1.2.2 Study 102: ONLY PRELIMINARY DATA SUBMITTED.

Study 102 ("ADVANTAGE") was a 12-week, randomized, double blind active controlled study of rofecoxib 25 mg/day and naproxen 1000 mg/day in approximately 5,500 patients with OA who were allowed to ASA 81 to 325 mg/day. The primary endpoint was GI symptoms. 12.1% and 12.8% of patients used low dose ASA in the rofecoxib and naproxen treatment group, respectively.

Reviewer's comment: This study was completed in March 2000. This large database was not included with this supplement submission. At the FDA request, preliminary data on GI and CV events were submitted in 12/21/00. The relatively short duration of the study (compared to VIGOR) is noted.

a. Serious GI events: Preliminary Results

There were 6 clinical upper GI events in the rofecoxib 25 mg group and 12 in the naproxen 1000 mg group.

Reviewer's comment: The small number of serious GI events and the relatively short duration of treatment do not allow statistical comparisons. However, this observation is consistent with the pattern seen in VIGOR.

b. Serious CV events: Preliminary results.

There were 5 myocardial infarctions (MI) in the rofecoxib 25 mg group and one MI in the naproxen 1000 mg group. Of the 5 MI in the rofecoxib group, 3 were in patients taking low dose ASA for cardiovascular prophylaxis. The patient with MI in the naproxen group was a non-ASA user.

Reviewer's comment: A trend towards an excess of MI's in the rofecoxib 25 mg group in a 12 week study is noted. This observation is consistent with the pattern seen in VIGOR.

The applicant proposes labeling that indicates [redacted]

Safety concerns have been raised based on the VIGOR study results regarding cardiovascular risks and overall relative risk associated with the use of rofecoxib compared to naproxen. These safety concerns require further investigation. A review of the safety database from the ADVANTAGE trial will allow for further global safety assessment of rofecoxib at currently labeled chronic doses and in subjects requiring cardioprotective doses of aspirin. Overall risk assessment should include review of this database before labeling changes are complete.

2.0 Safety of VIOXX in the original NDA

In addition to the new studies, this supplement refers to study 058 and 069 from the original NDA.

2.1 Study 058

Study 058 was a double-blind, randomized, placebo-controlled, 6-week study of rofecoxib 12.5 and 25 mg/day and nabumetone 1000 mg/day in elderly patients with OA. Seventy percent of patients were taking prophylactic ASA.

> *Reviwer's comment: Because of the small size and short duration, this study is inadequate to detect differences in clinically relevant adverse events between rofecoxib and nabumetone.*

2.2. Study 069

Study 069 was a pooled analysis of gastrointestinal events from all phase II and III OA studies conducted under the original NDA. The analysis compared PUB's between rofecoxib – pooled doses, despite the evidence of dose-related adverse events – and other NSAIDs (pooled data from ibuprofen 2400 mg/day, diclofenac 150 mg/day and nabumetone 1000 mg/day, each one with different risk of GI bleeding). These studies were of different duration (from 6 weeks to 86 months). Most patients were exposed for less than 6 months. Two hundred and sixty five received 50 mg QD for 6 months; the rest of the exposure to 50 mg was in acute pain studies. A total of 371 and 381 patients received 12.5 and 25 mg daily for more than one year. Of note, except for study 058 described above, all the phase II/III OA studies excluded patients taking low dose ASA.

> *Reviewer's comment: The Division has serious concerns with a combined analysis of studies of different length and dosing regimens. Furthermore, combining multiple different drugs within a single comparator arm may not be reflective of the risk of any one drug. These concerns were discussed extensively during the Advisory Committee Meeting of April 20, 1999. For a detailed review of study 069 the reader is referred to Dr. Goldkind's GI review of the original NDA 21-042.*

3.0 Post-marketing data.

Inherent limitations to the spontaneous report system are the lack of known denominator (number of patients at risk), the under-reporting of events and the multiple confounding variables. Despite these limitations, post marketing surveillance does inform in the evaluation of the safety profile of a drug. The safety profile of VIOXX is consistent with that of an NSAID.

3.1 Analyses of NSAID-related AE's

3.1.1 Reports of Gastrointestinal Bleeding.

From May 20, 1999 to October 25, 2000, thirty-seven deaths after experiencing GI bleeding, perforation or obstruction have been reported to the FDA AERS system in association with the use of rofecoxib. Risk factors for the development of serious gi bleeding with rofecoxib were the same as those for other NSAIDs: age, concomitant use of anti-platelet and anticoagulant agents and prior history of gastrointestinal bleeding.

Post-marketing surveillance does not allow adequate comparisons of frequency of serious gastrointestinal adverse events with non-selective NSAIDs but indicates that the potential for GI bleeding is still a concern.

Table 31. Summary of deaths due to GI complications reported to FDA AERS in association with the use of rofecoxib (May 1999 to October 1999).

Age in years	Mean 76, median 80, range 28 to 93
Gender	Male (14), Female (22), Unknown (1)
Year	1999 (3), 2000 (34)
Indication	Osteoarthritis (14), Acute pain (6), Unspecified arthritis (6), Other (6), Unknown (5)
Time to onset	Mean 43, median 21 (range, 0 to 131) days
Dose	At or below labeled range (24), Higher than labeled range (1), Unknown (12)
GI event	Hemorrhage (23), Perforation (7), Melena (4), Hematemesis (6), Erosions (1), Stenosis/Obstruction (1), Other (10)
Location	Gastric (13), Duodenal (5), Large intestine (2), Other (2), Unknown (15)
Pertinent PMH	Anemia (1), ASA allergy (1), sulfa allergy (1), Crohn's disease (1), CVA (1), Diabetes (1), Diverticulitis (1), Functional intestinal disorder (1), Gastrostomy (1), Previous GI bleed (1), Irritable bowel syndrome (1), Hepatic dysfunction (1), PUD (4)
Major event preceding bleed	Metastatic gastric cancer (1), Pancreatitis, hepatitis (1), Shock (1) Surgery (3)
Significant concomitant meds.	ASA (8), Clopidogril (2), Corticosteroid (2), Warfarin (6) Antacid, H2 blocker, or PPI (4)

Source: Joyce Weaver, Pharm.D., Safety Evaluator. Office of Post-marketing Drug Risk Assessment.

3.1.2 Drug interaction with coumadin.

In the original NDA, no clinically meaningful interaction with coumadin was found in normal volunteers. However, from May 20, 1999 to November 3, 1999, there were 18 post-marketing reports of concomitant use of rofecoxib and warfarin that indicated a possible drug interaction. The reported adverse events were GI hemorrhage (5), hematuria (1), hemoptysis (1), knee joint hemorrhage (1) retroperitoneal hemorrhage (1) and subdural hematoma without trauma (1) and one had significant INR/PT elevation without clinical symptoms. Eleven patients required hospitalization and the remaining required interventions. Fifteen patients discontinued VIOXX. Five patients required transfusion and seven received Vitamin K for reversal of coagulopathy. These post-marketing reports led to a modification of the VIOXX label, highlighting this potential drug interaction. (For a detailed review see Dr. Bonnel's review dated 01/10/00).

3.1.3 Renal related adverse events.

Although interstitial nephritis, papillary necrosis and acute and chronic renal failure were not observed in the original NDA database, some cases were reported within a few months of post-marketing surveillance. From May 1999 to October 2000, 142 unduplicated cases of renal failure were reported to the FDA AERS database. The patients were predominantly female and the average age was 73 years (range = 33 – 101 years). The dose of Vioxx was reported in 103 cases and fell within the recommended range of 12.5 to 50 mg once daily. The onset of adverse renal symptoms was reported in 100 cases and occurred at an average of approximately 33 days after the initiation of Vioxx; however, the median was 10 days. Thirty-two cases reported an onset of less than or equal to 3 days, including 14 cases at the 25 mg/day dose and 4 cases at the 12.5 mg/day dose. Nearly 70% of the cases required hospitalization and 15% reported the need for dialysis. Death attributed to Vioxx-initiated renal failure occurred in 6%. (For a detailed review see OPDRA report dated 2/14/2001).

3.1.5 Hematological events

From May 1999 to June 8, 2000 there were 89 unduplicated cases of hematological events. Of those, 31 showed a temporal relationship with rofecoxib use, including pancytopenia (4), agranulocytosis (5), leukopenia (5), thrombocytopenia (13), hemolytic anemia (3) and thrombocythemia (1). Most patients were female with an average age of 67 years. The median onset of events was 13 days. Nineteen reported positive dechallenge and three reported negative dechallenge on discontinuation of rofecoxib. Thirteen cases were potentially confounded by the presence of other medications with hematologic adverse events in their product labeling.

Cases involving thrombocytopenia provided detailed clinical information, good temporal associations, positive dechallenge information, and bone marrow biopsy evidence (4) to establish an association with rofecoxib use. The cases involving agranulocytosis, leukopenia, thrombocythemia, pancytopenia, and hemolytic anemia either lacked

sufficient clinical information, were small in number, or were confounded by the presence of co-suspect medications (methotrexate, gold, sulfasalazine, dipyrone, and allopurinol) which made it difficult to establish a clear role of rofecoxib as a causative agent. (For a detailed review the reader is referred to Dr. Bonnel's review dated 8/9/00).

3.1.6 Potential for anaphylactoid reactions.

From May to November, 1999 there were 46 immune system reports possibly associated with rofecoxib use. The severity of reactions varied and manifested as a generalized rash, swelling, urticaria, angioedema, dyspnea, or anaphylactoid reaction. Eight patients reported a history of "sulfa" allergies and one patient had an aspirin allergy. The majority of reactions was idiosyncratic and not related to triad allergy as warned in the labeling.

3.2. Additional post-marketing analyses: Cardiovascular events

Because of the increased incidence of cardiovascular thrombotic events found in the VIGOR study, an analysis of cardiovascular thrombotic events reported to the FDA AERS system was conducted by the Division of Drug Risk Evaluation . Postmarketing surveillance indicated a low incidence of spontaneous reports of thrombotic cardiovascular adverse experiences, with a reporting rate comparable to that observed in postmarketing surveillance of other non-cardiovascular drugs. While post-marketing surveillance is very helpful in detecting signals for uncommon events it is inadequate for assessing common events. Under-reporting may be a particularly relevant limitation in this case, because a few physicians would report to the FDA a myocardial infarction in an elderly patient.

In summary, Post-marketing surveillance indicates that the organ toxicities associated with rofecoxib are similar to other NSAIDs. Relative rates can not be estimated from post-marketing data.

III. Conclusions

1. GI safety

1. The sponsor demonstrated a statistically significant reduction in PUBs and complicated PUB's, associated with the use of rofecoxib compared to naproxen in this population of patients not considered by their physicians to have an indication for cardiovascular prophylaxis with low dose ASA.

   The cumulative incidence of PUB's was 1.8% and 3.9% (median exposure of 9 months) for rofecoxib and naproxen, respectively. Of note, this cumulative rate is very close to the 2 – 4% rate presented in the WARNING section of the NSAID template for patients treated for one year. The cumulative incidence of ***complicated*** **PUB's was 0.5 % and 1.2 %** in the rofecoxib and naproxen groups, respectively.

   The target population for anti-inflammatory drugs includes a substantial number of patients who will need low dose ASA for cardiovascular prophylaxis. Adequate data on the safety of the chronic co-use of rofecoxib and low dose ASA do not exist. Studies that allowed the concomitant use of rofecoxib and low dose ASA were of short duration and not powered to detect differences in serious GI and CV events. Therefore, the exclusion of patients using low dose ASA is a serious limitation to the generalizability of the findings of the VIGOR study.

   Different NSAIDs are associated with different risk of developing serious GI events. The only non-selective NSAID comparator included in this study was naproxen. Therefore, claims of GI superiority could be only be made in comparison to naproxen, not to all NSAIDs.

2. The post-marketing safety profile of rofecoxib is similar to other NSAIDs, including the risk of GI bleeding. From May 1999 to October 2000, the FDA post-marketing AER system received 37 unduplicated reports of death due to gastrointestinal complications associated with the use of rofecoxib. Despite a substantial risk reduction compared to naproxen in the VIGOR study, the risk of serious GI complications associated with rofecoxib is still a concern. Risk factors associated with serious GI complications are similar to those associated with conventional NSAIDs: age, prior history of ulcer disease, concomitant use of ASA, coumadin or other antiplatelet agents, and corticosteroids.

3. Data provided by the sponsor do not support removal of [redacted] from the VIOXX label.

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2. Cardiovascular safety

1. **The cumulative rate for serious CV/thrombotic events was 1.8% (n= 45) and 0.6% (n= 19)** in the rofecoxib and naproxen groups respectively over the 9-month period. The relative risk of developing serious CV/thrombotic events was more than twice in the rofecoxib group as compared to the naproxen group (RR= 2.37; 95% C.I 1.39, 4.06; p= 0.0016, based on risk per 100 patient years). The difference was mainly due to the difference in the number of myocardial infarction (MI): 20 in rofecoxib and 4 in naproxen (crude rate 0.5 % and 0.1% for rofecoxib and naproxen, respectively) (RR= 5.0; 95% C.I. 1.72, 14.3, based on risk per 100 patient years).

   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 was 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).

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 studies 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 new 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.

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.

IV. Recommendations for Regulatory Action: Approvable.

In order to adequately interpret the cardiovascular and overall safety results in the VIGOR study and provide adequate labeling information, review of the complete report of study 102 (ADVANTAGE) is necessary.

The applicant should be informed that labeling changes cannot be made until review of safety database from the ADVANTAGE study is complete.

Additional recommendations.

1. The [redacted] should not be removed from the VIOXX label. GI safety findings from this study should be included under the "Clinical Studies" section of the VIOXX label.

2. Information regarding pre-specified non-GI NSAID-associated adverse events should be displayed in the VIOOXX label.

3. Clinically relevant overall safety results (serious adverse events, discontinuations due to adverse events and deaths) observed in the VIGOR study should be included in the VIOXX label.

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Appendix 1. Financial Disclosure

Forms 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and 3455 (Disclosure of Financial Interest and Arrangements of Clinical Investigators) were signed by Richard N. Kender, Vice President, Financial Eval. & Analysis/Business Development, for Merck & Co., Inc.

Studies considered "covered studies" included: 088c (088 and 089), 085 and 090.

For study 088 the First Patient In (FPI) was January 14, 1999 and the Last Patient Out (LPO) was March 17, 2000. For study 089 the First Patient In (FPI) was January 15, 1999 and the Last Patient Out (LPO) was March 09, 2000. The cut-off date for financial information provided by the investigators was April 07, 2000. In compliance with the Financial Disclosure requirements, "significant payments of other sorts" information has been reviewed for the time period of February 02, 1999 through January 31, 2000 and included as appropriate.

On 6/29/00 the sponsor provided:

1. A list of investigators/subinvestigators who participated in study 088 and 089 (approximately 1400).
2. A list of investigators/subinvestigators who were certified by Merck & Co, Inc. regarding the absence of financial arrangements as defined in 21CRF 54.2 (approximately 1000)
3. A list of investigators/subinvestigators who did not provide financial information by cut-off date (approximately 400).
4. A list of investigators/subinvestigators who met the disclosure criteria regarding financial interests as defined in 21 CFR 54.2 because of equity interest in Merck [redacted] or payments of other sort [redacted] investigators).

On 10/6/2000 the sponsor provided financial information for protocols 085 and 090. For protocol 085 the first patient was enrolled in September 1998 and the last patient out was March 2, 1999. Financial information was reviewed from February 2, 1999 through March 2, 2000. For protocol 090 the first patient was enrolled October 20, 1998 and the last patient out was May 17, 1999. Financial information was reviewed from February 02, 1999 through May 17, 2000. For both protocols the cut-of date for the investigators to provide financial information was September 1, 2000.

The 10/6/00 submission included:

1. A list of investigators/subinvestigators who participated in studies 085 and 090 (approximately 1,500).
2. A list of investigators/subinvestigators who were certified by Merck & Co, Inc. regarding the absence of financial arrangements as defined in 21CRF 54.2 (approximately 1000)
3. A list of investigators/subinvestigators who did not provide financial information by cut-off date (approximately 600).
4. A list of investigators/subinvestigators who met the disclosure criteria regarding financial interests as defined in 21 CFR 54.2 because of equity interest in Merck [redacted] or payments of other sort [redacted] investigators from study 085 and 39 from study 090).

The 10/6/00 submission also included:

5. A list of investigators/subinvestigators from studies 088 and 089 identified after the original cut-off date of April 7, 2000 and through June 29, 2000 (approximately 90)
6. A list of investigators/subinvestigators identified after the cut-off date, who are certified by Merck regarding the absence of financial arrangements as defined in 21 CFR 54.2. (approximately 90)
7. A list of investigators/subinvestigators who did not provided financial information by cut-off date (only one)
8. A list of investigators/subinvestigators from studies 088 and 090 who met the disclosure criteria regarding financial interests as defined in 21 CFR 54.2 because of equity interest in Merck or payments of other sort — investigators).

Forms 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and 3455 (Disclosure of Financial Interest and Arrangements of Clinical Investigators) were signed by Richard N. Kender, Vice President, Financial Eval. & Analysis/Business Development, for Merck & Co., Inc. Approximately 1000 investigators/subinvestigators failed to provide financial disclosure information.

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Appendix 2. DEATHS in the VIGOR study.

Deaths on Rofecoxib 50 mg/day

1. Patient Allocation No.: 00324/088 **Therapy Start Date:** 31-Mar-1999 **Therapy Stop Date:** 20-Sep-1999 . **Serious Adverse Event (SAE):** Ventricular Fibrillation

This is a 69 year-old male with a history of RA, hypertension (HTN), knee prosthesis placement, purpura, and pedal edema. Concomitant medications included methotrexate (MTX), hydrochlorothiazide (HCTZ) and doxazosin. On rel day 174, the patient collapsed without apparent premonitory symptoms. Paramedics found the patient to be in ventricular fibrillation, and attempts to defibrillate were unsuccessful. The patient was in asystole upon arrival at the emergency room, where further attempts to resuscitate were unsuccessful and the patient expired. The investigator rated the ventricular fibrillation to be probably not related to rofecoxib.

2. Patient Allocation No.: 00229/088 **Therapy Start Date:** 15-Mar-1999 **Therapy Stop Date:** 26-Jun-1999 **(SAE):** Adult Respiratory Distress Syndrome

This is a 71 year-old female with a history of RA, HTN, rheumatoid lung, pulmonary fibrosis and pneumonitis. Concomitant medications included prednisone, felodipine, metoprolol, MTX, folic acid, acetaminophen, hydroxychloroquine (HCQ), and potassium. On rel day 50, the patient was hospitalized for a worsening of her interstitial lung disease. A bronchoscopy and transbronchial lung biopsy were both non-diagnostic. The patient was discharged on rel day 63. On rel day 132, the patient developed increasing dyspnea and was hospitalized. At admission, the patient was afebrile, with no sputum production, or pleuritic pain. However, the patient was noted to be markedly hypoxemic with a PO2 of 26 mmHg on room air. A chest x-ray revealed increasing bilateral infiltrates, that was diagnosed as adult respiratory disease. A chest x-ray indicated a progressive increase in right upper lobe infiltrate and left perihilar infiltrate, possibly secondary to infection. On rel day 138, the patient expired due to adult respiratory distress syndrome (ARDS). The investigator assessed the adult respiratory distress syndrome as not related to rofecoxib.

3. Patient Allocation No.: 00731/088 **Therapy Start Date:** 17-Mar-1999 **Therapy Stop Date:** 24-Nov-1999 **(SAE):** Pneumonia

This is a 77 year-old female with a history of RA, pulmonary fibrosis, osteoporosis. Screening lab results included: hemoglobin (Hgb) 14.0g/dL and hematocrit (Hct) 41.8. Concomitant medications included MTX, folic acid, calcium carbonate/vitamin D and fluticasone. On rel day 254, she presented to the emergency room with an increasing non-productive cough, dyspnea, mild pleural chest discomfort, lightheadedness, and general malaise. On physical exam she was afebrile; lungs had diffuse rales, rubs, and a few sonorous rhonchi. Blood pressure was 98/57 mmHg. An ECG showed sinus tachycardia at 114 bpm and a Q in AVF. Chest x-ray revealed scattered diffuse infiltrates. O2 saturation was in the low 80's. She was admitted to the hospital with the initial impression of pneumonia and secondary hypoxia. Laboratory showed a positive IgM mycoplasma antibody and an hematocrit of 37%. On approximately rel day 257, as the patient's condition deteriorated, her erythromycin was stopped and ofloxacin, IV steroids, and heparin were started. On rel day 266, labs showed Hgb of 9.8 g/dl, and Hct of 31.5%. Her platelet count was 98,000 per cumm. The patient also had an episode of melena. GI work-up was not pursued. The patient's condition continued to decline. She expired on rel day 269. An autopsy was not conducted. The investigator rated the pneumonia to be probably not related to rofecoxib.

4. Patient Allocation No.: 02560/088 **Therapy Start Date:** 27-May-1999 **Therapy Stop Date:** 23-Jun-1999 **SAE:** 1) Hemorrhagic Duodenal Ulcer, 2) Pneumonia, 3) Septic Shock

This is a 78 year-old male with a history of RA, hemorrhagic gastric ulcer (1995), mild COPD, hypertension, osteoporosis, asthma. Baseline lab results included: hemoglobin (Hgb) 12.7 mg/dL, hematocrit (Hct) 38%, BUN 38 mg/dl, and serum creatinine 1.5mg/dl. Concomitant medications included

MTX (suspect secondary therapy), diltiazem, HCTZ, irbesartan and calcitonin nasal spray. The patient was hospitalized for pneumonia from rel day 17 to rel day 22. He restarted rofecoxib on relative day 23.

On rel day 28, the patient notified the site of one episode of vomiting dark brown liquid, taking ranitidine for abdominal pain. The patient was seen at the site on rel day 29. A digital rectal exam revealed dark brown stool with a small amount of red material present. The patient had some dizziness with postural changes, but vital signs were within normal limits. Patient was treated with omeprazole and ferrous gluconate. Labs showed Hgb of 8.7 g/dl, Hct of 25.6% and platelet count of 355,000 per cumm. An outpatient endoscopy on rel day 30 revealed a large duodenal ulcer and severe esophagitis. *H.Pylori* results were negative, and the stool was positive for occult blood. On rel day 31, the patient awakened to go to the bathroom and fell to the floor. The patient was brought to the emergency room where he passed two brown/red colored stools. The patient received three units of packed red blood cells. On rel day 34, the patient was taken to the operating room for an oversew of a bleeding, penetrating duodenal ulcer, a pyloroplasty, and a truncal vagotomy.
Post-operatively, on rel day 37, patient was readmitted to the surgical intensive care unit because of a "recurrence of pneumonia". On rel day 41, the patient developed septic shock and renal failure and was placed on a ventilator. Patient expired on rel day 43. An autopsy was not performed. The primary cause of death was septic shock as a complication of pneumonia. The investigator rated the two incidences of pneumonia and septic shock to be definitely not related to study drug. The investigator rated the hemorrhagic duodenal ulcer to be probably related rofecoxib or to methotrexate.

> *(It appears to this reviewer that rather than recurrence of a pneumonia that had been resolved five days before the episode of gastrointestinal bleeding, the patient may have had nosocomial adquired pneumonia as a post-operative complication)*

5. Patient Allocation No.: 02662 / 088 **Therapy Start Date:** 20-Apr-1999 **Therapy Stop Date:** 15-May-1999 **SAEs** 1.) Perforating Hemorrhagic Gastric Ulcer, 2.) Subphrenic Abscess, 3.) Septic Shock

This is a 62 year-old female with a history of RA, COPD, chronic headaches, ecchymosis, and fatigue, who smokes up to 12 cigarettes per day. Concomitant medications included injectable gold preparation, prednisone and a multi-vitamin. On rel day 26 the patient presented at the emergency room with dyspnea and severe abdominal pain, nausea and diarrhea, plus fever and dehydration and appeared very pale. Rofecoxib was discontinued. The patient was admitted to the hospital with a blood pressure of 142/75 with tachycardia (170 bpm). Chest exam revealed diffuse wheezing on both sides. A chest X-ray revealed possible pulmonary congestion. An abdominal x-ray showed some air fluid levels with no obvious sign of obstruction. The patient's hemoglobin was 13.0 g/dl and her WBC count was 22.0 thou/mcl. She was treated with IV ciprofloxin, and bronchodilators. The patient was transferred to the ICU: heart rate 180 bpm, ECG demonstrated atrial, and was treated with digoxin and procainamide. On rel day 34, a CT scan showed subphrenic abscess and a gastric perforation and the patient underwent a partial gastrectomy. On rel day 40 the patient was discharged from the hospital.
On rel day 45 the patient reported to the emergency room lethargic, unable to answer questions, hypothermic, pale with cool dry skin and her extremities were mottled. The patient experienced ventricular fibrillation and died. The investigator rated the hemorrhagic perforated gastric ulcer to be probably related to rofecoxib, the septic shock to be definitely related to rofecoxib, and the subphrenic abscess to be definitely related to rofecoxib.

6. Patient Allocation No.: 01224 /088 **Therapy Start Date:** 22-Mar-1999 **Therapy Stop Date:** 01-May-1999 **SAEs:** 1) Acute Myocardial Infarction, 2) Multiple Organ Failure.

This is a 68 year old female with a history of RA, gout, osteoporosis, 30-40 year one pack a day smoking history. Concomitant medications included gold, prednisone, and raloxifene. On rel day 26 the patient experienced loose stools intermittently for two weeks. On rel day 37 she began to experience intermittent chest distress described as epigastric and mid-sternal burning beginning on rel day 37. On rel day 38, the patient developed a feeling of indigestion, and nausea. On rel day 40 the patient's heartburn worsened and she experienced pain and tingling in her left shoulder. Treatment included famotidine, aluminum hydroxide/magnesium hydroxide and loperamide hydrochloride. On rel day 41 the patient presented to the

emergency room with shoulder pain, left arm tingling, and chest distress. Findings were consistent with a non Q wave myocardial infarction. Rofecoxib was discontinued. Treatment included IV heparin and aspirin. On rel day 46 the patient underwent mitral valve replacement, tricuspid valve repair, and 4-vessel coronary artery bypass. The patient also underwent drainage of bilateral pleural effusions with bilateral tube thoracostomies. Postoperatively, the patient developed marginal cardiac output , progressive renal insufficiency, upper gastrointestinal bleeding, fever and leukocytosis. The patient's Hgb of 11.0 g/dl and Hct of 31.9% (on rel day 49) decreased to a Hgb of 9.1 g/dl and Hct of 25.9% by rel day 52. The patient's cardiac function continued to deteriorate and on rel day 52 the patient died due to cardiac failure and subsequent multi-organ dysfunction. The investigator rated the acute myocardial infarction and multiple organ failure resulting in death to be definitely not related to rofecoxib.

7. Patient Allocation No.: 00920 /088 **Therapy Start Date:** 05-Mar-1999 **Therapy Stop Date:** 25-Sep-1999 **SAE:** 1.) Complete heart block), 3.) Cerebrovascular Accident (with anoxic encephalopathy)

This is 68 year-old female with a history of RA, osteoporosis, HTN, hypercholesterolemia, and peptic ulcer. Concomitant medications included potassium, simvastatin, HCTZ, acetaminophen/propoxyphene napsylate, folic acid, MTX, prednisone, ranitidine, and alendronate sodium. On rel day 182 patient underwent surgical procedure for patellar fracture of the left knee. On rel day 184, the patient was discharged from the hospital and resumed rofecoxib. On rel day 205 the patient presented at the emergency room with cardiac arrest, which was presumed to be a bradyarrythmic arrest due to complete heart block. The patient was resuscitated, intubated, and received pressor support. That same day the patient was admitted to the hospital and rofecoxib was discontinued. A coronary angiogram on rel day 205 showed no coronary disease, and left ventricular function was preserved overall. A pulmonary angiogram performed that same day showed no evidence of pulmonary emboli. On rel day 206, a CT scan of the head showed progressive evidence of infarction; decorticate and decerebrate posturing were noted.. An electroencephalogram on rel day 208 showed minimal activity while the patient's neurological condition declined. On rel day 209, life support was withdrawn and the patient died. The suspected cause of death was complete heart block with underlying left bundle branch block, and hypoxia with hypoxic encephalopathy. The investigator rated the third degree atrioventricular block, cerebrovascular accident and patellar fracture to be definitely not related to rofecoxib.

8. Patient Allocation No.: 02759 /088 **Therapy Start Date:** 19-May-1999 **Therapy Stop Date:** 19-Aug-1999 **Adverse Event(s):** Myocardial Infarction

This is a 70 year-old male with a history of RA, hypercholesterolemia, and BPH and a family history of coronary artery disease. Concomitant medications included simvastatin and acetaminophen. On rel day 93, the patient experienced chest discomfort, further described as mild chest pain and took his last dose of rofecoxib. On rel day 94, the patient was found dead. The probable cause death was considered to be a myocardial infarction. The death certificate indicated that the immediate cause of death was arteriosclerotic cardiovascular disease. The investigator assessed the myocardial infarction as not resolved, and life threatening. The investigator rated the myocardial infarction to be definitely not related to rofecoxib.

9. Patient Allocation No.: 05687 /089 **Therapy Start Date:** 31-Mar-1999 **Therapy Stop Date:** 03-Jan-2000 **SAE(s):** 1.) Gastric Obstruction, 2.) Hemorrhagic Gastric Ulcer, 3.) Gastric Neoplasm.

This is a 53 year old male with a history of RA, dyspepsia and urolithiasis. Concomitant medication included prednisone, methotrexate, ranitidine, diclofenac sodium and chloroquine. As of rel day 258 the patient complained of persistent vomiting which was considered a symptom of gastric outlet obstruction. On rel day 273 the results of a physical examination were normal and the patient denied any pain. On rel day 279 an endoscopy revealed a large gastric ulcer (3 x 2 cm) with evidence of recent bleeding (no active bleeding was seen) and a large pyloric deformity causing a gastric outlet obstruction. The results of all laboratory tests were unremarkable and testing for *H. Pylori* was negative. On rel day 279 rofecoxib and all concomitant medications were discontinued. New treatment with omeprazol was initiated. On rel day 281 the patient was hospitalized. A second endoscopy was performed on rel day 282 and a gastric biopsy was obtained. The results of the endoscopy revealed no signs of bleeding. The results of the biopsy showed a moderately differentiated adenocarcinoma that was diagnosed as a gastric neoplasm. Laboratory testing, on

admission, revealed a depressed hematocrit of 31.3% and hemoglobin of 9.9 g/dl. An enteral tube for nutrition was inserted and the patient was discharged on rel day 283. On rel day 373 the patient died. The cause of death was attributed to the gastric neoplasm. The investigator rated the hemorrhagic gastric ulcer and the gastric outlet obstruction as disabling unresolved and probably related to the rofecoxib, and the gastric neoplasm as probably not related to rofecoxib.

10. Patient Allocation No.: 07285 /089 **Therapy Start Date:** 19-Apr-1999 **Therapy Stop Date:** 30-Jun-1999 **SAE:** Pneumonia.

This is a 71 year-old male with a history of RA. Concomitant medication included prednisone, MTX, and acetaminophen. On rel day 69, the patient complained of mild to moderate dyspnea. On rel day 71, a chest x-ray revealed acute bronchitis. Treatment included theophylline and trovafloxacin. On rel day 73, rofecoxib was discontinued. On rel day 75, the patient presented to the emergency room complaining of a worsening of the dyspnea. A chest x-ray revealed bilateral, severe pneumonia. On rel day 76, the patient was transferred to the intensive care unit where he expired. The investigator assessed the pneumonia as life threatening. The investigator rated the pneumonia to be probably not related to rofecoxib.

11. Patient Allocation No.: 08104 /089 **Therapy Start Date:** 07-May-1999 **Therapy Stop Date:** 14-Aug-1999 **SAE:** Acute Gastrointestinal Hemorrhage

This is a 57 year old male with a history of RA and LVH. Concomitant medication included prednisone. On rel day 101, the investigator was informed by patient's family that the patient was found dead at home. The investigator confirmed that there was evidence of gastrointestinal hemorrhage, prior to death. No autopsy was performed, as patient's family refused. The cause of death was recorded as acute gastrointestinal hemorrhage. The investigator felt that the acute gastrointestinal hemorrhage was possibly related to rofecoxib.

12. Patient Allocation No.: 05305 /089 **Therapy Start Date:** 15-Mar-1999 **Therapy Stop Date:** 16-Jan-2000 **SAE (s):** Cardiac Arrest

This is a 76 year-old female with a history of RA, and Sjogren's syndrome, anxiety, hypertension, pulmonary fibrosis, and posterolateral chronic myocardial ischemia. Concomitant medications included MTX, prednisone, alendronate sodium, calcium carbonate, folic acid, nifedipine, albuterol, beclomethasone and alprazolam. On rel day 309, the patient died at home. A family physician certified the death. The cause death was cardiopulmonary arrest. The investigator rated the cardiac arrest to be definitely not related to rofecoxib. *(I would classify this death as sudden death)*

13. Patient Allocation No.: 05316 /089 **Therapy Start Date:** 25-Mar-1999 **Therapy Stop Date:** 25-Jun-1999 **SAE(s):** 1.) Interstitial Lung Disease, 2.) Respiratory Failure

This is an 80 year-old male with a history of RA, BPH, gastritis, interstitial lung disease, tachyarrhythmia, and hypercholesterolemia. Concomitant medications included calcium carbonate, chloroquine, methotrexate, prednisone, and acetaminophen. On rel day 90, the patient experienced upper respiratory infection. On rel day 94, the patient was hospitalized due to acute respiratory insufficiency related to interstitial lung disease, and rofecoxib was discontinued. Treatment included antibiotics, prednisone and theophylline. On rel day 97, arterial blood gases included a PO2 of 49.2 mmHg and an O2 saturation of 86%. On rel day 104, the patient experienced tachyarrhythmia and oliguria. On rel day 105, lab values included a WBC of 24,300 thou/dL. The patient's respiratory condition progressively worsened, and the patient went into respiratory arrest. The patient did not recover from the interstitial lung disease and died on rel day 114. The cause of death was respiratory arrest due to interstitial lung disease. The investigator rated the interstitial lung disease to be probably not related to rofecoxib.

14. Patient Allocation No.: 08021 /089 **Therapy Start Date:** 07-May-1999 **Therapy Stop Date:** 18-Feb-2000 **(SAE):** 1.) Hip Fracture, 2.) Nosocomial Acquired Pneumonia, 3.) Respiratory Failure

This is a 84 year old female with a history of RA, HTN, Sjogren's syndrome, interstitial lung disease, osteoporosis, vertebral osteoarthrosis, myocardial infarction and anemia. Concomitant medications included methotrexate, prednisone, alendronate sodium, calcium carbonate, dextran 70, acetaminophen and losartan potassium. On rel day 289, the patient was hospitalized with a hip fracture and study therapy was discontinued. On rel day 292 a hip arthroplasty was performed . On rel day 294 the patient developed a nosocomial acquired pneumonia. On rel day 302 the patient died. The investigator listed the cause of death as respiratory arrest. The investigator assessed the nosocomial acquired pneumonia as life threatening and prolonged the patient's hospitalization. The investigator rated the hip fracture, nosocomial acquired pneumonia and respiratory arrest as not related to rofecoxib.

15. Patient Allocation No.: 05591/ 089 **Therapy Start Date:** 31-Mar-1999 **Therapy Stop Date:** 22-Oct-1999 **SAE:** Cerebrovascular Accident

This is a 52 year-old female with a history of RA, HTN, epigastric pain, and hematuria. Concomitant medications included chloroquine, methyldopa, and prednisone. On rel day 206, a computerized axial tomography of the head revealed the patient experienced a cerebrovascular accident, and rofecoxib was discontinued. This same day, physical examination showed the patient was experiencing bilateral mydriasis, and the patient was hospitalized. On rel day 208, the patient died. The cause of death was cerebrovascular accident. The investigator rated the cerebrovascular accident to be not related to rofecoxib.

16. Patient Allocation No.: 07620 / 089 **Therapy Start Date:** 04-May-1999 **Therapy Stop Date:** 03-Jun-1999 **SAE:** Dissecting Aortic Aneurysm

This is a 55 year-old female, with a history of RA, myocardial infarction, dyspepsia, and hypertension. Concomitant medications included chloroquine, hydrochlorothiazide, methotrexate, methyldopa, and prednisone. On rel day 31, the patient was admitted to the hospital. The patient had begun experiencing low back pain that same day, and received diclofenac sodium, dipyrone, and meperidine hydrochloride. Study therapy was discontinued on rel day 31. The patient died the same day. An autopsy was performed on rel day 32, and death was attributed to dissecting aortic aneurysm. The investigator rated the dissecting aortic aneurysm to be definitely not related to rofecoxib.

17. Patient Allocation No.: 06103 089 **Therapy Start Date:** 12-Mar-1999 **Therapy Stop Date:** 02-Jan-2000 **SAE:** Worsening of RA

This is a 65 year old female with a history of RA, interstitial pneumonitis, sinus bradycardia, ventricular dysfunction and hypereosinophilia. Concomitant medications included HCQ, prednisone and cisapride monohydrate. On rel day 152, the patient began to experience worsening of rheumatoid arthritis characterized mainly by worsening of the interstitial pneumonitis. On rel day 291 the patient complained of worsening of rheumatoid arthritis which was characterized by worsening of the interstitial pneumonitis, pulmonary fibrosis, pericarditis, vasculitis (with mild polyneuropathy of lower limbs and finger skin sclerosis) and an exacerbation of dry cough and dypsnea. On rel day 300 the patient was hospitalized and rofecoxib was discontinued. Hypoxemia was confirmed. On rel day 301 a thoracic CT scan confirmed interstitial pneumonitis and revealed pericardial effusion. On rel day 308 the patient was in a stable condition and discharged with oxygen. On rel day 340 the patient was re-hospitalized for worsening of symptoms of RA which had not resolved from the previous hospitalization. On rel day 341 the pulmonologist confirmed that the patient was in a terminal state. The patient died on rel day 344. The cause of death was due to worsening of rheumatoid arthritis. The investigator felt that the worsening of the rheumatoid arthritis was definitely not related to rofecoxib.

18. Patient Allocation No.: 07461 /089 **Therapy Start Date:** 20-Apr-1999 **Therapy Stop Date:** 17-May-1999 **Serious Adverse Event(s) (SAE):** 1.) Bacterial Sepsis, 2.) Pulmonary Superinfection

This is a 56 year-old female with a history of RA, HTN, epigastric pain, gammopathy, pulmonary anomaly and edema. Concomitant medications included calcium carbonate, methotrexate, amitriptyline, chlorthalidone, ferrous sulfate, chlorpromazine, nifedipine. On rel day 21, the patient complained of a

cough. On rel day 22, a chest x-ray revealed a pulmonary infection. On rel day 25, the patient was hospitalized for evaluation and treatment. On rel day 28, the patient was intubated, and study therapy was interrupted. Treatment included rifampin, isoniazid, and pyrazinamide. On rel day 37, the patient's condition worsened and she experienced septic shock. On rel day 47, the patient died. The investigator rated the pulmonary superinfection and bacterial sepsis to be not related to rofecoxib.

19. Patient Allocation No.: 07973 /089 **Therapy Start Date:** 21-May-1999 **Therapy Stop Date:** 13-Oct-1999 **SAE:** Myocardial Infarction

This is a 71 year-old male with a history of RA, asthma, anxiety, and insomnia. Concomitant medications included acetaminophen, methotrexate, salmeterol, fluticasone, and trimipramine. On rel day 147, the patient was found dead in his home. An autopsy was performed on rel day 153 revealed a large thrombus in the left anterior descending artery and coronary sclerosis. The cause of death was acute myocardial infarction. The investigator assessed the myocardial infarction as life threatening. The investigator rated the myocardial infarction to be definitely not related to rofecoxib.

20. Patient Allocation No.: 07553 /089 **Therapy Start Date:** 26-Apr-1999 **Therapy Stop Date:** 22-May-1999 **Serious Adverse Event(s) (SAE):** Congestive Heart Failure

This is a 51 year-old female with a history of RA, anxiety disorder, and varicose vein. Concomitant medications included bromazepam, and deflazacort. On rel day 27, the patient presented to the emergency room complaining of diarrhea since rel day 19. This same day, rofecoxib was discontinued. Treatment included IV fluids for dehydration. She was discharged from the emergency room, this same day. On rel day 28, the patient called the investigator, complaining of arthralgia. She presented to the emergency room that evening with dyspnea and cyanosis. Treatment included aminophylline, and lanatoside C. This same day, the patient died. The cause of death was cardiac insufficiency. The investigator assessed the congestive heart failure as life threatening. The investigator rated the congestive heart failure and death to be probably not related to rofecoxib.

21. Patient Allocation No.: 10078 089 **Therapy Start Date:** 08-Jun-1999 **Therapy Stop Date:** 05-Oct-1999 **Adverse Event(s) :** 1. Aplastic Anemia), 2.) Pneumonia, 3.) Bacterial Sepsis

This is a 54 year-old female with a history of RA, and urinary tract infection. Concomitant medications included prednisone and MTX.On rel day 120, the patient experienced weakness of the left arm, and was hospitalized, and rofecoxib was discontinued. A computed axial tomography of the head showed a hyperdense area, suggestive of a tumor. On rel day 129, an endoscopy revealed mild erosive esophagitis, hiatal hernia, and a healed duodenal ulcer which was judged by the investigator to be not clinically significant. On rel day 130, the patient had a fever, and pulmonary symptoms consistent with pneumonia. On rel day 131, a chest x-ray showed pulmonary infiltration. On rel day 133, a bone marrow biopsy confirmed aplastic anemia. On that same day, bacterial sepsis was also diagnosed. On rel day 134, cephalosporin C, ceftazidime pentahydrate, folinic acid, and metronidazole were administered. On rel day 136, the patient's level of consciousness and respiratory rate decreased. On rel day 137, the patient experienced septic shock; and expired. The primary cause of death was pneumonia, and the secondary cause was bacterial sepsis. The investigator assessed the pneumonia, aplastic anemia, and bacterial sepsis to be disabling. The investigator rated the pneumonia, aplastic anemia, bacterial sepsis, and brain neoplasm to be not related to rofecoxib.

22. Patient Allocation No.: 07689 089 **Therapy Start Date:** 26-Apr-1999 **Therapy Stop Date:** 09-Aug-1999 **SAE:** "Aortic Valve Stenosis" . This is a 60 year-old female with a history of RA, diabetes mellitus, and hypertension. Concomitant medications included enalapril maleate, glyburide, methotrexate, and prednisone. On rel day 107, the patient died suddenly at home. The coroner reported that the patient had cardiac hypertrophy and pulmonary congestion. The cause of death was idiopathic hypertrophic subaortic stenosis The investigator rated the aortic valve stenosis to be definitely not related to rofecoxib.

(There is no evidence of aortic valve stenosis. This death will be considered as sudden death)

Deaths on Naproxen 1000 mg/day

1. Patient Allocation No.: 02923 088 **Therapy Start Date:** 17-May-1999 **Therapy Stop Date:** 27-Oct-1999 **Adverse Event(s):** 1.) Cerebrovascular Accident; 2.) Acute Myocardial Infarction; 3.) Respiratory Failure; 4.) Shock; 5.) Arterial Thrombosis

This is a 60 year-old male with a history of RA, HTN, duodenal ulcer, cardiac catheterization, angiography, and carotid endarterectomy. The patient also had a history of smoking. Concomitant medications included methylprednisone, MTX, and nifedipine. On rel day 164 the patient was discovered by his spouse to be unresponsive. The patient was rushed to a local hospital where upon arrival his BP was 233/97 mmHg. He was alert and oriented, but did have right hemiparesis. An electrocardiogram (ECG) showed a wandering baseline, but was otherwise unremarkable compared to his baseline ECG. A computed axial tomography (CT) scan of the head revealed moderate atrophy, but was otherwise normal. The impression was that the patient had a massive left hemispheric acute cerebrovascular accident. On rel day 165, the patient developed respiratory failure, was intubated and airlifted to another hospital. Upon arrival, he was in a comatose state. He became hypotensive at 80/50 mmHg, and it was noted that his skin was mottled from the waist down. Lab values on rel day 165 included a CPK-MB of 186.2 g/ml, and a troponin of 0.06 ng/ml. Chest x-ray done on rel day 165 was normal. A non-contrast CT scan of the brain conducted at the new hospital on rel day 165 confirmed a left middle cerebral artery cerebrovascular accident, with no evidence of midline shift. A CT scan of the chest conducted on rel day 165 revealed a 2 cm filling defect in the left ventricle consistent with a clot. That same day, a CT scan of the abdomen and pelvis showed a distal aortic thrombosis. Lower and upper extremities were mottled and pallored with no palpable pulses. He rapidly continued decline in cardiopulmonary status. The family requested that no resuscitation be offered and the patient expired. The cause of death was felt to be a massive stroke, respiratory failure, acute myocardial infarction, an acute thromboembolism, and shock. The investigator rated the cerebrovascular accident, respiratory failure, acute myocardial infarction, arterial thrombosis, and shock to be definitely not related to naproxen.

2. Patient Allocation No.: 00815 088 **Therapy Start Date:** 11-May-1999 **Therapy Stop Date:** 13-Oct-1999 **Adverse Event(s) :** Metastatic carcinoma of unknown primary.

This is a 72 year-old male with a history of RA, HTN, lymphoma, and malignant skin neoplasm. Concomitant medications included MTX, folic acid, captopril, HCQ and prednisone. On rel day 133, the patient began to experience right upper quadrant pain, vomiting, and symptoms suggestive of gastroesophageal reflux disease (GERD). On rel day 156, he continued to have ongoing gastrointestinal upset, vomiting, and right upper quadrant tenderness and was seen by the investigator. The patient experienced a ten-pound weight loss since rel day 122. On rel day 156, naproxen was discontinued, and the patient was started on omeprazole. On rel day 161, the patient was still unable to tolerate fluids or solids. On rel day 164, an esophagogastroduodenoscopy (EGD) revealed erosive esophagitis, hiatal hernia, antral deformity with partial outlet obstruction and suspected tumor. A CT scan of the abdomen and pelvis revealed ascites, possible acute pancreatitis, and a 3 cm left adrenal mass. On rel day 166, a therapeutic paracentesis was performed with removal of 1305 ml of blood-tinged ascitic fluid. Cytology of the ascitic fluid revealed adenocarcinoma. On rel day 174, the patient was discharged from the hospital with a discharge diagnosis of metastatic adenocarcinoma with malignant ascites. On rel day 183, the patient expired with metastatic adenocarcinoma as the cause of death. The investigator rated the malignant neoplasm to be probably not related to naproxen.

3. Patient Allocation No.: 03097 /088 **Therapy Start Date:** 20-May-1999 **Therapy Stop Date:** 28-May-1999 **Adverse Event(s):** 1.) Perforating Gastric Ulcer, 2.) Acute Renal Failure, 3.) Peritonitis, 4.) Septic Shock, 5.) Pneumonia, 6.) Adult Respiratory Distress Syndrome

This is a 78 year-old female with a history of RA, epigastric discomfort, COPD, hypertension, hyperlipidemia, systolic heart murmur, osteoporosis. Concomitant medications included ramipril, methotrexate, prednisone, albuterol sulfate/ipratropium bromide inhaler, and alendronate sodium.
On rel day 9, the patient presented with upper abdominal pain, weakness, hypotension, and diarrhea. On the same day, laboratory assessments revealed a blood urea nitrogen (BUN) of 40 mg/dL , serum creatinine of

3.0 mg/dL, and uric acid of 9.3 mg/dL (increased from screening on rel day -9, when results were 30 mg/dL, 1.2 mg/dL, and 7.7 mg/dL, respectively). Hematology results on rel day 9 showed a hemoglobin (Hgb) of 9.8 g/dL, a hematocrit (Hct) of 30.7%, and a white blood cell (WBC) count of 19.9 thou/mcl (screening results were 10.6 g/dL, 33.3%, and 17.3 thou/mcl, respectively). On rel day 9, naproxen was discontinued and the patient was admitted to the hospital. On rel day 10, an abdominal x-ray showed free air under the diaphragm, and the patient underwent emergency surgery to repair a perforated peptic ulcer. Postoperatively the patient developed wheezing and hypoxia. A diagnosis of pneumonia was confirmed by bronchoscopy with broncho-aveolar lavage performed on rel day 19 which grew *Aspergillus sp.* She was treated with amphotericine B and developed uremia. On rel day 30, patient was diagnosed with an acute respiratory acidosis (due to severe ARDS). On rel day 31, the patient was noted to have increasing skin necrosis around mouth and lips, intermittent periods of bradycardia, and continued unresponsiveness. On rel day 32, the patient was removed from the ventilator upon request by the family and expired the same day. The investigator considered all six SAEs or rated the perforating gastric ulcer to be definitely related to naproxen, the acute renal failure to be possibly related to naproxen, the ARDS to be probably related to naproxen, and the peritonitis, septic shock, and pneumonia to be probably not related to naproxen.

4. Patient Allocation No.: 00981 **Protocol No:** 088 **Therapy Start Date:** 28-Apr-1999 **Therapy Stop Date:** 09-May-1999 **(SAE):** 1.) Non-infectious Pneumonitis, 2.) Rheumatoid Lung, 3.) Respiratory Failure

This is a 67 year-old female with a history of RA, hysterectomy, glaucoma,osteoporosis, and penicillin and morphine allergies Concomitant medications included levobunolol hydrochloride and acetaminophen/ propoxyphene napsylate monohydrate. On rel day 10, the patient developed a non-productive cough and insomnia. By rel day 12, the patient's symptoms worsened and she presented to the emergency room with a dry cough, progressively worsening shortness of breath, weakness and mild confusion. Arterial blood gases were consistent with hypoxia. The patient was intubated for respiratory failure. She developed metabolic acidosis and hypotension requiring treatment with dopamine. Chest x-ray showed bilateral infiltrates and bilateral pleural effusions, shallow respiration, and normal heart size with no evidence of congestive heart failure. On rel day 14 she was treated empirically for infection due to an elevated white blood cell count of 21.3 thou/mcl. On rel day 16, a neurological examination suggested diagnosis of encephalopathy with flaccidity (a questionable prolonged effect of sedation) and evidence of neuromuscular brain failure. On rel day 17, an open lung biopsy was consistent with interstitial pneumonia and rheumatoid lung. On rel day 28, the patient was taken off respiratory support and expired that same day. An autopsy was not done.
The investigator rated the non-infectious pneumonitis, rheumatoid lung, and respiratory failure to be probably not related to naproxen.

5. Patient Allocation No.: 02632 088 **Therapy Start Date:** 18-May-1999 **Therapy Stop Date:** 03-Jun-1999 **Serious Adverse Event(s) (SAE):** ?Acute Myocardial Infarction

This is a 70 year-old female with a history of rheumatoid arthritis, myocardial infarction (1978), atherosclerotic heart disease, hypertension, hypercholesterolemia, edema, and diabetes mellitus. Concomitant medications included methotrexate, prednisone, doxazosin, potassium, losartan metformin, glyburide, lovastatin, folic acid, and calcium . On rel day 17, the patient collapsed during a telephone conversation and was found by her husband, an hour later, who attempted to resuscitate her. The patient was rushed to the emergency room. Additional efforts to resuscitate her were unsuccessful. The patient was pronounced dead on arrival. The patient's last dose of naproxen was on rel day 17. The death certificate listed the cause of death as cardiopulmonary arrest. The investigator assessed the acute myocardial infarction as not resolved, and life threatening.
(There is no evidence of myocardial infarction. This death should be considered sudden death)

6. Patient Allocation No.: 02229 **Protocol No:** 088 **Therapy Start Date:** 27-May-1999 **Therapy Stop Date:** 27-Jan-2000 **Serious Adverse Event(s) (SAE):** Intracranial Hemorrhage

This is a 79 year-old female with a history of rheumatoid arthritis, hypertension, hematuria, anemia, osteoarthritis, osteopenia, abdominal aortic aneurysm, multinodular goiter, poor R-wave progression,

hypothyroidism, hydrochlorothiazide allergy, renal insufficiency. Concomitant medications included alendronate sodium, minocycline, L-thyroxine, and diltiazem. On rel day 250, the site had called the patient to schedule an end of study visit. The daughter reported that on rel day 247, her mother, the patient, had expired. On rel day 247, the patient had cried out for help, and when the daughter arrived, the patient was nauseated and complained of pain in her jaw. The patient became incontinent of urine and stool, then unresponsive. When the paramedics arrived, they intubated the patient, and transported her to the emergency room. Upon arrival, the patient's blood pressure was 108/60 mmHg with a pulse rate of 82 bpm and an oxygen saturation of 98%. It was noted that she had a dilated right pupil. The patient arrested. The patient was defibrillated and given epinephrine. She developed a pulse and was given dopamine. An ECG showed normal sinus rhythm with occasional atrial premature contractions. A chest x-ray was normal. Lab values included a partial thromboplastin time (APPT) of 57.6 seconds, a prothrombin time (PT) of 15.5 seconds, and an international normalized ratio (INR) of 1.7. The patient arrested again. The cause of death was felt to be due to intracranial hemorrhage. The investigator assessed the intracranial hemorrhage as ongoing at the time of death, and life threatening. The investigator rated the intracranial hemorrhage to be possibly related to naproxen. *(No evidence of intracranial hemorrhage)*

7. Patient Allocation No.: 07732 089 **Therapy Start Date:** 12-May-1999 **Therapy Stop Date:** 10-Jul-1999 **SAE:** Death, Unknown Cause

This is a 62 year-old male with a history of rheumatoid arthritis. Concomitant medications included chloroquine, and prednisone. On rel day 61, family members reported finding the patient dead in his residence. Family members related that the patient had complained of symptoms of a cough and chest pain on rel day 60. The cause of death on the death certificate was listed as unknown. The investigator rated the death to be probably not related to naproxen.

8. Patient Allocation No.: 07769 089 **Therapy Start Date:** 18-May-1999 **Therapy Stop Date:** 07-Feb-2000 **Serious Adverse Event(s) (SAE):** Myocardial Infarction. This is a 60 year-old male with a history of rheumatoid arthritis, hypertension, and atrial fibrillation. Concomitant medication included digoxin.

On rel day 246, the patient returned for a regularly scheduled visit, and no symptoms were reported. On rel day 266, the patient died waiting for a bus. The cause of death was myocardial infarction The investigator rated the myocardial infarction to be not related to naproxen. *(No evidence that this was a myocardial infarction)*

9. Patient Allocation No.: 10100 /089. **Therapy Start Date:** 01-Jun-1999 **Therapy Stop Date:** 07-Feb-2000 **Serious Adverse Event(s) (SAE):** Pneumonia

This is a 59 year-old female with a history of rheumatoid arthritis, osteoarthritis, osteoporosis, onychomycosis, iron deficiency anemia, and gastritis. The patient began naproxen therapy on 01-Jun-1999 (rel day 1). Concomitant medications included chloroquine, ferrous sulfate, methotrexate, and prednisone. On rel day 252, the patient took her last dose of naproxen. On rel day 253, the patient was hospitalized for bilateral pneumonia. On rel day 254, the patient died due to bilateral pneumonia. The investigator rated the pneumonia to be not related to naproxen.

10. Patient Allocation No.: 05590 089 **Therapy Start Date:** 31-Mar-1999 **Study Stop Date:** 28-Oct-1999 **Serious Adverse Event(s) (SAE):** 1.) Pneumonia, 2.) Electrolyte Imbalance

This is a 55 year-old postmenopausal female with a history of rheumatoid arthritis, hypertension, diabetes mellitus, epigastric pain, and varicose vein. Concomitant medication included prednisone, chloroquine, methotrexate, methyldopa, chlorpropamide, and acetaminophen. On rel day 215, the patient experienced pneumonia and electrolyte imbalance and subsequently died. Last day of naproxen was taken on rel day 212. The cause of death was pneumonia and electrolyte imbalance. The investigator rated the pneumonia and electrolyte imbalance to be probably not related to naproxen.

11. Patient Allocation No.: 09191 089 **Therapy Start Date:** 31-May-1999 **Therapy Stop Date:** 21-Feb-2000 **Serious Adverse Event(s) (SAE):** 1.) Necrotizing Hepatitis, 2.) Hepatic Failure, 3.) Hepatorenal Syndrome, 4.) Gastrointestinal Bleeding

This is a 63 year old female with a history of rheumatoid arthritis, anemia, osteoarthritis, obesity, urinary tract infections, and tonsillitis. Concomitant medication included methotrexate, acetomenophen and chloroquine. On rel day 267 the patient visited the clinic for her end-of-study visit and complained of upper quadrant pain, fatigue, nausea, and jaundice. The patient also reported "dark urine" since rel day 265. At this time acute hepatitis was diagnosed. On rel day 267 a hepatic ultrasound was performed, which revealed showed diffuse hepatic damage and cholelithiasis. Lab results included serum alanine aminotransferase (ALT) 430 IU/L, serum aspartate aminotransferase (AST) 708 IU/L, serum direct bilirubin 7.4 mg/dL, serum indirect bilirubin 6.3 mg/dL, and serum total bilirubin 13.7 mg/dL. On rel day 268 the patient was hospitalized. On that same day, tests for hepatitis B and hepatitis C were negative. On rel day 270, lab results included ALT 386 IU/L, AST 704 IU/L, direct bilirubin 7.5 mg/dL, and indirect bilirubin 6.2 mg/dL. The patient was classified with a hepatic encephalopathy grade III. On rel day 271, a hepatobiliary radionuclear scan was performed, which revealed diffuse hepatic damage. All hepatitis serologies were negative (A,B,C, delta, EBV, CMV). On rel day 279 the patient experienced gastrointestinal (GI) bleeding and was given 4 units of packed red cells (in the setting of an aPTT of 180 sec). On that same day, the encephalopathy was reclassified to grade IV; and the patient was diagnosed with hepatorenal syndrome. The patient began to experience generalized seizures. On rel day 282 clinical cerebral death was diagnosed and renal dysfunction observed. On rel day 285 a hepatic biopsy was performed, which revealed massive and acute hepatocellular necrosis. On that same day the patient died. The investigator rated the toxic hepatitis, GI bleeding, hepatorenal syndrome and acute hepatic failure as probably related to naproxen. *(HOWEVER, it may have been MTX)*

12. Patient Allocation No.: 06030 089 **Therapy Start Date:** 07-Apr-1999 **Therapy Stop Date:** 19-May-1999 **Serious Adverse Event(s) (SAE):** Lung Malignant Neoplasm

This is a 51 year-old male with a history of rheumatoid arthritis, anemia, dry cough, and hemorrhoids. Concomitant medications included azathioprine, folic acid, prednisone, and sulfasalazine. The patient reported a mild cough since rel day –14. On rel day –7, physical exam showed mild peripheral edema, with a regular heart rhythm at 100 bpm, and persistent cough that was treated symptomatically. On rel day 43, the patient experienced dyspnea and was hospitalized. This same day, naproxen was discontinued. A chest x-ray revealed a mass in the right hilar area, and right pleural changes. On rel day 44, a computed axial tomography (CT) of the chest showed a possible lung mass. This same day, a bronchoscopy, and a mediastinoscopy revealed an adenocarcinoma. Pulmonary functions and a pleural aspirate biopsy confirmed adenocarcinoma. The patient's condition was determined to be too advanced for surgery. On rel day 106, the patient died from carcinoma of the lung. The investigator rated the lung neoplasm to be not related to naproxen.

13. Patient Allocation No.: 06057 089 **Therapy Start Date:** 16-Apr-1999 **Therapy Stop Date:** 01-Nov-1999 **Serious Adverse Event(s) (SAE):** Myocardial Infarction

This is a 71 year-old male with a history of rheumatoid arthritis, hypertension, and gout. Concomitant medications included allopurinol/benzbromarone, methotrexate, amlodipine, nefedipine, amiloride hydrochloride plus hydrochlorothiazide, and hydrochlorothiazide/lisinopril. On rel day 200, the patient died suddenly at home. The cause of death was myocardial infarction. The investigator assessed the myocardial infarction as life threatening. The investigator rated the myocardial infarction to be not related to naproxen.

(No evidence that this was a myocardial infarction. This will should be considered as sudden death)

14. Patient Allocation No.: 06703 089 **Therapy Start Date**: 27-Apr-1999 **Therapy Stop Date**: 16-Nov-1999 **(SAE):** Intracranial Hemorrhage.

This is a 53 year-old female with a history of rheumatoid arthritis. Concomitant medications included methotrexate, prednisone, calcium carbonate, folic acid, and vitamin D. On rel day 204, the patient complained of headaches (non-serious adverse event) without any other symptoms. This same day, all medications were stopped, including naproxen. On rel day 205, she complained of persistent headaches, and suddenly lost consciousness and was admitted to the hospital, in a coma with left hemiplegia. On rel day 206, a computed axial (CT) tomography of the head showed an intracranial hemorrhage located in the parietotemporal region, and blood in the subarachnoid space with surrounding edema. On rel day 207, she developed respiratory failure and mechanical ventilation was initiated. Treatment included fluid and electrolyte infusion. On rel day 208, the patient experienced cranial nerve palsies (non reactive mydriasis). On rel day 209, the investigator identified bilateral pupillary abnormalities, absent corneal responses, and absent oculovestibular responses. On rel day 211, the patient died. The investigator assessed the intracranial hemorrhage as life threatening, and disabling. The investigator rated the intracranial hemmorhage to be probably not related to naproxen.

15. Patient Allocation No.: 06912/089 **Therapy Start Date:** 03-May-1999 **Therapy Stop Date:** 24-Jun-1999 **Serious Adverse Event(s) (SAE):** Pneumonia

This is a 76 year-old female with a history of rheumatoid arthritis, gastric ulcer, osteoporosis, and depressive disorder. Concomitant medications included calcium carbonate, fluoxetine, hydroxychloroquine, methotrexate, and prednisone. On rel day 52, the patient presented with fever and chest pain. A chest x-ray performed on rel day 52 indicated pneumonia. The patient was admitted to hospital on rel day 53 and naproxen was discontinued. On rel day 64, the patient experienced dyspnea and respiratory insufficiency, and subsequently died on rel day 66. The cause of death was reported as pneumonia. The investigator rated the pneumonia to be disabling and probably not related to naproxen.

Appendix 3. Summary of Adjudicated Serious Thromboembolic events in selected subgroups of patients in VIGOR (Sponsor's table. Safety update)

Subgroup	Trmt	N	Patients with Events	PYR[1]	Rates[2]	Relative Risk[3]	
						Estimate	95% CI
Males	Rofecoxib	824	20	548	3.65		
	Naproxen	814	7	556	1.26	0.34	(0.15, 0.81)
Females	Rofecoxib	3223	25	2149	1.16		
	Naproxen	3215	12	2142	0.56	0.48	(0.24, 0.96)
65+ years old	Rofecoxib	997	28	621	4.51		
	Naproxen	1070	13	662	1.97	0.43	(0.22, 0.84)
<65 years old	Rofecoxib	3050	17	2076	0.82		
	Naproxen	2959	6	2037	0.29	0.36	(0.14, 0.91)
Current smoker	Rofecoxib	790	17	516	3.29		
	Naproxen	779	5	533	0.94	0.28	(0.10, 0.76)
Ex/never smoker	Rofecoxib	3256	28	2180	1.28		
	Naproxen	3250	14	2165	0.65	0.50	(0.26, 0.96)
Cardiovascular history	Rofecoxib	238	16	147	10.92		
	Naproxen	216	5	139	3.60	0.33	(0.12, 0.90)
No cardiovascular history	Rofecoxib	3809	29	2550	1.14		
	Naproxen	3813	14	2559	0.55	0.48	(0.25, 0.91)
Hypertensive	Rofecoxib	1217	20	790	2.53		
	Naproxen	1168	12	762	1.58	0.62	(0.30, 1.27)
Not hypertensive	Rofecoxib	2830	25	1907	1.31		
	Naproxen	2861	7	1936	0.36	0.28	(0.12, 0.64)
Hypercholesterolemic	Rofecoxib	343	9	215	4.18		
	Naproxen	293	2	183	1.09	0.26	(0.06, 1.18)
Not hypercholesterolemic	Rofecoxib	3704	36	2482	1.45		
	Naproxen	3736	17	2515	0.68	0.47	(0.26, 0.83)
Diabetic	Rofecoxib	240	2	153	1.31		
	Naproxen	254	1	164	0.61	0.47	(0.01, 8.96)
Not diabetic	Rofecoxib	3807	43	2544	1.69		
	Naproxen	3775	18	2534	0.71	0.42	(0.24, 0.73)

[1]Patient-years at risk
[2]Per 100 PYR
[3]Relative risk of naproxen with respect to Rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.

Appendix 3 (cont). Summary of adjudicated Myocardial Infarctions by age group..

Summary of Adjudicated MIs Overall and by Age Group
with Rheumatoid Arthritis in VIGOR
Safety Update Report

Subgroup	Trmt	N	Patients with Events	PYR[1]	Rates[2]	Relative Risk[3]	
						Estimate	95% CI
Total Cohort	Rofecoxib	4047	20	2699	0.74		
	Naproxen	4029	4	2699	0.15	0.20	(0.07, 0.58)
65+ years old	Rofecoxib	997	10	622	1.61		
	Naproxen	1070	3	662	0.45	0.28	(0.08, 1.03)
<65 years old	Rofecoxib	3050	10	2076	0.48		
	Naproxen	2959	1	2037	0.05	0.10	(0.01, 0.80)

[1]Patient-years at risk
[2]Per 100 PYR
[3]Relative risk of naproxen with respect to rofecoxib from unstratified Cox model.

Appendix 4. Patients discontinued due to serious fatal and non-fatal clinical adverse experiences. (incidence 0.2%). Source: sponsor's table.

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Patients with one or more adverse experience	643	(15.9)	635	(15.8)
Patients with no adverse experience	3404	(84.1)	3394	(84.2)
Body As A Whole/Site Unspecified	**100**	**(2.5)**	**107**	**(2.7)**
Abdominal Distention	1	(0.0)	9	(0.2)
Abdominal Pain	26	(0.6)	48	(1.2)
Asthenia/Fatigue	9	(0.2)	7	(0.2)
Dizziness	22	(0.5)	7	(0.2)
Lower Extremity Edema	19	(0.5)	8	(0.2)
Cardiovascular System	**109**	**(2.7)**	**33**	**(0.8)**
Cerebrovascular Accident	10	(0.2)	3	(0.1)
Hypertension	23	(0.6)	4	(0.1)
Myocardial Infarction	13	(0.3)	3	(0.1)
Digestive System	**292**	**(7.2)**	**392**	**(9.7)**
Acid Reflux	9	(0.2)	6	(0.1)
Constipation	1	(0.0)	10	(0.2)
Diarrhea	27	(0.7)	18	(0.4)
Duodenal Ulcer	18	(0.4)	17	(0.4)
Dyspepsia	43	(1.1)	56	(1.4)
Epigastric Discomfort	19	(0.5)	49	(1.2)
Erosive Gastritis	4	(0.1)	9	(0.2)
Gastric Erosion	2	(0.0)	8	(0.2)
Gastric Ulcer	18	(0.4)	55	(1.4)
Gastritis	14	(0.3)	26	(0.6)
Gastroesophageal Reflux Disease	7	(0.2)	4	(0.1)
Gastrointestinal Bleeding	3	(0.1)	8	(0.2)
Gastrointestinal Disorder	7	(0.2)	8	(0.2)
Gastrointestinal Distress	2	(0.0)	7	(0.2)
Heartburn	28	(0.7)	28	(0.7)
Hemorrhagic Duodenal Ulcer	5	(0.1)	10	(0.2)
Hemorrhagic Gastric Ulcer	6	(0.1)	19	(0.5)
Nausea	34	(0.8)	32	(0.8)
Vomiting	6	(0.1)	11	(0.3)

Appendix 4 (cont). Patients discontinued due to serious fatal and non-fatal clinical adverse experiences (incidence 0.2% in one or more treatment groups). (Cont.). Source: sponsor's table.

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Eyes, Ears, Nose, And Throat	**20**	**(0.5)**	**11**	**(0.3)**
Hemic And Lymphatic System	**4**	**(0.1)**	**9**	**(0.2)**
Hepatobiliary System	**10**	**(0.2)**	**2**	**(0.0)**
Musculoskeletal System	**29**	**(0.7)**	**27**	**(0.7)**
Rheumatoid Arthritis	10	(0.2)	8	(0.2)
Nervous System	**44**	**(1.1)**	**24**	**(0.6)**
Headache	21	(0.5)	9	(0.2)
Psychiatric Disorder	3	(0.1)	10	(0.2)
Respiratory System	**23**	**(0.6)**	**13**	**(0.3)**
Skin And Skin Appendages	**42**	**(1.0)**	**37**	**(0.9)**
Pruritus	11	(0.3)	1	(0.0)
Rash	17	(0.4)	19	(0.5)
Urticaria	2	(0.0)	7	(0.2)
Urogenital System	**17**	**(0.4)**	**9**	**(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.

Appendix 5.

Table A. NDA 21-042. Percentage of patients with edema-related and hypertension-related adverse events in the phase II/III OA 6-month studies.

Placebo	Rofecoxib			Ibuprofen	Diclofenac
	12.5 mg	25 mg	50 mg	2400 mg	150 mg
N= 371	N= 490	N= 879	N= 379	N= 377	N=498
Patients with one or more edema related events					
2.7 %	5.9 %	7.1 %	9.5 %	4.8 %	3.5 %
Patients with one or more hypertension related events					
3.5 %	5.7 %	6.9 %	12.1 %	3.0 %	3.0 %

The incidence of discontinuation due to cardiovascular adverse events for rofecoxib 50 mg was similar to ibuprofen and diclofenac (1.6 %, 1.3 % and 2.0 % respectively) and was numerically higher than rofecoxib 12.5 and 25 mg (1.0 % and 0.9 % respectively). The incidence of edema-related and hypertension-related events was clearly dose-related

Appendix 6. Table B. NDA 21-042- Phase II/III OA program. Thromboembolic adverse events regardless of seriousness.

	6 week studies	6 month studies	6 month to 86 week
	N/n %	N/n %	N/n %
Placebo	**1/412 (0.2%)** Cerebrovascular accident	3/371 (0.8%) Acute myocardial infarction 2 Unstable angina	
Rofecoxib —	**0/149**		
Rofecoxib 12.5	**5/725 (0.7%)** Myocardial infarction Cerebrovascular accident Coronary artery disease Ischemic heart disease Angina pectoris	**7/490 (1.2%)** Cerebrovascular accident Myocardial infarction 2 Angina pectoris 3 CAD Ischemic heart disease	**7/550 (1.3%)** Angina pectoris 3 CVA CAD Ischemic heart disease Transient ischemic attack
Rofecoxib 25	**5/735 (0.8%)** Myocardial infarction 2 Unstable angina 2 Angina pectoris	**10/879 (1.0 %)** Transient ischemic attack 3 Myocardial infarction 2 Angina pectoris 3 Coronary artery disease 2	**6/547 (1.1%)** Angina pectoris 2 CVA 1 Coronary artery disease Ischemic heart disease Myocardial infarction
Rofecoxib 50	**1/97 (1.1%)** Angina pectoris	**4/379 (1.1%)** Cerebrovascular accident 3 Transient ischemic attack	**3/123 (2.4%)** CVA Coronary artery occlusion Myocardial infarction
Rofecoxib —	**(1/74) (1.4%)** Transient Ischemic Attack		
Ibuprofen 2400	**(2/470) (0.4%)** Cerebrovascular accident Angina pectoris	**2/377 (0.5%)** Angina pectoris 2	
Nabumetone 1500	0/115		**1/92 (1.1%)** Angina pectoris
Diclofenac 150	No studies	**9/498 (1.8%)** Cardiac arrest 2 Myocardial infarction 2 Angina pectoris 2 Coronary artery disease Unstable angina Cerebrovascular accident 2	**6/439 (1.3%)** Myocardial infarction Coronary artery occlusion Coronary artery disease 2 Angina pectoris 2

N/n = number of events/number of patients randomized.

In view of the concerns raised in the VIGOR study, a summary table of thromboembolic (TE) adverse events from NDA 21-042 is included in Table B. There seems to be a higher incidence of thromboembolic events with higher doses of rofecoxib, in long term studies, however, the number of events was small. None of the studies was powered to detect differences in serious cardiovascular thrombotic events. Data from these studies should not be pooled because they involved different treatment regimens and duration.

/s/

Maria Villalba
4/2/01 12:28:41 PM
MEDICAL OFFICER

Lawrence Goldkind
4/3/01 09:07:55 AM
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Jonca Bull
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APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Advisory Committee GI Briefing Document
Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products: HFD-550

NDA 21,042 S 007
21,052
Sponsor: Merck

Name of drug: Rofecoxib (Vioxx ™)

Dose: 50 mg

Subject of Consult: Review of Vioxx Gastrointestinal Outcomes Research Study (VIGOR)

Materials reviewed: Protocol and Completed Study Report 88C

Submission date: June 29, 2000

Reviewer: Lawrence Goldkind M.D.

Table of contents

Background

Vioxx (V) was approved in 1999 for the treatment of osteoarthritis (OA), acute pain and primary dysmenorrhea. The approved dose was 12.5 and 25mg/day for OA and 50 mg/day for acute pain and dysmenorrhea. This product is a highly selective inhibitor of cyclooxygenase-2 (COX-2). The drive to develop highly selective cyclooxygenase (COX) inhibitors was based on the hopes that the safety profile would be improved compared to less selective COX inhibitors. Upper gastrointestinal ulcers complicated by pain, bleeding and perforation are a labeled complication of NSAIDs. Of the two isoforms, COX-1, a constituitively-generated enzyme has been considered critical to the maintenance of the upper gastrointestinal mucosal integrity. Physiological mechanisms that are linked to "maintenance" effects of COX-1 generated prostaglandins include gastric mucous production, bicarbonate secretion and mucosal blood flow. Inhibition of this enzyme has been linked to the gastrointestinal toxicity of NSAIDs. COX-2 is upregulated in inflammatory conditions. Since the identification of the second isoform of COX, it has been hoped that selective inhibition of this isoform would effectively treat inflammatory conditions and pain with less gastrointestinal toxicity. The original NDA included extensive safety data related to upper gastrointestinal ulceration that are reflected in the product label. V was associated with fewer endoscopically defined (as opposed to symptomatically defined) ulcers compared to ibuprofen. The studies reviewed to date have not differentiated V from all NSAIDs studied in terms of gastrointestinal symptoms and clinically meaningful ulcers. Some symptoms appear to be more commonly associated with V compared to the other NSAIDs studied while some were more common in specific comparators.

Comparative safety claims are susceptible to bias selectively defining the events of interest without incorporating other potentially important toxicities. Comparative study of symptoms and clinically relevant outcomes must be linked to dose and specific comparator. Comparative study of safety and subsequent safety claims are intrinsically different than the well ploughed area of drug efficacy. Efficacy is typically established for a particular beneficial effect. Study can therefore be based on prespecified definitions, objectives, instruments of measurement and statistical analysis. Safety by comparison is

multifaceted and therefore less easily studied and quantified. Specific safety claims other than those associated with ultimate endpoints such as death or permanent disability are difficult to study in an unbiased way that includes the concept of overall safety.

Upper gastrointestinal toxicity has been identified as a major health risk associated with the use of NSAIDs. Some estimates of the number of deaths due to the complications of gastrointestinal bleeding and perforation attributed to these products as a class are in the range of 10-20,000 per year in the United States. Based on these estimates, NSAIDs contain a generic warning of GI risk. Thus, gastrointestinal toxicity appears to be an appropriate specific safety issue for study. COX-2 selective inhibitors hold the promise of having less GI toxicity than less selective agents. Just as relative specificity of COX isoenzyme inhibition exists, so does the possibility of **relative** specificity of GI safety. Available information about the toxicity of NSAIDs suggests that each NSAID most likely has a somewhat unique profile. The study of relative safety has been limited by the difficulties inherent in safety studies compounded by the difficulties in comparative studies of many agents, at different doses, over long periods of time, using different endpoints in heterogeneous populations. The presence of generic products further discourages large expensive comparative studies.

The most daunting challenge in the study of GI safety is that the most important outcomes of bleeding, obstruction and perforation are rare events, estimated to occur in less than several percent of patients on chronic NSAIDs per year. (The estimates of perforations, ulcers and bleeding that appear in the GI warning section of NSAID labels include ulcers associated with pain alone without the more serious complications). Therefore, large studies are required.

Once the morbid outcomes of bleeding, obstruction and perforation are excluded, it becomes difficult to define an appropriate safety comparison for NSAIDs. The majority of ulcers are painless and up to 30% of patients on NSAIDs experience abdominal pain. The correlation between UGI symptoms and mucosal damage is weak. Gastric adaptation to the effects of NSAIDs is well documented. This produces new difficult questions. Is abdominal pain less or more significant than other GI symptoms such as diarrhea, nausea or vomiting? Are such symptoms more relevant than other toxicities such as renal or hepatic damage?

The original NDA database suggested that V did **not** differentiate from the comparators studied in terms of symptoms as it did for endoscopic ulcers. Based on the absence of evidence for a distinctly different safety profile in terms of clinically meaningful outcomes, the current product label includes the same warnings regarding gastrointestinal toxicity that less selective NSAIDs have. Based on the theoretical advantages of COX selectivity discussed previously and the endoscopic data that appears in the product label, V has been proposed by some as "safer" than previously approved NSAIDs. Although it is tempting to accept the development of asymptomatic ulcers as a meaningful endpoint and a surrogate for clinically relevant outcomes, there is inadequate evidence to date to accept this as fact. The clinical outcome trial entitled, "MUCOSA" published in 1995 in conjunction with other studies of endoscopically defined ulcers associated with the use of NSAIDs and misoprostol are suggestive of a correlation. This study did not have

prespecified outcomes and a statistical plan to allow for conclusions. Furthermore, MUCOSA cannot be extrapolated to all other potentially "gastroprotective" drugs.

Therefore, adequate evidence of a uniquely improved GI safety profile for V based on asymptomatic endoscopically defined ulcers was not established in the original NDA.

Databases are inadequate at the time of marketing to fully define the safety profile of a new drug. This is particularly true of new molecular entities and drug classes. (Some authors contend that COX-2 selective agents represent a new class. The World Health Organization has placed such agents in a separate class than traditional NSAIDs that are less selective.) The wide acceptance as evidenced by the many millions of prescriptions in the first year of marketing reflects acceptance of V as a safer alternative to traditional NSAIDs. However, clinically relevant safety endpoints are rare and may be missed in a database of even several thousand subjects. Authors outside the FDA have voiced concern over this issue as well. The following excerpt from a lead editorial in the September 2000 Rheumatology journal highlights this issue.

> " While it is still true that Cox-1 is expressed constitutionally in most cells and Cox-2 is induced in sites of inflammation and other pathology, recent careful work has clarified several physiological situations in which Cox-2 inhibitors in the clinic are understood only partly at present...
>
> The driving force behind the rapid and forceful cooperation between basic science and drug development was concern about the serious toxicities of conventional NSAIDs and aspirin, not least the increased fatalities resulting from gastrointestinal bleeding and ulcer perforation. Those who are skeptical about extrapolation form databases such as ARAMIS are referred to a Finnish study that identified 30 fatalities from the use of NSAIDs in that country in a single year. Cox-2 is up-regulated in the inflamed joint, and the hypothesis was that selective inhibition of the inducible Cox-2 isoenzyme would offer therapeutic efficacy without this severe toxicity. Endoscopic data from clinical trials support this hypothesis, ***but information about the risk of serious events, i.e. bleeding and perforation is still not at hand. New insights into the biologic function of Cox-2 should caution us from the uncritical use of Cox-2 inhibitors. There is a convincing evidence from published trials that celecoxib is equivalent but not superior to conventional NSAIDs in the symptomatic control of osteoarthritis and rheumatoid arthritis. However, long-term safety data can be established only with time and, as with all new types of drugs, we should be vigilant in recognizing possible new types of problems. The questions that must still be addressed concern the ultimate consequences of selective inhibition of Cox-2 and its biological functions"*** [1]
>
> (bolding and italics added for emphasis by reviewer)

Another author in a review article in the New England Journal of Medicine stated that:

" In spite of enthusiasm for these promising new agents NSAIDs, some questions remain regarding their highly selective inhibition of cyclo-oxygenase-2. For example, cyclo-oxygenase-2 might generate endogenous prostanoids that are biologically active....

..although the highly selective cyclo-oxygenase-2 inhibitors offer considerable promise in the treatment of inflammatory arthritidies, careful surveillance will be important to determine their ultimate benefit and safety profile." [2]

The Division and the sponsor have agreed that evidence was needed regarding clinically meaningful upper gastrointestinal events as well as a large controlled database for overall safety assessment. While, upper gastrointestinal tract injury was the primary and prespecified endpoint, the sponsor and the Division shared the concerns noted by the above reference #1.

The VIGOR trial was conducted to establish a safety profile based on a large database to allow for meaningful study of clinically relevant outcomes.

APPEARS THIS WAY
ON ORIGINAL

Clinical Studies

088C: A double blind, Stratified, Parallel-group study to assess the incidence of PUBs during chronic treatment with V or naproxen in patients with Rheumatoid Arthritis

The original protocol and relevant amendments appear in appendix 1.

Studies 088 and 089 were two identical arms of a single international study that were intended to for combined analysis (088C). All comments apply to both protocols.

Objectives:

Primary

1. To determine the incidence rate of PUBs in patients with rheumatoid arthritis (RA) taking 50 mg V daily compared to patients taking naproxen, 1000mg daily

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

Secondary

1. To assess the incidence of confirmed and unconfirmed PUBs in patients with RA taking 50 mg V daily compared to patients taking naproxen 1000 mg daily

2. To assess the incidence of complicated PUBs in patients with RA taking 50 mg MK-0966 daily compared to patients taking naproxen 1000 mg daily

3. To compare the efficacy of treatment of RA with V or naproxen as evaluated by the patient and investigator global assessment of disease activity and the discontinuation due to lack of efficacy

Reviewer's Comments related to objectives

Endpoint: PUB

This endpoint is a composite. The current GI warning on NSAID labels uses the term "PUB (perforation, ulcer, bleed)" to describe the GI events widely described in the medical literature at the time of the development of this section of NSAID labels. The medical literature at the time of development of this NSAID warning template was not standardized as to the definition of a PUB. This acronym in fact defines a symptomatic ulcer with or without serious morbidity. Such a term does define a clinically relevant endpoint. It represents ulcers identified during an evaluation of patients experiencing symptoms serious enough to warrant a physician intervention. Such an event must by definition be relevant to the patient. There are several difficulties with this endpoint as the primary endpoint of study in a controlled trial.

A. *Many patients on NSAIDs including V experience UGI symptoms that are consistent with ulcer symptoms that in fact are not related to ulcers. Up to 50% of patients on NSAIDs experience dyspepsia. Up to 15% discontinue therapy due to such symptoms.[2] Only a fraction of these patients have ulcers on UGI endoscopy. Thus, there are a significant number of patients who will have gastroduodenal ulcers on endoscopy without causal association with symptoms. The rate of such events would be even higher in a clinical trial where protocol driven ascertainment or bias within the clinical trial setting identifies ulcers that would not be identified in clinical practice. In clinical practice patients without alarm symptoms on NSAIDs are generally taken off presumed offending medication without any further sequelae. Therefore the use of the endpoint PUB in a clinical trial introduces a somewhat artificial entity that does not have the degree of clinical relevance that is inherent in the more clearly defined endpoint "POB" (perforation, obstruction or bleed).The*

sponsor has identified "complicated PUB" (the equivalent of POB) as a secondary endpoint.

B. *Symptomatic ulcers, whether clinically or protocol derived do not represent the same severity of endpoint as POB. Only a small fraction of ulcers are thought to result in a clinically serious outcome. In the original NDA database for V the vast majority of ulcers identified were protocol derived and not related to any symptoms. A composite outcome should contain endpoints with similar clinical importance. The correlation between symptomatic ulcers and complicated ulcers is too weak to consider the two in the same endpoint of a prospective study. In fact, clinically silent ulcers that present with a complication rather than pain symptoms are felt to be potentially more dangerous since they do not provide warning of any underlying pathology. Therefore symptomatic ulcers may be uniquely inappropriate for inclusion in a composite endpoint of a serious outcome. The current NSAID warning used the endpoint "PUB" due to the limitations of the available data at the time of conception. This endpoint is not inherently the most appropriate composite endpoint to be studied prospectively. Furthermore, symptomatic ulcers are so much more common that POBs that the outcome would be primarily determined by the symptomatic ulcer results and therefore are most accurately defined as such. Separate analyses of POBs and symptomatic ulcers allow for a more meaningful and accurate understanding of the data. The sponsor has designated POBs as a well-controlled and well-defined secondary endpoint of study. In fact, the inclusion of both PUB and POB as important endpoints will allow for a further understanding of these composite endpoints in relation to one another for future trial design as well as scientific understanding of the correlation of parameters of UGI safety related to NSAIDs.*

Endpoint: "All bleeds"

The criteria for this endpoint is found in the protocol reproduced in the appendix under section 5.5.1.6. This endpoint does not establish a new well documented meaningful endpoint that adds to the PUB and POB endpoints. If the intended endpoint was all UGI bleeding, a subset of the well-documented PUBs could be used. If the intent was to compare all significant GI bleeding (below the duodenum) in view of the lack of platelet effect and possibly diminished small bowel and colonic toxicity of a COX-2 selective agent a more rigorous approach may have been employed.

a. *The adverse event terms used for screening should have been prespecified*

b. *Witnessed bleeding or occult positive stool or some prespecified degree of fall in hemoglobin should have been pre-defined*

The criteria chosen may include self-reported dark colored stool/diarrhea or scant hemorroidal bleeding. The scenario of undocumented reports of melena or LGI bleeding

has been seen frequently by this reviewer upon review of case report forms from clinical trials, particularly when GI outcomes are of interest.

Dose selection

The dose choice of 50 mg for V is the labeled dose for acute pain and twice the labeled dose for OA. As ***V is not approved for the treatment of RA****, it is unclear what the relationship of the tested dose will have to this population. The dose of naproxen is within the commonly used range for the treatment of OA and RA. While the NSAID comparators have been in use for years and have well-established dose ranges in practice, V is a relatively new molecular entity and has a less well established efficacy and dose ranging profile. A labeled safety advantage related to UGI events may suggest to consumers that there is room to "push" the dose of a drug with proposed analgesic as well as anti-inflammatory properties. This phenomenon of "dose creep" is particularly relevant in the treatment of pain when currently available therapies leave most patients with some residual pain (absence of total pain relief). The widely held expectation that new COX-2 selective agents will have little to no potential for UGI toxicity requires a robust proof of principle.* ***Comparative safety claims therefore would be most meaningful for a high dose V. If general safety concerns prevent such doses the robustness of safety comparisons is less substantial and extrapolations from GI specific to general safety profiles could prove dangerous in practice.***

Selection of comparator

The selection of naproxen 1000mg is a reasonable choice. This is a widely used NSAID for pain, OA and RA. Generalizability is limited with the use of one comparator. As there is a range of GI toxicity within the NSAID class (albeit imperfectly characterized), a panel of several drugs across the spectrum would offer stronger support for a different class in terms of GI toxicity.

Disease model

The choice of disease is unusual, as V is not approved for the treatment of RA. Therefore the relevance of the results may be limited based on the patient population and dose selected. RA has been described as a higher risk condition compared to OA or the general population for GI toxicity with NSAID use. The largest and best-controlled data for the comparison of OA and RA appears in the CLASS trial published in 2000. This study suggested little difference in risk between these conditions in ambulatory patients. Therefore, safety ***comparisons*** *should be generalizable from RA to other rheumatological conditions. Absolute safety profile may be different for other clinical conditions, particularly those with higher morbidity overall.*

Hypothesis generating objectives

The large size of the trial will allow for assessment of other less common toxicities such as renal and cardiovascular effects. The inclusion in the final protocol of an adjudication process for cardiovascular effects and the collection of extensive laboratory information will provide a unique database for the safety of V as well as naproxen. Statistical comparisons however, will be difficult for relatively small differences in the face of the multiplicity of potential comparisons and the inherent post-hoc nature of such comparisons.

Reviewer's comments related to study design

The study size was based on a 90% power of identifying a 50% reduction in the incidence of PUBs at a 0.05% alpha level assuming a 2.25% annual incidence of PUBs in the naproxen group.

The study was well designed with adequate detail provided for randomization, double-blinding, and appropriately timed follow-up. An optimal study of chronic drug safety involves long term follow-up. The treatment period for this study was defined as the period until the last randomized patient had been observed for 6 months or 95 events had accrued. An amendment later extended the number of events to 120.

The absence of a screening endoscopy in a study population recently on NSAIDs may allow for the inclusion and therefore incorrect attribution of some ulcers, particularly early in the study. This design however is appropriate for an optimal risk assessment generalizable to clinical settings.

Exclusion criteria

1. *Subjects with a history of any illness or significant abnormalities on prestudy clinical evaluation that, in the opinion of the investigator, contraindicates a 1-2 year course of therapy with an NSAID were excluded. Subjects with significant active angina pectoris, congestive heart failure, suboptimally controlled hypertension or recent stroke or TIA were excluded as well. Subjects with a history of MI or coronary artery bypass graft surgery within prior year were explicitly excluded. Patients with health problems associated with morbid obesity were also excluded.* ***These exclusions are reasonable but significantly limit the generalizability of results. Thus, overall safety conclusions regarding the safety in sicker patients and particularly those with cardiovascular and renal disease will be substantially limited.***

2. ***Patients on any aspirin, including low doses were excluded. This exclusion prevents any confounding of PUB results that may be attributable to the effects of aspirin. However, the use of aspirin is so common in current preventive medicine practice***

that the generalizability of results will be substantially limited by the exclusion of patients that have the broad range of conditions that warrant low dose aspirin.

Conclusion regarding study design

1. *The endpoint of POB is of greatest significance as a true clinically serious outcome measure. The symptomatic ulcer however, represents a clinically meaningful additional endpoint.*

2. *The dose of 50 mg is appropriate if a safety advantage based on the COX-2 hypothesis is to be tested. Ultimate use of this dose may be common based on the phenomenon of dose creep seen with analgesics as well as perceptions of a safety advantage over less selective COX inhibitors*

3. *Although not approved for use in RA, the comparative safety data may be generalizable to other populations at similar risk for NSAID toxicity.*

4. *The exclusion of subjects with significant active cardiovascular disease represents a serious limitation of the current study. Patients with RA may be at higher risk of these conditions. Safety conclusions may not be valid for the substantial percentage of patients who may be exposed to Vioxx who have active cardiovascular disease.*

5. *The exclusion of even low dose aspirin users seriously limits the generalizability of this study to an important segment of the population.*

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Results

Demographics

Sponsor tables 16,17 and 19 display demographic data.

The groups were evenly divided for relevant factors. The demographic composite indicates that:

1. *80% of subjects were between the ages of 40 and 65*
2. *80% of subjects were female*
3. *20-25% of subjects were ARA III and 2% were ARA IV*
4. *Less than 8% of subjects had a history of symptomatic ulcers and approximately 2% had a history of UGI perforation, obstruction or bleed.*
5. *Over 50% of subjects were taking steroids or DMARDs at the time of entry*

Table 16

Baseline Patient Characteristics by Treatment Group (Continuous Variables)

Treatment Group	N	Mean (SD)		Median	Range
Age (Years)					
Rofecoxib	4047	58.0	(9.5)	58.0	34.0 to 88.0
Naproxen	4029	58.2	(9.6)	58.0	37.0 to 89.0
Total	8076	58.1	(9.5)	58.0	34.0 to 89.0
Weight (kg)					
Rofecoxib	4045	72.2	(17.7)	69.5	31.0 to 193.2
Naproxen	4027	71.9	(17.0)	69.7	35.0 to 150.6
Total	8072	72.1	(17.3)	69.6	31.0 to 193.2
Height (cm)					
Rofecoxib	4026	161.8	(10.2)	161.0	115.0 to 203.2
Naproxen	4010	161.8	(10.0)	161.0	126.0 to 195.6
Total	8036	161.8	(10.1)	161.0	115.0 to 203.2
Duration of Rheumatoid Arthritis (Years)					
Rofecoxib	4043	10.9	(9.6)	8.0	0.0 to 69.0
Naproxen	4024	10.7	(9.4)	8.0	0.0 to 61.0
Total	8067	10.8	(9.5)	8.0	0.0 to 69.0

Data Source: [4.6; 4.10]

Table 17

Baseline Patient Characteristics by Treatment Group (Categorical Variables)

Baseline Demographics	Rofecoxib (N=4047)		Naproxen (N=4029)		Total (N=8076)	
	n	(%)	n	(%)	n	(%)
Gender						
Female	3223	(79.6)	3215	(79.8)	6438	(79.7)
Male	824	(20.4)	814	(20.2)	1638	(20.3)
Ethnic Group						
White	2761	(68.2)	2750	(68.3)	5511	(68.2)
Black	207	(5.1)	202	(5.0)	409	(5.1)
Asian	101	(2.5)	85	(2.1)	186	(2.3)
Hispanic	501	(12.4)	516	(12.8)	1017	(12.6)
Multi-racial	464	(11.5)	466	(11.6)	930	(11.5)
Other	13	(0.3)	10	(0.2)	23	(0.3)
Study Region						
U.S.	1748	(43.2)	1750	(43.4)	3498	(43.3)
Multinational	2299	(56.8)	2279	(56.6)	4578	(56.7)
Age Group						
<40	10	(0.2)	11	(0.3)	21	(0.3)
40-54	1521	(37.6)	1527	(37.9)	3048	(37.7)
55-64	1519	(37.5)	1421	(35.3)	2940	(36.4)
65-74	800	(19.8)	857	(21.3)	1657	(20.5)
75+	197	(4.9)	213	(5.3)	410	(5.1)
Prior History of PUBs						
Yes	314	(7.8)	316	(7.8)	630	(7.8)
No	3733	(92.2)	3713	(92.2)	7446	(92.2)
ARA Status [1.1.12]						
I	881	(21.8)	830	(20.6)	1711	(21.2)
II	2160	(53.4)	2199	(54.6)	4359	(54.0)
III	928	(22.9)	932	(23.1)	1860	(23.0)
IV	78	(1.9)	68	(1.7)	146	(1.8)

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Table 17 (Cont.)

Baseline Patient Characteristics by Treatment Group (Categorical Variables)

Baseline Demographics	Rofecoxib (N=4047)		Naproxen (N=4029)		Total (N=8076)	
	n	(%)	n	(%)	n	(%)
Treatment for Rheumatoid Arthritis at Study Entry						
Corticosteroids	2260	(55.8)	2263	(56.2)	4523	(56.0)
Methotrexate	2263	(55.9)	2269	(56.3)	4532	(56.1)
Other DMARDs[†]	1847	(45.6)	1826	(45.3)	3673	(45.5)
History of Cardiac Disease						
Yes	1884	(46.6)	1838	(45.6)	3722	(46.1)
No	2163	(53.4)	2191	(54.4)	4354	(53.9)
Smoking Status						
Unknown	1	(0.0)	0	(0.0)	1	(0.0)
Never Smoked	2128	(52.6)	2150	(53.4)	4278	(53.0)
Ex-Smoker	1128	(27.9)	1100	(27.3)	2228	(27.6)
Current Smoker	790	(19.5)	779	(19.3)	1569	(19.4)
Number Cigarettes/24 Hours						
<11/day	404	(51.1)	409	(52.5)	813	(51.8)
11 to 20/day	271	(34.3)	252	(32.3)	523	(33.3)
>20/day	115	(14.6)	118	(15.1)	233	(14.9)
Number of Alcoholic Drinks Per Week						
Unknown	0	(0.0)	1	(0.0)	1	(0.0)
None	2994	(74.0)	2984	(74.1)	5978	(74.0)
1 to 4	866	(21.4)	864	(21.4)	1730	(21.4)
5 to 7	101	(2.5)	88	(2.2)	189	(2.3)
8 to 10	54	(1.3)	56	(1.4)	110	(1.4)
>10	32	(0.8)	36	(0.9)	68	(0.8)

Table 19

Number (%) of Patients With Secondary Diagnoses of Clinical Upper GI Events (PUBs) (Gastroduodenal Perforation, Obstruction, Ulcer, and Upper Gastrointestinal Bleed)

	Rofecoxib (N=4047)	Naproxen (N=4029)	Total (N=8076)
	n (%)	n (%)	n (%)
Prior History of Clinical Upper GI Event (PUB) (Total)	**314 (7.8)**	**316 (7.8)**	**630 (7.8)**
Gastroduodenal Ulcer	**287 (7.1)**	**289 (7.2)**	**576 (7.1)**
Gastric Ulcer	163 (4.0)	157 (3.9)	320 (4.0)
Duodenal Ulcer	104 (2.6)	110 (2.7)	214 (2.7)
Peptic Ulcer[†]	29 (0.7)	37 (0.9)	66 (0.8)
Associated Perforation	18 (0.4)	17 (0.4)	35 (0.4)
Associated Obstruction	2 (0.1)	6 (0.2)	8 (0.1)
Upper GI Bleed	**91 (2.3)**	**93 (2.3)**	**184 (2.3)**

[†] Exact location unknown.
Patients may appear in more than 1 row but are counted only once in each relevant row.

Data Source: [4.15]

GI outcome results

Database audit:

Approximately 50% of endpoint packages were reviewed. Adjudication appeared to be consistently applied.

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Endpoint results:

Table 12 displays the extent of exposure in the study. Figures 4 and 5 also indicate the exposure data as subjects at risk for each 2-month interval.

Sponsor figures 3,4 and 5 tables 22, 23, 24, 26, 31 and 32 display the most relevant GI results.

These results suggest that the endpoint PUB reasonably predicts the ***relative risk*** *of true complicated events (POB). The* ***actual event rate*** *tables indicate that rates of POBs and PUBs are quite different and should not be intermingled when discussing the* ***absolute*** *risks of serious/lifethreatening events versus symptomatic adverse events. The cumulative risk of PUBs was 1.8 and 3.9 for the V and naproxen respectively. The POB rates were 0.4 and 0.9 respectively for a study with a mean exposure of 8 months.* ***The rate for PUBs in both groups is quite similar to the range for the 3-6 months and one-year exposures that appears in the current GI warning section of NSAID labels (1% at 3-6 months and 2 to 4 percent at one year).***

The current study suggests that potentially life-threatening events (POBs) make up a fraction of the total UGI events associated with these products. GI safety must be assessed within the overall safety profile of a drug. As discussed in the background section, labeling a selective GI safety advantage in the absence of a commensurate or improved overall safety profile compared to other products in the same class may give a false impression to consumers. Thus safety profiles must be carefully analyzed based on events of comparable severity and seriousness. The reader is referred to the general safety review by Dr. Villalba.

The relative rates for the first month appear comparable for the PUB and POB endpoints. The event rates begin to diverge after 1 month. This may be due to the small number of events however, short term use does not appear to be associated with an advantage in UGI safety in the V group in this study. Results for NSAID naive subjects may be different in short-term use.

The current study is consistent with prior studies that suggest gastric ulcers (as opposed to duodenal ulcers) represent the vast majority of UGI events.

Table 12

Time in Study[†]

Cohort	Treatment Group	Duration of Follow-Up (Months)					
		N	Mean	SD	Median	Range	Inter-Quartile Range
Overall	Rofecoxib	4047	8.0	3.1	9.0	0.5 to 13.0	7.5 to 10.1
	Naproxen	4029	8.0	3.1	9.0	0.5 to 12.7	7.6 to 10.1
	Total	8076	8.0	3.1	9.0	0.5 to 13.0	7.6 to 10.1
U.S.	Rofecoxib	1748	7.5	3.6	8.5	0.5 to 13.0	4.4 to 10.3
	Naproxen	1750	7.5	3.5	8.5	0.5 to 12.7	4.4 to 10.3
	Total	3498	7.5	3.6	8.5	0.5 to 13.0	4.4 to 10.3
Multi-national	Rofecoxib	2299	8.4	2.7	9.2	0.5 to 12.3	8.0 to 10.0
	Naproxen	2279	8.4	2.6	9.2	0.5 to 12.2	8.1 to 10.0
	Total	4578	8.4	2.7	9.2	0.5 to 12.3	8.0 to 10.0

[†] Up to 14 days past discontinuation.

Data Source: [4.8]

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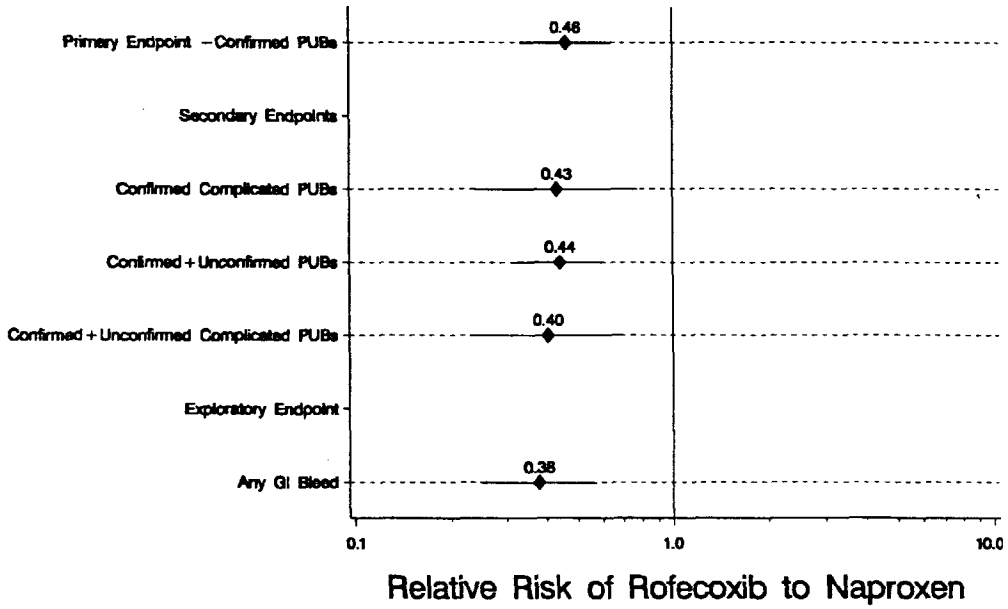
Figure 3

Relative Risk of Rofecoxib to Naproxen With 95% CI† Primary, Secondary, and Exploratory GI Endpoints



†95.44% CI for Primary Endpoint (adjusted for interim analysis)

Data Source: [4.3; 4.15]

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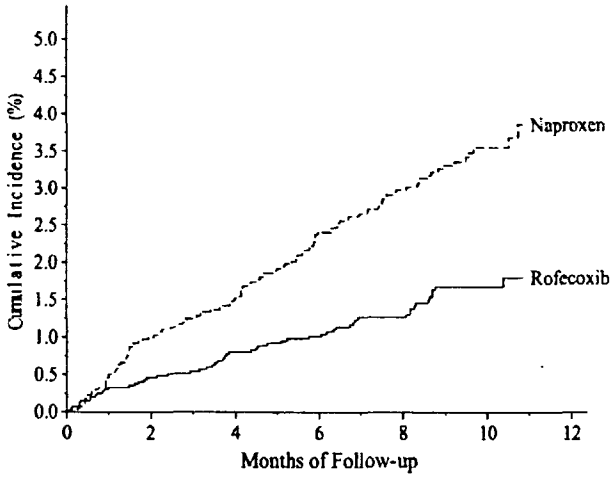
Figure 4

Primary Endpoint—Confirmed PUBs
Time-to-Event Plot (All-Patients-Randomized)

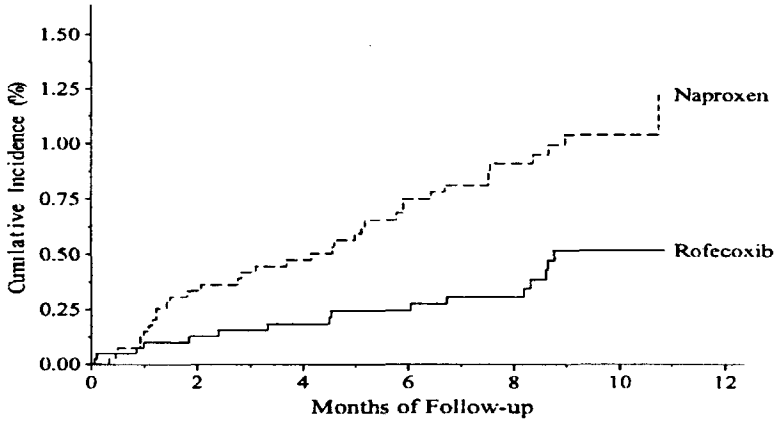


# at Risk							
Rofecoxib	n=4047	3641	3402	3180	2806	1073	533
Naproxen	n=4029	3644	3389	3163	2796	1071	513

Data Source: [4.8; 4.15]

Figure 5

Confirmed Complicated PUBs
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

Data Source: [4.8; 4.15]

Table 22

Summary of Gastrointestinal Safety Endpoints

Endpoint	Treatment Group	N	Number of Patients With Events	PYR†	Rates‡	Proportionality Assumption p-Value	Relative Risk¶		
							Estimate	95% CI‖	p-Value
Primary-confirmed PUBs	Rofecoxib	4047	56	2697	2.08	0.378	0.46	(0.33, 0.64)	<0.001
	Naproxen	4029	121	2694	4.49				
Secondary Endpoints									
Confirmed, complicated PUBs	Rofecoxib	4047	16	2699	0.59	0.648	0.43	(0.24, 0.78)	0.005
	Naproxen	4029	37	2698	1.37				
Confirmed and unconfirmed PUBs	Rofecoxib	4047	58	2697	2.15	0.471	0.44	(0.32, 0.60)	<0.001
	Naproxen	4029	132	2693	4.90				
Confirmed and unconfirmed complicated PUBs	Rofecoxib	4047	17	2699	0.63	0.739	0.40	(0.23, 0.71)	0.002
	Naproxen	4029	42	2697	1.56				
Exploratory Endpoint									
Any GI bleed	Rofecoxib	4047	31	2698	1.15	0.707	0.38	(0.25, 0.57)	<0.001
	Naproxen	4029	82	2694	3.04				

† Patient-years at risk.
‡ Per 100 PYR.
¶ Relative risk of rofecoxib with respect to naproxen from Cox model stratified by prior history of PUBs (and study region for confirmed and unconfirmed PUBs).
‖ 95.44% CI for primary endpoint.

Data Source: [4.3; 4.6; 4.15]

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Table 23

Analysis of Confirmed PUBs
All-Patients-Randomized

	Rofecoxib (N=4047)	Naproxen (N=4029)
Patients with events	56	121
Patient-years at risk	2697	2694
Rate[†]	2.08	4.49
Cumulative incidence[‡]	1.80	3.87
Relative Risk[§]		
Estimate	0.46	
95.44% CI	(0.33, 0.64)	
p-Value	<0.001	

† Per 100 patient-years at risk.
‡ At end of study but while at least 500 patients are at risk in each treatment group. Note: Cumulative incidence is from the survival analysis, it may not equal (number patients with events/N) x 100.
§ Of rofecoxib to naproxen from Cox model stratified by prior history of PUBs.
Proportional hazard assumption was met: p-value=0.378.
Treatment-by-PUB history not significant: p-value=0.874.

Data Source: [4.15]

Table 24

Number (%) of Types of Confirmed PUBs (Primary Endpoints)

Primary Endpoint	Rofecoxib (N=4047) n (%)	Naproxen (N=4029) n (%)
Confirmed PUBs	**56 (1.38)**	**121 (3.00)**
Gastroduodenal perforations	3 (0.07)	4 (0.10)
Gastric ulcers	28 (0.69)	81 (2.01)
Duodenal ulcers	27 (0.67)	39 (0.97)
Gastric outlet obstructions	1 (0.02)	0 (0.00)
Upper GI bleeds	14 (0.35)	35 (0.87)

Patients may be counted in more than 1 row, but are only counted once within a row.

Data Source: [4.15]

Table 26

Number (%) of Types of Confirmed, Complicated PUBs

Secondary Endpoint	Rofecoxib (N=4047) n (%)	Naproxen (N=4029) n (%)
Confirmed Complicated PUBs	**16 (0.40)**	**37 (0.92)**
Gastroduodenal perforations	3 (0.07)	4 (0.10)
Gastric ulcers	1 (0.02)	6 (0.15)
Duodenal ulcer	3 (0.07)	5 (0.12)
Gastric outlet obstructions	1 (0.02)	0 (0.00)
Upper GI bleeds	12 (0.30)	32 (0.79)

Patients may be counted in more than 1 row, but are only counted once within a row.

Data Source: [4.15]

Table 31

Analysis of Any GI Bleed
All-Patients-Randomized

	Rofecoxib (N=4047)	Naproxen (N=4029)
Patients with events	31	82
Patient-years at risk	2698	2694
Rate[†]	1.15	3.04
Cumulative incidence[‡]	1.00	2.59
Relative Risk[§]		
Estimate	0.38	
95% CI	(0.25, 0.57)	
p-Value	<0.001	

† Per 100 patient-years at risk.
‡ At end of study but while at least 500 patients are at risk in each treatment group. Note: Cumulative incidence is from the survival analysis, it may not equal (number patients with events/N) x 100.
§ Of rofecoxib to naproxen from Cox model stratified by prior history of PUBs.
Proportional hazard assumption was met: p-value=0.707.
Treatment-by-PUB history not significant: p-value=0.244.

Data Source: [4.3; 4.15]

Table 32

Number (%) of Types of GI Bleeds

Exploratory Endpoint	Rofecoxib (N=4047) n (%)	Naproxen (N=4029) n (%)
Any GI Bleed	**31 (0.77)**	**82 (2.04)**
Upper GI bleed	21 (0.52)	58 (1.44)
Lower GI bleed†	11 (0.27)	24 (0.60)

† Lower GI bleeds include all GI bleeds that were not of esophageal, gastric or duodenal origin.
Patients may be counted in more than 1 row, but are only counted once within a row.

Data Source: [4.3]

Subgroup analysis

Figure 11 and tables 12.3.1, 12.3.2, 12.3.3, 12.3.5, 12.3.6, 12.3.7, 12.3.8, 12.3.9, 12.3.10 and 12.3.11 display the result of subgroup analyses. The trend for lower relative risk is maintained in the subgroups displayed.

Findings of interest:

1. The absolute risk of PUBs appeared to be meaningfully higher in the subpopulation **not** taking NSAIDs at baseline compared to the group not recently on NSAIDs. These data are displayed in table 12.3.10. This finding is consistent with the concept of "gastric adaptation" that has been identified in short-term endoscopic studies in the past. The current data represent validation of this concept as a clinically relevant phenomenon. This finding is consistent with the concept of falling risk with continued exposure of NSAIDs. The current database does not show a meaningful fall in risk over time. The CLASS study recently reviewed did show a fall in the risk over time in the risk of PUBs and POBs in the traditional NSAID groups (ibuprofen and diclofenac) but not in the celecoxib group. These two large databases do not offer a consistent picture of risk over time for COX inhibitors, regardless of COX-2 selectivity.

2. Subjects with a prior history of PUB experienced a four-fold increase in risk of PUBs in the current study. The relative risk associated with the use of V compared to naproxen is maintained in this subpopulation (0.44). The **absolute** risk in the V group with a history of a PUB was nearly double the rate in the naproxen group that did **not**