Pylori		Positive H. Pylori	
	Rofecoxib	Naproxen	Rofecoxib	Naproxen
N	2244	2260	1740	1712
Patients with events	21	67	34	54
Patient-years at risk	1470	1486	1186	1170
Rate†	1.43	4.51	2.87	4.62
Relative Risk‡				
Estimate	0.32		0.62	
95% CI	(0.19, 0.52)		(0.40, 0.95)	
Model Effects: Positive vs. Negative H. Pylori (Combined Treatments)§				
Estimate	1.27			
95% CI	(0.94, 1.70)			
Model Effects: Treatment by Subgroup Interaction‡				
p-Value	0.043			

† Per 100 patient-years at risk.
‡ Cox model includes treatment, subgroup, and treatment by subgroup interaction.
§ Cox model includes treatment and subgroup main effect.
‖ Serology was measured by the HM-CAP method. Values ≤100 were considered negative.

Data Source: [4.9; 4.15]

Table 12.3-8

Confirmed PUBs
Analysis of Treatment by ASCVD History
All-Patients-Randomized

	No History ASCVD		ASCVD History	
	Rofecoxib	Naproxen	Rofecoxib	Naproxen
N	3809	3813	238	216
Patients with events	55	114	1	7
Patient-years at risk	2550	2555	148	139
Rate†	2.16	4.46	0.68	5.04
Relative Risk‡				
Estimate	0.48		0.13	
95% CI	(0.35, 0.67)		(0.02, 1.09)	
Model Effects: ASCVD History vs. No ASCVD History (Combined Treatments)§				
Estimate	0.85			
95% CI	(0.42, 1.73)			
Model Effects: Treatment by Subgroup Interaction‡				
p-Value	0.235			

† Per 100 patient-years at risk.
‡ Cox model includes treatment, subgroup, and treatment by subgroup interaction.
§ Cox model includes treatment and subgroup main effect.

Data Source: [4.10; 4.15]

Table 12.3-9

Confirmed PUBs
Analysis of Treatment by Indication for Aspirin Use—FDA Rules
All-Patients-Randomized

	Not Indicated for Cardioprotective Aspirin—FDA Rules		Indicated for Cardioprotective Aspirin—FDA Rules	
	Rofecoxib	Naproxen	Rofecoxib	Naproxen
N	3877	3878	170	151
Patients with events	55	116	1	5
Patient-years at risk	2592	2592	106	102
Rate†	2.12	4.47	0.95	4.91
Relative Risk‡				
Estimate	0.47		0.19	
95% CI	(0.34, 0.65)		(0.02, 1.64)	
Model Effects: Indicated for Cardioprotective Aspirin vs. Not (Combined Treatments)§				
Estimate	0.88			
95% CI	(0.39, 1.99)			
Model Effects: Treatment by Subgroup Interaction‡				
p-Value	0.412			

† Per 100 patient-years at risk.
‡ Cox model includes treatment, subgroup, and treatment by subgroup interaction.
§ Cox model includes treatment and subgroup main effect.

Data Source: [4.10; 4.15]

Table 12.3-10

Confirmed PUBs
Analysis of Treatment by Baseline NSAID Use Interaction
All-Patients-Randomized

	No Baseline NSAID Use		Baseline NSAID Use	
	Rofecoxib	Naproxen	Rofecoxib	Naproxen
N	703	688	3344	3341
Patients with events	14	33	42	88
Patient-years at risk	455	435	2242	2260
Rate†	3.07	7.59	1.87	3.89
Relative Risk‡				
Estimate	0.41		0.48	
95% CI	(0.22, 0.76)		(0.33, 0.69)	
Model Effects: Baseline NSAID Use vs. No Baseline NSAID Use (Combined Treatments)§				
Estimate	0.54			
95% CI	(0.39, 0.76)			
Model Effects: Treatment by Subgroup Interaction‡				
p-Value	0.645			

† Per 100 patient-years at risk.
‡ Cox model includes treatment, subgroup, and treatment by subgroup interaction.
§ Cox model includes treatment and subgroup main effect.

Data Source: [4.5; 4.15]

Table 12.3-11

Confirmed Complicated PUBs
Analysis of Treatment by Study Region Interaction
All-Patients-Randomized

	U.S.		Non-U.S.	
	Rofecoxib	Naproxen	Rofecoxib	Naproxen
N	1748	1750	2299	2279
Patients with events	10	21	6	16
Patient-years at risk	1096	1094	1603	1604
Rate†	0.91	1.92	0.37	1.00
Relative Risk‡				
Estimate	0.48		0.38	
95% CI	(0.22, 1.01)		(0.15, 0.96)	
Model Effects: Baseline NSAID Use vs. No Baseline NSAID Use (Combined Treatments)§				
Estimate	0.49			
95% CI	(0.28, 0.84)			
Model Effects: Treatment by Subgroup Interaction‡				
p-Value	0.700			

† Per 100 patient-years at risk.
‡ Cox model includes treatment, subgroup, and treatment by subgroup interaction.
§ Cox model includes treatment and subgroup main effect.

Data Source: [4.6; 4.15]

Overall conclusions:

1. ***The sponsor has demonstrated a statistically significant reduction associated with the use of V compared to naproxen at the endpoints of symptomatic, bleeding obstructing and perforating UGI ulcers (PUBs) as well as serious events including bleeding, obstruction and perforation (POBs).***

2. ***Absolute risk assessment requires separating out PUBs and POBs to allow for a meaningful analysis of overall risk based on seriousness of the outcome described. A comparison of overall safety requires assessment of the entire database of adverse events. The medical officer's review by Dr. Villalba addresses this issue.***

3. ***The relative risk reduction associated with the use of V compared to naproxen is maintained in all important subgroups. The absolute risk associated with V in high risk subjects (elderly, prior PUB history, steroid use) remains in the range suggested in the current GI warning template. Patients with poor overall health status, particularly those with cardiovascular disease were to a certain extent excluded based on the composite of multiple exclusion criteria in the current study. The relative and absolute UGI safety cannot be extrapolated to this population. Prescribing physicians as well as patients should be aware of these facts in the context of any proposed labeling change based on the current study.***

4. ***The substantial differences in absolute rates of PUBs in different subgroups based on concomitant disease, history of PUBs, medication, and age highlight the difficulties and risks in extrapolating absolute risk rates beyond the population studied. A study with even slight differences in inclusion criteria, exclusion criteria and population enrolled would likely result in substantially different absolute rates, although the relative rates to comparators may be maintained. There will be a strong incentive to cross-compare to other large outcome studies or controlled databases. Such an approach is to be discouraged and may be highly misleading.***

5. ***Conclusions regarding study 069 that was submitted in the original NDA and resubmitted in the current supplement may be found in the GI Medical Officers review of the original NDA dated May 5, 1999***

Appendix 1

Relevant protocol provisions and amendments

APPEARS THIS WAY
ON ORIGINAL

4. STUDY HYPOTHESES AND OBJECTIVES

4.1 Primary Hypotheses

1. The risk of confirmed PUBs (gastroduodenal perforations, symptomatic ulcers, gastric outlet obstructions, or upper-GI bleeds) during the treatment period will be reduced in the group of patients with rheumatoid arthritis taking 50 mg rofecoxib daily, compared to the group of patients with rheumatoid arthritis taking naproxen 1000 mg daily [3.2].

2. Rofecoxib administered at a dose of 50 mg daily will be safe and well tolerated.

4.2 Secondary Hypothesis

1. The risk of confirmed and unconfirmed PUBs during the treatment period will be reduced in the group of patients with rheumatoid arthritis taking 50 mg rofecoxib daily compared to the group of patients with rheumatoid arthritis taking naproxen 1000 mg daily.

4.2 Secondary Hypothesis (Cont.)

2. The risk of confirmed complicated PUBs during the treatment period will be reduced in the group of patients with rheumatoid arthritis taking 50 mg rofecoxib daily compared to the group of patients with rheumatoid arthritis taking naproxen 1000 mg daily.

4.3 Primary Objectives

1. To determine the relative risk of confirmed PUBs in patients with rheumatoid arthritis taking 50 mg rofecoxib daily compared to patients taking naproxen, 1000 mg daily.

2. To study the safety and tolerability of rofecoxib in patients with rheumatoid arthritis.

4.4 Secondary Objectives

1. To assess the relative risk of confirmed and unconfirmed PUBs in patients with rheumatoid arthritis taking 50 mg rofecoxib daily compared to patients taking naproxen 1000 mg daily.

2. To assess the relative risk of complicated PUBs in patients with rheumatoid arthritis taking 50 mg rofecoxib daily compared to patients taking naproxen 1000 mg daily.

3. To assess the efficacy of treatment of rheumatoid arthritis with rofecoxib or naproxen as evaluated by the Patient and Investigator Global Assessment of Disease Activity and the discontinuation rates due to lack of efficacy.

4.5 Exploratory Objectives

1. To determine relative risk of occurrence of bleeding from any location in the GI tract in patients taking 50 mg rofecoxib daily, compared to patients taking naproxen 1000 mg daily.

2. To assess the efficacy of treatment of rheumatoid arthritis with 50 mg rofecoxib daily compared to patients taking naproxen 1000 mg daily as evaluated by the modified Health Assessment Questionnaire.

5. INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan

This active-comparator-controlled, parallel-group, stratified, double-blind, multicenter study was conducted under in-house blinding procedures to further evaluate the long-term safety of rofecoxib compared with naproxen. Patients with rheumatoid arthritis who met entry criteria were randomized to rofecoxib 50 mg once a day, or naproxen 500 mg twice a day. The primary endpoint of this study was the occurrence of PUBs and a key secondary endpoint was the occurrence of complicated PUBs (see Section 5.5.1.5 for detailed endpoint definitions). All events identified by the investigators as potential PUBs were adjudicated by a blinded Case Review Committee that had final say on the classification of all such events as described in detail below in Section 5.5.1.4. The study was to terminate after a minimum of 120 PUBs and 40 complicated PUBs had been confirmed by the Case Review Committee and the study had run at least 6 months from the date of the last patient randomized, whichever came last.

5.2 Detailed Description of Study Design

Patients with a history of RA who were thought to require treatment with NSAIDs for at least 1 year were permitted to enter the study. After a minimum of a 3-day washout of NSAIDs, patients with RA who met the entry criteria were randomized to rofecoxib 50 mg once daily or naproxen 500 mg twice a day. There were no "flare" criteria for entry into this study. Allocation was stratified according to whether the patient had a prior history of a PUB due to the increased risk of experiencing a significant upper GI event associated with such a history. At the screening visit, patients were instructed that they were permitted to take acetaminophen or other analgesics (except for NSAIDs or aspirin) for rescue medication. Choice of rescue therapy was at the discretion of the investigator. Intra-articular, intramuscular, and oral steroids were permitted during the study. Topical creams or lotions containing NSAIDs or salicylates were not permitted during the study. Disease-Modifying Anti-Rheumatic Drugs (DMARDs) were allowed during the study. These could be initiated or the dose may have been changed at the discretion of the investigator during the course of the study. (Treatment with cyclosporin was not allowed during the study.)

The duration of the study was expected to be 1 to 1.5 years based on the time needed to observe at least 120 PUBs and 40 complicated PUBs.

5.2 Detailed Description of Study Design (Cont.)

Clinic visits occurred at screening, randomization, and Weeks 6, 17, 35, and 52. Thereafter, patients would have been seen approximately every 4 months (Weeks 69, 87, and 104) had the study continued, until the termination of the study. At the termination of the study, patients were called in for an end-of-study visit. Patients were asked to remain off NSAIDs for 14 days after the end-of-study visit. Every effort was made to bring all patients back for this visit.

Efforts were made to keep in contact with the patients between clinic visits. Patients were contacted by phone at Week 10 and then every 4 months thereafter (Weeks 26 and 43). The primary endpoint for this study was the occurrence of confirmed PUBs. The key secondary endpoint was confirmed complicated PUBs. Other clinical endpoints included: confirmed and unconfirmed PUBs, confirmed and unconfirmed complicated PUBs, bleeding from any location in the GI tract; discontinuation due to lack of efficacy, Patient Global Assessment of Disease Activity, Investigator Global Assessment of Disease Activity, and Modified Health Assessment Questionnaire. Safety was monitored by repeat clinical and laboratory assessments throughout treatment and adverse events monitored throughout treatment for 14 days following completion of treatment or last dose of study therapy for discontinued patients.

Patients were encouraged to remain in the study for the full duration of the study. However, if patients were unwilling to continue study medication, they were asked to return for a discontinuation visit within 48 hours.

Patients were asked to remain off NSAIDs for 14 days after the discontinuation visit. In addition, they were contacted by telephone 14 days after the last dose of medication to ascertain whether any adverse events had occurred. Lastly, they were telephoned 45 days after the last dose of study medication and at the conclusion of the study (i.e., when they were to have concluded the study had they continued) to ascertain whether a PUB had occurred. Every effort was made to remain in contact with these patients.

Indiscriminate use of low-dose H_2 blockers was to be avoided. Initiation of high-dose H_2 blockers (defined as any dose higher than ranitidine 75 mg twice a day [or 150 mg once daily], famotidine 10 mg twice a day [or 20 mg once daily], cimetidine 200 mg twice a day [or 400 mg once daily], nizatidine 75 mg twice a day [or 150 mg once daily]), proton-pump inhibitors, sucralfate, or misoprostol during the study required discontinuation of the patient from the study. In addition, the use of low-dose aspirin was prohibited in the study, since even low-dose aspirin can affect gastric mucosal integrity. Furthermore, patients who required the use of low-dose aspirin as cardioprotective prophylaxis were excluded from study entry.

5.2 Detailed Description of Study Design (Cont.)

Clinical suspicion of GI bleeding or other possible GI complications were investigated by the appropriate clinical procedures. Any gastric or duodenal ulcers, obstructions, or perforations detected during the workup of GI symptoms or suspected bleeding were classified in accordance with guidelines provided in the Endpoint Classification Document [3.2]. These patients were discontinued from the study. In addition to the standard 14-day follow-up phone call, patients with a possible study endpoint (PUB) were contacted 6 weeks after the occurrence of the event to collect health care resource utilization information (completion of HCCR form).

Events that were determined by the investigator to be possible study endpoints were reported to headquarters, and the investigator was asked to assemble an endpoint package. Endpoint packages were sent to the Case Review Committee for final adjudication.

5.2.1 NSAID Washout

After prestudy laboratory tests were verified to be within defined limits by the central laboratory and the investigator, patients that fulfilled all entry criteria and had signed an informed consent were contacted by telephone. NSAID users were instructed to discontinue their current NSAID regimen.

After an initial evaluation, patients were given 3 stool hemoccult cards. Patients were instructed to return to the clinical research center for repeat evaluation and randomization 3 days after discontinuing their NSAIDs. At the randomization visit and prior to randomization, the 3 stool hemoccult cards were collected and developed. If necessary, the randomization visit occurred 3 to 14 days following Visit 1.

5.3 Selection of the Study Population

5.3.1 Inclusion Criteria

1. Patient was male or female, was at least 50 years of age or was 40 to 49 years of age and was taking chronic oral corticosteroids, had a clinical diagnosis of rheumatoid arthritis, and was judged by the investigator to require chronic NSAID therapy for at least 1 year.

2. Female patients must have demonstrated a serum beta human chorionic gonadotropin (β-hCG) level consistent with a nongravid state at the prestudy visit and must have agreed to remain abstinent, use oral birth control pills or single-barrier contraception (such as: partner using condom or patient using diaphragm, contraceptive sponge, or intrauterine [IUD]) beginning at least 7 days prior to treatment and continuing at least 14 days after the end-of-study visit or a discontinuation visit. Women who were postmenopausal or status posthysterectomy or tubal ligation were exempt from this requirement. (Postmenopausal was defined as no menses for the previous 1 year. If cessation of menses was within 18 months, follicle-stimulating hormone [FSH] must have been documented as elevated into the postmenopausal range prestudy.)

3. Except rheumatoid arthritis, the patient was judged to be in general reasonable health, based on medical history, physical examination, and laboratory screening tests, enabling him or her to complete the trial without anticipated serious comorbid event.

4. Patient was able to understand and complete the study questionnaires.

5. Patient understood the study procedures and agreed to participate in the study by giving written informed consent.

5.3.2 Exclusion Criteria

1. Patient had a history of the following:

   Other inflammatory arthritis (e.g., systemic lupus, spondyloarthropathy, polymyalgia rheumatica). Note: Patients with a history of gout were allowed to

enroll into the study; however, additional NSAID therapy was not allowed for treatment of exacerbations during the course of the study. Patients with rheumatoid arthritis and secondary Sjögrens disease or fibromyalgia were permitted to enter the study.

2. The patient was, in the opinion of the investigator, mentally or legally incapacitated such that informed consent could not be obtained or the patient could not read or comprehend written material.

3. The patient had a history of any illness or had significant abnormalities on prestudy clinical or laboratory evaluation that, in the opinion of the investigator, contraindicated a 1- to 2-year course of therapy with a NSAID such as naproxen.

   Note: Patients with low hemoglobin values [3.2; 3.8] must have had a history of chronic anemia or at least 2 stable baseline values which were repeated at least 1 week apart. An algorithm for assessing out-of-range laboratory values was provided [3.2; 3.8].

4. The patient had a documented history of ulcer or upper GI bleeding within the recent past which was thought by the investigator to mandate that NSAID therapy be given with concurrent proton-pump inhibitors, misoprostol or other medications not allowed per study protocol.

5. Patient had a history of gastric, biliary, or small intestinal surgery that caused malabsorption.

6. The patient had evidence of impaired renal function, defined as estimated creatinine clearance ≤30 mL/min. (Creatinine clearance estimated as follows—Men: [140-age] x weight [kg]/[serum creatinine [mg/dL] x 72]; Women: [0.85] [140-age] weight [kg]/[serum creatinine [mg/dL] x 72).

7. The 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 or coronary arterial bypass grafting more than 1 year prior to study start may have participated if they did not require any concomitant medication excluded in this protocol. However, if a patient developed unstable angina or a myocardial infarction during the study they must have discontinued from the study.)

8. The patient had uncontrolled hypertension (diastolic blood pressure >95 mm Hg, or systolic blood pressure >165 mm Hg).

5.3 Selection of the Study Population (Cont.)

9. The patient had a history of stroke or transient ischemic attack (TIA) within the previous 2 years. (Note: If a patient had a TIA or stroke during the study they must have been discontinued from the study.)

10. The patient had active hepatitis/hepatic disease.

11. Patient had a history of neoplastic disease (exceptions: (a) patients with adequately treated basal cell carcinoma or carcinoma in situ of the cervix, and (b) patients with other malignancies that had been successfully treated ≥5 years prior to screening, where in the judgment of both the investigator and treating physician, appropriate follow-up had revealed no evidence of recurrence from the time of treatment through the time of screening). Patients with a history of leukemia, lymphoma, or myeloproliferative disease were ineligible for the study regardless of the time since treatment.

12. Patient was currently a user (including "recreational use") of any illicit drugs, or had a history of drug or alcohol abuse within the past 5 years.

13. Patient was allergic to or had hypersensitivity (e.g., bronchoconstriction in association with nasal polyps) to aspirin, naproxen, and other NSAIDs. (Note: Patients with a history of a potential idiosyncratic allergic reaction [e.g., rash] to a single NSAID in the past but who tolerated at least 2 other NSAIDs without hypersensitivity reactions may have participated).

14. Patient had morbid obesity and demonstrated significant health problems stemming from their obesity.

15. Patient had a positive result for the fecal occult blood screening test at baseline.

16. Patient had a history of esophageal or gastric surgery. (Patients with a history of simple closure of a perforation greater than 3 months prior to the beginning of the study were allowed to be enrolled. In addition, patients with a history of a simple hiatal hernia repair may have been enrolled.)

17. Patient had a history of inflammatory bowel disease.

18. Patient had a history of a bleeding diathesis.

5.3 Selection of the Study Population (Cont.)

19. The patient was excluded from participation in the study if the following medications had been used:

    - Misoprostol or sucralfate within the past 1 month.

    - Recent sustained use (any period longer than 4 consecutive days during the month prior to study start) of H_2 blockers (e.g., cimetidine, ranitidine, famotidine, nizatidine), or a proton-pump inhibitor (e.g., omeprazole, lansoprazole) at prescription doses, or doses indicated for treatment of active gastroduodenal ulcers. (Note: Use of antacids or over-the-counter doses of ranitidine (75 mg twice a day or 150 mg once daily), famotidine [10 mg twice a day or 20 mg once daily], cimetidine [200 mg twice a day or 400 mg once daily], and nizatidine [75 mg twice a day or 150 mg once daily] prior to randomization were not grounds for exclusion.)

    - Ongoing cyclosporin A treatment.

20. Patients taking aspirin, even low-dose (325 mg or less, daily or every other day) or other antiplatelet agents (e.g., ticlopidine) may not have enrolled in the study. Patients were not to stop taking low-dose aspirin or ticlopidine in order to participate. Exceptions: Patients taking aspirin solely as treatment of their rheumatoid arthritis may have participated in this study after discontinuation of their aspirin during the washout period. Patients were also excluded if use of antiplatelet agents (other than NSAIDs) within the following year was anticipated.

21. Patients were excluded from the study if the following concomitant medications were required: warfarin, or heparin (or low molecular weight heparin). Patients taking digoxin or lithium were not excluded from the study; however, baseline serum drug levels should have been drawn at Visit 1 and should have been monitored in the first few weeks of the study since naproxen and other NSAIDs can increase blood levels of these medications.

22. Other chronic medications had not been used at a stable dosage for at least 2 weeks.

23. Patient had donated a unit of blood or plasma or participated in another clinical study with an investigational agent within the last 4 weeks. The patient could not have participated in any other clinical study with an investigational agent during the course of this study.

24. Patient had previously been enrolled in a rofecoxib clinical study. Note: Patients previously enrolled in a rofecoxib study and allocated to placebo may have participated in this study. Identification of treatment allocation in prior rofecoxib studies must have been verified by the Merck Monitor.

5.4.3 Method of Assigning Patients to Treatment Groups

Patient allocation was stratified according to whether the patient had prior history of a PUB. Within each allocation range, those patients who had a history of a PUB were entered into Stratum 1 and those who did not into Stratum 2.

Within each allocation schedule, patients in Stratum 1 were assigned allocation numbers (ANs) sequentially starting with the highest number at each site and proceeding sequentially to the lower numbers. Patients in Stratum 2 were assigned ANs sequentially starting with the lowest number at each site and proceeding sequentially to higher numbers.

5.4.4 Selection of Doses in the Study

The selection of dose for this study was based both upon the compilation of Phase III safety data in osteoarthritis [1.2.3; 1.2.7; 1.2.8; 1.2.11; 1.2.14 to 1.2.17 to 1.2.20; 1.2.28; 2.1.2] and RA pilot efficacy and dose-ranging studies [1.2.1; 2.1.1]. The Phase IIb RA dose-ranging study demonstrated that 25 and 50 mg were equally efficacious in the treatment of RA. Both doses were superior to placebo and were safe and well tolerated. In Part II of Protocol 068, both 25 and 50 mg demonstrated efficacy similar to naproxen 500 mg twice daily [2.2.1; 2.2.2]. The choice of rofecoxib 50 mg ensured that the safety of the drug was studied at a dose that is anticipated to be 2 times the maximum dose for the treatment of both osteoarthritis and rheumatoid arthritis. Comparing this dose of rofecoxib to the most commonly used dose of a standard nonselective NSAID would provide the most rigorous testing of the GI safety of rofecoxib.

Naproxen is a widely prescribed NSAID that is a dual COX-1/COX-2 inhibitor approved for the treatment of rheumatoid arthritis. In most countries worldwide, the recommended dose for the treatment of rheumatoid arthritis is 500 to 1000 mg per day. However, in some countries, the dose may be increased to a maximum of 1500 mg per day when a higher level of anti-inflammatory/analgesic activity is required. The dose chosen for naproxen in this study (500 mg 2 times a day) is the most commonly used dose for the treatment of rheumatoid arthritis and was anticipated to provide similar efficacy to rofecoxib 50 mg. Therefore, the safety profile was actually biased against rofecoxib; the dose of 50 mg is anticipated to be 2 times greater than the dose indicated for RA whereas the dose of naproxen used in this study was within the recommended dose range for the drug.

Table 4

Study Flow Chart

	Scheduled Office/Clinic Visits										
			Treatment Week							End of Study Visit	Discontinuation Visit
Visit ID:	Screening	Randomization	6	17 (Month 4)	35 (Month 8)	52 (Month 12)	69† (Month 16)	87† (Month 20)	104† (Month 24)		
Visit Number:	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	End	D
Review entry criteria and study procedures	X	X									
Obtain informed consent††	X										
Document medical history	X										
Stool hemoccult	X										
Review concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Discontinue prestudy nonsteroidal anti-inflammatory drugs (NSAIDs)	X‡										
Vital signs and weight#	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X									X	X
Document interim history/monitor for study endpoints/adverse experiences		X	X	X	X	X	X	X	X	X	X
Develop stool hemoccult cards		X									
Retrieve used study medication				X	X	X	X	X	X	X	X
Complete blood count (CBC); serum chemistry	X‡,¶		X			X			X	X‡	X‡
Hemoglobin, hematocrit				X	X		X	X			
Serum for β-human chorionic gonadotropin (β-hCG)‖	X										
Urine for β-hCG‖			X	X	X	X	X	X	X	X	X
Urinalysis	X		X							X	X

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Table 4 (Cont.)

Study Flow Chart

	Scheduled Office/Clinic Visits										
			Treatment Week							End of Study Visit	Discontinuation Visit
Visit ID:	Prestudy	Randomization	6	17 (Month 4)	35 (Month 8)	52 (Month 12)	69† (Month 16)	87† (Month 20)	104† (Month 24)		
Visit Number:	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	End	D
Serum for archive; plasma for archive		X		X		X		X		X	X
Electrocardiogram (EKG)	X										
Dispense study medication		X		X	X	X	X	X	X		
Count study medication tablets				X	X	X	X	X	X	X	X
Modified Health Assessment Questionnaire		X	X							X	X
Patient global assessment of disease activity	X	X	X	X		X		X	X	X	X
Investigator global assessment of disease activity		X	X	X		X		X	X	X	X
Distribute investigational study identification card and appointment reminder cards	X	X	X	X	X	X	X	X	X		

† If study still ongoing.
‡ Patients who were on NSAIDs were to be called after laboratory tests had been evaluated and were told to stop NSAIDs and to return for Visit 2 after a 3-day washout period.
§ Serum chemistry obtained following 8-hour fast.
‖ For premenopausal woman only.
¶ Baseline levels of digoxin and lithium should have been drawn for patients taking these medications.
# Obtained vital signs post 10 minutes of rest.
†† Permission should have been obtained to collect medical records and copies of endoscopy or radiographic reports should an endpoint occur.

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Table 5

Phone Visits

Visit ID: Visit Number:	Pre-screening 0	Treatment Week Week 10 Month 2.5 P4	Week 26 Month 6 P5	Week 43 Month 10 P6	Week 60[3] Month 14 P7	Week 78 Month 18 P8	Week 95[3] Month 22 P9	End of Study for Enrolled and Discontinued Patients	14 Days Post Last Dose of Study Therapy	45 Days Post Discon-tinuation
Prescreen patients to determine if they meet entry criteria that can be screened by phone	X									
Schedule Screening Visit 1	X									
Encourage patient compliance and participation in study		X	X	X	X	X	X			
Review concomitant medication restrictions		X	X	X	X	X	X			
Monitor for interim study endpoints		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]		X[4]	
Monitor for adverse events, interim gastrointestinal (GI) endpoints										
Monitor for GI endpoints								X[4,5]		X[5]

[1] If study still ongoing.
[2] Suspicion of a possible endpoint prompted an unscheduled visit and/or retrieval of additional information.
[3] Schedule end-of-study visit for those patients currently enrolled in study and on study drug. Priority given to patients who reported a possible PUB. Eight-hour fast required.
[4] If a discontinued patient reported a possible PUB, then all documenting information was obtained.
[5] Did not need to be performed for patients who completed the study. However, should the investigator have become aware of a serious adverse experience (SAE) or endpoint which occurred within 14 days post last dose of study therapy, these should have been reported.

Data Source: [3.2]

5.5.1.2 Documentation of Potential Endpoints

All potential endpoints occurring in the study were identified, documented and submitted for adjudication. The investigators were instructed as to the endpoint definitions and criteria for confirmation. At each investigator meeting, and in periodic newsletters, the potential signs and symptoms of upper GI endpoints and standard work-ups for these signs and symptoms were reviewed. However, it was the ultimate responsibility of the investigator to determine if a case qualified as a potential endpoint based on the specific clinical presentation. A properly completed significant GI Event Form (GICL), and a concise but complete clinical narrative of the case, both signed by the investigator, were required for a potential endpoint to be submitted for adjudication. The GICL worksheet was designed for purposes of investigator documentation of a potential endpoint. Instructions for the completion of the GICL were given to all investigators. Patients were asked to sign medical releases so that medical records could be obtained for any endpoint reported.

As part of the field procedures manual, all investigators were given instructions as to how to collect source documentation for and report potential endpoints, and store records related to them. Confidentiality of patient identifying information was maintained.

In addition, to the instructions given to the investigators, extensive efforts were made to ensure that endpoints did not inadvertently go unreported. Field monitoring and in-house data review personnel were instructed to review worksheets and the database for terms which may have been indicative of an endpoint or gastrointestinal work-up (e.g., gastric ulcer, GI bleeding, positive stool hemoculls, endoscopies). Specific queries of the database were designed to look for these terms. When such terms were found, the investigator was requested to assess the event and determine if a GI endpoint had occurred. At all times, the decision to report an upper GI endpoint was made by the investigator.

All patients who discontinued early from the GI Outcomes study who did not have a GI endpoint reported were followed via telephone for the occurrence of an endpoint. To elicit this information, patients were asked about recent hospitalizations, GI work-ups and physician visits for GI-related events. These telephone contacts occurred at 14 and 45 days postdiscontinuation, and at study completion. The informed consent in the primary protocol covered the data proposed for patient follow-up. The Discontinued Patient Follow-up (DPF) Form was used to collect safety data regarding endpoints occurring after the usual 14-day postdiscontinuation follow-up. Important ancillary data, including concomitant medications, excessive alcohol use, and other relevant data were collected on the DPF as well.

5.5.1.5 Adjudication Criteria for Upper-GI Perforations, Ulcers, Obstructions, and Bleeds

Specific endpoint adjudication criteria were established and prespecified to allow the CRC to confirm the diagnosis reported by the investigator and determine whether the endpoint was clinically complicated (Table 6) . The CRC adjudicated each endpoint with respect to the confirmatory criteria first, followed by adjudication with respect to the clinically complicated criteria. Potential endpoints judged to meet the prespecified criteria by a majority of the CRC (2 of 3) were adjudicated as "confirmed." Similarly, an endpoint judged to meet the clinically complicated criteria by a majority of the CRC was adjudicated as "complicated." Thus, there were 4 classes of endpoints (confirmed and complicated, confirmed and uncomplicated, unconfirmed and complicated, and unconfirmed and uncomplicated). The CRC adjudicated an event as being "not an upper-GI event", if by majority opinion, the potential endpoint did not involve the upper-GI tract as defined (e.g., a case reported as an upper GI bleed by the investigator was determined by the committee to be a lower GI bleed based on the case documentation). In addition, the CRC may have reclassified a potential endpoint if there was sufficient evidence to do so (e.g., a pyloric channel ulcer reported as a "gastric ulcer" may have been reclassified as a "duodenal ulcer" based on the endoscopy report). All adjudications by the committee were final.

Table 6

Endpoint Adjudication Criteria

Event	Criteria for Confirmed Event	Criteria for Confirmed Complicated Events
Gastric or Duodenal Perforation due to Active Gastric Ulcer (GU) or Duodenal Ulcer (DU)	Report of gastric or duodenal perforation (excluding perforation caused by a malignant ulcer) confirmed by 1 or more of the following: 1. Endoscopy 2. Surgery 3. Unequivocal radiographic results consistent with free intraperitoneal air or extravasation of contrast media 4. Autopsy	All gastric or duodenal perforations are classified as complicated.

Table 6 (Cont.)

Endpoint Adjudication Criteria

Event	Criteria for Confirmed Event	Criteria for Confirmed Complicated Events
Obstruction due to Active Gastric Ulcer (GU) or Duodenal Ulcer (DU)	Postprandial nausea and vomiting lasting for at least 24 hours **AND** evidence of narrowing of the distal stomach, pylorus, or duodenum due to a nonmalignant ulcer documented by: 1. Endoscopy 2. Surgery 3. Radiography 4. Autopsy	All obstructions are classified as complicated
Development of Active Gastric Ulcer (GU) or Duodenal Ulcer (DU)	Report of GU or DU confirmed by one or more of the following: 1. Endoscopy 2. Surgery 3. Unequivocal radiological evidence of active GU or DU on upper-GI series with contrast 4. Autopsy	GU or DU associated with a confirmed upper-GI hemorrhage as defined under Development of Upper-GI Hemorrhage, criteria 1, 2, or 3.

Table 6 (Cont.)

Endpoint Adjudication Criteria

Event	Criteria for Confirmed Event	Criteria for Confirmed Complicated Events
Development of Upper-GI (esophageal, gastric, or duodenal) Hemorrhage	Report of upper-GI hemorrhage fulfilling one or more of the following: 1. Healthcare provider witnessed frank hematemesis (distinguished from blood tinged or streaked emesis), including coffee-grounds vomitus, **OR** healthcare provider-witnessed frank blood or coffee grounds by gastric aspiration or lavage (distinguished from scant coffee-grounds that clear rapidly) 2. Healthcare provider witnessed frank melena (distinguished from other dark stool, e.g., that due to bismuth salts). 3. Active upper-GI bleeding documented by endoscopy, angiography, or surgery. 4. Heme-positive stool associated with a documented upper-GI lesion judged by the healthcare provider to be the source of the bleeding **AND** associated with either of the following: a) Significant bleeding/volume loss b) Stigmata of recent bleeding (visible vessel, pigmented spot or clot on ulcer base) on endoscopy	1. Upper-GI hemorrhage associated with significant bleeding/volume loss (1).

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Table 6 (Cont.)

Endpoint Adjudication Criteria

Event	Criteria for Confirmed Event	Criteria for Confirmed Complicated Events
	5. Patient reported hematemesis or melena associated with a documented upper-GI lesion judged by the healthcare provider to be the source of the bleeding **AND** associated with 1 or more of the following: a) Significant bleeding/volume loss b) Stigmata of recent bleeding (visible vessel, pigmented spot or clot on ulcer base) on endoscopy	1. Upper-GI hemorrhage associated with significant bleeding/volume loss (1).
(1) Criteria for significant bleeding/volume loss: One or more of the following (a, b, c, or d) is temporally related to the event: a. Decrease in hemoglobin ≥2 gm/dL (or ≥6% drop in hematocrit if hemoglobin not available). b. Evidence of orthostatic (sitting to standing, or lying to sitting) changes; one or more of: (i) pulse rate increase of >20 beats per minute (BPM), (ii) decrease in systolic blood pressure (SBP) >20 mm Hg, (iii) decrease in diastolic blood pressure (DBP) >10 mm Hg. c. Other evidence of significantly reduced circulatory volume (e.g., significant hypotension corrected by volume replacement). d. Transfusion of blood or packed red blood cells.		

Data Source: [3.2]

5.5.1.6 Criteria for Exploratory "All GI Bleed" Analysis

One of the following predefined criteria needed to be met to be included in the analysis of clinically significant bleeds from any location in the GI tract:

a. Upper GI bleeds adjudicated by the CRC as confirmed or unconfirmed.

b. Adverse experiences suggestive of a lower GI bleed or GI bleed of unspecified location were identified from the adverse experience and serious adverse experience (SAE) forms. The adverse experience terms to be included were identified prior to unblinding. See [3.5] for a listing of included terms. To be included in this analysis, those adverse experiences must have met 1 of the following criteria:

   - Reported as a SAE;
   - Resulted in discontinuation of the patient from the study;
   - Associated with a 2-gm drop in hemoglobin from baseline within 14 days before the start date of the event and/or 30 days after.

c. Upper GI bleeds adjudicated by the CRC as "not an upper GI event" were included in this analysis if it met 1 of the following criteria:

   - Reported as a SAE.
   - Associated with a 2-gm drop in hemoglobin from baseline within 14 days before the start date of the event and or 30 days after.

5.7.1 Statistical and Analytical Plans to Address Study Objectives

5.7.1.1 Primary Objectives

The relative risk of confirmed PUBs in patients with rheumatoid arthritis taking 50 mg rofecoxib daily compared with patients taking naproxen 1000 mg daily was evaluated using the Cox proportional hazard model via SAS PROC PHREG (a procedure in SAS that does Cox proportional hazard model analyses) [3.5] with treatment as an explanatory factor and stratum of prior history of PUBs as a stratification factor.

The overall safety and tolerability of rofecoxib in patients with rheumatoid arthritis was evaluated by comparing the incidence of clinical and laboratory adverse experiences between treatment groups. A prespecified listing of potentially relevant safety parameters was examined. In addition, the percents of patients exceeding defined limits of change and mean values for clinical and laboratory safety measurements were compared among treatments.

5.7.1.2 Secondary Objectives

The relative risk of confirmed complicated PUBs in patients with rheumatoid arthritis taking 50 mg rofecoxib daily compared with patients taking naproxen 1000 mg daily was evaluated using the same method described for the primary PUB endpoint.

The relative risk of confirmed and unconfirmed PUBs in patients with rheumatoid arthritis taking 50 mg rofecoxib daily compared with patients taking naproxen 1000 mg daily was evaluated using the Cox proportional hazard model via SAS PROC PHREG [3.5] with treatment as an explanatory factor, and stratum of prior history of PUBs and study region effects (U.S. versus multinational) as stratification factors.

The relative risk of confirmed and unconfirmed complicated PUBs in patients with rheumatoid arthritis taking 50 mg rofecoxib daily compared with patients taking naproxen 1000 mg daily was evaluated using the same method described for the primary PUB endpoint.

The efficacy of treatment of rheumatoid arthritis with rofecoxib or naproxen was evaluated using 95% CI on the difference between treatment groups in average change from baseline for Patient and Investigator Global Assessment of Disease Status and by comparing the discontinuation rates due to lack of efficacy.

5.7.1.3 Exploratory Objectives

The relative risk of occurrence of bleeding from any location in the GI tract in patients taking 50 mg rofecoxib daily versus patients taking naproxen 1000 mg daily was evaluated using the same method described for the primary PUB endpoint.

5.7.2.3 Criteria to Determine a Positive Study

The trial was to be considered a positive study if a significant ($p<0.050$) reduction in the risk of confirmed PUBs in the rofecoxib 50-mg daily group compared to the naproxen 1000-mg daily group was found and if a trend ($p\leq0.20$) was found for the reduction in risk of confirmed complicated PUBs.

5.7.2.4 Power and End of Study Stopping Rule

The study was planned to stop when a minimum of 120 patients experienced confirmed PUB events, 40 patients experienced confirmed complicated PUB events, or 6 months after the last patient was randomized, whichever came last.

For the primary gastrointestinal safety hypothesis, the targeted number of patients with events of 120 provided at least 97% power ($\alpha=0.05$, 2-tailed) to detect a reduction in risk of at least 50%. This calculation accounted for 1 interim analysis described in 5.7.3.3. The targeted number of patients with complicated PUB events of 40 provided more than 80% power to show a trend ($p\leq0.20$) if the reduction in confirmed complicated PUBs due to rofecoxib was $\geq50\%$ and more than 80% power to show a statistically significant effect ($p<0.05$) if the reduction due to rofecoxib was $\geq60\%$. The targeted sample size of 3500 patients per treatment group assumed that the upper-GI side effects of perforations, ulceration, obstructions, and bleeding would occur in 2 to 4% of RA patients treated with NSAIDs for 1 year and was chosen to provide a reasonable study duration under varying assumptions about dropout rates and patient accrual.

5.7.3 Statistical/Analytical Methods and Issues

5.7.3.1 Approaches to Analyses

5.7.3.1.1 All-Patients-Randomized Approach

The primary approach for gastrointestinal safety endpoints was based on an All-Patients-Randomized (APR) population, i.e., all patients randomized were included based on their randomized treatment assignment. The primary time frame for the analysis of the PUB data included a 14 day postdiscontinuation follow-up period. Since most of the endpoints are analyzed as time-to-first-event, no values were imputed.

5.7.3.4 Assessment of Consistency of Treatment Effects Across Subgroups

To explore whether treatment effects were consistent across different subgroups, treatment-by-factor interactions were evaluated for the primary endpoint in the All-Patients-Randomized population. The patient characteristics and baseline covariates of interest were:

- Prior history of PUBs (yes/no)
- Study region (U.S./non-U.S.)
- Age group (<65 years/≥65 years)
- Ethnic group (Caucasian/Other)
- Gender (female/male)
- Baseline use of systemic corticosteroids (yes/no)

For each subgroup variable listed above, a Cox regression model was performed for the primary endpoint and included the treatment, subgroup, and treatment-by-subgroup interaction. The interactions were tested at α=0.05 significance level. When an interaction is not significant, the main treatment effect is interpreted reasonably as the effect averaged over the different levels of the subgroup factor.

Summary statistics (cases, patient-years at risk, incidence rates, relative risk, and 95% confidence interval for relative risk) were presented within the subgroups for the primary endpoint.

5.7.3.5 Multiplicity

There was only 1 primary endpoint and one primary treatment group comparison defined for VIGOR, and the interim analysis was conducted using sequential stopping boundaries. For the primary endpoint in the final analysis, the p-values and confidence intervals quoted were adjusted to reflect the interim analyses. Secondary analyses were used to support and help interpret the primary analyses, and thus, no p-value adjustment for multiplicity was applied other than the adjustment for the interim analysis.

No p-value adjustments were applied to the numerous safety evaluations to be overly conservative with regard to missing items of interest.

5.7.3.7 Other Safety Analyses

Safety and tolerability were assessed by statistical and/or clinical review of all safety parameters, including adverse experiences, laboratory values, and vital signs, as described in this section. All patients randomized were included in the safety analyses. Formal statistical tests focused on prespecified safety concerns while estimates were provided for all other parameters. The following variables were tested (described in the following sections) in the analysis of adverse experiences: discontinuations due to Digestive adverse experiences including abdominal pain, discontinuations due to hypertension, discontinuations due to edema, discontinuations due to renal-related adverse experiences, discontinuations due to hepatic-related adverse experiences, and congestive heart failure (CHF).

Dual COX-1/COX-2 inhibitors such as naproxen inhibit platelet aggregation via suppression of serum levels of thromboxane B2 which is a product of platelet-derived COX-1. Naproxen, like aspirin and unlike other NSAIDs such as diclofenac and meloxicam, has been shown to maximally inhibit platelet aggregation throughout its dosing interval [1.2.23; 1.2.24]. In contrast,

rofecoxib, a specific inhibitor of COX-2 does not suppress serum levels of TXB_2, and therefore has been shown to have no effect on platelet aggregation [1.2.23; 1.2.24]. Low-dose cardioprotective aspirin was not allowed in this study since even low-dose aspirin can affect gastric mucosal COX-1. Therefore, there was the theoretical possibility that naproxen, through its effects on platelet aggregation, may have provided cardioprotective effects not provided by rofecoxib, resulting in a lower incidence of thromboembolic events in the naproxen treatment group. To assess this possibility, cardiovascular thrombotic or embolic serious adverse experiences (SAEs) were adjudicated by an independent committee as a part of a program-wide effort. Procedures for handling these SAEs and the analytic methods to be used were defined in separate documents that can be found in [3.2]. The adjudicated events, as opposed to the reported SAEs, were considered primary. Results of these analyses are described in the Cardiovascular Events Analysis [2.1.6].

5.7.3.7.1 Adverse Experiences

Survival analysis methods were used to analyze prespecified adverse experiences. For such adverse experiences, time-to-event was analyzed and cases, patient-years at risk, relative risk, CIs, and p-values were determined. p-Values and 95% CIs for relative risk ratios (rofecoxib versus naproxen group) were computed using the Cox proportional hazard model with treatment as the explanatory factor. Numbers, proportions, and 95% CIs on the difference in proportions [3.5] were provided for all other adverse experiences.

Prespecified adverse experiences included:

- Serious clinical adverse experiences (overall)
- Drug-related (possibly, probably, definitely) clinical adverse experiences (overall)
- Clinical adverse experiences leading to study discontinuation (overall)
- Discontinuations due to Digestive adverse experiences including abdominal pain
- Discontinuations due to edema-related adverse experiences
- Discontinuations due to hypertension-related adverse experiences

- Discontinuations due to renal-related adverse experiences (clinical and/or laboratory adverse experiences)
- Discontinuations due to hepatic-related adverse experiences (clinical and/or laboratory adverse experiences)
- CHF adverse experiences
- Serious laboratory adverse experiences (overall)
- Drug-related (possibly, probably, definitely) laboratory adverse experiences (overall)
- Laboratory adverse experiences leading to study discontinuation (overall)

5.8.2 Protocol Amendments

The original protocol was amended 4 times. All amendments were made prior to unblinding of the database, after frozen file, and before the first interim analysis. Major changes included in the amendments were as follows:

1. The primary hypothesis was changed from an assessment of "cumulative incidence" to "relative risk" to better conform with the planned statistical analyses.
2. Secondary hypotheses assessing the relative risk in the 2 treatment groups of: (a) confirmed and unconfirmed PUBs; and (b) confirmed complicated PUBs were added. After discussions with the Steering Committee and regulatory agencies, the importance of obtaining sufficient data on complicated endpoints was made clear. Therefore the secondary hypotheses were added and the end-of-study stopping rule was changed such that a minimum of 40 confirmed complicated endpoints was required in addition to a minimum of 120 PUBs.
3. Endpoint definitions were refined after receiving feedback from regulatory agencies. These revised endpoint definitions were used by the Case Review Committee to adjudicate all endpoints.
4. At the request of regulatory agencies, the modified HAQ was added as an exploratory efficacy measurement in the United States.

References

1. Wollheim FA, Selective Cox-2 inhibition in man-therapeutic breakthrough or cosmetic advance? Rheumatology, 2000; 39:935-38
2. Wolfe MM Lichtenstein DR and Singh G, Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs, NEJM. 1999; 340:1888-99

/s/

Lawrence Goldkind
3/22/01 03:38:21 PM
MEDICAL OFFICER

Jonca Bull
4/3/01 09:15:10 AM
MEDICAL OFFICER

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Consultative Review and Evaluation of Clinical Data

NDA (Serial Number)	**21042**
Sponsor:	**Merck**
Drug:	**Vioxx**
Proposed Indication:	
Material Submitted:	**Blinded cardiovascular adjudication package**
Consult Date:	**7/13/01**
Date Received / Division:	**9/05/01**
Date Review Completed:	**9/28/01**
Reviewer:	**Eric P. Bastings, MD**

1. Introduction

The ADVANTAGE study was submitted in 3/30/01 as part of the complete response to an approvable letter for NDA 21-0421s007. This is a 12-week, 6,000-patient study comparing rofecoxib 25 mg and naproxen 1000 mg in patients with osteoarthritis. The study protocol allows the use of low dose aspirin for cardiovascular prophylaxis. As part of the protocol, cardiovascular events involving the CNS were referred to a cerebrovascular adjudication committee. Six cases were referred for consultation because of questions about the adjudication appropriateness. The object of the consult is to reclassify these cases based on the adjudication guidelines.

2. Adjudication Guidelines For Cerebrovascular Events (non fatal)

I classified the cases submitted according to the adjudication guidelines provided by the sponsor. These guidelines are summarized here below:

2.1 Ischemic Cerebrovascular Stroke with adequate documentation to subclassify etiology as follows:

An ischemic cerebrovascular stroke is defined as focal neurological disturbance of the central nervous system affecting higher integrated functioning, cranial nerves, motor, sensory, brainstem, cerebellar or spinal cord, alone or in combination in the absence of witnessed epileptic seizure or known history of migraine. Signs and symptoms persist longer than 24 hours. A diagnosis of ischemic stroke can be made provided brain imaging done within 48 hours discloses no sign of hemorrhage. Subtypes of ischemic cerebrovascular stroke are as follows:

2.1.1 Ischemic Cerebrovascular Stroke due to large-artery atherosclerosis

These patients will have clinical and brain imaging findings consistent with stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis.

2.1.2 Ischemic Cerebrovascular Stroke due to cardioembolism

This category includes patients with arterial occlusions AND at least one cardiac source for an embolus (Table 1).

Table 1: Sources of cardioembolism

Sources of Cardioembolism
Mechanical prosthetic valve
Mitral stenosis
Atrial fibrillation
Left atrial/atrial appendage thrombus
Sick sinus syndrome
Myocardial infarction (<6 months)
Left ventricular thrombus
Dilated cardiomyopathy
Akinetic left ventricular segment
Atrial myxoma
Infective endocarditis
Mitral valve prolapse
Mitral annulus calcification
Atrial septal aneurysm
Patent foramen ovale
Left atrial
Atrial flutter
Bioprosthetic cardiac valve
Nonbacterial thrombotic endocarditis
Congestive heart failure
Hypokinetic left ventricular segment

2.1.3 Small-artery occlusion (lacune)

This category includes patients whose cerebrovascular strokes exhibit one of the traditional syndromes:

- **Pure motor hemiplegia:** hemiplegia with or without dysarthria; CT or MRI usually reveals a lesion in the lenticulostriate artery territory (internal capsule, corona radiata).
- **Pure sensory lacune:** a pure sensory lacune will exhibit hemisensory deficit with usual CT or MRI evidence of a lacune in the lateral thalamus or parietal white matter.
- **Dysarthria/clumsy hand syndrome:** severe dysarthria, central facial weakness and associated dysarthria and clumsiness of the affected hand. The CT or MRI usually shows a lacune in the contralateral pons.
- **Ataxic Hemiparesis:** characterized by ataxia and weakness of the leg more than in the arm. The degree of ataxia is out of proportion to the weakness. The lesion is located in the corona radiate near the internal capsule or the ventral pons.

2.1.4 Ischemic Cerebrovascular Stroke of other determined etiology

This category includes patients lacking evidence of other major ischemic stroke categories and lacking evidence of non-atherosclerotic vasculopathies, hypercoagulable states or hematologic disorders.

2.2 Ischemic Cerebrovascular Stroke without Adequate Documentation to subclassify etiology

The subtype cause of ischemic stroke cannot be classified based on existing documentation.

2.3 Cerebrovascular venous thrombosis

An event which consists of documented signs and symptoms of occlusion of an intracranial vein or venous sinus, supported by CT, MRI or angiography.

2.4 Transient Ischemic Attack

An event which consists of documented focal neurologic deficit which resolves completely within 24 hours without residua and is not associated with a new abnormality on brain imaging.

2.5 Hemorrhagic Cerebrovascular Stroke or Hemorrhagic Change

An event with a focal neurologic deficit with documented evidence of intracranial blood products on imaging studies or spinal fluid analysis.

2.6 Non thrombo-embolic event

An event unrelated to thrombotic/thromboembolic conditions.

2.7 Unable to adjudicate

Insufficient data or other reason.

3. Case review

3.1 Case 0215 4378 (— case No 211)

Adjudication committee diagnosis	Reviewer's diagnosis
Non thrombo-embolic event.	Ischemic cerebrovascular stroke with adequate documentation to subclassify: due to large-artery atherosclerosis (confirmed strictly by criteria)

3.1.1 Adverse experience report (as presented in submission)

This 72 year old female developed a carotid artery obstruction on blinded study therapy. The patient has hyperlipidemia (1995), mild depression (1997), and a history of thyroid nodule (1995), breast implant capsular rupture (1999), carotid artery obstruction (1995), fibrocystic breast disease, mastectomy with reconstruction (1978), mini-cerebrovascular accident (1995), hysterectomy, and carotid endarterectomy (1995).

The patient was randomized for the study on 06-Oct-1999. On 07-Oct-1999, the patient was allocated to receive the blinded study therapy. Concomitant therapy included pravastatin sodium, estradiol, bupropion HCL, aspirin and clopidogrel bisulfate. On 30-

Oct-1999, study therapy was discontinued. On 31-Oct-1999, the patient developed numbness and weakness of her right hand.

[Reviewer's note: there is confusion about the lateralization of weakness in the file: the descriptive provided by the sponsor states "numbness and weakness of her right hand", but the hospital discharge summary, consulting physician (internist?) AND surgeon's note state LEFT hemiparesis. Based on this information, I consider the diagnosis of left hemiparesis to be the right one.]

Since these were symptoms that were similar to what she had experienced in the past due to carotid artery blockage, her family took her to the hospital. A computed axial tomography was performed, which revealed a possible blockage of the right carotid artery. The patient was then referred to her cardiovascular surgeon. On 03-Nov-1999, a carotid artery imaging study was performed which revealed "severe stenosis secondary to soft plaque or thrombus noted in the left common carotid artery at the site of the previous common artery endarterectomy and the internal and external carotid arteries were widely patent".

[Reviewer's note: again, the narrative appears inaccurate. The narrative states "severe stenosis secondary to soft plaque or thrombus noted in the left common carotid artery at the site of the previous common artery endarterectomy and the internal and external carotid arteries were widely patent", but the SAE report, discharge summary, surgical note, and angiography report all list "stenosis of the right CCA". However, the Doppler reports contains an error, since the graph of large vessels shows a severe to critical right CCA stenosis, with handwritten confirmatiom of this, but the typed protocol states "severe stenosis ...noted in the left CCA". The typed protocol is obviously wrong, and misleading. From all records, I retain a diagnosis of RIGHT CCA STENOSIS.]

On 05-Nov-1999, that patient was hospitalized and an angiography was performed. This is protocoled as "patient is status post prior right carotid endartectomy. There is irregularity of the distal common carotid artery with two areas of stenosis. One measures approximately 60% in diameter and is weblike – the other measures about 40% in diameter. 30% diameter stenosis of the left internal carotid artery".

[Reviewer's note: the angiography detailed protocol clarifies the right lateralization of the CCA stenosis].

On 06-Nov-1999, an endarterectomy was performed without complications. On 08-Nov-1999, the patient was discharged from the hospital. The reporting physician felt that the carotid artery obstruction was definitely not related to the study medication.

3.1.2 Diagnostic test results

Head CT (31-Oct-1999): right occipital infarction of indeterminate age. Question of low attenuation of the left occipital lobe as well. Reviewer's note: this head CT was performed very early after symptoms onset and can certainly have missed an acute stroke.

A repeat study (CT or MRI) within 48 hours would have been very useful to identify a possible infarct.

Carotid ultrasound (03-Nov-1999):
Verified result: severe to critical right CCA stenosis.
Listed results: severe stenosis secondary to soft plaque or thrombus noted in the left common carotid artery at the site of the previous common carotid artery endarterectomy.

[Reviewer's note: see section 3.1.1 for explanation of discrepancy.]

Angiography (05-Nov-1999): irregularity of the right distal common carotid artery (CCA) with two areas of stenosis. One measures approximately 60% diameter and is weblike; the other measures approximately 40% diameter.

3.1.3 Reviewer's comments

There is a major confusion about the lateralization of both the lateralization of hemiparesis AND the lateralization of CCA stenosis in the file provided by the sponsor (see section 3.1.1 for details). After verification, I conclude that hemiparesis was LEFT and CCA stenosis RIGHT.

This patient had a history of right carotid endarterectomy (CEA) 5 years prior to her new symptoms of left hemiparesis. This patient had direct evidence (during the repeat CEA of 06-Nov-1999) of both a stenosis and an acute thrombus in the right common carotid artery (CCA). She has several vascular risk factors (hyperlipoproteinemia, hypertension, previous stroke, coronary artery disease, smoking – but discontinued for indefinite amount of time), but has also developed an new right ICA thrombus, which may have been induced by the study drug, natural progression of atherosclerosis or both. It is unclear why she discontinued the study drug 1 day prior to the reported date of symptoms onset.

The surgical note states that the patient "has developed severe stenosis" over the past 6 months. I have no information on what study or observation this statement is based on. The surgical note also states that the patient "had 2 small transient ischemic attacks, the last of which was actually a minor stroke, with mild weakness and dyspraxia of the left upper limb". Neurological exam was reported "grossly intact", with left upper extremity monoparesis on 5-Nov-99.

Impression: this patient had a left hemiparesis lasting over 24 hours, with evidence of stenosis and thrombus of the right common carotid artery, with symptom onset within 48 hours of receiving the study drug.

Diagnosis: ischemic cerebrovascular stroke due to large-artery atherosclerosis.

3.2 Case 0386 3155 — Case No 209)

Adjudication committee diagnosis	Reviewer's diagnosis.
Ischemic cerebrovascular stroke with adequate documentation to subclassify: Small artery occlusion (lacune), confirmed strictly by criteria.	Unable to adjudicate. Acute chorea of undetermined etiology, possibly related to hyperglycemia.

3.2.1 Adverse experience report (as presented in submission)

This 77 year old female patient developed chorea secondary to a possible cerebrovascular accident while on blinded therapy. The patient has hypertension, hyperlipidemia, edema, dyspepsia, hypothyroidism, and diabetes mellitus. On 18-Jun-1999, she was allocated to receive the study drug. Concomitant therapy included omeprazole, atenolol, nifedipine, atorvastatin calcium, levothyroxine sodium, clopidogrel bisulfate, temazepam, rosiglitazone maleate, potassium chloride and furosemide. On 05-Aug-1999, a physician reported that the patient developed abnormal head and arm movements and was hospitalized. She was diagnosed with dyskinesia of unknown cause. On 09-Aug-1999 therapy with the study medication was discontinued. The patient subsequently recovered. Follow-up information received from a physician indicated that the adverse event was changed from dyskinesia to "chorea secondary to a possible small cerebrovascular accident." The occurrence of a CVA has not been confirmed. The patient was treated with haloperidol (dose and duration unknown) and the event resolved. On 09-Aug-1999, the patient was discharged. Further follow-up information received in the patient's discharge summary indicated that the patient had no history of use of neuroleptics or psychiatric disorders. On 09-Aug-1999, a MRI brain scan showed lacunar type infarctions bilaterally in the caudate region and an old hemorrhagic infarct in the right putamen and bilateral thalamic lacuna. The patient's medications were gradually adjusted and the chorea was markedly improved by the time of discharge. The reporting physician felt that the patient's experience was not related to therapy with the study medication.

3.2.2 Diagnostic test results

Brain MRI (08-Aug-1999): There is hyperintense signal noted within the putamen on the left. This is suspicious for subacute hemorrhage. There are small punctate foci of abnormal signal scattered throughout the regions of the internal capsules bilaterally. These are few in number but are suspicious for small lacunar infarcts. There is subtle lateral bowing of the anterior aspect of the body of left lateral ventricle. This is consistent with atrophy of the head of left caudate nucleus. Several small punctate foci of abnormal signal are seen scattered throughout the subcortical white matter of the cerebral hemisphere bilaterally. These are consistent with small deep focal areas of ischemia and/or infarct. Signal void elicited from the carotid and basilar artery is consistent with patency.

3.2.3 Reviewer's comments

This patient apparently developed acute left hemibody choreic movements, for which a vascular origin was suspected. She had no prior psychiatric history or prior use of neuroleptics. She had several vascular risk factors (diabetes, hypertension, hypercholesterolemia). MRI showed evidence of basal ganglia lacunes, without clear

evidence of an acute infarct. The abnormal movements lasted for over 24 hours. The patient was reported as well improved at discharge on 8-Sep-99.

Paraclinical investigations were very limited, and there was no vascular imaging or cardiac imaging done. Onset of symptoms was relatively sudden, in an elderly patient. This suggests a symptomatic causes of chorea, such as drug-induced or toxic, metabolic (i.e. hyperthyroidism), immunologic (i.e. systemic lupus erythematosus), or vascular, as opposed to Huntington's disease and other neurodegenerative disorders. Hyperglycemia has been also reported as a possible metabolic cause of chorea, and it is important to notice that the patient has hyperglycemia exceeding 450 during her hospital stay. Various immunological causes have not been excluded either.

Impression: the diagnosis of lacunar stroke is not confirmed strictly by criteria, as the adjudication committee has assessed. Acute choreic symptoms can (rarely) be caused by a lacunar infarct, but can also be related to metabolic imbalances, such as hyperglycemia present in this patient. I can not concur with a definite diagnosis of stroke in this patient.

Diagnosis: unable to adjudicate. Acute chorea of undetermined cause (possibly related to hyperglycemia).

3.3 Case 0283 2182 —Case 222)

Adjudication committee diagnosis	Reviewer's diagnosis.
Ischemic cerebrovascular stroke without adequate documentation to subclassify;	Unable to adjudicate. Possible migraine variant.

3.3.1 Adverse experience report (as presented in submission)

This 58 year old menopausal female developed transient ischemic attacks while on blinded study therapy. The patient has a herpetic infection, allergies, cardiac murmur, dry skin, rashes, and history of allergic cough and intermittent anemia. The patient's maternal family history includes the development of transient ischemic attacks at age 52 with symptoms including dysphagia. The patient entered the study and on 21-Jul-1999, the patient was randomized and allocated to receive the study drug. Other concomitant therapy included famciclovir and conjugated estrogenic hormones medroxyprogesterone 17-acetate. On 05-Aug-1999, the patient began therapy with baby aspirin for general health. On 16-Aug-1999, the patient experienced a transient ischemic attack (TIA) manifested as difficulty with speech, and left arm and left leg weakness, which lasted two hours. The patient was treated with baby aspirin 81mg, daily, which was discontinued on 11-Sep-1999. On 17-Sep-1999, the patient started therapy with aspirin 325 mg daily for treatment of the TIA. Between 23-Sep-1999 and 12-Oct-1999 a second TIA occurred, again manifested as a transient episode of dysphagia, which lasted 24 hours. The patient did not seek medical attention for the second episode. On 12-Oct-1999 blinded study therapy was discontinued. As of 12-Oct-1899 the patient recovered from the TIA's. The primary investigator felt that the multiple TIA's were disabling and serious due to other medical event, and were not related to blinded study therapy (?).

3.3.2 Diagnostic tests

Head CT –C (24-Sep-1999): negative.

Carotid ultrasound (24-Sep-1999): negative.

Echocardiogram (27-Sep-1999): normal.

3.3.3 Reviewer's comments

This case narrative is very confusing. The neurology consult note of 17-Sep-99 (for possible seizure) states that the patient had a "feeling of head being filled with water", and the sudden onset of a severe right hemicrania, along with speech difficulties. In addition to the "adverse experience report", there is an "adverse event report" which states that the second "TIA" (or episode) was a transient episode of aphasia (?), initially reported starting on 19-Sep-99 and resolved on 20-Sep-99, but later reported as occurring sometime between 23-Sep-99 and 12-Oct-99. The reason for replacing the exact date by a 3-week interval is unclear to me. I believe that a clear explanation for that change should be requested. The duration of the second episode might have exceeded 24 hours, and but the exact duration is unclear. This patient possibly had a baseline left hemiparesis, with unclear date of onset (a Merck memo states 1993 [?]) or etiology. This suggests that the left-sided weakness reported with the first episode of August 99 might have been premorbid. The left-sided weakness was reported as being "on and off" since 1993.

Neurological note of 17-Sep-99 reports on exam 5/5 muscle strength in all 4 extremities, with a left pronator drift (?) and equivocal plantar reflexes.

On 23-Sep-99, a progress note mentions that the neurologist felt that the TIA was probably hereditary related (?), and that the patient had had one episode of dizziness since. There was no mention of the episode of 19-Sep-99.

On 12-Oct-99, it was noted that she had had another incidence of dizzy feeling, with everything "going gray" and a subsequent headache. It is unclear if this corresponds to the "second TIA".

On 23-Nov-99, the assessment was questionable TIA versus autoimmune disorder.

Impression: Poor and confusing documentation. The first episode of neuro-deficit in August 99 was apparently mostly speech difficulties (aphasia? Dysarthria?), with a duration of several hours, in the context of a severe right hemicrania. A second episode was also characterized by headache, this time with dizziness and some vision difficulties. Paraclinical evaluations were negative, and the patient had no vascular risk factors. The diagnosis of TIA is very questionable. The report misses any personal of family history of migraine headache, which would be very useful to obtain.

The episodes of left hemiparesis reported by the patient over several years (and with no neuroimaging/vascular imaging abnormalities) might correspond to migraine equivalents. It would be useful to know if these early episodes of hemiparesis were accompanied by

headache. Interestingly, these episodes are reported since 1993 (when the patient was age 52), and they may correspond to the time of menopause, when it is not rare to have the onset or worsening of migraine headache. Findings on neurological exam did not support a definite left sided weakness. I can not support a diagnosis of TIA based on the information provided to me.

Diagnosis: Based on clinical judgment, I favor a diagnosis of migraine variant (?).

3.4 Case 0580 6099 — Case No 296)

Adjudication committee diagnosis	Reviewer's diagnosis.
Ischemic cerebrovascular stroke with adequate documentation to subclassify: Small artery occlusion (lacune), based on clinical judgment.	Ischemic cerebrovascular stroke with adequate documentation to subclassify: Small artery occlusion (lacune), based on clinical judgment.

3.4.1 Adverse experience report (as presented in submission)

This 80 year old male developed a neurological disorder while on blinded study therapy. The patient has glaucoma (1999), constipation, dizziness, diaphragmatic elevation (1989), hyperlipidemia (1999), hypertension (1999), and a cardiac arrhythmia (1999). The patient has a history of skin cancer (1971), benign prosthetic hyperplasia (1960), appendectomy (1933), tinnitus (1969), and excision of a benign lump on the roof of his mouth (March 1999). On 27-Oct-1999, the patient was randomized and on 28-Oct-1999, the patient was allocated to receive the blinded study drug for the treatment of osteoarthritis. Concomitant therapy included latanoprost, ascorbic acid, vitamin E, vitamins, saw palmetto, mineral oil and an over the counter cold and flu therapy (not further specified). The investigator reported that on 07-Jan-2000, the patient had a sudden onset of dizziness and double vision during his morning walk. The patient was referred to a neurologist who suspected a right mid-brain infarct. An echocardiogram showed "aortic valvular sclerosis without evidence of hemodynamically significant aortic stenosis. Mild mitral insufficiency. Marked concentric left ventricular hypertrophy with preserved systolic function and associated mild left atrial enlargement. Moderate enlarged aortic root. Mild tricuspid insufficiency without evidence of pulmonary hypertension. Diastolic flow pattern across the mitral valve compatible with appeared diastolic relaxation." The magnetic resonance imaging (MRI) revealed "small focal evidence of the cortex. Altered signal. (?)" The magnetic resonance angiography (MRA) showed nearing of the right external carotid artery origin with minimal luminal irregularity of the left internal carotid artery without evidence of hemodynamically significant stenosis.

The neurologist consult report confirmed the diagnosis of a right mid brain infarct. The investigator stated that based on the above the patient was believed to have had a reversible ischemic neurologic deficit. The neurologist reported that the patient had attended physical therapy for vestibular rehabilitation. The patient was also referred to a cardiologist due to abnormal echocardiogram results. Study medication was discontinued on 10-Jan-2000. The investigator felt that the right mid brain infarct was not related to

study medication and was serious due to "other medical event". At the time of this report, the patient had not recovered from the right mid brain infarct.

Follow up received from the reporting physician indicated that the event name had been clarified to be ischemic neurological deficit. The results of the MRI/MRA were listed as negative and confirmed the findings (?). The physician reported in progress notes from 18-Jan-00, that the subjected experienced diplopia and dizziness/vertigo. On 02-Feb-2000, he reported a "reversible ischemic neurologic deficit", with a diagnosis of vertigo. On 02-Feb -2000, the patient recovered from the neurological disorder. Additional information is not expected.

3.4.2 Diagnostic test results

Brain MRA (10-Jan-2000): The circle of Willis is within normal limits. No proximal branch occlusions, aneurysm formation or significant stenosis is identified. Both internal carotid arteries are patent. There may be a mild luminal irregularity on the left without evidence of hemodynamically significant stenosis. There is narrowing of the origin of the right external carotid artery of unknown clinical significance. Also of note is anterograde flow of both vertebral arteries.

Echocardiography (?-Jan-2000): Aortic valvular sclerosis without evidence of hemodynamically significant aortic stenosis. Mild mitral insufficiency. Marked concentric left ventricular hypertrophy with preserved systolic function and associated mild left atrial enlargement. Moderate enlarged aortic root. Mild tricuspid insufficiency without evidence of pulmonary hypertension. Diastolic flow pattern across the mitral valve compatible with appeared diastolic relaxation.

Brain MRI (10-Jan-2000): There are periventricular and deep white matter changes scattered throughout the brain in a pattern and distribution that is entirely within normal limits for a patient of that age. This is consistent with mild white matter degeneration and small vessel ischemic changes. No definite cortical infarction is seen. There is a small focal left insular cortex area of altered signal, however.

3.4.3 Reviewer's comments

There are multiple inconsistencies in that adverse experience report. The neurology consultant note of 10-Jan-2000 reports that the patient had a discrete right upper and lower extremity dysmetria and a right internuclear opthlamoplegia. That note also mentions a sudden onset of symptoms "last Friday", which corresponds to 07-Jan-01. This establishes a diagnosis of completed deficit, and not TIA as the "reversible ischemic event" diagnosis in the adverse experience report suggests. On 27-Jan-2000, the patient was noted to have made "good progress" and "feel much steadier. This implies to me that the patient was not normalized at that time, which would have been mentioned. The patient was reported normalized on 2-Feb-2000.

The MRI protocol of "small focal evidence of the cortex. Altered signal" as related in the adverse experience report does not make any sense. I assume this is a transcription error

form the neurology consultant, but is has been reproduced in the adverse event report without explanation. The echocardiogram showed several abnormalities, and a diagnosis of micro-embolism to the posterior circulation is possible.

Conclusion: Overall, the symptoms suggest a right pontine infarction, presumably lacunar in a patient with a history of hypertension, although again I can not exclude a micro-embolism.

Diagnosis: Right pontine stroke, likely lacunar, with no strict confirmation by criteria.

3.5 Case 0702 6480 (⟶ Case No 227)

Adjudication committee diagnosis	Reviewer's diagnosis.
Ischemic cerebrovascular stroke without adequate documentation to subclassify.	Ischemic cerebrovascular stroke without adequate documentation to subclassify.

3.5.1 Adverse experience report (as presented in submission)

This 59 year old female patient developed a cerebrovascular accident while on blinded study therapy. The patient has insomnia, osteoporosis, a morphine allergy, and a history of a right cerebral hemorrhage in 1985. On 14-Oct-1999, the patient was randomized for entry into the study. On 15-Oct-1999, the patient was allocated to receive the study drug. Concomitant therapy included acetaminophen 325mg PRN, as rescue medication. Other concomitant therapy included alendronate sodium, zolpidem tartrate, and estradiol/ norethindrone acetate. On 10-Nov-1999 the patient presented to the emergency room with acute onset of disorientation, memory difficulty, thickened speech, and left hemiparesis. At that time the subject was admitted to the hospital for evaluation and blinded study therapy was interrupted. On 10-Nov-1999 a cranial computed axial tomography (CT) showed no acute intracranial abnormality, and a Holter monitor test was "relatively normal" with occasional premature atrial contractions and premature ventricular contractions (considered non-serious events). On 11-Nov-1999 a carotid ultrasound showed no evidence of hemodynamically significant stenosis in the right or left internal carotid arteries. An echocardiogram was also performed that day which showed no evidence of significant regional wall motion abnormality, well preserved left ventricular ejection fraction, and mild mitral regurgitation (considered non-serious). On 13-Nov-1999 the patient recovered from the cerebrovascular accident, was discharged from the hospital, and resumed blinded study therapy. The primary investigator felt that the cerebrovascular accident was probably not related to blinded study therapy. Additional information is not expected.

3.5.2 Diagnostic test results

Holter monitoring (11-Nov-1999): occasional PACs and PVCs.

Carotid ultrasound (11-Nov-1999): no evidence of hemodynamically significant stenosis. Vertebrals identified with anterograde flow.

Echocardiography (11-Nov-1999): no evidence of significant regional wall motion abnormality. Mild mitral regurgitation.

Head CT C- (11-Nov-1999): no acute intracranial abnormality. Patient had residual lesions form her ICH and craniotomy, and a "clip" artefact.

3.5.3 Reviewer's comment

This patient had a prior history of stroke in 95 (ICH) and hyperlipidemia, and active smoking. She had residual left hemiparesis from the 95' ICH, but presented a sudden onset of left hemiparesis and dysarthria on 09-Nov-99, along with some disorientation, memory difficulties, double vision and vertigo. On exam on 10-Nov-99 (neurology consultant), she still had dysarthria along with a mild left hemiparesis, proportional (4/5). Sensory exam was grossly normal. Cranial nerve exam was normal. The neurologist suspected a posterior circulation event. Head CT was done less than 48 hours after onset, and with no contrast, so that an acute ischemic lesion may have been missed.

Impression: Left proportional hemiparesis, dysarthria, diplopia (poorly characterized), disorientation lasting over 24 hours, with essentially negative paraclinical investigations, and recovery after about 4 days.

Diagnosis: Stroke, likely in the posterior circulation.

3.6 Case 0810 6272 — Case No 173)

Adjudication committee diagnosis	Reviewer's diagnosis.
Transient Ischemic attack	Unable to adjudicate

3.6.1 Adverse experience report (as presented in submission)

This 76-year-old male patient developed a transient ischemic attack while on blinded study therapy. The patient has macular degeneration, phlebitis, hypertension, a history of coronary bypass, and dyspnea. On 19-Oct-1999, the patient was randomized for entry into the study. On 20-Oct-1999, the patient was allocated to receive the study medication. Concomitant therapy included acetominophen 325mg PRN, as rescue medication. Other concomitant therapy included vitamin E, ascorbic acid, and multi-vitamins. On 25-Oct-1999 the patient reported to the primary investigator that in the evening on 20-Oct-1999 he suffered a "mini stroke' which lasted 30 minutes. At that time, the patient did not seek medical attention, but he discontinued blinded study therapy due to the event. The patient reported that on 22-Oct-1999 he suffered a second 'mini stroke" which lasted for 30 minutes, and was hospitalized for further testing.

During hospitalization, the patient was observed to not have developed subsequent transient ischemic attacks. A chest x-ray performed during hospitalization showed the prior median sternotomy, atherosclerosis of the aorta, left ventricle prominence, and was otherwise normal. A computed axial tomography scan was "negative" (not further

specified). An electrocardiogram showed sinus bradycardia (non-serious) with a rate of 50 and non-specific T-wave abnormality (non-serious). A carotid duplex scan showed that despite tortuosity of the internal carotid arteries, there was no focal area stenosis or significant narrowing. An echocardiogram was "technically limited' but showed possible apical thrombosis with what appeared to be significant apical hypokinesis. The electrocardiogram also showed mild aortic stenosis and mild tricuspid valvular insufficiency. The patient was placed on therapy with intravenous heparin for the possible thrombus in the apical portion of the left ventricle.

The primary investigator felt that the possible apical thrombosis with significant apical hypokinesis might have been the cause of the transient ischemic attacks. On 27-Oct-1999 the patient recovered and was discharged on therapy with warfarin sodium for the possible thrombus, naproxen sodium salt for osteoarthritis, and enalapril maleate for hypertension. The reporting physician felt that the transient ischemic attacks were probably not related to blinded study therapy.

3.6.2 Diagnostic tests

Carotid ultrasound (24-Oct-1999): Despite tortuosity of the internal carotid arteries, there is no focal area of stenosis or significant narrowing.

Chest X-Ray (22-Oct-1999):prior median stemotomy. Atherosclerosis of the aorta, left ventricular prominence.

Head CT (22-Oct-1999): Negative.

Echocardiography (25-Oct-1999): Technically limited, possible apical thrombosis with apical thrombosis with apical hypokinesis. Mild aortic stenosis. Mild tricuspid valvular insufficiency.

Electrocardiogram (?-Oct-1999): Sinus bradycardia (50), non specific T-wave abnormalities.

3.6.3 Reviewer's comments

"Mini-stroke" were apparently two episodes of left-sided numbness. Head CT was with no contrast, and done within 24 hours of the second episode. Again, this exam might have missed an acute infarct. MRI with diffusion weighted imaging would have been very useful in this instance. Documentation for this case is particularly weak, especially for symptoms progression and clinical exam. The adverse experience reports states that the patient "recovered on 27-Oct-99", which is 7 days after the first episode. Does this mean that the patient has been symptomatic for 7 days, or is the 30 minutes duration of both episodes accurate?

Impression: Episodes X2 of left sided numbness, lasting 30 minutes (?), with apical hypokinesia and possible ventricular thrombus. Very poor documentation. It is unclear if these episodes of numbness represent documented episodes of neurological deficit, and

therefore match the definition of TIA adopted by the adjudication committee. In this situation, I am unable to adjudicate.

Diagnosis: Possible TIAs X2 (subcortical right hemispheric ischemia), with possible cardio-embolic origin. Uanble to adjudicate.

Eric P. Bastings, M.D.
Medical Reviewer

J. Feeney, MD _____

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ON ORIGINAL