In view of the cardiovascular findings the sponsor conducted a subgroup analysis of patients identified as potential candidates for cardiovascular prophylaxis with low dose ASA by retrospective chart review in this study. This post-hoc analysis showed that the risk of developing a CV/thrombotic event was 14.3% and 2.9% per 100 patients years, for rofecoxib and naproxen, respectively) (RR= 4.89; 95% C.I. 1.41, 16.88; p= 0.012). For those patients in whom neither prospective physician assessment nor retrospective chart review suggested need for low dose ASA use, the risk of developing a CV/thrombotic event was 1.2% and 0.6% per 100 patient years, for rofecoxib and naproxen, respectively. (RR= 1.88; 95% C.I. 1.03, 3.45; p=0.041). Twelve of the twenty MI in the rofecoxib group and all four MI in the naproxen group were in patients who were not candidates for prophylactic aspirin, based on the sponsor's post hoc chart review.

2. The sponsor has suggested a possible cardio-protective effect of naproxen as the sole explanation for the cardiovascular findings in this study. Several issues are raised by this suggestion:

    a. Inhibition of endothelial prostacyclin synthesis (a potent vasodilator and anti-platelet agent) by selective COX-2 inhibitors has been demonstrated in pre-clinical studies. The potential effect of unopposed thromboxane A2 production (due to lack of effect on platelet COX-1) has raised concern over a possible pro-thrombotic effect of selective COX-2 inhibitors.
    b. There are no placebo-controlled studies of naproxen in the prevention of cardiovascular thrombotic events.
    c. The effect size of naproxen in this study (58% decrease risk of serious CV thrombotic events as compared to rofecoxib over a 9-month period) exceeds that reported in the literature for an anti-platelet agent in a primary or secondary prevention setting (review Table 14).
    d. Other studies (085, 090 and 102) suggest a trend of excess of MI in the rofecoxib group as compared to the active comparators.

3. The sponsor recommends that patients with known cardiovascular risk should be on prophylactic low dose ASA, however, outstanding issues are:

    a. Whether the addition of low dose ASA will abolish the GI advantage of rofecoxib over naproxen.
    b. Whether any of the differences in cardiovascular findings seen between rofecoxib and naproxen groups will be prevented by low dose ASA
    c. Whether patients at no risk of cardiovascular disease (by standard risk factors) taking rofecoxib should be on low dose ASA.

    There are no adequate data available to answer these questions. The sponsor proposes that studies 085, 090 and 058 support the safety of the concomitant use of rofecoxib and ASA. Each of these three studies was designed as an efficacy trial and neither the size (less than 1000 patients on rofecoxib taking into account all three studies) nor the duration (6 weeks) was adequate to detect significant differences in

serious GI or CV events. A total of 161 patients were exposed to rofecoxib and aspirin. The dose of rofecoxib used in 085 and 090 was one fourth of the dose used in the VIGOR study.

4. In addition to the CV/thrombotic events, rofecoxib had a higher incidence of discontinuations due to HTN-related events [n= 28 (0.7%)] as compared to naproxen [n= 6 (0.2%)] and a higher incidence of CHF-related events [n= 19 (0.5%)] as compared to naproxen [n= 9 (0.2%)]. More patients in the rofecoxib group required additional cardiovascular medication as compared to the naproxen group.

5. Study 102 was a 5,500-patient study that compared rofecoxib (25 mg/day) and naproxen (1000 mg/day) for 12 weeks and allowed the use of low dose ASA. This large database contains valuable information about the concomitant use of rofecoxib and low dose ASA as well as the overall safety of rofecoxib compared to naproxen at a dose labeled for chronic use.

2.2.3. Overall safety in the VIGOR study

This risk reduction in relevant GI events did not translate into an overall safety benefit of rofecoxib over naproxen. GI safety must be assessed within the overall safety profile of a drug. Evaluation of safety by routine parameters showed no advantage of rofecoxib over naproxen:

	Rofecoxib 50 mg N=4047 (%)	Naproxen 1000 mg N=4029 (%)
a. Deaths	22 (0.5)	15 (0.4)
b. Serious AEs	378 (9.3)	315 (7.8)
c. Dropouts due to AEs	643 (15.9)	635 (15.8)
d. Serious lab AEs	3 (0.1)	0 (0)
e. Dropouts due to lab AEs	22 (0.5)	12 (0.3)
f. Hospitalizations	338 (8.4)	263 (6.6)

Body systems with the highest rate of SAE's were the Cardiovascular (2.5 and 1.1% for rofecoxib and naproxen, respectively – crude rates -) and Digestive systems (1.2 and 2.4% for rofecoxib and naproxen, respectively – crude rates -).

Other than GI and CV, the safety profile of rofecoxib and naproxen showed a similar pattern and was consistent with that of the NSAID class, although the number of non-GI NSAID-related (liver, renal, HTN and edema-related) AE's were consistently higher in the rofecoxib group. Safety profiles must be carefully analyzed based on events of comparable severity and seriousness. In the VIGOR study the potential advantage of decreasing the rate of complicated PUB's was counterbalanced by the increased rate of developing serious non-GI events (particularly cardiovascular events).

It is of note that this study employed rofecoxib 50 mg/day, a dose twice the highest recommended dose for chronic use in OA. However, 50 mg/day is the dose approved

for the treatment of acute pain and post-marketing data indicate that some patients take the 50 mg dose for more than a few days. Additionally, a superior organ-specific GI safety profile may be interpreted by some as enhanced overall safety, encouraging the "dose-creep" phenomenon. Therefore, the VIOXX label should reflect the overall safety data generated in this study.

A. Background

1. General background

VIOXX (rofecoxib) is a non-steroidal anti-inflammatory drug (NSAID) with selective cyclooxygenase 2 (COX-2) inhibitory properties. It was approved for marketing in the U.S. in May 1999 for the treatment of acute pain in adults, dysmenorrhea and the signs and symptoms of osteoarthritis (OA).

The NSAID class includes a heterogeneous group of drugs with different degree of selectivity for COX-1 and COX-2 isoforms. In addition to COX inhibition, NSAIDs may have other, non-prostaglandin mediated effects that contribute to their toxicity. Serious NSAID-class related adverse events are not common but potentially fatal. Individual NSAIDs are associated with different preferential organ toxicity and in particular, different degrees of gastrointestinal (GI) toxicity [Fries et al, The relative toxicity of NSAIDs. *Arthritis Rheum,* 34 (1991); Henry et al., Variability in risk of GI complications with individual NSAIDs: results of a collaborative meta-analysis. *BMJ,* 312, (1996)].

The NSAID class label includes the following WARNINGS and PRECAUTIONS:

WARNINGS
- Risk of GI bleeding, ulcer, perforation in patients treated chronically
- Potential for severe allergic reactions in patients allergic to ASA or other NSAIDs (also under CONTRAINDICATIONS)
- Advanced renal disease
- Pregnancy – premature closure of the ductus arteriosus.

PRECAUTIONS
- Hepatic effects
- Renal effects
- Hematologic effects
- Fluid retention and edema
- Drug interactions (coumadin, lithium, cimetidine, others)

Based on the safety profile demonstrated in the original NDA database VIOXX carries the Warnings and Precautions section of the NSAID class, including the risk of gastrointestinal (GI) bleeding, as follows:

> **WARNINGS**
>
> **Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation:**
> Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common

and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Reviewer's comment: The percentage of GI events that appears in the GI warning section of NSAID labels includes symptomatic but uncomplicated ulcers as well as complicated ulcers.

In addition to the above paragraph, the VIOXX label states:

It is unclear, at the present time, how the above rates apply to VIOXX (see CLINICAL STUDIES, Special Studies, *Upper Endoscopy in Patients with Osteoarthritis*).

Safety data from two endoscopic studies in which ibuprofen was the active comparator are included under the Clinical Studies section of the label.

2. Administrative history.

In 11/5/98 the applicant, Merck Research Laboratories met with members of the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products to discuss the design of a large and simple trial to assess the gastrointestinal safety profile of rofecoxib. In addition to answering specific questions that the sponsor posed regarding a draft protocol submitted prior to this meeting, the Division pointed out to several study design issues. Some of these issues were:

- the importance of defining complicated ulcers as a primary endpoint in addition to symptomatic ulcers.
- the importance of using twice the highest recommended dose of rofecoxib
- the importance of allowing inclusion of patients on low dose ASA
- the importance of including multiple comparators to add robustness/ generalizability to the study
- the need to provide adequate support for including only RA patients
- the importance of including efficacy endpoints to allow safety comparisons relative to efficacy.

- the need to reconsider the interim analysis design (mainly because of the concern that early termination would insufficiently address safety issues other than the GI primary endpoint)

The VIGOR protocol was submitted to the FDA in 12/6/98. The applicant chose to use VIOXX 50 mg (twice the highest dose recommended in OA). At that time, (and up to today), the efficacy of VIOXX in RA had not been demonstrated although the sponsor anticipated that 25 mg would be the recommended dose in RA. The applicant agreed to modify the criteria for confirmed GI events and to add the modified Health Assessment Questionnaire to the efficacy assessments. The applicant chose to keep the exclusion of patients on low dose ASA, to keep a single active comparator and to keep the planned interim analysis.

The VIGOR study, also referred as 088c, had two separate cohorts: a domestic cohort (study 088) and an international cohort (study 089), involving approximately 1,400 investigators/ subinvestigators. Study 088 was conducted in 194 centers. Study 089 was conducted in 130 centers. Each enrolled approximately 10-20 patients. A few U.S. centers enrolled more than 50 patients. International centers tend to enroll larger number of patients. Several international centers enrolled 80 to 100 patients.

The original protocol was amended four times. All amendments were done prior to unblinding of the database. Most relevant changes were as follows:

- The primary hypothesis was changed from "the cumulative incidence" to "the relative risk" of confirmed PUBs.
- A secondary hypothesis was added regarding the relative risk of confirmed *complicated* PUBs.
- The modified HAQ was added.
- Serum salicylate and NSAID levels were added to the laboratory measurements.
- Special instructions were given to investigative sites for documentation of serious vascular adverse events.
- Subsequently, prior to the interim analysis, the end-of-study stopping rule was changed such that a minimum number of PUBs would be 120 instead of 95.

3. Financial Disclosure

Financial disclosure information was provided by approximately 1,000 of the 1,400 investigators involved in the VIGOR study (Appendix 1). In compliance with the regulatory requirement for the sponsor to demonstrate "due diligence" (CFR part 54.4), multiple request for this information were made to Clinical Investigators who did not respond. Merck & Co., Inc. has stated that it has not entered into any financial arrangement with any of the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study (21 CFR 54.2(a)). The fact that these were double blind, multicenter studies - with independent adjudication endpoints in the case of VIGOR- would minimize any potential bias.

4. Relevant clinical issues in this submission

Based on the results of the present submission and data from pooled studies submitted in the original NDA the applicant proposes to remove the [redacted] and to include a brief paragraph describing GI risk under the Precautions section of the VIOXX label. By doing so, VIOXX would distance itself from the NSAIDs class.

The following issues have been raised during this review:

- The generalizability of the GI findings of the VIGOR study to a general population, since a substantial part of the target population also has clinical indications for the use of low dose ASA. As low dose ASA affects mucosal integrity, rofecoxib might loose its relative GI superiority to naproxen in this population.

- The generalizability of the GI findings to NSAIDs other than the one included as active comparator in this study. Superiority to one NSAID does not imply superiority to the whole spectrum of NSAIDs.

- Remaining GI risk as evidenced by remaining serious complicated GI events in this review and in post-marketing surveillance.

- Cardiovascular safety issues.

- Potential danger of generalizing specific organ-safety to overall safety.

B. Data reviewed in NDA 21-042/052 s/007

The safety of rofecoxib was evaluated by looking at studies in the current submission, data in the original NDA database and by evaluation of post-marketing safety reports. The current submission included 3 new studies and two studies from the original NDA. These studies are summarized in Tables 1 and 2. An additional study conducted under ——— (rofecoxib) is summarized in Table 3.

Table 1. NDA 21-042/S007. New studies in this submission

	Design	Dz.	Treatment (mg/day)	N	ASA allowed
Study 088c "VIGOR"	"Large and simple" Multicenter, double-blind, randomized, active controlled, median 9 months f.u.	RA	Rofecoxib 50 Naproxen 1000	4027 4049	NO
Study 085	Multicenter, double-blind, randomized, placebo and active-controlled, six- week duration	OA	Rofecoxib 12.5 Nabumetone 1000 Placebo	424 410 208	YES
Study 090			Rofecoxib 12.5 Nabumetone 1000 Placebo	390 392 196	10-15%

Table 2. Data from original NDA submission (December, 1998)

	Design	Dz.	Treatment (mg/day)	N	ASA allowed
069	Pooled studies of 6 to 86 weeks duration, including two 6-month endoscopic studies. Most patients exposed <6 months.	OA	Rofecoxib 12.5, 25 and 50 (pooled)	3357	NO
			Ibuprofen 2400 Dclofenac 150 Nabumetone 1000 (pooled)	1564	
			Placebo (6 weeks)	514	
058	Same as 085 and 090 but in Elderly 65 years	OA	Rofecoxib 12.5 Rofecoxib 25 Nabumetone 1000 Placebo	56 118 115 52	YES 60-70%

Table 3. Additional study – Study 102

Study 102* "Advantage"	Multicenter, double-blind, randomized, active controlled, 12-week duration	OA	Rofecoxib 25 Naproxen 1000	2799 2789	YES** 12-13%

* This study had been completed by March 2000 but not submitted as part of this supplement. FDA reviewers requested the complete report of this study in November 2000.

1. New studies in this submission

1.1 Study 088c. VIOXX Gastrointestinal Outcomes Research Study (VIGOR)

The VIGOR study was a multicenter (324 centers), randomized, active-controlled study that compared rofecoxib 50 mg/day with naproxen 1000 mg/day (approximately 4000 patients per arm) in a population of patients with rheumatoid arthritis (RA). The use of low dose ASA was not allowed in this study. Patients with significantly active cardiovascular disease were excluded from the protocol (MI or CABG < 1 year, TIA or stroke < 2 years). Patients deemed by the investigator to require low dose ASA for cardiovascular prophylaxis at the time of screening, were excluded from the protocol.

Reviewer's comment: The exclusion of patients taking low dose ASA seriously limits the generalizability of any results to the general population.

Rofecoxib 50 mg is twice the highest recommended dose for chronic use in osteoarthritis (OA) and it is the dose approved for the treatment of acute pain. In clinical studies, the analgesic effect of a single dose of 50 mg was similar to 550 mg of naproxen sodium or 400 mg of ibuprofen.

Reviewer's comment: Multiple dose studies in acute pain lasted up to five days. Rofecoxib 50 mg/day is not approved for chronic use. However, post-marketing usage data indicates that some patients are given prescriptions for the 50 mg/day dose for periods longer than five days. (——— data from May 1998 to October 2000 showed that —— of VIOXX 50 mg dose appearances were for ———— days).

Naproxen 500 mg twice a day is the maximum labeled dose for chronic use in OA and RA. The label states that up to 1500 mg/day can be use for short term. Naproxen 500 mg single dose is approved for acute pain.

VIGOR was a safety study. The primary endpoint was the incidence of PUB's (perforation, symptomatic ulcer, bleeding). The secondary endpoint of the study was the incidence of complicated PUB's (also called POB's: perforation, obstruction and bleeding, excluding symtomatic but uncomplicated ulcers). General safety parameters were also analyzed.

Reviewer's comment: For a detailed description of the protocol and statistical analysis plan the reader is referred to Dr. Goldkind's review.

Of note, the 50 mg dose is twice the anticipated recommended dose in RA. However, the efficacy of the 25 mg dose in RA remains to be demonstrated. VIGOR was not an efficacy study. Standard efficacy endpoints such as swollen joints, tender joints and CRP or ESR were not measured.

1.1.1 Disposition

Approximately 30% of patients discontinued from each treatment arm. Discontinuations due to lack of efficacy and adverse events were about the same (approximately 6% and 16% respectively) for both rofecoxib and naproxen. A high number of patients withdrew their consent. The timing of discontinuation due to consent withdrawal appears similarly distributed in both treatment groups.

Reviewer's comment: Random evaluation of forty CRF's from patients who withdrew consent indicates that some of them were actually discontinued due to adverse events or lack of efficacy, but errors in the classification were similarly distributed in both treatment groups.

Table 4. VIGOR. Patient accounting (source: sponsor's table)

Patient Accounting

	Rofecoxib 50 mg	Naproxen 1000 mg	Total
	n (%)	n (%)	n (%)
TOTAL PATIENTS	4047 (100.0)	4029 (100.0)	8076 (100.0)
COMPLETED TRIAL	2862 (70.7)	2880 (71.5)	5742 (71.1)
DISCONTINUED TRIAL	1185 (29.3)	1149 (28.5)	2334 (28.9)
Clinical adverse experience	645 (15.9)	636 (15.8)	1281 (15.9)
Laboratory adverse experience	22 (0.5)	12 (0.3)	34 (0.4)
Lack efficacy	256 (6.3)	263 (6.5)	519 (6.4)
Lost to follow-up	6 (0.1)	4 (0.1)	10 (0.1)
Patient discontinued for other	27 (0.7)	30 (0.7)	57 (0.7)
Patient moved	17 (0.4)	16 (0.4)	33 (0.4)
Patient withdrew consent	138 (3.4)	130 (3.2)	268 (3.3)
Protocol deviation	74 (1.8)	58 (1.4)	132 (1.6)

Data Source [4.7]

1.1.1.2. Demographics characteristics

There were no substantial differences in the demographics and baseline characteristics of each treatment group regarding age, weight, height, ethnic group, smoking, alcohol use, duration of RA, ARA class or history of cardiac disease. Approximately 80% of the population were female, approximately 70% were Caucasian and approximately 25% were 65 years; 43% of patients were enrolled in the US and 57% as part of the international cohort; 46 % had a history of cardiac disease. Patients with a recent history of myocardial infarction (<2 years), recent history of cerebrovascular accident (<1 year) and unstable angina were not allowed in the protocol. Approximately 56% of patients were taking concomitant corticosteroids and also 56% were taking concomitant methotrexate (MTX) in each treatment group. The mean dose of corticosteroids was 5 mg/day in both treatment arms. The mean dose of MTX 7.5 mg/week in both treatment arms.

1.1.1.3 Exposure

The median duration of follow up in the VIGOR study was 9 months. There were no meaningful differences in the duration of follow-up between treatment groups.

Table 5. Exposure in the VIGOR study.

Treatment	Entry	2 mos	4 mos	6 mos	8 mos	10 mos	11 mos
Rofecoxib	4047	3645	3407	3181	2806	1072	440
Naproxen	4029	3647	3395	3173	2800	1074	432

Source: Table 13, 088c study report, page 94.

1.1.1.4 Safety results

1.1.1.4.1 Deaths in the VIGOR study

There were 37 deaths for all causes: 22 in the rofecoxib and 15 in the naproxen groups, respectively (Table 6).

The most frequent cause of death was cardiovascular and infectious. Few patients died of complications that could be typically attributed to NSAID therapy. Four patients died of gastrointestinal complications: three in the rofecoxib arm (one of them with gastric carcinoma) and one in the naproxen arm.

> *Reviewer's comment: The cause of death for patient **2560, study 088** (rofecoxib) was listed by the sponsor as pneumonia. This patient had gastrointestinal bleeding due to a penetrating doudenal ulcer. He developed fever and pneumonia as a post-operative complication.*

There were sixteen deaths that could be attributed to cardiovascular events: nine on rofecoxib and seven on naproxen. Most of the cardiovascular deaths in both arms were in patients with cardiovascular risks such as hypertension, hypercholesterolemia, diabetes, smoking, and prior documented history of coronary artery disease.

> *The cause of death for patient **7689, study 089** (rofecoxib) is listed as Aortic Valve Stenosis (AVS). However, there is no documentation of AVS in the CRF. The cause of death for patients **2632, 7769 and 6057, study 089**, (all on naproxen) are listed as myocardial infarction, however, there was no documentation of MI in the CRF's. FDA reviewers consider these cases as sudden death. (See review by Dr. Targum).*

Eight patients died of pneumonia: five in the rofecoxib arm (two of them complicated with bacterial sepsis - one of them in the setting of aplastic anemia **(10078, study 089)** and three in the naproxen arm. The high number of patients with infectious complications is likely related to the concomitant use of MTX and prednisone in this population.

Four patients died of worsening of pre-existing interstitial lung disease: three in the rofecoxib arm and one in the naproxen arm. Two of these patients were taking concomitant MTX, both in the rofecoxib group.

One patient **(9191, study 088)** died of hepatic necrosis right after completing treatment with naproxen. The patient was receiving concomitant MTX 2.5 mg three times a week. Both MTX and naproxen may be implicated in this death.

Conclusions

Review of the deaths suggests that there is no overall safety benefit of rofecoxib over naproxen expressed in terms of mortality. There were numerically more deaths due to GI complications, CV events, infections and worsening of interstitial lung disease in the rofecoxib group than in the naproxen group. However, the small number of events does not allow meaningful comparisons. Narrative of all deaths are presented in Appendix 2.

Table 6. NDA 21-042/s007. VIGOR. Deaths in patients treated with Rofecoxib 50 mg.

ID/ Study	Age/ Gender	Rel[1] (days)	Serious adverse event	Other RA meds	Medical history
324/088	69 F	174	Ventricular fibrillation/sudden death	MTX	HTN
229/088	70 F	132	Adult respiratory distress syndrome	MTX, HCQ, Pred	HTN, pulm fibrosis
731/088	77 F	254	Pneumonia	MTX	Pulmonary fibrosis
2560/088	78 M	41	Penetrating duodenal ulcer, pneumonia, septic shock.	MTX	GI bleeding, COPD
2662/088	62 F	26	Perforating hemorrhagic gastric ulcer, subphrenic abcess, septic shock.	Gold, Prednisone	COPD, smoker
1224/088	68 F	46	Myocardial infarction, multiple organ failure.	Gold, Predinsone	Smoker, gout
920/088	68 F	205	Cerebrovascular accident; complete heart block.	MTX, Prednisone	HTN, chol, GI ulcer
2759/088	69 M	94	Myocardial infarction.		chol, family hx CAD
5687/089	53 M	283	Gastric neoplasm.	MTX, Pred, CQ	
7285/089	71 M	69	Pneumonia.	MTX, Prednisone	
8104/089	57 M	101	Gastrointestinal bleeding.	Prednisone	
5305/089	75 F	309	Cardiac arrest. Sudden death.	MTX, Prednisone	HTN, CAD, pulm fibr.
5316/089	80 M	90	Interstitial lung disease.	MTX, CQ, Pred	Pulm fibr., gastritis
8021/089	84 F	302	Hip fracture, pneumonia, respiratory failure	MTX, Prednisone	HTN, Pulm fibr., MI
7620/089	55 F	31	Dissecting aortic aneurism	MTX, Pred, CQ	HTN, MI, dyspepsia
5591/089	51 F	206	Cerebrovascular accident.	Prednisone, CQ	HTN
6103/089	65 F	340	Worsening rheumatoid arthritis (lung).	Prednisone, HCQ	Interst pneumonitis
7461/089	56 F	25	Pulmonary infection. Bacterial sepsis.	MTX	HTN, gammopathy
7973/089	71 M	147	Myocardial infarction.	MTX	Asthma
7553/089	51 F	28	CHF? Unknown cause of death.		
10078/089	54 F	133	Aplastic anemia.Pneumonia. Sepsis.	MTX, Prednisone	
7689/089	60 F	206	Sudden death. *	MTX, Prednisone	HTN, DM

Source Table 54 of 088c study report; medical reviewer's review of narratives and CRFs. ** Cause of death listed as Aortic Valve Stenosis but there is no documentation of A.S. in the autopsy.

Table 6 (cont). NDA 21-042/s007. VIGOR. Deaths in patients treated with Naproxen 1000 mg.

ID/ Study	Age/ Gender	Rel[1] (days)	Serious adverse event	Other RA meds	Medical history
923/088	60 M	164	Cerebrovascular accident; myocardial infarction?; aortic thrombosis.		HTN, CAD, smoker, GI ulcer, prior carotid sx.
815/088	72 M	133	Metastatic neoplasm of unknown primary	MTX, HCQ, Pred	HTN, lymphoma
3097/088	78 F	9-29	Perforating gastric ulcer, septic shock.	MTX, Prednisone	HTN, dyspepsia, COPD
981/088	66 F	12-28	Respiratory failure. Pneumonitis. RA lung.		
2632/088	70 F	17	Sudden death*	MTX, Prednisone	HTN, MI, DM, chol
2229/088	79 F	247	Cerebrovascular accident. Intracraneal hemorrage.		HTN, renal insuff.
7732/089	62 M	61	Unknown cause of death/ sudden death*.	CQ, Prednisone	
7769/089	58 M	266	Sudden death.*		HTN, Atrial fibrillatio
10100/089	58 F	253	Pneumonia.	MTX, Pred, CQ	Gastritis
5590/089	55 F	215	Pneumonia. Electrolyte imbalance.	MTX, Pred, CQ	HTN, DM, dyspepsia
9191/089	62 F	260	Hepatic necrosis.	MTX[1], APAP, CQ	
6030/089	51 M	44-106	Lung malignant neoplasm.	AZA, Pred, SSZ	
6057/089	60 M	200	Sudden death.*	MTX	HTN, gout
6703/089	53 F	205	Intracranial hemorrhage	MTX, Prednisone	
6912/089	76 F	52	Pneumonia.	MTX, HCQ, Pred	Gastric ulcer, depression

Source Table 54 of 088c study report; medical reviewer's review of narratives and CRFs. * Cause of death listed as myocardial infarction but there were no documented MI in the CRF. [1] MTX 2.5 mg three times a week.

1.1.1.4.2 Serious adverse events

A serious adverse experience (SAE) is any adverse experience occurring at any dose that: results in death or is life threatening or results in a persistent or significant disability/incapacity or results in or prolongs an existing inpatient hospitalization or is a congenital anomaly/birth defect . Also other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Table 7. Serious adverse experience by body system

	Rofecoxib (N=4047) n (%)	Naproxen (N=4029) n (%)
Patients with one or more serious[1] adverse experience	378 (9.3)	315 (7.8)
Body As A Whole/Site Unspecified	51 (1.3)	35 (0.9)
Cardiovascular System[2]	101 (2.5)	46 (1.1)
Digestive System[3]	48 (1.2)	97 (2.4)
Endocrine System	4 (0.1)	0 (0.0)
Eyes, Ears, Nose, And Throat	13 (0.3)	4 (0.1)
Hemic And Lymphatic System	8 (0.2)	7 (0.2)
Hepatobiliary System	11 (0.3)	8 (0.2)
Immune System	1 (0.0)	1 (0.0)
Metabolism And Nutrition	2 (0.0)	0 (0.0)
Musculoskeletal System	83 (2.1)	70 (1.7)
Nervous System	14 (0.3)	7 (0.2)
Psychiatric Disorder	7 (0.2)	3 (0.1)
Respiratory System	52 (1.3)	39 (1.0)
Skin And Skin Appendages	31 (0.8)	20 (0.5)
Urogenital System	32 (0.8)	23 (0.6)

Source: Modified from appendix 4.17.4 of 088c study report. Patients may appear under more than one category, but only once within one category. [1] Estimate 1.5 (0.3, 2.8); [2] Estimate 1.4 (0.7, 2..0); [3] Estimate-1.2 (-1.8, -0.6).

Overall, the incidence of SAE's was 9.3% and 7.8% in the rofecoxib and naproxen groups, respectively. SAE's were numerically higher in the rofecoxib group for all body systems except the digestive system. The highest percentage of serious events was observed for events related to the cardiovascular system for rofecoxib (2.5%) and the digestive system for naproxen (2.5%), followed by the musculoskeletal system in the rofecoxib group (2.1%).

Table 8. VIGOR. Listing of serious adverse experience by body system. Events with incidence >=0.1% or more (source: sponsor's table)

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Patients with one or more adverse experience	378	(9.3)	315	(7.8)
Patients with no adverse experience	3669	(90.7)	3714	(92.2)
Body As A Whole/Site Unspecified	**51**	**(1.3)**	**35**	**(0.9)**
Bacterial Infection	2	(0.0)	3	(0.1)
Bacterial Sepsis	3	(0.1)	2	(0.0)
Chest Pain	6	(0.1)	4	(0.1)
Dehydration	4	(0.1)	2	(0.0)
Fever	2	(0.0)	3	(0.1)
Lower Extremity Edema	3	(0.1)	0	(0.0)
Procedure Complication	3	(0.1)	0	(0.0)
Trauma	3	(0.1)	6	(0.1)
Cardiovascular System	**101**	**(2.5)**	**46**	**(1.1)**
Acute Myocardial Infarction	3	(0.1)	4	(0.1)
Angina Pectoris	2	(0.0)	6	(0.1)
Atrial Fibrillation	5	(0.1)	4	(0.1)
Cerebrovascular Accident	13	(0.3)	5	(0.1)
Congestive Heart Failure	12	(0.3)	3	(0.1)
Coronary Artery Disease	2	(0.0)	3	(0.1)
Deep Venous Thrombosis	5	(0.1)	1	(0.0)
Hypertension	9	(0.2)	0	(0.0)
Myocardial Infarction	19	(0.5)	5	(0.1)
Transient Ischemic Attack	2	(0.0)	3	(0.1)
Unstable Angina	7	(0.2)	1	(0.0)
Digestive System	**48**	**(1.2)**	**97**	**(2.4)**
Duodenal Ulcer	3	(0.1)	5	(0.1)
Erosive Gastritis	3	(0.1)	0	(0.0)
Gastric Ulcer	4	(0.1)	13	(0.3)
Gastritis	4	(0.1)	8	(0.2)
Gastrointestinal Bleeding	2	(0.0)	7	(0.2)
Gastrointestinal Perforation	3	(0.1)	3	(0.1)
Hemorrhagic Duodenal Ulcer	5	(0.1)	8	(0.2)
Hemorrhagic Gastric Ulcer	2	(0.0)	15	(0.4)
Intestinal Diverticulitis	0	(0.0)	3	(0.1)
Lower Gastrointestinal Hemorrhage	2	(0.0)	3	(0.1)
Vomiting	1	(0.0)	4	(0.1)

Table 8 (cont). Serious adverse events with incidence>= 0.1% in study 088c.

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Patients with one or more adverse experience	378	(9.3)	315	(7.8)
Patients with no adverse experience	3669	(90.7)	3714	(92.2)
Endocrine System	**4**	**(0.1)**	**0**	**(0.0)**
Diabetes Mellitus	3	(0.1)	0	(0.0)
Eyes, Ears, Nose, And Throat	**13**	**(0.3)**	**4**	**(0.1)**
Hemic And Lymphatic System	**8**	**(0.2)**	**7**	**(0.2)**
Anemia	5	(0.1)	2	(0.0)
Hepatobiliary System	**11**	**(0.3)**	**8**	**(0.2)**
Cholecystitis	4	(0.1)	4	(0.1)
Metabolism And Nutrition	**2**	**(0.0)**	**3**	**(0.1)**
Musculoskeletal System	**83**	**(2.1)**	**70**	**(1.7)**
Back Pain	0	(0.0)	3	(0.1)
Elbow Fracture	1	(0.0)	3	(0.1)
Femoral Fracture	3	(0.1)	7	(0.2)
Hip Fracture	10	(0.2)	6	(0.1)
Humeral Fracture	6	(0.1)	0	(0.0)
Intervertebral Disc Displacement	3	(0.1)	2	(0.0)
Joint Infection	0	(0.0)	3	(0.1)
Patellar Fracture	4	(0.1)	1	(0.0)
Rheumatoid Arthritis	17	(0.4)	23	(0.6)
Vertebral Fracture	1	(0.0)	3	(0.1)
Nervous System	**14**	**(0.3)**	**7**	**(0.2)**
Sciatica	3	(0.1)	0	(0.0)
Psychiatric Disorder	**7**	**(0.2)**	**3**	**(0.1)**
Depressive Disorder	3	(0.1)	1	(0.0)
Respiratory System	**52**	**(1.3)**	**39**	**(1.0)**
Bronchitis	3	(0.1)	3	(0.1)
Chronic Obstructive Pulmonary Disease	3	(0.1)	0	(0.0)
Dyspnea	4	(0.1)	0	(0.0)
Interstitial Lung Disease	3	(0.1)	0	(0.0)
Pneumonia	22	(0.5)	25	(0.6)
Respiratory Failure	1	(0.0)	3	(0.1)
Skin And Skin Appendages	**32**	**(0.8)**	**20**	**(0.5)**
Basal Cell Carcinoma	17	(0.4)	6	(0.1)
Cellulitis	5	(0.1)	6	(0.1)
Erysipelas	1	(0.0)	3	(0.1)
Skin Abscess	3	(0.1)	0	(0.0)
Skin Malignant Neoplasm	4	(0.1)	3	(0.1)
Skin Ulcer	3	(0.1)	0	(0.0)

Table 8 (cont). Serious adverse events with incidence>= 0.1% in study 088c.

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Urogenital System	**32**	**(0.8)**	**23**	**(0.6)**
Breast Malignant Neoplasm	6	(0.1)	3	(0.1)
Urinary Tract Infection	5	(0.1)	3	(0.1)
Uterine Hemorrhage	3	(0.1)	2	(0.0)
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a body system. The same patient may appear in different body systems.				

Serious adverse events by body system with incidence >= 2 % in at least one treatment group will be discussed in the following section.

1.1.1.4.2.1 Serious adverse events related to the Digestive system.

Forty eight (1.2%) and 97 (2.4%) events of the digestive system met the regulatory definition of a serious event in the rofecoxib and naproxen groups, respectively (Table 8).

> *Reviewer's comment: Serious Digestive events included events such as vomiting and diverticulitis. Not all PUB's - primary endpoint of the study- met the definition of serious events.*

Table 9. PUB's[1] and **complicated** PUB's[2] confirmed by the CRC[3] in the VIGOR study

	N	Events n	Cum Rate[4]	PYR[5]	Rate per 100 PYR	Relative risk[6]		
						Estimate	95%CI	p-value
PUB's								
Rofecoxib	4047	56	**1.8 %**	2697	2.08	0.46	0.33, 0.64	< 0.001
Naproxen	4049	121	**3.9 %**	2694	4.49			
Complicated PUB's								
Rofecoxib	4047	16	**0.5 %**	2699	0.59	0.43	0.24, 0.78	0.005
Naproxen	4049	37	**1.2 %**	2698	1.37			

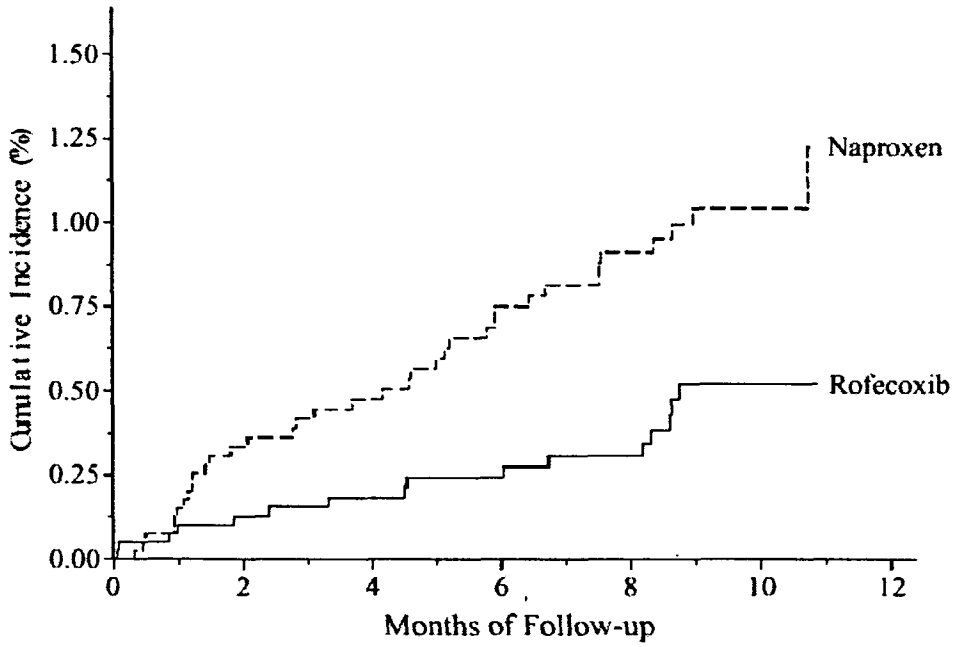
[1] Perforations, symptomatic ulcers and GI bleedings. [2]Excludes uncomplicated ulcers. [3]Adjudicated by the Case Review Committee. [4]Cumulative rate. [5]Patient-years at risk. [6]Relative risk of rofecoxib compared to naproxen. Source: sponsor's tables 22, 23, 24, 26 and 31 of 088c study report.

Of note, the sponsor successfully demonstrated a risk reduction of clinically relevant GI adverse events for rofecoxib compared to naproxen. The study succeeded in

demonstrating a lower risk of PUB's and complicated PUB's for rofecoxib compared to naproxen.

Symptomatic ulcers do not represent the same severity of endpoint as complicated PUBs. Only a fraction of symptomatic ulcers result in a clinically serious outcome. Time to event plot for complicated PUB's is presented in Figure 1.

Figure 1. Confirmed *complicated* PUB's in the VIGOR study (secondary endpoint). Time to event plot (all patients randomized).



# at Risk							
Rofecoxib	n=4047	3644	3407	3181	2806	1072	533
Naproxen	n=4029	3646	3394	3170	2800	1074	514

Source: sponsor's Figure 5, s007 submission). Cumulative rate for complicated PUB's was 0.5% and 1.2% for rofecoxib and naproxen, respectively.

The inclusion of a single comparator (naproxen) limits the generalizability of the findings to non-selective NSAIDs with less COX-1 activity than naproxen (eg. diclofenac, nabumetone and etodolac).

Different NSAIDs inhibit COX-1 and COX-2 in varying degrees (Cryer and Feldman, COX-1 and COX-2 selectivity of widely used NSAIDs, American Journal of Medicine, 104 (1998); Lipsky, Defining COX-2 inhibitors, Journal of Rheumatology, 27 (2000).

For a detailed GI safety review, the reader is referred to Dr. Goldkind's review.

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1.1.1.4.2.2. Serious adverse events related to the Cardiovascular system

Serious cardiovascular adverse events were observed in 101 (2.5%) and 46 (1.1%) of patients on rofecoxib and naproxen respectively. Most common serious events in the cardiovascular system were thrombotic, hypertension, and congestive heart failure (CHF) adverse events. For a detailed review of CV adverse events the reader is referred to Dr. Targum's review. Serious cardiovascular events considered by the investigator to be thrombotic in nature were referred to three Cardiovascular Adjudication Committees (Cardiac, Peripheral vascular and Cerebrovascular committees). Of the 64 and 32 events referred for adjudication from the rofecoxib and naproxen groups respectively, 47 and 19 were confirmed by the Cardiovascular Adjudication Committees. Of note, as per the sponsor's Standard Operating Procedures, [redacted]

In addition to the SOP [redacted] the sponsor conducted an analysis of thrombotic events using the Antiplatelet Trialists' Collaboration composite endpoint (APTC). This endpoint is widely used in clinical trials of anti-platelet agents and therefore allows for some comparison to other trials published in the literature. The APTC endpoint excludes unstable angina, TIA and peripheral vascular events and includes hemorrhagic strokes.

Although the number of serious CV/thrombotic events were a little different depending on the definition used, the findings were very consistent: the relative risk of developing cardiovascular thrombotic events was roughly twice for the rofecoxib group as compared to the naproxen group.

1.1.1.4.2.2.1 Serious CV thrombotic events

As seen in Table 10, the cumulative rate for **serious adjudicated CV/thrombotic events was 1.8% and 0.6%** for rofecoxib and naproxen, respectively. The list of adjudicated events is presented in table 11.

Table 10. VIGOR. Analysis of adjudicated serious thrombotic cardiovascular adverse experiences

	Patients with events (%)	Cumulative rate	PYR[1]	Rates per 100 PYR	Relative risk[2]		
					Estimate	95%CI	p
All patients randomized							
Rofecoxib (4047)	45	1.81 %	2697	1.67	2.37	1.39, 4.06	0.0016
Naproxen (4027)	19	0.6 %	2698	0.70			

PYR: Patient years at risk. Relative risk for rofecoxib as compared to naproxen based on rates per 100 patient years. (Modified from sponsor table 9 of the safety update. Cumulative rate and relative risk estimate calculated by Dr. Qian Li, FDA statistician).

Table 11. VIGOR. Summary of adjudicated serious Thrombotic Cardiovascular adverse events (Source: modified from Sponsor's table)[1]

Event	Rofecoxib N= 4047 (%)	Naproxen N= 4029 (%)
Number of patients w/events	**47**	**20**
Cardiovascular death	**6 (0.1)**	**6 (0.1)**
Fatal acute myocardial infarction	2	0
Fatal hemorrhagic stroke	1	1
Fatal ischemic stroke	0	1
Sudden cardiac death	3	4
Cardiac event (non-fatal)	**23 (0.6)**	**7 (0.2)**
Acute myocardial infarction	18	4
Unstable angina pectoris	5	3
Cerebrovascular event (non-fatal)	**12 (0.3)**	**7 (0.2)**
Hemorrhagic stroke	1	0
Ischemic cerebrovascular stroke	9	7
Transient ischemic attack	2	0
Peripheral vascular event (non-fatal)	**6 (0.1)**	**1 (0.0)**
Peripheral arterial thrombosis	1	0
Peripheral venous thrombosis	5	1

[1] As per SOP,

CV thrombotic events in different subgroups of patients (by age, sex, prior history of cardiovascular disease, smoking, etc) were consistently higher in the rofecoxib treatment group (Appendix 3).

The protocol mandated that patients with recent or significantly active cardiovascular disease be excluded from the protocol. Patients with recent MI or CABG (<1 year), patients with recent TIA/stroke (<2 years) and patients deemed by the investigator to require prophylactic ASA or anticoagulation at the time of enrollment were excluded from the study. Patients on low dose ASA were not to stop therapy in order to enter the study.

The sponsor retrospectively identified 321 patients (4%) enrolled in this study with past medical history of cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, stable angina, coronary artery bypass surgery or percutaneous coronary intervention who might have benefited from the use of low dose ASA.

> *The validity of this retrospective identification of patients is unclear. By protocol, patients with active cardiovascular disease were excluded. The investigator's clinical judgement at the time of enrollment appears to be more relevant than a retrospective chart review.*

An analysis in this subgroup of patients retrospectively identified by the sponsor as candidates for low dose ASA showed that the risk of developing CV thrombotic events was five times higher in the rofecoxib group compared to the naproxen group (14.3% and 2.9% respectively, per 100 patient years of exposure). For those patients in whom neither prospective nor retrospective chart review suggested need for low dose ASA use, the risk was still twice in the rofecoxib group compared to the naproxen group (1.2% and 0.6%, respectively, per 100 patient years).

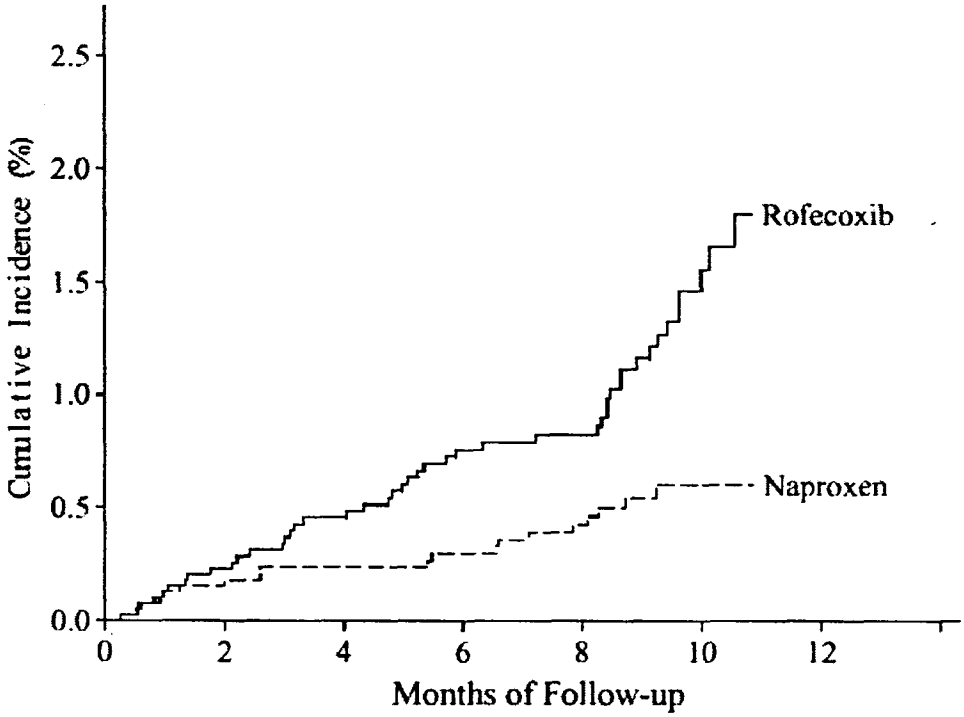
Table 12. VIGOR. Adjudicated thrombotic cardiovascular serious adverse experiences. Subgroup analyses by sponsor's retrospective identification of patients who may have benefited from low dose ASA.

	N	Patients with events (%)	PYR[1]	Rates[2]	Relative risk[3]		
					Estimate	95%CI	p
All patients randomized							
Rofecoxib	4047	45 (1.1%)	2697	1.67	2.37	1.39 – 4.06	0.0016
Naproxen	4029	19 (0.5%)	2698	0.70			
Potential candidate for low dose ASA[5]							
Rofecoxib	170	15 (8.8%)	105	14.29	4.89	1.41 - 16.88	0.0122
Naproxen	151	3 (2.0 %)	102	2.94			
Not candidate for low dose ASA							
Rofecoxib	3877	30 (0.8%)	2592	1.16	1.88	1.03 – 3.45	0.041
Naproxen	3838	16 (0.4%)	2596	0.62			

[1] Patient-years at risk. [2] Per 100 patients years. [4] Relative risk of rofecoxib with respect to naproxen. [5] Patients with past medical history of cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, stable angina, coronary artery bypass surgery or percutaneous coronary intervention. (Source: modified from sponsor's Table 9 of the safety update, Estimate calculated by Dr. Qian Li, FDA statistician).
VIGOR study. Myocardial Infarctions. Subgroup analyses by sponsor's retrospective identification of patients who may have benefited from low dose ASA.

Twelve of the twenty MI in the rofecoxib group and all four MI in the naproxen group were in patients who were not candidates for prophylactic aspirin, based on the sponsor's post hoc chart review (The relative risk of MI in this subgroup is still three times higher for rofecoxib).

Figure 2. Confirmed Thrombotic CV serious adverse experiences in the VIGOR study. Time to event plot (all patients randomized). RR 2.37 for rofecoxib compared to naproxen (p = 0.0016). (Source, Sponsor's Figure 1 of safety update).



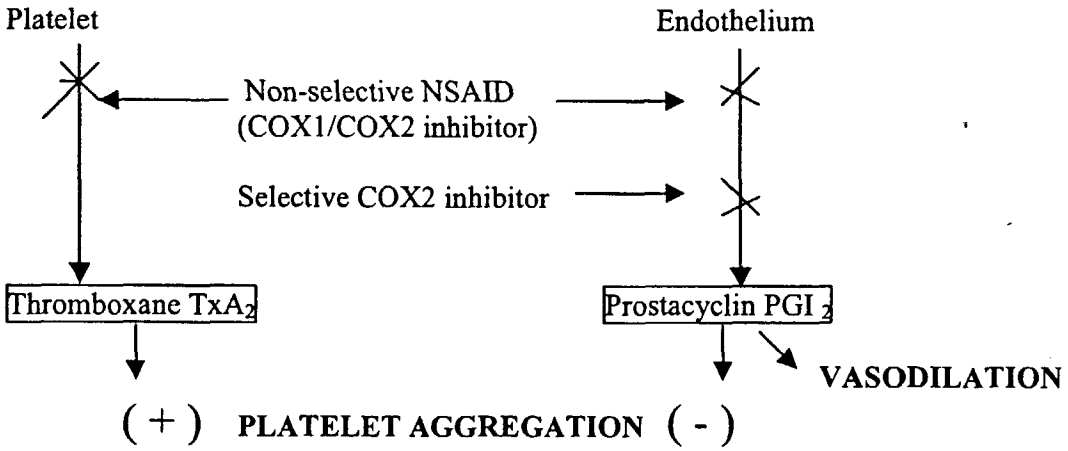
# at Risk						
Rofecoxib	n=4047	3643	3405	3177	2806	1067 531
Naproxen	n=4029	3647	3395	3172	2798	1073 514

There are several potential explanations for this difference in cardiovascular events:

Hypothesis #1. The difference in serious CV thrombotic events may due to the prothrombotic effects of rofecoxib.

Prostacyclin (PGI2) is a potent vasodilator and platelet inhibitor. COX-2 has been implicated as a major source of PGI2 biosynthesis in humans [McAdam et al. Systemic biosynthesis of prostacyclin by COX-2: The human pharmacology of a selective inhibitor of COX-2, PNAS, January 1999] (Fig 3). Animal studies also suggest an important role for PGI2 in mediating inflammation and in preventing thrombosis [Murata et al. Altered pain perception and inflammation response in mice lacking prostacyclin receptor. Nature, 388, 1997].

Figure 3. Potential pro-thrombotic effect of selective COX-2 inhibitors



Modified from McAdam et al. (PNAS, Vol 97, January 1999)

Inhibition of PGI2 synthesis without inhibition of the production of thromboxane TXA2, may shift the hemostasis towards a pro-thrombotic state.

Hypothesis #2: The difference in serious CV thrombotic events may be due to the potent and sustained anti-platelet effect of naproxen.

1. To support this hypothesis, the sponsor refers to a study conducted under the original NDA (study 061) that looked at the selectivity of rofecoxib and other NSAIDs based on biochemical markers and indices of platelet function.

To summarize study 061, 76 healthy women, age 18 to 45, were randomized to receive placebo, rofecoxib 12.5 mg/day, rofecoxib 25/day, meloxicam 15 mg/day, diclofenac 150 mg/day, ibuprofen 2400 mg/day or naproxen 1000 mg/day for six days. Blood samples for platelet aggregation, bleeding time, serum TXB2 generation in clotting whole blood (as an assay of COX-1 activity), LPS-induced PGE2 generation in whole blood (as a measure of COX-2 activity) and urinary prostanoids were obtained before and post treatment. The degree of inhibition of COX-1 was assessed by the weighted average inhibition (WAI) and peak inhibition of TXB2 generation *(platelets do not have COX-2, therefore, selective COX-2 inhibitors are not anticipated to decrease thromboxane production).* The degree of inhibition of COX-2 was assessed by LPS-induced PGE2 generation *(both, selective and non-selective NSAIDs are supposed to decrease PGE2 generation*). A summary of the results of this study is presented in Table 13.

Table 13. NDA 21-042. Summary results of study 061. Selectivity of rofecoxib and other NSAIDs based on biochemical markers and indices of platelet function (Day 6).

	Placebo	Rofecox 12.5	Rofecox 25	Meloxi	Diclofe	Ibuprof	Naprox
COX-1 activity							
Mean TBX2 WAI [1] (%)	-5.2	7.98	6.65	53.28	49.5	88.65	94.4
P value vs. placebo		< 0.05		< 0.001			
Mean peak inhibition of TBX2 (%)	6.5	18.1	14.2	65.4	88.2	95.2	95.3
P value vs. placebo		< 0.05		< 0.001			
COX-2 activity							
Mean LPS-induced PGE2 WAI [2] (%)	-2.3	66.7	69.7	77.5	93.9	71.4	71.5
P value vs. placebo		0.001					
Mean peak inhibition of LPS-induced PGE2	10.8	75.4	77.1	83.7	96.5	89.2	84.2
		0.001					
Platelet inhibition activity							
WAI of Platelet aggregation [3] (%)	-4.1	1.4	1.3	1.8	21.5	77.0	88.3
P value vs. placebo	No significant				< 0.001		
Mean change in bleeding time (minutes)	-0.17	0.06	0.64	-1.10	0.33	1.57	2.54
P value vs. placebo	No significant					< 0.002	< 0.001

[1]TBX2 WAI: weighted average inhibition of production of thromboxaneB2 (measure of COX-1 activity). [2]LPS-induced PGE2 WAI: weighted average inhibition of generation of PGE2 (measure of COX-2 activity). [3] weighted average inhibition of platelet aggregation using arachidonic acid as agonist.

The sponsor points out that the ability of naproxen to inhibit thromboxane generation (almost 95.3 %) and platelet aggregation may explain the lower incidence of cardiovascular thrombotic events in the VIGOR study. However, ibuprofen provides a similar degree of thromboxane inhibition than naproxen (95.2 %) as well as significant inhibition of platelet aggregation and bleeding time, therefore it would also be expected to show some "cardioprotective" effects.

Of note, the degree of inhibition of peak thromboxane production with rofecoxib (14 - 18 %) was also statistically significantly different from placebo (p <0.05). However, inhibition was less than with any of the non-selective NSAIDs, particularly ibuprofen and naproxen.

2. The sponsor submitted to the IND a report of a 28,000 patient-meta-analysis of several rofecoxib studies, using the APTC endpoint. This meta-analysis included all phase II b and III OA clinical program (also referred by the sponsor as study 069); studies 085, 090 and 102; three recently completed studies in RA, two recently completed studies in [redacted] and ongoing studies in Alzheimer's and [redacted]

Of note, study 069 had been submitted to the original NDA 21-042 and studies 085 and 090 were submitted along with VIGOR as part of the current supplemental application. The other studies have not been submitted to the Agency for review.

The applicant compared the number of CV thrombotic events in rofecoxib (12.5, 25 and 50mg dose) to the number of events among patients receiving naproxen 1000 mg/day, and to the number of events among other non-selective NSAIDs (diclofenac 150 mg/day, nabumetone 1000 mg/day and ibuprofen 2400 mg/day) plus placebo, and concluded that the risk of CV/thrombotic events in the rofecoxib group (all doses) was no different from non-selective NSAIDs other than naproxen and similar to placebo.

Reviewer's comment: The sponsor's meta-analysis has serious methodological limitations:

1. *It pools studies of different length (4 weeks to 86 months). Most of the were short (< 6 months). As shown in Figure 2., the cumulative incidence of CV thrombotic AE's for rofecoxib and naproxen start to diverge at approximately 3 months, but the difference increases after 8 months of follow up.*

2. *It pools studies using different doses of rofecoxib. The analysis assumes that there is no dose response for rofecoxib (most doses were 25 mg/day (1/2 and ¼ of the dose used in the VIGOR study). Only approximately 700 patients were exposed to the 50 mg dose for at least 6 months.*

3. *It pools different comparators that may be associated with different risk of thrombotic events. Only diclofenac is representing the non-selective NSAID group after 6 months.*

This meta-analysis is not adequate to address the concern raised in a randomized, prospective study in a large number of patients using a single dose of rofecoxib and a single comparator for a median follow up of 9 months.

There are several arguments against the beneficial naproxen effect being the sole explanation for the difference in cardiovascular thrombotic events in the VIGOR study:

a) *There are no prospective placebo-controlled trials with naproxen to support the assumption that naproxen or any other NSAID associated with reversible inhibition of platelet aggregation are effective in decreasing the risk of cardiovascular events.*

b) *The VIGOR study population was considered by their physicians not to require cardiovascular prophylaxis at the time of entry. (A retrospective chart review conducted by the sponsor identified 4% of patients who had one or more risk factors and would have benefited from prophylactic ASA). With the caveat that the populations are very different, an 80% reduction in risk of myocardial infarction for naproxen relative to rofecoxib in the VIGOR study exceeds the effect size of ASA compared to placebo for primary or secondary prevention in clinical trials published in the literature.*

Table 14. Summary of published randomized clinical trials of Aspirin for primary prevention of vascular disease [1]

Name of study (year of publication)	Patients randomized	Duration (years)	Population [% women] (mean age)	Risk reduction MI	ASA Treatment
Physicians Health study (1989)	22,071	5 (mean)	Healthy male physicians (53)	**44%**	325 QOD
British Doctor' Trial (1988)	5,139	6 (mean)	Healthy male physicians (61)	**4%**	500 mg QD
Early Treatment of diabetic Retinopathy (1992)	3,711	[2]	Men and women [44%] with diabetes mellitus (60)	**15%**	325 mg QD
Thrombosis Prevention Trial (1998)	2,540	5	Men with coronary risk factors (57)	**29%**	75 mg QD
HTN Optimal Treatment study (1998)	18,790	4 (mean)	Men and women [47%] with HTN & diastolic BP from 100-115 mm Hg (62)	**35%**	75 mg QD
PPP. Collaborative Group of the Primary Prevention Project (2001)[3]	4,495	3.5	Men and women [58%] One or more CV risk factor (64)	**31%**	100 mg QD

[1] Modified from Hart et al. Aspirin for the primary prevention of stroke and other major vascular events, meta-analysis and hypotheses. *Archives of Neurology*, March 2000. [2] Exact patient-years of follow-up were not published. [3] Roncaglioni et al. Low dose aspirin and Vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet*, January 2001.

Of note, a secondary analysis of important vascular events in the Physician's Health Study showed risk reduction of 18%; a similar analysis in the PPP study showed a risk reduction of 23%. These analyses included cardiovascular deaths, non-fatal MI and non-fatal stroke (similar to the APTC composite endpoint). In the VIGOR study, there was a 51% decrease in APTC endpoints in the naproxen group as compared to the rofecoxib group.

The hypothesized cardio-protective effect of naproxen in the VIGOR study would be impressive, particularly considering that the risk reduction would have occurred over 9 months while most anti-platelet trials follow patients for 3 to 6 years.

c) *Other studies (085, 090 and 102) to be described later in this review, suggest trends towards higher rates of myocardial infarction in the rofecoxib group compared to active control groups. Of note, these studies involved lower doses and duration of exposure to rofecoxib than the VIGOR trial and allowed the use of low dose ASA.*

Hypothesis #3: It is possible that both, hypotheses #1 and #2, as well as additional unknown factors may account for the cardiovascular results in VIGOR.

The rheumatoid arthritis population is known to have a higher cardiovascular risk than the osteoarthritis population. Several factors have been implicated to explain the elevated cardiovascular risk, such as the chronic use of corticosteroids, high levels of homocysteine and circulating antiphospholipid antibodies in some patients.

1.1.1.4.2.2.1 Serious CV other than thrombotic events (HTN and CHF)

Serious HTN-related and CHF-related events were also higher in the rofecoxib group. Edema-related and HTN-related events are dose related and had been observed in the original NDA database (Appendix 5).

HTN related

Ten (0.2%) and one patients (0%) had a serious hypertension-related adverse experience in the rofecoxib and naproxen groups, respectively. There were no episodes of malignant hypertension and none was associated with end-organ damage. Of the 10 serious adverse experiences in the rofecoxib treatment group: 4 resulted in discontinuation of study therapy and 3 occurred while the patient had discontinued study medication (two of them had discontinued due to non-serious adverse events of edema and hypertension and one of them because of the need to start prophylactic aspirin). All of the serious adverse experiences resolved with either changes in hypertension medication or initiation of new therapies.

Congestive heart failure (CHF)

Fifteen patients developed serious CHF: 13 (0.3%) in the rofecoxib group and 3 (0.1%) in the naproxen group. Additionally, two and one patient developed pulmonary edema in the rofecoxib and naproxen group respectively. It is not clear whether these events of CHF are related only to fluid retention and edema. There might be an ischemic component to these events.

1.1.1.4.2.3. Serious adverse events related to the musculoskeletal system

Eighty three (2.1%) and 70 (1.7%) events met the definition of a serious event in the musculoskeletal system. This category includes fractures, worsening of RA, trauma and others.

There were 41 (1%) and 29 (0.7%) fractures (all sites) in the rofecoxib and naproxen groups, respectively. Bones most commonly involved were the femur (15 and 13 patients on rofecoxib and naproxen respectively) and humerus (6 and 0 patients on rofecoxib and naproxen respectively) but all areas of the skeleton were involved.

> *Reviewer's comment: The number of fractures in this study appears to be high. However, this is a population at high risk of osteoporosis because of the chronic use of steroids. It would be interesting to know the background fracture rate for this population. This study was not powered to detect differences in SAE's other than GI and the difference in the incidence of fractures between the rofecoxib and naproxen arm may not be significant. However, COX-2 is involved in regulation of bone metabolism and concerns have been raised regarding the long term bone*

effects of COX-2 inhibitors.

1.1.1.4.2.3 Renal related SAE's

Of the 50 and 36 patients with renal-related adverse experiences in the rofecoxib and naproxen groups, respectively, one and four had serious events, respectively. Only one of the naproxen patients, was a drug-related serious renal-related adverse experience.

AN 439 (rofecoxib) had serious adverse experiences of hypertension and renal failure. This was a 52 year old woman with RA with no history of HTN. Approximately two months into the study she developed edema of lower extremities that was managed with diazide PRN. Four months later, she was diagnosed with labile hypertension (BP of 240/120) and was given furosemide and Altace, for about a week. Her creatinine rose from 0.8mg/dL at entry, to 1.7 mg/dL. At this point rofecoxib was discontinued and the patient was treated with lopressor, 50 mg bid. (This patient was included in the analysis of serious HTN related adverse events).

> *Renal failure appears to be secondary to furosemide treatment and probably not to NSAID related renal toxicity. However, HTN was likely related to the use of rofecoxib.*

AN 882 (naproxen) developed renal insufficiency in the setting of dehydration, gastritis, and esophagitis. The renal insufficiency resolved with rehydration.

> *This event may have been related to a decrease in glomerular filtration rate, a typical NSAID-related renal toxicity.*

AN 1824 (naproxen) developed acute renal failure due to obstructive uropathy in the setting of bilateral renal calculi.

AN 2720 (naproxen) was hospitalized for right flank pain. Work up included an intravenous pyclogram which revealed a non-functioning left kidney consistent with an obstruction. Cystoscopy revealed a left ureteral stricture. The patient continued on study therapy.

> *In these two cases renal failure developed in the setting of obstructive uropathy. Thise reviewer does not consider these events to be NSAID-related renal toxicity.*

AN 3097 (naproxen) was hospitalized for a perforated gastric ulcer. Her course was complicated by ARDS, peritonitis, septic shock, pneumonia and acute renal failure. The patient expired due to these complications.

> *This reviewer does not consider this case to be NSAID-related renal toxicity; the patient developed renal failure in the setting of septic shock and multiorgan failure.*

In addition to the above adverse experiences there were 2 serious adverse experiences **(AN 8299** nephrotic syndrome [rofecoxib] and **AN 7066** proteinuria [naproxen]) not considered treatment related. Both patients had been receiving concomitant gold therapy.

1.1.1.4.2.4 Serious Liver-related events

There were seven serious liver-related adverse events: four in the rofecoxib and three in the naproxen groups. All were female. The age range was 41 to 84 years. By protocol, chemistries were measured at entry, week 6 and week 52 (end of study visit). The earliest case presented increased LFT's on day 34. One case showed increased LFT's at the discontinuation visit. One patient in each treatment group discontinued from study therapy due to serious hepatic-related adverse experiences. The investigator assessed all cases as possibly related to study drug. However, two of the rofecoxib and one of the naproxen patients (the patient who died) were taking concomitant MTX, therefore, MTX may have played a role in liver toxicity.

The narrative of the patient who died is included in this section (AN 9191). This patient was mentioned under section 1.1.1 (Deaths).

AN 9191 (naproxen) is a 62-year-old Mulatto female, with a history of RA. Concomitant medications included chloroquine, acetaminophen, chlorpheniramine and MTX. Baseline, Day –7, laboratory results included: serum ALT 51 IU/L (normal range was 0 to 48 IU/L), serum AST 41 IU/L (normal range was 0 to 42 IU/L), serum alkaline phosphatase 79 IU/L (normal range was 20 to 125 IU/L), and serum total bilirubin was 0.7 mg/dL (normal range was 0.0 to 1.3 mg/dL). At the 6-week assessment, LFT's were also normal. On Day 268, during the end-of-study visit, the patient complained of right upper quadrant pain, fatigue, nausea, jaundice and dark urine; and the patient was hospitalized. Laboratory results included: AST 780 IU/L, ALT 504 IU/L, serum alkaline phosphatase 237 IU/L, serum total bilirubin 14.7 mg/dL, serum direct bilirubin 4.0 mg (normal range was 0.0 to 0.4 mg/dL, and serum indirect bilirubin 10.7 mg/dL (normal range was 0.0 to 1.3 mg/dL). Hepatitis serology was negative. Liver biopsy confirmed the diagnosis of toxic hepatitis, which was assessed by the investigator as probably related to naproxen. On Day 277, the hepatitis progressed to hepatic failure; which then progressed to hepatorenal syndrome, on Day 279. On Day 285, the patient expired.

> *Reviewer's comment: the CRF for this patient states that the patient started MTX 2.5 mg three times a week for 7 months prior to study entry. The patient was also taking acetaminophen (unknown dose).*

1.1.1.4.2.5 Potential for severe allergic reactions

Four patients, all in the rofecoxib group, had serious adverse experiences that could potentially be considered allergic in nature. (exanthema **(AN 6563),** anaphylactic shock

(AN 7885), skin erythema **(AN 7888),** and anaphylactoid reaction **(AN 8413)** Of these, only the skin erythema was assessed by the investigator to be related to study therapy.

In addition to these patients, there were 3 episodes of angioedema, 2 reported with rofecoxib **(AN 7246 and AN 10222),** and 1 with naproxen **(AN 8215).** The episodes in the rofecoxib group were determined to be drug related by the investigator; one resulted in discontinuation from study therapy. The episode reported with naproxen was determined to be probably not drug related and did not necessitate discontinuation of study therapy.

> *Of note, patients with known allergic reactions to ASA or NSAIDs had been excluded from the study, the risk of developing serious allergic reactions is probably higher than what appears in this study.*

1.1.1.4.3 Dropouts due to adverse events

Approximately 16% of patients discontinued from each treatment arm due to an adverse experience. As seen in Table 15, the number of discontinuations due to adverse events by body system were similar in both treatment groups, except for gastrointestinal and cardiovascular events. The number dropouts was numerically higher in the rofecoxib group compared to the naproxen group for most body systems, except for Body as a whole, Digestive system and Psychiatric disorder categories. A complete list of events leading to discontinuation in the VIGOR trial is presented in Appendix 3.

Looking at the overall number of patients who discontinued due to adverse events, and the number of patients who had serious adverse experiences it is clear that half of the adverse events leading to discontinuation did not meet the definition of a serious event. This difference in the overall comparison is driven by discontinuations in the Digestive body system.

Table 15. Dropouts due to adverse experiences and serious adverse events by body system (incidence >=0.2%)

	Rofecoxib (N=4047) n (%)		Naproxen (N=4029) n (%)	
Number (%) of patients with one or more adverse experience	Serious 378 (9.3)	Dropouts 643 (15.9)	Serious 315 (7.8)	Dropouts 635 (15.8)
Body As A Whole/Site Unspecified	51 (1.3)	100 (2.5)	35 (0.9)	107 (2.7)
Cardiovascular System	101 (2.5)	109 (2.7)	46 (1.1)	33 (0.8)
Digestive System	48 (1.2)	292 (7.2)	97 (2.4)	392 (9.7)
Eyes, Ears, Nose, And Throat	13 (0.3)	20 (0.5)	4 (0.1)	11 (0.3)
Hemic And Lymphatic System	8 (0.2)	4 (0.1)	7 (0.2)	9 (0.2)
Hepatobiliary System	11 (0.3)	10 (0.2)	8 (0.2)	2 (0.0)
Musculoskeletal System	83 (2.1)	29 (0.7)	70 (1.7)	27 (0.7)
Nervous System	14 (0.3)	44 (1.1)	7 (0.2)	24 (0.6)
Psychiatric Disorder	7 (0.2)	3 (0.1)	3 (0.1)	10 (0.2)
Respiratory System	52 (1.3)	23 (0.6)	39 (1.0)	13 (0.3)
Skin And Skin Appendages	31 (0.8)	42 (1.0)	20 (0.5)	37 (0.9)
Urogenital System	32 (0.8)	17 (0.4)	23 (0.6)	9 (0.2)

Source: Modified from appendix 4.17.4 and 4.17.2 of 088c study report. Patients may appear under more than one category, but only once within one category.

The incidence of gastrointestinal events leading to discontinuation (a category that includes bleeding and non-bleeding symptomatic ulcers) was a numerically higher in the naproxen than in the rofecoxib groups (7.2% and 9.7%, respectively). Approximately 300 patients discontinued from the rofecoxib arm due to digestive system adverse events but only 48 patients (one every six patients) had a serious event (1.2 %). Similarly, approximately 400 patients discontinued from the naproxen arm but only 97 (one every four patients) had a serious event (2.4%). Discontinuations in the digestive system included symptomatic gastric ulcer (18 in rofecoxib, 55 in naproxen), gastritis (14 in rofecoxib, 26 in naproxen), epigastric discomfort (19 in rofecoxib, 49 in naproxen), dyspepsia (43 in rofecoxib and 56 in naproxen), and constipation (1 rofecoxib, 10 in naproxen). Serious gastrointestinal complications such as gastrointestinal bleeding and hemorrhagic ulcers were twice more common in the naproxen that the rofecoxib arm.

Of note, for cardiovascular events, most of the events leading to discontinuation met the definition of a serious event.

The overall incidence of cardiovascular events leading to discontinuations was three times higher in the rofecoxib group compared to the naproxen group (109 patients - 2.7% - vs. 33 patients - 0.8% -, respectively). Discontinuation due to hypertension related events was four times higher on rofecoxib than on naproxen (28 patients - 0.7% vs. 6 patients - 0.2%, respectively). There were six cases of discontinuation due to congestive heart failure (CHF) on rofecoxib (0.1%) and none on naproxen.

Discontinuations due to cardiovascular thrombotic events were two fold higher in the rofecoxib than the naproxen group. (See serious cardiovascular events).

1.1.1.4.4 Pre-specified NSAID-related adverse events

The protocol included a pre-specified analysis of discontinuations due to NSAID related AE's (GI, edema-related, HTN-related, renal and liver-related AE's) as well as an analysis of CHF events.

Table 16: VIGOR. Results of pre-specified safety analyses

Type of Adverse Experience	Treatment	N	Events	Rates	Relative Risk		
					Estimate	95%CI	p-value
Discontinuations due to GI and abdominal pain	rofecoxib naproxen	4047 4029	307 416	11.47 15.62	0.73	(0.63, 0.85)	<0.001
Discontinued due to edema-related AEs	rofecoxib naproxen	4047 4029	25 13	0.93 0.48	1.92	(0.98, 3.75)	0.057
Discontinued due to hypertension-related AEs	rofecoxib naproxen	4047 4029	28 6	1.04 0.22	4.67	(1.93, 11.28)	<0.001
Discontinued due to hepatic disease AEs	rofecoxib naproxen	4047 4029	10 3	0.37 0.11	3.33	(0.92, 12.11)	0.067
Discontinuations due to renal related AE's*	rofecoxib naproxen	4047 4029	*	*	*	*	*
CHF AEs	rofecoxib naproxen	4047 4029	19 9	0.70 0.33	2.11	(0.96, 4.67)	0.065
Lab AEs leading to discontinuation	rofecoxib naproxen	4047 4029	22 12	0.82 0.44	1.83	(0.91, 3.71)	0.091

Source: modified from sponsor Tables 66 to 75. **Due to discrepancy between analysis submitted by the sponsor and the number of patients who actually had renal-related discontinuations, the sponsor's analysis is omitted from this table.*

1.1.1.4.4.1 Dropouts due to Renovascular adverse experiences.

NSAIDs are known to cause decreases in glomerular filtration rate sometimes resulting in overt renal decompensation. Since COX1 and COX2 isoforms express in different parts of the nephron, it was initially hypothesized that COX-2 inhibitors might spare some of the renal effects of non-selective NSAIDs. Data submitted in the original NDA 21-042 have made clear that rofecoxib does not spear the kidney. Rofecoxib shows a clear dose-response relationship in terms of renal effects. Post-marketing surveillance has confirmed the potential renal toxicity of rofecoxib.

> *Reviewer's comment: Discontinuations due to renal-related adverse experiences reported in this study included: serum creatinine increased, blood urea nitrogen increased, renal failure, and renal insufficiency. Since the original data provided by the sponsor (8 patients on rofecoxib and 7 patients on naproxen) did not match the discontinuation datatsets, narratives of patients who presented discontinuations due to renal ae's were provided by the sponsor in response to the medical reviewer.*

Table 17. VIGOR. Discontinuations due to renal-related AE's. Revised information [1]

Rofecoxib 50 mg (N = 4049)					Naproxen 1000 mg (N = 4027)				
9 (0.2%)					5 (0.1%)[11]				
Pt #	Age/sex	Hx [2]	Creatinine[3] (mg/dL)	Onset day	Pt #	Age/sex	Hx	Creatinine[3] (mg/dL)	Onset day
693	64/F	HTN	1.7	150	541	72/F	HTN	1.6	29
746	69/M	HTN	1.9	218	882	66/F	HTN	2.6	45[8]
1782	66/F	HTN	2.1	72[4]	1267	56/F	-	2.5	300
1837	63/F	HTN	1.7	117[5]	3588	77/M	CRI	2.2	43[9]
2000	51/F	HTN	1.5	93	1097	77/M	HTN/CRI	2.4	40[10]
2281	65/F	-	1.3	90					
2403	56/F	-	1.7	109					
5137	73/M	HTN/DM	*	36[6]					
7312	71/F	HTN	1.5	129[7]					

[1] Data submitted 2/25/01. [2] Pertinent medical history: HTN: hypertension; DM: Diabetes Mellitus; CRI; chronic renal insufficiency. [3] Normal range 0.5-1.4 mg/mL. [4] Event associated with GI bleeding, pancytopenia and sepsis. [5] Event associated with abdominal pain. [6] Creatinine 149 mol/L (normal 50-125 mol/L). [7] Secondary to initiation of enalapril for worsening HTN. [8] Event associated with GI bleeding and pancytopenia. [9] Patient had a history of prostatic carcinoma with baseline creatinine of 1.5 mg/dL. [10] Baseline creatinine 2.0. [11] In addition, patient 1824 was discontinued due to increased BUN and creatinine due to bilateral ureteral obstruction.

As seen in this table, ten out of fourteen cases of creatinine increase occurred in patients who had hypertension. Two cases (one in each group) were associated with GI bleeding and pancytopenia, both in patients taking concomitant MTX.

Although the number of cases of renal insufficiency was small in both groups, rofecoxib 50 mg was associated with more cases than naproxen 500 mg twice a day in the VIGOR study. All nine patients discontinued from the rofecoxib group due to creatinine increase had a normal serum creatinine at screening. Two of the five patients discontinued from the naproxen group had pre-existing renal insufficiency.

1.1.1.4.5 Hospitalizations

An analysis of hospitalizations provided by the sponsor at the reviewer's request was consistent with the findings that overall safety favored naproxen, mainly due to an excess of cardiovascular events in the rofecoxib group, compared to the naproxen group.

Table 18. VIGOR. Hospitalization by body system.

	Rofecoxib (N=4047) n (%)	Naproxen (N=4029) n (%)
Patients with one or more hospitalizations	338 (8.4)	263 (6.6)
Cardiovascular	65 (1.6)	24 (0.6)
Gastrointestinal	29 (0.7)	49 (1.2)
Hematologic	12 (0.3)	7 (0.2)
Hepatobiliary	7 (0.2)	6 (0.1)
Renal	6 (0.1)	6 (0.1)
Other	219 (5.4)	144 (3.6)

Source: Modified from response to FDA request submitted 2/2/01. Patients may appear under more than one category, but only once within one category.

Table 19. VIGOR. Hospitalizations due to cardiovascular related adverse events

	Rofecoxib (N=4047) n (%)	Naproxen (N=4029) n (%)
Patients hospitalized for a cardiovascular adverse event	65 (1.6)	24 (0.6)
a. Cardiac		
Arrythmia	38 (0.9)	20 (0.5)
Angina	12 (0.3)	10 (0.2)
MI	20 (0.5)	5 (0.1)
b. Hypertension	9 (0.2)	0 (0.0)
c. Peripheral vascular	3 (<0.1)	3 (<0.1)
d. Thrombophlebitis	5 (1.2)	1 (<0.1)
e. Cerebrovascular	19 (0.5)	9 (0.2)

Source: modified from sponsor's response to FDA request. Patients may appear under more than one category.

The number of cardiovascular related hospitalizations was almost three times higher in the rofecoxib group as compared to the naproxen group. Main differences in the number of hospitalizations were due to myocardial infarction, hypertension, thrombophlebitis and cerebrovascular events.

Reviewer's comment: Cerebrovascular events include hemorrhagic and non-hemorrhagic events. There were only two and one confirmed hemorrhagic events in the rofecoxib and naproxen group, respectively. If, as the sponsor has proposed, naproxen has such a potent anti-platelet effect, one would expect to see more patients with hemorrhagic events in the naproxen group.

1.1.1.4.6 Most common Adverse Events

Table 20 indicates that for all body system except the digestive system, the incidence of adverse events was higher for rofecoxib than naproxen. The differences were statistically significantly different for the Cardiovascular, Digestive and Nervous body system.

Table 20. VIGOR. Most common Clinical Adverse Experience by body system (2%)

	Rofecoxib (N=4047) n (%)	Naproxen (N=4029) n (%)
Patients with one or more adverse experience	2872 (71)	2824 (70.1)
Body As A Whole/Site Unspecified	1071 (26.5)	1003 (24.9)
Cardiovascular System[1]	590 (14.6)	390 (9.7)
Digestive System[2]	1320 (32.6)	1449 (36.0)
Eyes, Ears, Nose, And Throat	450 (11.1)	397 (9.9)
Metabolism And Nutrition	128 (3.2)	132 (3.3)
Musculoskeletal System	630 (15.6)	613 (15.2)
Nervous System[3]	456 (11.3)	356 (8.8)
Psychiatric Disorder	108 (2.7)	92 (2.3)
Respiratory System	346 (8.5)	343 (8.5)
Skin And Skin Appendages	508 (12.6)	410 (10.2)
Urogenital System	372 (9.2)	341 (8.5)

Source: Modified from appendix 4.17.4 of 088c study report. Patients may appear under more than one category, but only once within one category. [1] Estimate 4.9, (95% CI 3.5, 6.3); [2] Estimate –3.3, (95% CI –5.4, -1.3); [3] Estimate 2.4, (95% CI 1.1, 3.8).

> *Of note, the nervous system includes a heterogeneous group of symptoms such as headaches, peripheral neuropathy, insomnia, paresthesias. A statistically significant difference was noted for headaches (190 and 140 in rofecoxib and naproxen respectively) and muscular spasms (18 and 5 in rofecoxib and naproxen group respectively). The clinical significance of these findings is unclear.*

1.1.1.4.7 Laboratory adverse experiences (LAE's)

Laboratory adverse experiences occurred in 10.4 and 9.2% of patients in rofecoxib and naproxen groups, respectively.

Table 21. Laboratory adverse experiences (LAE's) summary.

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
With at least one laboratory test postbaseline	4006		3999	
With one or more LAE's	418	(10.4)	368	(9.2)
With serious LAE's				
Who died	2	(0.0)	0	(0.0)
Discontinued due to LAE's	0	(0.0)	0	(0.0)
	22	(0.5)	12	(0.3)

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once in a body system. The same patient may appear in different body systems. Source: NDA table 60.

There were no significant changes from baseline in chemistry and hematology laboratory parameters in any group. The number of patients with laboratory AE's with incidence >0.2% is presented in table 22.

Serious laboratory adverse experiences.

Three serious laboratory adverse experiences occurred in the rofecoxib group:
1) one case of neutropenia on day 266, 2) one case of leukopenia (AN 7058) and platelets decreased in a patient with worsening vasculitis and pneumonia (AN 7575), on day 300, respectively). 3) An additional patient died of pneumonia in the setting of aplastic anemia and sepsis (patient 10078). None was assessed by the investigator to be study drug related. The three cases were judged by the investigator to be related to methotrexate.

Discontinuations due to LAE's

More patients discontinued due to LAE's from the rofecoxib group (22), compared to the naproxen group (12). The difference was due to higher number of patients with liver-related enzymes and serum creatinine increase as well as hemoglobin and platelet decrease in the rofecoxib group compared to the naproxen group.

Table 22. VIGOR. Number of patients with laboratory adverse experiences (incidence >0.2% in one or more treatment groups) (source: Table 62 of sNDA 007)

Adverse Experience	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n/m	(%)	n/m	(%)
Patients with one or more adverse experience	418/4006	(10.4)	368/3999	(9.2)
Patients with no adverse experience	3588/4006	(89.6)	3631/3999	(90.8)
Blood Chemistry	**187/3994**	**(4.7)**	**133/3997**	**(3.3)**
Alanine Aminotransferase Increased	73/3988	(1.8)	41/3992	(1.0)
Alkaline Phosphatase Increased	25/3987	(0.6)	18/3991	(0.5)
Aspartate Aminotransferase Increased	65/3989	(1.6)	34/3992	(0.9)
Blood Urea Nitrogen Increased	20/3989	(0.5)	9/3992	(0.2)
Gamma-Glutamyl Transpeptidase Increased	23/522	(4.4)	12/464	(2.6)
Hyperglycemia	17/3988	(0.4)	16/3992	(0.4)
Serum Creatinine Increased	38/3988	(1.0)	27/3995	(0.7)
Hematology	**289/3997**	**(7.2)**	**267/3997**	**(6.7)**
Eosinophils Increased	2/3987	(0.1)	13/3988	(0.3)
Hematocrit Decreased	105/3993	(2.6)	106/3997	(2.7)
Hemoglobin Decreased	134/3995	(3.4)	148/3997	(3.7)
Leukocytes Decreased	10/3993	(0.3)	14/3993	(0.4)
Leukocytes Increased	7/3993	(0.2)	9/3993	(0.2)
Platelets Decreased	13/3990	(0.3)	5/3990	(0.1)
Platelets Increased	10/3990	(0.3)	7/3990	(0.2)
Urinalysis	**105/3972**	**(2.6)**	**77/3974**	**(1.9)**
Bacteriuria	19/70	(27.1)	9/67	(13.4)
Erythrocyturia	22/3972	(0.6)	5/3974	(0.1)
Hematuria	12/3972	(0.3)	6/3974	(0.2)
Leukocyturia	26/2021	(1.3)	18/1831	(1.0)
Proteinuria	17/3972	(0.4)	15/3973	(0.4)

Although a patient may have had two or more laboratory adverse experiences, the patient is counted only once in a body system. The same patient may appear in difference body systems.
* Incidence based on the total number of patients in each treatment group.
n/m = number of patients with laboratory adverse experiences/number of patients for whom the laboratory test was recorded.

1.1.1.4.7.1 Liver-related laboratory AE's

Hepatic related AE's were reported by 90 (2.2%) and 49 (1.2%) patients in the rofecoxib and naproxen groups, respectively. The most common hepatic-related adverse experience was ALT increased, occurring in 1.8 and 1.0% of patients in the rofecoxib and naproxen groups, respectively.

As seen in Table 10, the number of patients with elevated liver function tests (LFT's) was numerically higher in the rofecoxib than in the naproxen group. For ALT, AST and GGT, the number of patients with increased values was almost twice in the rofecoxib than the naproxen group. There were no serious liver related laboratory AE's.

In this study, 0.5 and 0.3% of patients on rofecoxib and 0.2 and 0.3% of patients on naproxen had at least 1 single (nonconsecutive) AST and ALT value >3 times the ULN, respectively.

Of the 90 and 49 patients with hepatic-related adverse experiences in the rofecoxib and naproxen groups, respectively, only 4 patients (all in the rofecoxib group) met predefined limits of change for serum ALT and only 1 patient (in the rofecoxib group) met predefined limits of change for serum aspartate aminotransferase (defined as: In patients with normal baselines, consecutive values >3 times the ULN or 1 value >3 times the ULN associated with study drug discontinuation; in patients with abnormal baselines, consecutive values that are >2 times the baseline value and >3 times the ULN or 1 value >3 times the ULN associated with study drug discontinuation).

The remaining patients did not meet the predefined limits criteria or elevations were transient and did not necessitate discontinuation of study therapy. No patient in either treatment group exceeded the predefined limit of change established for serum bilirubin (1.8 times ULN) and alkaline phosphatase (3 times ULN).

These criteria are more stringent than the ones used in the original NDA (a single value x2and >ULN) . With the current definition a patient could have repeated values twice the ULN and not be considered as exceeding predefined limits of change.

At the reviewer's request, the sponsor conducted an analysis of events using less stringent criteria.

Table 23. Analysis of LFT Values Exceeding the Limits of Change (Source: sponsor's table, response to FDA request submitted 1/10/01).

Laboratory Test	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n/N	(%)	n/N	(%)
ALT (U/L)				
In patients with one or more values >2 times baseline and >ULN	150/3971	(3.8)	101/3979	(2.5)
In patients with consecutive values >2 times baseline and >ULN or one or more values >2 times baseline and > ULN associated with study drug discontinuation	20/3971	(0.5)	10/3979	(0.25)
AST (U/L)				
In patients with one or more values >2 times baseline and >ULN	114/3972	(2.9)	87/3980	(2.2)
In patients with consecutive values >2 times baseline and >ULN or one or more values >2 times baseline and > ULN associated with study drug discontinuation	11/3972	(0.3)	8/3980	(0.2)

This analysis again shows that the number of patients with abnormal ALT and AST values was numerically higher in the rofecoxib compared to the naproxen group. Approximately 10% of patients with one single value >2 and ULN had consecutive values >2 and ULN.

1.1.1.4.7.2 Renal related Laboratory AE's

Renal-related clinical and laboratory adverse experiences were reported by 50 (1.2%) and 36 (0.9%) of patients in the rofecoxib and naproxen groups, respectively. The most common renal-related adverse experience in both treatment groups was serum creatinine increased (transient elevations), occurring in 37 (1.0%) and 27 (0.7%) of patients in the rofecoxib and naproxen groups, respectively.

Only 4 and 3 patients in the rofecoxib and naproxen group respectively met predefined limits of change for serum creatinine (defined as consecutive values with an actual increase of 0.5 mg/dL and >ULN or 1 value with an increase of 0.5 mg/dL and >ULN that was associated with study drug discontinuation). All 7 of these patients discontinued due to their renal-related adverse experience.

The remaining patients with renal-related adverse experiences had elevations less than 0.5 mg/dL or had elevations of 0.5 mg/dL or more which were transient and did not necessitate discontinuation of study therapy.

This criterion is more stringent than the one used in the original NDA (a single value increased by 0.5mg/ML and >ULN.

At the reviewer's request, the sponsor provided an analysis of changes of 25% over baseline.

Table 24. Number (%) of Patients With Serum Creatinine Increase 25% above Baseline (source: sponsor's table, response to FDA request submitted 01/10/01)

Laboratory Test	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n/m	(%)	n/m	(%)
Serum Creatinine				
In patients with increase of 25%	1082/3970	(27.3)	856/3979	(21.5)
In patients with consecutive values with Increase of 25% or one or more values with increase 25% associated with study drug discontinuation	294/3970	(7.4)	208/3979	(5.2)

The number of patients with creatinine increase at or above 25% from baseline was higher in the rofecoxib group (27%) compared to the naproxen group (21.5%). Approximately 1/3 and ¼ of patients with a single abnormal value 25% had consecutive abnormal values.

1.1.1.4.7.3 Hematology

In general, there were no substantial differences in the percentage of patients with abnormal hematologic laboratory values. The number of patients with hemoglobin decreased was numerically higher in the naproxen group (148 patients, 3.7%) compared

with the rofecoxib group (137 patients, 3.4%). There were more patients with platelets decreased in the rofecoxib group than in the naproxen group (0.3% and 0.1%, respectively). The three serious cases of laboratory AE's in the VIGOR study were in the hematologic system, in the rofecoxib group, in patients taking concomitant MTX.

1.1.1.4.7.4 Other laboratory tests

Bacteriuria, erytrhocyturia and hematuria were more common among patients in the rofecoxib group. The clinical significance of these observations is unclear.

In general, analyses of laboratory predefined limits of change not associated with prespecified adverse events (such as electrolytes, calcium, BR and platelet counts) showed no significant differences between groups. Of note, changes in sodium (hyponatremia and hypernatremia) were relatively high in both groups, compared to other electrolytes.

Hyponatremia (defined as a decrease by 8 units and below lower limit of normal) was more frequent with rofecoxib than with naproxen (1% and 0.5% respectively). This difference was statistically significant. The relatively high incidence of hyponatremia may be in part explained by fluid retention and edema.

1.1.1.4.8 Vital signs

Overall, the data indicate that rofecoxib 50 mg is associated with small increases in systolic, and to a lesser extent, diastolic blood pressure compared to baseline. No clinically important changes in body weight were observed in either treatment group.

Table 25. VIGOR. Summary statistics for vital signs.

Parameter	Treatment Group	N	Baseline Mean	Treatment Period Mean	Change From Baseline			
					Mean	SD	Median	Range
Diastolic blood pressure (mm Hg)	Rofecoxib	3997	78.2	79.9	1.7	7.5	1.3	
	Naproxen	4002	78.1	78.2	0.1	7.5	0.0	
Systolic blood pressure (mm Hg)	Rofecoxib	3997	128.7	133.2	4.6	12.7	4.0	
	Naproxen	4002	128.8	129.8	1.0	12.3	0.0	
Weight (Kg)	Rofecoxib	3992	72.1	72.7	0.6	2.4	0.5	
	Naproxen	3993	71.9	72.5	0.5	2.4	0.5	

* Baseline: Visit 2.0, after the NSAID washout period. (source: sponsor's table)

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1.1.1.4.9 Adverse Experiences in Methotrexate Users

There were no differences in the overall incidence of clinical adverse experiences, drug-related clinical adverse experiences, or serious clinical adverse experiences for patients who took or did not take concomitant MTX for treatment of RA. There were no significant differences in the overall incidence of adverse events by body system between MTX and non-MTX users for each treatment.

Table 26. VIGOR. Adverse experience summary in MTX users and non-MTX users

	MTX Users		MTX Non-users	
	Rofecoxib 50 N = 2385 %	Naproxen 1000 N = 2387 %	Rofecoxib 50 N = 1662 %	Naproxen 1000 N = 1642 %
Clinical AE's				
With one or more AE's	1716 (71.9)	1701 (71.3)	1156 (69.6)	1123 (68.4)
With serious AE's	223 (9.4)	190 (8.0)	155 (9.3)	125 (7.6)
Who died	15 (0.6)	10 (0.4)	7 (0.4)	5 (0.3)
Discontinued due to AE's	362 (15.2)	345(14.5)	281 (16.9)	290 (17.7)
Discontinued due to SAE's	84 (3.5)	74 (3.1)	59 (3.5)	53 (3.2)
Discontinued due to SAE's drug- related	39 (1.6)	39 (1.6)	16 (1.0)	29 (1.8)
Laboratory AE's				
With one lab test post baseline	2372	2374	1634	1625
With one or more AE's	257 (10.8)	240 (10.1)	161 (9.9)	128 (7.9)
Discontinued due to AE's	13 (0.5)	6 (0.3)	9 (0.6)	6 (0.4)

Source Appendix 4.21, Study 088c of s007.

No differences in the overall incidence of laboratory adverse experiences were observed between patients taking or not taking concomitant methotrexate for RA. Liver function tests (ALT and AST) were consistently higher in rofecoxib as compared to naproxen. MTX use did not seem to increase the risk of LFT abnormalities in either rofecoxib or naproxen.

Table 27. VIGOR. Liver-related laboratory adverse experiences in MTX users and non-users

	MTX users		MTX non-users	
	Rofecoxib 50 (N 2385)	Naproxen (N=2387)	Rofecoxib (N=1662)	Naproxen (N=1642)
ALT	48 (2.0)	28 (1.2)	25 (1.5)	13 (0.8)
AlkPhos	12 (0.5)	13 (0.5)	13 (0.8)	5 (0.3)
AST	44 (1.9)	23 (1.0)	21 (1.3)	11 (0.7)
GGT	12 (0.5)	7 (0.3)	11 (0.7)	5 (0.3)

1.1.1.4.10 Analysis of concomitant therapies

There were no substantial differences in the number of patients who took concomitant medications, except for those related to the cardiovascular system.

Table 28. VIGOR. Number (%) of Patients With Specific Prior and Concomitant Therapies for CV disease (Incidence =1.0% in One or More Treatment Groups) by Drug Category

	Rofecoxib 50 mg N= 4047 (%)			Naproxen 1000 mg N= 4027 (%)		
	Prior	Concomitant	New	Prior	Concomitant	New
Cardiac Therapy	87 (2.1)	154 (3.8)	**(1.7)**	97 (2.4)	137 (3.4)	**(1.0)**
Antihypertensive	95 (2.3)	119 (2.9)	**(0.6)**	76 (1.9)	85 (2.1)	**(0.2)**
Diuretic	423 (10.5)	624 (15.4)	**(4.9)**	430 (10.7)	540 (13.4)	**(2.7)**
Beta Blocking Agent	330 (8.2)	429 (10.6)	**(2.4)**	336 (8.3)	389 (9.7)	**(1.4)**
Calcium Channel Blocker	338 (8.4)	440 (10.9)	**(2.5)**	316 (7.8)	371 (9.2)	**(1.4)**
Angiotensin System	476 (11.8)	647 (16.0)	**(4.2)**	441 (10.9)	525 (13.0)	**(2.1)**

Modified from sponsor's tables. A patient may have had two or more therapies.

Patients in both groups required new cardiovascular therapy. More patients required concomitant therapy for a cardiovascular condition in the rofecoxib group as compared to the naproxen group.

1.1.1.5 VIGOR study - Efficacy Results

Of note, the 50 mg dose is twice the anticipated recommended dose in RA. However, the efficacy of the 25 mg dose in RA remains to be demonstrated.

The efficacy parameters in this study were Patient's and Investigator's Global Assessment of Disease Status (measured on the Likert scale from 0 to 4), the modified HAQ (consisting of 8 questions measured on a scale of 0 to 3) and discontinuations due to lack of efficacy. Efficacy endpoints routinely followed in efficacy trials such as swollen and tender joints and markers of inflammation such as CRP or ESR were not recorded in this study.

There were no differences between treatments in their effects on patient and investigator global assessments of disease status and the modified HAQ. However, Intra-articular and oral steroids as well as changes in doses of DMARDs and non-NSAID analgesics were allowed throughout the study, therefore, it the lack of differences in efficacy between arms is not unexpected.
Discontinuations due to lack of efficacy were low in both treatment groups and there was no difference between the treatment groups.

Adequate Phase III efficacy studies designed to test efficacy hypotheses are required.

1.1.1.6 VIGOR Summary of findings

1. Gastrointestinal findings:

The study succeeded in the GI primary and secondary endpoints. The relative risk of developing clinically meaningful GI events was almost half for rofecoxib compared to naproxen (RR= 0.46 and 0.43 for PUBs and complicated PUBs, respectively). However, generalization of the GI findings to a general population is limited by the exclusion of patients on low dose ASA. Generalization of the GI findings to other less selective NSAIDs requires an assumption of relative homogeneity in GI toxicity across the spectrum of traditional NSAIDs. This assumption is incorrect.

2. Cardiovascular findings:

The risk of serious cardiovascular thrombotic events associated with rofecoxib use was over two fold higher compared to naproxen use (RR = 2.37). The incidence of dropouts due to hypertension was almost five times higher in the rofecoxib group as compared to the naproxen group. The incidence of CHF was also twice in the rofecoxib group. More patients in the rofecoxib group required initiation of cardiovascular medications compared to the naproxen group. Fluid retention/edema and HTN are dose related and had been observed in the original NDA. The mechanism for the CHF may have been related to fluid retention and edema, but an ischemic component can not be ruled out.

The reason for the excess in cardiovascular thrombotic events in the rofecoxib group as compared to the naproxen group is not clear. The anti-platelet effect of naproxen may partially explain the difference. However, concerns regarding the potential prothrombotic effects of selective COX-2 inhibitors have been raised in the past because selective COX-2 inhibition decreases the synthesis the prostacyclin, a potent vasodilator and anti-platelet agent. The effect size of naproxen as a putative cardioprotective agent exceeds the expectations for an antiplatelet drug in a population not considered to be at increased cardiovascular risk by traditional risk factors, particularly over such a short period of time.

3. Overall safety:

The superior organ-specific GI safety did not translate into an overall benefit for the rofecoxib group, mainly due to an excess of serious cardiovascular events in the rofecoxib group as compared to the naproxen group. Other than GI and CV, the safety profile of rofecoxib was consistent with that of an NSAID. It is of not that this study employed rofecoxib 50 mg/day, a dose twice the highest recommended dose for chronic use in OA. However, 50 mg/day is the dose approved for the treatment of acute pain.

4. Efficacy: The study was not designed to address the efficacy of rofecoxib.

1.2 New Studies submitted in this supplement application. Studies that allowed low dose ASA.

1.2.1 Studies 085 and 090

1.2.1.1 Study design, demographics and disposition.

Studies 085 and 090 were six-week, placebo controlled studies in patients with OA, comparing rofecoxib 12.5 mg/day to nabumetone 1000 mg/day. The studies were designed as efficacy studies in patients with OA. Both studies used a 2:2:1 randomization scheme (rofecoxib/ nabumetone/placebo). Each active treatment arm involved approximately 400 patients. Patients were permitted to take low-dose aspirin (81 mg or less, once daily) for cardioprotective benefit.

There were no substantial differences in the demographic and clinical characteristics at baseline in each treatment group, in each study: 70% of patients were female; 87% were Caucasian; mean age was approximately 63 years (range 35 o 92 years). Nearly one fifth of the patients (18%) reported a history of GI adverse experiences associated with NSAID use, and (16)% had stopped arthritis medication due to stomach or abdomen problems.

In study **085**, 62 to 66% of patients had prior history of CV disease. In study **090**, 55% to 60% of patients had prior history of CV disease. Approximately 40% of patients had a prior history of HTN.

In study 085, overall, 11.9% of patients took low-dose aspirin during this trial. The frequency of low-dose aspirin use was comparable among treatment groups: 10.8, 13.9, and 10.1% in the rofecoxib, nabumetone, and placebo treatment groups, respectively.
In study 090, overall, 12.2% of patients took low-dose aspirin during this trial. The frequency of low-dose aspirin use was comparable among treatment groups: 11.5, 12.0, and 13.8% in the rofecoxib, nabumetone, and placebo treatment groups, respectively.

1.2.1.2 Safety results

Table 29. Clinical AE summary of studies 085 and 090

	Rofecoxib 12.5 mg (N=814)	Nabumetone 1000 mg (N=802)	Placebo (N=404)
Number (%) of patients:	n (%)	n (%)	n (%)
with one or more adverse experiences	432 (53)	390 (48.6)	188 (46.5)
with serious adverse experiences	13 (1.6)	10 (1.2)	2 (0.5)
discontinued due to an adverse experience	53 (6.5)	41 (5.1)	13 (3.2)
discontinued due to a serious AE	10 (1.2)	4 (0.5)	1 (0.3)

(Source: pooled data from Table 33 and 34 of studies 085 and 090). † Considered by the investigator to be possibly, probably, or definitely drug-related.

1.2.1.2.1 Deaths. There were no deaths.

1.2.1.2.2 Serious Adverse Events (SAE's):

Twelve, four and one patient discontinued due to a serious AE from the rofecoxib 25, nabumetone 100 and placebo groups, respectively.

There were three serious gastrointestinal complications: one lower GI bleeding in the nabumetone group and two cases of cholecystitis, one in each active treatment group. There were no PUB's.

There were six cases of serious cardiovascular events in the rofecoxib group (4 myocardial infarctions and 2 cerebrovascular accidents); three in the nabumetone group (1 myocardial infarction, 1 coronary artery disease and 1 CHF) and one coronary artery occlusion in the placebo group.

1.2.1.2.3. Discontinuations due to AE's

The incidence of discontinuations due to clinical and laboratory AE's were similar in both active treatment groups.

Discontinuations in the Digestive system were similar in both active groups and higher than placebo. Discontinuations in the CV system were twice in the rofecoxib 12.5 mg dose than in nabumetone 1000 mg dose.

Table 30. Discontinuations due to clinical AEs in study 085 and 090

	Rofecoxib 12.5 mg (N=814)	Nabumetone 1000 mg (N=802)	Placebo (N=404)
	n (%)	n (%)	n (%)
Body As A Whole/Site Unspecified	13 (1.6)	11 (1.4)	4 (1)
Cardiovascular System	10 (1.2)	3 (0.4)	1 (0.2)
Digestive System	19 (2.3)	18 (2.2)	0
Musculoskeletal System	5 (0.6)	9 (1.1)	3 (0.7)
Nervous System	6 (0.7)	4 (0.5)	0
Respiratory System	2 (0.2)	2 (0.2)	1 (0.2)
Skin And Skin Appendages	6 (0.7)	2 (0.2)	3 (0.7)
Urogenital System	0	1 (0.2)	1 (0.2)

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

1.2.1.2.4. Most common adverse events

Overall, body systems with the highest incidence of clinical adverse experiences were body as a whole (approximately 20%), the digestive system (14%), and the nervous system (12 %, mainly headache). Incidences of clinical adverse experiences by body system were generally comparable among treatment groups.

1.2.1.2.5. Laboratory AE's

Two patients in the rofecoxib 25 mg group, one in the nabumetone 1000 mg group and one patient on placebo discontinued due to laboratory AE's.

Conclusions:

Population size, dose and duration limit the value of these studies in assessing the safety of chronic rofecoxib use. However, there were 6 cardiovascular thrombotic events in the rofecoxib group and two in the nabumetone group. The number of events is too small to allow statistical comparisons but results for this lower dose of rofecoxib in these short-term studies appear to follow the pattern observed in the VIGOR study for CV thrombotic events.

The sponsor proposes to use studies 085 and 090, along with study 058 (a small study from the original NDA) to support the safety of the co-use of rofecoxib and low dose ASA. However, these studies were 6-week efficacy studies and therefore inadequate in size and duration to detect differences in serious adverse events. For comparison, VIGOR protocol included approximately 4000 patients per arm and provided a 95% power (α =0.05, two tailed) to detect a reduction in risk of at

least 50% in the primary gastrointestinal safety hypothesis. The mean duration of treatment was 9 months. Cumulative rates of serious GI events in the VIGOR study showed that events start to separate by week 4 but the difference increases with time. Cumulative rates of cardiovascular thrombotic events in VIGOR show that maximum differences are observed after 8 months of treatment.