TABLE OF CONTENTS

TABLE OF CONTENTS (CONT.)

TABLE OF CONTENTS (CONT.)

LIST OF TABLES

LIST OF TABLES (CONT.)

LIST OF TABLES (CONT.)

LIST OF FIGURES

LIST OF FIGURES (CONT.)

LIST OF FIGURES (CONT.)

Glossary of Terms

Term	Definition
ADVANTAGE	**A**ssessment of **D**ifferences between **V**IOXX™ **A**nd **N**aproxen **T**o **A**scertain **G**astrointestinal tolerability and **E**ffectiveness. 12-Week study in over 5500 OA patients. Rofecoxib 25 mg versus naproxen 1000 mg
APPROVe	**A**denomatous **P**olyp **PR**evention **O**n **V**IOXX™ study. 3-year study in over 2500 patients with resected colon polyp. (Adjust to 10 point type)
APTC	**A**nti-**P**latelet **T**rialists' **C**ollaboration
APTC combined endpoint	myocardial infarction, stroke, or vascular death. Based on events confirmed by adjudication except for studies antedating the adjudication SOP
ASCVD	Athersclerotic cardiovascular disease
Clinical upper GI event	confirmed PUB
Complicated PUB	the subset of more severe PUBs: perforations, gastric outlet obstruction due to ulcer, and major upper GI bleeds
Complicated upper GI event	confirmed complicated PUB
Confirmed thrombotic cardiovascular serious adverse experience	a potential cardiac, cerebrovascular, or peripheral vascular arterial or venous thrombotic event that was confirmed by an external independent adjudication committee
Confirmed/unconfirmed complicated PUB	a complicated PUB confirmed (unconfirmed) by the external independent adjudication committee
Confirmed/unconfirmed PUB	a PUB confirmed (unconfirmed) by the external independent adjudication committee
Investigator reported thrombotic cardiovascular serious adverse experience	an investigator report of a potential cardiac, cerebrovascular, or peripheral vascular arterial or venous thrombotic event
PGI_2	prostacyclin
PGI-M	prostacyclin metabolite: 2,3-dinor-6-keto-prostaglandin F1 alpha
POB	see complicated PUB
PUB	gastroduodenal **P**erforation, symptomatic gastroduodenal **U**lcer, or upper GI **B**leed
TXA_2	Thromboxane A_2
TXB_2	Thromboxane B_2
VICTOR	**V**IOXX™ **I**n colorectal **C**ancer **T**herapy: definition of **O**ptimal **R**egime Study. Separate 2- and 5-year studies in a total of 7000 patients with completely resected Dukes B or C colon cancer. Rofecoxib 25 mg vs. placebo.

VIGOR	**VI**OXX™ **G**I **O**utcomes **R**esearch Study. Median duration 9 month (maximum 13 month) study in over 8000 RA patients. Rofecoxib 50 mg vs. naproxen 1000 mg.
ViP	**V**IOXX™ **i**n **P**rostate Cancer Prevention Study. 6-Year study in over 15,000 men with PSA between 2.5 and 10. Rofecoxib 25 mg vs. placebo.

Executive Summary

INTRODUCTION

For patients with arthritis, an important question in choosing appropriate therapy is the relative risks and benefits amongst their options. Although comparison to placebo is useful in understanding the efficacy and safety profile of each product, none of the agents developed for symptomatic relief in osteoarthritis or rheumatoid arthritis has the safety profile of placebo. Starting with the first use of salicylates, followed by aspirin, butazolidin, indomethacin and others, agents in the class of nonsteroidal antiinflammatory drugs (NSAIDs) have been the mainstay for the clinical relief of arthritis symptoms. Given their long history of use, it was believed that the efficacy and safety profile of NSAIDs was understood. NSAID use was associated with an increased risk of serious gastrointestinal (GI) adverse effects including upper GI ulceration and bleeding [1; 2; 3], as well as renovascular adverse effects such as fluid retention and hypertension [4; 5]. These agents could also increase bleeding [6; 7; 8; 9; 10; 11]. These adverse effects were related to the same mechanism by which these drugs relieved pain and inflammation: the inhibition of cyclooxygenase (COX) [12]. With the discovery of COX-2, an isoform of cyclooxygenase that was upregulated by mediators of inflammation as well as by certain growth factors and tumor promoters, and that was not expressed constitutively in gastric mucosa, the COX-2 hypothesis was framed[13]. This hypothesis proposed that a selective inhibitor of COX-2 would have efficacy similar to non-selective inhibitors of COX-1 and COX-2 but with improved GI safety. Rofecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor that was developed to provide efficacy similar to nonselective NSAIDs with an improved GI safety profile and without effects on platelets.

In the initial clinical program, rofecoxib was shown to be effective in the relief of the signs and symptoms of osteoarthritis (OA), treatment of primary dysmenorrhea, and management of acute pain; it was approved by FDA in 1999. Subsequent approvals were received for the relief of the signs and symptoms of rheumatoid arthritis (RA) (2002) and juvenile rheumatoid arthritis (JRA) (2004), and treatment of acute migraine attacks (2004). A significant GI benefit versus naproxen was demonstrated in the VIOXX™[1] Gastrointestinal Outcomes Research (VIGOR) study in 2000 [14]. VIGOR also demonstrated higher cardiovascular (CV) event rates in patients treated with rofecoxib 50 mg daily than in patients treated with naproxen 500 mg twice daily, due primarily to a difference in the incidence of myocardial infarctions between groups. That finding differed from the CV safety profiles that were shown in large studies that compared rofecoxib to placebo and non-naproxen NSAIDS in OA or rofecoxib 25 mg in Alzheimer's Disease patients and in a pooled analysis of studies across the clinical development program [15]. Those analyses revealed no discernable difference in the CV safety profile of rofecoxib compared to placebo or non-naproxen NSAID comparators.

[1] VIOXX is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

Labeling approved in 2002 reflected the data on GI and CV results up to that time, and included a direction to use caution in prescribing rofecoxib for patients with ischemic heart disease. Additional updates of the CV and GI data were provided to agencies and published as new information became available. In Sep-2004, an increased risk of CV events with rofecoxib versus placebo was noted beginning after 18 months of daily treatment in the Adenomatous Polyp PRevention On VIOXX™ (APPROVe) study. The mechanism for the increased risk with rofecoxib was uncertain. Although the frequency of these events were low and the risk did not appear to be elevated compared to placebo during the first 18 months of use, a decision was made to voluntarily withdraw rofecoxib from the marketplace. This was done in the interest of patient safety, given the questions raised by the data and the availability of alternative therapies without placebo controlled data suggesting an increase in CV risk. Merck voluntarily withdrew rofecoxib from the marketplace on September 30, 2004.

The attached background document for the Arthritis Advisory Committee Meeting provides an overview of the available GI, renovascular, and CV safety data on rofecoxib. The review of CV safety data is organized around a chronologic framework of information known at various points throughout the rofecoxib development program to reflect the timing when key data became available with regard to GI and CV safety information. The following provides a high-level summary and discussion of the information within the rofecoxib background document and, for ease of review, is cross-referenced to the appropriate section of the document in which the data are provided.

SUMMARY

GI Safety (Section 2)

The demonstration that NSAID-induced gastropathy was due to inhibition of prostaglandin synthesis [12], and the identification of two isoforms of cyclooxygenase (COX), a constitutively expressed COX-1 and a second, inducible isoform, COX-2, that was not expressed constitutively in the stomach, led to the COX-2 hypothesis[13]. This hypothesis stated that selective pharmacologic inhibition of COX-2 would be expected to be as effective as inhibition of both COX isoforms in relieving pain and inflammation but with reduced GI toxicity compared to non-selective NSAIDs.

Initial clinical pharmacology studies in normal volunteers assessed surrogate markers of intestinal endothelial injury and demonstrated that rofecoxib use was associated with no increase in fecal RBCs loss compared to placebo [16] and no increase in intestinal permeability [17]. In contrast, non-selective NSAIDs increased both markers of GI injury. Furthermore, using gastric biopsies it was demonstrated that rofecoxib did not suppress prostaglandin synthesis in the stomach of volunteers whereas nonselective NSAIDs produced pronounced suppression [18].

There were 3 major clinical components to the GI safety assessment of rofecoxib. First, endoscopy studies analyzed the difference in cumulative $\geq$3 mm ulcer rates over 12-24 weeks between rofecoxib, placebo and non-selective NSAIDs. Second, a combined analysis of upper GI clinical events was performed, based on the prospective collection and adjudication of these events in the clinical program. The initial GI analysis pooled

data from the 8 Phase IIb/III OA studies in the original NDA. Updates to this analysis used the same methodology and pooled all studies of greater than four weeks duration in which rofecoxib was compared to a non-selective NSAID in the Phase IIb to V clinical development program, with the exception of VIGOR. These studies included rofecoxib doses of 12.5, 25 or 50 mg and. The VIGOR study was the third component of the GI safety program. This was a large outcomes study in 8076 patients with rheumatoid arthritis that randomized patients to treatment with rofecoxib 50 mg, twice the highest dose recommended for chronic use, versus naproxen 1000 mg daily, a common clinical dose, and analyzed the incidence of confirmed upper GI clinical events. There was limited use of concomitant aspirin in the studies in the pooled analysis and the VIGOR outcomes study excluded concomitant aspirin use at any dose. Aspirin was excluded because of its potential confounding effect on the rates of GI mucosal injury due to its inhibition of COX-1 activity which would have made a rigorous test of the COX-2 hypothesis impossible.

Endoscopy Studies (Section 2.4.1)

Two endoscopy studies were carried out to assess cumulative rates of endoscopic ≥3 mm ulcers in patients with osteoarthritis taking rofecoxib 25 mg or 50 mg, placebo or ibuprofen 2400 mg daily and reported individually and as a combined analysis. In each study, the rates of ≥ 3 mm ulcers by 12 weeks in the rofecoxib groups were significantly lower than the corresponding rate with ibuprofen and in the combined analysis the rates with rofecoxib 25 mg were comparable to placebo. These studies showed that this GI safety advantage for both rofecoxib 25 mg and 50 mg versus ibuprofen was maintained at 24 weeks as well. In a similarly designed 12-week endoscopy study in RA patients treated with rofecoxib 50 mg once daily or naproxen 1000 mg daily, treatment with rofecoxib was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with naproxen.

Analyses of Adjudicated GI Events (Sections 2.2 and 2.3)

A rigorous adjudication of all potential upper GI clinical outcomes from all studies containing any dose of rofecoxib was performed by an external expert, independent, blinded Case Review Committee (CRC). The expert panel used prespecified criteria to determine whether events were confirmed, and whether they were clinically complicated. Gastroduodenal perforation, symptomatic gastroduodenal ulcer (with or without obstruction), and upper GI bleed were identified as "PUB" events. "Complicated PUB" events were defined as gastroduodenal perforation, gastric outlet obstruction due to an ulcer, or a major upper GI bleed.

Pooled GI Analysis (Section 2.4.2)

Results for the pooled GI analysis are reviewed from the final update to this analysis (data to Feb-2003) to allow explorations of the data that were not possible in the initial analysis available in 1998 at the time of the original NDA. This final update included PUBs from the 20 Phase IIb to V trials from the rofecoxib development program excluding VIGOR with average duration greater than 4 weeks in which rofecoxib was

compared to a non-selective NSAID. There were a total of 17,072 patients with osteoarthritis (15 trials) or rheumatoid arthritis (5 trials) studied. Overall, the analyses in this pooled dataset demonstrated a 64% reduction in the rate of confirmed upper GI PUBs with rofecoxib versus combined NSAIDs. The incidence of confirmed PUBs over 24.8 months was significantly lower with rofecoxib vs. combined NSAIDs (rate/100 patient-years 0.74 vs. 1.87; relative risk 0.36, 95% CI 0.24, 0.54). Similar findings were demonstrated with complicated PUB endpoints as well. Differences were consistent across subgroups and with the individual NSAID comparators ibuprofen, naproxen and diclofenac.

GI Safety From VIGOR (Section 2.4.3)

The VIGOR GI outcomes trial in 8076 patients with rheumatoid arthritis demonstrated that rofecoxib 50 mg was associated with significantly fewer PUBs and complicated PUBs than the non-selective NSAID naproxen 1000 mg daily. There was a 54% reduction in the rate of confirmed upper GI clinical events (PUBs) with rofecoxib versus naproxen (rates of 2.08 vs. 4.49 per 100 patient-years; relative risk 0.46, 95% CI 0.33, 0.64; $p<0.001$). Similar results were found for confirmed complicated events (rates of 0.59 vs. 1.37 per 100 patient-years for rofecoxib versus naproxen, respectively; relative risk 0.43, 95% CI 0.24, 0.78; $p=0.005$). Differences were consistent across subgroups. A post-hoc analysis of VIGOR data revealed a reduced risk of clinical lower GI events compared to naproxen as well. Lower GI events were defined as: gross rectal bleeding (other than melena) associated with a hemoglobin decrease >2 g/dL or hospitalization, or positive test for fecal occult blood associated with a hemoglobin decrease >2 g/dL and negative upper endoscopy; hospitalization for intestinal perforation, obstruction, ulceration, or diverticulitis.

Additional GI Data (Sections 2.4.4 and 2.5)

The addition of low-dose aspirin to rofecoxib appears to result in a degree of mucosal GI injury similar to that of ibuprofen alone based on assessment of the cumulative incidence of ulcers ≥3 mm in a 12-week endoscopy study. Ibuprofen combined with low dose aspirin was not evaluated in this study. Data from a recently completed 7-day endoscopy trial in healthy subjects suggest that the GI risk of a COX-2 inhibitor plus aspirin may be lower than a nonselective NSAID plus aspirin. However, long term clinical data confirming this benefit have not been presented. Placebo-controlled data from studies in Alzheimer's disease and colon polyp prevention suggest that rofecoxib 25 mg is associated with a higher rate of upper GI clinical events than is placebo. Thus, as indicated in its labeling, although rofecoxib significantly reduces the risk of GI injury from NSAIDs, it does not completely eliminate the risk.

GI Conclusions

The analyses of PUBs for rofecoxib in both the VIGOR study and the pooled analysis of 20 phase IIb to V studies demonstrate the superior upper GI safety profile of rofecoxib when compared to non-selective NSAIDS. Results in the 12-24 week endoscopy studies

of cumulative ulcers ≥3 mm also support this improved GI safety profile versus non-selective NSAIDs. Post hoc data from the VIGOR study suggest that rofecoxib was also associated with a reduction in clinically important lower GI events compared with nonselective NSAIDs.

Renovascular Safety (Section 3)

Edema, CHF, and hypertension are known renovascular effects of COX-2 inhibition and have been observed with all nonselective NSAIDs and COX-2 inhibitors [4; 5; 19; 20; 21]. These side effects of inhibiting COX-2 are mechanism-based, are known to be dose-related, and are reflected in NSAID class labeling. Renovascular effects were monitored in the rofecoxib program as a prespecified safety endpoint.

Approach to Analyses

To evaluate the clinical impact of potential renovascular effects, a composite of edema-related and hypertension-related adverse experiences was defined. The composite terms were prespecified to provide greater precision than the individual adverse experience terms when comparing treatment groups. In addition, congestive heart failure adverse experiences were evaluated in a prespecified manner. Individual adverse experience terms were also reviewed for trends in the data.

Renovascular Safety Data (Sections 3.2 to 3.3)

Overall, the data indicate that rofecoxib is associated with the development of edema-related and hypertension related adverse experiences generally consistent with the effects of fluid retention typically observed for NSAIDs. Edema-related adverse experiences generally occurred early, and were mild, transient, and infrequently led to discontinuations. CHF was rare in all populations, including the elderly. Most of the hypertension adverse experiences were mild to moderate in intensity and discontinuation due to hypertension adverse experiences was infrequent (data provided in Sections 3.2 to 3.3). At the 25 mg dose, rofecoxib use was generally associated with small increases in mean systolic blood pressure (2 to 4 mm Hg) compared to placebo and increases of mean diastolic blood pressure <2 mm Hg. Changes in mean systolic blood pressure with rofecoxib exhibited a dose-related pattern in 6-week OA studies with increases of 1.1 to 5.1 mm Hg across the rofecoxib doses 12.5 to 50 mg. These changes approximate the increase of 5 mm Hg in mean arterial pressures reported for NSAIDs in two meta-analyses [4; 5]. In general, hypertension adverse experiences also appeared to be dose related with 12.5 mg displaying rates lower than 25 mg, and both of these doses with rates lower than rofecoxib 50 mg, which is above the therapeutic dose range for chronic treatment. Rofecoxib 50 mg displayed higher rates of edema and hypertension adverse experiences than therapeutic doses of comparator NSAIDs. While in general the incidence of renovascular adverse experiences within the therapeutic dose range of rofecoxib (12.5 and 25 mg) is similar to NSAIDs, in some studies (RA Phase III) the 25 mg dose had a higher incidence than the comparator NSAID, naproxen. This difference from naproxen was not replicated however, in a 12-week study in OA patients (ADVANTAGE).

Cardiovascular Safety Prior to Sep-2004 APPROVe Trial Results (Section 4)

An overview of the evolving understanding of CV safety of rofecoxib is organized around a chronologic framework of information known at various points throughout the rofecoxib development program.

Evolution of Prostaglandin Biology (Section 4.1.1)

Cyclooxygenase and its prostanoid products have important roles in hemostasis. Prostacyclin (PGI_2), a product thought to be derived primarily through the activity of endothelial cell COX-1 and COX-2, is a vasodilator and inhibitor of platelet aggregation [22; 23]. Serum thromboxane A_2 (TXA_2), largely a product of platelet COX-1, is a vasoconstrictor and promoter of platelet aggregation. Aspirin, a well recognized antiplatelet agent and inhibitor of platelet TXA_2 synthesis, is effective in decreasing the risk of cardiovascular thrombotic events in patients at risk for such events [24]. Aspirin's antiplatelet effect is mediated through its near complete, irreversible inhibition of platelet COX-1 activity [25].

At the time of the initiation of the Phase IIb/III OA program (Jun-1995), there was no suggestion that a selective COX-2 inhibitor might be prothrombotic. However there were suggestions in the literature that at least some NSAIDs might be cardioprotective through the inhibition of COX-1 [26; 27]. As expected for a selective COX-2 inhibitor, rofecoxib was shown to have no inhibitory effect on platelet thromboxane production and therefore did not have any effects on platelet aggregation.

Several months prior to the completion of the OA Phase III studies, data from clinical pharmacology studies demonstrated that the selective COX-2 inhibitors rofecoxib and celecoxib reduced the urinary excretion of the prostacyclin metabolite PGI-M [28; 19]. These data indicated that COX-2 was the predominant cyclooxygenase isoform involved in systemic prostacyclin production and it was hypothesized by the authors that at least some of the COX-2-dependent systemic prostacyclin was derived from endothelium. It was further hypothesized that inhibition of endothelial prostacyclin synthesis by a selective COX-2 inhibitor without the inhibition of platelet thromboxane synthesis as would be obtained with a non-selective inhibitor of both COX-1 and COX-2 could theoretically alter the hemostatic balance between prostacyclin and thromboxane. This imbalance, if present, could theoretically be prothrombotic and lead to an increase in the risk of thrombotic cardiovascular events. The data from the above rofecoxib clinical pharmacology study were submitted to the FDA as part of the original rofecoxib NDA in 1998.

Cardiovascular Clinical Results in Phase IIb/III OA Studies (Section 4.1.2)

An initial review of CV data was included in the rofecoxib NDA, which was submitted to the FDA in Nov-1998. These analyses included data on approximately 5,400 OA patients from 8 double-blind, placebo-controlled and active-comparator studies. Although somewhat limited with respect to the comparison to placebo, in these studies, similar rates of investigator-reported thrombotic cardiovascular serious adverse

experiences were seen with rofecoxib, placebo, and comparator NSAIDs (ibuprofen, diclofenac, or nabumetone) with a relative risk (95% CI) of 0.92 (0.50, 1.67) for rofecoxib compared to non-selective NSAIDs. There were no individual thrombotic events such as myocardial infarction or stroke whose rates suggested an imbalance between the groups and Kaplan-Meier plots of cumulative incidence over time did not suggest between-group differences. Collectively, these data did not support the hypothesis that selective COX-2 inhibitors might be associated with an increase in thrombotic CV events as had been theorized. These data were reviewed with both the Arthritis Advisory Committee in 1999, which concluded that rofecoxib had a favorable risk/benefit profile, as well as with FDA, which approved rofecoxib in May-1999 for the relief of the signs and symptoms of osteoarthritis, for the management of acute pain in adults, and for the treatment of primary dysmenorrhea.

CV Adjudication Standard Operating Procedure (SOP) (Section 4.1.5)

Several hypotheses had been proposed to suggest possible effects of selective COX-2 inhibitors and/or of non-selective NSAIDs on CV event rates [29; 27; 30]. These included hypotheses suggesting a decrease in CV events with all agents that inhibit COX-2, a decrease of events with non-selective NSAIDs that inhibit COX-1, and an increase in events with agents that selectively inhibit COX-2 but not COX-1 [28; 19]. Although there had been no imbalance in CV events in the Phase III OA database, Merck initiated a CV Adjudication Standard Operating Procedure (Adjudication SOP) in the second half of 1998 to systematically collect and adjudicate potential cardiovascular thrombotic serious adverse experiences from all future studies with its selective COX-2 agents. The basis of the Adjudication SOP was a blinded systematic review by an expert panel of cardiologists, neurologists, and vascular medicine internists of serious adverse experiences reported by site investigators. These adverse experiences were prespecified in the Adjudication SOP as potential thrombotic cardiovascular events (referred to in this background document as Investigator Reported Thrombotic CV Serious Adverse Experiences). The report of such an event triggered a procedure whereby additional information was collected and the event was adjudicated. None of the members of the 3 expert panels (one each for cardiac events, cerebrovascular events, peripheral vascular events) was a Merck employee or a site investigator for any of the Merck selective COX-2 inhibitor studies. Events confirmed by adjudication are referred to in this document as Confirmed Thrombotic CV Serious Adverse Experiences.

The primary endpoint outlined in the original Adjudication SOP was the Confirmed Thrombotic CV Serious Adverse Experience endpoint. This endpoint was considered primary for all studies included in the SOP which also encompassed VIGOR. Data from individual studies are reported using this endpoint or, if from a study antedating the SOP, using the Investigator Reported endpoint. Prior to undertaking a pooled analysis of the data, which included the unadjudicated Phase IIb/III data, the decision was made to prespecify the Antiplatelet Trialists' Collaboration (APTC) combined endpoint, for all pooled analyses which included studies which were not part of the CV Adjudication SOP. The APTC combined endpoint includes cardiovascular death, death due to unknown

causes, fatal hemorrhage, myocardial infarction, and stroke. These "hard events" have a high confirmation rate during adjudication, an important characteristic since the data from the Phase IIb/III OA studies and the RA Phase IIb study were not subject to adjudication. Results have been highly consistent between analyses based on the APTC and Confirmed Thrombotic CV Serious Adverse Experience endpoints.

CV Findings From the VIGOR study (Section 4.2)

VIGOR was the first trial with rofecoxib to utilize the CV Adjudication SOP. In March of 2000, the preliminary results of VIGOR became available. Although the GI benefit of rofecoxib was clear in the VIGOR study, an imbalance in thrombotic cardiovascular adverse experiences favoring naproxen was observed. A total of 64 patients had one or more events during VIGOR that were adjudicated as confirmed thrombotic events by the committees; 45 of 4047 patient in the rofecoxib group and 19 of 4029 patients in the naproxen group. The relative risk (95% CI) for confirmed thrombotic events for rofecoxib compared to naproxen was 2.38 (1.39, 4.00). The difference between treatment groups could be observed starting approximately 1 month after the initiation of treatment and was due primarily to a lower incidence of myocardial infarctions in the naproxen group. Multiple statistical analyses indicated that the relative risk observed between treatment groups for a confirmed thrombotic cardiovascular serious adverse experiences did not vary significantly over time.

Subgroup analyses were performed including an analysis based on baseline risk for a cardiovascular event and analyses based on blood pressure parameters. There were no statistically significant subgroup by treatment interactions for the following subgroups: age, gender, history of a CV risk factor and past history of atherosclerotic cardiovascular disease.

More patients in the rofecoxib 50 mg group in VIGOR (twice the highest recommended chronic dose) had hypertension adverse experiences than in the naproxen group. Although the difference in thrombotic cardiovascular serious adverse experiences was larger than one may have anticipated given the small between-group differences in blood pressure, it was nonetheless important to examine the data to determine if the known renovascular effects of rofecoxib 50 mg accounted for the cardiovascular findings of VIGOR. A number of different analyses were carried out to evaluate the relationship between blood pressure and confirmed thrombotic CV events. This included an analysis based on reports of hypertension adverse experiences and analyses based on blood pressure measurements. None of these analyses revealed an association between hypertension and the imbalance of thrombotic cardiovascular events. Thus, differential effects of the two study treatments on blood pressure did not appear to explain the imbalance in confirmed thrombotic CV events in VIGOR, although some contribution of blood pressure could not completely be excluded.

Placebo-Controlled Interim Data From the Alzheimer's Disease Program (2000; Section 4.2.3)

The data from the Phase IIb/III OA program reviewed in the original NDA for rofecoxib had not revealed an increased risk of investigator reported thrombotic cardiovascular serious adverse experiences on rofecoxib compared to either placebo or non-naproxen NSAIDs. To better understand the significance of the new cardiovascular results of VIGOR, an interim analysis was carried out for two large, ongoing placebo-controlled studies in elderly patients with early Alzheimer's disease. These ongoing trials provided a large dataset comparing rofecoxib 25 mg with placebo, rather than the naproxen comparator evaluated in VIGOR. Importantly, the Alzheimer's studies provided extensive experience in an elderly population at increased risk for serious thrombotic cardiovascular events.

A preliminary review of the Alzheimer's data in Mar-2000 and submitted to the FDA in Jun-2000 showed no increase in investigator reported cardiovascular event rates for rofecoxib compared to placebo, and numerically similar rates of specific events in both groups. In preparation for the Feb-2001 FDA Arthritis Advisory Committee meeting, a second interim analysis of the cardiovascular data from the placebo controlled Alzheimer's studies occurred in Sep-2000 with consistent findings. The relative risk (95% CI) for rofecoxib compared to placebo was 0.85 (0.53, 1.35). These year 2000 analyses were based on unadjudicated investigator reported Thrombotic CV Serious Adverse Experiences, since at that time, few of the events had been adjudicated. Subsequent analyses were performed on adjudicated data and were consistent with the initial analyses.

Anti-platelet Effects of Naproxen 500 mg Twice Daily (Section 4.2.4.1 to 4.2.4.4)

In order to understand the biologic basis for the difference in CV event rates between rofecoxib and naproxen, it was important to review all available information on the potential anti-platelet and CV effects of naproxen. As early as 1977, the potential for non-selective NSAIDs to inhibit platelet aggregation was recognized [7]. As clinical use of NSAIDs increased, the ENT literature discussed an association between NSAID therapy and epistaxis [6]. Inhibition of platelet aggregation with increased bleeding after non-selective NSAID administration was noted in the urologic, neurosurgical, and ophthalmologic surgical literature [8; 9; 10; 11]. The effects of NSAIDs on platelet aggregation were found to be related to the inhibition of COX-1 mediated TXA2 synthesis and it was recognized that the effect of an NSAID on platelet aggregation was related to the duration of the drug's effect on TXA2 synthesis [31; 32].

It is generally accepted that, to persistently inhibit platelet aggregation and serve as a vascular-protective agent, near-complete inhibition (>90%) of TXA_2 synthesis sustained over time is needed [25]. The effect of chronic therapy with non-aspirin COX-1/COX-2 inhibitors (the nonselective NSAIDs) on the incidence of cardiovascular thrombotic events has not been well characterized. Indeed, little if any placebo-controlled clinical trial data have been published for NSAIDs other than aspirin. Although nonselective NSAIDs inhibit platelet COX-1 activity, this inhibition is reversible. Thus, the ability of

a nonselective NSAID to provide potent and sustained antiplatelet effects that mimic aspirin's antiplatelet properties [33; 34; 33; 35] (and thus potentially to effect aspirin-like vascular-protection) is highly dependent on the unique COX-1/COX-2 potency and pharmacokinetic profiles of each of these compounds.

Several studies have demonstrated that the nonselective COX-1/COX-2 inhibitors vary in the magnitude and time course of their effects on platelet function [33]. One study performed by Merck in collaboration with external investigators compared the effects of lower doses of rofecoxib and several nonselective COX-1/COX-2 inhibitors on thromboxane generation and platelet function. Patients were randomized to receive either placebo, rofecoxib 12.5 or 25 mg daily, diclofenac 50 mg 3 times daily, ibuprofen 800 mg 3 times daily, or naproxen 500 mg 2 times daily [33]. These data show a gradient of anti-aggregatory effects for the different drugs. Therapy with rofecoxib did not meaningfully inhibit platelet aggregation, having an effect similar to placebo. Diclofenac 50 mg three times daily had an intermediate effect resulting in less than 40% inhibition and ibuprofen 800 mg three times daily showed near-complete inhibition (≥90%) at peak, although it was not maintained across the dosing interval. Only naproxen 500 mg twice daily resulted in near-complete inhibition of platelet aggregation that was maintained across its dosing interval (comparable to the results obtained in a separate study with aspirin. Consistent with these findings, >90% inhibition across the dosing interval of platelet TXB2 production was only obtained with naproxen and not the other NSAIDs [33].

Consistent with these data, therapy with placebo, rofecoxib, and diclofenac did not result in a prolongation of bleeding time whereas therapy with naproxen prolonged bleeding time by ~79%. This effect of naproxen on bleeding time was similar to the reported effect of aspirin (50 to 100% prolongation [33; 34; 22; 36]).

Clinical Trials Evaluating the Vascular-Protective Properties of Nonselective NSAIDs (Section 4.2.4.5)

Although there have been no cardiovascular outcomes trials with naproxen, there is evidence for the vascular-protective efficacy of flurbiprofen and indobufen, two nonselective NSAIDs which also exhibit potent antiplatelet properties [27; 26]. Flurbiprofen treatment has been shown to prolong bleeding time and was evaluated for a cardioprotective effect compared with placebo, in the setting of coronary plaque rupture. In one study, 464 patients who were successfully treated for acute myocardial infarction by thrombolysis and/or coronary angioplasty were randomized to receive either placebo or flurbiprofen 50 mg twice daily for 6 months. Therapy with flurbiprofen was associated with a >50% reduction in the incidence of reinfarction and coronary revascularization at 6 months and a 71% reduction in the risk of myocardial infarction when compared with placebo treatment. This study specifically addressed the effects of flurbiprofen in the context of an active disease state.

There are many studies which support the cardioprotective effects of the nonselective NSAID indobufen. Clinical studies have compared the effects of indobufen with placebo, aspirin, warfarin, or ticlopidine in patients with intermittent claudication

resulting from peripheral vascular disease, in the prophylaxis of thromboembolism in patients with heart disease, in the prophylaxis of occlusion of coronary and femoropopliteal artery bypass grafts, and in the secondary prevention of thrombotic events following transient ischemic attack (TIA) and stroke. Collectively, these randomized double-blind clinical studies showed that indobufen treatment was associated with cardioprotective effects superior to placebo and similar to aspirin or warfarin although not as effective as ticlopidine.

The data from these studies suggest that nonselective COX-1/COX-2 inhibitors with potent and sustained platelet COX-1 inhibitory properties result in vascular-protective properties similar to those observed with aspirin [37; 38]. Recent public announcements of a possible increased cardiovascular risk with a low dose of naproxen sodium (220 mg twice daily) do not preclude a cardioprotective effect of naproxen at 500 mg twice daily. The details have not been made available at the time of writing this background package.

Cardiovascular Event Rates on Naproxen Relative to Selective COX-2 Inhibitors (Section 4.2.4.6)

Although not available at the time of VIGOR, more recent data further identify a consistent difference in thrombotic cardiovascular events between selective COX-2 inhibitors and naproxen but not between selective COX-2 inhibitors and other non-selective NSAIDs. To date, published data on all COX-2 inhibitors have shown rates of CV events similar to NSAIDs other than naproxen. [15; 39; 40; 41]. In the Phase IIb/III OA program as noted above, the incidence of CV events was similar on rofecoxib and the comparator NSAIDs ibuprofen, diclofenac and nabumatone. In contrast, in clinical studies comparing selective COX-2 inhibitors to naproxen 500 mg twice daily [15; 39], the rates of CV events with naproxen have been lower than with selective COX-2 inhibitors. Although it has been argued that CV event rates with celecoxib are similar to naproxen with a relative risk of 0.85 for celecoxib:naproxen [40], the data were limited with only 4 events and less then 400 patient-years exposure in the naproxen group, and the 95% CI were wide (0.29 to 2.46), limiting the ability to draw a conclusion.

The largest single trial comparing a selective COX-2 inhibitor with naproxen was the TARGET study with lumiracoxib. The TARGET study, which enrolled over 18,000 patients, was designed to assess GI outcomes but a key secondary objective was to measure and compare a composite endpoint of cardiovascular morbidity and mortality. TARGET consisted of 2 substutdies of equal size with one comparing lumiracoxib to ibuprofen 800 mg 3x daily and the other lumiracoxib to naproxen 500 mg 2x daily [39]. In TARGET, the hazard ratio (95% CI) of confirmed or probable APTC events for lumiracoxib versus ibuprofen was 0.76 (0.41, 1.40) while the hazard ratio (95% CI) of confirmed or probable APTC events for lumiracoxib versus naproxen was 1.46 (0.89, 2.37). The differences between lumiracoxib and ibuprofen and between lumiracoxib and naproxen were not significant (0.3775 and 0.1313, respectively), and the treatment by substudy interaction resulted was not significant (p=0.1145). However, the TARGET study was not powered for the cardiovascular endpoint. The hazard ratio for the APTC combined endpoint in the lumiracoxib versus naproxen substudy is not inconsistent with the findings with rofecoxib. [39]

Pooled Analysis of Adjudicated CV Events From All Rofecoxib Clinical Trials (2000; Section 4.2.5)

A pooled analysis with all data available from across the rofecoxib development program was performed in September 2000, including the two ongoing trials in Alzheimer's disease already described above. All Phase IIb to V studies of at least 4 weeks duration which included either placebo and/or active-comparator nonselective NSAID controls were included in the pooled analysis. The pooled analysis thus included data from the Phase IIb/III OA, VIGOR, ADVANTAGE, and Alzheimer's Disease studies discussed above as well as data from the RA Phase IIb/III program in which rofecoxib was compared to placebo and naproxen, and from postmarketing (Phase V) studies such as Protocols 085 and 090 in which rofecoxib was compared to placebo and nabumetone. The pooled analysis was a prespecified ongoing project; the results were periodically updated as additional sets of data became unblinded. The primary endpoint for the pooled analysis was the APTC combined endpoint. Data for naproxen were analyzed separately from other NSAIDs due its demonstrated potent and sustained antiplatelet effect which would potentially provide cardioprotective effects not present in the other NSAIDs. The comparisons of interest were:

- Naproxen versus rofecoxib.
- Other (non-naproxen) NSAIDs versus rofecoxib.
- Placebo versus rofecoxib.

Data from over 28,000 patients on either rofecoxib or nonselective NSAID/placebo in Phase IIb to V clinical studies were analyzed. The relative risk of the APTC endpoint in naproxen users versus rofecoxib users was consistent with the results observed in VIGOR, with a decreased incidence of APTC events on naproxen. Similar to the finding in the Alzheimer's disease and OA programs, there was no discernable difference in rofecoxib CV risk compared with placebo and non-naproxen comparators. Given the potential for aspirin use to confound the results of the analysis, a subgroup analysis was conducted only in patients who were not taking aspirin/clopidogrel prior to study start. This subgroup analysis, which included >88% of the events, provided consistent results with the primary approach.

To investigate whether rofecoxib dose could have contributed to the imbalance of thrombotic cardiovascular serious adverse experiences in VIGOR, data from the pooled analysis were explored to investigate evidence for a dose effect on the thrombotic cardiovascular event rates. Although the data were limited by small numbers of CV events, they did not provide evidence in favor of a dose-relationship for rofecoxib in APTC events.

VIGOR CV Conclusions (2000; Section 4.2.6)

In assessing the imbalance in thrombotic cardiovascular events in VIGOR, all of the relevant available data were reviewed. The data regarding platelet and bleeding time effects for naproxen described above substantiated its potent antiplatelet effects.

Randomized clinical trials had already established a reduction in cardiovascular risk associated with the use of nonselective NSAIDs with potent antiplatelet effects. The clinical trial data did not demonstrate an increased cardiovascular risk for rofecoxib in either the Alzheimer's population versus placebo or the Phase IIb/III OA population versus non-naproxen NSAIDs and were inconsistent with a CV risk as large as had been seen in VIGOR. The weight of the evidence was most consistent with no prothrombotic effect of rofecoxib and a cardioprotective benefit of naproxen.

Study of CV Outcomes With Rofecoxib (Section 4.3.1)

At the time VIGOR completed, several large placebo controlled studies were already underway: the Alzheimer's Disease studies discussed above and the APPROVe study. The APPROVe study, an outcomes study evaluating the ability of rofecoxib to diminish the recurrence of colon polyps in patients with a prior colorectal adenoma had started screening patients in Dec-1999 and enrolling patients in Feb-2000. Each of these two datasets would have individually been sufficiently powered to demonstrate a prothrombotic effect of rofecoxib of a magnitude similar to the difference observed in VIGOR between rofecoxib and naproxen, if such an effect were to exist. Indeed, in final data for each there were more confirmed thrombotic CV events than in VIGOR.

However, in order to evaluate further the risk of thrombotic cardiovascular events with rofecoxib, Merck decided to conduct a cardiovascular outcomes study. One approach considered was to study the use of rofecoxib in arthritis patients and compare the risk of rofecoxib with a nonselective NSAID. Also considered was a study in acute coronary syndrome patients. This was rejected for a variety of reasons as described in section 4.3.1. However, the expanding database of studies versus placebo with rofecoxib and the emerging data on possible chemopreventative benefits of COX-2 inhibition provided an alternative means to address this question in populations which could be approached using placebo-controlled studies.

Thus, it was decided to develop a cardiovascular outcome protocol for rofecoxib based on a combined analysis of placebo-controlled studies with rofecoxib in patients with a broad spectrum of CV risks and with clinical conditions for which placebo controlled efficacy trials were ethical to conduct.

The CV outcome protocol consisted of the following studies:

- APPROVe – a study comparing rofecoxib 25 mg to placebo; already initiated during 2000s
- VICTOR – a study to assess the ability of rofecoxib to prolong disease-free and overall survival in patients with resected colon cancer; initiated in 2002.
- ViP – a third study examining the ability of rofecoxib to prevent prostate cancers in men at risk; initiated in 2003 after discussions with regulatory agencies.

Together, these 3 studies would provide information in over 25,000 patients on thrombotic CV events that would all be adjudicated per Merck's SOP. The combined analysis had its own protocol and data analysis plan, and as its primary safety outcome

the confirmed thrombotic CV serious adverse experience endpoint. An External Safety Monitoring Board was to monitor the CV safety for these 3 combined studies as data became available; however, given the sequence of events, the combined ESMB never met. The protocol for the combined study of CV outcomes was finalized in Oct-2002 and it was submitted to and discussed with FDA and with the regulatory agency in the UK, the reference member state (RMS) for the EU registration.

Continual Monitoring of Ongoing Studies (Section 4.3.2)

At the time of VIGOR, Merck made a commitment to continue to update our pooled analysis of CV events.

The first pooled analysis was based on data available in Sep-2000 and published in Circulation in 2001 by Konstam *et al.* [15]. The OA Phase IIb/III Study Extensions were completed by 2001; the final OA data along with any other new and updated data available at the time were included in an updated pooled analysis that was provided to FDA in Jul-2001. The results were consistent with the original analysis discussed above. The RA Phase IIb/III Study Extensions were completed in 2001; the final RA data along with any other new and updated data available at the time were included in an updated pooled analysis based on Jan-2002 data that were submitted to regulatory agencies in the 2nd quarter 2002 and published by Weir *et al.* in 2003 [42]. The Alzheimer's Disease studies completed in 2003; the final Alzheimer's disease data along with any other new and updated data available at the time were included in the final update to the pooled analysis based on Jun-2003 data. These data were provided to Regulatory agencies and to the APPROVe ESMB in the late 2003 to early 2004 timeframe. In the final data from the Alzheimer's studies the overall rate of confirmed thrombotic CV events was not elevated on rofecoxib compared with placebo. The final CV pooled analysis encompassed a period of up to 4 years of follow-up in more than 32,000 patients representing over 19,300 patient-years of experience with rofecoxib or comparator agents. The data continued to demonstrate similarity between rofecoxib and placebo or non-naproxen NSAIDs and to demonstrate a significant difference for rofecoxib compared with naproxen.

In the final Alzheimer's Disease data the overall relative risk for rofecoxib 25 mg with respect to placebo of confirmed thrombotic CV serious adverse experiences was 1.01 (95% CI 0.67, 1.53) (Section 4.3.2.2). A non-constant relative risk for rofecoxib over placebo was observed over time and there appeared to be a decreased risk for events in the rofecoxib group for the first 18 months of the trial followed by an increased risk in the rofecoxib group after 18 months. However, as discussed below, the pooled analysis did not reveal a pattern of changing relative risk over time in any of the data sets. Thus, given the overall relative risk of 1.01 in the Alzheimer's Disease studies, it was interpreted that the variability in relative risk over time represented chance variation about the mean and was not a clinically meaningful observation.

The final pooled analysis in 2003 of cardiovascular events in the rofecoxib clinical trials program continued to demonstrate similarity between rofecoxib and placebo or non-naproxen NSAIDs and to demonstrate a significant difference for rofecoxib compared

with naproxen (Section 4.3.2.3). As alluded to above, because of the finding of a non-constant relative risk in the Alzheimer's studies, the pooled data were analyzed by duration intervals in order to examine if the relative risk changed with duration of exposure to study drug. The point estimates for the relative risks across the chosen time points approximated 1 for the placebo-controlled and non-naproxen-controlled data sets and no trend was observed in the naproxen controlled data set. Given these data, there was no clear evidence to support an increased risk in the >12 month time period.

Subgroup analyses (by rofecoxib dose, baseline CV risk, and aspirin use) were carried out for each data set within the final pooled CV data. The estimated rate of APTC events for rofecoxib 50 mg was greater than for 25 mg. This was due to an imbalance in the number of thrombotic strokes in studies completed prior to the implementation of the CV Adjudication SOP. There was no apparent dose-related effect of rofecoxib on the risk of sustaining a myocardial infarction. There were no statistically significant imbalances in relative risk between the subgroups of patients at an increased baseline CV risk versus those not at an increased risk for the APTC combined endpoint. Data in aspirin users were limited. There was no treatment-by-subgroup interaction and no apparent difference in relative risk between aspirin users and non-users in any of the data sets. In consideration of the APPROVe findings, additional subgroup analyses are being conducted.

Efficacy Data From Alzheimer's Disease Studies

No beneficial effect of rofecoxib was observed in the treatment of Alzheimer's Disease [43; 44] and the data in the prevention study were conflicting [45]. While the primary endpoint demonstrated a higher rate of conversion to Alzheimer's Disease compared to placebo, this finding was not supported by any of the secondary endpoints in the trial (see APPENDIX 2).

Mortality (Section 4.3.3)

The incidences of overall mortality and of cardiovascular mortality were generally similar across treatment groups in the rofecoxib program. In the OA and RA studies, patients were not followed after discontinuation. The standard tabulation method included patients who died while taking study therapy or those who had a fatal adverse event that started within 14 days of the last dose of study therapy. In the Alzheimer's Disease prevention study (Protocol 078), and in APPROVe, patients who discontinued were followed until study termination, allowing a true ITT analysis of mortality in addition to the on-drug analysis.

In VIGOR, RA Phase IIb/III, and in the ADVANTAGE study, differences in the rates of mortality were not seen for rofecoxib compared to naproxen or rofecoxib compared to placebo.

In the OA studies, mortality incidences were significantly lower on rofecoxib than comparator NSAIDs (diclofenac, ibuprofen, and nabumetone); 5 (0.13 per 100 patient-years) deaths on rofecoxib and 8 (0.26 per 100 patient-years) deaths for the nonselective NSAID comparator.

In the Alzheimer's Disease studies, the total number of deaths was not inconsistent with that expected for an elderly population. However, the incidence was significantly higher on rofecoxib than placebo: 36 (2.1 per 100 patient-years) patients in the rofecoxib group and 19 (1.0 per 100 patient-years) in the placebo group in the on-drug period of the primary safety period. One study included a three month randomized withdrawal period during which an additional 3 deaths occurred (all randomized to placebo for the initial treatment period and the withdrawal period). The difference between rofecoxib and placebo in on-drug mortality did not reflect any increases in particular types of events to suggest causality in the Alzheimer's studies [43; 45]. Of these deaths, 11 in the rofecoxib group and 5 in the placebo group were thrombotic cardiovascular deaths. These final data were consistent with the interim data that had been included in the rofecoxib label in 2002: 8 thrombotic cardiovascular deaths in the rofecoxib group and 3 in the placebo group. There were an additional 6 deaths in the off-drug period for Protocol 091 (4 assigned to rofecoxib and 2 assigned to placebo). None of these deaths were due to thrombotic cardiovascular events. Off-drug follow-up mortality data for Protocol 078 were available for less than half the patients and the median duration of off-drug follow-up was longer in the rofecoxib group. There were 22 deaths (17 in patients assigned to rofecoxib and 5 in patients assigned to placebo); 12 of these (11 in the rofecoxib group and 1 in the placebo group) occurred more than 48 weeks after treatment discontinuation. Eight of these 22 off-drug deaths in Protocol 078 were due to thrombotic cardiovascular events. Data from APPROVe are provided below.

Observational Studies of CV Risk in Patients Prescribed Rofecoxib (Section 5)

Observational studies are helpful in evaluating associations and generating hypotheses. They are particularly advantageous in situations where there is limited clinical trial evidence of an uncommon or rare adverse event. However, they are non-randomized and non-blinded, thus more prone to bias than randomized clinical trials and for that reason are considered to be weaker than randomized experiments for establishing causality. [46; 47; 48]

A number of observational studies of cardiovascular thrombotic risk with the use of rofecoxib have been presented or published. Currently, seven have been published in peer-reviewed journals.[49; 50; 51; 52; 53; 54; 55] Two of them are open-label studies of rofecoxib in clinical practice with no comparator.[51; 49] and one is a "prescription event monitoring" study [53] where physicians are solicited by regulatory agencies to provide safety information regarding newer drugs they have prescribed. The remainder are comparative studies. In two the authors conclude there is no difference in risk with rofecoxib compared with non-use of NSAIDs.[52; 55] One also indicates no difference in risk compared with other NSAIDs or COX-2 inhibitors.[52] The others [50; 54] are inconsistent with each other and with clinical trial evidence, In one [50], rofecoxib only at doses greater than 25 mg was significantly associated with an increased risk of serious coronary heart disease among patients who were "new users" compared with non-users of NSAIDs. In the other [54] rofecoxib (all doses combined) was associated with a significantly increased risk of acute MI compared to celecoxib (all doses combined). This increased risk however was demonstrated only during the first 90 days of use, after which the risk was similar. The authors also concluded a difference between rofecoxib

and no NSAID use although this difference did not reach statistical significance (p=0.054). Therefore, the comparative observation studies do not provide clear conclusions about the cardiovascular safety profile of rofecoxib. Given the inherent limitations of observational and cohort studies, and the superiority of clinical trial data for decision making, we placed greater weight on the consistent findings in our large clinical trials data base than on the inconsistent observations that arose from these epidemiologic analyses.

CV Safety Results From the APPROVe Study (September 2004; Section 6)

The APPROVe study was a multicenter, randomized, placebo-controlled double-blind clinical trial in 2586 patients to determine whether 156 weeks (3 years) of treatment with rofecoxib would reduce future adenoma occurrence in patients with a history of colorectal adenomas. Patients who completed the year 3 colonoscopy, with removal of all identified polyps, would be eligible to participate in an off-drug 1 year study extension. Approximately 1400 patients had enrolled in the extension as of 09-Dec-2004, and these patients were planned to have a year 4 colonoscopy at the end of the 1 year extension to evaluate the potential for accelerated adenomatous polyp recurrence; during the extension, blinding to the base study treatment assignments was to be maintained. As described above, a key CV safety endpoint was prespecified.

The primary cardiovascular safety endpoint was the incidence of confirmed thrombotic CV events. APPROVe was one of 3 placebo-controlled studies that contributed to the CV Outcomes protocol for rofecoxib. Data on confirmed CV events in APPROVe were to have been combined with data from the other 2 studies based on a prespecified analysis plan; however, given the decision by the external safety monitoring board (ESMB) to stop the APPROVe study based on the CV data, the data are being analyzed separately. The final ESMB meeting was on 17-Sep-2004, and the committee recommended that participating patients be instructed to discontinue study treatment. The ESMB has indicated that they believed that early termination at this time would not adversely impact the planned efficacy analysis using the Year 3 colonoscopy results which would be important for a full assessment of risk/benefit in this population. In accordance with the protocol, this recommendation was first discussed with the executive committee of the APPROVe administrative committee and then with the entire administrative committee. The administrative committee agreed with the recommendation to discontinue the study and this was communicated to Merck on the evening of Thursday 23-Sep-2004. Patients were notified to stop study drug on 30-Sep-2004, and Merck also announced on that day that the drug was being voluntarily withdrawn from the market.

The cardiovascular safety data in this background document represent the preliminary data that were provided to the ESMB for their meeting on 17-Sep-2004. The data that will be presented at the Advisory Committee in Feb-2005 will be based on the final data which will be available in late Jan-2005.

Efficacy Data From APPROVe (Section 6.1)

The cumulative adenoma recurrence rates were significantly lower with rofecoxib vs. placebo for both primary and secondary endpoints. The cumulative Year 0 to 3 recurrence rate for colorectal adenomas was 40.9% for rofecoxib and was 54.8% for

placebo. The relative risk for rofecoxib versus placebo was 0.75 with a 95% confidence interval of (0.67, 0.83) which was significantly less than 1 ($p<0.001$). This result supported the primary hypothesis for the trial.

Overall Safety From APPROVe (Section 6.1)

As anticipated, there was an increased risk of hypertension, congestive heart failure and edema associated with rofecoxib treatment compared to placebo, consistent with the previously documented adverse event profile of both NSAIDs and coxibs. Discontinuations were more frequent in the rofecoxib patient group; the three most common causes of discontinuation were hypertension, increased blood pressure and peripheral edema. Overall mortality was similar in both treatment groups: 5 deaths in each group while taking study therapy or within 14 days of discontinuing, and an additional 15 deaths (8 in the rofecoxib and 7 in the placebo groups) off-drug in the ITT analysis. As discussed above, although the absolute rates were low, confirmed upper GI events occurred more frequently with rofecoxib than placebo.

Cardiovascular Safety Results From APPROVe (Sections 6.1 and 6.2)

A total of 70 patients (45 in the rofecoxib 25 mg group and 25 in the placebo group) had one or more confirmed thrombotic CV serious adverse events as determined by an independent blinded adjudication committee. Treatment with rofecoxib was associated with an overall relative risk of 1.96 (95% CI: 1.20, 3.19) compared to placebo for the development of confirmed thrombotic cardiovascular serious adverse events, due primarily to a higher incidence of acute myocardial infarction and ischemic cardiovascular stroke.

A Kaplan-Meier analysis of the cumulative incidence of confirmed thrombotic cardiovascular serious adverse events over time showed that the separation of the cumulative incidence curves for rofecoxib and placebo did not begin until after 18 months of chronic treatment. Prior to 18 months there was no apparent difference in the cumulative incidence of these events in the two groups as evidenced by the overlapping plots. The changing pattern of hazard ratio over time was confirmed by the failed test for proportionality of hazards ($p=0.006$). Results for the first 18 months of treatment in APPROVe were consistent with prior placebo-controlled and non-naproxen NSAID controlled data. The difference between rofecoxib and placebo beginning after 18 months appears to mostly reflect a flattening of the placebo curve after 18 months compared with the preceding 18 months. Analyses of cardiovascular risk factors, including blood pressure, did not reveal any consistent associations that might explain the increased risk of thrombotic cardiovascular events in the rofecoxib group. Baseline characteristics of those patients with events after 18 months were comparable between the treatment groups. Results for analysis of the APTC endpoint over time were similar.

DISCUSSION

The COX-2 hypothesis proposed that a selective COX-2 inhibitor would have efficacy similar to a non-selective inhibitor of COX-1 and COX-2 but with superior GI safety. This element of the COX-2 hypothesis deserves emphasis. It was not anticipated that

selective COX-2 inhibitors would provide symptomatic benefit with an adverse effect profile like that of placebo. Rather, it was intended that the analgesic and anti-inflammatory benefit of nonselective NSAIDs could be experienced with a reduced risk of NSAID-related gastropathy. The rofecoxib development program was designed to test the COX-2 hypothesis by comparing rofecoxib to non-selective NSAIDs across a number of diseases and conditions. To a substantial extent, the rofecoxib development program validated the COX-2 hypothesis. However, at this time, at least relative to placebo, rofecoxib demonstrated in the APPROVe study an increased risk of CV events that was first seen beginning after 18 months of chronic therapy. Whether a similar increased risk would be observed relative to nonselective NSAIDs without potent and sustained antiplatelet effects is an as yet unanswered question.

Efficacy and GI Benefit

The early goals of the rofecoxib program were achieved by showing similar efficacy to the nonselective NSAIDs in the treatment of OA and acute pain and improved GI safety based on fecal red blood cell loss, intestinal permeability, endoscopic ulcer studies, and an initial pooled analysis of clinical upper GI events in OA patients. The VIGOR study in RA patients further substantiated the GI benefit of rofecoxib over naproxen and an update to the pooled analysis confirmed a GI benefit over ibuprofen and diclofenac. Additional studies demonstrated efficacy of rofecoxib in reducing the signs and symptoms of both adult and juvenile rheumatoid arthritis and in the treatment of acute migraine attacks. These data confirmed the core components of the COX-2 hypothesis that a selective COX-2 inhibitor would have efficacy similar to a non-selective COX inhibitor with improved GI safety.

Although the risk of GI toxicity with rofecoxib was shown to be substantially lower than with non-selective NSAIDs, the risk is not completely eliminated as revealed in large placebo-controlled studies. Further, in patients taking low-dose aspirin with rofecoxib, the cumulative incidence of endoscopic ulcers was similar to patients taking ibuprofen. Nonetheless, there is evidence to suggest a benefit for the use of selective COX-2 inhibitors in patients taking low-dose aspirin compared to nonselective NSAIDs plus aspirin. However, long term clinical data confirming this benefit have not been presented. Finally, it is of interest that rofecoxib use was associated with a lower incidence of clinical lower GI events compared to non-selective NSAIDs. A similar benefit for celecoxib is suggested by recent data from capsule endoscopy studies [56]. This was an unanticipated additional benefit of the class.

Interpreting Cardiovascular Risk pre-APPROVe

A second finding of the VIGOR study was the imbalance of thrombotic cardiovascular serious adverse experiences resulting in a greater risk for rofecoxib than for naproxen. Analyses of the data did not demonstrate particular subgroups of patients at increased relative risk based either on baseline demographic factors or on blood pressure responses during the study. At that time, two principle hypotheses were put forth to explain those data. The first hypothesis was that inhibition of COX-2 might lead to reduction in endothelial prostacyclin, altering the balance between prostacyclin and thromboxane

towards thrombosis. It was hypothesized that this imbalance could theoretically lead to an increase in the risk of cardiovascular events. The second hypothesis was that the anti-platelet effects of naproxen 500 mg twice daily could have been cardioprotective in the VIGOR study. Both hypotheses were considered feasible and the data available at that time was extensively reviewed and analyzed. A third hypothesis at that time, that the findings of VIGOR were due to chance, could not be excluded as the trial was not specifically designed to evaluate CV safety.

To assess the first hypothesis, data from rofecoxib clinical trials were evaluated. Data from the OA trials showed similar risks of thrombotic cardiovascular events for rofecoxib versus non-naproxen NSAIDs. Data from the ongoing Alzheimer's disease studies comparing rofecoxib to placebo also showed similarity in cardiovascular event rates compared with placebo. These data suggested that rofecoxib 25 mg, the maximal dose recommended for chronic use, was not prothrombotic in comparison to placebo and the pooled data on rofecoxib across all doses (mean dose approximately 25 mg) suggested no prothrombotic effect in comparison to the non-naproxen NSAIDs studied (mostly ibuprofen and diclofenac). Although VIGOR was conducted with a 50 mg rofecoxib dose, analysis of data across the rofecoxib development program available at that time did not demonstrate dose-related trends in thrombotic cardiovascular events. Thus, the weight of the evidence at that time indicated that rofecoxib was not prothrombotic and did not increase the rates of thrombotic cardiovascular events. These data were extensively reviewed at the FDA Arthritis Advisory Committee meeting in February 2001.

As to the second hypothesis, data from previous studies had shown that some nonselective NSAIDs with potent and sustained platelet COX-1 inhibitory properties (such as indobufen and flurbiprofen) could result in vascular-protective properties similar to those observed with aspirin [38]. In this regard, the antiplatelet properties of naproxen 500 mg twice daily were further reviewed. The effects of rofecoxib and the nonselective NSAIDs diclofenac, ibuprofen, and naproxen on thromboxane (TXB_2) generation and platelet function had been evaluated in clinical pharmacology studies. Results of these studies showed no inhibitory effects for rofecoxib on TXB_2 synthesis and platelet aggregation and a gradient of inhibitory effects for the nonselective NSAIDs. Among the nonselective NSAIDs studied, naproxen when dosed at 500 mg twice daily had the most potent inhibitory effects on TXB_2 and platelet aggregation and analysis of the time-course of inhibition showed that, among the non-selective NSAIDs studied, only naproxen's inhibition of platelet aggregation persisted at high level across the dosing interval from peak to trough at a magnitude similar to that of aspirin. Further support of naproxen's antiplatelet effects in the VIGOR study was provided by evaluation of adverse experiences typically associated with antiplatelet effects, such as ecchymosis and epistaxis. In VIGOR, naproxen 500 mg twice daily was shown to result in a 2.1 to 3.5 fold increase in the incidence of such adverse experiences compared with rofecoxib. Although the magnitude of a hypothesized cardioprotective effect of naproxen was large, the confidence intervals for the effect size were also fairly large and were not inconsistent with an aspirin-like effect, at least in a relatively higher risk population of patients such

as those with chronic inflammatory disease. Finally, the TARGET trial with lumiracoxib, which was published in 2004, further suggests a lowering of CV event rates with naproxen but not ibuprofen compared to selective COX-2 inhibitors [39].

In considering whether naproxen 500 mg twice daily could be cardioprotective, we recognized that there were no clinical studies that assessed cardiovascular events with naproxen to support (or refute) the hypothesis, although clinical studies with indobufen and flurbiprofen provided evidence that reversible COX-1 inhibitors with pharmacologic properties similar to naproxen could protect against thrombotic vascular events. Epidemiological data available at that time for nonselective NSAIDs other than aspirin were limited and generally grouped the non-aspirin NSAIDs together. However, given the clinical trial data available, the weight of the evidence was most consistent with a cardioprotective benefit of naproxen and no prothrombotic effect of rofecoxib. Subsequent epidemiologic studies on the ability of naproxen to reduce the risk of thrombotic cardiovascular events have been inconsistent. The strongest findings for reduction in risk have been in RA patients, a population most likely to use the 500-mg dose twice daily on a consistent basis [57]. The implications of the more recent announcement of an increased risk of cardiovascular thrombotic events in patients taking naproxen sodium 220 mg twice daily (equivalent to 200 mg naproxen twice daily) do not preclude a cardioprotective effect of naproxen 500 mg twice daily. At the time of writing this background package these new data were not publically available. In the absence of a better understanding of the mechanisms for the findings in APPROVe and in the absence of a placebo control in VIGOR, it is difficult retrospectively to apply the new information from APPROVe to VIGOR.

At the time the VIGOR results were known, large placebo-controlled studies of rofecoxib had already been initiated, including the Alzheimer's disease studies and APPROVe. These trials were large enough and of sufficient duration to reveal whether rofecoxib was associated with an increased cardiovascular risk of a magnitude similar to the difference from naproxen observed in VIGOR. In addition, the APPROVe study was being monitored by an external data safety monitoring board so that, if a signal appeared, Merck would be notified. Moreover, in 2002, Merck initiated a cardiovascular outcome protocol to pool data from 3 large studies in chemoprevention which would study rofecoxib 25 mg vs. placebo in over 25,000 patients.

During this period Merck continued to monitor and disclose the results of its ongoing programs. Throughout this time, Merck's clinical trials data from its OA program comparing rofecoxib to non-naproxen NSAIDs and from the Alzheimer's Disease program comparing rofecoxib to placebo, and pooled analyses of data across all the clinical program, continued to support its interpretation that rofecoxib did not increase the risk of cardiovascular thrombotic events in comparison to either placebo or non-naproxen NSAIDs, although a difference from naproxen remained evident. Subgroup analyses of updated pooled data based on baseline demographic factors and aspirin usage did not reveal patients in whom there was an increased relative risk with rofecoxib. Data on duration and dose were limited but overall did not support the implication that these parameters had an effect on the relative risk of cardiovascular thrombotic events.

As noted above, other clinical trials data reported in this time frame supported the view that the cardiovascular data with naproxen 500 mg twice daily were different from those obtained with other commonly prescribed NSAIDs and selective COX-2 inhibitors. In all of these selective COX-2 inhibitor programs, the data suggested no difference in thrombotic cardiovascular event rates between selective COX-2 inhibitors and ibuprofen or diclofenac.

Also in this time frame, data from retrospective observational studies on the cardiovascular safety of rofecoxib, celecoxib, and NSAIDs became available. Although such observational studies can be useful to generate hypotheses, especially when there are consistent findings across several data bases and the magnitude of the observed effect is large [58], in general these studies need to be interpreted with caution. This was especially true for studies comparing the selective COX-2 inhibitors to non-selective NSAIDs. Selective COX-2 inhibitors were restricted by managed care organizations and channeled to the types of patients who had an increased risk for both GI and CV events whereas non-selective NSAIDs were used in younger, healthier patients. Overall, the results of these observational studies were inconsistent with respect to differences between users of selective COX-2 inhibitors and non-selective NSAIDs, between NSAID users and non-users, and with respect to dosage effects. In several instances, stated conclusions were based on a limited numbers of events. Although we carefully followed this literature, we believed that our clinical trials database was more robust and provided higher quality data than these observational or retrospective database studies. Therefore greater weight was placed on clinical data in decision making and, in that regard, believed that the study of cardiovascular outcomes we had initiated would be able to definitively answer the question. The more recent revelation from a celecoxib clinical study versus placebo of an increased cardiovascular risk of similar or greater magnitude to that observed in the rofecoxib APPROVe study is in sharp contradiction from the conclusions of epidemiologic retrospective database studies and further illustrates the limited ability of retrospective studies to account for all the variables that can impact an assessment of risk.

Given the strong GI data, the large CV safety databases in the Alzheimer's disease studies demonstrating similar rates of thrombotic cardiovascular events on rofecoxib 25 mg and placebo, and the large CV safety database in OA patients demonstrating similar rates of thrombotic cardiovascular events on rofecoxib and non-naproxen NSAIDs, we believed that rofecoxib did not increase the risk of thrombotic cardiovascular events, that the risk benefit of rofecoxib over older NSAIDs was clearly in favor of rofecoxib, and that our labeling for rofecoxib was appropriate and reflected the state of knowledge at the time. Indeed, rofecoxib was the only agent marketed in the US with a proven GI benefit compared to nonselective NSAIDs. FDA-approved labeling for rofecoxib reflected both the GI benefit and conflicting cardiovascular data.

When we learned the APPROVe data at the end of Sep-2004, we immediately acted based on the new data.

Interpreting Cardiovascular Risk post-APPROVe

Data from the APPROVe study confirm the findings in our other clinical trial databases that there is no evidence for an increase in the relative risk of sustaining a thrombotic CV event for the rofecoxib group versus placebo over the first 18 months of treatment. However, in APPROVe, the risk of thrombotic CV events in patients taking rofecoxib 25 mg began to diverge from placebo beginning after 18 months of chronic therapy; over time the difference became significant. The mechanism(s) of the CV safety findings from APPROVe were uncertain.

At the time, many hypotheses were proposed to explain the APPROVe findings. These included hypotheses based on molecule specific effects unrelated to the inhibition of COX-2, hypotheses based on the inhibition of COX-2 which proposed that all NSAIDs could increase the risk of thrombotic cardiovascular events versus placebo, and hypotheses based on an imbalance in inhibition of COX-2 versus COX-1 which proposed that selective COX-2 inhibitors and not non-selective NSAIDs would increase the risk. With regard to the molecule-specific hypothesis, one study suggested that there was sulfone-mediated oxidation of LDL by rofecoxib and that molecules with a sulfonamide moiety such as celecoxib and valdecoxib would not have this effect [59]. Recent revelations regarding the increased cardiovascular risk of celecoxib and valdecoxib would seem to render this hypothesis untenable. Other theories about the protective properties of sulfonamides were also raised. There were also hypotheses proposing that differences among these agents in their relative tendencies to affect blood pressure were the basis for the findings. However, the available evidence did not support such an association. Moreover, the increased risk of thrombotic cardiovascular events observed in APPROVe was greater than what would be predicted by the observed changes in blood pressure. With regard to mechanism-based hypotheses, some suggested that selective COX-2 inhibition may promote atherosclerosis [60; 61; 62] (while still others offered the promise of reduced atherosclerotic progression based on an anti-inflammatory benefit).

Thus, the mechanism of the CV safety findings from APPROVe are uncertain. At the time of the APPROVe results, no other non-aspirin NSAIDs or selective COX-2 inhibitors had been studied in this large a patient group for this duration. Although Merck recognized that rofecoxib benefited many patients and believed that it could have remained on the market with labeling to reflect these new findings, we were unaware of CV data similar to APPROVe with other products and, at that time, believed that the withdrawal of rofecoxib best served the interest of patients.

Although there were several questions raised by the new findings in APPROVe, comparison of the pattern of cardiovascular findings in APPROVe and VIGOR reveals notable differences. In VIGOR, examination of the cumulative incidence curves suggests a difference between rofecoxib and naproxen began starting approximately 1 month after therapy whereas in APPROVe a difference from placebo was not discernible until after 18 months of therapy. The inhibition of platelet aggregation and tendency to form clots is the presumed mechanism of aspirin's efficacy at low dose to reduce the risk of thrombotic cardiovascular events. This effect is seen early after starting low-dose aspirin

therapy. An opposite effect to increase clotting would similarly be anticipated to start early if that were the basis for the rofecoxib findings. The data in APPROVe for a late separation of event rates suggests that an effect of rofecoxib to increase clotting is not sufficient as the sole explanation. The data in VIGOR of an early separation in event rates mimics what has been seen with aspirin and is consistent with a change in the hemostatic balance. Whereas rofecoxib has not been shown in a variety of pharmacology studies to affect platelet aggregation, naproxen has. However, because naproxen is a reversible COX inhibitor, in order to manifest a clinical benefit, naproxen would need to be taken continuously with few off-drug intervals and at a dose sufficient to provide near complete inhibition of platelet thromboxane synthesis across a 12-hour dosing interval. Those conditions were met in the design of VIGOR. For these reasons and for the reasons enumerated elsewhere in the document, Merck continues to believe that the weight of evidence continues to support the hypothesis that naproxen provided a cardioprotective benefit in VIGOR and that the anti-platelet effects of naproxen 500 mg twice daily could account for differences in CV events observed for naproxen in comparison to selective COX-2 inhibitors. In the absence of a better understanding of the mechanisms for the findings in APPROVe and in the absence of a placebo control in VIGOR, it is difficult retrospectively to apply the new information from APPROVe to VIGOR.

Shortly after the APPROVe data were announced, data were released from a study in which the perioperative administration of valdecoxib and parecoxib increased the risk of cardiovascular events in patients who had undergone coronary artery bypass graft surgery. This study confirmed a similar observation from a smaller study [63]. Also, in response to APPROVe, a re-analysis of CV events in ongoing colon polyp prevention studies with celecoxib was performed. On 17-Dec-2004, it was announced publicly that celecoxib 400 and 800 mg daily increased the risk of thrombotic CV events compared to placebo in one colon polyps prevention trial but that an increased risk was not observed with celecoxib 400 mg in another colon polyps trial [64]. And on December 20, it was announced that patients in an Alzheimer's Disease prevention study taking naproxen sodium 220 mg twice day but not celecoxib 200 mg twice daily had a numeric increase in thrombotic cardiovascular events compared to patients taking placebo. At the time of writing this background package, the data that prompted these announcements have not been made publically available. Thus, it is difficult to draw conclusions at this time on the implications of these new findings for the other drugs in this class including COX-2 selective inhibitors and non-selective NSAIDs or to assess topics such as the effects of dose and duration. Although the data suggest that the CV findings may represent a class effect, it is unclear at this time how extensive the class might be: selective COX-2 inhibitors, all NSAIDs, or the subset of NSAIDs without potent and sustained COX-1 inhibitory effects.

Implications of These Findings and Next Steps

The therapeutic options for patients with arthritis and chronic pain are limited. For the near term, NSAIDs and selective COX-2 inhibitors are effective agents with certain benefits and risks both in absolute terms and relative to each other. Although we do not

yet understand all the mechanisms for the new CV findings, there are ample efficacy and clinical safety data available to inform clinical decision making. Physicians and patients should discuss the benefits and risks of these agents and incorporate the new information into their decision making. New and ongoing studies will likely continue to inform on this topic and should be taken into account in any product labeling. In the long term, new therapeutic options are clearly needed.

CONCLUSIONS

- Rofecoxib was the only approved selective COX-2 inhibitor with a demonstrated advantage over nonselective NSAIDs in decreasing the risk of clinical upper GI events. A benefit over nonselective NSAIDs in patients taking concomitant low dose aspirin has been suggested but not conclusively established.
- Rofecoxib use, like all NSAIDs, is associated with renovascular adverse experiences that are mechanism based and dosed related. In general, these effects with rofecoxib are similar to the effects seen with other NSAIDs.
- The data from rofecoxib clinical trials shows a similar incidence of thrombotic cardiovascular events with rofecoxib 25 mg compared to placebo over the first 18 months of chronic usage or from non-naproxen NSAIDs.
- The incidence of thrombotic cardiovascular events is lower on naproxen 500 mg twice daily than rofecoxib. The difference is apparent shortly after initiation of therapy.
- In APPROVe, the risk of thrombotic CV events in patients taking rofecoxib 25 mg began to diverge from placebo beginning after 18 months of chronic therapy; over time the difference became significant. Long term data for rofecoxib in comparison to non-naproxen NSAIDs has not revealed a difference but are limited.
- The mechanism(s) for the increased risk of thrombotic cardiovascular events in the APPROVe study are uncertain.
- There are as yet no long-term data to suggest a difference in the incidence of thrombotic cardiovascular events in selective COX-2 inhibitors compared to nonselective NSAIDs such as ibuprofen and diclofenac that do not have potent and sustained antiplatelet effects.
- It is premature to draw conclusions at this time on the implications of the new findings with rofecoxib, celecoxib, and naproxen for the other drugs in this class including COX-2 selective inhibitors and non-selective NSAIDs or to assess topics such as the effects of dose and duration. Although the data suggest that the CV findings represent a class effect, it is unclear at this time how extensive the class might be: selective COX-2 inhibitors, all NSAIDs, or the subset of NSAIDs without potent and sustained COX-1 inhibitory effects.
- Physicians and patients should discuss the benefits and risks of these agents and incorporate the new information into their decision making. New and ongoing studies will likely continue to inform on this topic and should be taken into account in any product labeling.

1. Introduction

This portion of the background document provides the data on rofecoxib, a cyclooxygenase-2 (COX-2) selective inhibitor, to support the summary and discussion of the findings provided in the executive summary. Rofecoxib received approvals for the treatment of osteoarthritis (OA), rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), primary dysmenorrhea, migraine, and acute pain. To date, rofecoxib was the only approved COX-2 selective inhibitor to demonstrate definitively a significant gastrointestinal benefit versus nonselective NSAIDs, in this case naproxen.

The main focus of this document is the safety information from clinical studies including gastrointestinal, renovascular, and cardiovascular safety. The chronologic description of the information below provides a framework for the rofecoxib development program within the context of cardiovascular safety monitoring.

1.1 Organization of Document

The document is divided into several major sections. Section 2 provides a summary of the gastrointestinal safety data. These data confirm the premise of the COX-2 hypothesis and provide the foundation of the GI sparing effect noted with rofecoxib versus traditional non-selective NSAIDs. This section is followed by a summary of the renovascular safety including data for parameters typically associated with the mechanism based side effects associated with NSAID use including edema and hypertension.

Sections 4 through 7 focus on the cardiovascular safety data for rofecoxib. Section 4 presents data prior to the knowledge of the APPROVe results and is presented in a chronological format. The data are presented in the order in which they were accrued and evaluated so that the reviewer may better understand and assess what information regarding the cardiovascular safety of this drug was known at each step along the clinical development path of rofecoxib. The CV section includes a brief overview of the mortality data for the rofecoxib program. Section 5 outlines the epidemiological studies and is followed by the CV safety data from APPROVe in Section 6. Section 7 discusses postmarketing data with rofecoxib. Section 8 provides overall conclusions.

The data for GI safety are presented according to their patient population and/or comparator. The section is comprised of the VIGOR study (in RA patients), endoscopy studies in OA and RA patients, and a pooled analysis of all 20 rofecoxib Phase IIb to V OA and RA studies in which rofecoxib was compared with a non-selective NSAID. The primary comparison was to the pooled NSAID group; comparisons to individual NSAID comparators are also provided. In addition, GI safety is presented for placebo controlled studies – 2 studies in Alzheimer's disease patients and the APPROVe study.

The data for renovascular safety are presented according to their exposure and/or patient population (e.g., OA and RA) and are further broken out by comparator. In addition, renovascular safety is presented for large placebo controlled studies – 2 studies in Alzheimer's disease patients and one study in patients with colon polyps (APPROVe).

The data for CV safety are presented chronologically starting with the 1998 Phase IIb/III OA studies, followed by the 2000 VIGOR data and the placebo-controlled Alzheimer's Disease interim results. This is followed by presentation of a pooled analysis of rofecoxib Phase IIb to V studies first performed in 2000 and updated through 2003 in which the data are analyzed versus different comparators (e.g., placebo, naproxen, and non-naproxen NSAIDS). When completed, the pooled analysis encompassed all 28 Phase IIb to V studies ≥4 weeks duration, more than 32,000 patients, and over 19,300 patient-years of experience. The CV safety section concludes with a presentation of the APPROVe data.

A summary of the studies in the rofecoxib development program are provided in Table 1, Table 2, and Table 3. These tables display a comprehensive list of the Phase IIb to V studies which are the basis of the GI and CV analyses presented in this document. As described below in Section 1.2, these analyses included all of the data from studies ≥4 weeks in duration in which rofecoxib was compared to non-selective NSAIDs or placebo. The tables are organized into three data sets: the Placebo-Controlled, Non-Naproxen NSAID-Controlled, and Naproxen-Controlled data sets.

In the GI analysis, results were consistent for the naproxen- and non-naproxen NSAID-controlled data and the datasets were combined into a single NSAID-controlled data set. In the CV analysis, different results were obtained for the naproxen- and non-naproxen NSAID-controlled data sets and differences had been observed in pharmacology studies of these agents. Therefore, the data sets were analyzed separately.

Each table includes the number of patients, the date the first patient was enrolled (First Patient In), and the date the last patient completed (Last Patient Out) each study. As the data in this document are often reported by groupings of studies (e.g., Phase IIb/III OA Studies), these grouping are further delineated in the tables as Study Populations. In addition, Figure 1 provides an over-all time line for the main study populations described in this document. Of note, individual patients may be counted in more than one dataset due to some studies having a placebo- and active comparator-controlled initial study period followed by an active comparator-controlled Part II or extension period.

Table 1

Summary of Rofecoxib Studies
Placebo-Controlled Data Set

		Rofecoxib		Placebo			
Population	Study No.	N	PYR†	N	PYR†	FPI	LPO
RA Phase IIb/III	PN 068	332	49	168	24	12/17/1997	6/17/2001
	PN 096	459	97	301	58	4/1/1999	4/25/2001
	PN 097	612	137	299	62	5/11/1999	3/6/2001
	098+103	219	55	221	56	7/6/1999	7/6/2000
	All RA	1622	338	989	201	12/17/1997	6/17/2001
OA Phase IIb/III in NDA	PN 029	378	46	145	16	4/29/1996	9/30/1999
	PN 033	446	66	69	9	4/14/1997	11/18/1997
	PN 040	486	72	74	11	5/14/1997	1/1/1998
	PN 044	381	154	177	52	1/13/1997	2/18/1998
	PN 045	388	157	194	61	3/4/1997	2/18/1998
	PN 058	174	21	52	6	8/1/1997	7/27/1999
Add'l OA	PN 083	98	21	100	21	4/20/1998	2/9/2000
	PN 085	424	61	208	28	9/17/1998	3/3/1999
	PN 090	390	56	196	27	10/26/1998	5/17/1999
	PN 136	399	95	816	201	12/19/2000	2/5/2002
	All OA	3564	750	2031	432	4/29/1996	2/5/2002
ALZ	PN 078	723	1369	728	1563	4/29/1998	4/23/2003
	PN 091	346	292	346	367	2/10/1999	11/30/2000
	PN 126	380	186	376	192	4/1/2000	5/30/2001
	All ALZ	1449	1847	1450	2121	4/29/1998	4/23/2003
Other	PN 118	102	15	58	8	1/2000	7/2000
	PN 120	252	28	128	14	1/8/2000	6/27/2000
	PN 121	210	23	100	11	12/28/1999	6/16/2000
	PN 125	89	23	83	22	4/4/2000	6/29/2001
	PN 129	8	3	9	4	11/2000	4/2002
	APPROVe	1287	3041	1299	3315	2/8/2000	9/30/2004‡
	All OTH	1948	3133	1677	3374	12/28/1999	9/30/2004
ALL COMBINED		**8583**	**6068**	**6147**	**6129**	**4/29/1996**	**9/30/2004**

OA = Osteoarthritis, RA = Rheumatoid Arthritis, and ALZ = Alzheimers Studies.
FPI = First patient in (based on randomization visit), LPO = Last patient out (date of last visit) except APPROVe.
† Patient-years at risk.
‡ Date dosing was terminated by Merck

Table 2

Summary of Rofecoxib Studies
Non-Naproxen NSAIDs-Controlled Data Set

Population	Study No.	Rofecoxib		Non-Naproxen NSAIDs		FPI	LPO	Comparator
		N	PYR†	N	PYR†			
OA Phase IIb/III in NDA	PN 029	479	527	92	137	4/29/1996	9/30/1999	Diclofenac 150 mg
	PN 033	446	66	221	32	4/14/1997	11/18/1997	Ibuprofen 2400 mg
	PN 034	463	635	230	309	9/15/1996	6/1/2000	Diclofenac 150 mg
	PN 035	516	645	268	315	11/15/1996	10/12/1999	Diclofenac 150 mg
	PN 040	486	72	249	37	5/14/1997	1/1/1998	Ibuprofen 2400 mg
	PN 044	381	154	184	60	1/13/1997	2/18/1998	Ibuprofen 2400 mg
	PN 045	388	157	193	64	3/4/1997	2/18/1998	Ibuprofen 2400 mg
	PN 058	199	130	128	79	8/1/1997	7/27/1999	Nabumatone 1500 mg
Add'l OA	PN 083	136	121	148	127	4/20/1998	2/9/2000	Ibuprofen 2400 mg
	PN 085	424	61	410	59	9/17/1998	3/3/1999	Nabumetone 1000 mg
	PN 090	390	56	392	57	10/26/1998	5/17/1999	Nabumetone 1000 mg
	PN 136	399	95	400	94	12/19/2000	2/5/2002	Ibuprofen 2400 mg
	PN 902	453	67	456	66	12/29/1998	1/29/2001	Arthrotec™ (50 mg diclofenac/200 mcg misoprostol) BID
ALL COMBINED		**5160**	**2788**	**3371**	**1434**	**4/29/1996**	**2/5/2002**	

OA = Osteoarthritis.

FPI = First patient in (based on randomization visit), LPO = Last patient out (date of last visit)

† Patient-years at risk.

Table 3

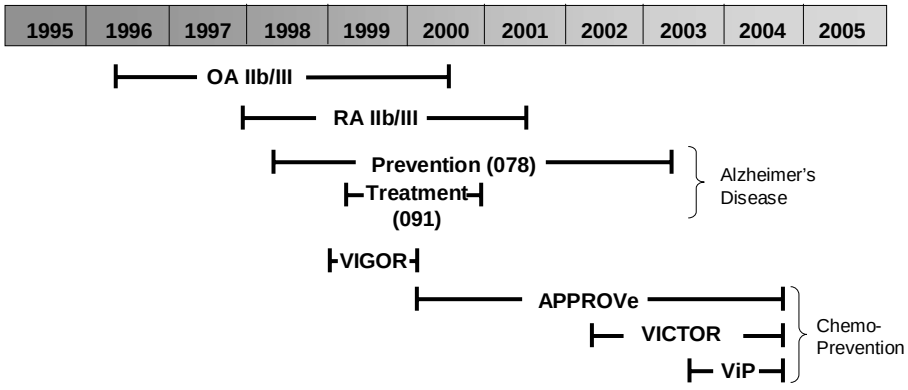
Summary of Rofecoxib Studies
Naproxen-Controlled Data Set

		Rofecoxib		Rofecoxib			
Population	Study No.	N	PYR†	N	PYR†	FPI	LPO
RA Phase IIb/III	PN 068	511	788	86	132	12/17/1997	6/17/2001
	PN 096	554	604	254	308	4/1/1999	4/25/2001
	PN 097	726	995	270	361	5/11/1999	3/6/2001
	098+103	219	55	220	51	7/6/1999	7/6/2000
Add'l RA	VIGOR	4047	2807	4029	2809	1/6/1999	3/17/2000
	All RA	6057	5249	4859	3661	12/17/1997	6/17/2001
OA	Advantage	2785	640	2772	629	3/27/1999	4/10/2000
	PN 901	470	70	473	70	10/2/1998	11/11/2000
	All OA	3255	710	3245	699	10/2/1998	11/11/2000
ALL COMBINED		**9312**	**5958**	**8104**	**4360**	**12/17/1997**	**6/17/2001**

OA = Osteoarthritis. RA = Rheumatoid Arthritis.
FPI = First patient in (based on randomization visit), LPO = Last patient out (date of last visit)
† Patient-years at risk.

Figure 1

Timeline of Rofecoxib Study Populations



1.2 Collection of Data

Through the rofecoxib development program, the standard data collection for all adverse experiences included patients on drug and extending to 14 days after last dose of study therapy. Therefore, all analyses described follow this standard unless otherwise specified. In addition to this standard collection of information, ITT mortality data is provided for the Alzheimer's Disease Program and the APPROVe study; these studies prespecified to follow patients long term after discontinuing study therapy.

2. Summary of Gastrointestinal Safety

This section summarizes the rationale and the gastrointestinal (GI) safety data for the development of rofecoxib, a selective cyclo-oxygenase-2 (COX-2) inhibitor, and the gastrointestinal (GI) safety data which supported its approval as a drug with an improved GI safety profile versus non-selective NSAIDs.

2.1 Rationale for the Development of Rofecoxib

NSAIDs are the most widely used class of drugs for treatment of pain and inflammation with more than 70 million prescriptions and over 30 billion over-the-counter tablets sold annually in the United States alone. The most significant drawback of NSAIDs is their tendency to cause gastrointestinal (GI) ulceration, obstruction, perforation and/or bleeding (PUBs), which may be life threatening [65; 1; 2; 66]. Patients at increased risk of GI complications include those with advanced age, those taking multiple NSAIDs including aspirin even at low doses, patients with a previous history of an upper GI PUB, those taking concomitant corticosteroids, and possibly patients who are also infected with *H. pylori*. Thus, NSAID induced GI toxicity is an important clinical problem with significant public health implications.

The demonstration that NSAID-induced gastropathy was due to inhibition of prostaglandin synthesis, and the definition of two isoforms of cyclooxygenase (COX), a constitutively expressed COX-1 and a second, inducible isoform, COX-2, that was not expressed constitutively in the stomach, led to the COX-2 hypothesis [13]. This hypothesis stated that selective pharmacologic inhibition of COX-2 would be expected to be as effective as inhibition of both COX isoforms in relieving pain and inflammation but with reduced GI toxicity compared to non-selective NSAIDs.

2.2 Gastrointestinal Adjudication Standard Operating Procedure (SOP)

A fundamental objective of the rofecoxib development program was to confirm the COX-2 hypothesis through a rigorous adjudication of all potential upper GI clinical outcomes. To accomplish this goal, all cases of suspected clinical upper GI perforations, gastroduodenal ulcers, or bleeds (PUBs) from all studies containing any dose of rofecoxib were submitted to an external expert, independent, blinded Case Review Committee (CRC). Blinded investigators monitored clinical trials for suspected upper-GI perforations, ulcers, and bleeds. If, in the judgment of the investigator, any PUB events occurred, medical records were sent to the CRC for review. The expert panel, which was also blinded to treatment, used prespecified criteria to determine whether events were confirmed, and whether they were clinically complicated. All adjudication decisions by the committee were final.

2.3 Definition of Adjudicated Endpoints

The following adjudication endpoints were prespecified to be analyzed: (1) confirmed PUBs, (2) confirmed plus unconfirmed PUBs, (i.e. all investigator reported PUBs) (3) confirmed clinically complicated PUBs (a subset of confirmed PUBs), and (4) confirmed plus unconfirmed clinically complicated PUBs (a subset of confirmed plus unconfirmed PUBs). "PUB" was defined as a gastroduodenal perforation, symptomatic gastroduodenal ulcer (with or without obstruction), or upper GI bleed; "complicated PUB" was defined as a gastroduodenal perforation, gastric outlet obstruction due to an ulcer, or a "major" upper GI bleed (as defined by clinical and laboratory evidence of large volume blood loss, such as orthostatic changes in vital signs, need for transfusion of blood products, decrease in hemoglobin ≥2 gm/dL, or other evidence of significantly reduced circulatory volume). An event was considered "confirmed" if it was confirmed by the independent CRC according to prespecified criteria which also allowed the CRC to determine if the event was clinically "complicated" or not [67]; the specific final diagnosis (e.g. gastric or duodenal ulcer, GI bleeding event, etc.) was assigned by the CRC. The CRC could also classify a potential event as "not an upper GI event."

2.4 GI Safety Results in OA and RA Patients

Initial clinical pharmacology studies in normal volunteers assessed surrogate markers of intestinal endothelial injury and demonstrated that rofecoxib use was associated with no increase in fecal RBCs loss compared to placebo [16] and no increase in intestinal permeability [17]. In contrast, non-selective NSAIDs increased both markers of GI injury. Furthermore, using gastric biopsies it was demonstrated that rofecoxib did not suppress prostaglandin synthesis in the stomach of volunteers whereas nonselective NSAIDs produced pronounced suppression [18].

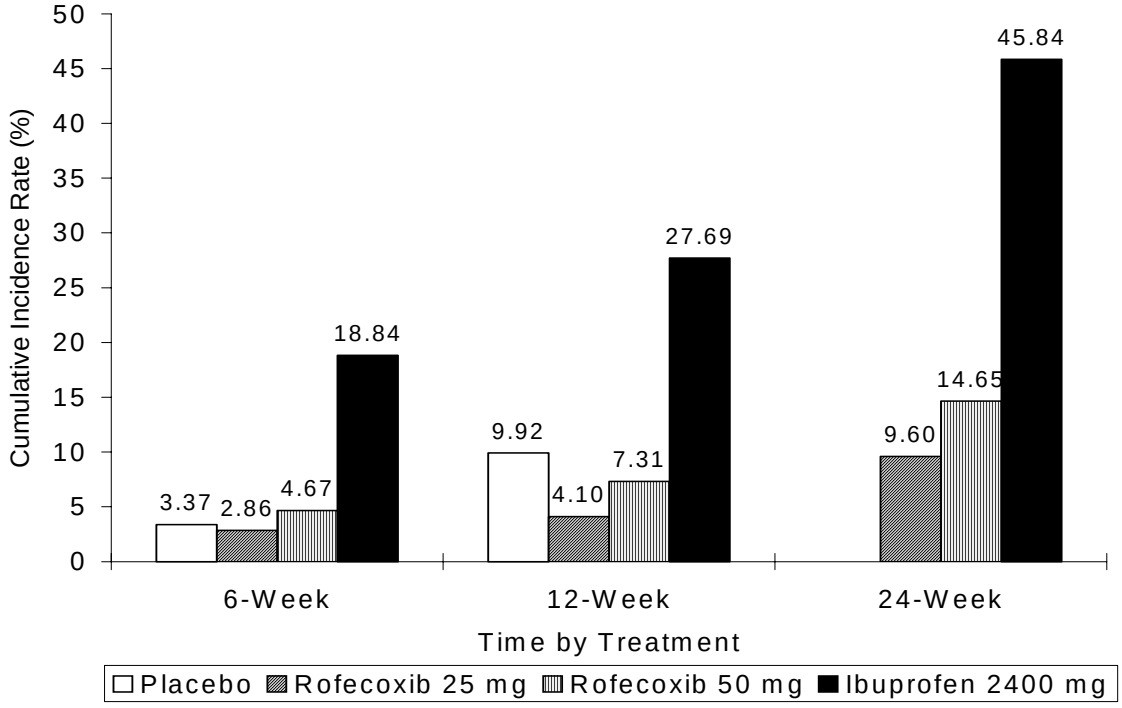
There were 3 major clinical components to the GI safety assessment of rofecoxib in OA and RA patients. First, endoscopy studies analyzed the difference in cumulative ≥3 mm ulcer rates over 12-24 weeks between rofecoxib, placebo and non-selective NSAIDs. In addition, a combined analysis of upper GI clinical events, or PUBs, was performed, based on the prospective collection and adjudication of these events in the clinical program. The initial PUB analysis pooled data from the 8 Phase IIb/III OA studies in the original NDA. Updates to this analysis used the same methodology and pooled all studies in which rofecoxib was compared to a non-selective NSAID of greater than four weeks duration in the Phase IIb to V clinical development program, with the exception of the large GI outcomes study, known as VIGOR. This document will focus on the results from the final update to this analysis which is sufficiently large to allow additional explorations of the data that were not possible in the initial analysis available in 1998 at the time of the original NDA. The Vioxx GI Outcome Research Study, known as VIGOR, was the third component of the GI safety program. There was limited use of concomitant aspirin in the studies in the pooled analysis, and the VIGOR outcomes study excluded concomitant aspirin use at any dose. Aspirin users had been excluded because aspirin inhibits COX-1 activity. Allowing its use would confound the ability to interpret studies that had been designed as a rigorous test of the COX-2 hypothesis.

2.4.1 Endoscopy Studies in OA and RA Patients

Two endoscopy studies were carried out to assess cumulative rates of endoscopic ≥3 mm ulcers in patients with osteoarthritis taking rofecoxib 25 mg or 50 mg, placebo or ibuprofen 2400 mg daily and reported individually and as a combined analysis [68; 69], In each study, the rates of ≥3 mm ulcers by 12 weeks in the rofecoxib groups were significantly lower than the corresponding rate with ibuprofen and in the combined analysis the rates with rofecoxib 25 mg were comparable to placebo. These studies showed that this GI safety advantage for both rofecoxib 25 mg and 50 mg versus ibuprofen was maintained by 24 weeks, as well (Figure 2). A similarly designed endoscopy study was done in patients with rheumatoid arthritis taking rofecoxib 50 mg, placebo or naproxen 1000 mg daily and the results were similar to those in the OA patients [70].

Figure 2

Cumulative Incidence Rate
of Endoscopic Gastroduodenal Ulcers (≥3 mm)
Rofecoxib Versus Ibuprofen in OA Patients
(Protocols 044/045)



N=158 N=186 N=178 N=167

p<0.001 ibuprofen versus placebo, rofecoxib 25 mg, rofecoxib 50 mg at Week 6 and Week 12.
p<0.001 ibuprofen versus rofecoxib 25 mg, rofecoxib 50 mg at Week 24.

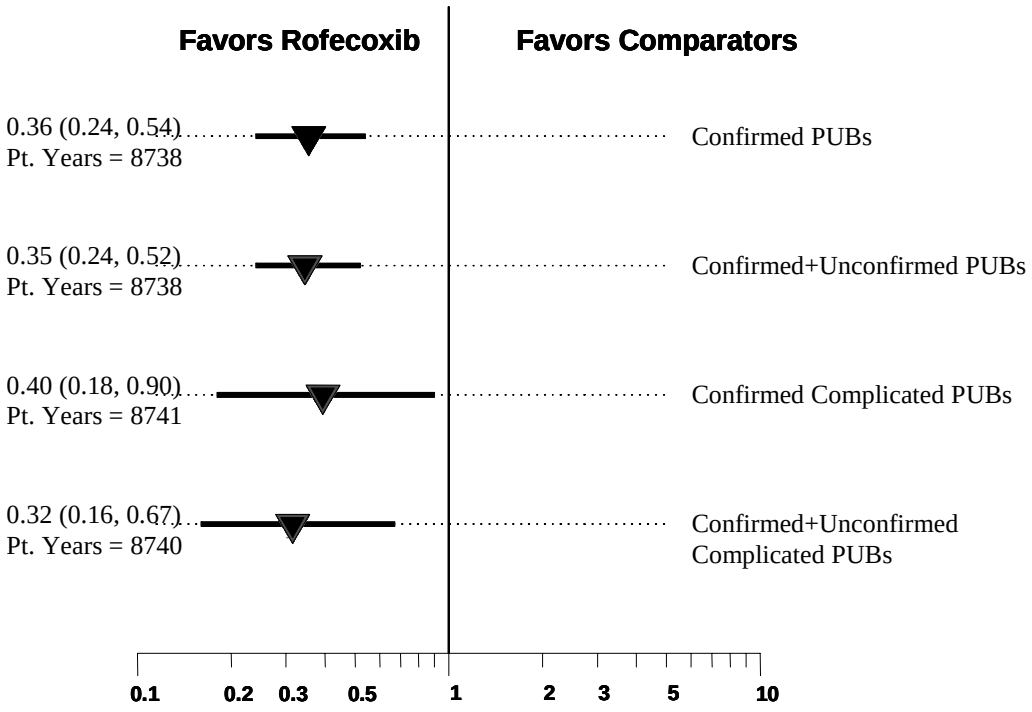
2.4.2 Pooled Analysis of Phase IIb to V Studies With Rofecoxib

A pooled analysis was performed of PUBs in the 20 Phase IIb to V trials from the rofecoxib development program excluding VIGOR with average duration greater than 4 weeks and in which rofecoxib was compared to a non-selective NSAID. This analysis based on data to Feb-2003 is the most recent update to the initial pooled PUB data presented with the original NDA both of which have been published [67; 71]. There were a total of 17,072 patients with either osteoarthritis (15 trials) or rheumatoid arthritis (5 trials) studied. Overall, the analyses in this pooled dataset demonstrated a 64% reduction in the rate of confirmed upper GI PUBs with rofecoxib versus combined NSAIDs. The incidence of confirmed PUBs over 24.8 months was significantly lower with rofecoxib vs. combined NSAIDs (rate/100 patient-years 0.74 vs. 1.87; relative risk 0.36, 95% CI 0.24, 0.54). Similar findings were demonstrated for confirmed complicated PUBs, the types of events associated with the increased risk for GI hospitalization and death with non-selective NSAIDs, and with the investigator reported PUB endpoints, as well Figure 3).

In the pooled analysis, evaluation of PUB data as a function of dose showed a lower relative risk with 12.5 mg and 25 mg versus the 50 mg dose for confirmed and confirmed plus unconfirmed PUBs, suggesting that the benefit observed in VIGOR with rofecoxib 50 mg compared to naproxen 1000 mg is a conservative estimate [72].

Figure 3

Pooled Analysis of PUBs
Rofecoxib Versus NSAIDs Combined
Relative Risk (95% CIs)

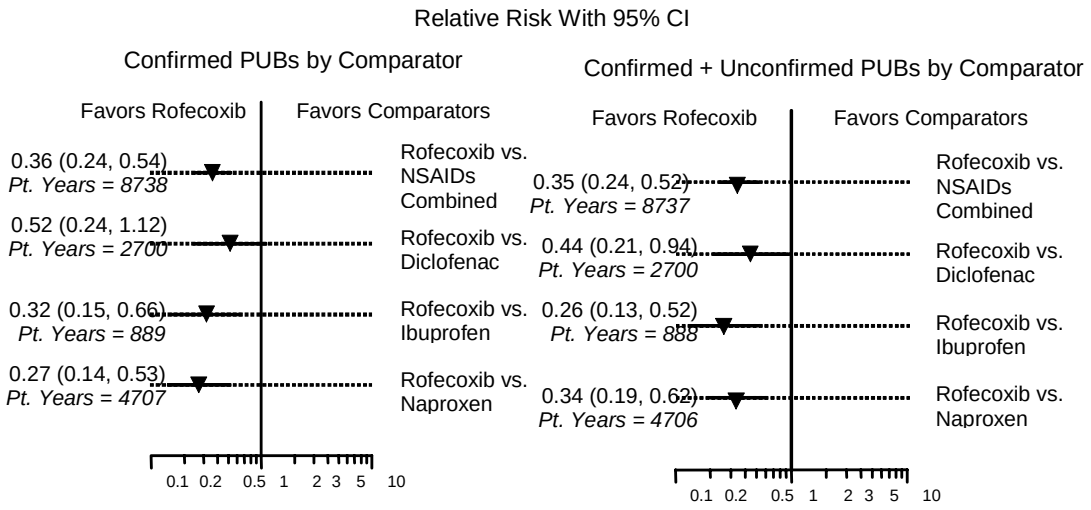


Note: Relative risk via Cox proportional hazard model estimates.

A subgroup analysis was conducted to assess consistency of the data across each of the individual NSAID comparators. It is important to recognize that the results of the studies in this pooled analysis were neither intended nor powered to detect a significant reduction in PUBs with each individual NSAID. Therefore, the subgroup analysis should only be used to assess consistency amongst the subgroups and not statistical significance in each. The combined NSAIDs comparator group in this pooled rofecoxib dataset included over 7,000 patients taking either ibuprofen 800 mg three times daily (N=995), diclofenac 50 mg three times daily (N=1046), nabumetone 1000 or 1500 mg daily (N=930), or naproxen 500 mg twice daily (N=4075). Two of the 3 nabumetone studies, totaling 802 patients in the nabumetone group, were only 6 weeks in duration. In all 3 nabumetone studies, there were no PUBs recorded in the nabumetone group and only two PUB events recorded in the rofecoxib group. Given the short average duration of exposure, and since the number of events was too few to allow meaningful analyses, the nabumetone studies were not included in the subgroup analysis. The results of the subgroup analysis demonstrate reductions of 50 to 70% in relative risk between rofecoxib and each individual NSAID comparator, consistent with the primary result versus all NSAIDs combined (Figure 4).

Figure 4

Pooled Analysis of PUBs
Rofecoxib Versus Combined and Individual NSAIDs



2.4.3 Vioxx GI Outcomes Research Trial (VIGOR)

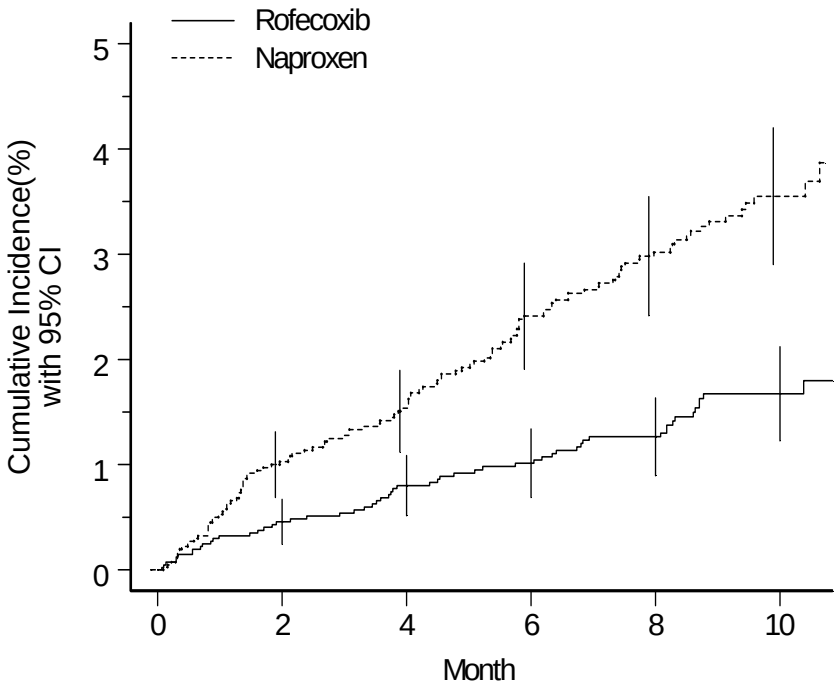
The VIGOR GI outcomes trial in 8076 patients with rheumatoid arthritis demonstrated that patients taking rofecoxib 50 mg had significantly fewer PUBs and complicated PUBs than patients taking the non-selective NSAID naproxen 1000 mg daily [14]. The

rofecoxib 50 mg dose studied in VIGOR was twice the highest recommended and approved dose for chronic daily use. In spite of this maximal dose, there was a 54% reduction in the rate of confirmed upper GI clinical events (PUBs) with rofecoxib versus naproxen. This is displayed in the Kaplan-Meier (KM) plot in Figure 5 (rates of 2.08 vs. 4.49 per 100 patient-years; relative risk 0.46, 95% CI 0.33, 0.64; p<001). In this plot the number of patients at risk displayed along the x-axis at a given point in time is representative of the number of patients remaining in the study at those time points and therefore, are reflective of the patient number and duration of therapy throughout the study. Similar results were found for the other PUB endpoints including the more severe endpoint of confirmed complicated events (rates of 0.59 vs. 1.37 per 100 patient-years for rofecoxib versus naproxen, respectively; relative risk 0.43, 95% CI 0.24, 0.78; p=0.005) (Figure 6). Consistent findings were found across various subgroups of various PUB risk factors, as well [14].

Figure 5

Kaplan-Meier Estimates of Cumulative Incidence of
Confirmed PUBs— Primary Endpoint

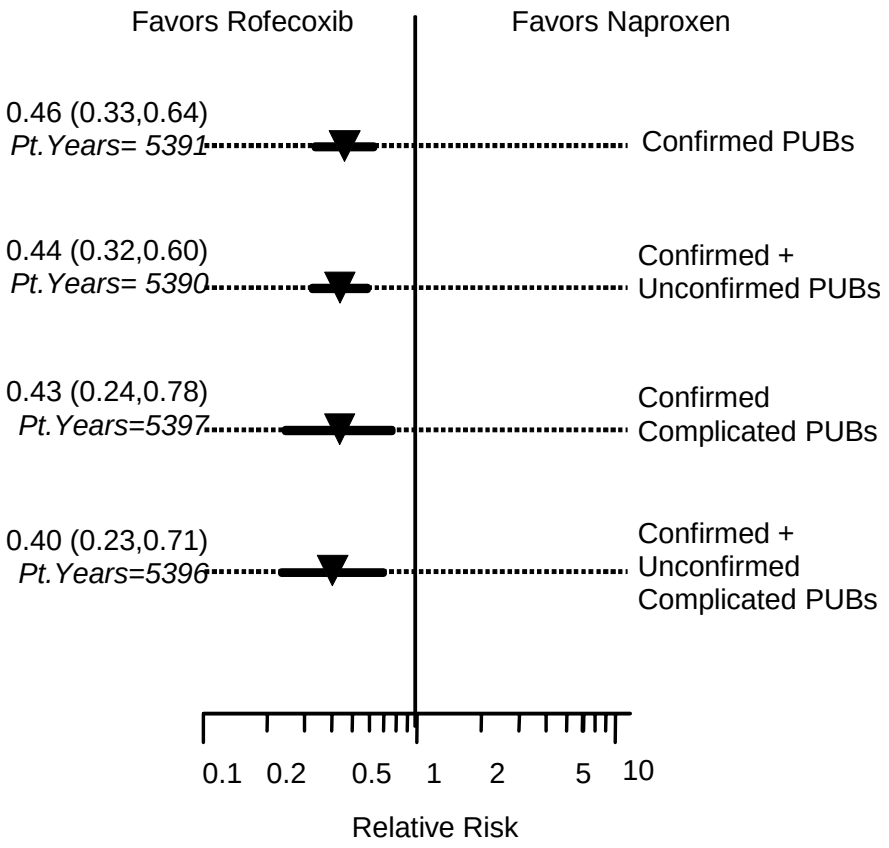
(All Patients Randomized) VIGOR Study



Patients at Risk						
Rofecoxib	4047	3641	3402	3180	2806	1073
Naproxen	4029	3644	3389	3163	2796	1071

Figure 6

Relative Risk (95% CIs)
Confirmed and Unconfirmed PUBs
Rofecoxib 50 mg Versus Naproxen in VIGOR



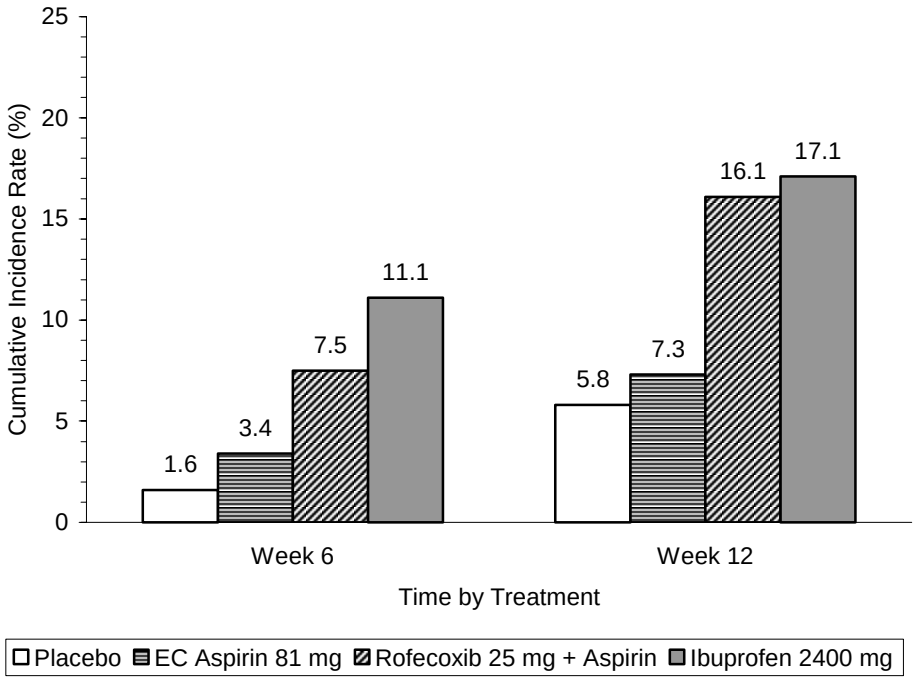
2.4.4 Endoscopy Data With Rofecoxib Plus Aspirin

The data above from VIGOR confirmed the COX-2 hypothesis and demonstrated the superior GI safety of rofecoxib compared to non-selective NSAIDs. As noted above, to rigorously assess the COX-2 hypothesis, patients taking low-dose aspirin at baseline were excluded from almost all of these studies because aspirin inhibition of COX-1 would confound the interpretation of the data. To investigate the GI safety of rofecoxib in patients taking low-dose aspirin, a 12-week endoscopy study was conducted in over 1600 OA patients treated with low-dose enteric coated (EC) aspirin 81 mg daily, low-dose EC aspirin 81 mg plus rofecoxib 25 mg daily, ibuprofen 2400 mg daily, or placebo [73].

The design of this study was similar to the earlier endoscopy studies described above. There was no significant difference over 12 weeks in the cumulative incidence of endoscopic gastroduodenal ulcers ≥3mm in patients taking low-dose aspirin plus rofecoxib 25 mg as compared to those taking ibuprofen 2400 mg daily alone (Figure 7). Although an NSAID plus aspirin would be the alternative treatment choice to a coxib plus aspirin in clinical practice, patients taking low-dose aspirin plus ibuprofen were not studied because it was thought unethical to expose OA patients not requiring aspirin to this combination and the placebo control in the study precluded the study of patients with cardiovascular disease in whom low dose aspirin was indicated.

Figure 7

Life-Table Cumulative Incidence of Gastroduodenal Ulcer (≥3 mm)
Rofecoxib 25 mg plus Low Dose Aspirin Endoscopy Study



EC= Enteric Coated

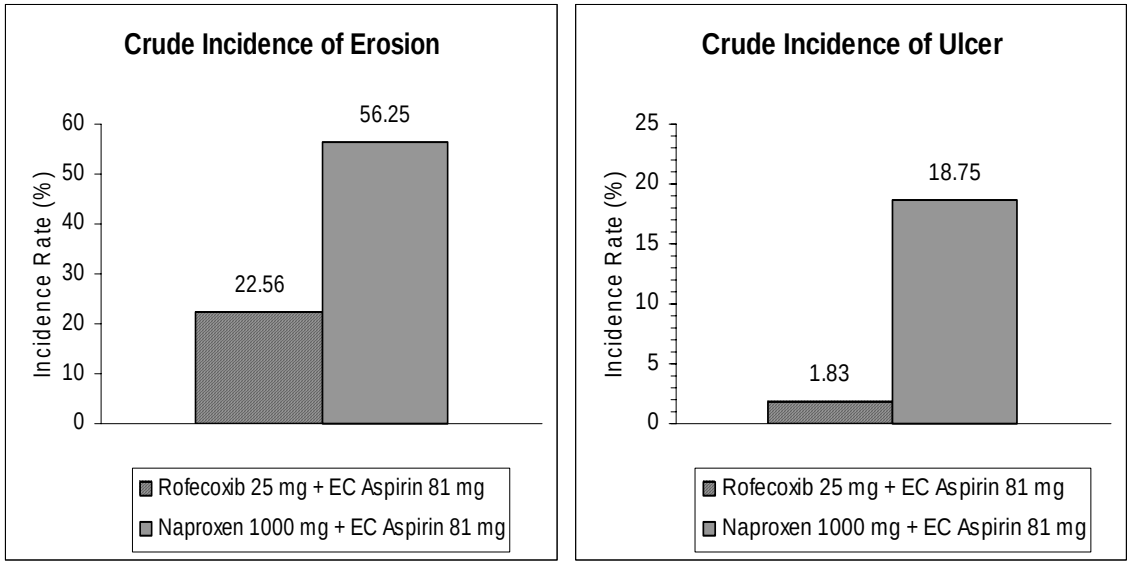
A recently completed 7-day endoscopy study in healthy subjects demonstrated significantly less gastroduodenal injury as measured by erosion scores ≥2 on a 0-4 scale and ulcers of any size with rofecoxib 25 mg plus EC-aspirin 81 mg daily versus naproxen 500 mg twice daily plus enteric-coated (EC)-aspirin 81 mg (rates of ulcers: 1.83% [95% CI= 0.38, 5.25] for rofecoxib + aspirin versus 18.75 [95% CI=10.08, 30.46] for naproxen

+ aspirin, p<.001) (Figure 8) (recent unpublished data). Longer term endoscopy or GI clinical outcomes data are not available for rates of GI mucosal injury with rofecoxib plus low-dose aspirin.

Although the addition of aspirin to rofecoxib appears to increase the degree of upper GI mucosal injury when compared to rates of injury versus rofecoxib alone based on previous similarly designed endoscopy studies, it is still unclear whether this degree of injury is lower than that of an NSAID plus low-dose aspirin. The short term endoscopy data above with concomitant aspirin with either rofecoxib or naproxen suggest this may be true. Further studies are needed to more fully evaluate the relative risk of GI mucosal injury between an NSAID plus aspirin versus a selective COX-2 inhibitor such as rofecoxib, plus aspirin.

Figure 8

Incidence of Gastroduodenal Erosion Score ≥2 and Ulcer Among Subjects Rofecoxib 25 mg plus EC Aspirin 81 mg Versus Naproxen 1000 mg plus EC Aspirin 81 mg Over 7 Days



EC= Enteric Coated

2.4.5 Summary of GI Safety in Active Comparator-Controlled Studies

The clinical data on upper GI PUBs and endoscopic ulcers presented above in active comparator controlled studies strongly supports the improved GI safety profile of rofecoxib versus non-selective NSAIDs. Patients taking rofecoxib with low-dose aspirin 81 mg daily or the non-selective NSAID ibuprofen alone without aspirin have rates of endoscopic gastroduodenal ulceration that are similar. The GI benefit for a selective

COX-2 inhibitor plus low dose aspirin versus a nonselective NSAID plus low dose aspirin remains an open question.

2.5 Data From Placebo-Controlled Studies

The initial pooled analysis in the NDA (see Section 2.4.2) was a combined analysis of all eight major phase IIb/III studies in OA patients available at the time of the original NDA filing for rofecoxib in 1999. Analysis of placebo-controlled data was not a prespecified endpoint because of the small number of anticipated PUB events due to the size of the enrolled placebo group. Nonetheless, results of testing of rofecoxib versus placebo were presented in the filing for completeness since these were the only placebo-controlled data at that time. The data showed that in 3357 patients taking rofecoxib versus 514 patients taking placebo across 4 months, the rates per 100 patient-years for rofecoxib versus placebo were 2.10 vs. 3.58, with the cumulative incidence of confirmed PUBs 0.79% for rofecoxib and 1.23 % for placebo; the difference in cumulative incidence did not reach statistical significance (relative risk 0.60 rofecoxib versus placebo; 95% CI 0.20,1.82; p=0.365) [67].

Subsequently, more extensive controlled data in over 1000 patients taking placebo versus rofecoxib 25 mg became available from the analysis of the PUB data from studies 078 and 091 performed in patients with mild cognitive impairment and Alzheimer's disease patients, respectively. In contrast to the earlier pooled, placebo-controlled data available from the original NDA filing, the rates for confirmed and confirmed complicated PUBs observed in the protocols 078 and 091 combined analysis were higher in the rofecoxib group than in the placebo group. The rate/100-patient years (95% CI) for confirmed PUBs in the rofecoxib group was 1.07, (0.68,1.71) and in the placebo group was 0.26 (0.11,0.62). For confirmed complicated PUBs, the rates/100-patient years were 0.78 (0.45,1.34) for rofecoxib and 0.21 (0.08,0.55) for placebo. Note that despite the advanced age of the population studied (> 65 years), the rates of confirmed PUBs and confirmed complicated PUBs were low in the rofecoxib 25 mg group in comparison to previously reported rates in placebo- and active comparator-controlled studies.

Similar data for rofecoxib versus placebo were found in the APPROVe study which was a placebo-controlled trial designed to examine the efficacy of rofecoxib 25 mg daily in preventing the recurrence of colon polyps in patients at high risk of developing recurrent polyps and colorectal cancer. In this study, in which preliminary PUB data became available in November 2004, with 2586 total patients evaluated, the rate of developing a confirmed PUB was 0.82 (95% CI: 0.56, 1.25) for the rofecoxib group (25/3051 events per patient years exposure) versus 0.18 (95% CI: 0.07, 0.39) (6/3330 events per patient years exposure) for patients on placebo.

These data, plus the placebo controlled data from the Alzheimer's disease studies, represent many more patient-years of exposure than the early placebo controlled data available at the time of the original NDA filing in 1998. These more recent data suggest that patients treated with rofecoxib 25 mg daily appear to have had a higher rate of confirmed PUBs than those taking placebo, in contrast to the more limited early placebo-controlled PUB and endoscopy study data that was available at the NDA filing. As

highlighted previously, comparisons to placebo must be viewed in the context of benefit in the untreated population.

2.6 Lower GI Safety Results

NSAIDs also appear to increase the risk of lower GI clinical events, including lower GI bleeding, perforation, intestinal obstruction, ulcerations and symptomatic diverticular disease [74]. A *post hoc* analysis was carried out of serious lower GI events from the VIGOR megatrial comparing rofecoxib 50 mg once daily, twice the highest recommended dose for chronic daily use, versus naproxen 500 mg twice daily. Lower GI events were defined as: gross rectal bleeding (other than melena) associated with a hemoglobin decrease >2 g/dL or hospitalization, or positive test for fecal occult blood associated with a hemoglobin decrease >2 g/dL and negative upper endoscopy; hospitalization for intestinal perforation, obstruction, ulceration, or diverticulitis. There was a significant decrease in the rate of lower GI events with rofecoxib versus naproxen with rates of serious lower GI events per 100 patient years of 0.41 for rofecoxib and 0.89 for naproxen (relative risk 0.46, 95% CI: 0.22,0.93, p=0.032). The rates per 100 patient-years calculated for all serious GI events combined (i.e. complicated upper GI events plus serious lower GI events) from the VIGOR GI outcomes study, was 0.96 for rofecoxib and 2.26 for naproxen (relative risk of 0.43; 95% CI: 0.27,0.67, p<0.001)[75]. Therefore, rofecoxib 50 mg once daily was associated with a reduction in combined risk of complicated upper and serious lower GI events of 57% versus naproxen 500 mg twice daily.

2.7 GI Safety Conclusions for Rofecoxib

- Analyses of PUBs for rofecoxib in both the VIGOR GI outcomes study with over 8,000 patients and in the pooled analysis of 20 phase IIb to V studies with over 17,000 patients demonstrate that rofecoxib has a superior upper GI safety profile when compared to non-selective NSAIDs.
- Results in the 12 to 24 week surveillance endoscopy studies also support an improved safety profile for rofecoxib versus non-selective NSAIDs.
- Data from a single 12 week endoscopy study (protocol 136) with rofecoxib 25 mg plus low-dose EC-aspirin 81 mg suggest that the concomitant administration of low-dose aspirin with rofecoxib may result in an increased rate of GI ulceration or other complications compared to the use of rofecoxib alone.
- Recent placebo-controlled data from studies with longer treatment exposure suggest that rofecoxib is associated with a higher rate of upper GI injury than is placebo.
- A post-hoc analysis of serious lower GI events from the VIGOR GI outcomes trial indicates an improved lower GI safety profile for rofecoxib versus naproxen.

3. Renovascular Effects

3.1 Background

Edema, CHF, and hypertension are known renovascular effects of COX-2 inhibition and have been observed with all nonselective NSAIDs and COX-2 inhibitors. These side effects of inhibiting cyclooxygenase in the kidney are mechanism-based, dose-related, and are reflected in NSAID class labeling. Renovascular effects were monitored in the rofecoxib program as a prespecified safety endpoint.

Approach to Analyses

To evaluate the clinical impact of potential renovascular effects, edema and hypertension were evaluated as composites of edema-related and hypertension-related adverse experiences. Adverse experiences were reported by investigators based on their clinical judgment. The composite terms were prespecified in order to provide greater precision than the individual adverse experience terms when comparing treatment groups. In addition, congestive heart failure adverse experiences were evaluated in a prespecified manner. Specific terms that comprise each AE category are listed at the beginning of sections 3.2.1 and 3.2.2. Statistical analysis of difference in these adverse experiences is presented if prespecified in the analysis plan.

Frequently occurring AEs within a category were also examined individually, especially to analyze any dose-related trends and differences between rofecoxib and active comparators. In addition, mean changes in diastolic and systolic blood pressure are briefly discussed for each study population.

Datasets

Data are presented first in Section 3.2 for OA and RA patients, as these are the populations in whom chronic dosing was indicated and correspondingly represent the largest patient populations in whom we have data. The populations included in the OA and RA section include the 6-week/6-month OA population, the ADVANTAGE studies, the RA Phase IIb/III Studies, and the VIGOR study. This section is followed by a presentation of the data from large placebo controlled trials (Alzheimer's disease and APPROVe) in Section 3.3.

The 6-week/6-month OA population provided data from the OA Phase IIb/III program and is comprised of 6-week placebo-controlled studies, two 6-month endoscopy studies which included a 4 month placebo-controlled period, and the first 6 months of two 1-year trials. This is the population represented in the approved rofecoxib label from which safety information in OA patients was derived. Consistent with labeling, data for the approved chronic and acute doses (12.5 - 50 mg) and the comparators, ibuprofen and diclofenac, are presented. The ADVANTAGE studies were two 12-week, naproxen-controlled trials in OA patients which evaluated rofecoxib 25 mg and naproxen 1000 mg. These data are presented to provide data for a different comparator than the 6-week/6-month OA studies. Although a single Phase III OA study with nabumetone as a comparator was performed, this study exclusively involved octogenarian OA patients. Because any nabumetone data would have been exclusively derived from this distinct

population, the nabumetone data from this study are not included in the rofecoxib labeling or in the analyses below. The rofecoxib data from this study is included in the approved labeling and the analyses presented herein because, when combined with the rofecoxib data from the other studies, it added to the safety profile relevant to the indicated population.

Renovascular safety data in the RA Phase IIb/III Population comes from studies up to 1 year in duration: a single Phase IIb and two Phase III studies. This is the population represented in the approved rofecoxib label from which general safety information in RA patients is derived. The VIGOR study was a GI endpoint driven study in RA patients with a median duration of 9 months. Importantly, this study only included a 50 mg dose of rofecoxib, twice the maximum recommended chronic dose, in comparison with naproxen 1000 mg.

The large placebo-controlled studies evaluated rofecoxib 25 mg in Alzheimer's Disease and in the APPROVe study. The Alzheimer's Disease program consisted of a 4-year study to assess efficacy in the treatment of Mild Cognitive Impairment and a 15-month study to assess efficacy of rofecoxib in delaying Alzheimer's progression. A third study in Alzheimer's disease, a replicate of the Mild Cognitive Impairment study, was intended as an additional 15-month study but was terminated early after the original 15-month study failed to demonstrated efficacy; therefore it is not included. In the 15-month study, the majority of patients randomized to rofecoxib received active treatment for only 12 months and placebo thereafter; therefore the results of the first 12 months of treatment are provided. The APPROVe study was a 3-year prevention study in patients with a history of colon polyps.

The baseline characteristics are shown for the different populations in Table 4. Consistent with the rofecoxib program, patients in the OA studies were generally older than those in the RA studies and a previous medical history of hypertension was common in all populations.

Table 4
Baseline Patient Characteristics in Rofecoxib Studies Shown
In Renovascular Safety Analyses

	OA 6-week/ 6-month N=4650	ADVANTAGE (3 month OA) N=5557	RA Phase IIb/III (1 year) N=1245	VIGOR (RA) (median 9 mo.) N=8076	Alzheimer's (combined) N=2149	APPROVe N=2586
	(%)	(%)	(%)	(%)	(%)	(%)
Age						
Mean age	63	63	54	58	75	59
Gender						
Female	73	71	81	80	39	38
Male	27	29	19	20	61	62
Medical History of Hypertension	39	45	25	29	36	35

3.2 Data in OA and RA Patients

3.2.1 Edema and CHF

Edema-related adverse experiences included the following terms: edema, fluid retention, hand swelling, lower extremity edema, peripheral edema, upper extremity edema. CHF-related terms included CHF and left cardiac failure.

6-Week/6-Month OA and ADVANTAGE Populations

In the 6-Week/6-Month population, the incidence of edema-related adverse experiences was 2.3% for placebo; 4.9, 6.6, and 9.5% for rofecoxib 12.5, 25, and 50 mg, respectively; and 5.3 and 5.0% for ibuprofen and diclofenac, respectively. The overall incidence of edema in the doses approved for chronic use of rofecoxib was generally similar to comparator NSAIDs.

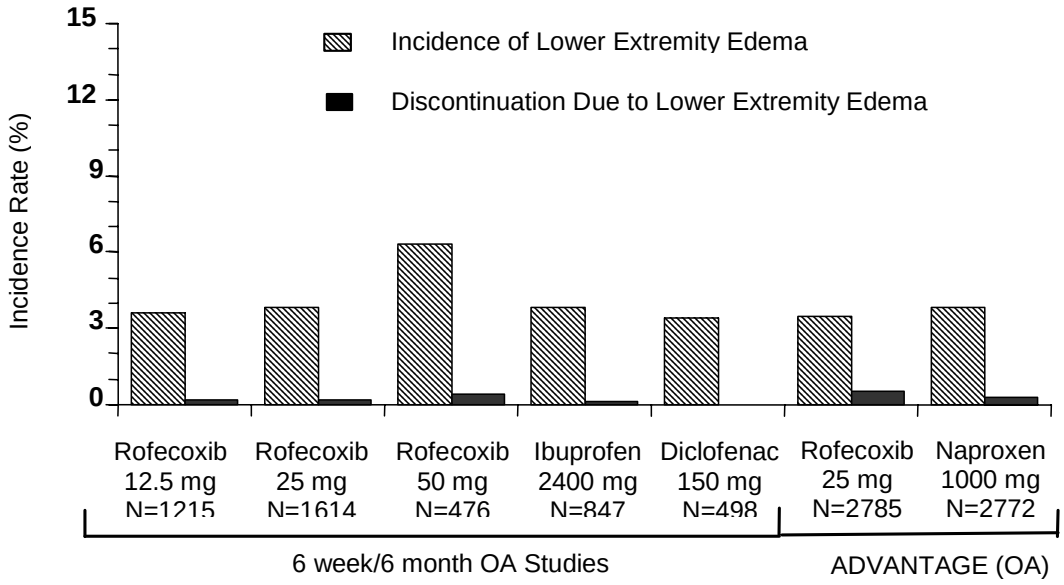
Overall discontinuations due to edema-related adverse experiences were low (<1%) across all treatment groups with no clinically important differences between any dose of rofecoxib and placebo. The percentage of patients who discontinued due to an edema-related adverse experience was 0.0% for placebo; 0.6, 0.6, and 0.8% for rofecoxib 12.5, 25, and 50 mg, respectively; 0.2 and 0.2% for ibuprofen and diclofenac, respectively.

In ADVANTAGE, the incidence of edema-related adverse experiences was 5.5% for rofecoxib 25 mg and 5.2% for naproxen. Discontinuations due to edema-related adverse experiences were low: 0.7% for rofecoxib 25 mg and 0.4% for naproxen.

The most common edema-related adverse experience in these two populations was lower extremity edema. Incidence and discontinuations due to lower extremity edema are presented in Figure 9 for the OA populations. The incidence of edema is highest for the rofecoxib 50 mg dose in the 6 week/6 month population; however the incidence is similar for the doses approved for osteoarthritis, rofecoxib 12.5 and 25 mg, compared with ibuprofen and diclofenac. In ADVANTAGE, the incidence of edema was similar for rofecoxib 25 mg and naproxen.

Figure 9

Incidence of Lower Extremity Edema Adverse Experiences and Discontinuations
Phase IIb/III OA Studies and ADVANTAGE Studies



Although rare, CHF is one of the more clinically significant manifestations of the fluid retention that can be caused by nonselective NSAIDs and COX-2 inhibitors. Therefore, an integrated analysis of CHF and left cardiac failure was conducted. In the 6-week/6-month studies, the incidence of CHF was 0.0% for placebo; 0.4, 0.1, and 0.0% for rofecoxib 12.5, 25, and 50 mg, respectively; and 0.4 and 0.8% for ibuprofen and diclofenac, respectively. In the ADVANTAGE study, the incidence of CHF was 0.4% for rofecoxib and 0.2% for naproxen. There were no clinically important mean changes in body weight in the 6-week/6-month OA studies; these data were not analyzed for the ADVANTAGE studies.

RA IIb/III Studies up to 1 Year and VIGOR Populations

In the RA program, the incidence of edema was generally similar among the doses of rofecoxib and naproxen.

In the RA Phase IIb/III population, the incidence of edema-related adverse experiences was 7.3% for rofecoxib 25 mg, 6.6% for rofecoxib 50 mg and 5.1% for naproxen 1000 mg.

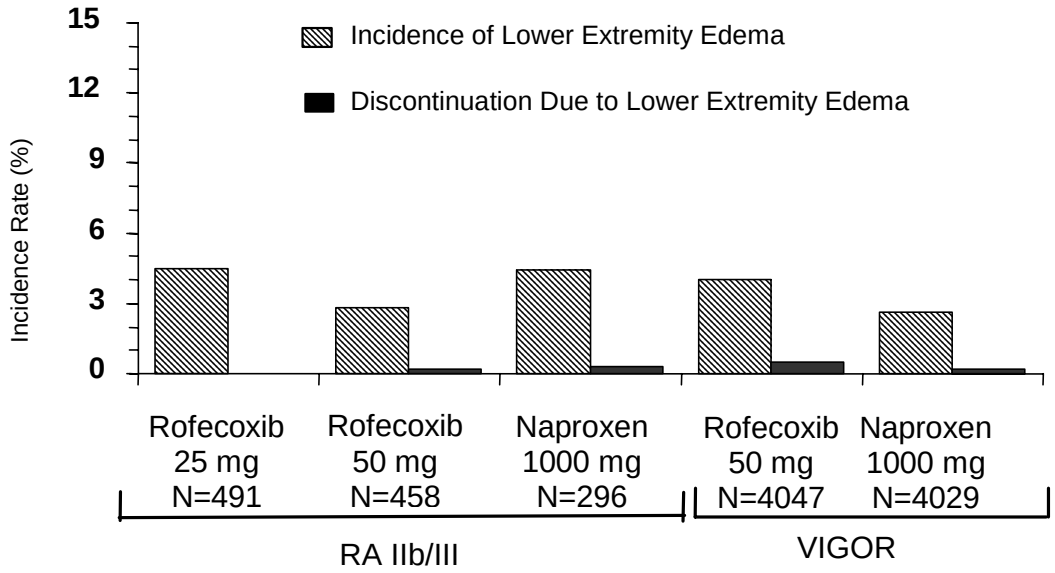
Overall discontinuations due to edema-related adverse experiences were low (<1%) across the treatment groups. The percentage of patients who discontinued due to an edema-related adverse experience was 0.2% for rofecoxib 25 mg, 0.9% for rofecoxib 50 mg and 0.3% for naproxen.

In VIGOR, the incidence of edema-related adverse experiences was 5.4% for rofecoxib 50 mg and 3.6% for naproxen. Discontinuation due to edema-related adverse experiences was prespecified for statistical analysis in VIGOR. The incidence was 0.6% of patients in the rofecoxib group and 0.3% of patients in the naproxen group (p=0.057).

The most common edema-related adverse experience in these two populations was lower extremity edema. Incidence and discontinuations due to lower extremity edema are presented in Figure 10.

Figure 10

Incidence of Lower Extremity Edema
Adverse Experiences and Discontinuations
RA IIb/III Studies up to 1 Year and VIGOR Study



The overall incidences of CHF were low in all treatment groups. In the RA Phase IIb/III population, the incidence of CHF adverse experiences was 0.0% for rofecoxib 25 mg, 0.4% for rofecoxib 50 mg and 0.0% for naproxen. In VIGOR the incidence of CHF was 0.5% for rofecoxib 50 mg and 0.2% for naproxen. The rate of CHF adverse experiences in VIGOR was not statistically significantly different between the 2 treatment groups (p=0.065 for prespecified test of difference in relative risk between groups.) There were no clinically important mean changes in body weight in the VIGOR or Phase IIb/III RA study population.

3.2.2 Hypertension

Hypertension-related adverse experiences included the following terms: blood pressure increased, borderline hypertension, diastolic hypertension, hypertension, hypertensive crisis, hypertension uncontrolled with medication, systolic hypertension, and uncontrolled hypertension.

6-Week/6-Month OA and ADVANTAGE Populations

Dose-related trends in hypertension for OA patients were observed for rofecoxib with a numerically higher incidence at 50 mg, a dose not recommended for chronic use. At the doses approved for osteoarthritis, 12.5 and 25 mg, rofecoxib users had incidences of hypertension which were similar to or slightly higher than with the comparator NSAIDs.

In the 6-Week/6-Month population, the incidence of hypertension-related adverse experiences was 2.2% for placebo; 4.4, 5.5, and 10.1% for rofecoxib 12.5, 25, and 50 mg, respectively; and 3.5 and 3.0% for ibuprofen and diclofenac, respectively.

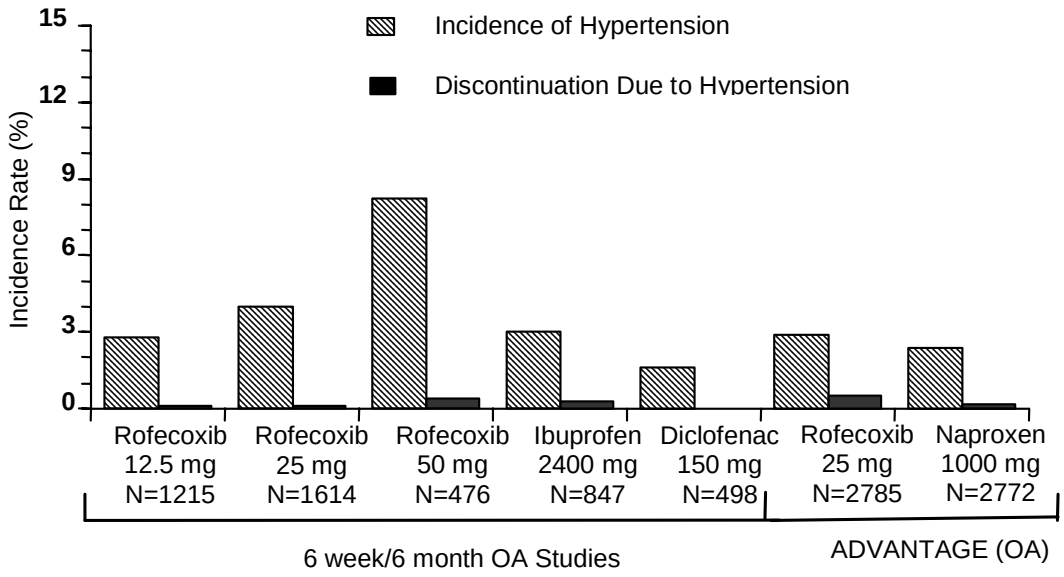
Overall discontinuations due to hypertension-related adverse experiences were low (<1%) across all treatment groups. The percentage of patients who discontinued due to a hypertension-related adverse experience was 0.0% for placebo; 0.1, 0.1, and 0.4% for rofecoxib 12.5, 25, and 50 mg, respectively; 0.4 and 0.0% for ibuprofen and diclofenac, respectively.

In ADVANTAGE, the incidence of hypertension-related adverse experiences was 3.2% for rofecoxib 25 mg and 2.6% for naproxen. Discontinuations due to hypertension-related adverse experiences were low: 0.5% for rofecoxib 25 mg and 0.3% for naproxen.

The most common hypertension-related adverse experience in these two populations was hypertension. Incidence and discontinuations due to hypertension are presented in Figure 11.

Figure 11

Incidence of Hypertension Adverse Experiences and Discontinuations
Phase IIb/III OA Studies and ADVANTAGE Study



RA IIb/III Studies up to 1 Year and VIGOR Populations

In the RA populations, hypertension-related adverse experiences for rofecoxib 25 mg (the dose approved for RA) were higher than observed on naproxen. This was different from results in the OA 6-week/6-month population and ADVANTAGE population where 25 mg was generally similar to the comparator NSAIDs. These differences were reflected in the rofecoxib label for RA. Similar to the OA studies, hypertension-related adverse experiences were higher with rofecoxib 50 mg than comparator NSAIDs.

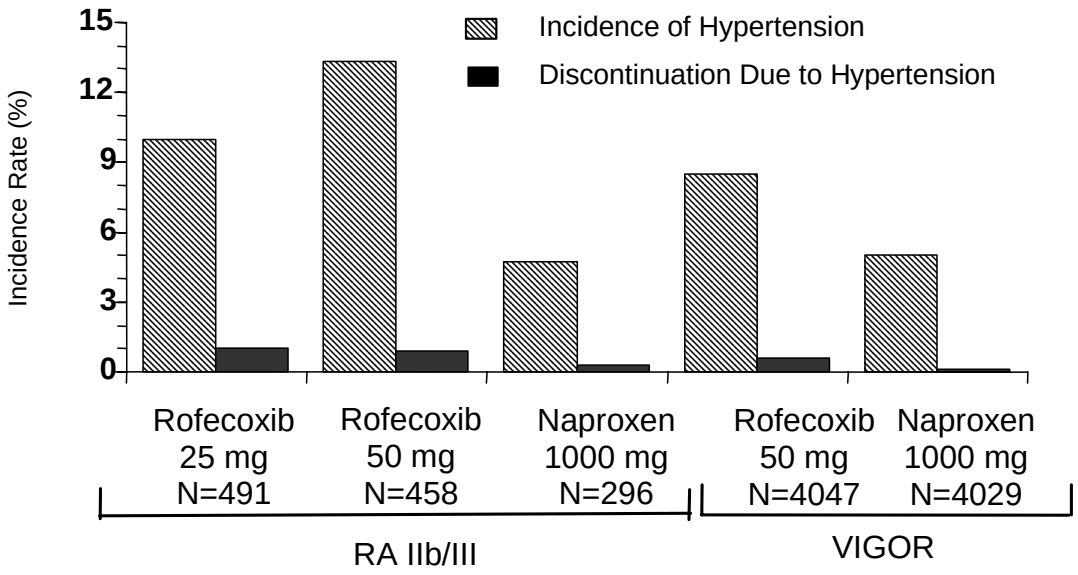
In the RA Phase IIb/III population, the incidence of hypertension-related adverse experiences was 12.0% for rofecoxib 25 mg, 15.5% for rofecoxib 50 mg and 5.4% for naproxen 1000 mg. The percentage of patients who discontinued due to a hypertension-related adverse experience was 1.2% for rofecoxib 25 mg, 0.9% for rofecoxib 50 mg and 0.3% for naproxen.

In VIGOR, the incidence of hypertension-related adverse experiences was 9.7% for rofecoxib 50 mg and 5.5% for naproxen. Discontinuation due to edema-related adverse experiences was prespecified for statistical analysis in VIGOR. The incidence was low, but significantly higher in the rofecoxib group ($p<0.001$): 0.7% for rofecoxib 50 mg and 0.1% for naproxen.

The most common hypertension-related adverse experience in these two populations was hypertension. Incidence and discontinuations due to hypertension are presented in Figure 12.

Figure 12

Incidence of Hypertension Adverse Experiences and Discontinuations
RA IIb/III Studies up to 1 Year and VIGOR Study



Mean Changes in Systolic and Diastolic Blood Pressure

Mean changes in blood pressure are reported relative to the baseline measurement. In both OA and RA studies, baseline measurements of blood pressure were performed at a single randomization visit after NSAID washout. In some studies, blood pressure values were an average of 2 or 3 readings while in other studies they represented a single reading.

6-Week/6-Month OA and ADVANTAGE Populations

Mean changes in diastolic and systolic blood pressure were evaluated in the 6-Week/6-Month studies. Compared with the values at baseline, small dose related increases in mean diastolic blood pressure were noted after 6 weeks of study therapy: 0.4 to 1.4 mm Hg across the rofecoxib doses from 12.5 to 50 mg and 1.0 mm Hg for ibuprofen. Changes in mean systolic blood pressure exhibited a similar dose-related pattern for

rofecoxib (1.1 to 5.1 mm Hg across rofecoxib doses 12.5 to 50 mg) and ibuprofen (3.3 mm Hg). Smaller changes in mean diastolic blood pressure were noted after 6 months for rofecoxib and these changes were not dose-related (ranging from -0.6 for rofecoxib 50 mg to 1.1 mm Hg for rofecoxib 25 mg), diclofenac (0.2 mm Hg), and ibuprofen (-1.1 mm Hg). Small changes in mean systolic blood pressure were present after 6 months for rofecoxib (1.9 to 2.1 mm Hg across the doses of rofecoxib from 12.5 to 25 mg), diclofenac (0.7 mm Hg), and ibuprofen (1.7 mm Hg).

In ADVANTAGE, the magnitude of the systolic blood pressure effects was small over the 12 week study period. Mean increases in systolic blood pressure were 1.0 mm Hg and 0 mm Hg in the rofecoxib 25 mg and naproxen groups, respectively. Mean increases in diastolic blood pressure were 0.3 mmHg and -0.7 mmHg in the rofecoxib and naproxen groups, respectively.

RA IIb/III Studies up to 1 Year and VIGOR Populations

In the Phase IIb/III RA studies, the magnitude of the systolic blood pressure changes from baseline in the 25-mg rofecoxib treatment group generally ranged between 0.8 for the 25-mg and 3.6 mm Hg for the 50-mg rofecoxib groups. Results for the 25-mg rofecoxib, 50-mg rofecoxib and naproxen treatment groups showed no clear effect for diastolic blood pressure; changes ranged between 0.4 for the 25-mg and 2.2 mm Hg for the 50-mg rofecoxib groups.

In VIGOR, the mean change from baseline for systolic blood pressure in the rofecoxib 50 mg was 4.6 mm Hg; the mean change from baseline in diastolic blood pressure was 1.7 mm Hg. The increases in blood pressure were observed early in the course of treatment and then remained fairly stable over the treatment period. In the naproxen group, mean changes from baseline in systolic and diastolic blood pressure were 1.0 and 0.1 mm Hg, respectively.

3.3 Data From Large Placebo-Controlled Studies

Edema, CHF, and hypertension are known renovascular effects of COX-2 inhibition and have been observed with all nonselective NSAIDs and COX-2 inhibitors. These side effects of inhibiting cyclooxygenase are mechanism-based and dose-related. Not unexpectedly, differences from placebo in renovascular adverse experiences are observed in large placebo-controlled studies.

3.3.1 Edema and CHF

Alzheimer's Disease Studies (Protocols 078 and 091) and APPROVe Study

As in the previous section, p-values are provided for pre-specified analyses.

In Protocol 078, the incidence of edema-related adverse experiences was 10.0% for rofecoxib 25 mg and 7.7% for placebo during a treatment period of up to 48 months (p=0.139). Discontinuations due to edema-related adverse experiences were low (<1%) and not significantly different: 0.8% for rofecoxib 25 mg and 0.0% for placebo .

In Protocol 091, the incidence of edema-related adverse experiences was 3.8% for rofecoxib 25 mg and significantly higher than for placebo (1.2%) (p=0.046) during a 12 month treatment period. Discontinuations due to edema-related adverse experiences were low: 0.3% for rofecoxib 25 mg and 0.0% for placebo.

In the APPROVe study population, the incidence of edema-related adverse experiences was 8.1% for rofecoxib 25 mg and 6.0% for placebo during a 36 month treatment period (p=0.016). Overall discontinuations due to edema-related adverse experiences were low (<1%); 0.9% for rofecoxib 25 mg and 0.4% for placebo (p=0.082).

The most common edema-related adverse experience in the Alzheimer's population was peripheral edema and lower extremity edema for protocols 078 and 091, respectively, In protocol 078, the incidence of peripheral edema was numerically greater for rofecoxib (8.7%) than placebo (6.7%) during a treatment period of up to 48 months and discontinuations due to peripheral edema were low, but greater for rofecoxib (0.7%) than placebo (0.0%). In protocol 091, lower extremity edema was 3.8% for rofecoxib and 2.0% for placebo over a 12 month period; there were no discontinuations in either group. In APPROVe, a number of different edema-related AEs were reported with no one AE being most common. Therefore, only the composite term of edema-related AEs is discussed.

In both Alzheimer's Disease studies, the overall incidences of CHF were low and not significantly different between treatment groups. In Protocol 078, the incidence of CHF adverse experiences was 2.2% for rofecoxib 25 mg and 2.6% for placebo (p=0.733). In Protocol 091, the incidence of CHF was 3.2% for rofecoxib and 1.4% for placebo (p=0.205). The incidence of CHF was also low in the APPROVe study but significantly higher for rofecoxib (0.7%) than for placebo (0.1%) (p=0.015). There were no clinically important mean changes in body weight, an independent assessment of fluid overload, in the Alzheimer's disease studies.

3.3.2 Hypertension

Alzheimer's Disease Studies and APPROVe Study

In Protocol 078 which encompassed a treatment period up to 48 months, the incidence of hypertension-related adverse experiences was significantly higher for rofecoxib 25 mg (24.3%) than for placebo (15.9%) (p=0.001). Discontinuations due to hypertension-related adverse experiences were similar in both treatment groups: 1.8% for rofecoxib 25 mg and 1.4% for placebo.

In Protocol 091, which encompassed a 12-month treatment period, the incidence of hypertension-related adverse experiences was significantly higher for rofecoxib 25 mg (9.0%) than for placebo (3.2%) (p=0.002). Discontinuations due to hypertension-related adverse experiences were low: 0.6% for rofecoxib 25 mg and 0.0% for placebo.

In APPROVe, the incidence of hypertension-related adverse experiences was 27.7% for rofecoxib 25 mg and was significantly higher than placebo (15.9%) (p<0.001) during a 36 month treatment period. The percentage of patients who discontinued due to a hypertension-related adverse experience was 2.5% for rofecoxib 25 mg and significantly higher than for placebo (0.5%) (p<0.001).

The most common hypertension-related adverse experience in these two populations was hypertension, which was generally greater for rofecoxib than placebo; discontinuations were low in both treatment groups.

In Protocol 078, the incidence of hypertension was greater for rofecoxib (18.4%) than placebo (11.5%) over a treatment period of up to 48 months. Discontinuations due to hypertension were low and similar in the rofecoxib (1.4%) and placebo (1.0%) groups. In protocol 091, hypertension was 6.9% for rofecoxib and 3.8% for placebo over a 12 month period; discontinuations were low in both groups (0.3% for rofecoxib and 0.0% for placebo). In APPROVe, hypertension was numerically greater in the rofecoxib group (23.4%) compared to placebo (13.0%) during a 36 month treatment period. Discontinuations for hypertension were also numerically greater for rofecoxib (1.5%) than placebo (0.4%).

Mean Changes in Systolic and Diastolic Blood Pressure

Small changes in mean blood pressure were noted in the different placebo-controlled studies.

In Protocol 078, in the rofecoxib group, mean changes from baseline in systolic blood pressure ranged from -0.6 to 2.2 mm Hg at individual study visits; mean changes from baseline in diastolic blood pressure ranged from -1.4 to 0.2 mm Hg at individual study visits. In the placebo group, initial decreases of -4.1 mm Hg systolic blood pressure and -0.8 mm Hg diastolic blood pressure at the Month 4 time point persisted through Month 48.

In Protocol 091, mean changes from baseline in systolic blood pressure ranged from 1.3 to 4.1 mm Hg at individual study visits in the 25-mg rofecoxib group compared to a mean change from baseline of -3.1 to 1.4 mm Hg at individual study visits in the placebo group. Changes from baseline in other vital signs, including diastolic blood pressure, were not notable.

In the APPROVe study, in the rofecoxib group, mean changes from baseline in systolic blood pressure ranged from 2.3 to 3.9 mm Hg at individual study visits and mean changes from baseline in diastolic blood pressure ranged from 0.3 to 1.4 mm Hg at individual study visits. In the placebo group the mean changes from baseline in systolic blood pressure ranged from -1.4 to 0.7 mm Hg at individual study visits and mean changes from baseline in diastolic blood pressure ranged from -1.1 to -0.5 mm Hg at individual study visits.

3.4 Renovascular Safety Summary

Overall, the data indicate that rofecoxib is associated with a low incidence of dose-dependent edema-related and hypertension-related adverse experiences generally consistent with the effects of fluid retention typically observed for NSAIDs.

Edema-related adverse experiences generally occurred early, and were mild, transient, and infrequently lead to discontinuations. CHF was rare in all populations, including the elderly. Most of the hypertension adverse experiences were mild to moderate in intensity

and discontinuation due to hypertension adverse experiences was infrequent. At the 25-mg dose, rofecoxib use was generally associated with small increases in mean systolic blood pressure 2 to 4 mm Hg compared to placebo and increases of mean diastolic blood pressure <2 mm Hg (data not shown). Changes in mean systolic blood pressure with rofecoxib exhibited a dose-related pattern in 6-week OA studies with increases of 1.1 to 5.1 mm Hg across the rofecoxib doses 12.5 to 50 mg. These findings are consistent with two meta-analyses which demonstrated an increase in mean arterial blood pressure of approximately 5 mm Hg with the use of NSAIDs [4; 5]. In general, hypertension adverse experiences also appear to be dose dependent with 12.5 mg displaying rates lower than 25 mg, and both of these doses with rates lower than rofecoxib 50 mg, which is above the therapeutic dose range for chronic treatment. Rofecoxib 50 mg displayed somewhat higher rates of edema and hypertension adverse experiences than therapeutic doses of comparator NSAIDs. While in general, the incidence of renovascular adverse experiences within the therapeutic dose range of rofecoxib (12.5 and 25 mg) is similar to NSAIDs, in some studies (RA Phase III studies) the 25 mg dose had a higher incidence than the comparator NSAID, naproxen. This difference from naproxen was not replicated however, in a 12-week study in OA patients (ADVANTAGE).

3.5 Renovascular Safety Conclusions

- Renovascular effects of NSAIDs including fluid retention, edema, and hypertension are mechanism-based adverse experiences associated with the use of NSAIDs including rofecoxib.
- Clinical trials with rofecoxib at daily doses of 12.5 and 25 mg in patients with osteoarthritis have shown effects on hypertension and edema similar to those observed with comparator NSAIDs.
- In clinical trials of rofecoxib at daily doses of 25 mg in patients with rheumatoid arthritis the incidence of hypertension was twice as high in patients treated with rofecoxib as compared to patients treated with naproxen 1000 mg daily. A difference from naproxen was not reproduced in the ADVANTAGE study in OA patients.
- Renovascular adverse experiences of NSAIDs are dose related. Compared to chronic use of rofecoxib 12.5 or 25 mg, there is an increased frequency with chronic use of rofecoxib at daily doses of 50 mg, a dose not recommended for chronic use.
- Similar to clinical doses of other NSAIDs, use of rofecoxib 25 mg is associated with small increases compared to placebo in mean systolic blood pressure <5mm Hg and mean increases of mean diastolic blood pressure <2mm Hg.

4. CV Safety in Rofecoxib Prior to Sep-2004 APPROVe Trial Results

This section of the document describes the cardiovascular safety data for the rofecoxib development program prior to obtaining the results for the APPROVe study in September 2004. The CV safety data presented represent all the data from all studies ≥4 weeks in duration in which rofecoxib was compared to non-selective NSAIDs and also include the large placebo controlled program in Alzheimer's Disease. The data from APPROVe are presented separately. The data are presented chronologically.

4.1 Cardiovascular Information at Time of the 1998 Original NDA

4.1.1 Clinical Pharmacology

Several months prior to the completion of the OA Phase III studies, data from two studies demonstrated that the selective COX-2 inhibitors celecoxib and rofecoxib reduced the urinary excretion of a prostacyclin metabolite [19; 28]

4.1.1.1 The Effects of Aspirin, Selective COX-2 Inhibitors, and Nonselective NSAIDs on Platelet Thromboxane Metabolism and Function

Cyclooxygenase and its prostanoid products have important roles in hemostasis. Prostacyclin (PGI_2), a product thought to be derived primarily through the activity of endothelial cell COX-1 and COX-2, is a vasodilator and inhibitor of platelet aggregation. Serum thromboxane A_2 (TXA_2), largely a product of platelet COX-1, is a vasoconstrictor and promoter of platelet aggregation [22; 23]. Aspirin, a well recognized antiplatelet agent and inhibitor of platelet TXA_2 synthesis, is effective in decreasing the risk of cardiovascular thrombotic events in patients at risk for such events. Aspirin's antiplatelet effect is mediated through its near complete, irreversible inhibition of platelet COX-1 activity [25]. Even low-dose aspirin (≥81 mg/day) achieves nearly complete inhibition of platelet TXA_2 production [34]. This effect on platelets is irreversible because these nonnucleated cells cannot replace the COX-1 enzyme that is permanently acetylated and inactivated by aspirin.

Non-selective NSAIDs reversibly inhibit COX-1 and had been shown to affect platelet function and, in some circumstances, increase bleeding due to the inhibition of clotting. At the time of the initiation of the Phase IIb/III OA program (June 1995), the prevailing theory was that inhibition of COX-2 would have no effect on platelet thromboxane (TxB_2). The hypothesis from these observations was that COX-2-selective inhibitors would not be expected to have the cardioprotective properties of aspirin as they would not affect platelet function. At that time, there was no suggestion that a selective COX-2 inhibitor might be prothrombotic. However there were suggestions in the literature that at least some NSAIDs might be cardioprotective through the inhibition of COX-1 [37; 26; 38].

As expected for a selective COX-2 inhibitor, rofecoxib was shown to have no inhibitory effect on platelet thromboxane generation and therefore did not have any effects on platelet aggregation [19].

4.1.1.2 The Effects of Selective COX-2 Inhibitors and of Nonselective NSAIDs on Prostacyclin Synthesis

Endothelial cells express abundant COX-1 but had been shown in vitro to express COX-2 *only* under certain pathologic conditions or under sheer stress [76; 77]. However, the experimental data were limited in this area. Merck collaborated with external investigators to further investigate the effects of selective COX-2 inhibitors on renal function. An additional analysis examined effects on systemic prostacyclin production [19]. Similar research had been performed using celecoxib [28]. These studies

demonstrated that selective COX-2 inhibitors reduced the urinary excretion of the prostacyclin metabolite PGI-M. These data demonstrated that COX-2 was important in systemic prostacyclin production. In these experiments, selective COX-2 inhibitors and nonselective NSAIDs appeared to inhibit the excretion of PGI-M to a similar extent (50-70%). Thus, the data were interpreted to suggest that COX-2 was the dominant cyclooxygenase isoform involved in systemic prostacyclin production. With the advent of better measurement techniques, subsequent experiments have shown clinical doses of non-selective NSAIDs such as naproxen inhibit the excretion of the prostacyclin metabolite PGI-M to a somewhat greater extent than clinical doses of selective COX-2 inhibitors, suggesting that both COX isoforms participate in systemic prostacyclin production, although COX-2 is the dominant component.

The experiments cited above did not reveal the source of the COX-2-dependent systemic prostacyclin. Although prostacyclin is produced in endothelium, it is also produced in other tissues such as lung. Nonetheless, based on the earlier experiments showing that cultured endothelial cells could upregulate COX-2 expression in certain conditions, it was hypothesized that at least some of the COX-2-dependent systemic prostacyclin was derived from endothelium. It was hypothesized that inhibition of endothelial prostacyclin synthesis by a selective COX-2 inhibitor without the inhibition of platelet thromboxane synthesis as would be obtained with a non-selective inhibitor of both COX-1 and COX-2 could theoretically alter the hemostatic balance between prostacyclin and thromboxane. And it was hypothesized that this imbalance could theoretically be prothrombotic and lead to an increase in the risk of thrombotic cardiovascular events. The data from this study were submitted to the FDA as part of the original NDA in 1998.

Since 1998, we and other researchers have investigated the potential source of the prostacyclin metabolites in urine that are decreased after administration of either non-selective NSAIDs or selective COX-2 inhibitors [19; 28]. Rabbit and dog studies conducted by Merck Frosst laboratories have suggested that arterial prostacyclin production is mediated by COX-1 rather than COX-2 [78; 79]. Others have come to similar conclusions based on studies in rat tissues [80]. Further, in an arm laceration study that measured prostacyclin metabolites at the site of injury, Tuleja and colleagues [81] observed that rofecoxib did not reduce prostacyclin metabolite levels and concluded that in human microvasculature, COX-1, and not COX-2, appears to be the source of prostacyclin. Nevertheless, experiments with cultured human endothelial cells under sheer stress reveals an upregulation of COX-2 expression [77]. Thus, to this day, the origin of COX-2 dependent systemic prostacyclin remains to be established.

4.1.2 Cardiovascular Clinical Results in Phase IIb/III OA Studies

Analyses of Thrombotic Cardiovascular Serious Adverse Experiences Rates in Rofecoxib Users Versus NSAIDs or Placebo: 1998

An initial review of CV data was included in the rofecoxib NDA, which was submitted to the FDA in Nov-1998 and discussed at the FDA Arthritis Advisory Committee meeting in Apr-1999. Specific analyses were undertaken in light of the data suggesting

that COX-2 inhibition decreased prostacyclin as noted above. This analysis included data on approximately 5,400 OA patients from 8 double-blind, placebo-controlled and active-comparator studies. Although somewhat limited with respect to the comparison to placebo, similar rates of investigator-reported thrombotic cardiovascular serious adverse experiences were seen with rofecoxib, placebo, and comparator NSAIDs in these studies (ibuprofen, diclofenac, or nabumetone).

Six of the OA protocols included a placebo comparator. These placebo-controlled data, however, had only few events due to the short exposure times involved. The overall duration of exposure in placebo-controlled periods was 516 patient years for the combined rofecoxib (all doses) group and 156 years for the placebo group. The primary active comparators in the OA program were diclofenac 150 mg and ibuprofen 2400 mg. Nabumetone 1500 mg was also used as a comparator in one 6-week study (Protocol 058) and accounted for only 30 patient-years of exposure (4% of the comparator data). The average daily dose of rofecoxib was approximately 25 mg. The overall extent of exposure in active comparator-controlled periods was 1657 patient-years for the combined rofecoxib (all doses) group and 706 patient-years for the combined nonselective NSAID (all comparators) group. Patient baseline risk factors are presented in Table 5 and Table 6.

Throughout the remainder of this document, a set of standard data are presented for each CV analysis: baseline characteristics, relative risk tables, summary tables by class of terms and Kaplan-Meier (KM) plots. The relative risk tables provide the number of patients with events per 100 patient years (PYR). This rate per 100 patient years of exposure is used to calculate the relative risk. The rate per 100 patient years takes into account the patient exposure to each drug, unlike crude incidence which calculates the number of events per 100 patients. The summary tables by class of terms summarize the CV events by treatment group and type of event and present number of events, percentage of patients with events, and rates. The percentages shown represent the number of events per 100 patients (crude incidence) and do not take into account the patient exposure. The rates represent the number of events per 100 patient-years of exposure. The KM plots are time-to-event plots that show the cumulative incidence rate for the endpoint evaluated, and changes in hazard over time. In these plots the number of patients at risk displayed along the x-axis at a given point is representative of the number of patients remaining in the study at those time points. Kaplan-Meier estimates are imprecise when the number of patients remaining at risk is small at the end of the study and it is recommended that the plot be curtailed when approximately 10 to 20% of patients remain in follow-up [82]. This approach was generally followed; Kaplan-Meier curves were truncated when there were around 10 to 20% of patients remaining at risk in any treatment group (or ~150-200 patients). Such a truncation was just for the plot; any events occurring after the truncation time point were still retained in the analyses of crude proportions, patient-year adjusted incidence rates and relative risks and also displayed in the relevant tables.

Table 7 displays the rates and relative risk of patients having investigator-reported thrombotic cardiovascular serious adverse experiences in the Phase IIb/III Placebo-Controlled and nonselective NSAID OA Populations. These included cardiac, cerebrovascular, and peripheral vascular (arterial and venous) events; the set of adverse experience terms matches the set ultimately implemented as part of Merck's Standard Operating Procedure for the systematic collection and adjudication of potential cardiovascular thrombotic serious adverse experiences (see Section 4.1.4 below). Thus, although the OA Phase IIb/III program data were obtained before initiation of this SOP and were not subject to adjudication, the approach to the data is similar to that ultimately used in the SOP.

The incidences of patients having investigator-reported thrombotic cardiovascular serious adverse experiences in these OA studies were similar between the rofecoxib and nonselective NSAID comparator treatment groups and between rofecoxib and placebo groups (Table 7). Summaries of the investigator-reported thrombotic cardiovascular serious adverse experience event types in the various treatment groups are in Table 8 and Table 9. There are no individual thrombotic CV serious adverse experiences whose rates suggest an imbalance between the groups. Table 8 displays the cumulative incidence rates of investigator-reported thrombotic CV serious adverse experiences in the nonselective-NSAID population displayed as Kaplan-Meier plots. As the Phase IIb/III OA data are composed of a large number of studies with differing durations, there is no way to appropriately reflect the duration in a single value. The number of patients at risk indicated in the KM plot provide this type of information as they are reflective of the patient number and duration of therapy throughout the study. Collectively, these data did not suggest that rofecoxib might be associated with an increase in thrombotic CV events as previously theorized.[19; 28].

Table 5

Baseline Risk Factors in the Rofecoxib Phase IIb/III OA Studies
Placebo-Controlled Population (1998)

	Placebo (N=711)		Rofecoxib (N=2253)	
	n	(%)	n	(%)
Age				
Percent <65 Years Old	406	(57.1)	1226	(54.4)
Percent ≥65 Years Old	305	(42.9)	1027	(45.6)
Gender				
Female	514	(72.3)	1650	(73.2)
Male	197	(27.7)	603	(26.8)
Cardiovascular Risk Factors				
Any Cardiovascular Risk Factor	380	(53.4)	1250	(55.5)
Hypertension	254	(35.7)	876	(38.9)
Diabetes Mellitus	22	(3.1)	79	(3.5)
Hypercholesterolemia	130	(18.3)	379	(16.8)
Current Smoker	93	(13.1)	266	(11.8)
Hx of Symptomatic ASCVD	58	(8.2)	173	(7.7)
Increased CV Risk[†]	145	(20.4)	437	(19.4)

[†] 2 or More Risk Factors for coronary artery disease or a history of symptomatic ASCVD
ASCVD= atherosclerotic cardiovascular disease

Table 6

Baseline Risk Factors in the Rofecoxib Phase IIb/III OA Studies
Nonselective NSAIDs Controlled -Population (1998)

	Rofecoxib (N=3358)		Nonselective NSAIDs (N=1565)	
	n	(%)	n	(%)
Age				
Percent <65 Years Old	1813	(54.0)	832	(53.2)
Percent ≥65 Years Old	1545	(46.0)	733	(46.8)
Gender				
Female	2444	(72.8)	1141	(72.9)
Male	914	(27.2)	424	(27.1)
Cardiovascular Risk Factors				
Any Cardiovascular Risk Factor	1888	(56.2)	894	(57.1)
Hypertension	1337	(39.8)	634	(40.5)
Diabetes Mellitus	146	(4.3)	71	(4.5)
Hypercholesterolemia	588	(17.5)	290	(18.5)
Current Smoker	377	(11.2)	177	(11.3)
Hx of Symptomatic ASCVD	259	(7.7)	116	(7.4)
Increased CV Risk†	681	(20.3)	324	(20.7)

† 2 or More Risk Factors for coronary artery disease or a history of symptomatic ASCVD
ASCVD= atherosclerotic cardiovascular disease

Table 7

Absolute Rate and Relative Risk (95% CI)
Investigator-Reported Thrombotic Cardiovascular
Serious Adverse Experiences
Rofecoxib Phase IIb/III OA Studies (1998)

Study	Treatment Group	N	Patients With Events	PYR†	Rate‡	Relative Risk (95% CI)
Phase IIb/III Studies Combined	Rofecoxib 12.5/25/50 mg	2253	14	516	2.71	1.06 (0.34, 3.23)
	Placebo	711	4	156	2.57	
Phase IIb/III Studies Combined	Rofecoxib 12.5/25/50 mg	3357	34	1657	2.05	0.92 (0.50, 1.67)
	Nonselective NSAIDS§	1564	16	706	2.27	

† Patient-years at risk.
‡ Per 100 PYR.
§ diclofenac, ibuprofen, nabumetone.

Table 8

Summary of Patients with Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences by Class of Terms
Rofecoxib and Placebo
Phase IIb/III OA Studies (1998)

	Rofecoxib (N=2253) (PYR=516)		Placebo (N=711) (PYR=156)	
	n (%)[†]	Rate[‡]	n (%)[†]	Rate[‡]
Patients with one or more investigator-reported thrombotic cardiovascular serious adverse experiences	14 (0.6)	(2.7)	4 (0.6)	(2.6)
Cardiac	**7 (0.3)**	**(1.4)**	**3 (0.4)**	**(1.9)**
Myocardial Infarction	3 (0.1)	(0.6)	2 (0.3)	(1.3)
Unstable Angina	2 (0.1)	(0.4)	1 (0.1)	(0.6)
Coronary Artery Disease	2 (0.1)	(0.4)	0 (0.0)	(0.0)
Cerebrovascular	**6 (0.3)**	**(1.2)**	**1 (0.1)**	**(0.6)**
Cerebrovascular Accident	4 (0.2)	(0.8)	1 (0.1)	(0.6)
Transient Ischemic Attack	2 (0.1)	(0.4)	0 (0.0)	(0.0)
Peripheral Vascular	**1 (0.0)**	**(0.2)**	**0 (0.0)**	**(0.0)**
Deep Venous Thrombosis	1 (0.0)	(0.2)	0 (0.0)	(0.0)

PYR=Patient-years at risk
[†] Crude incident (n/Nx100).
[‡] Events per 100 patient-years (PYR).

Note: Patient with multiple events may be counted more than once under different terms but only once in the "One or More" category.

Table 9

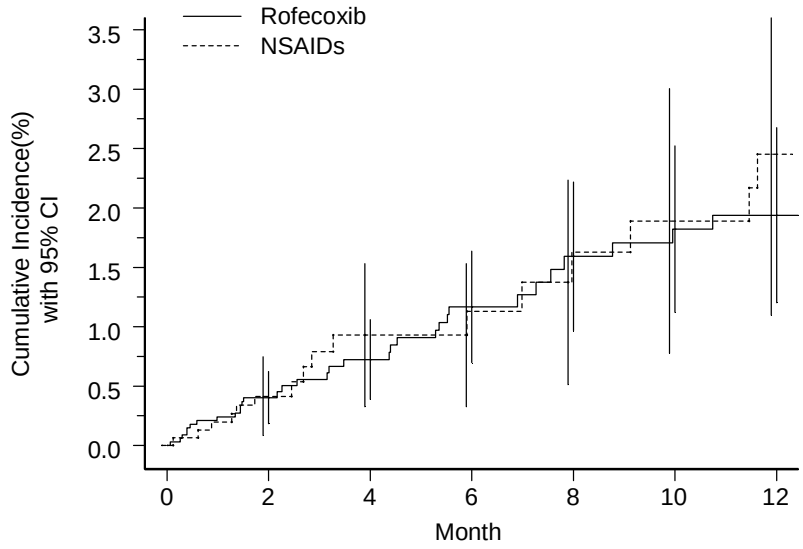
Summary of Patients with Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences
Rofecoxib and Nonselective NSAID
Phase IIb/III OA Studies (1998)

	Rofecoxib (N=3357) PYR=1657		Nonselective NSAIDs (N=1564) PYR=706	
	n (%)[†]	Rate[‡]	n (%)[†]	Rate[‡]
Patients with one or more investigator-reported thrombotic cardiovascular serious adverse experiences	34 (1.0)	(2.1)	16 (1.0)	(2.3)
Cardiac	**18 (0.5)**	**(2.1)**	**12 (0.8)**	**(1.7)**
Cardiac Arrest	0 (0.0)	(0.0)	2 (0.1)	(0.3)
Acute Myocardial Infarction	3 (0.1)	(0.2)	0 (0.0)	(0.0)
Myocardial Infarction	5 (0.1)	(0.3)	3 (0.2)	(0.4)
Coronary Artery Occlusion	1 (0.0)	(0.1)	1 (0.1)	(0.1)
Unstable Angina	2 (0.1)	(0.1)	0 (0.0)	(0.0)
Angina Pectoris	2 (0.1)	(0.1)	4 (0.3)	(0.6)
Coronary Vasospasm	1 (0.0)	(0.1)	0 (0.0)	(0.0)
Coronary Artery Disease	4 (0.1)	(0.2)	2 (0.1)	(0.3)
Cerebrovascular	**9 (0.3)**	**(0.5)**	**3 (0.2)**	**(0.4)**
Cerebrovascular Accident	6 (0.2)	(0.4)	3 (0.2)	(0.4)
Transient Ischemic Attack	3 (0.1)	(0.2)	0 (0.0)	(0.0)
Peripheral Vascular	**7 (0.2)**	**(0.4)**	**1 (0.1)**	**(0.1)**
Arterial Occlusion	1 (0.0)	(0.1)	0 (0.0)	(0.0)
Deep Venous Thrombosis	4 (0.1)	(0.2)	0 (0.0)	(0.0)
Peripheral Vascular Disorder	1 (0.0)	(0.1)	0 (0.0)	(0.0)
Pulmonary Embolism	1 (0.0)	(0.1)	0 (0.0)	(0.0)
Vascular Insufficiency	0 (0.0)	(0.0)	1 (0.1)	(0.1)

PYR=Patient-years at risk
[‡]Crude incident (n/Nx100).
[‡] Events per 100 patient-years (PYR).
Note: Patient with multiple events may be counted more than once under different terms but only once in the "One or More" category.

Figure 13

Kaplan-Meier Estimates of Cumulative Incidence (95% CI) of
Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences
Rofecoxib and Nonselective NSAIDs
Phase IIb/III OA Studies (1998)



Patients at Risk							
Rofecoxib	3357	2074	1679	1169	891	849	786
NSAIDs	1564	896	675	493	389	369	337
Cumulative Events							
Rofecoxib	0	13	19	26	30	32	33
NSAIDs	0	6	10	10	12	14	16

4.1.3 CV Conclusions Original NDA

- Data in the original NDA were consistent with the interpretation that the incidence of thrombotic cardiovascular serious adverse experience with rofecoxib was similar to placebo and to the nonselective NSAIDs studied.

4.1.4 Results of 1999 Arthritis Advisory Committee Meeting and NDA Approval

The Arthritis Advisory Committee reviewed the efficacy data for rofecoxib in OA, acute pain, and primary dysmenorrhea and the safety data including the general, GI, and CV safety data in April 1999. It was concluded that rofecoxib had a favorable risk/benefit profile and should be approved. The FDA approved rofecoxib in May 1999 for the relief of the signs and symptoms of osteoarthritis (12.5 and 25 mg), for the management of acute pain in adults (50 mg), and for the treatment of primary dysmenorrhea (50 mg).

4.1.5 CV Adjudication Standard Operating Procedure (SOP)

To better assess the cardiovascular safety of its selective COX-2 inhibitors, Merck initiated an Adjudication Standard Operating Procedure (CV Adjudication SOP) in the second half of 1998 to systematically collect and adjudicate potential cardiovascular thrombotic serious adverse experiences from all future studies with its selective COX-2 agents. This Adjudication SOP was initiated on the basis of three questions raised in the literature: 1) the potential for selective COX-2 agents to cause an imbalance between thromboxane and prostacyclin production and thus have a prothrombotic effect [28; 19], 2) an indication that some nonselective NSAIDs through their ability to inhibit platelet thromboxane production may have a cardioprotective effect [29; 27; 30], and 3) studies that demonstrated the expression of COX-2 in atheroma and which proposed that COX-2 might be involved in plaque rupture. It was proposed that COX-2 inhibitors might inhibit plaque rupture and be cardioprotective. [83; 84]

The basis of the Adjudication SOP was a blinded systematic review by an expert panel of cardiologists, neurologists, and vascular medicine internists of serious adverse experiences reported by site investigators. These adverse experiences were prespecified in the CV Adjudication SOP as potential thrombotic cardiovascular events (referred to in this document as Investigator-Reported Thrombotic CV serious adverse experiences). The report of such an event triggered a procedure whereby additional information was collected and the event was adjudicated. None of the members of the 3 expert panels (cardiac events, cerebrovascular events, peripheral vascular events) was a Merck employee or a site investigator for any of the rofecoxib or etoricoxib studies. Events confirmed by adjudication are referred to in this document as Confirmed Thrombotic CV Serious Adverse Experiences.

The purpose of the CV Adjudication SOP was: (1) to improve accuracy in diagnosis across a heterogeneous group of study investigators in different nations and having different clinical specialties; and (2) to standardize the evaluation of thrombotic cardiovascular serious adverse experiences across ongoing clinical studies of rofecoxib.

The VIOXX GI Outcomes Research Study (VIGOR) which evaluated rofecoxib 50 mg and naproxen 1000 mg was initiated in January 1999 and was the first study to utilize the CV Adjudication SOP. From that point on, all ongoing or newly initiated studies followed the CV Adjudication SOP. Thus, except for the OA Phase IIb/III studies and the rheumatoid arthritis Phase IIb study, which had completed their initial study periods and had been unblinded prior to the time the SOP was initiated, all studies discussed in this document were subject to the CV Adjudication SOP.

The analysis of cardiovascular outcomes in trials of rofecoxib as described in the Adjudication SOP did not envision a separate analysis of individual trials. Individual trials would likely be underpowered with respect to subgroup and exploratory analyses necessary to understand any observed differences in event rates. Instead, the SOP was designed to examine the combined incidence of cardiovascular outcomes across a broad range of patients in all post-Phase III OA trials of rofecoxib initiated by or after the

second quarter 1998. However, based on a request from the VIGOR Data Safety Monitoring Board, a separate analysis of thrombotic cardiovascular serious adverse experiences in VIGOR was performed.

4.1.5.1 CV Endpoints

The primary endpoint outlined in the original CV Adjudication SOP was the Confirmed Thrombotic CV Serious Adverse Experience endpoint. With respect to cardiovascular analyses, this endpoint was considered primary for all studies included in the CV Adjudication SOP. Prior to undertaking a pooled analysis of the data, which included the Phase IIb/III data, the decision was made to prespecify the Antiplatelet Trialists' Collaboration (APTC) combined endpoint, for all pooled analyses which included studies which were not part of the CV Adjudication SOP. There were several reasons for this decision. First the APTC combined endpoint was the endpoint most commonly used in combined analyses of studies investigating antiplatelet agents such as aspirin. It was widely accepted and allowed comparison between results obtained for rofecoxib and results of the anti-platelet agents. The APTC combined endpoint consisted of cardiovascular death, death due to unknown causes, fatal hemorrhage, myocardial infarction, and stroke. This endpoint includes "hard events" that have a high confirmation rate during adjudication, an important characteristic since the data from the Phase IIb/III OA studies and the RA Phase IIb study were not subject to adjudication as they were initiated and completed (aside from ongoing extensions) prior to the initiation of the Adjudication SOP. Overall, the results have been highly consistent between analyses based on the APTC and Confirmed Thrombotic CV serious adverse experience endpoints. Table 10 outlines the different terms included in the APTC endpoint and the Confirmed Thrombotic Cardiovascular Serious Adverse Experience endpoint.

Table 10

Serious Adverse Events Included in the Confirmed Thrombotic Cardiovascular Serious Adverse Experience and APTC Combined Endpoints

Adjudication Committee Categories for Cardiovascular Events	Confirmed Thrombotic Cardiovascular Event	APTC† Combined Endpoint
Thrombotic Events		
Cardiac Events		
Acute MI	√	√
Fatal: acute MI	√	√
Unstable angina pectoris	√	
Sudden and/or unexplained death	√	√
Resuscitated cardiac arrest	√	√
Cardiac thrombus	√	
Peripheral Vascular Events		
Pulmonary embolism	√	
Fatal: pulmonary embolism	√	
Peripheral arterial thrombosis	√	
Fatal: peripheral arterial thrombosis	√	√
Peripheral venous thrombosis	√	
Cerebrovascular Events		
Ischemic cerebrovascular stroke	√	√
Fatal: ischemic cerebrovascular stroke	√	√
Cerebrovascular venous thrombosis	√	
Fatal: cerebrovascular venous thrombosis	√	√
Transient ischemic attack	√	
Hemorrhagic Events		
Hemorrhagic cerebrovascular stroke‡		√
Fatal: hemorrhagic cerebrovascular stroke‡		√
Fatal: hemorrhagic deaths of any cause		√

† APTC = Antiplatelet Trialists' Collaboration.
‡ These events are included as investigator-reported events but not Confirmed Thrombotic CV events.

4.2 VIGOR (First Patient Enrolled: 06-Jan-1999/Completed: 17-Mar-2000)

As described in Section 2.4, the Vioxx GI Outcomes Research Study (VIGOR) was designed primarily to assess the GI safety of rofecoxib versus naproxen. Also, as described in Section 4.1.4, VIGOR was the first study in which the CV Adjudication SOP was applied. VIGOR was initiated Jan-1999 before the regulatory approval of rofecoxib in the US or the EU and the protocol stated that potential thrombotic cardiovascular serious adverse experiences were to be adjudicated. The data became available in Mar-2000, after the original NDA was approved.

4.2.1 CV Safety From VIGOR

A total of 8076 patients were randomized in the VIGOR study to either rofecoxib 50 mg, twice the highest recommended dose for chronic use, or naproxen 1000 mg, a common clinical dose. The 50 mg dose was chosen in consultation with the FDA to provide a rigorous assessment of the GI safety of rofecoxib. The mean duration of study therapy was 8 months (median: 9 months) for both treatment groups. Baseline CV risk factors are presented in Table 11. Importantly, because VIGOR was designed to test the hypothesis that a selective COX-2 inhibitor would have improved GI safety compared to a dual COX-1/COX-2 inhibitor, and because aspirin inhibits COX-1, concomitant aspirin use was not allowed in VIGOR to avoid confounding of the assessment of the primary hypothesis. Thus patients who would clinically be considered appropriate candidates for low dose aspirin for cardioprotection were not supposed to be randomized into the trial.

In March of 2000, the preliminary results of the VIGOR study became available. These data were based on a prespecified plan to include data available as of Feb-2000 in the primary analysis. Although the GI benefit was clear in the VIGOR study, an imbalance in thrombotic cardiovascular adverse experiences favoring naproxen was observed. Within the same month, the data were released publicly via a press release, and submitted to the FDA and other regulatory agencies, communicated to investigators, ethics committees, and included in the investigator brochure and informed consent. These data were also presented in a scientific meeting and submitted for publication in May-2000. Draft label changes to reflect the GI and CV data were submitted to the FDA in Jun-2000. A safety update report which included the final GI and CV data, that is, all events reported after the prespecified cut off date for the primary analysis, was submitted in Oct-2000. These final data were presented at the Feb-2001 FDA Arthritis Advisory Committee meeting and are the data included in this background package.

A total of 96 patients (64 in the rofecoxib group and 32 in the naproxen group) had 1 or more thrombotic CV serious adverse experiences which were referred to the CV adjudication committee as Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences. Of these, 64 patients had one or more events during VIGOR that were adjudicated as thrombotic events by the committees (hereafter referred to as Confirmed Thrombotic Cardiovascular Serious Adverse Experiences) (Table 12). The overall incidence of Confirmed Thrombotic CV serious adverse experiences in VIGOR is presented by treatment group in Table 13. Therapy with naproxen was associated with a lower risk for the development of Confirmed Thrombotic CV serious adverse experiences, due primarily to a lower incidence of coronary events. Multiple statistical analyses described in detail below of the proportionate hazard revealed that the relative risk between treatment groups for a confirmed thrombotic cardiovascular serious adverse experiences did not vary significantly over time. A summary of the event types is displayed in Table 13 and the Cumulative incidence rate of Confirmed Thrombotic CV serious adverse experiences is displayed in Figure 14.

Table 11

Patient Baseline Demographics and Cardiovascular Risk
VIGOR (2000)

Demographic	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Age				
Percent <65 Years Old	3050	(75.4)	2959	(73.4)
Percent ≥65 Years Old	997	(24.6)	1070	(26.6)
Gender				
Female	3223	(79.6)	3215	(79.8)
Male	824	(20.4)	814	(20.2)
Cardiovascular Risk Factors				
Any Cardiovascular Risk Factor	2047	(50.6)	1988	(49.3)
Hypertension	1217	(30.1)	1168	(29.0)
Diabetes Mellitus	240	(5.9)	254	(6.3)
Hypercholesterolemia	343	(8.5)	293	(7.3)
Current Smoker	790	(19.5)	779	(19.3)
Hx of Symptomatic ASCVD	170	(4.2)	151	(3.7)
Increased CV Risk[†]	604	(14.9)	570	(14.1)

[†] 2 or More Risk Factors for coronary artery disease or a history of symptomatic ASCVD
ASCVD= atherosclerotic cardiovascular disease

Table 12

Absolute Rate and Relative Risk (95% CI)
Confirmed Thrombotic Cardiovascular
Serious Adverse Experiences
VIGOR (2000)

Event Category	Treatment Group	N	Patients With Events	PYR[‡]	Rates[‡]	Relative Risk[§]	
						Estimate	95% CI
All thrombotic Events	Rofecoxib	4047	45	2697	1.67	2.38	(1.39, 4.00)
	Naproxen	4029	19	2698	0.70		

[‡] Per 100 patient-years at risk (PYR).
[§] Relative risk of rofecoxib with respect to naproxen from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.
Although a patient may have had 2 or more serious adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Table 13

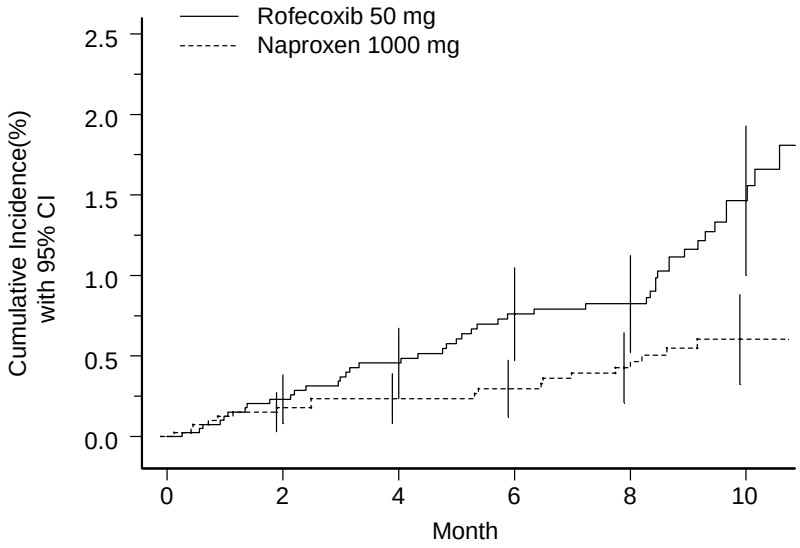
Summary of Patients With Confirmed Thrombotic Cardiovascular Serious Adverse Experiences:VIGOR (2000)

	Rofecoxib (N=4047) PYR=2697		Naproxen (N=4029) PYR=2698	
	n (%)[†]	Rate[‡]	n (%)[†]	Rate[‡]
Patients with One or More **Thrombotic Cardiovascular Serious Adverse Experiences**	**45 (1.1)**	**(1.7)**	**19 (0.5)**	**(0.7)**
Cardiac Events	**28 (0.7)**	**(1.0)**	**10 (0.2)**	**(0.4)**
Acute Myocardial Infarction	20 (0.5)	(0.7)	4 (0.1)	(0.1)
Sudden Cardiac Death	3 (0.1)	(0.1)	4 (0.1)	(0.1)
Unstable Angina Pectoris	5 (0.1)	(0.2)	3 (0.1)	(0.1)
Cerebrovascular Events	**11 (0.3)**	**(0.4)**	**8 (0.2)**	**(0.3)**
Ischemic Cerebrovascular Stroke	9 (0.2)	(0.3)	8 (0.2)	(0.3)
Transient Ischemic Attack	2 (0.0)	(0.1)	0 (0.0)	(0.0)
Peripheral Vascular Events	**6 (0.1)**	**(0.2)**	**1 (0.0)**	**(0.0)**
Peripheral Arterial Thrombosis	1 (0.0)	(0.0)	0 (0.0)	(0.0)
Peripheral Venous Thrombosis	5 (0.1)	(0.2)	1 (0.0)	(0.0)

PYR=Patient-years at risk
[†] Crude incident (n/Nx100).
[‡] Events per 100 patient-years (PYR).
Note: Patient with multiple events may be counted more than once under different terms but only once in the "One or More" category.

Figure 14

Kaplan-Meier Estimate of Cumulative Incidence (95% CI) of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
VIGOR (2000)



Patients at Risk						
Rofecoxib 50 mg	4047	3643	3405	3177	2806	1067
Naproxen 1000 mg	4029	3647	3395	3172	2798	1073

Preliminary inspection of the Kaplan-Meier time-to-event plots suggested that the rofecoxib group showed a different hazard rate pattern than the naproxen group. Particularly, the event data between Month 8 to Month 12 as compared to those prior to Month 8 could cast doubt on the constant hazard ratio assumption between the two groups. Several statistical analyses as described below were performed to determine if there were statistically significant departures from the proportional hazard assumption, i.e., the assumption that the hazard ratio between rofecoxib and naproxen was constant over time.

The first analysis assessed the treatment-by-log(time) effect in the Cox PH model. A non-significant result ($p>0.2$) implied that the hazard ratio did not vary to any significant degree over time. A second analysis examined the correlation between the individual Schoenfeld residuals (observed treatment covariate minus expected) from the fitted Cox PH model and the log-transformed CV event times. No significant departure from the proportional hazard assumption was seen. A third analysis involved fitting a Weibull parametric survival model to the CV event time data. Two separate forms of the Weibull model were fit to the CV event data. The first such model utilized a common shape parameter, but different scale parameters for each of the two treated groups. For this

model, the common shape parameter was not significantly different from 1, indicating no statistical departure from constant hazard rates for each group according to this model, and hence, a constant risk ratio as a result. The second Weibull model allowed for different shape parameters for the two treated groups. The fit from this model was not significantly improved relative to the original model. A fourth analysis utilized Zelen's exact test to check if the risk ratios between the two treatment groups were relatively constant over discrete, equal time intervals of the study period. The test was performed multiple times with the data divided in each iteration into 2-, 4-, or 8-month intervals ($p \geq 0.159$). In addition to these statistical analyses, the assumption of proportional hazards was further assessed either through graphic representations of the estimated hazard rates by the models chosen or by comparing the estimates from different models. Although the power of each of these tests is admittedly limited, results of these analyses all yielded the conclusion of no significant departure from proportional hazards, that is, the hazard ratio between rofecoxib and naproxen was relatively constant over time.

The FDA, however, reached a somewhat different conclusion based on their statistical analyses. They concluded that relative risk could not be used to characterize the findings as the data did not support the assumption of a hazard rate that was constant over the 12 months of the study. They concluded that the rofecoxib group tended to show a different hazard rate pattern than the naproxen group. Based on the 8-12 month event data for rofecoxib, in particular, FDA argued that these data cast doubt on the constant hazard rate assumption for that group.

4.2.2 VIGOR Subgroup Analyses

In an attempt to investigate further and understand the imbalance observed in Confirmed Thrombotic CV serious adverse experiences in VIGOR, subgroup analyses were performed including an analysis based on baseline risk for a cardiovascular event and analyses based on blood pressure parameters.

There were no subgroup by treatment interactions for the following subgroups: age, gender, history of a CV risk factor and past history of atherosclerotic cardiovascular disease.

Thrombotic Cardiovascular Serious Adverse Experiences Analyzed by Baseline CV Risk.

In this analysis, patients with 2 or more risk factors for CV disease or a history of symptomatic atherosclerotic cardiovascular disease at baseline were deemed the increased risk subgroup. Although the absolute risk of a thrombotic CV adverse experience is higher in such patients, the relative risk of a confirmed thrombotic CV serious adverse experience was similar regardless of baseline risk status (Table 14).

Table 14

Absolute Rate and Relative Risk (95% CI)
Confirmed Thrombotic Cardiovascular Serious Adverse Experience
Subgroup Analysis by Baseline CV Risk
VIGOR (2000)

Subgroup	Treatment	n/N (%)	Patient-Years	Rate[†]	Relative Risk[‡] (95% CI)
Total Cohort	Rofecoxib	45/4047 (1.1)	2697	1.67	2.38 (1.39, 4.00)
	Naproxen	19/4029 (0.5)	2698	0.70	
Increased Risk	Rofecoxib	21/604 (3.5)	386	5.44	2.86 (1.18, 8.33)
	Naproxen	7/570 (1.2)	370	1.89	
Without Increased Risk	Rofecoxib	24/3443 (0.7)	2311	1.04	2.00 (0.97, 4.35)
	Naproxen	12/3459 (0.3)	2328	0.52	

n/N=the number of patients with events/total number of patients, CI=Confidence Interval.

[†] Number of events per 100 patient-years.

[‡] Relative risk of rofecoxib with respect to naproxen from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.

Thrombotic Cardiovascular Serious Adverse Experiences Stratified by Changes in Blood Pressure in VIGOR

In VIGOR, consistent with the use of a dose of rofecoxib twice as high as the maximal approved dose for chronic use, more patients in the rofecoxib 50 mg group had hypertension adverse experiences than in the naproxen group. Although the difference in thrombotic cardiovascular serious adverse experiences was larger than one would anticipate given the small between-group differences in observed blood pressure, it was nonetheless important to examine the data to determine if the known renovascular effects of rofecoxib 50 mg accounted for the cardiovascular findings of VIGOR.

A number of different analyses were carried out to evaluate the relationship between blood pressure and Confirmed Thrombotic CV serious adverse experiences. This included an analysis based on reports of hypertension adverse experiences and analyses based on blood pressure measurements. Neither analysis revealed an association with the imbalance of thrombotic cardiovascular events. The analyses based on blood pressure measurements are provided. As there was very little effect of rofecoxib on diastolic blood pressure, the limited analyses of diastolic blood pressure are not shown.

Table 15 shows an analysis of thrombotic cardiovascular events stratified by changes in systolic blood pressure using two stratification approaches – the first from <-5 mm Hg to >10 mm Hg is based on equal-sized quartiles of patients and the second from <-10 mm

Hg to ≥25 mm Hg is based on equal-sized increments of systolic blood pressure. In this analysis, data on patients with events are only included up until the time of the event. Differences are noted in the rates across the various categories of blood pressure changes; however, no consistent trend in the relative risk across the strata could be identified.

Table 15

Absolute Rate and Relative Risk (95% CI)
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
Subgroup Analysis by Changes in Systolic Blood Pressure
VIGOR (2000)

Change in Systolic BP	Trmt	N	Patients With Events	PYR†	Rates‡	Relative Risk§ 95% CI
Overall	Rofecoxib	3992	39	2693	1.45	
	Naproxen	3998	14	2694	0.52	2.78 (1.52, 5.26)
Systolic BP ranges from <-5 mm Hg to >10 mm Hg						
<-5 mmHg	Rofecoxib	776	9	503	1.79	
	Naproxen	1131	6	763	0.79	2.33 (0.83, 6.67)
-5 to <2.5 mmHg	Rofecoxib	977	10	654	1.53	
	Naproxen	1076	1	715	0.14	11.11 (1.41, 100)
2.5 to 10 mmHg	Rofecoxib	1065	6	728	0.82	
	Naproxen	1002	1	687	0.15	5.56 (0.68, ---)
>10 mmHg	Rofecoxib	1174	14	809	1.73	
	Naproxen	789	6	529	1.13	1.52 (0.58, 3.85)
Systolic BP ranges from <-10 mm Hg to ≥25 mm Hg						
<-10 mmHg	Rofecoxib	383	6	253	2.38	3.45 (0.72, 20.0)
	Naproxen	634	3	429	0.70	
-10 to <10mmHg	Rofecoxib	2258	18	1527	1.18	3.85 (1.45, 11.11)
	Naproxen	2427	5	1648	0.30	
10 to <25 mmHg	Rofecoxib	1113	9	758	1.19	1.28 (0.43, 3.85)
	Naproxen	810	5	544	0.92	
≥25 mmHg	Rofecoxib	238	6	155	3.88	2.86 (0.34, 100)
	Naproxen	127	1	73	1.37	

† Patient-years at risk

‡ Per 100 PYR

§ 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.

Blood Pressure Measurements in Patients With and Without Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in VIGOR

Changes in blood pressure measurements were compared in patients with and without Confirmed Thrombotic CV serious adverse experiences. In both treatment groups, mean systolic blood pressure in patients who had Confirmed Thrombotic CV serious adverse experiences were 6 to 9 mm Hg higher at baseline compared to patients without events. However, mean changes from baseline in systolic and diastolic blood pressure were similar in rofecoxib patients with and without Confirmed Thrombotic CV serious adverse experiences. In addition, the percent of patients with elevations in blood pressure which exceeded 20 mm Hg in systolic blood pressure or 10 mm Hg in diastolic blood pressure was similar in patients with and without Confirmed Thrombotic CV serious adverse experiences. Lastly, there was no correlation between the magnitude of change in blood pressure and the risk of sustaining a Confirmed Thrombotic CV serious adverse experience. Consistent with the relatively short duration of the trial, differences between treatment groups in blood pressure changes did not appear to serve as an explanation for the difference observed in thrombotic cardiovascular event rates, although some contribution of blood pressure could not completely be excluded.

Conclusions

Although there was a difference in the relative risk of patients who had confirmed thrombotic CV serious adverse experiences in VIGOR, it was not clear based on the VIGOR data alone, whether this was due to an increase in the risk in the rofecoxib group or a decreased risk in the naproxen group. The VIGOR data were further evaluated through subgroup analyses including evaluations based on baseline cardiovascular risk and evaluations based on blood pressure changes during the study. No differences were noted when assessing these two parameters. In the absence of a placebo control in VIGOR no definitive conclusions could be drawn from the VIGOR data alone with regard to the cause of the imbalance in CV events. Therefore, additional rofecoxib data were evaluated to try to answer this question.

4.2.3 Evidence Against a Prothrombotic Effect of Rofecoxib: Placebo-Controlled Interim Data From the Alzheimer's Disease Program (Data From Sep-2000 Provided)

The data from the Phase IIb/III OA program reviewed in the original NDA for rofecoxib had not revealed an increased risk of thrombotic cardiovascular serious adverse experiences on rofecoxib compared to either placebo or non-naproxen NSAIDs. To better understand the significance of the new cardiovascular results of VIGOR, an interim analysis was carried out for two large, ongoing placebo-controlled studies in elderly patients with early Alzheimer's disease (Protocols 078 and 091). These ongoing trials provided a large dataset comparing rofecoxib 25 mg with placebo, rather than the naproxen comparator evaluated in VIGOR. Importantly, the Alzheimer's studies provided extensive experience in an elderly population at increased risk for serious thrombotic cardiovascular events.

An initial review was performed on data unblinded in Mar-2000 and submitted to the FDA and other regulatory agencies in Jun-2000. The interim analyses of the data from these trials did not demonstrate an increase in cardiovascular event rates for rofecoxib compared to placebo; indeed the event rate was numerically lower on rofecoxib. In preparation for the Feb-2001 FDA Advisory Committee meeting, a second interim analysis of the cardiovascular data from the placebo-controlled Alzheimer's studies occurred in Sep-2000 and are presented below. These year 2000 analyses were based on unadjudicated investigator-reported Thrombotic CV serious adverse experiences, since at that time, few of the events had been adjudicated. Subsequent analyses (see Section 4.3.3.2) were performed on adjudicated data and were consistent with the initial analyses.

4.2.3.1 Thrombotic Cardiovascular Serious Adverse Experiences in Alzheimer's Disease Studies (Protocols 078 and 091) – Interim Analysis (Sep-2000)

Protocol 078 was a 4-year placebo-controlled, parallel-group, double-blind study in 1406 patients to evaluate the effects of rofecoxib 25 mg daily on the prevention of Alzheimer's disease and cognitive decline in patients ≥65 years of age with mild cognitive impairment. Protocol 091 was a placebo-controlled, parallel-group, 15-month, double-blind study in 682 patients to evaluate the efficacy and safety of rofecoxib 25 mg in slowing the progression of symptoms of Alzheimer's disease. As of 15-Sep-2000, more than 2090 patients had been randomized into the 2 studies combined. At the time of the interim analysis, the total extent of exposure in each treatment group was approximately 1200 patient-years.

Patients who were taking aspirin or other antiplatelet agents for cardiovascular protection, or who had an indication for the approved use of aspirin for cardiovascular-protective effect were excluded from enrollment in both of these studies. However, because these patients were elderly and might have been at risk for atherosclerotic cardiovascular disease complications, therapy with aspirin or clopidogrel was allowed if, during the study period, the investigator determined that it was indicated. Table 16 outlines the baseline risk factors of the Alzheimer's patients. These patients were older and at a relatively higher risk for Thrombotic CV serious adverse experiences compared with the overall patient population in VIGOR or in the OA Phase IIb/III studies.

The relative risk and incidence of patients with investigator-reported Thrombotic CV serious adverse experiences is presented for the 2 studies combined (Table 17 and Table 18). The relative risk (95% CI) of 0.85 (0.53, 1.35) does not suggest an increased risk of sustaining a Thrombotic CV serious adverse experience with rofecoxib. The subgroup of terms constituting myocardial infarction was similar between rofecoxib and placebo. The breakdown of event types by term is found in Table 18. Of note, the incidences of cardiac events and specifically MI-related events were similar for rofecoxib (9 events) and placebo (12 events). There were 9 cerebrovascular events in the rofecoxib group and 19 in the placebo group.

The cumulative incidence rates indicating the number of patients at risk at specific time points for rofecoxib and placebo are in Figure 15. None of the data evaluated in this interim analysis indicated that rofecoxib 25 mg was associated with an increased risk for CV events.

Table 16

Patient Baseline Demographics and Cardiovascular Risk
in Protocols 078 and 091
Patients With Mild Cognitive Impairment
or Early Alzheimer's Disease (Sep-2000)

Demographic	Rofecoxib 25 mg (N=1069)		Placebo (N=1074)	
	n	(%)	n	(%)
Age				
Percent <65 Years Old	52	(4.9)	57	(5.3)
Percent ≥65 Years Old	1017	(95.1)	1017	(94.7)
Gender				
Female	435	(40.7)	406	(37.8)
Male	634	(59.3)	668	(62.2)
Cardiovascular Risk Factors				
Any Cardiovascular Risk Factor	614	(57.4)	590	(54.9)
Hypertension	406	(38.0)	361	(33.6)
Diabetes Mellitus	107	(10.0)	108	(10.1)
Hypercholesterolemia	250	(23.4)	255	(23.7)
Current Smoker	70	(6.5)	73	(6.8)
Hx symptomatic ASCVD	164	(15.3)	152	(14.2)
Increased CV Risk[†]	289	(27.0)	282	(26.3)

[†]History of ≥2 risk factors or a history of symptomatic ASCVD
ASCVD = atherosclerotic cardiovascular disease

Table 17

Absolute Rates and Relative Risk (95% CI)
Investigator-Reported Thrombotic Cardiovascular
Serious Adverse Experiences in Protocols 078 and 091
Patients With Mild Cognitive Impairment or Early Alzheimer's Disease (Sep-2000)

Study	Treatment Group	N	Patients With Events	PYR[†]	Rate[‡]	Relative Risk (95% CI)
Protocols 091/078 combined	Rofecoxib 25 mg	1041	32	1146	2.81	0.85 (0.53, 1.35)
	Placebo	1050	40	1221	3.31	

[†] Patient-years at risk.
[‡] Per 100 PYR.

Table 18

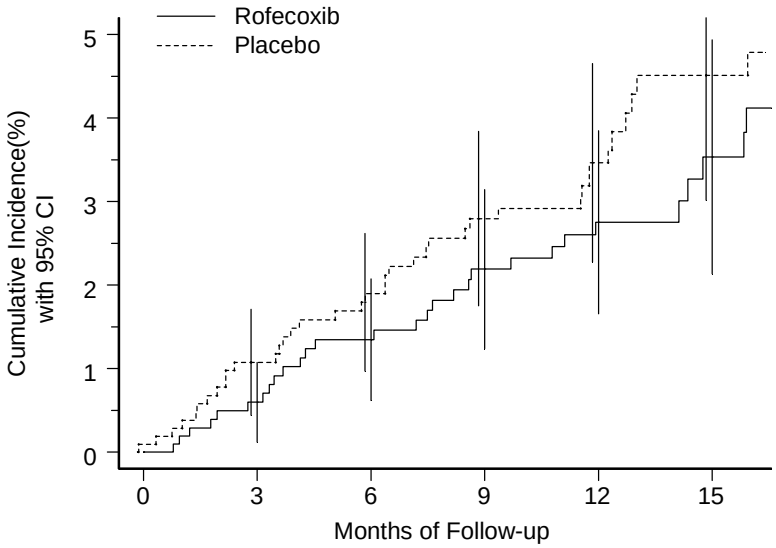
Summary of Patients with Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences in Protocols 078 and 091
Patients With Mild Cognitive Impairment or Early Alzheimer's Disease (Sep-2000)

Endpoint Term	Rofecoxib (N=1041) PYR=1146		Placebo (N=1050) PYR=1221	
	n (%)†	Rate‡	n (%)†	Rate‡
Patients with One or More **Thrombotic Cardiovascular Serious Adverse Experiences**	**32 (3.1)**	**(2.8)**	**40 (3.8)**	**(3.3)**
Cardiac Events	**21 (2.0)**	**(1.8)**	**19 (1.8)**	**(1.6)**
Acute Myocardial Infarction	2 (0.2)	(0.2)	3 (0.3)	(0.2)
Angina Pectoris	1 (0.1)	(0.1)	4 (0.4)	(0.3)
Cardiac Arrest	1 (0.1)	(0.1)	0 (0.0)	(0.0)
Coronary Artery Disease	7 (0.7)	(0.6)	3 (0.3)	(0.2)
Coronary Artery Stenosis	1 (0.1)	(0.1)	1 (0.1)	(0.1)
Myocardial Infarction	7 (0.7)	(0.6)	8 (0.8)	(0.7)
Non-Q-Wave Myocardial Infarction	0 (0.0)	(0.0)	1 (0.1)	(0.1)
Unstable Angina	1 (0.1)	(0.1)	2 (0.2)	(0.2)
Ventricular Fibrillation	1 (0.1)	(0.1)	0 (0.0)	(0.0)
Ventricular Tachycardia	0 (0.0)	(0.0)	2 (0.2)	(0.2)
Cerebrovascular Events	**9 (0.9)**	**(0.8)**	**19 (1.8)**	**(1.6)**
Carotid Artery Obstruction	1 (0.1)	(0.1)	7 (0.7)	(0.6)
Cerebrovascular Accident	2 (0.2)	(0.2)	5 (0.5)	(0.4)
Lacunar Infarction	0 (0.0)	(0.0)	1 (0.1)	(0.1)
Transient Ischemic Attack	6 (0.6)	(0.5)	6 (0.6)	(0.5)
Peripheral Vascular Events	**2 (0.2)**	**(0.2)**	**3 (0.3)**	**(0.2)**
Deep Venous Thrombosis	0 (0.0)	(0.0)	1 (0.1)	(0.1)
Femoral Artery Occlusion	0 (0.0)	(0.0)	1 (0.1)	(0.1)
Intracranial Hemorrhage	0 (0.0)	(0.0)	1 (0.1)	(0.1)
Pulmonary Embolism	1 (0.1)	(0.1)	0 (0.0)	(0.0)
Thrombosis	1 (0.1)	(0.1)	0 (0.0)	(0.0)
Vascular Graft Occlusion	0 (0.0)	(0.0)	1 (0.1)	(0.1)

PYR=Patient-years at risk
† Crude incident (n/Nx100).
‡ Events per 100 patient-years (PYR).
Note: Patient with multiple events may be counted more than once under different terms but only once in the "One or More" category.

Figure 15

Kaplan-Meier Estimate of Cumulative Incidence (95% CI) of Investigator Reported Thrombotic Cardiovascular Serious Adverse Experiences in Protocols 078 and 091
Patients With Mild Cognitive Impairment or Early Alzheimer's Disease (Sep-2000)



Patients at Risk						
Rofecoxib	1041	947	879	769	640	359
Placebo	1050	991	930	816	693	376

4.2.4 Evidence Supporting a Possible Cardioprotective Effect of Naproxen 500 mg Twice Daily in VIGOR

Based on an understanding of the literature in 2000 and the hypotheses that had been proposed up to that time, the data from VIGOR suggested two principal possibilities: 1) rofecoxib was responsible for the imbalance in CV events due to a prothrombotic effect, or 2) the imbalance in CV events was attributable to an effect of naproxen. In addition, the play of chance could not be formally excluded. In assessing these possibilities, the clinical trial data available for both the placebo-controlled Alzheimer's Disease studies and the placebo and non-naproxen NSAID-controlled OA Phase IIb/III studies provided support that rofecoxib was not prothrombotic. Therefore, it was important to evaluate all of the evidence to support or refute that a nonselective NSAID like naproxen could be responsible for the difference observed in VIGOR. In order to address this question, it was important to understand the cardioprotective effects of agents such as aspirin.

The acute cardiovascular syndromes such as myocardial infarction, share a common underlying pathophysiology: the rupture of an arterial atherosclerotic plaque [85]. Plaque fissuring or rupture results in exposure of thrombogenic material to circulating blood, leading to clot formation with partial or complete occlusion of coronary or cerebrovascular blood flow and ischemia or infarction. Patients with a history of symptomatic atherosclerotic cardiovascular disease have a significant chronic risk of developing a spontaneous plaque rupture that can lead to platelet-mediated thrombosis and potentially catastrophic ischemic events [86; 87; 88]. Effective pharmacologic antagonism of platelet function using antiplatelet agents such as aspirin has been clearly documented to reduce the incidence of fatal and nonfatal cardiovascular thrombotic events in these patients [86]. Thus, aspirin therapy has become a central component of chronic risk management in these patients [89].

4.2.4.1 The Mechanism of Action for the Vascular-Protective Properties of Aspirin

The anti-platelet properties of aspirin are mediated through its effects on prostaglandin metabolism [22]. The prostaglandins thromboxane (TXA_2) and prostacyclin (PGI_2) play a major role in the development and control of thrombus formation by modulating platelet activation, adhesion, and aggregation and vascular tone in response to plaque rupture. TXA_2 is produced by activated platelets [22] and has pro-aggregatory and vasoconstrictive effects [22]. As discussed in section 4.1.1.2, PGI_2 is produced by the vasculature where it inhibits platelet aggregation and acts as an arterial vasodilator [22]. Platelets contain COX-1 but not COX-2 and produce TXA_2 following activation through a COX-1 dependent process [22]. Of note, it was also known that there are other non-prostanoid anti-platelet and vasodilatory mediators produced by the endothelium such as nitric oxide, which are not affected by cyclooxygenase inhibitors and which could serve in addition to prostacyclin in processes that counter-regulate the effects of thromboxane [90].

Aspirin irreversibly acetylates and inactivates COX-1 and COX-2. In platelets, this inhibition leads to significant reductions in TXA_2 synthesis and inhibition of platelet activation, adhesion, and aggregation. The inhibitory effects of aspirin on nucleated cells is less marked, because unlike platelets, nucleated cells are able to synthesize new COX-1 and COX-2 molecules. This is especially true for low-dose aspirin where the net effect of therapy is profound inhibition of platelet function with minimal effects on systemic prostacyclin production. Clinically, this inhibition is manifested as an increase in bleeding time, and from a patient care perspective, improved outcomes following atherosclerotic plaque rupture but with an increased risk of minor and major bleeding events.

4.2.4.2 Comparison of the Effects of Selective Cox-2 Inhibitors and Nonselective NSAIDs/Aspirin on COX-1-Related Platelet Metabolism: Clinical Pharmacology

As early as 1977, the potential for non-selective NSAIDs to inhibit platelet aggregation was recognized [7]. As clinical use of NSAIDs increased, the ENT literature discussed an association of NSAID therapy with epistaxis, and inhibition of platelet aggregation with increased bleeding after non-selective NSAID administration was noted in the urologic , neurosurgical, and ophthalmologic surgical literature as well [6; 8; 9; 10; 11]. As discussed in Section 4.1.1, the effects of NSAIDs on platelet aggregation were found to be related to the inhibition of COX-1 mediated TXA_2 synthesis [31] and it was recognized that the effect of an NSAID on platelet aggregation was related to the duration of the drug's effect on TXA_2 synthesis [32].

It is thought that, to serve as a vascular-protective agent, near-complete inhibition of TXA_2 synthesis sustained over time is needed [25]. The effect of chronic therapy with non-aspirin COX-1/COX-2 inhibitors (the nonselective NSAIDs) on the incidence of cardiovascular thrombotic events has not been well characterized. Although nonselective NSAIDs inhibit platelet COX-1 activity, this inhibition is reversible. Thus, the ability of a nonselective NSAID to provide potent and sustained antiplatelet effects that mimic aspirin's antiplatelet properties (and thus potentially to effect aspirin-like vascular-protection) is highly dependent on the unique COX-1/COX-2 potency and pharmacokinetic profiles of each of these compounds. In contrast to the nonselective NSAIDs or aspirin, selective COX-2 inhibitors such as celecoxib and rofecoxib do not have these platelet inhibitory effects because platelets do not express COX-2 [91].

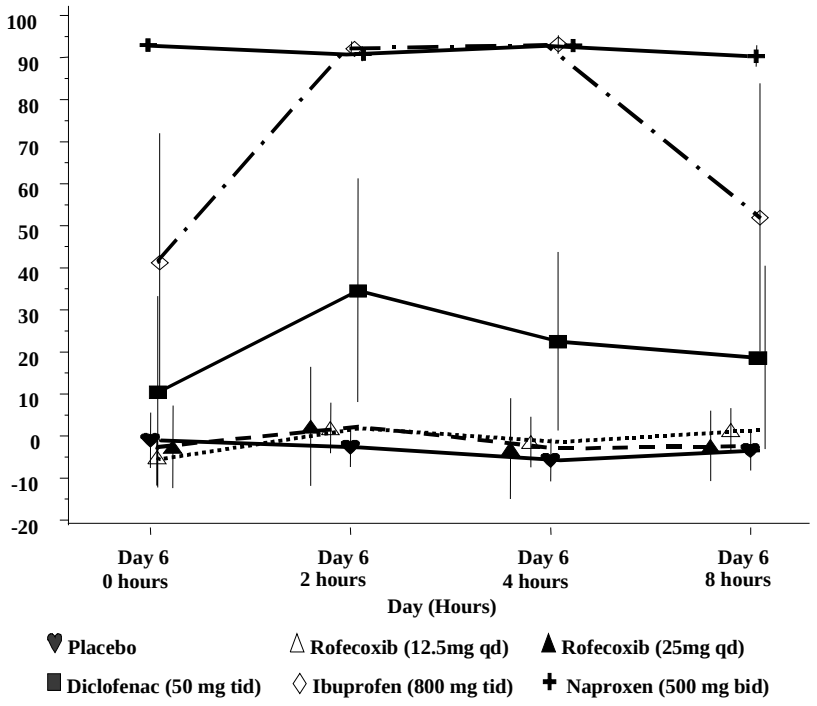
Several studies have demonstrated that the nonselective NSAIDs vary in the magnitude and time course of their effects on platelet function. These studies evaluated the effects of the NSAIDs on thromboxane metabolism and platelet aggregation in normal subjects. TXA_2 synthesis by platelets was monitored by measuring serum TXB_2 generated in clotting whole blood. As blood coagulates, platelets synthesize and release TXA_2. The synthesis of TXA_2 is dependent on COX-1. TXA_2 is converted rapidly and non-enzymatically to TXB_2 which is stable and measurable. In addition to the measurement of these prostanoid metabolites, effects on platelet aggregation and bleeding time were studied.

Studies reported in the original rofecoxib NDA explored the platelet effects of rofecoxib. Protocol 061 compared the effects of rofecoxib and several nonselective NSAIDs on thromboxane generation and platelet function [33]. Patients were randomized to receive 6 days of therapy with either placebo, rofecoxib 12.5 or 25 mg daily, diclofenac 50 mg 3 times daily, ibuprofen 800 mg 3 times daily, or naproxen 500 mg 2 times daily. The effects of these therapies on COX-1 activity were assessed by measuring the inhibition of TXB_2 generation and arachidonic acid-induced platelet aggregation at steady state. On day 6, measurements were taken prior to (trough) and at several times points after dosing. Protocol 063 investigated the effect of low-dose aspirin (81 mg) on TXB_2 and platelet aggregation and assessed the subsequent effect of rofecoxib 50 mg on the aspirin-induced inhibition of TXB2 and platelet aggregation.

The inhibition of platelet aggregation across the dosing intervals observed in Protocol 061 are displayed in Figure 16. In this figure, the effect of each drug is displayed across its recommended dosing interval. Because the study was performed at steady-state, measurements at 0 hours represent the trough values for the previous dose. These data show a gradient of anti-aggregatory effects when the pharmacodynamics of each drug is taken into account. Rofecoxib had an effect similar to placebo and diclofenac had an intermediate effect. Although ibuprofen showed near maximal inhibition of platelet aggregation at peak, it was not maintained across the dosing interval. Only naproxen 500 mg twice daily resulted in near maximal inhibition of platelet aggregation that was maintained across its dosing interval. The inhibition observed for naproxen in Protocol 061 was similar to that observed for aspirin in Protocol 063. Consistent with these findings, >90% inhibition across the dosing interval of platelet TXB2 production was only obtained with naproxen 500 mg twice daily and not the other NSAIDs [33].

Figure 16

Percent Inhibition From Baseline Platelet Aggregation by
Time Point* on Day 6 Using Arachidonic Acid as Agonist (Mean ±90% CI)



Also consistent with these data, therapy with placebo, rofecoxib, and diclofenac did not result in a prolongation of bleeding time whereas therapy with naproxen 500 mg twice daily prolonged bleeding time by ~79% [33]. This effect of naproxen on bleeding time is similar to the reported effect of aspirin (50 to 100% prolongation) [35; 33; 34; 22; 36].

In fact, differences in the antiplatelet effects of the various nonselective NSAIDs are reflected in their product circulars. The diclofenac United States package circular states that "Diclofenac increases platelet aggregation time but does not affect bleeding time;" the ibuprofen package circular states "Ibuprofen can inhibit platelet aggregation but, unlike aspirin, its effect on platelet function is reversible, quantitatively less, and of shorter duration;" while the package circular for naproxen in the United States and other countries states that "Naproxen may reduce platelet aggregation and prolong bleeding time", and is associated with a risk of bleeding [92; 93; 94; 92; 93].

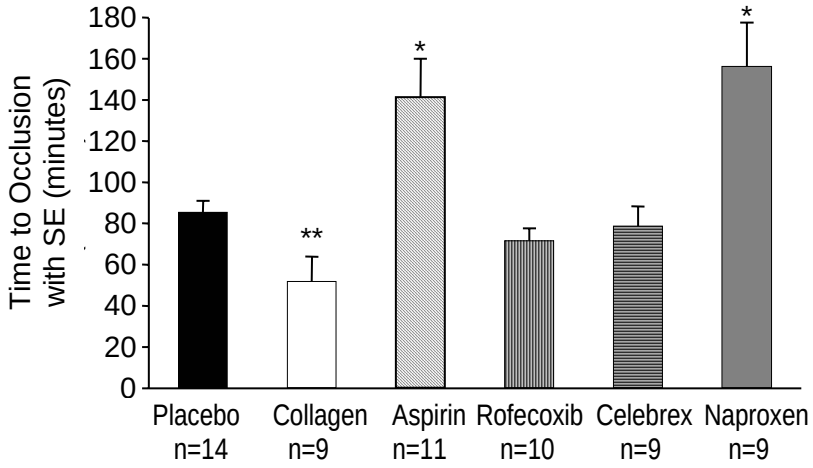
Thus, these data demonstrate a gradient of antiplatelet effects among the nonselective NSAIDs and rofecoxib, indicating that certain nonselective NSAIDs such as naproxen, with both potent and sustained antiplatelet effects might provide aspirin-like anti-platelet effects when appropriately dosed and used continuously. Similar results have been reported by other investigators [95] for the antiplatelet effects of naproxen, celecoxib, and valdecoxib [96].

4.2.4.3 Comparison of the Vascular Protective Effects of Naproxen/Aspirin in Preclinical Models of Vascular Injury

Additional preclinical data consistent with naproxen having an antithrombotic effect come from studies in the African green monkey Figure 17. In this model, animals exposed for 5 days to placebo, rofecoxib, celecoxib, naproxen, collagen, or aspirin were evaluated following electrolytic injury to the carotid artery and jugular vein. The aspirin arm was designed to be a positive control to represent effects of an antiplatelet agent. The collagen arm was designed to be a positive control to represent effects of a prothrombotic agent. COX-2 inhibition with either rofecoxib or celecoxib had no demonstrated effect on either arterial or venous thrombosis compared to placebo. Those treated with naproxen, however, demonstrated significantly prolonged times to both arterial and venous thrombosis compared to placebo. The time to thrombosis in the aspirin group had similar outcomes to naproxen; a significantly prolonged time to arterial thrombosis and a numerically increased time to venous thrombosis. The results of this study suggest that COX-2 inhibition has no effect on thrombosis and that naproxen exhibits antithrombotic effects similar to aspirin.

Figure 17

Time to Occlusion in Carotid Artery – African Green Monkey
Model of Thrombosis



**p=0.06; Collagen < Placebo

*p<0.05; Aspirin & Naproxen > Placebo

4.2.4.4 Clinical Evidence of an Antiplatelet Effect of Naproxen 500 mg Twice Daily in the VIGOR Study

Treatment with anti-platelet agents such as aspirin is associated with an increased risk of minor and major episodes of bleeding. In VIGOR, naproxen was associated with a higher incidence of minor bleeding events relative to rofecoxib (2.7 versus 1.9%, difference = -0.8%, 95% CI: -1.4%, -0.1%). The largest differences between naproxen and rofecoxib occurred in those events typically associated with antiplatelet effects, such as ecchymosis and epistaxis. For these adverse experiences, naproxen therapy was associated with a 2.1- and 3.5-fold increase incidence relative to rofecoxib therapy, respectively. These results are consistent with the differences in antiplatelet properties observed in clinical pharmacology studies between potent nonselective COX-1/COX-2 inhibitors such as naproxen 500 mg twice daily and the selective COX-2 inhibitors such as rofecoxib and celecoxib [19; 28].

4.2.4.5 Clinical Trials Evaluating the Vascular-Protective Properties of Nonselective NSAIDs

Although there have been no cardiovascular outcomes trials with naproxen, there is evidence for the vascular-protective efficacy of flurbiprofen and indobufen, two nonselective NSAIDs which exhibit potent antiplatelet properties. Flurbiprofen treatment

has been shown to prolong bleeding time and was evaluated for a cardioprotective effect compared with placebo in the setting of coronary plaque rupture [27]. In this study, 464 patients who were successfully treated for acute myocardial infarction by thrombolysis and/or coronary angioplasty were randomized to receive either placebo or flurbiprofen 50 mg twice daily for 6 months. Use of aspirin or ticlopidine during the treatment period was not allowed. The primary endpoint was recurrent MI or reocclusion of the infarct-related coronary artery. Therapy with flurbiprofen was associated with a >50% reduction in the incidence of reinfarction and coronary revascularization at 6 months [27] and a 71% reduction in the risk of myocardial infarction when compared with placebo treatment. The benefit was observed regardless of whether the patients underwent thrombolysis or percutaneous transluminal coronary angioplasty as therapy for the index myocardial infarction. This study specifically addressed the effects of flurbiprofen in the context of acute cardiovascular disease.

The data on the cardioprotective effects of the nonselective NSAID indobufen are even more compelling, although they are not as extensive as available for aspirin or clopidogrel. Clinical studies compared the effects of indobufen with placebo, aspirin, warfarin, or ticlopidine in patients with intermittent claudication resulting from peripheral vascular disease, in the prophylaxis of thromboembolism in patients with heart disease, in the prophylaxis of occlusion of coronary and femoropopliteal artery bypass grafts, and in the secondary prevention of thrombotic events following transient ischemic attack (TIA) and stroke [29; 37; 26; 38]. Collectively, these randomized double-blind clinical studies showed that indobufen treatment was associated with cardioprotective effects superior to placebo and similar to aspirin or warfarin although not as effective as ticlopidine

When compared to placebo, indobufen therapy for 26 months was associated with a 65% reduction in the risk of a primary event (defined as fatal and nonfatal ischemic stroke and pulmonary embolism, fatal myocardial infarction and nonfatal systemic embolism and TIA) and reduced the risk of stroke 3-fold in patients with heart disease who were at risk of thromboembolism [26]. When evaluated for the prevention of saphenous vein graft occlusion in patients undergoing coronary artery bypass graft surgery indobufen therapy resulted in a significant reduction in the incidences of vein graft occlusion at 1 month and at 1 year, when compared with aspirin plus dipyridamole [37]. When evaluated for the secondary prevention of thrombotic events in patients with nonrheumatic atrial fibrillation and a recent (<15 days) cerebral ischemic episode, no difference was noted for patients treated with indobufen versus warfarin over 1 year of treatment [38].

The data from these studies suggest that nonselective COX-1/COX-2 inhibitors with potent and sustained platelet COX-1 inhibitory properties result in vascular-protective properties similar to those observed with aspirin and the anticoagulant agent warfarin.

4.2.4.6 Clinical Trials Demonstrating a Difference in Cardiovascular Event Rates Between Naproxen and Other Selective COX-2 Inhibitors

Although not available at the time of VIGOR, more recent data further identify a consistent difference in thrombotic cardiovascular events between selective COX-2 inhibitors and naproxen but not between selective COX-2 inhibitors and other non-selective NSAIDs. To date, published data on all COX-2 inhibitors have shown rates of CV events similar to NSAIDs other than naproxen. [15; 39; 40; 41]. In the Phase IIb/III OA program as noted above, the incidence of CV events was similar on rofecoxib and the comparator NSAIDs ibuprofen, diclofenac and nabumatone. In contrast, in clinical studies comparing selective COX-2 inhibitors to naproxen 500 mg twice daily [15; 39], the rates of CV events with naproxen have been lower than with selective COX-2 inhibitors. Although it has been argued that CV event rates with celecoxib are similar to naproxen with a relative risk of 0.85 for celecoxib:naproxen [40], the data were limited with only 4 events and less then 400 patient-years exposure in the naproxen group, and the 95% CI were wide (0.29 to 2.46), limiting the ability to draw a conclusion.

The largest single trial comparing a selective COX-2 inhibitor with naproxen was the TARGET study with lumiracoxib [97]. The TARGET study, which enrolled over 18,000 patients, was designed to assess GI outcomes but a key secondary objective was to measure and compare a composite endpoint of cardiovascular morbidity and mortality. TARGET consisted of 2 substudies of equal size with one comparing lumiracoxib to ibuprofen 800 mg 3x daily and the other lumiracoxib to naproxen 500 mg 2x daily [39]. In TARGET, the hazard ratio (95% CI) of confirmed or probable APTC events for lumiracoxib versus ibuprofen was 0.76 (0.41, 1.40) while the hazard ratio (95% CI) of confirmed or probable vascular events for lumiracoxib versus naproxen was 1.46 (0.89, 2.37). The differences between lumiracoxib and ibuprofen and between lumiracoxib and naproxen were not significant (0.3775 and 0.1313, respectively), and the treatment by substudy interaction result was nonsignificant (p=0.1145). However, the TARGET study was not powered for the cardiovascular endpoint. The hazard ratio for the APTC combined endpoint in the lumiracoxib versus naproxen substudy is not inconsistent with the findings with rofecoxib [39].

4.2.4.7 Weight of the Evidence in Favor of an Antithrombotic and Potential Cardioprotective Benefit of Naproxen 500 mg Twice Daily (Sep-2000)

In assessing the imbalance in thrombotic cardiovascular events in VIGOR, all of the possible data available were reviewed. The data regarding platelet and bleeding time effects for naproxen described above clearly substantiate its potent antiplatelet effects. Randomized clinical trials had also suggested a reduction in cardiovascular risk associated with the use of nonselective NSAIDs with potent antiplatelet effects.

The available clinical trial data were not suggestive of an increased cardiovascular risk for rofecoxib in either the Alzheimer's population versus placebo or the Phase IIb/III OA population versus non-naproxen NSAIDs (See Figure 18). The weight of the evidence was most consistent with no prothrombotic effect of rofecoxib and a cardioprotective benefit of naproxen.

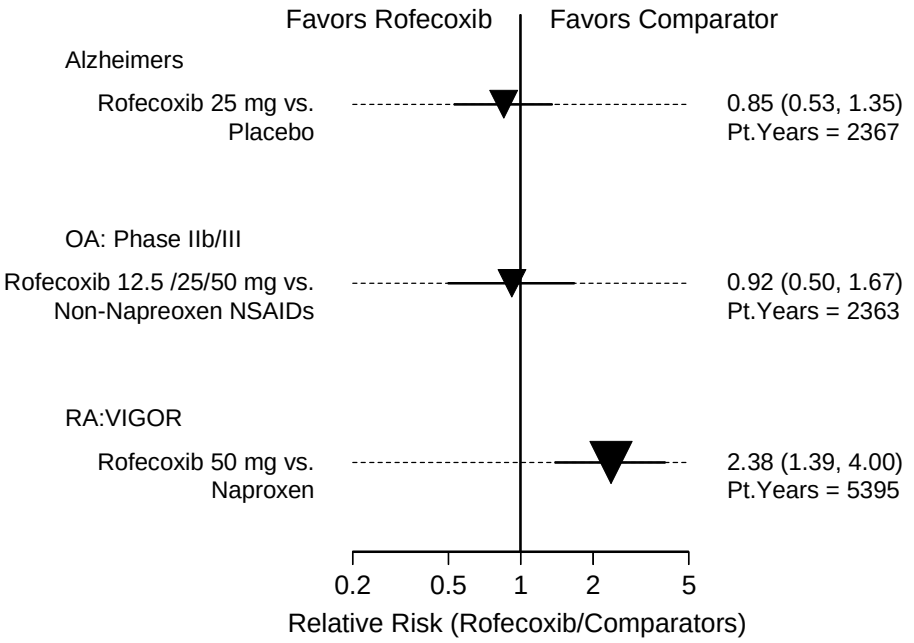
In considering the possibility that naproxen provided a cardioprotective benefit in VIGOR, it was important to determine if the estimate for a putative cardioprotective effect was reasonable based on published data for aspirin, the paradigmatic antiplatelet COX-1 inhibitor. The APTC combined endpoint for the VIGOR data allows one to compare the effect size in VIGOR with the effects of antiplatelet drugs reported in a large meta-analysis [98] and thus determine if it is reasonable to hypothesize an antiplatelet and therefore, cardioprotective effect of naproxen in VIGOR. The risk reduction for the APTC combined endpoint in the meta-analysis of antiplatelet drugs was 25% (overall combined data). The "risk reduction" and 95% CI of the APTC combined endpoint for naproxen versus rofecoxib was 49% (95% CI: 9, 71%). Although the point estimate for "risk reduction" in VIGOR is greater than in the meta-analysis, the meta-analysis result is within the 95% CI of the VIGOR result.

Studies have suggested that aspirin has a larger relative benefit in higher risk patients defined either by levels of C-reactive protein (CRP) [99]or as defined clinically[98]. In the Physician's Health Study, the risk reduction for myocardial infarction ranged from 13.9% in the quartile of patients with the lowest level of CRP to 55.7% in the quartile with the highest CRP levels [99]. In the antiplatelet drugs meta-analysis, a greater risk reduction was seen in higher risk patients (37% reduction of the APTC combined endpoint in patients with coronary artery disease and ~50% reduction in patients with unstable angina or post-angioplasty)[98]. The patients in VIGOR all had RA, RA patients generally have higher CRP levels than patients without inflammatory disease, and RA patients have an increased risk of coronary artery disease and are a recognized high risk group for coronary artery disease [100; 101; 102].

Thus, the results in VIGOR were thought to be consistent with an antiplatelet and therefore cardioprotective effect of naproxen.

Figure 18

Relative Risk (95% CI)
Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences for Alzheimer's Disease and OA Phase IIb/III Studies; and Confirmed Thrombotic CV Serious Adverse Experiences for VIGOR
(Data Available in 9/2000)



4.2.5 Pooled Analysis of Thrombotic Cardiovascular Events: Rofecoxib or Nonselective NSAID Users Across All Rofecoxib Clinical Trials Using the Antiplatelet Trialists' Collaboration (APTC) Combined Endpoint (Original Pooled Analysis, Sep-2000)

In addition to the clinical studies described above, the rofecoxib clinical program had included several smaller studies in diverse patient populations. To provide a global assessment of cardiovascular outcomes across the rofecoxib clinical program at the time of VIGOR completion, Merck conducted a pooled analysis of all relevant studies completed and unblinded in early Sep-2000, as well as the two ongoing trials in Alzheimer's Disease as described above. The focus of the pooled analysis was to improve precision in the estimate of relative risks for the development of a thrombotic CV event between rofecoxib and naproxen, rofecoxib and placebo, and rofecoxib and non-naproxen NSAIDs, and to determine if the conclusions from the individual studies described above (VIGOR, OA Phase IIb/III, Alzheimer's Disease) would be either altered or strengthened by inclusion of all relevant data.

All Phase IIb to V studies of at least 4 weeks duration which included either placebo and/or active-comparator nonselective NSAID controls were included in the pooled analysis. The pooled analysis thus included data from the Phase IIb/III OA, VIGOR, ADVANTAGE, and Alzheimer's Disease studies discussed above as well as data from the RA Phase IIb/III program in which rofecoxib was compared to placebo and naproxen, and from postmarketing (Phase V) studies such as Protocols 085 and 090 in which rofecoxib was compared to placebo and nabumetone. Studies in which rofecoxib was compared with celecoxib or that were conducted in healthy volunteers were excluded. The celecoxib studies were excluded because they did not provide data to address the questions being asked; that is, comparisons to nonselective NSAIDs and placebo. Examination of these data revealed similar rates of events on the 2 selective COX-2 agents: 2 events in 2363 patients (0.08% crude incidence for rofecoxib and 2 events in 1535 patients (0.13% crude incidence) for celecoxib. The pooled analysis was a prespecified ongoing project; the results were periodically updated as additional sets of data became unblinded.

As discussed previously, the primary endpoint for the pooled analysis was the APTC combined endpoint. The primary objective of the pooled analysis was to estimate the incidence rates of the APTC combined endpoint in patients treated with nonselective NSAIDs (naproxen, and other NSAIDs examined separately) or placebo compared to those treated with rofecoxib. Naproxen was analyzed separately from other NSAIDs due to its demonstrated potent and sustained antiplatelet effect which would potentially provide cardioprotective effects not present in the other NSAIDs. The comparisons of interest were:

- Naproxen versus rofecoxib.
- Other (non-naproxen) NSAIDs versus rofecoxib.
- Placebo versus rofecoxib.

Over 28,000 patients had been treated with either rofecoxib or nonselective NSAID/placebo in Phase IIb to V clinical studies by Sep-2000. Baseline patient characteristics are in Table 19, Table 20, and Table 21 for the naproxen, non-naproxen nonselective NSAID, and placebo populations, respectively.

The results of the pooled analysis, which were reviewed at the FDA Arthritis Advisory Committee meeting on 08-Feb-2001, are displayed in Figure 19 using a standard relative risk plot. The triangle represents the point estimate of the relative risk, with the size of the triangle proportional to the number of patient years included in the analysis. The relative risk of the APTC combined endpoint in naproxen users versus rofecoxib users was consistent with the results observed in VIGOR and with a decreased incidence of the APTC combined endpoint in the naproxen group compared to the rofecoxib group. Because of the potential for aspirin use to confound the results of the analysis, a subgroup analysis was conducted only in patients who were not taking aspirin/clopidogrel prior to study start. This subgroup analysis, which included >88% of the events, provided consistent results with the primary approach.

Table 19

Patient Baseline Demographics and CV Risk
Pooled Analysis
Rofecoxib Versus Naproxen (Sep-2000)

Demographic	Rofecoxib (N=9083)		Naproxen (N=7870)	
	n	(%)	n	(%)
Age				
Percent <65 years old	6214	(68.4)	5228	(66.4)
Percent ≥65 years old	2869	(31.6)	2642	(33.6)
Gender				
Female	6984	(76.9)	6015	(76.4)
Male	2099	(23.1)	1855	(23.6)
Cardiovascular Risk Factors				
Any cardiovascular risk factor	4834	(53.2)	4205	(53.4)
Hypertension	3117	(34.3)	2782	(35.3)
Diabetes mellitus	691	(7.6)	659	(8.4)
Hypercholesterolemia	1405	(15.5)	1134	(14.4)
Current smoker	1226	(13.5)	981	(12.5)
Hx of symptomatic ASCVD	499	(5.5)	451	(5.7)
Increased CV risk[†]	1700	(18.7)	1460	(1.6)

[†] History of ≥2 risk factors for coronary disease or a history of symptomatic atherosclerotic cardiovascular disease
ASCVD = atherosclerotic cardiovascular disease

Table 20

Patient Baseline Demographics and Cardiovascular Risk
Pooled Analysis
Rofecoxib Versus Other NSAIDS (Sep-2000)

Demographic	Rofecoxib (N=4549)		Other NSAIDs (N=2755)	
	N	(%)	n	(%)
Age				
Percent <65 years old	2499	(54.9)	1510	(54.8)
Percent ≥65 years old	2050	(45.1)	1245	(45.2)
Gender				
Female	3256	(71.6)	1966	(71.4)
Male	1293	(28.4)	789	(28.6)
Cardiovascular Risk Factors				
Any cardiovascular risk factor	2589	(56.9)	1601	(58.1)
Hypertension	1816	(39.9)	1104	(40.1)
Diabetes mellitus	380	(8.4)	217	(7.9)
Hypercholesterolemia	818	(18.0)	554	(20.1)
Current smoker	480	(10.6)	291	(10.6)
Hx of symptomatic ASCVD	357	(7.8)	215	(7.8)
Increased CV risk[†]	1021	(22.4)	631	(22.9)

[†]History of ≥2 risk factors for coronary disease or a history of symptomatic atherosclerotic cardiovascular disease
ASCVD = atherosclerotic cardiovascular disease

Table 21

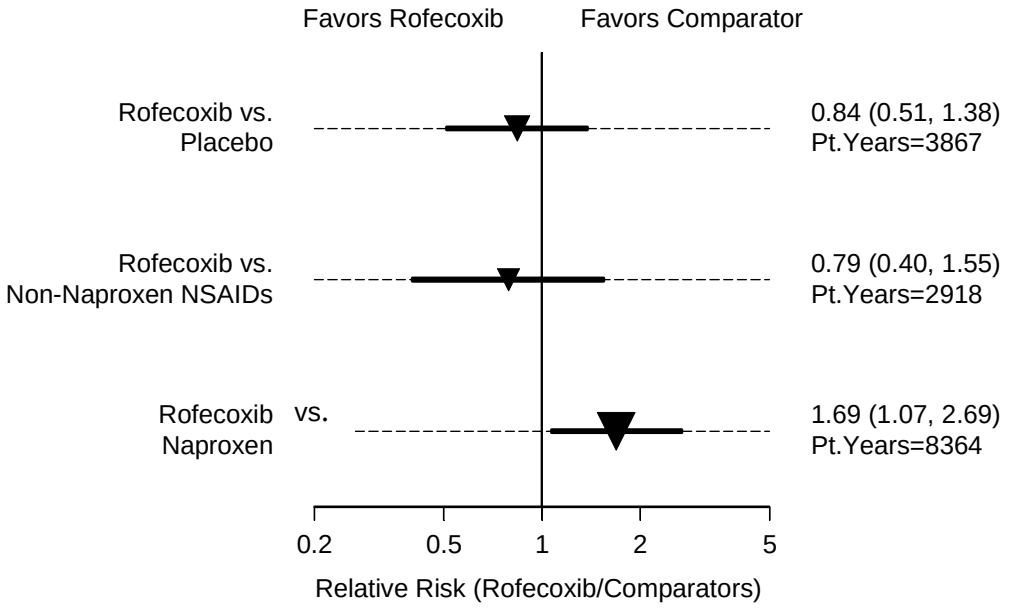
Patient Baseline Demographics and Cardiovascular Risk
Pooled Analysis
Rofecoxib Versus Placebo (Sep-2000)

Demographic	Rofecoxib (N=6290)		Placebo (N=3482)	
	n	(%)	n	(%)
Age				
Percent <65 years old	3396	(54.0)	1676	(48.1)
Percent ≥65 years old	2894	(46.0)	1806	(51.9)
Gender				
Female	4258	(67.7)	2157	(61.9)
Male	2032	(32.3)	1325	(38.1)
Cardiovascular Risk Factors				
Any cardiovascular risk factor	3420	(54.4)	1828	(52.5)
Hypertension	2182	(34.7)	1098	(31.5)
Diabetes mellitus	491	(7.8)	308	(8.8)
Hypercholesterolemia	1104	(17.6)	592	(17.0)
Current smoker	807	(12.8)	457	(13.1)
Hx of symptomatic ASCVD	490	(7.8)	292	(8.4)
Increased CV risk[†]	1306	(20.8)	728	(20.9)

[†]History of ≥2 risk factors for coronary disease or a history of symptomatic atherosclerotic cardiovascular disease
ASCVD = atherosclerotic cardiovascular disease

Figure 19

Relative Risk (95% CIs)
Pooled Analysis of APTC Combined Endpoint at the Time of VIGOR Completion,
Rofecoxib Versus Comparator Agents (September 2000 Data)



4.2.5.1 Pooled Analysis of APTC Combined Endpoint Data by Rofecoxib Dose (September 2000 Data)

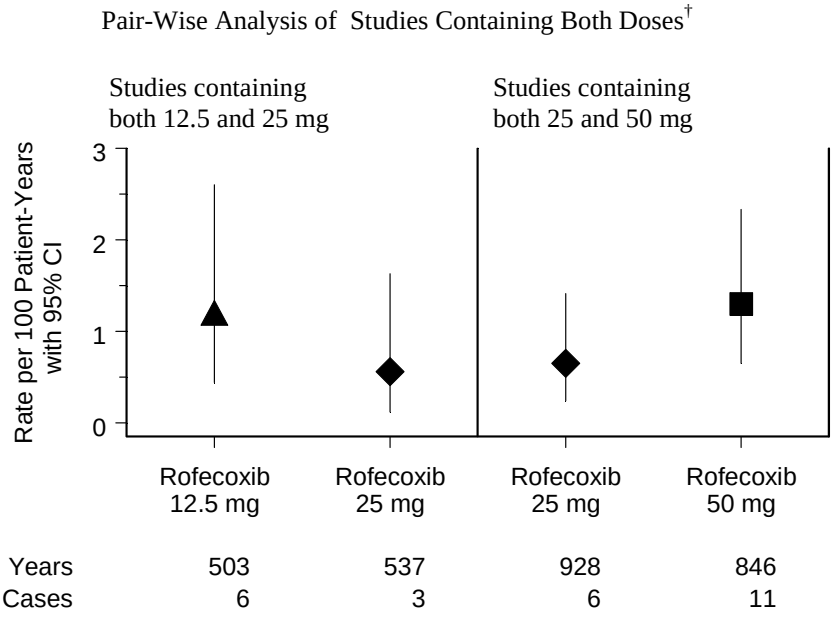
Although the aggregate data in the pooled analysis was important in confirming the data observed in the Alzheimer's Disease and OA programs and establishing the low likelihood of a prothrombotic effect with rofecoxib, VIGOR studied rofecoxib 50 mg and these other databases were based either on pooled rofecoxib doses or just the 25-mg dose. To investigate whether rofecoxib dose could have contributed to the imbalance of thrombotic cardiovascular serious adverse experiences in VIGOR, data from the pooled analysis were explored to investigate evidence for a dose effect on the thrombotic cardiovascular event rates.

To compare incidence rates and relative risks across doses, one needs to combine data from different studies. An important factor therefore is which studies can be combined. In general in such an analysis for a dose-related outcome, studies should be combined only if each study contains the two treatments that are being compared. Therefore, the approach, referred to as a pair-wise analysis, is the most rigorous approach and is based on a dose analysis which includes data only from those studies which contained both doses being analyzed. As only one small study (Protocol 029) contained all 3 doses of rofecoxib, a pair-wise analysis was done by combining studies that contained the approved chronic doses of 12.5 and 25 mg and studies containing 25 and 50 mg. The 50-mg dose was not recommended for chronic use.

Three studies contributed to the comparison of rofecoxib 12.5 and 25 mg. There were a total of 9 patients with CV events: 6 on rofecoxib 12.5 mg in 503 patient-years of exposure and 3 on 25 mg in 537 patient-years. Six studies contributed to the comparison of rofecoxib 25 and 50 mg. There were a total of 17 patients with CV events: 6 on rofecoxib 25 mg in 928 patient-years of exposure and 11 on 50 mg in 846 patient-years. Consistent with the small number of events, the confidence intervals for the rates are widely overlapping. Overall, the data are limited by small numbers of CV events but do not provide evidence in favor of a dose-relationship for APTC events.

Figure 20

APTC Combined Endpoint Stratified by Dose Analysis of Cardiovascular Events
Rates per 100 Patient-Years (95% CIs)
Pooled Analysis (Sep-2000 Data)



† Comparison of 12.5 mg and 25 mg doses used studies that administered those two doses and comparison of 25 mg and 50 mg doses used studies that administered those two doses.

4.2.6 Cardiovascular Conclusions – VIGOR

- The VIGOR study showed a lower incidence of confirmed serious cardiovascular thrombotic events in patients treated with naproxen 500 mg once daily as compared to patients treated with rofecoxib 50 mg twice daily. This finding was largely due to a difference in the incidence of myocardial infarction between the groups.
  - Subgroup analyses did not reveal demographic variables associated with an increased relative risk.
  - Analyses of the differential effects of the two study treatments on blood pressure did not explain the imbalance in confirmed thrombotic CV events in VIGOR.
  - Analyses of relative risks over time were most consistent with a constant relative risk.
- Data from the other studies in the rofecoxib clinical program did not suggest a prothrombotic effect of rofecoxib
  - In the Alzheimer's Disease studies, there was a similar incidence of serious cardiovascular thrombotic events in patients treated with rofecoxib 25 mg once daily as compared to patients treated with placebo.
  - A pooled analysis of data across the rofecoxib development program confirmed the findings in the OA, Alzheimer's Disease, and VIGOR studies of a similar rate of CV thrombotic events in patients taking rofecoxib compared to either placebo or non-naproxen NSAIDs. The rate of thrombotic events was lower in patients taking naproxen
  - Analyses did not reveal a relationship between rofecoxib dose and the incidence of thrombotic cardiovascular events.
  - Subgroup analyses revealed that relative risk was similar in patients with or without baseline risk factors for CV events.
- Data on naproxen and other non-selective NSAIDs with potent and sustained antiplatelet effects were consistent with the ability of naproxen 500 mg twice daily to provide a cardioprotective benefit when used continuously as in a clinical study.
  - Review of clinical and preclinical pharmacologic data on naproxen revealed that naproxen 500 mg twice daily inhibits platelet thromboxane production and aggregation and, in animal models, thrombosis to a degree similar to aspirin and greater than that seen with ibuprofen 800 mg three times daily or diclofenac 50 mg three times daily.
  - Review of clinical literature revealed that other non-aspirin NSAIDs with potent and sustained antiplatelet effects could provide a cardioprotective benefit.
  - Subsequent studies with lumiracoxib were consistent with a difference in thrombotic cardiovascular events between naproxen and another selective COX-2 inhibitor, lumiracoxib, but not between ibuprofen and lumiracoxib.

- Naproxen's label, in distinction from the diclofenac or ibuprofen labels, describes an increased incidence of bleeding; there was a higher incidence of epistaxis and ecchymoses with naproxen compared to rofecoxib in VIGOR.
- The 95% CI for the magnitude of the difference in VIGOR of thrombotic cardiovascular events between naproxen and rofecoxib was consistent with the size of the effect in a large meta-analysis of aspirin versus placebo in lowering the risk of these events.

- The weight of the evidence supported that in VIGOR naproxen provided a cardioprotective benefit.

4.2.7 Outcome of Feb-2001 Advisory Committee Meeting and Final FDA Decisions on the VIGOR Supplemental NDA

The preliminary results from the VIGOR trial were submitted to the FDA and made available to the public through a press release in Mar-2000 within a month of the data being unblinded, and a supplementary NDA was submitted in Jun-2000. A safety update report including the final VIGOR data was submitted in Oct-2000. The FDA assembled the Arthritis Advisory Committee in Feb-2001 to assess the gastrointestinal and cardiovascular safety data from VIGOR. The advisory committee, composed of an outside group of experts, recommended that the label for rofecoxib should include the gastrointestinal and cardiovascular information observed in VIGOR. The committee advised that the NSAID-class warning regarding GI adverse events should be modified, but not removed, from the rofecoxib label. The Advisory Committee noted that one cannot conclude from the VIGOR data alone whether the difference in CV event rates observed in the study entirely represented a decrease in naproxen users, or an increase in rofecoxib users and therefore stated that the cardiovascular data should be presented in the label for prescribers to interpret, rather than providing a conclusion.

In Apr-2001, the FDA issued an Approvable letter for the VIGOR supplemental NDA application and requested updated safety analyses in order to adequately interpret the cardiovascular and overall safety results in the VIGOR study and provide adequate labeling information. The safety update analyses were provided to FDA in Jul-2001. Responses to additional requests for analyses based on the new data were provided to FDA through the end of 2001. Also, in this time frame, efficacy and safety data from the adult rheumatoid arthritis program were submitted as an additional NDA supplement. This information complimented the VIGOR data, a trial which was performed solely in RA patients.

In April 2002, the rofecoxib label was updated to include 1) a new indication for use of rofecoxib in the relief of the signs and symptoms of rheumatoid arthritis in adults, 2) a modification of the NSAID-class warning regarding gastrointestinal safety, 3) the CV data from VIGOR and the ongoing Alzheimer's Disease studies, along with a statement that the significance of these data is unknown, 4) a direction to use caution in prescribing rofecoxib for patients with ischemic heart disease, 5) additional safety information on

rofecoxib 50 mg, and 6) the statement that the chronic use of rofecoxib 50 mg is not recommended. Merck issued a "Dear Health Care Provider" letter detailing these changes to the rofecoxib label.

4.3 Ongoing Activities Post-VIGOR Through September-2004

4.3.1 Study of CV Outcomes (Protocol Developed 2002)

At the time VIGOR completed, several large placebo controlled studies were already underway: the Alzheimer's Disease studies and the APPROVe study. The Alzheimer's Disease program consisted of the two Alzheimer's Disease studies (Protocols 078 and 091). A third Alzheimer's Disease study had been initiated in 2000, identical in design to Protocol 091. This latter study was terminated early after Protocol 091 failed to demonstrate efficacy. Because patient exposure was relatively short in this 3rd study compared to the other 2 Alzheimer's Disease studies, the data from this 3rd study are not combined with the others in the Alzheimer's Disease analyses. Data from the 3rd Alzheimer's Disease study are included in the pooled analyses of all studies. The APPROVe study, an outcomes study evaluating the ability of rofecoxib to diminish the recurrence of colon polyps in patients with a prior colorectal adenoma had started screening patients in Dec-1999 and enrolling patients in Feb-2000. Either of these two datasets would have been sufficiently powered to demonstrate a prothrombotic effect of rofecoxib of a magnitude similar to the difference observed in VIGOR between rofecoxib and naproxen. Indeed, in final data for each there were more confirmed thrombotic CV events than in VIGOR.

In order to evaluate further the risk of thrombotic cardiovascular events with rofecoxib, Merck decided to conduct a cardiovascular outcomes study. In Dec-2001 Merck announced that it would conduct CV Outcomes studies with its COX-2 inhibitors. One approach considered was to study the use of rofecoxib in arthritis patients and compare the risk of rofecoxib with a nonselective NSAID. This design could address the question of relative risk between rofecoxib and the nonselective NSAID. The second approach considered was to study rofecoxib in comparison to placebo in patients who did not require chronic NSAID therapy and who could therefore ethically be enrolled in a long-term, placebo-controlled study. This latter design could address the question of relative risk between rofecoxib and placebo. After consultation with experts, Merck decided to develop a cardiovascular outcome protocol for rofecoxib based on a placebo-controlled design.

To implement a placebo-controlled cardiovascular outcomes protocol for rofecoxib, a strategy was devised to compare rofecoxib to placebo in a novel population in whom a potential benefit of selective COX-2 inhibitors had been proposed. Again, several designs were considered. One design proposal was in high-risk patients with acute coronary syndrome. As alluded to above, because COX-2 is expressed in atheroma and was thought to be linked to plaque rupture, the inhibition of COX-2 was proposed as a possible mechanism to stabilize plaques. After extensive discussion with consultants,

this design was ultimately rejected for several reasons. First, these patients are medically unstable and the risk of giving them an agent with a known (albeit reduced) risk for causing GI hemorrhage and small risk of fluid retention and CHF, was considered excessive in comparison to the potential benefit. Second, in any such study, all patients would need to take aspirin which had the potential to mask a potential prothrombotic effect of rofecoxib if one should be present. Third and finally, it was unclear how to extrapolate these data to the larger population of arthritis patients with a spectrum of CV risks in whom rofecoxib was indicated.

However, the expanding database of studies versus placebo with rofecoxib and the emerging data on possible chemopreventative benefits of COX-2 inhibition [103; 104] provided an alternative means to develop a cardiovascular outcomes protocol in populations which could be approached using placebo-controlled studies. Thus, it was decided to develop a cardiovascular outcome protocol for rofecoxib based on a combined analysis of placebo-controlled chemoprevention studies with rofecoxib in patients with a broad spectrum of CV risks. The APPROVe study comparing rofecoxib 25 mg to placebo was already initiated, and a second study also comparing rofecoxib and placebo was to be started in 2002: VICTOR – a study to assess the ability of rofecoxib to prolong disease-free time and overall survival in patients with resected colon cancer. The third study was to assess the ability of rofecoxib to prevent prostate cancers in men at risk (ViP) and was initiated in 2003 after discussions with regulatory agencies. Together, these 3 studies (APPROVe, VICTOR and ViP) would provide information in over 25,000 patients on thrombotic cardiovascular events that would all be adjudicated per Merck's SOP. The combined analysis had its own protocol and data analysis plan and as its primary safety outcome the confirmed thrombotic CV serious adverse experience endpoint. An External Safety Monitoring Board was to monitor the CV safety for these 3 combined studies as data became available; however, given the sequence of events, the combined ESMB never met. The protocol for the combined study of CV Outcomes was finalized in October 2002 and it was submitted to and discussed with FDA and with the regulatory agency in the UK (the reference member state for the EU registration.) Preliminary results from the APPROVe study became available in September 2004 and are discussed in Section 6.

4.3.2 Continual Monitoring of Ongoing Studies (2001 to 2004)

At the time of VIGOR, Merck made a commitment to continue to update our pooled analysis of CV events. The OA Phase IIb/III Study Extensions were completed by 2001 and included in an updated pooled analysis based on Mar-2001 data that was provided to FDA in Jul-2001 as part of the updated safety data requested in the VIGOR Approvable action letter received by Merck in Apr-2001.

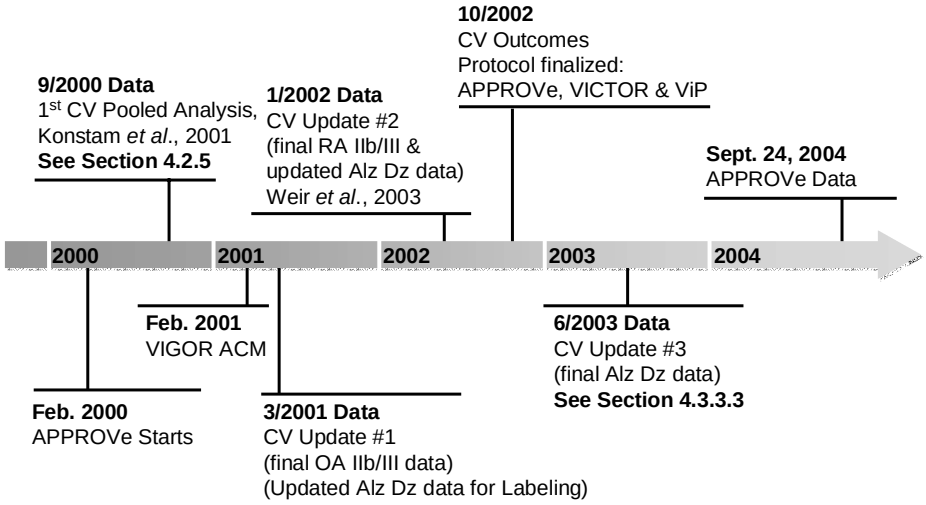
The RA Phase IIb/III Study Extensions were completed later in 2001 and were included in an updated pooled analysis based on a Jan-2002 data cutoff. These data were submitted to regulatory agencies in the 2nd quarter 2002 and published in 2003 [42].

The Alzheimer's Disease studies were completed in 2003 and were included in the final update to the pooled analysis based on a final data cutoff of June 2003 .

Shown below are the final data from the OA Phase IIb/III program (Section 4.3.2.1), the Alzheimer's Disease program (Section 4.3.2.2), and the final CV pooled analysis (Section 4.3.2.3). The final CV pooled analysis encompassed a period of up to 4 years of follow-up in more than 32,000 patients representing over 19,300 patient-years of experience with rofecoxib or comparator agents. Figure 21 highlights the major updates to the pooled analyses of CV events outlined above.

Figure 21

Timeline of Major Updates to the CV Pooled Analysis



4.3.2.1 Final OA IIb/III CV Data

The placebo-controlled portions of the OA Phase IIb/III studies were completed at the time of the original NDA, however the double-blinded extensions with non-naproxen NSAIDs were not completed and fully analyzed until 2001. Table 22 and Table 23 contains the final number of events and relative risk for the non-naproxen NSAIDs data set. Figure 22 presents the cumulative incidence of investigator reported Thrombotic CV serious adverse experiences. The results are consistent with the original analysis and demonstrate similar rates of events in the rofecoxib and non-naproxen NSAID treatment groups.

Table 22

Absolute Rate and Relative Risk (95% CI)
Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences
OA Phase IIb/III: Non-Naproxen NSAIDs (Final Data 2001)

Study	Treatment Group	N	Patients With Events	PYR[†]	Rate[‡]	Relative Risk (95% CI)
Phase IIb/III Studies Combined	Rofecoxib 12.5/25/50 mg	3358	50	2381	2.10	0.98 (0.60, 1.62)
	Nonselective NSAIDS[§]	1565	22	1030	2.14	

[†] Patient-years at risk.
[‡] Per 100 PYR.
[§] diclofenac, ibuprofen, nabumetone

Table 23

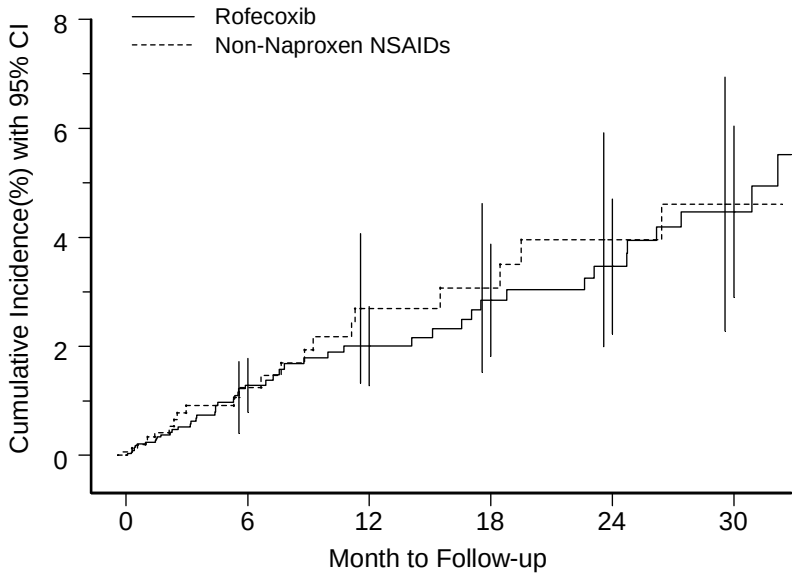
Summary of Patients With Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences
OA Phase IIb/III: Non-Naproxen NSAIDs (Final Data 2001)

Category	Rofecoxib (N=3358) (PYR=2381)		Non-Naproxen NSAIDs (N=1565) (PYR=1030)	
	n (%)[†]	(Rate)[‡]	n (%)[†]	(Rate)[‡]
Patients With One or More Thrombotic Cardiovascular Serious Adverse Experiences	**50 (1.5)**	**(2.1)**	**22 (1.4)**	**(2.1)**
Cardiac Events	31 (0.9)	(1.3)	15 (1.0)	(1.5)
Acute myocardial infarction	10 (0.3)	(0.4)	4 (0.3)	(0.4)
Unstable angina pectoris	4 (0.1)	(0.2)	0 (0.0)	(0.0)
Angina pectoris	5 (0.1)	(0.2)	4 (0.3)	(0.4)
Sudden/unknown cause of death	2 (0.1)	(0.1)	3 (0.2)	(0.3)
Coronary artery occlusion	3 (0.1)	(0.1)	1 (0.1)	(0.1)
Coronary artery disease	6 (0.2)	(0.3)	3 (0.2)	(0.3)
Coronary vasospasm	1 (0.0)	(0.0)	0 (0.0)	(0.0)
Cerebrovascular Events	**17 (0.5)**	**(0.7)**	**6 (0.4)**	**(0.6)**
Cerebrovascular accident	9 (0.3)	(0.4)	4 (0.3)	(0.4)
Transient ischemic attack	6 (0.2)	(0.3)	1 (0.1)	(0.1)
Vascular insufficiency	1 (0.0)	(0.0)	1 (0.1)	(0.1)
Carotid artery obstruction	1 (0.0)	(0.0)	0 (0.0)	(0.0)
Peripheral Vascular Events	5 (0.1)	(0.2)	1 (0.1)	(0.1)
Deep venous thrombosis	5 (0.1)	(0.2)	0 (0.0)	(0.0)
Peripheral vascular disorder	0 (0.0)	(0.0)	1 (0.1)	(0.1)

Note: Patient with multiple events may be counted more than once in different terms but only once in one term.
PYR=Patient-years at risk
[†] Crude incident (n/Nx100)
[‡] Events per 100 patient-years (PYR)

Figure 22

Kaplan-Meier Estimates of Cumulative Incidence (95% CI) of Investigator Reported Thrombotic Cardiovascular Serious Adverse Experiences
OA Phase IIb/III: Nonselective NSAIDs in
(Final Data 2001)



Patients at Risk						
Rofecoxib	3358	1245	849	534	448	261
Non-Naproxen NSAIDs	1565	541	368	237	184	105

4.3.2.2 Alzheimer's Disease CV Safety – Final Analysis (Jun-2003 Data)

An interim analysis of data from Protocols 078 and 091 had been performed based on Sep-2000 data in preparation for the 2001 Advisory Committee Meeting and was presented in Section 4.2.3. A subsequent interim analysis based on data through Mar-2001 was submitted to FDA in Jul-2001 as part of the updated safety data requested in the VIGOR Approvable action letter. These Mar-2001 data were the basis for the placebo-controlled data included in the final VIGOR label of Apr-2002. A final analysis of the Alzheimer's data was carried out at the completion of Protocol 078 in 2003. These data are presented below. The results of the final data from the Alzheimer's studies showed that the overall rate of Confirmed Thrombotic CV serious adverse experience was similar on rofecoxib compared with placebo.

Confirmed Thrombotic CV Serious Adverse Experiences

Table 24 reports the incidence of confirmed thrombotic CV serious adverse experiences and the relative risk for rofecoxib versus placebo in the Alzheimer's studies. Table 25 summarizes the confirmed thrombotic CV serious adverse experiences by class of terms and treatment. A non-constant relative risk of rofecoxib over placebo was observed over time (p=0.011), therefore the estimated relative risk of 1.01 should be interpreted as the average relative risk over time, indicating that the incidence of events was similar in both groups over the 4-year treatment period.

In examining the time-to-event curves (Figure 23), and consistent with the non-constant relative risk, there appeared to be a decreased risk for events in the rofecoxib group for the first 18 months of the trial followed by an increased risk in the rofecoxib group after 18 months. Given the overall relative risk of 1.01, one could interpret the non-constant hazard either as variability in the data or as indicating different risks over time for the different periods of the study.

The data were further examined with regard to types of events observed. The incidence of MI was generally similar in both groups; the incidence of sudden cardiac death was numerically greater on rofecoxib. However, the incidence of cerebrovascular stroke was numerical greater on placebo. In both Protocol 078 and 091 there were fewer Confirmed Thrombotic CV serious adverse experiences on rofecoxib compared with placebo in the <18 month treatment period. During this time period, in Protocol 091 there were 4 and 12 Confirmed Thrombotic CV serious adverse experiences and in Protocol 078 there were 12 and 20 events on rofecoxib and placebo, respectively. The data beyond 18 months period comes solely from Protocol 078. During this time period in Protocol 078, there were 26 and 16 events on rofecoxib and placebo, respectively. Analysis of data from 0 to 15 months (the period common to the 2 protocols) indicated that the treatment effect of rofecoxib over placebo was consistent across the 2 studies (p=0.502). As presented in Section 4.3.2.3, the pooled analysis did not reveal a pattern of changing relative risk over time in any of the data sets. Thus, given the overall relative risk of 1.01 in the Alzheimer's Disease studies, it was interpreted that the variability in relative risk over time represented chance variation about the mean and was not a clinically meaningful observation.

Figure 23 displays the Kaplan-Meier estimates from 0 to 36 months of the time to Confirmed Thrombotic CV serious adverse experiences by treatment groups. [105]

Table 24

Absolute Rate and Relative Risk (95% CI)
Thrombotic Cardiovascular Serious Adverse Experiences
Protocols 078 and 091 (Final Data Jun-2003)

Study	Treatment Group	N	Patients With Events	PYR[†]	Rate[‡]	Relative Risk (95% CI)
Protocols 091/078 Combined	Rofecoxib 25 mg	1069	42	1661	2.53	1.01 (0.67, 1.53)
	Placebo	1074	48	1917	2.50	

[†] Patient-years at risk.
[‡] Per 100 PYR.

Table 25

Summary of Patients with Thrombotic Cardiovascular Serious Adverse Experiences
by Class of Terms: Protocols 078 and 091 (Final Data Jun-2003)

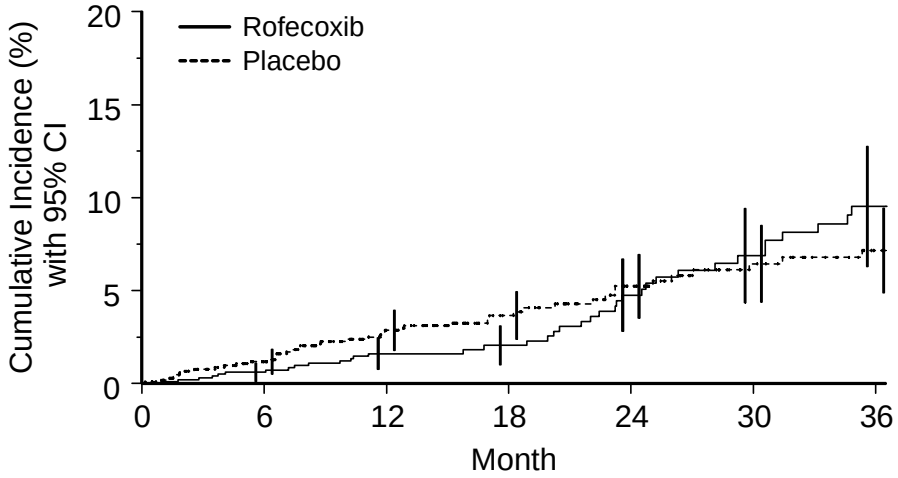
	Rofecoxib 25 mg (N=1069) (PYR=1661)		Placebo (N=1074) (PYR=1917)	
Endpoint Terms	n (%)[†]	Rate[‡]	n (%)[†]	Rate[‡]
Number of patients with ≥1 Confirmed Thrombotic Cardiovascular Event	42 (3.9)	2.5	48 (4.5)	2.50
Cardiac Events	29 (2.7)	1.7	25 (2.3)	1.3
Acute myocardial infarction	14 (1.3)	0.8	14 (1.3)	0.7
Fatal acute myocardial infarction	2 (0.2)	0.1	1 (0.1)	0.1
Sudden cardiac death	8 (0.7)	0.5	4 (0.4)	0.2
Unstable angina pectoris	7 (0.7)	0.4	9 (0.8)	0.5
Cerebrovascular Events	14 (1.3)	0.8	20 (1.9)	1.0
Fatal ischemic cerebrovascular stroke	1 (0.1)	0.1	0 (0.0)	0.0
Ischemic cerebrovascular stroke	6 (0.6)	0.4	17 (1.6)	0.9
Transient ischemic attack	7 (0.7)	0.4	3 (0.3)	0.2
Peripheral Vascular Events	0 (0.0)	0.0	5 (0.5)	0.3
Peripheral arterial thrombosis	0 (0.0)	0.0	1 (0.1)	0.1
Peripheral venous thrombosis	0 (0.0)	0.0	3 (0.3)	0.2
Pulmonary embolism	0 (0.0)	0.0	1 (0.1)	0.1

Note:Patients with multiple events may be counted more than once in different terms, but only once in each term.
PYR=Patient-years at risk
[†] Crude incidence (100 × n/N).
[‡] Events per 100 patient-years (PYR)[‡] Events per 100 patient-years (PYR)

Figure 23

Kaplan-Meier Estimates of Cumulative Incidence (95% CI) of

Thrombotic Cardiovascular Serious Adverse Experiences
Protocols 078 and 091 (Final Data Jun-2003)



Patients at Risk

Rofecoxib	1069	878	707	415	318	226	185
Placebo	1074	939	797	463	385	283	243

4.3.2.3 Updates to Pooled Analysis of CV Events Based on APTC Combined Endpoint – Final Update Based on Jun-2003 Data

As outlined above, the CV pooled analysis was updated as data became available and provided to regulatory agencies and were published. The 2003 final update to the CV pooled analysis included over 32000 patients, representing more than 19300 patient-years at risk.

4.3.2.3.1 Primary Findings

The final results of the APTC combined endpoint for the updated 2003 CV pooled analysis are in Figure 24. These results were generally consistent with the initial pooled analysis from Sep-2000 presented in Section 4.2.3. The data continued to demonstrate similarity between rofecoxib and placebo or non-naproxen NSAIDs and a significant difference for rofecoxib compared with naproxen. The relative risk of 1.61 for rofecoxib compared to naproxen would correspond to an approximately 38% reduction of events on naproxen compared with rofecoxib.

Since event rates had changed over time in the Alzheimer's studies, the pooled data were analyzed by duration intervals in order to examine if the relative risk changed according to duration of exposure to study drug. No consistent pattern was seen in this analysis which is displayed in Figure 25. The time points for this analysis were chosen because they divided the data into roughly equal-sized segments based on patient-years of exposure. The point estimates for the relative risks across the chosen time points approximate 1 for the placebo-controlled and non-naproxen-controlled data sets and no trend is observed in the naproxen controlled data set. Given these data, there was no clear evidence to support an increased risk in the >12 month time period.

Figure 24

Relative Risk (95% CIs)
APTC Combined Endpoint
Pooled Analysis (Final CV Update Based on Jun-2003 Data)

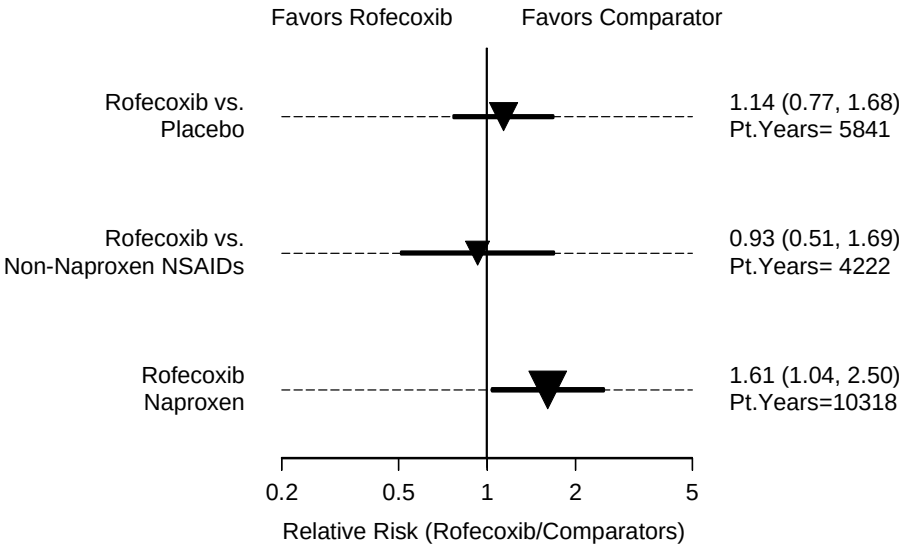
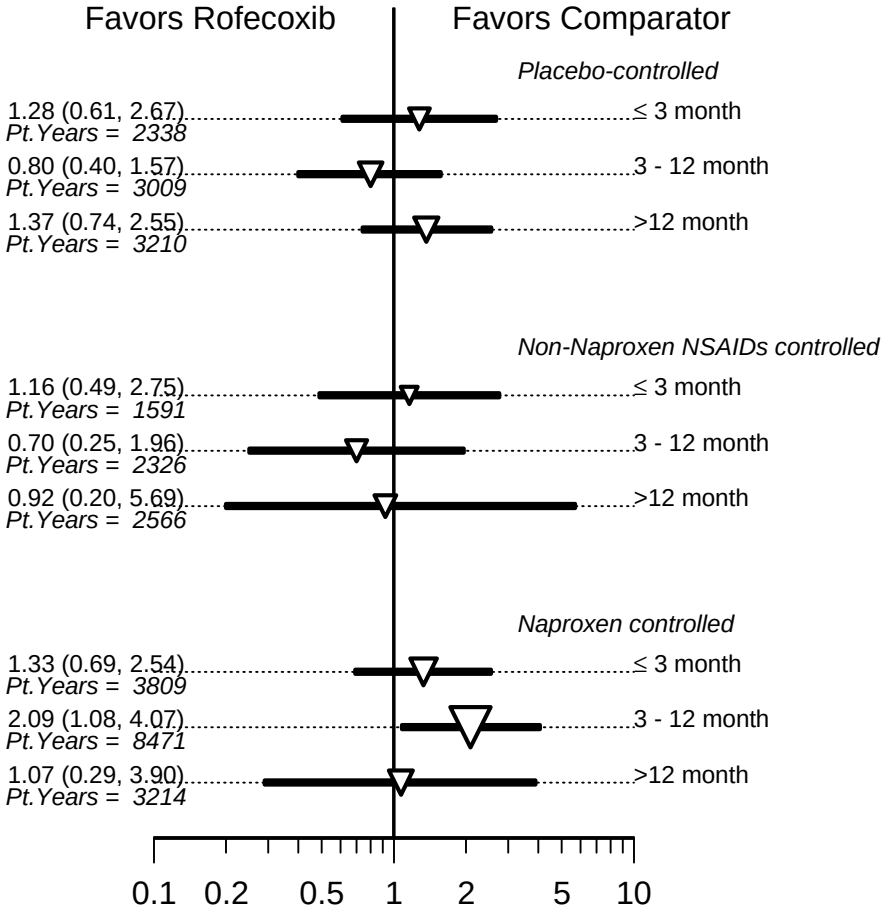


Figure 25

Relative Risk (95% CIs)
APTC Combined Endpoint
Subgroup Analysis by Duration
Pooled Analysis (Final CV Update Based on Jun-2003 Data)



4.3.2.3.2 Subgroup Analyses

In order to understand further any potential differences that might contribute to a different relative cardiovascular risk with rofecoxib, several subgroup analyses were carried out for each data set within the final pooled CV data. Given the difference observed in the relative risk for rofecoxib versus naproxen and the lack of difference when rofecoxib was compared with non-naproxen NSAIDs, an analysis of the APTC combined endpoint stratified by comparator was carried out. The effect of dose was also

examined. Subgroup analyses compared patients with an increased CV risk to patients without an increased CV risk based on baseline characteristics of known cardiovascular risk factors. A subgroup analysis was also carried out for aspirin user versus non aspirin users as it was likely that aspirin users were taking aspirin to mitigate a known cardiovascular risk.

4.3.2.3.2.1 Pooled Analysis of APTC Combined Endpoint Data by Rofecoxib Dose - Final Data Cutoff Jun-2003

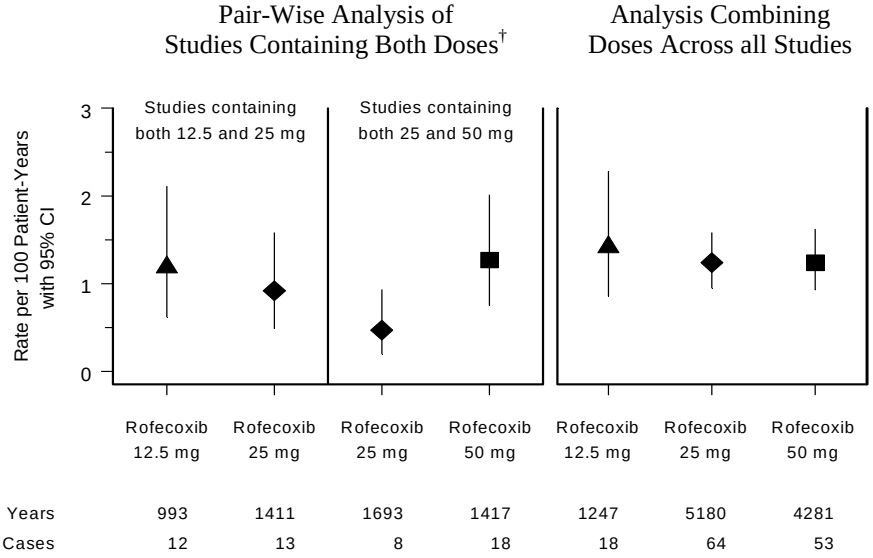
CV event rates by rofecoxib dose were determined for the chronic exposure populations by analyzing the individual doses across all studies combined using 2 different stratification approaches. This section updates the analyses initially presented in Section 4.2.5.1.

The rates per 100 patient-years (95% CI) for the primary pair-wise analysis for the APTC combined endpoint are displayed in the left 2 panels of Figure 26. The estimated rate for 25 mg is less than for 12.5 mg, and the confidence intervals are broadly overlapping for the 2 doses that were recommended for chronic use. However, the estimated rate for 50 mg was greater than for 25 mg. Review of the individual events demonstrated that the imbalance between rofecoxib 50 mg and rofecoxib 25 mg was due to an imbalance in the number of thrombotic strokes: 10 in patients taking rofecoxib 50 mg and 1 in patients taking 25 mg. Of note, 8 of the 10 events in the 50 mg group occurred in studies which were not adjudicated as they occurred in studies that had been completed prior to the implementation of the CV Adjudication SOP.

The right panel of Figure 26 displays the rates per 100 patient-years (95% CI) for rofecoxib combined across all studies (secondary analysis).

Figure 26

APTC Combined Endpoint
Stratified by Rofecoxib Dose
Rates Per 100-Patient Years (95% CIs)
Pooled Analysis (From Final CV Update Based on Jun-2003 Data)



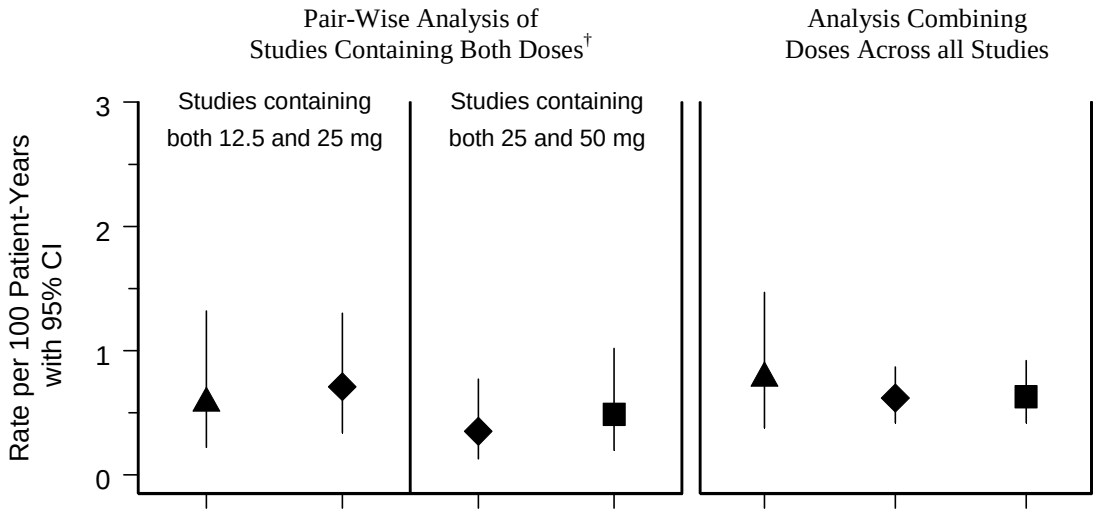
†Comparison of 12.5 mg and 25 mg doses used studies that administered those two doses and comparison of 25 mg and 50 mg doses used studies that administered those two doses.

Due to questions raised in the epidemiology literature specifically examining the effect of dose on myocardial infarction as well as the fact that the signal in VIGOR was an imbalance in MI with rofecoxib 50 mg, an additional analysis exploring the effect of dose for the MI endpoint was carried out. Figure 27 displays the pair-wise analysis and the analysis across all studies for myocardial infarction. The rates of myocardial infarction are similar across doses of rofecoxib including 12.5 mg and 25 mg and extending to 50 mg. This was observed for the most rigorous evaluation provided by the pair-wise analysis as well as the comprehensive analysis across all studies. Small differences were observed but CIs were broadly overlapping.

Thus there was no apparent dose-related effect of rofecoxib on the risk of sustaining a myocardial infarction.

Figure 27

Clinical Studies by Rofecoxib
Myocardial Infarction Stratified by Rofecoxib Dose
Rates per 100 Patient-Years (95% CI)
Pooled Analysis (From Final CV Update Based on Jun-2003 Data)



Pt. Years	993	1411	1693	1417	1247	5180	4281
No. Cases	6	10	6	7	10	32	27

4.3.2.3.2.2 Pooled Analysis of APTC Combined Endpoint by Baseline CV Risk - Final Data Cutoff Jun-2003

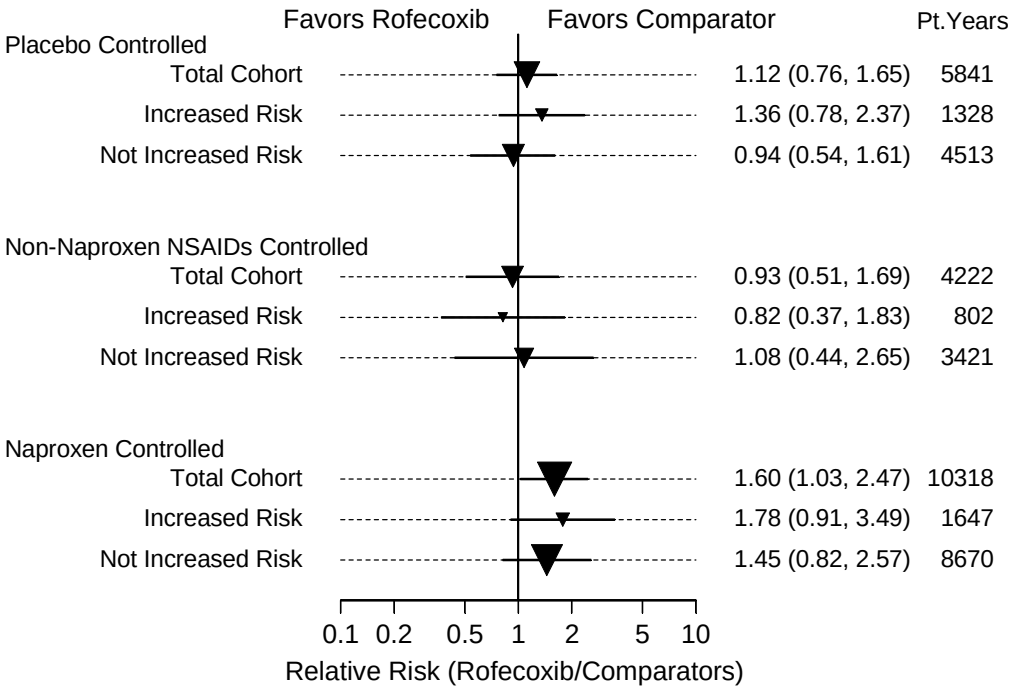
In order to further evaluate the cardiovascular safety of rofecoxib, subgroup analyses of patients defined as being at an increased cardiovascular risk were undertaken. Patients at increased risk in the pooled analysis were defined as having 2 or more risk factors (hypertension, hypercholesterolemia, diabetes, and smoking) or a history of symptomatic arthrosclerotic cardiovascular disease (ASCVD). Patients with 1 or no risk factors and without a prior history of ASCVD were considered to be not at an increased risk. Figure 28 displays the relative risk (95% CI) for the placebo controlled, non-naproxen controlled, and naproxen controlled data sets for patients at an increased risk and those not at an increased risk within each dataset. As expected, the overall rates are higher in the groups of patients at an increased risk, however, the relative risks are similar between the treatment groups and consistent with the overall analyses.

Additionally, treatment by subgroup interaction analyses found no significant interaction indicating that, within each comparison, there were no statistically significant imbalances in relative risk between the subgroups of patients at an increased risk versus those not at an increased risk.

Figure 28

Relative Risk (95% CIs) of Cardiovascular Events in

Subgroup Analysis by Baseline CV Risk
APTC Combined Endpoint
Pooled Analysis (From Final CV Update Based on Jun-2003 Data)



4.3.2.3.2.3 Pooled Analysis of APTC Combined Endpoint by Aspirin Use - Final Data cutoff Jun-2003

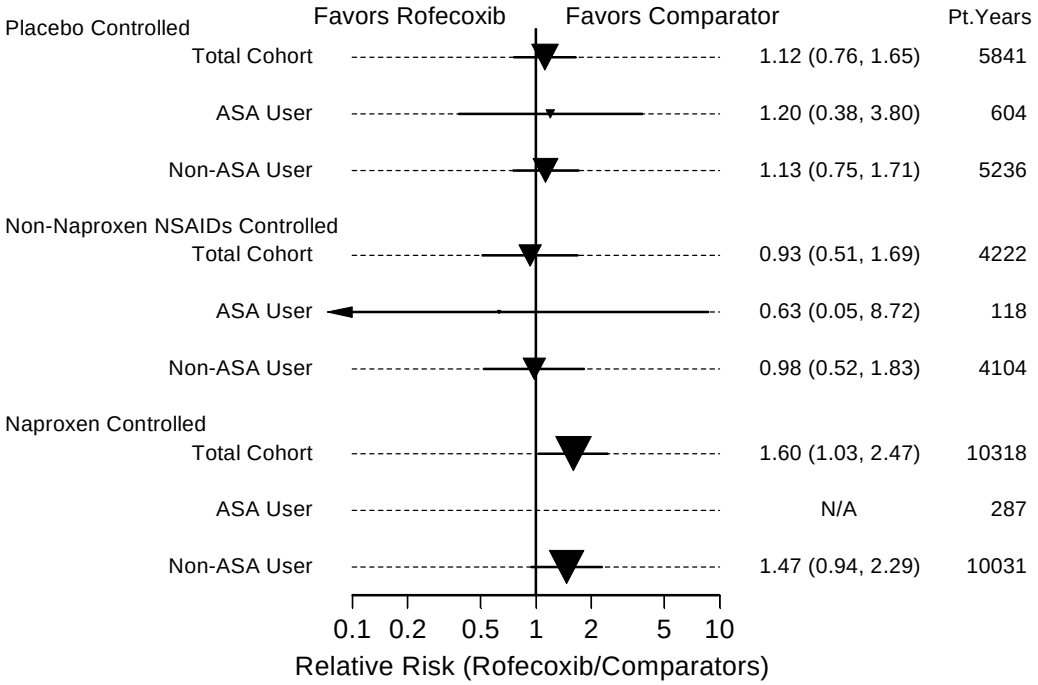
Subgroup analyses for aspirin/non-aspirin users for the 3 data sets (rofecoxib versus placebo, rofecoxib versus non-naproxen NSAIDs, and rofecoxib versus naproxen) are in Figure 29. Aspirin/non-aspirin users were defined as patients who took aspirin ≥50% of the time while on study therapy and for patients who had a cardiovascular event which contributed to the analysis only the time prior to the event was considered. Aspirin and

the antiplatelet therapies were considered together and the generic terms used were: aspirin, clopidogrel, clopidogrel bisulfate, ticlopidine, and ticlopidine hydrochloride. Only a small percentage of patients used these therapies (~4% to 7%); therefore, these subgroup analyses should be interpreted with caution as very few events occurred in aspirin users versus limiting the interpretability of results for this subgroup.

Event rates (per 100 patient-years), relative risks (95% CIs) for the APTC combined endpoint for aspirin/non-aspirin-users and the total cohort for the rofecoxib versus placebo, rofecoxib versus non-naproxen NSAIDs, and rofecoxib versus naproxen data sets are in Figure 29. There were no treatment-by-subgroup interactions and no apparent differences in the rates of the APTC combined endpoints for aspirin/non-aspirin users and the overall cohort in the 3 data sets.

Figure 29

Relative Risk (95% CIs)
Subgroup Clinical Studies
Analysis by Aspirin Use†
APTC Combined Endpoint
Pooled Analysis (From Final CV Update Based on Jun-2003 Data)



Note: ASA users were patients who took aspirin ≥50% of the time while on study therapy and for patients who had a cardiovascular event which contributed to the analysis only the time prior to the event was considered.

4.3.3 Mortality - Final Data Cutoff Jun-2003

The incidences of overall mortality and of cardiovascular mortality were generally similar across treatment groups in the rofecoxib program. Deaths were attributed to one of the treatment groups if the adverse experience leading to death began within 14 days of the patient's discontinuing study therapy. In some studies the mortality incidence was numerically lower with rofecoxib than the control group, while in others the rate with rofecoxib was numerically higher than in the control group. Figure 30 displays the rates per 100 patient years (95% CI) for the different populations.

In the OA studies, mortality incidences were significantly lower on rofecoxib than comparator NSAIDs (diclofenac, ibuprofen, and nabumetone); 5 deaths on rofecoxib and 8 deaths for the nonselective NSAID comparator. Of these deaths, 3 in the rofecoxib group and 4 in the nonselective NSAID group were thrombotic cardiovascular deaths; a rate of 0.13 versus 0.26 per 100 patient years for the rofecoxib and nonselective NSAID groups, respectively.

In the Alzheimer's Disease studies, Protocol 091 (12-month study followed by 3 month randomized withdrawal period) and Protocol 078 (4-year study), the total number of deaths was not inconsistent with that expected for an elderly population. However, the incidence was significantly higher on rofecoxib than placebo. Figure 30 displays the mortality rates (95% CIs) per 100 patient years. During the primary safety period of the studies (12 months for Protocol 091), a total of 55 deaths occurred in patients who were taking study treatment or from fatal adverse events that started within 14 days of the last dose (36 or 2.1 per 100 patient years for rofecoxib and 19 or 1.0 per 100 patient years for placebo). Patients died from a range of causes that were consistent with expectations for an elderly population, and there was no specific pattern as to the cause of death in either treatment group [43; 45]. Of these deaths, 11 in the rofecoxib group and 5 in the placebo group were due to confirmed thrombotic cardiovascular events. These final data were consistent with the interim data that had been included in the rofecoxib label in 2002: 8 deaths in the rofecoxib group and 3 in the placebo group due to confirmed thrombotic cardiovascular events. Based on these data, it was concluded that the difference between rofecoxib and placebo in overall mortality did not reflect any increases in particular types of events to suggest causality in the Alzheimer's studies. An additional 3 deaths occurred in the 3-month randomized withdrawal phase of Protocol 091 (all randomized to placebo for the initial treatment period and the withdrawal period).

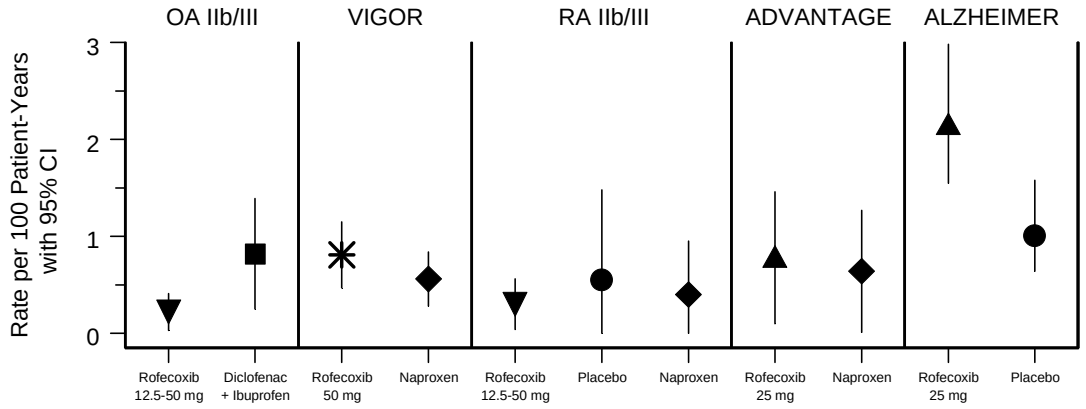
In addition to the analysis of on-drug mortality discussed in the paragraphs above, an ITT analysis of mortality was conducted for the Alzheimer's program. There were an additional 6 deaths in the off-drug period for Protocol 091 (4 assigned to rofecoxib and 2 assigned to placebo). None of these deaths were due to thrombotic cardiovascular events. Off-drug follow-up mortality data for Protocol 078 were available for less than half the patients (N=356 for rofecoxib, N=307 for placebo); the median duration of off-drug follow-up in these patients was 29 weeks in the rofecoxib group and 20 weeks in the placebo group. There were 22 deaths in the off-drug period for Protocol 078 (17 in

patients assigned to rofecoxib and 5 in patients assigned to placebo); 12 of these (11 in the rofecoxib group and 1 in the placebo group) occurred more than 48 weeks after treatment discontinuation. Eight of these 22 off-drug deaths in Protocol 078 were due to thrombotic cardiovascular events.

Other than the imbalances discussed above for the OA Phase IIb/III program and for the Alzheimer's program, in other large databases (VIGOR, RA Phase IIb/III, and APPROVe), differences in the rates of mortality were not seen for rofecoxib compared to naproxen or rofecoxib compared to placebo.

Figure 30

On-Drug Mortality
Rates Per 100 Patient Years (95% CI)
(Jun-2003 Data)



Patient Years	2390	1032	4047	4029	1665	183	512	640	630	1677	1891
No. Events	5	8	22	15	5	1	2	5	4	36	19

4.3.4 Summary—Cardiovascular Events in the Clinical Trials Program for Rofecoxib (Through Aug-2004)

There was a large amount of data on cardiovascular safety available through August 2004. Our assessments were based on the largest safety database ever developed for any NSAID or selective COX-2 inhibitor with the exception of aspirin: over 32,000 patients representing over 19,000 patient-years on rofecoxib or comparator agents. There were approximately 7300 patients on rofecoxib representing over 3000 patient years in the

placebo-controlled data set. In the non-naproxen NSAID data set there were over 5100 patients on rofecoxib representing over 2800 patient years. In the naproxen data set there were 9300 patients on rofecoxib with over 5900 patient years. Although there was a clear difference between rofecoxib and naproxen, the pooled analyses comparing both placebo and non-naproxen NSAIDs showed similar rates of cardiovascular events for rofecoxib and the comparison groups. Importantly, the majority of the placebo-controlled data was from the Alzheimer's disease program and included elderly patients at increased risk for cardiovascular disease.

Extensive subgroup analyses did not identify a patient population that might have a higher relative cardiovascular risk for rofecoxib compared to either placebo or nonselective NSAIDs. In addition, analyses by dose did not show an effect that could explain the VIGOR findings.

In addition, the preclinical, clinical pharmacology and clinical trials data were consistent with the potential for a potent and sustained antiplatelet effect of naproxen 500 mg twice daily. The magnitude of the decreased risk of cardiovascular events with naproxen 500 mg twice daily compared to rofecoxib, when the relative risk and 95% confidence intervals are taken into account, is not inconsistent with the reduction observed with antiplatelet therapy. As discussed above, subsequent studies suggest a difference between other selective COX-2 inhibitors and naproxen but not between COX-2 inhibitors and either non-naproxen NSAIDs or placebo [39].

Overall, the data available through Aug-2004 did not suggest that rofecoxib increased the cardiovascular risk relative to placebo or non-naproxen NSAIDs. The totality of the clinical trial data through Aug-2004 was most consistent with naproxen having provided a relative cardioprotective benefit and argued against a prothrombotic effect of rofecoxib.

4.3.5 Conclusions—Cardiovascular Events in the Clinical Trials Program for Rofecoxib (Through Aug-2004)

- Final data from the OA and Alzheimer's clinical programs were consistent with the interim 1998 OA and 2000 Alzheimer's Disease data and supported the interpretations of VIGOR from 2000.
- Final data from the pooled analysis of thrombotic cardiovascular events with rofecoxib were consistent with the year 2000 analysis and supported the earlier interpretation that the difference in thrombotic cardiovascular events between rofecoxib and naproxen 500 mg twice daily but not between rofecoxib and placebo or between rofecoxib and non-naproxen NSAIDs was most consistent with a cardioprotective effect of naproxen.
    - Analyses of cardiovascular events stratified by dose did not reveal findings that explained the imbalance of events noted in VIGOR.
    - Analyses of cardiovascular events stratified by time did not identify consistent differences in relative risk over time.
    - Subgroup analyses did not identify an increased relative risk in patients with particular demographic factors.

- The weight of the evidence continued to support that in VIGOR naproxen provided a cardioprotective benefit.

5. Data from Epidemiology Studies

Observational Studies of Cardiovascular Thrombotic Risk in Patients Prescribed Rofecoxib

Observational studies are helpful in evaluating associations and generating hypotheses. They are particularly advantageous in situations where there is limited clinical trial evidence of an uncommon or rare adverse event. However, they are more prone to bias than randomized clinical trials and for that reason are considered to be weaker than randomized experiments for establishing causality. It is generally held that to establish causality with observational data one must see consistent, strong associations in a number of studies in different settings. Further credibility is lent to observational data when the temporal relationship between exposure and disease is clearly established, when there is evidence of a dose-response, and when there is experimental evidence that is consistent with the observational data. However, even when such criteria are met, conclusions about cause and effect from observational data may still be contradicted by clinical trial evidence, as was seen for the risk of cardiovascular disease in the observational studies of hormone replacement therapy as compared to that defined by subsequent clinical trials [46; 47; 48].

A number of observational studies of cardiovascular thrombotic risk with the use of rofecoxib have been presented or published. Currently, seven have been published in peer-reviewed journals [49; 50; 51; 52; 53; 54; 55]. Two of them are open-label studies of rofecoxib in clinical practice with no comparator [51; 49] and one is a monitoring study [53]. The remainder are comparative studies. In two the authors conclude there is no difference in risk with rofecoxib compared with non-use of NSAIDs [52; 55]. One also indicates no difference in risk compared with other NSAIDs or COX-2 inhibitors [52]. The others [50; 54] are inconsistent with each other and with clinical trial evidence, In one [50], rofecoxib only at doses greater than 25 mg was significantly associated with an increased risk of serious coronary heart disease among patients who were “new users” compared with non-users of NSAIDs. In the other [54] rofecoxib (all doses combined) was associated with a significantly increased risk of acute MI compared to celecoxib (all doses combined). This increased risk however was demonstrated only during the first 90 days of use, after which the risk was similar. The authors also concluded a difference between rofecoxib and no NSAID use although this difference did not reach statistical significance (p=0.054). Therefore, the comparative observation studies do not provide clear conclusions about the cardiovascular safety profile of rofecoxib. This section briefly summarizes the observational literature on this topic.

5.1 Observational Studies Published in the Peer-Reviewed Literature to Date

5.1.1 Open-Label and Monitoring Studies

Zacher 2002

Zacher published a post -marketing surveillance study in Germany to assess the efficacy and tolerability of rofecoxib in the treatment of OA in 2002 [49]. A total of 80,371 patients being treated with rofecoxib for the first time or being switched to rofecoxib, from among 11,851 office-based physicians specializing in rheumatology, orthopedics, internal medicine, or general medicine participated in the study. Patients were treated with rofecoxib 12.5 mg or 25 mg once daily (the dose range approved in Germany for OA) at the discretion of prescribing physicians. Adverse events that occurred during the study were elicited by questioning patients at their second visit and recorded on forms provided for that purpose. The timing of the second (final) visit was at the discretion of the investigator; 28 days was recommended. Three deaths were recorded during the study (~1 per 2222 patient-years), of which 2 were considered unrelated to rofecoxib use. The third was attributed to a posterior myocardial infarction in a 75-year-old woman. A causal relationship with rofecoxib was not suspected, but could not be excluded. No further information about cardiovascular thrombotic adverse events was provided.

Bannwarth 2003

In 2003 Bannwarth presented a 24-week, open label study of 2896 patients in France with knee or hip OA that evaluated the CV safety profile of rofecoxib. Patients were treated with rofecoxib starting at a 12.5 mg once daily dose, and increased to 25 mg at Week 4 or Week 12 in case of insufficient efficacy [51]. The study population was 70.3% female and had a mean age of 66.8 years. There were a total of 6 thrombotic arterial events (1 MI and 5 strokes). The rate per 100 patient-years rate (95% CI) of MI and stroke with rofecoxib was 0.09 (0.0, 0.50) and 0.45 (0.16, 01.05). The authors concluded the results provided evidence for a lack of excess CV events in OA patients treated with rofecoxib 12.5 to 25 mg.

Layton 2003

In Jun-2003, the UK Drug Safety Research Unit performed a Prescription Event Monitoring Study of rofecoxib during the period Jul through Nov-1999 to compare the incidence rates of selected thromboembolic (cardiovascular, cerebrovascular and peripheral venous thrombotic) events reported for patients prescribed rofecoxib and meloxicam in general practice. [53] Patients were identified from dispensed prescriptions written by general practitioners (GPs) for meloxicam during the period Dec-1996 to Mar-1997, and rofecoxib during the period Jul to Nov-1999. Questionnaires (“green cards”) requesting details of events recorded during/after treatment, indication and potential risk factors (including age, sex and NSAIDs prescribed within 3 months of treatment) were posted to prescribing GPs approximately 9 months after the first prescription for each

patient. The manuscript does not report the response rate for the return of the green cards for patients prescribed rofecoxib, although a preliminary report received in advance of the publication indicated 40% were returned, of which 90% (N=15,268 patients) had useful clinical data and were therefore used in the study. Incidence rates of the first of each type of event were calculated; crude and age- and sex-adjusted RRs were obtained using regression modeling. During the 9 months after starting treatment, there were 21 (0.14%) and 19 (0.10%) reported cardiovascular events, 74 (0.48%) and 52 (0.27%) cerebrovascular events, and 6 (0.05%) and 20 (0.10%) peripheral venous thrombotic events for rofecoxib and meloxicam, respectively. Adjusting for the age and gender, the RR for cerebrovascular events was 1.68 (95% CI 1.15, 2.46), for peripheral venous thrombotic events 0.29 (0.11, 0.78)], and for the cardiovascular events was 1.38 (95% CI 0.71, 2.67), for rofecoxib vs. meloxicam respectively.

The authors concluded a relative increase in the rate of cerebrovascular events, a relative reduction in peripheral venous thrombotic events in users of rofecoxib compared with meloxicam, and no difference in the rate of cardiovascular thromboembolic events. They noted the incidence of these three types of events was low (less than 0.5%). In addition, the nature of the data collection process, the low rate of return of the green cards, and the comparison of data from two different calendar periods makes these results particularly difficult to interpret.

5.1.2 Comparative Observational Studies

Ray *et al.* 2002

In January 2002 **Ray et al.** published a retrospective cohort study, using the Tennessee Medicaid database, that assessed the occurrence of serious coronary heart disease (CHD: acute MI or cardiac death), in patients taking rofecoxib, celecoxib or other NSAIDs.[50] Among 251,046 NSAID users and 202,916 non-users there were 5,316 events. Use of rofecoxib at doses greater than 25 mg was significantly associated with an increased risk (RR 1.93; 95% CI 1·09–3·42) of serious CHD among patients who were “new users” compared with non-users of NSAIDs. This result was based on only 12 exposed cases. There was no evidence of increased risk among users of rofecoxib at doses of 25 mg or less, celecoxib, naproxen or ibuprofen.

Mamdani *et al.* 2003

In February 2003 **Mamdani et al.** published a population-based, retrospective cohort study among 66,964 elderly patients taking COX-2 inhibitors, naproxen and non-aspirin NSAIDs and 100,000 controls not using these drugs using administrative databases in Ontario, Canada.[52] A total of 701 events occurred during the study period. The rates of acute MI among the drugs studied were not different from each other nor were any of them different from controls not using NSAIDs.

Solomon *et al.* 2004

In 2004 **Solomon et al.** published a case-control study to assess the risk of acute MI among users of rofecoxib, celecoxib, and NSAIDs among 54,475 elderly recipients of NJ/PA Medicare who also received pharmaceutical benefits.[54] This study was first

presented at the American College of Rheumatology meeting in 2003 and was sponsored by Merck. The study included 10,895 cases and 4 controls per case. No significant difference in risk was found comparing rofecoxib to ibuprofen, naproxen, other NSAIDs, and to those not taking NSAIDs. Rofecoxib (all doses combined) was associated with a significantly increased risk (OR 1.24; 95% CI 1.05 to 1.46) of acute MI compared to celecoxib (all doses combined). Analyses comparing comparable doses of rofecoxib and celecoxib (i.e., >25mg compared with >400mg) were not performed. Of note, in the final logistic regression model, the use of HMG Co-A reductase inhibitors did not protect against MI (adjusted OR 1.0, 95% CI 0.94, 1.04), and use of hormone replacement therapy was protective for MI (adjusted OR 0.88, 95% CI 0.79, 0.98). These results contrast the findings from randomized clinical trials of HRT and statin treatment. The elevated risk with rofecoxib vs. celecoxib was also seen in dose-specific analyses (rofecoxib ≤25 mg and >25 mg vs. celecoxib ≤200 and >200, respectively). The risk was higher with rofecoxib during the first 90 days of use but not thereafter. The authors also concluded a difference between rofecoxib and no NSAID use although this difference did not reach statistical significance (p=0.054).

Kimmel *et al.* 2004

Kimmel et al. published an incident case-control study to determine the effect of COX-2 inhibitors on risk of nonfatal myocardial infarction (MI) in December 2004 [106; 55]. Seventeen hundred eighteen cases with a first, nonfatal MI admitted to one of 36 hospitals in a 5-county area near Philadelphia, PA, USA were identified. Controls were randomly selected from the same counties. All cases (n=1718) and controls (n=6800) were interviewed via telephone about medication use and risk factors for MI. Among cases, 27 (1.57%), 18 (1.05), and 319 (18.56%) were exposed to rofecoxib, celecoxib, and non-selective NSAIDs respectively. Among controls, 78 (1.15%), 87 (1.28%), and 2144 (31.53%) were exposed to rofecoxib, celecoxib, and non-selective NSAIDs respectively. There was no increased risk for CV events comparing rofecoxib to non-users of NSAIDS; the adjusted OR for rofecoxib users was 1.16 (95% CI 0.70, 1.93). Compared to non-users of NSAIDS the adjusted OR for celecoxib users was 0.43 (0.23, 0.79) and for nonselective NSAID users was 0.61 (0.52–0.71). Because celecoxib and NSAIDs had a lower risk than non-users of NSAIDs, comparisons with rofecoxib to the other drugs studies were all elevated. The authors concluded celecoxib and rofecoxib had different effects on the odds of MI. This study was partly funded by Merck and Pfizer.

5.2 Additional Comparative Observational Studies

Six comparative observational studies [107; 108; 109; 110; 111; 112] have been presented and published in abstract form only to date. The Kaiser Permanente Database study presented by Graham and Campen in 2004 are the same study, which also appears to be an extension of the study presented by Levy in 2002. Therefore there are only four unique studies among the six published abstracts [108; 112; 110; 111].

Of the four unique studies published in abstract form only, two concluded rofecoxib was not associated with an increased risk of MI when compared with other non-selective NSAIDs [110; 111]. The others indicated an increased risk with rofecoxib relative to some of the comparators considered.

The study by Whelton *et al.* was conducted among patients with hypertension and compared rofecoxib with non-use of NSAIDs, celecoxib and non-selective NSAIDs [108]. The authors concluded that rofecoxib significantly increased the risk of acute MI or stroke compared with non-users of NSAIDS (RR 2.45, 95% CI 1.71, 3.51) while there was no increased risk among users of celecoxib or non-selective NSAIDs. Of note is that the study included only 841 patients treated with rofecoxib, the number of events with rofecoxib is not reported, and the diagnostic codes used to identify the endpoints included diagnoses that were not specific to acute MI or stroke.

The Kaiser Permanente study initially found no elevation in risk with rofecoxib compared with naproxen or ibuprofen [107]. The more recent extension/update to this study was presented at 2 meetings in 2004: by Graham at the International Society for PharmacoEpidemiology (ISPE) annual meeting in August, and by Campen at the American College of Rheumatology (ACR) annual meeting in October. The abstract of this study submitted to ISPE did not contain results [109]. The abstract submitted to ACR contained data that was different from that which was ultimately presented at both the ISPE and ACR meetings [112]. The ACR abstract reported the estimated RR (95% CI) of acute cardiac events with current use of specific NSAIDS compared with remote NSAID use (exposure ended more than 60 days before the index date) as: celecoxib 0.77 (0.60-0.99), ibuprofen 1.13 (1.00-1.30), naproxen 1.11 (0.96-1.30), rofecoxib ≤25mg/d 1.02 (0.71-1.46), rofecoxib > 25mg/d 5.04 (0.94-27.06). The results for rofecoxib >25 mg was based on 5 exposed cases and 7 exposed controls [112]. The data presented at the meetings included different, and statistically significant results, for rofecoxib>25mg (OR 3.15, 95% CI 1.14, 8.75) based on 10 exposed cases and 8 exposed controls. Other results of this study were that rofecoxib ≤25 mg had an increased risk compared with celecoxib, and several other NSAIDs increased the risk of AMI and sudden cardiac death compared with remote use of NSAIDs.

An additional retrospective cohort study, sponsored by Merck, has been conducted among patients ages 40-64 who used NSAIDS by prescription from 1999-2001 [113]. Final results of this study became available in September 2004, were submitted for publication on October 21, 2004, and are currently under review. The study assessed rates of MI or unstable angina pectoris (UAP) in relation to use of rofecoxib, celecoxib, diclofenac, and ibuprofen. Compared with the combined referent group of ibuprofen or diclofenac, the relative risk of MI or UAP with rofecoxib use was 1.35 (95% CI 1.09-1.68) and that for celecoxib was 1.03 (0.83, 1.27). The risk did not vary significantly by duration of use or dose.

In November 2004 Aetna Inc, released a report of a case-control study done using their administrative health care databases to examine whether COX-2 inhibitors are associated with new acute MI [114]. Cases were all plan members with an admission or urgent/emergent emergency department visit for acute MI (ICD-9 code 410) during the period Jan-2002 through May-2004. Controls were randomly selected age-and gender-matched members without such an event during the study period. Use of rofecoxib,

celecoxib, valdecoxib, naproxen and "other NSAIDs" was determined for the time windows 1 to 14 and 1 to 90 days prior to the index date. For exposure in the 1 to 14 day window, the adjusted OR (95% CI) for rofecoxib was 1.5 (1.1, 1.7) compared with no NSAIDs, and 1.3 (0.9, 1.7) compared with "other NSAIDS." For celecoxib, the adjusted OR (95% CI) was 1.4 (1.1, 1.7) compared with no NSAIDs, and 1.2 (0.9, 1.6) compared with other NSAIDs. For valdecoxib, the adjusted OR (95% CI) was 0.8 (0.5, 1.2) compared with no NSAIDs and 0.7 (0.4, 1.1) compared with other NSAIDs. Similar results were seen in sensitivity analyses and in the analyses that used the 1 to 90 day exposure window. The authors concluded that rofecoxib and celecoxib were associated with a significantly higher risk of MI than non-use of NSAIDs. This study has not been publicly presented in a scientific forum.

5.3 Summary of Epidemiological Reports

All of the above studies suffer to some extent from limitations of observational studies using health care databases. These include, but are not limited to, possible bias resulting from:

- Failure to measure or completely control for differences in characteristics of the groups being compared. It is known that COX-2 inhibitors are preferentially prescribed over non-selective NSAIDs to older patients and to those with higher baseline risk of MI (i.e., "channeling") [115; 116; 117; 118; 119]. While the studies described have attempted to control for differential prescribing of COX-2 inhibitors and NSAIDs, limited information is available from claims databases to allow for complete control of such differences;
- Lack of information regarding important potential confounders, such as use of over-the-counter medications (e.g. aspirin or other NSAIDs), cigarette smoking, alcohol consumption, physical activity, and diet, is not available in most of these observational studies;
- Misclassification of exposure, particularly that due to unknown compliance with prescribed therapy;
- Misclassification of outcomes resulting from the lack of endpoint verification through clinical chart review.

In addition, it is generally accepted that small relative risks (i.e. <2.0) in observational studies may easily arise due to confounding or bias, as discussed by Temple [58].

Thus, prior to the results of the APPROVe study, only five observational studies comparing the risk of coronary events with rofecoxib vs. no treatment, or treatment with selective or non-selective NSAIDs had been published in peer-reviewed journals. One study showed no elevation in risk for rofecoxib compared with no NSAID use or with other selective or non-selective NSAIDs [52]. The other four [50; 53; 54; 55] were inconsistent with each other with respect to the effect of rofecoxib on CV risk, both in terms of risk vs. different comparators and in terms of risk of different endpoints. The

greatest elevation in risk was based on a very small number of exposed cases at higher doses of rofecoxib. The elevations in risk were in the range that could be explained by bias or residual confounding [58]. Furthermore, those studies which showed an increased risk with rofecoxib were not consistent with the data from the APPROVe trial, which showed an elevated risk with rofecoxib 25 mg vs. placebo that was apparent after, but not before, 18 months of therapy.

Given the inherent limitations of observational and cohort studies, and the superiority of clinical trial data for decision making, we placed greater weight on the consistent findings in our large clinical trials data base than on the inconsistent observations that arose from these epidemiologic analyses.

6. Cardiovascular Safety Results From APPROVe (September 2004)

APPROVe Study Design

Colorectal carcinomas and precursor adenomas are associated with increased cyclooxygenase (COX)-2 expression [120]. Epidemiologic studies suggest that regular use of nonselective COX inhibitors is associated with a reduced risk of colorectal neoplasia [121]. Randomized controlled clinical studies have shown that treatment with non-selective and COX 2-selective NSAIDs can cause regression of colorectal adenomas [122; 123; 124; 125].

APPROVe (Adenomatous Polyp PREvention On Vioxx) was a multicenter (~107 centers in 30 countries), randomized, placebo-controlled double-blind clinical trial to determine whether 156 weeks (3 years) of treatment with rofecoxib would reduce future adenoma occurrence in patients with a history of colorectal adenomas. Because of the ongoing questions about cardiovascular risk a key cardiovascular safety endpoint was prespecified.

Patients (≥40 years) with a recent history of 1 or more histologically confirmed adenomas were randomized to receive placebo or 25 mg rofecoxib. Randomization was stratified according to chronic use of low-dose aspirin (allowed in up to 20% of subjects to avoid potentially confounding effects of aspirin on polyp recurrence). Only patients not anticipated to need chronic NSAID therapy (including analgesic doses of aspirin) during the trial were entered.

Patients were excluded if they had uncontrolled hypertension (diastolic >95 mm Hg or systolic >165 mm Hg), angina or congestive heart failure symptoms at rest or with minimal activity. Patients with a history of myocardial infarction, coronary angioplasty or coronary arterial bypass grafting were included unless the event occurred within a year prior to enrollment. Patients with a history of stroke or transient ischemic attack were included unless it had occurred within 2 years prior to enrollment.

The primary endpoint was the cumulative incidence of patients who have a recurrence of adenoma(s) in the subgroup of patients with an “increased-risk” qualifying exam (baseline adenoma ≥ 1 cm, villous component, ≥ 2 adenomas, age <55, family history of

colorectal cancer). Cumulative recurrence risk with any baseline adenoma was a secondary endpoint. All adenoma assessments were conducted by a central study pathologist. Data were analyzed by the Cochran-Mantel-Haenzel test, and the time-stratified relative risk was the primary measure of treatment effect.

The primary cardiovascular safety endpoint was the incidence of confirmed thrombotic cardiovascular serious adverse experiences; confirmed thrombotic cardiovascular serious adverse experiences were adjudicated in accordance with the Merck SOP for the Surveillance, Monitoring, and Adjudication of Acute Thrombotic and Embolic Vascular Events and Deaths in Clinical Trials of COX-2 Specific Inhibitors. APPROVe was one of 3 placebo-controlled studies that contributed to the Cardiovascular Outcomes protocol for rofecoxib. Data on confirmed thrombotic cardiovascular serious adverse experiences in APPROVe were to be combined with data from the other 2 studies based on a prespecified analysis plan. Given the decision by the ESMB to stop the study based on the APPROVe data, they are being analyzed separately.

After a 6-week placebo run-in period, 2586 patients were randomized to either rofecoxib 25 mg or placebo in a 1:1 ratio (stratified by low-dose aspirin use). In all patients, colonoscopies were performed at Week 52 (Year 1) and Week 156 (Year 3) or at the time of study therapy discontinuation. The first patient was enrolled in Feb-2000 and the last patient enrolled was Nov-2001. The last patient was scheduled to complete the treatment phase of the study and have a year 3 colonoscopy at the end of Nov-2004. Patients who completed the year 3 colonoscopy, with removal of all identified polyps, were eligible to participate in an off-drug 1 year study extension.

Approximately 1550 patients had enrolled in the extension as of 09-Dec-2004, and these patients were planned to have a year 4 colonoscopy at the end of the 1 year extension to evaluate the potential for accelerated adenomatous polyp recurrence; during the extension, blinding to the base study treatment assignments was to be maintained.

Monitoring of Safety in APPROVe

Safety parameters were monitored on a regular basis by an External Safety Monitoring Board (ESMB) with regular meetings and review of unblinded data approximately every half year. During the course of the study, the ESMB communicated twice that investigators should be reminded of the need to monitor blood pressure and ultimately recommended to discontinue patients from the study if blood pressure was not controlled (diastolic >95 mm Hg or systolic >165 mm Hg).

The final ESMB meeting was on 17-Sep-2004, and the committee recommended that participating patients be instructed to discontinue study treatment. The ESMB has indicated that they believed that early termination at this time would not adversely impact the planned efficacy analysis using the Year 3 colonoscopy results which would be important for a full assessment of risk/benefit in this population.

In accordance with the protocol, this recommendation was first discussed with the executive committee of the APPROVe administrative committee and then with the entire administrative committee. The administrative committee agreed with the

recommendation to discontinue the study and this was communicated to Merck on the evening of Thursday 23-Sep-2004. Patients were notified to stop study drug on 30-Sep-2004. It was also announced on that day that Merck had decided to voluntarily withdraw the drug from the market.

The cardiovascular safety data in this background document represents the preliminary dataset which was the basis for the report provided to the ESMB for their meeting on 17-Sep-2004. The data that will be presented at the Advisory Committee Meeting in Feb-2005 will be based on the final data which will be available in late Jan-2005.

Baseline Characteristics

The baseline characteristics of the patients were similar in both treatment groups (Table 26). The risk factors for colorectal adenomas (Table 27) and cardiovascular (Table 26) disease were similarly distributed.

A patient was defined as being at increased cardiovascular risk if they had a past history of symptomatic atherosclerotic cardiovascular disease or 2 or more of the following: history of diabetes, history of hypercholesterolemia, history of hypertension and cigarette use. An aspirin user was defined as patient who took any dose of aspirin, clopidogrel, clopidogrel bisulfate, ticlopidine, and ticlopidine hydrochloride for at least 50% of the time while on study therapy, and did not start any of these medications after a confirmed thrombotic cardiovascular serious adverse event.

Table 26

Baseline Patient Demographics and Baseline Cardiovascular Risks in APPROVe

Demographic	Rofecoxib (N=1287)		Placebo (N=1299)	
	n	(%)	n	(%)
Age				
Percent ≥65 Years Old	385	(29.9)	385	(29.6)
Gender				
Male	804	(62.5)	805	(62.0)
Cardiovascular Risk Factors				
Hypertension	463	(36.0)	445	(34.3)
Diabetes Mellitus	115	(8.9)	111	(8.5)
Hypercholesterolemia	373	(29.0)	338	(26.0)
Current Smoker	279	(21.7)	285	(21.9)
Increased Cardiovascular Risk[†]	379	(29.4)	341	(26.2)
Aspirin Use				
Low Dose Aspirin User At Baseline	213	(16.6)	204	(15.7)
Concomitant Aspirin User[§]	247	(19.2)	239	(18.4)

[†] 2 or more risk factors for coronary artery disease or past medical history of either cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable or stable angina, coronary artery bypass graft surgery, or percutaneous coronary intervention).

[§] Use of any dose of aspirin, clopidogrel, clopidogrel bisulfate, and ticlopidine ≥50% of time on study therapy

Table 27

Baseline Patient Colorectal Cancer Risk Characteristics in APPROVe

	Rofecoxib 25 mg (N=1287)		Placebo (N=1299)	
	n	%	N	%
Number of Adenomas				
≥2 Adenomas	488	(37.9)	434	(33.4)
Maximum Size of Adenomas				
≥1 cm	436	(33.9)	430	(33.1)
First Degree Family History of Colorectal Cancer or Polyps				
Yes	439	(34.1)	420	(32.3)
Adenoma With Tubulovillous or Villous Characteristics				
Yes	151	(11.7)	176	(13.6)
Age at first-identified Colorectal Adenomas				
<55 years	436	(33.9)	444	(34.2)
Increased-risk Patients *				
Yes	1019	(79.2)	1002	(77.1)
Advanced Adenomas				
Yes	371	(28.8)	374	(28.8)
* Patients with an "increased-risk" qualifying exam (baseline adenoma ≥ 1 cm, villous component, >2 adenomas, age <55, family history of colorectal cancer				

6.1 Primary Analyses

Based on the preliminary analysis of November 2004, the cumulative adenoma recurrence rates were significantly lower with rofecoxib vs. placebo for both primary and secondary endpoints. For the increased-risk patient population, among the 923 patients in the rofecoxib group who had colonoscopies during the 3-year treatment period, 350 had the recurrence of colorectal adenomas; among the 953 patients in the placebo group who had colonoscopies during the 3-year treatment period, 489 had the recurrence of colorectal adenomas. The cumulative Year 0 to 3 recurrence rates for colorectal adenomas was 40.9% for rofecoxib and was 54.8% for placebo. The relative risk for rofecoxib versus placebo was 0.75 with a 95% confidence interval of (0.67, 0.83) which was significantly less than 1 ($p<0.001$). This preliminary result supported the primary hypothesis for the trial. A similar reduction in the Year 0 to 3 recurrence rates was seen in the all-patient population where the relative risk for rofecoxib versus placebo was 0.75 with a 95% confidence interval of (0.68, 0.82).

Overall Safety Results

Table 28 provides data on prespecified general adverse experiences observed in APPROVe. Prespecified safety analyses were done for selected adverse experiences of particular interest, including edema-related, hypertension-related, congestive heart failure-related, hepatic-related, digestive and renal-related adverse experiences (Table 29) as well as clinical upper GI events (see section 2.5 Data from Placebo-Controlled Studies) and confirmed thrombotic cardiovascular serious adverse experiences (Table 30)

There was an increased incidence of hypertension, congestive heart failure and edema associated with rofecoxib treatment compared to placebo, consistent with the previously documented adverse event profile of both non-selective NSAIDs and selective COX-2 inhibitors. Discontinuations were more frequent in the rofecoxib patient group; the three most common causes of discontinuation were hypertension, increased blood pressure and peripheral edema (not shown).

Table 28

Prespecified General Adverse Experiences in APPROVe

	Rofecoxib 25 mg (N=1287)		Placebo (N=1299)	
Number (%) of Patients	n	(%)	n	(%)
With one or more AEs	1223	(95)	1234	(95.0)
With drug-related[†] clinical AEs	453	(35.2)	364	(28.0)
With serious clinical AEs	330	(25.6)	273	(21.0)
Who died	5	(0.4)	5	(0.4)
Discontinued due to a clinical AE	181	(14.1)	129	(9.9)
Discontinued due to a laboratory AE	12	(0.9)	6	(0.5)
Discontinued due to a serious AE	69	(5.4)	53	(4.1)

[†] Assessed by the investigator to be possibly, probably, or definitely drug-related.

Table 29

Prespecified Adverse Experiences of Particular Interest in APPROVe

	Rofecoxib 25 mg (N=1287)		Placebo (N=1299)	
Number (%) of Patients:	N	(%)	N	(%)
With edema-related AEs	104	(8.1)	78	(6.0)
With hypertension-related AEs	357	(27.7)	207	(15.9)
With congestive heart failure AEs	16	(1.2)	4	(0.3)
With hepatic-related lab AEs	47	(3.7)	48	(3.7)
Discontinued due to a digestive AE including abdominal pain	40	(3.1)	28	(2.2)
Discontinued due to an edema-related AE	12	(0.9)	5	(0.4)
Discontinued due to a hypertension-related AE	32	(2.5)	6	(0.5)
Discontinued due to a renal-related AE	1	(0.1)	0	(0)
Discontinued due to a hepatic-related AE	2	(0.2)	0	(0)

Mortality

All deaths were adjudicated to determine whether cardiovascular in etiology.

In the preliminary dataset provided to the ESMB on 17th September 2004, the following mortality information was available:

- A total of 10 patients died within 14 days of discontinuing blinded therapy: 5 patients in each treatment group. Eight deaths were thrombotic cardiovascular events with 4 in each treatment group.
- A total of 15 patients died more than 14 days after discontinuing blinded therapy but within 3 years of randomization (that is, the prespecified study period). Eight deaths were in patients treated with rofecoxib (3 thrombotic) and 7 deaths were in patients treated with placebo (1 thrombotic).

Cardiovascular Safety Results

A total of 118 patients (74 in the rofecoxib 25-mg group and 44 in the placebo group) had one or more investigator-reported cardiovascular serious adverse experiences.

Primary Analysis of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences

Seventy patients had one or more events that were determined to be confirmed thrombotic cardiovascular serious adverse experiences by an independent blinded Adjudication Committee. The risk of patients having 1 or more confirmed thrombotic cardiovascular serious adverse experiences was 1.48 per 100 patients-years for the rofecoxib 25-mg group and 0.75 per 100 patients-years for the placebo group. Treatment

with rofecoxib was associated with an overall relative risk of 1.96 compared to placebo for the development of a confirmed thrombotic cardiovascular serious adverse experience (Table 30), due primarily to a higher incidence of acute myocardial infarction and ischemic cardiovascular stroke, as illustrated in Table 31.

Table 30

Absolute Rate and Relative Risk (95% CI)
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
in APPROVe

Event Category	Treatment Group	N	Patients With Events	PYR†	Rates‡	Relative Risk	
						Estimate	95% CI
Confirmed thrombotic Events	Rofecoxib	1287	45	3041	1.48	1.96	(1.20, 3.19)
	Placebo	1299	25	3315	0.75		

† Patient-years at risk.
‡ Per 100 patient-years at risk (PYR).

Table 31

Summary of Patients With Confirmed Thrombotic Cardiovascular Adverse Experiences by Class of Terms Summary of Confirmed in APPROVe

	Rofecoxib 25 mg (N=1287) (PYR=3041)		Placebo (N=1299) (PYR=3315)	
	N (%)†	Rate‡	n (%)†	Rate‡
Patients with One or More **with Confirmed Thrombotic Cardiovascular Serious Adverse Events**	45 (3.5)	(1.5)	25 (1.9)	(0.8)
Cardiac Events	30 (2.3)	(1.0)	11 (0.8)	(0.3)
Acute myocardial infarction	20 (1.6)	(0.7)	8 (0.6)	(0.2)
Fatal acute myocardial infarction	1 (0.1)	(0.0)	3 (0.2)	(0.1)
Sudden cardiac death	3 (0.2)	(0.1)	1 (0.1)	(0.0)
Unstable angina pectoris	7 (0.5)	(0.2)	4 (0.3)	(0.1)
Cerebrovascular Events	15 (1.2)	(0.5)	7 (0.5)	(0.2)
Fatal ischemic cerebrovascular stroke	0 (0.0)	(0.0)	0 (0.0)	(0.0)
Ischemic cerebrovascular stroke	11 (0.9)	(0.4)	6 (0.5)	(0.2)
Transient ischemic attack	5 (0.4)	(0.2)	2 (0.2)	(0.1)
Peripheral Vascular Events	3 (0.2)	(0.1)	7 (0.5)	(0.2)
Peripheral arterial thrombosis	1 (0.1)	(0.0)	1 (0.1)	(0.0)
Peripheral venous thrombosis	2 (0.2)	(0.1)	4 (0.3)	(0.1)
Pulmonary embolism	0 (0.0)	(0.0)	2 (0.2)	(0.1)

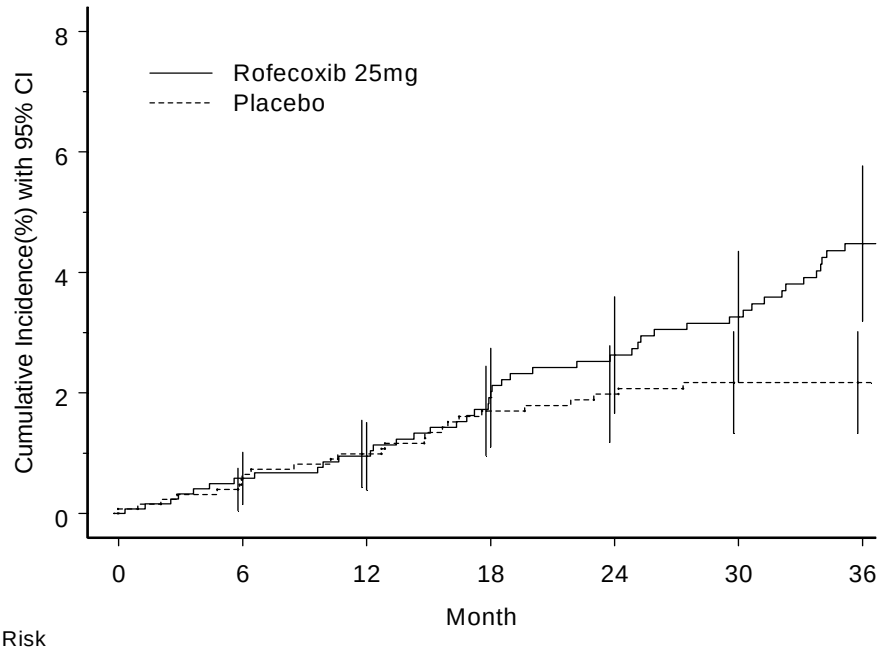
† Crude incident (n/Nx100).
‡ Events per 100 patient-years (PYR).
Note: Patients may be counted in more than one row but are only counted once within a row

A Kaplan-Meier analysis (Figure 31) of the cumulative incidence of confirmed thrombotic cardiovascular serious adverse events over time shows that the separation of the trend lines for rofecoxib and placebo did not begin until after 18 months of continuous daily treatment. Prior to 18 months there was no apparent difference in the cumulative incidence of these events in the two groups as evidenced by the overlapping lines. The changing pattern of treatment effect over time was confirmed by the failed test for proportionality of hazards (p=0.006). The difference between rofecoxib and placebo beginning after 18 months appears to primarily reflect a relative flattening of the placebo curve after 18 months compared with the preceding 18 months (Figure 31). Baseline characteristics of those patients with events beginning after 18 months were comparable between the treatment groups (data not shown).

Results for analysis of the APTC combined endpoint over time were similar.

Figure 31

Kaplan-Meier Estimates of Cumulative Incidence of Confirmed Thrombotic Cardiovascular Adverse Experiences Plot for Confirmed Thrombotic in APPROVe



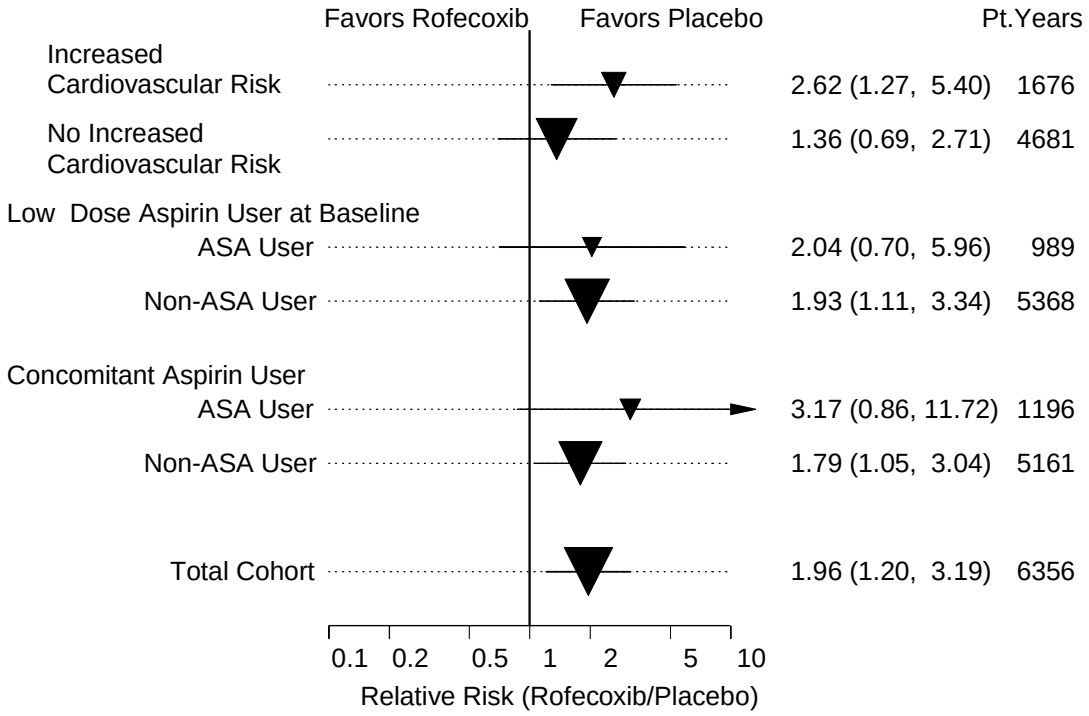
Patients at Risk							
Rofecoxib 25mg	1287	1123	1050	986	935	898	411
Placebo	1299	1192	1148	1079	1039	1002	470

6.2 Subgroup Analyses

Subgroup analyses were performed to assess whether any clinical risk factors could be identified as potential explanations for the imbalance in cardiovascular events observed. The following subgroup analyses were done: age ≥65, past history of cardiovascular event, increased cardiovascular risk (as defined previously), low dose aspirin use at baseline, concomitant aspirin use, presence of the history of diabetes, and history of hypertension. Although there were no statistically significant treatment by subgroup interactions for any of the subgroups, indicating no significant departure from consistency of treatment effects across subgroups, numeric trends in the data suggested the possibility of a higher relative risk in patients who at baseline were defined as being at increased risk for cardiovascular disease. The data for subgroups defined by increased cardiovascular risk, low dose aspirin use at baseline, and concomitant aspirin use are shown in Figure 32.

Figure 32

Relative Risk (95% CIs)
Subgroup Analysis by CV Risk and Aspirin Use: Confirmed
Cardiovascular Serious Adverse Experiences
(Events Within 14 Days After Discontinuation of Study Therapy) in APPROVe



Increased Risk = Increased Cardiovascular Risk, defined as 2 or more risk factors for coronary artery disease or past medical history of either cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable or stable angina, coronary artery bypass graft surgery, or percutaneous coronary interventions

Concomitant Aspirin User = Patient using any dose of aspirin, clopidogrel, clopidogrel bisulfate, or ticlopidine ≥ 50% of time on study therapy

Note: No significant subgroup interactions in the subgroups defined by low dose aspirin use, concomitant aspirin use, or baseline cardiovascular risk

6.2.1 Analysis of Blood Pressure Changes and Risk of Having Serious Cardiovascular Thrombotic Adverse Experiences

Mean blood pressure increases of 3.3 mm Hg (systolic) and 0.9 mm Hg (diastolic) were observed in the rofecoxib group relative to baseline and mean blood pressure decreases of 0.4 mm Hg (systolic) and 0.8 mm Hg (diastolic) were observed in the placebo group relative to baseline. There are no data to reference for evaluation of the consequences of sustained (>12 months) pharmacologically induced blood pressure increases such as associated with non-selective NSAID and selective COX-2 inhibitor therapy.

In order to investigate the potential relationship between blood pressure changes and serious cardiovascular thrombotic adverse events further, patients were categorized according to their change from baseline in mean arterial blood pressure at 4 weeks. Since changes in blood pressure in the rofecoxib group appeared to have stabilized by that time, and as there had only been 2 CV events during the first 4 weeks of the study (1 in each treatment group), this analysis provided an assessment of whether the magnitude of the change in blood pressure could have been predictive of relative risk for a CV event. The rofecoxib:placebo relative risks for a confirmed thrombotic serious cardiovascular adverse event were similar across quartile categories of blood pressure change (Table 32). Similar results were obtained in an analysis based on change in mean arterial pressure at Week 17.

Table 32

Absolute Rates and Relative Risk (95% CI)
Confirmed Thrombotic Cardiovascular Serious AEs
by Subgroup of Changes in MAP at Week 4 in APPROVe

Change From Baseline BP	Rofecoxib (N=1266) Events/Patient-Years (Rate x100), N	Placebo (N=1279) Events/Patient-Years (Rate x100), N	Relative Risk(95% CI)
Overall	45/3038 (1.48), 1266	25/3296 (0.76), 1279	1.95 (1.20, 3.18)
<-4.6	8/615 (1.30), 256	6/1031 (0.58), 400	2.23 (0.77, 6.42)
-4.6 to 0	13/802 (1.62), 334	7/878 (0.80), 343	2.02 (0.81, 5.06)
0 to 5.8	7/760 (0.92), 321	7/711 (0.99), 275	0.93 (0.33, 2.65)
>5.8	17/861 (1.98), 355	5/676 (0.74), 261	2.67 (0.99, 7.23)

An analysis was also performed in which mean arterial blood pressure at all time points during the study was included as a time-varying co-variate in the model of treatment effects (Table 33). In this analysis, data on patients with events are only included up until the time of the event. Mean arterial blood pressure did not have a significant effect on confirmed thrombotic cardiovascular serious adverse events in this analysis (p=0.748), and its inclusion as a covariate did not materially modify the treatment difference (rofecoxib:placebo relative risk [95% CI] = 2.01 [1.22, 3.31]). There was no significant treatment by covariate interaction.

Table 33

Relative Risks (95% CIs)
Effect of Change From Baseline in MAP at Visit Prior to Cardiovascular Event
on Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in APPROVe

Effect	RR (95% CI)	p-Value
With Confirmed Thrombotic Cardiovascular Serious Adverse Event		
TREATMENT	2.01 (1.22, 3.31)	0.006
Time-varying COVARIATE*	1.00 (0.97, 1.02)	0.748
STRATUM§	1.39 (0.77, 2.51)	0.272
* The value of MAP at the visit before the event time was used as the covariate.		
§ Aspirin user/ Non-aspirin user (at baseline)		

Additional exploratory analyses of association of confirmed thrombotic cardiovascular serious adverse experiences with categories of baseline, on treatment, and change from baseline in systolic and diastolic BP were carried out, and revealed no important or consistent findings (data not shown).

Risk of Patients Having Thrombotic CV Serious Adverse Experiences Analyzed by Absolute BP at Baseline or During Therapy

The effect of baseline blood pressure on the rates of patients having confirmed thrombotic cardiovascular serious adverse experiences was explored. Baseline blood pressure measurements were taken at visit 2 after a 6-week placebo run-in period. Table 34 presents the numbers of patients with confirmed thrombotic cardiovascular serious adverse experiences by category of baseline BP. Baseline, pretreatment elevations in blood pressure were associated in both treatment groups with an increased incidence of cardiovascular events, as expected from the known association between hypertension and cardiovascular risk. In all BP categories (from low to high), the relative risk of patients having a cardiovascular event was higher in the rofecoxib group than in the placebo group. This effect was greatest for patients with diastolic BP of 80 to 84 mm Hg or systolic BP of 120 to 129 mm Hg at baseline.

Table 34

Absolute Rates and Relative Risk (95% CI)
Analysis by Baseline Blood Pressure and Confirmed Thromboembolic
Serious AEs in APPROVe

Baseline Blood Pressure	Rofecoxib (N=1287) Events/Patient-Year (rate x100)	Placebo (N=1299) Events/Patient-Year (rate x100)	Comparison Relative Risk (95% CI)
DBP≥100 or SBP≥160	5/176 (2.84)	3/191 (1.57)	1.81 (0.35, 11.63)
DBP 90-99 or SBP 140-159	13/857 (1.52)	11/1030 (1.07)	1.42 (0.64, 3.18)
DBP 85-89 or SBP 130-139	14/753 (1.86)	8/709 (1.13)	1.65 (0.69, 3.93)
DBP 80-84 or SBP 120-129	9/707 (1.27)	2/809 (0.25)	5.13 (1.11, 23.75)
DBP <80 and SBP <120	4/548 (0.73)	1/576 (0.17)	4.21 (0.42, 207.13)

DBP = diastolic blood pressure; SBP = systolic blood pressure.

Table 35 presents the numbers of patients having a confirmed thrombotic cardiovascular serious adverse experience by category of blood pressure attained at any time post-randomization up to the discontinuation of study therapy. The rates of CV events were greater for patients in the rofecoxib group who experienced an elevated blood pressure during the study compared to the other patients.

Table 35

Rates Per 100 Patient-Years
Confirmed
Thrombotic Serious Adverse Experiences by Analysis of Blood
Pressure During Study in APPROVe

On-Treatment Blood Pressure	Rofecoxib (N=1268) Events/Patient-Year (rate x 100)	Placebo (N=1286) Events/Patient-Year (rate x 100)
DBP<100 and SBP<160	20/2062 (0.97)	20/2515 (0.80)
DBP≥100 or SBP≥160 (Once)	13/454 (2.86)	2/413 (0.48)
DBP≥100 or SBP≥160 (Two or more times)	12/525 (2.29)	3/386 (0.78)

DBP = diastolic blood pressure; SBP = systolic blood pressure

Relative risk (95% CI) for time-varying covariate defined as 1 once (DBP≥100 or SBP≥160) was true: 2.29 (1.37, 3.82); treatment effect: 1.83 (1.12, 2.99). Treatment by covariate interaction p-value: 0.105

Relative risk (95% CI) for time-varying covariate defined as 1 if (DBP≥100 or SBP≥160) was true at the visit before the event time otherwise defined as 0: 1.44 (0.66, 3.15); treatment effect: 1.97 (1.20, 3.24). Treatment by covariate interaction p-value: 0.474

Relationship of Blood Pressure to Cardiovascular Outcomes

Data from epidemiologic studies like the Framingham study [126] and more recent meta-analyses [127] have permitted estimates of the magnitude of cardiovascular risk and the types of events associated with elevations in blood pressure. These epidemiologic studies suggest that an increase of 20 mm Hg in systolic blood pressure or 10 mm Hg in diastolic blood pressure is associated with an approximately 2-fold increase in cardiovascular events [127]. Data from clinical and epidemiologic meta-analyses shows that reducing diastolic blood pressure over 5 to 6 years by 5 to 6 mm Hg in hypertensives reduces the risk of stroke by 35 to 40% and coronary heart disease by 20 to 35% (epidemiologic studies) or 14% (clinical studies) [128]. In rofecoxib-treated patients in APPROVe, the mean difference at individual study visits from pre-treatment baseline blood pressure ranged from 2.3 to 3.9 mm Hg for systolic blood pressure and from 0.3 to 1.4 mm Hg for diastolic blood pressure (see Section 3.3).

These epidemiological studies have shown that elevations in blood pressure are consistently associated with a greater risk of cerebrovascular events than cardiac events. Furthermore, the benefit of blood pressure reduction is greater for cerebrovascular outcomes than for cardiac outcomes [129]. In the APPROVe study, cardiac events were more numerous than cerebrovascular events.

Thus, drug-related increases in blood pressure would not appear to account for the magnitude of the increased risk of cardiovascular events observed for rofecoxib compared to placebo in APPROVe, although a small contribution of blood pressure to the overall result cannot be excluded.

Summary: Blood Pressure Changes and Risk of Having Serious Cardiovascular Thrombotic Adverse Experiences

The majority of analyses performed did not reveal significant associations between blood pressure and relative risk for CV events in the APPROVe study. In one analysis, the relative risk for CV events was greatest in patients with increases in systolic blood pressure ≥160 mm Hg. The lack of consistency with any of the other BP analyses performed limits the ability to draw conclusions from this single association.

6.3 APPROVe Summary

The study validates the primary efficacy hypothesis but revealed unexpected safety findings. Daily administration of rofecoxib was associated with a significantly reduced rate of adenoma recurrence compared with placebo. The study also showed an increased risk of patients having confirmed thrombotic cardiovascular serious adverse experiences with rofecoxib 25 mg. The risk began to diverge from placebo beginning after 18 months of chronic therapy; over time the difference became significant. Results for the first 18 months of treatment in APPROVe did not indicate any meaningful difference

between rofecoxib and placebo and were consistent with prior placebo-controlled and non-naproxen NSAID controlled data. Analyses of cardiovascular risk factors, including blood pressure, did not reveal any important association that might provide insight into origin of the increased risk of patients having thrombotic cardiovascular events associated with rofecoxib therapy beginning after 18 months of continuous therapy. There was no difference in mortality between the treatment groups.

6.4 APPROVe Conclusions

- The incidence of thrombotic cardiovascular events with rofecoxib 25 mg was similar to placebo over the first 18 months of continuous usage, consistent with the other data in the rofecoxib development program.
- The risk of thrombotic CV events in patients taking rofecoxib 25 mg began to diverge from placebo beginning after 18 months of chronic therapy; over time the difference became significant.
- Analyses of cardiovascular risk factors, including blood pressure, did not reveal any consistent association that might provide insight into the increased risk of thrombotic cardiovascular risk factors associated with rofecoxib therapy after 18 months.
- There was no difference in mortality between the treatment groups.
- The mechanism(s) for the increased risk versus placebo starting after 18 months of continuous therapy of thrombotic cardiovascular events are uncertain.

7. Postmarketing Data

Postmarketing surveillance is an important signal detection tool after a new drug enters the market. The first suspicion of rare and non-mechanism based adverse events not detected in clinical trials usually arises from spontaneous reporting systems. For common adverse events, i.e. coronary heart disease (CHD), however, the background rate (640 to 1,100 per 100,000 patient years in the U.S.) often is so much higher than the reported rate (3.5 per 100,000 patient-years of exposure worldwide, market introduction through 30-September-2004; Health Care Provider reports) that no conclusion of an association or an increased risk can be drawn. Similarly, mechanism based adverse events, i.e., fluid retention and hypertension from NSAID use, are expected to occur and therefore are not systematically reported by health care practitioners for drugs of the same class; hence no conclusions can be drawn regarding the magnitude of risk. Therefore, it is generally accepted that post marketing surveillance cannot be used to evaluate such adverse events, which only can be studied in clinical trials and/or observational studies.

It is also generally accepted that spontaneous reporting systems can only produce signals of potential cause – effect relationships because the information is most often incomplete and the systems are sensitive to multiple biases like time on market – reporting highest during the first years, media attention – leading to increased reporting, channeling high risk patients to new treatments etc. For irreversible effects it is impossible to make valid causal inferences from spontaneous reports since two important criteria for causality evaluation – dechallenge and rechallenge are not applicable. Typical examples of such effects are cardiovascular events like thromboembolism including acute myocardial infarctions and cerebrovascular events. Such events can therefore only be evaluated in

formal studies where the risk of the outcome is compared between exposed and non-exposed. Furthermore, spontaneous reports cannot be used to compare the risk of one type of AE between different drugs, a fact recognized by the FDA and other experts.

8. Overall Conclusions

- Rofecoxib was the only approved selective COX-2 inhibitor with a demonstrated advantage over nonselective NSAIDs in decreasing the risk of clinical upper GI events. A benefit over nonselective NSAIDs in patients taking concomitant low dose aspirin has been suggested but not conclusively established.
- Rofecoxib use, like all NSAIDs, is associated with renovascular adverse experiences that are mechanism based and dosed related. In general, these effects with rofecoxib are similar to the effects seen with other NSAIDs.
- The data from rofecoxib clinical trials shows a similar incidence of thrombotic cardiovascular events with rofecoxib 25 mg compared to placebo over the first 18 months of chronic usage or from non-naproxen NSAIDs.
- The incidence of thrombotic cardiovascular events is lower on naproxen 500 mg twice daily than rofecoxib. The difference is apparent shortly after initiation of therapy.
- In APPROVe, the risk of thrombotic CV events in patients taking rofecoxib 25 mg began to diverge from placebo beginning after 18 months of chronic therapy; over time the difference became significant. Long term data for rofecoxib in comparison to non-naproxen NSAIDs has not revealed a difference but are limited.
- The mechanism(s) for the increased risk of thrombotic cardiovascular events in the APPROVe study are uncertain.
- There are as yet no long-term data to suggest a difference in the incidence of thrombotic cardiovascular events in selective COX-2 inhibitors compared to nonselective NSAIDs such as ibuprofen and diclofenac that do not have potent and sustained antiplatelet effects.
- It is premature to draw conclusions at this time on the implications of the new findings with rofecoxib, celecoxib, and naproxen for the other drugs in this class including COX-2 selective inhibitors and non-selective NSAIDs or to assess topics such as the effects of dose and duration. Although the data suggest that the CV findings represent a class effect, it is unclear at this time how extensive the class might be: selective COX-2 inhibitors, all NSAIDs, or the subset of NSAIDs without potent and sustained COX-1 inhibitory effects.
- Physicians and patients should discuss the benefits and risks of these agents and incorporate the new information into their decision making. New and ongoing studies will likely continue to inform on this topic and should be taken into account in any product labeling.

9. List of References

1. Fries JF. NSAID gastropathy: the second most deadly rheumatic disease? Epidemiology and risk appraisal. J Rheumatol 1991;18(Suppl 28):6-10.

2. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Eng J Med 1999;340(24):1888-99.

3. Griffin MR. Epidemiology of nonsteroidal anti-inflammatory drug-associated gastrointestinal injury [With Discussion]. Am J Med 1998;104(3A):23s-9s, 41s-2s.

4. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. Arch Intern Med 1993;153:477-84.

5. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994;121(4):289-300.

6. Livesey JR, Watson MG, Kelly PJ, Kesteven PJ. Do patients with epistaxis have drug-induced platelet dysfunction? Clin Otolaryngol 1995;20:407-10.

7. Morse EE. Effects of drugs on platelet function. Ann Clin Lab Sci 1977;1:68-72.

8. Cheng JC, Siegel LB, Katari B, Traynoff SA, Ro JO. Nonsteroidal anti-inflammatory drugs and aspirin: a comparison of the antiplatelet effects. Am J Ther 1997;4(2-3):62-5.

9. Wierod FS, Frandsen NJ, Jacobsen JD, Hartvigsen A, Olsen PR. Risk of haemorrhage from transurethral prostatectomy in acetylsalicylic acid and NSAID-treated patients. Scand J Urol Nephrol 1998;32(2):120-2.

10. Niemi T, Tanskanen P, Taxell C, Juvela S, Randell T, Rosenberg P. Effects of nonsteroidal anti-inflammatory drugs on hemostasis in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg Anesthesiol 1999;11(3):188-94.

11. Tsirbas A, McNab AA. Secondary haemorrhage after dacryocystorhinostomy. Clin Experiment Ophthalmol 2000;28(1):22-5.

12. Whittle BJR, Higgs GA, Eakins KE, Moncada S, Vane JR. Selective inhibition of prostaglandin production in inflammatory exudates and gastric mucosa. Nature 1980;284:271-3.

13. Vane J. Towards a better aspirin. Nature 1994;367:215-6.

14. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Eng J Med 2000;343(21):1520-8.

15. Konstam MA, Weir MR, Reicin A, Shapiro D, Sperling RS, Barr E, et al. Cardiovascular Thrombotic Events in Controlled, Clinical Trials of Rofecoxib. Circulation 2001;104:1-9.

16. Hunt RH, Bowen B, Mortensen ER, Simon TJ, James C, Cagliola A, et al. A randomized trial measuring fecal blood loss after treatment with rofecoxib, ibuprofen, or placebo in healthy subjects. Am J Med 2000;109:201-6.

17. Sigthorsson G, Crane R, Simon T, Hoover M, Quan H, Bolognese J, et al. COX-2 inhibition with rofecoxib does not increase intestinal permeability in healthy subjects: a double blind crossover study comparing rofecoxib with placebo and indomethacin. Gut 2000;47:527-32.

18. Cryer B, Gottesdiener K, Gertz B, Wong P, Feldman M. In vivo effects of rofecoxib, a new cyclooxygenase (COX)-2 inhibitor, on gastric mucosal prostaglandin (PG) and serum thromboxane B-2 (TXB-2) synthesis in healthy human [Abstract]. Gastroenterology 1999;116(4):A 141.

19. Catella-Lawson F, McAdam B, Morrison BW, Kapoor S, Kujubu D, Antes L, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther 1999;289(2):735-41.

20. Gertz BJ, Krupa D, Bolognese JA, Sperling RS, Reicin A. A comparison of adverse renovascular experiences among osteoarthritis patients treated with rofecoxib and comparator non-selective non-steroidal anti-inflammatory agents. Curr Med Res Opin 2002;18(2):82-91.

21. Schwartz JI, Vandormael K, Malice MP, Kalyani RN, Lasseter KC, Holmes GB, et al. Comparison of rofecoxib, celecoxib, and naproxen on renal function in elderly subjects receiving a normal-salt diet. Clin Pharmacol Ther 2002;72(1):50-61.

22. Awtry EH, Loscalzo J. Aspirin. Circulation 2000;101:1206-18.

23. Bunting S, Moncada S, Vane JR. The prostacyclin-thromboxane A2 balance: pathophysiological and therapeutic implications. Br Med Bull 1983;39:271-6.

24. Lewis HD, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. N Eng J Med 1983;309:396-403.

25. Reilly IAG, FitzGerald GA. Inhibition of thromboxane formation in vivo and ex vivo: implications for therapy with platelet inhibitory drugs. Blood 1987;69(1):180-6.

26. Fornaro G, Rossi P, Mantica PG, Caccia ME, Aralda D, Lavezzari M, et al. Indobufen in the prevention of thromboembolic complications in patients with heart disease: a randomized, placebo-controlled, double-blind study. Circulation 1993;87:162-4.

27. Brochier ML. Evaluation of flurbiprofen for prevention of reinfarction and reocclusion after successful thrombolysis or angioplasty in acute myocardial infarction. Eur Heart J 1993;14:951-7.

28. McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci USA 1999;96:272-7.

29. Wiseman LR, Fitton A, Buckley MM. Indobufen: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in cerebral, peripheral and coronary vascular disease. Drugs 1992;44(3):445-64.

30. Schönbeck U, Sukhova GK, Graber P, Coulter S, Libby P. Augmented expression of cyclooxygenase-2 in human atherosclerotic lesions. Am J Pathol 1999;155(4):1281-91.

31. Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. J Clin Pharmacol 1995;35:209-19.

32. Drvota V, Vesterqvist O, Green K. Effects of non-steroidal anti-inflammatory drugs on the in vivo synthesis of thromboxane and prostacyclin in humans. Adv Prostaglandin Thromboxane Leukot Res 1991;21A:153-6.

33. Van Hecken A, Schwartz JI, Depré M, De Lepeleire I, Dallob A, Tanaka W, et al. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen and naproxen on COX-2 versus COX-1 in healthy volunteers. J Clin Pharmacol 2000;40:1-12.

34. Greenberg HE, Gottesdiener K, Huntington M, Wong P, Larson P, Wildonger L, et al. A new cyclooxygenase-2 inhibitor, rofecoxib (VIOXX®), did not alter the antiplatelet effects of low-dose aspirin in healthy volunteers. J Clin Pharmacol 2000;40:1509-15.

35. Zeigler ZR. Non-occlusive bleeding times may improve the value of ivy bleeding times. Thromb Haemost 1990;63(3):371-4.

36. De Caterina R, Giannessi D, Boem A, Bernini W, Battaglia D, Michelassi C, et al. Equal antiplatelet effects of aspirin 50 or 324 mg/day in patients after acute myocardial infarction. Thromb Haemost 1985;54(2):528-32.

37. Cataldo G, Heiman F, Lavezzari M, Marubini E. Indobufen compared with aspirin and dipyridamole on graft patency after coronary artery bypass surgery: results of a combined analysis. Coron Artery Dis 1998;9:217-22.

38. Bhana N, McClellan KJ. Indobufen. An updated review of its use in the management of atherothrombosis. Drugs Aging 2001;18(5):369-88.

39. Farkouh ME, Kirshner H, Harrington RA, Ruland S, Verheugt FWA, Schnitzer TJ, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the therapeutic arthritis research and gastrointestinal event trial (TARGET), cardiovascular outcomes: randomised controlled trial. Lancet 2004;364:675-84.

40. White WB, Faich G, Whelton A, Maurath C, Ridge NJ, Verburg KM, et al. Comparison of thromboembolic events in patients treated with celecoxib, a cyclooxygenase-2 specific inhibitor, versus ibuprofen or diclofenac. Am J Cardiol 2002;89:425-30.

41. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. JAMA 2000;284(10):1247-55.

42. Weir MR, Sperling RS, Reicin A, Gertz BJ. Selective cox-2 inhibition and cardiovascular effects: a review of the rofecoxib development program. Am Heart J 2003;146:591-604.

43. Reines SA, Block GA, Morris JC, Liu G, Nessly ML, Lines CR, et al. Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. Neurology 2004;62:66-71.

44. Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, et al. Effects of rofecoxib or naproxen vs placebo on alzheimer disease progression: a randomized controlled trial. JAMA 2003;289(21):2819-26.

45. Thal LJ, Ferris SH, Kirby L, Block GA, Lines CR, Yuen E, et al. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. Neuropsychopharmacology 2005, in press.

46. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280(7):605-13.

47. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and estrogen/progestin replacement study follow-up (HERS II). JAMA 2002;288(1):49-57.

48. FDA Statement on the Results of the Women's Health Initiative (8/13/2002). Women's health initiative (WHI) results signal need for reassessment of risks and benefits of conjugated equine estrogens/medroxyprogesterone acetate (prempro) in postmenopausal women. http://www.fda.gov/cder/drug/safety/WHI_statement.htm (accessed 9/11/03).

49. Zacher J, Schattenkirchner M. Patient and physician satisfaction with rofecoxib in osteoarthritis: results of a post-marketing surveillance study in primary care in germany. Curr Med Res Opin 2002;18(4):229-36.

50. Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. Lancet 2002;360:1071-3.

51. Bannwarth B, Trèves R, Euller-Ziegler L, Rolland D, Ravaud P, Dougados M. Adverse events associated with rofecoxib therapy. Results of a large study in community-derived osteoarthritic patients. Drug Safety 2003;26(1):49-54.

52. Mamdani M, Rochon P, Juurlink DN, Anderson GM, Kopp A, Naglie G, et al. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. Arch Intern Med 2003;163:481-6.

53. Layton D, Heely E, Hughes K, Shakir SAW. Comparison of the incidence rates of thromboembolic events reported for patients prescribed rofecoxib and meloxicam in general practice in England using prescription-event monitoring (PEM) data. Rheumatol 2003;42(11):1342-53.

54. Solomon DH, Schneeweiss S, Glynn RJ, Kiyota Y, Levin R, Mogun H, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 2004;109:2068-73.

55. Kimmel SE, Berlin JA, Reilly M, Jaskowiak J, Kishel L, Strom BL. Risk of myocardial infarction by type of cyclooxygenase-2 inhibitor. [Abstract]. Circulation 2003;108(17, Suppl. IV):IV 752.

56. Goldstein J, Eisen G, Blair L, Gralnick I, Fort J, Brown R, et al. (Abstract #284) Abnormal Small Bowel Findings Are Common in Healthy Subjects Screened for a Multi-Center, Double Blind, Randomized, Placebo-Controlled Trial Using Capsule Endoscopy. [Abstract]. Gastroenterology 2003;124(4 Suppl. 1):A37.

57. Watson DJ, Rhodes T, Cai B, Guess HA. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. Arch Intern Med 2002;162:1105-10.

58. Temple R. Meta-analysis and epidemiologic studies in drug development and postmarketing surveillance. JAMA 1999;281(9):841-4.

59. Walter MF, Jacob RF, Day CA, Dahlborg R, Weng Y, Mason RP. Sulfone COX-2 inhibitors increase susceptibility of human LDL and plasma to oxidative modification: comparison to sulfonamide COX-2 inhibitors and NSAIDs. Atherosclerosis 2004;177:235-43.

60. Kobayashi T, Tahara Y, Matsumoto M, Iguchi M, Sano H, Murayama T, et al. Roles of thromboxane A_2 and prostacyclin in the development of atherosclerosis in apoE-deficient mice. J Clin Invest 2004;114(6):784-94.

61. Egan KM, Lawson JA, Fries S, Koller B, Rader DJ, Smyth EM, et al. COX-2 derived prostacyclin confers atheroprotection on female mice. Science 2004:1-4 plus supporting material.

62. Pratico D, Tillmann C, Zhang Z-B, Li H, FitzGerald GA. Acceleration of atherogenesis by COX-1-dependent prostanoid formation in low density lipoprotein receptor knockout mice. PNAS 2001;98(6):3358-63.

63. Ott E, Nussmeier NA, Duke PC, Feneck RO, Alston RP, Snabes MC, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg 2003;125(6):1481-92.

64. Pfizer statement on new information regarding cardiovascular safety of Celebrex. Dosing in long-term cancer studies suspended due to increased cardiovascular risk in one study; preliminary analysis of second long-term cancer study shows no increased cardiovascular risks. http://www.pfizer.ca/english/newsroom/press%20releases/default.asp?s=1&year=2004&releaseID=149 1/10/2005

65. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991;115(10):787-96.

66. Tramèr MR, Moore RA, Reynolds DJM, McQuay HJ. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. Pain 2000;85:169-82.

67. Langman MJ, Jensen DM, Watson DJ, Harper ES, Zhoa PL, Quan H, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDS. JAMA 1999;282(20):1929-33.

68. Hawkey C, Laine L, Simon T, Beaulieu A, Maldonado-Cocco J, Acevedo E, et al. Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2000;43(2):370-7.

69. Laine L, Harper S, Simon T, Bath R, Johanson J, schwartz H, et al. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Gastroenterology 1999;117(4):776-83.

70. Hawkey CJ, Laine L, Simon T, Quan H, Shingo S, Evans J. Incidence of gastroduodenal ulcers in patients with rheumatoid arthritis after 12 weeks of rofecoxib, naproxen, or placebo: a multicentre, randomised, double blind study. Gut 2003;52:820-6.

71. Watson DJ, Yu Q, Bolognese JA, Reicin AS, Simon TJ. The upper gastrointestinal safety of rofecoxib vs. NSAIDs: an updated combined analysis. Curr Med Res Opin 2004;20(10):1539-48.

72. Memo to Maller E from Qinfen Y: Pooled Analysis of Upper GI PUBs by Rofecoxib Dose, 2004.

73. Laine L, Maller ES, Yu C, Quan H, Simon T. Ulcer formation with low-dose enteric-coated aspirin and the effect of COX-2 selective inhibition: a double blind trial: Gastroenterology. Unpublished observations 2003.

74. Bjarnason I, Hayllar J, Macpherson AJ, Russell AS. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. Gastroenterology 1993;104(6):1832-47.

75. Laine L, Connors LG, Reicin A, Hawkey CJ, Burgos-Vargas R, Schnitzer TJ, et al. Serious lower gastrointestinal clinical events with nonselective NSAID or Coxib Use. Gasteroenterology 2003;124(2):288-92.

76. Habib A, Créminon C, Frobert Y, Grassi J, Pradelles P, Maclouf J. Demonstration of an inducible cyclooxygenase in human endothelial cells using antibodies raised against the carboxyl-terminal region of the cyclooxygenase-2. J Biol Chem 1993;268(31):23448-54.

77. Topper JN, Cai J, Falb D, Gimbrone MAJ. Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. Proc Natl Acad Sci USA 1996;93:10417-22.

78. Singer IL, Kawka DW, Cunningham P, Ouellett M, Riendeau D. COX-1 is the major Isoform of cyclooxygenase co-localized with prostacyclin synthase in normal dog aortic endothelium [Abstract]. Inflamm Res 2003;52:S88, IS/18.

79. Wong E, Huang JQ, Tagari P, Riendeau D. Effects of COX-2 inhibitors on aortic prostacyclin production in cholesterol-fed rabbits. Atherosclerosis 2001;157:393-402.

80. Warner TD, Vojnovic I, Giuliano F, Jiménez R, Bishop-Bailey D, Mitchell JA. Cyclooxygenase 1, 2, and 3 and the production of prostaglandin I_2: investigating the activities of acetaminophen and cyclooxygenase-2-selective inhibitors in rat tissues. J Pharmacol Exp Ther 2004;310(2):642-7.

81. Tuleja E, Mejza F, Cmiel A, Szczeklik A. Effects of cyclooxygenase inhibitors on vasoactive prostanoids and thrombin generation at the site of microvascular injury in healthy men. Arterioscler Thromb Vasc Biol 2003;23:1111-5.

82. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet 2002;359:1686-9.

83. Baker CSR, Hall RJC, Evans TJ, Pomerance A, Maclouf J, Creminon C, et al. Cyclooxygenase-2 is widely expressed in atherosclerotic lesions affecting native and transplanted human coronary arteries and colocalizes with inducible nitric oxide synthase and nitrotyrosine particularly in macrophages. Arterioscler Thromb Vasc Biol 1999;19:646-55.

84. Cipollone F, Prontera C, Pini B, Marini M, Fazia M, De Cesare D, et al. Overexpression of functionally coupled cyclooxygenase-2 and prostaglandin E synthase in symptomatic atherosclerotic plaques as a basis of prostaglandin E_2-dependent plaque instability. Circulation 2001;104:921-7.

85. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92(3):657-71.

86. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81-106.

87. Juul-Möller S, Edvardsson N, Jahnmatz B, Rosen A, Sørensen S, Ömblus R, et al. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. Lancet 1992;340(8833):1421-5.

88. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-39.

89. Hennekens CH, Dyken ML, Fuster V. Aspirin as a therapeutic agent in cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 1997;96(8):2751-3.

90. Simon DI, Stamler JS, Jaraki O, Keaney JF, Jr., Osborne JA, et al. Antiplatelet properties of protein S-nitrosothiols derived from nitric oxide and endothelium-derived relaxing factor. Arterioscler Thromb 1993;13:791-9.

91. Patrignani P, Sciulli MG, Manarini S, Santini G, Cerletti C, Evangelista V. COX-2 is not involved in thromboxane biosynthesis by activated human platelets. J Physiol Pharmacol 1999;50(4):661-7.

92. Physicians' Desk Reference. EC-NAPROSYN® (naproxen) delayed-release tablets; NAPROSYN® (naproxen) tablets; ANAPROX®/ANAPROX® DS (naproxen sodium) tablets; NAPROSYN® (naproxen) suspension [Package Insert]. 54 ed. Montvale (NJ): Medical Economics Company, Inc., 2000:2631-4.

93. Physicians' Desk Reference. CATAFLAM® diclofenac potassium immediate-release tablets; VOLTAREN® diclofenac sodium delayed-release (enteric coated) tablets; VOLTAREN®-XR diclofenac sodium extended-release tablets [Package Insert]. 53 ed.Montvale (NJ): Medical Economics Company, Inc., 1999:2001-4.

94. U.S. Package Insert: Ibuprofen: 2003.

95. Capone ML, Tacconelli S, Sciulli MG, Grana M, Ricciotti E, Minuz P, et al. Clinical pharmacology of platelet, monocyte, and vascular cyclooxygenase inhibition by naproxen and low-dose aspirin in healthy subjects. Circulation 2004;109:1468-71.

96. Leese PT, Talwalker S, Kent JD, Recker DP. Valdecoxib does not impair platelet function. Am J Emerg Med 2002;20(4):275-81.

97. Collantes E, Curtis SP, Lee KW, Casas N, McCarthy T, Melian A, et al. A multinational randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis. BMC Family Practice 2002;3(10):1-10.

98. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.

99. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336(14):973-9.

100. Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, et al. The mortality of rheumatoid arthritis. Arthritis Rheum 1994;37(4):481-94.

101. Myllykangas-Luosujärvi RA, Aho K, Isomäki HA. Mortality in rheumatoid arthritis. Semin Arthritis Rheum 1995;25(3):193-202.

102. Wållberg-Jonsson S, Öhman M-L, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. J Rheumatol 1997;24(3):445-51.

103. Taketo MM. Cyclooxygenase-2 inhibitors in tumorigenesis (Part II). J Natl Cancer Inst 1998;90(21):1609-20.

104. Baron JA, Sandler RS. Nonsteroidal anti-inflammatory drugs and cancer prevention. Annu Rev Med 2000;51:511-23.

105. MRL Statistical Report: Clinical safety of rofecoxib versus placebo in the VIOXX (rofecoxib)/MK-0966 Alzheimer's disease (AD) studies (Protocol 078 and Protocol 091): Analysis of confirmed thrombotic events, confirmed Antiplatelet Trialists' Collaboration (APTC) events, investigator-reported thrombotic events, all-cause mortality and thrombotic cardiovascular mortality , 10-Dec-2003.

106. Kimmel SE, Berlin JA, Reilly M, Jaskowiak J, Kishel L, Chittams J, et al. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. Ann Intern Med 2005;142(3):1-9.

107. Levy GD, Cheetham TC, Shoor S. Cohort analysis myocardial Infarction risk and COX2 use in the Kaiser large observational thrombosis study (KLOTS). [Abstract]. Arth & Rheum 2002;46(Suppl. 9):S377.

108. Whelton A, Spalding WM, White WB, Reeves MJ, Suh SS, Fort JG. Rofecoxib increases cardiovascular events in arthritis patients but celecoxib and nonspecific nonsteroidal anti-inflammatory drugs do not: results from a large New England Health Care claims database. [Abstract]. JACC 2004;415A.

109. Graham DJ, Campen D, Cheetham C, Hui R, Spence M, Ray WA. Risk of acute cardiac events among patients treated with cyclooxygenase-2 selective and non-selective nonsteroidal anti-inflammatory drugs [Abstract]. Pharmacoepidemiology Drug Safety 2004;13:S287-S288.

110. Rahme E, Kong SX, Watson DJ, Toubouti Y, LeLorier J. Association between rofecoxib, diclofenac/ibuprofen and hospitalization for acute myocardial infarction. [Abstract]. Pharmacoepidemiology Drug Safety 2004;13:S235.

111. Shaya FT, BLume SW, Blanchette CM, Mullins CD, Weir MR. Cardiovascular risk of selective cyclooxygenase-2 inhibitors compared to other nonsteroidal anti-inflammatory agents: an observational study of a Medicaid population. (659) [Abstract]. Pharmacoepidemiology Drug Safety 2004;13:S234-S235.

112. Campen DH, Graham D, Cheetham C, Shoor S, Levy G, Hui R, et al. Risk of acute cardiac events among patients treated with cyclooygenase-2 selective and non-sSelective-nonsteroidal anti-inflammatory drugs. [Abstract]. Arth & Rheum 2004;50(Suppl. 9):S657.

113. Velentgas P, West W, Walker AM. Velentgas P, West W, Walker AM. Cardiovascular risk of COX-2 inhibitors and other non-aspirin NSAIDs. Pre-publication draft. Submitted Oct 2004.

114. Memo to Yothers K, Seligman P from Scheid S: Aetna, 14-Nov-2004.

115. Zhao SZ, Burke T, Pettitt D, Henderson SC, Von Allmen H. Baseline risk of cardiovascular disorders among new users of ibuprofen, naproxen, diclofenac, and celecoxib [Abstract]. Ann Rheum Dis 2002;61(Suppl 1):341.

116. Wolfe F, Flowers N, Burke TA, Arguelles LM, Pettitt D. Increase in lifetime adverse drug reactions, service utilization, and disease severity among patients who will start COX-2 specific inhibitors: quantitative assessment of channeling bias and confounding by indication in 6689 patients with rheumatoid arthritis and osteoarthritis. J Rheumatol 2002;29(5):1015-22.

117. Gimeno V, Castellsague J, Maguire A, Eaton S, McQuay LJ, Zhou X, et al. Gastrointestinal and cardiovascular characterization of users of valdecoxib and other COX-2 specific inhibitors. [Abstract]. Pharmacoepidemiology Drug Safety 2004;13:S236.

118. Levesque L, Brophy JM, Zhang B, Bourgault C. Cox-2 selective inhibitors and cardiovascular outcomes in an elderly population. [Abstract]. Pharmacoepidemiology Drug Safety 2004;13:S49.

119. Teeling M, Bennett K, Feely J. Are Cox-2 selective inhibitors preferentially prescribed in patients on aspirin therapy? [Abstract]. Pharmacoepidemiology Drug Safety 2004;13:S286.

120. Eberhart CE, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, Dubois RN. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. Gastroenterology 1994;107(4):1183-8.

121. Sandler RS. Aspirin and other nonsteroidal anti-inflammatory agents in the prevention of colorectal cancer. In: DeVita VT, Hellman S, Rosenberg SA, eds. Important Advances in Oncology 1996. Philadelphia: Lippincott-Raven, 1996:123-37.

122. Giardiello FM, Hamilton SR, Krush AJ, Piantadosi S, Hylind LM, Celano P, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med 1993;328(18):1313-6.

123. Steinbach G, Lynch PM, Phillips RKS, Wallace MH, Hawk E, Gordon GB, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Eng J Med 2000;342(26):1946-52.

124. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003;348(10):891-9.

125. Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med 2003;348(10):883-90.

126. Dawber TR, Kannel WB, Revotskie N, Stokes J, Kagan A, Gordon T. Some factors associated with the development of coronary heart disease: six years' follow-up experience in the Framingham study. Am J Public Health 1959;49:1349-56.

127. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. The Lancet 2002;360:1903-13.

128. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. The Lancet 1990;335(8692):765-74.

129. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, et al. Blood pressure, stroke, and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990;335:827-38.

APPENDIX 1

Emerging Data on Prostaglandin Biology Relevant to the Cardiovascular System

Over the course of the clinical development of rofecoxib, there has been an evolution in the understanding of the biology of the pathways affected by the inhibition of COX-1 and COX-2. Although there are no definitive data, mechanisms have been proposed to explain the reasons why selectively inhibiting COX-2 might be associated with an increase in cardiovascular risk. Both clinical and preclinical data on the cardiovascular effects of selective COX-2 inhibition reveal mixed results with some studies showing a benefit, some no effect, and others a possible deleterious effect.

The identification of COX-2 in atherosclerotic lesions in humans and in fatty streaks of $apoE^{-/-}$ and $LDL^{-/-}$ mice has spurred an interest in the role of COX-2 in the pathogenesis of atherosclerosis [1; 2; 3; 4]. Animal models of atherosclerosis examining the effects of COX-2 inhibition on lesion size provide inconclusive correlation. In short term (3 to 12 week) studies in $apoE^{-/-}$ mice, mice treated with COX-2 selective inhibitors had increased, decreased, and no change in the size of atherosclerotic lesions [5; 4; 6; 7]. In longer terms studies (>15 weeks), neither the COX-2 selective inhibitors celecoxib, MF-tricyclic, or the non-selective NSAID sulindac had a significant effect on the size of atherosclerotic lesions [8; 9]. In LDL-/- mice, 6 weeks of treatment with the COX-2 inhibitor rofecoxib reduced lesion size [4], while treatment for 18 weeks with the COX-2 inhibitor nimesulide had no significant effect [3]. Overall, the majority of mouse studies indicate no detrimental effects of COX-2 inhibition, and several indicate potential benefits on atherogenesis.

A variety of studies have explored the pathogenesis of atherosclerosis using mice with targeted deletions in specific prostanoid receptors. These results must be interpreted in light of the knowledge that NSAIDs or COX-2 selective inhibitors produce between 60 and 75% inhibition of the enzyme at clinical doses [10]. In addition, inhibitors affect the synthesis of a broad range of prostanoids rather than targeting a single molecular species. The data from cross breeding experiments suggest that loss of the IP (prostacyclin) receptor potentiates atherosclerosis in $apoE^{-/-}$ mice while loss of the TP (thromboxane) receptor is partially protective [11; 12]. As both COX-1 and COX-2 may be involved in the synthesis of thromboxane and prostacyclin, depending on the cell type and stimulus, the significance of these findings for non-selective NSAIDs and COX-2 selective inhibitors is not clear. The observation that the phenotype of mice with targeted deletion of prostacyclin synthase is not similar to that of the IP knockout mouse is further evidence that the results of receptor knockout experiments may not be directly extrapolated to situations in which prostanoid synthesis is decreased [13].

Numerous animal studies have examined the effect of COX-2 gene deletion and selective inhibition on myocardial infarction (MI), in one study, and thrombosis (references from Lynch memo) [14; 15; 16; 17; 18]. Overall, these studies indicate no detrimental effects

of COX-2 selective inhibitors compared with nonselective NSAIDs. An internal MRL preclinical study assessed the effect of selective COX-2 inhibition versus nonselective inhibition with aspirin and naproxen on arterial and venous thrombosis in an African green monkey model of carotid artery and jugular vein electrolytic injury. Five day oral dosing regimens were selected to achieve levels of inhibition of COX-1 and COX-2 similar to those achieved in clinical use with non-selective and selective COX-2 inhibitors, respectively. The COX-2 selective inhibitors used were rofecoxib and celecoxib while the nonselective NSAIDs were Naproxen and aspirin. This primate study demonstrated no effect of COX-2 inhibition with rofecoxib or celecoxib on either arterial or venous thrombosis. In contrast, naproxen significantly prolonged times to both arterial and venous thrombosis. Aspirin significantly prolonged time to arterial thrombosis, and tended, albeit non-significantly, to increase time to venous thrombosis. This study suggested that COX-2 inhibition demonstrated no effect on acute arterial or venous thrombosis, while naproxen was associated with significantly longer times to arterial and venous thrombosis.

Recent animal experiments have demonstrated that both COX-1 and COX-2 may play a role in late ischemic preconditioning, an experimental paradigm in which myocardium or brain is subjected to short periods of ischemia followed by complete occlusion of the artery. Pre-conditioning has been observed to reduce infarct size. Non-selective NSAIDs and selective COX-2 inhibitors abolish this pre-conditioning response [19; 20; 21]. Both COX-1 and COX-2 null mice, as well as wild-type mice treated with non-selective NSAIDs, lose the last ischemic pre-conditioning response, suggesting that both enzymes may be involved in this prostanoid-dependent mechanism of cardioprotection [22]. The significance of this finding for human disease states is unknown and untestable. However, both non-selective NSAIDs and COX-2 inhibitors produced similar effects in this model system so that effects unique to selective COX-2 inhibition are not anticipated.

The overall effects of COX-2 inhibition or deletion on cardiovascular risk are unclear at this time as the aggregate data do not provide a clear signal. Comprehensive literature reviews of animal models suggest that COX-2 inhibition is associated with a full range of outcomes, including positive benefit, no effect, and deleterious outcomes. The animal model effects of COX-2 inhibition should be extrapolated to effects in humans with extreme caution as there is no clear established relationship between these animal models and human disease.

References

1 Schönbeck U, Sukhova GK, Graber P, Coulter S, Libby P. Augmented expression of cyclooxygenase-2 in human atherosclerotic lesions. Am J Pathol 1999;155(4):1281-91.

2 Baker CSR, Hall RJC, Evans TJ, Pomerance A, Maclouf J, Creminon C, et al. Cyclooxygenase-2 is widely expressed in atherosclerotic lesions affecting native and transplanted human coronary arteries and colocalizes with inducible nitric oxide synthase and nitrotyrosine particularly in macrophages. Arterioscler Thromb Vasc Biol 1999;19:646-55.

3 Pratico D, Tillmann C, Zhang Z-B, Li H, FitzGerald GA. Acceleration of atherogenesis by COX-1-dependent prostanoid formation in low density lipoprotein receptor knockout mice. PNAS 2001;98(6):3358-63.

4 Burleigh ME, Babaev VR, Oates JA, Harris RC, Gautam S, Riendeau D. Cyclooxygenase-2 promotes early atherosclerotic lesion formation in LDL receptor-deficient mice. Circulation 2002;105:1816-23.

5 Rott D, Zhu J, Burnett MS, Zhou YF, Zalles-Ganley A, Ogunmakinwa J, et al. Effects of MF-tricyclic, a selective cyclooxygenase-2 inhibitor, on atherosclerosis progression and susceptibility to cytomegalovirus replication in apolipoprotein-E knockout mice. J Am Coll Cardiol 2003;41(10):1812-9.

6 Krul ES, Napawan N, Butteiger DT, Hayes K, Krause L, Frierdich GE, et al. Atherosclerosis is reduced in cholesterol-fed ApoE(-/-) mice administered an ASBT inhibitor or a selective COX-2 inhibitor [Abstract]. Arterioscler Thromb Vasc Biol 2002;(P409):1.

7 Belton OA, Duffy A, Toomey S, Fitzgerald DJ. Cyclooxygenase isoforms and platelet vessel wall interactions in the apolipoprotein E knockout mouse model of atherosclerosis. Circulation 2003;108:3017-23.

8 Olesen M, Kwong E, Meztli A, Kontny F, Seljeflot I, Arnesen H, et al. No effect of cyclooxygenase inhibition on plaque size in atherosclerosis-prone mice. Scand Cardiovasc J 2002;36:362-7.

9 Bea F, Blessing E, Bennett BJ, Kuo CC, Campbell LA, Kreuzer J, et al. Chronic inhibition of cyclooxygenase-2 does not alter plaque composition in a mouse model of advanced unstable atherosclerosis. Cardiovasc Res 2003;60:198-204.

10 Van Hecken A, Schwartz JI, Depré M, De Lepeleire I, Dallob A, Tanaka W, et al. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen and naproxen on COX-2 versus COX-1 in healthy volunteers. J Clin Pharmacol 2000;40:1-12.

11 Kobayashi T, Tahara Y, Matsumoto M, Iguchi M, Sano H, Murayama T, et al. Roles of thromboxane A_2 and prostacyclin in the development of atherosclerosis in apoE-deficient mice. J Clin Invest 2004;114(6):784-94.

12 Egan KM, Lawson JA, Fries S, Koller B, Rader DJ, Smyth EM, et al. COX-2 derived prostacyclin confers atheroprotection on female mice. Science 2004:1-4 plus supporting material.

13 Yokoyama C. Prostacyclin-deficient mice develop ischemic renal disorders, including neprhosclerosis and renal infarction. Circulation 2002;106:2397-403.

14 LaPointe MC, Mendez M, Leung A, Tao Z, Yang X-P. Inhibition of cyclooxygenase-2 improves cardiac function after myocardial infarction in the mouse. Am J Physiol Heart Circ Physiol 2004;286:H1416-H1424.

15 Scheuren N, Jacobs M, Ertl G, Schorb W. Cyclooxygenase-2 myocardium in stimulation by angiotensin-II in cultured cardiac fibroblasts and role at acute myocardial infarction. J Mol Cell Cardiol 2002;34:29-37.

16 Saito T, Rodger IW, Hu F, Shennib H, Giaid A. Inhibition of cyclooxygenase-2 improves cardiac function in myocardial infarction. Biochem Biophys Res Commun 2000;273(2):772-5.

17 Saito T, Rodger IW, Shennib H, Hu F, Tayara L, Giaid A. Cyclooxygenase-2 (COX-2) in acute myocardial infarction: cellular expression and use of selective COX-2 inhibitor. Can J Physiol Pharmacol 2003;81:114-9.

18 Hennan JK, Huang J, Barrett TD, Driscoll EM, Willens DE, Park AM, et al. Effects of selective cyclooxygenase-2 inhibition on vascular responses and thrombosis in canine coronary arteries. Circulation 2001;104:820-5.

19 Shinmura K, Xian-Liang T, Wang Y, Xuan Y, Liu S, Takano H. Cyclooxygenase-2 mediates the cardioprotective effects of the late phase of ischemic preconditioning in conscious rabbits. PNAS 2000;97(18):10197-202.

20 Guo Y, Bao W, Wu W, Shinmura K, Tang X, Bolli R. Evidence for an essential role of cyclooxygenase-2 as a mediator of the late phase of ischemic preconditioning in mice. Basic Res Cardiol 2000;95:479-84.

21 Alcindor D, Krolikowski JG, Pagel PS, Warltier DC, Kersten JR. Cyclooxygenase-2 mediates ischemic, anesthetic and pharmacologic preconditioning in vivo. Anesthesiology 2004;100:547-54.

22 Camitta MGW, Gabel SA, Chulada P, Bradbury A, Langenbach R, Zeldin DC, et al. Cyclooxygenase-1 and -2 knockout mice demonstrate increased cardiac ischemia/reperfusion injury but are protected by acute preconditioning. Circulation 2001;104:2453-8.

APPENDIX 2

Summary of Efficacy Findings from Rofecoxib Alzheimer's Disease Studies

1. Introduction

A total of 3 studies were initiated to investigate the efficacy of rofecoxib 25 mg for slowing the progression of symptoms in patients with Alzheimer's disease (AD). These include 2 Merck studies (Protocols 091 and 126) and the Alzheimer's Disease Cooperative Study (ADCS). Because proof of efficacy in AD typically requires improvement on cognition and another domain such as an overall clinical rating or activities of daily living, these studies assessed multiple endpoints. An additional Merck study (Protocol 078) investigated the efficacy of rofecoxib for delaying a diagnosis of AD in patients with Mild Cognitive Impairment (MCI). Patients with MCI are at increased risk for developing AD compared with the normal elderly subjects. The study employed similar assessments to those used in the AD trials. The main findings from each study are summarized below.

2. Protocol 091 [1]

2.1 Design

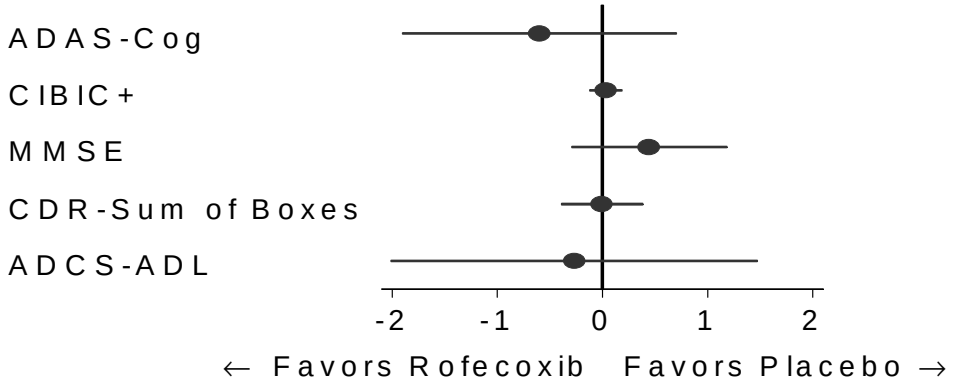
Protocol 091 was a randomized, multicenter, double-blind, placebo-controlled, 12-month, intent-to-treat (ITT) study in patients at least 50 years of age with mild or moderate possible or probable AD. Patients were randomized to receive rofecoxib (N=346) or placebo (N=346). Efficacy measures included assessments of cognition (AD Assessment Scale – cognitive subscale [ADAS-Cog], Mini-Mental State Exam [MMSE]), clinical ratings (Clinical Dementia Rating [CDR], Clinician's Interview Based Impression of Change with caregiver input [CIBIC+]), and activities of daily living (ADCS Activities of Daily Living scale [ADCS-ADL]).

2.2 Results

The efficacy findings at Month 12 are summarized in Figure 1. There were no statistically significant differences between treatments.

Figure 1

Month 12 Mean (95% CI) Treatment Differences in Changes from Baseline in Protocol 091



2.3 Conclusions

Rofecoxib had no effect on the progression of symptoms in AD patients in this study.

3. Protocol 126

3.1 Design

This study had an identical design to Protocol 091.

3.2 Results

The study was terminated early when the results from Protocol 091, indicating no effect of rofecoxib, became known. Due to the early termination, only 1% of the 758 randomized patients completed the planned 12 months of treatment, too few to allow an analysis of the primary endpoint (ADAS-Cog score at Month 12). Analyses of efficacy data at earlier time points of 3, 6, and 9 months were generally consistent with those from Protocol 091 in showing no effect of rofecoxib on progression of AD. Out of 20 comparisons performed with no adjustment for multiplicity, there was 1 statistically significant finding consisting of a treatment difference in favor of placebo on the ADAS-Cog at 6 months of 1.08 points [95% CI: 0.11, 2.05], p=0.029. This small difference was not replicated at the 3- or 9-month time points, or on other measures. No treatment difference on the ADAS-Cog at 6 months was seen in Protocol 091 which had nearly twice the sample size at this time point.

3.3 Conclusions

The results from Protocol 126 were generally consistent with those from Protocol 091 in suggesting no effect of rofecoxib on progression of AD.

4. ADCS Trial [2]

4.1 Design

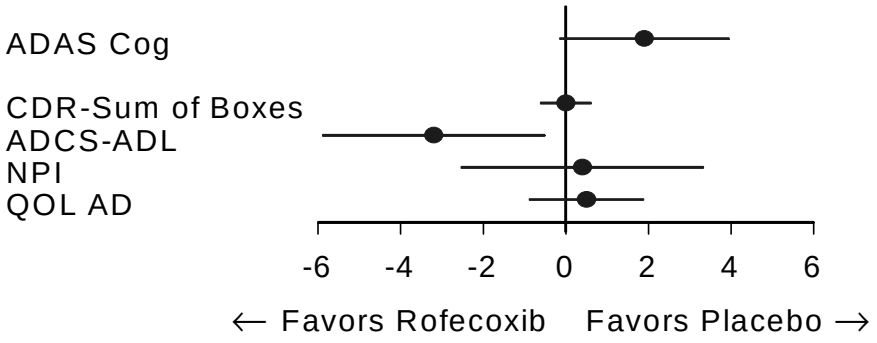
This was a randomized, multicenter, double-blind, placebo-controlled, 12-month, study in patients at least 50 years of age with mild or moderate probable AD. Patients were randomized to receive rofecoxib 25 mg (N=111), naproxen 220 mg (N=118), or placebo (N=122). Efficacy measures included assessments of cognition (ADAS-Cog), clinical ratings (CDR), activities of daily living (ADCS-ADL), quality of life (AD Quality of Life scale [QOL-AD]), and neuropsychiatric symptoms (Neuropsychiatric Inventory [NPI]).

4.2 Results

The efficacy findings at Month 12 for rofecoxib versus placebo are summarized in Figure 2. There were no statistically significant differences between treatments. There were also no significant differences between naproxen and placebo (data not shown). It should be noted that the statistical comparison for the primary endpoint of the ADAS-Cog at Month 12 was adjusted for multiplicity because there were 2 primary comparisons (rofecoxib versus placebo and naproxen versus placebo); the unadjusted p-value for the comparison of rofecoxib versus placebo was 0.044. The rofecoxib ADAS-Cog score at Month 12 appeared to be an outlier relative to other time points (Aisen, personal communication). Some secondary analyses favored rofecoxib (trend toward slower decline on the ADCS-ADL, and longer time to institutionalization).

Figure 2

Month 12 Mean (95% CI) Treatment Differences in Changes From Baseline in the ADCS Trial



Note: The 95% CIs shown in this illustrative plot are created from data presented in the manuscript [2], and are without statistical adjustments for either multiplicity or baseline factors.

4.3 Conclusions

The results from the ADCS trial were generally in line with those from Protocol 091, indicating no consistent effect of rofecoxib on progression of AD.

5. Protocol 078

The primary findings from this study were presented at the 42nd annual meeting of the American College of Neuropsychopharmacology, December 7-11, 2003 [3] and have been accepted for publication [4].

5.1 Design

Protocol 078 was a randomized, multicenter, placebo-controlled, double-blind, 4-year ITT study to investigate the efficacy of rofecoxib 25 mg for delaying a diagnosis of AD in patients at least 65 years of age with MCI. These patients were expected to progress to AD at a rate of 15% per year. Patients were randomized to receive rofecoxib (N=725) or placebo (N=732). The primary endpoint was the number of patients in each treatment group who were diagnosed with possible or probable AD according to NINCDS-ADRDA criteria [5]. Investigator diagnoses confirmed as possible or probable AD by a blinded independent endpoint adjudication committee (EAC) were included in the analysis. The endpoint adjudication process is described in more detail in section 5.3.2 below. Other assessments consisted of cognitive test measures (ADAS-Cog, MMSE, Selective Reminding Test [SRT; a word recall test]), clinical ratings (CDR), and activities of daily living (Blessed Dementia Scale – Activities of Daily Living [BDS-ADL]).

The study was one of the first prevention trials to be initiated in an MCI population. The intention was to run the study until 220 diagnoses of AD had been made, which it was anticipated would take 2 years based on an expected conversion rate of 15% per year. The study was extended to 4 years due to lower than expected conversion rates and high discontinuation rates, and then terminated early after 189 confirmed diagnoses of AD had been made. The study was terminated early because the steadily decreasing accrual of endpoints made it likely that continuation until completion would have yielded little further useful information. Approximately 45% of the total number of randomized patients discontinued the study prematurely and 40% of the total number of randomized patients completed the study on-drug.

5.2 Results of Pre-specified Analyses

In the primary ITT analysis, the hazard ratio for conversion to possible or probable AD unexpectedly favored placebo (Figure 3). The difference was not further increased in an analysis restricted to the on-drug population (Figure 3). The estimated annual diagnosis rates were 6.4% in the rofecoxib group and 4.5% in the placebo group. The treatment difference was evident at the earliest evaluation (4 months) and was proportional over time. No differences between treatments were observed on other commonly measured endpoints in AD trials including assessments of cognition, clinical ratings, and activities of daily living (Figure 4).

Figure 3

Rofecoxib:Placebo Hazard Ratios (95% CI) for Diagnosis of AD

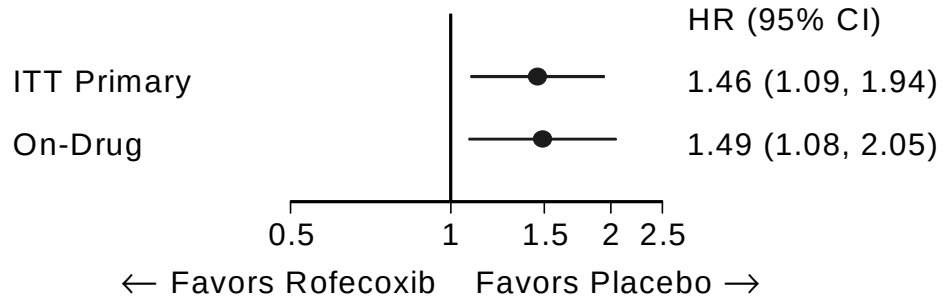
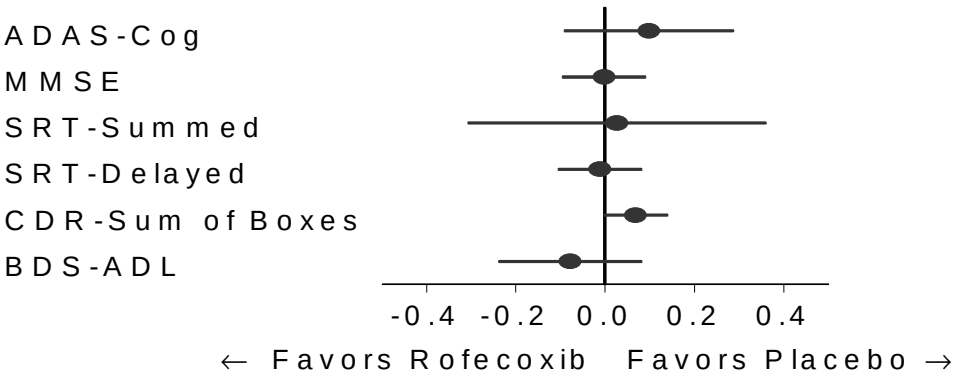


Figure 4

Comparison Between Rofecoxib and Placebo In Terms of Annual Slopes (95% CI) for Secondary Measures



5.3 Results of Post-hoc Analyses

In order to further explore the unexpected findings on the primary endpoint suggesting that rofecoxib might accelerate a diagnosis of AD, a number of post hoc analyses were conducted. The analyses addressed the following questions: 1) Was there any evidence for biases that may have influenced the results? 2) Was the treatment difference maintained in patients with the most certain AD diagnosis? 3) Was there any evidence that rofecoxib might have contributed to an AD diagnosis through cardiovascular effects? 4) Was there any evidence that rofecoxib might have been associated with non-specific cognitive effects that could have been misinterpreted as conversion to AD? 5) Could the findings be replicated in an independent dataset?

5.3.1 Potential Biases

5.3.1.1 Imbalances Between Groups

The observation that the separation between treatment groups in rates of AD diagnosis was apparent from 4 months (the earliest time point assessed) but did not increase over time, raised the possibility that there may have been an imbalance between the groups at baseline or which arose during the study. There was no evidence of a major imbalance for measured variables, including severity of impairment. To more fully investigate the possible contribution of baseline and post-randomization variables, an analysis was performed adjusting for factors which showed an effect, at a significance level of $p<0.10$, on progression to AD. Those factors correlated with greater likelihood of progression to AD were lower baseline MMSE score stratum (24-26), female gender, age >75, and prior ginkgo use. Factors associated with a decreased risk of progressing to AD were longer duration of concomitant NSAID use, and concomitant use of statins. In the analysis which adjusted for these factors, the statistical significance of the hazard ratio was reduced (1.31 [95% CI: 0.98, 1.75], $p = 0.065$). (Presence of the apolipoprotein ε4 allele was also a risk factor but was not included in the model because information was missing for a substantial proportion of patients.) This suggests that the treatment difference may have been partly due to imbalances between the groups.

5.3.1.2 Differential Discontinuations

As noted above, only 40% of the total number of randomized patients completed the study on-drug. The high drop-out rate complicates interpretation of the results and raises the potential that differential discontinuations may have influenced the results. No major imbalance was noted with regard to reasons for discontinuation, although the categories used to classify the reasons may have been too broad to be informative. For example "withdrew consent" was the largest single categorization, accounting for over half the discontinuations in each treatment group. The relatively large proportion who withdrew consent may have been partly due to the fact that patients were asked to sign a new consent form after 2 years (the original planned study duration) and were unwilling to extend their initial commitment. An analysis was performed to determine if the baseline characteristics of patients who discontinued differed by treatment group. The analysis included baseline efficacy measures, demographics, vital signs, laboratory measures, and

prior medications. Of those who discontinued, placebo patients had higher baseline ADAS-Cog scores, indicative of greater cognitive impairment and presumably greater risk of progression to AD, than patients randomized to rofecoxib (p=0.034 in a logistic regression model). In the subgroup of discontinued patients who had at least 1 on-treatment evaluation (about a third of discontinuers had no on-treatment evaluation), the change from baseline to last evaluation time point scores on the ADAS-Cog, MMSE, and CDR-sum of boxes were similar between the treatment groups (data not shown).

5.3.2 Effect of Type of AD Diagnosis

Cases of dementia (any cause) diagnosed by the investigator were adjudicated by a blinded EAC consisting of 3 experts who were sent copies of the patient's case report forms and medical records. Each expert reviewed the case independently and indicated whether the event was a confirmed event of AD (yes/no; if yes, whether possible AD or probable AD), non-AD dementia (yes/no), or non-dementia. The primary analysis included those events in which ≥2 of the adjudicators confirmed the diagnosis of AD as possible or probable according to NINCDS-ADRDA criteria [5]. Out of a total of 195 investigator-reported cases of dementia (190 possible or probable AD and 5 non-AD dementia), 189 were adjudicated as confirmed AD (the endpoint for the primary analysis). Of the 189 confirmed AD cases, 154 were adjudicated as probable AD (≥2 adjudicators classified as probable AD), 25 were adjudicated as possible AD (≥2 adjudicators classified as possible AD), and in the remaining 10 there was a split judgment (1 adjudicator classified as probable AD, 1 adjudicator classified as possible AD, and 1 adjudicator classified as either non-AD dementia or non-dementia). Of these adjudicated diagnoses, probable AD represents the most certain diagnostic category; the FDA had requested an analysis restricted to patients with probable AD in the Protocol 091 treatment trial of patients with possible or probable AD. Analyses of the Protocol 078 data were therefore performed to see if the treatment difference was maintained or enhanced in those patients with the most certain diagnosis.

In the analysis of the 154 patients with adjudicated probable AD, the rofecoxib:placebo hazard ratio was reduced in the primary ITT model (1.20 [95% CI: 0.88, 1.65], p=0.256). In the analysis of the remaining 35 patients (those with either adjudicated possible AD or a split judgment), the hazard ratio was increased in the primary ITT model (3.84 [95% CI: 1.74, 8.45], p=0.001). One key distinction between probable AD and possible AD is presence of a confounding factor in the case of a possible AD diagnosis [5]. An attempt was made to determine the reasons for the latter 35 events being adjudicated as non-probable AD, based on the adjudicator's written comments. Since multiple reasons were often given within and between adjudicators for their diagnosis, the approach taken was that a neurologist reviewed the comments and made an overall judgment as to what appeared to be the primary confounding reason for the less certain AD diagnosis. Based on this approach, the primary reasons were: non-AD dementia (e.g., Lewy body dementia) - 9 cases; little evidence of disease progression - 8 cases; depression - 7 cases; cardiovascular disease - 7 cases; other (e.g. delirium) - 4 cases. In order to more objectively assess the possibility that cardiovascular factors might have been a major determinant of the non-probable diagnoses, the number of events in which ≥2 adjudicators made any mention of cardiovascular factors in their comments was

determined. This included any mention of stroke or infarct on the CT/MRI brain scan performed at the time of diagnosis, but excluded mention of non-specific generalized white matter abnormalities. This approach may have been over-inclusive by counting non-clinically-relevant lesions and static pre-existing lesions (it should be noted than brain scans were not performed at baseline). To ensure an all-inclusive analysis, the analyzed dataset also included 2 cases adjudicated to be non-AD dementia, and 2 cases with a split AD/non-AD dementia/non-dementia EAC judgment, in addition to the above 35 patients. Using this approach, the comments for 12 of the 39 non-probable-AD diagnoses included any mention of cardiovascular factors by ≥2 adjudicators. In both evaluations, therefore, cardiovascular factors did not appear to be the primary determinant of the majority of non-probable-AD diagnoses.

In summary, the results from this exploratory analysis indicated that the finding on the primary endpoint was not confirmed in the 154 patients who had the most certain AD diagnosis. The treatment difference appeared to be increased in the remaining 35 patients with a less certain AD diagnosis, but the interpretation of this finding is unclear.

5.3.3 Cardiovascular Effects and AD Diagnosis

5.3.3.1 Relation of AD Diagnosis to Blood Pressure Changes

Rofecoxib and other NSAIDs can cause small mean increases in blood pressure, and there is some evidence in the literature to suggest that increased blood pressure might be associated with an increased risk of dementia. We therefore performed three post hoc analyses to evaluate whether the rofecoxib:placebo risk ratio for diagnosis of AD increased as a function of increased blood pressure change. In the first analysis, change from baseline in mean arterial blood pressure at month 4 was calculated for each patient. The rofecoxib:placebo odds ratios for diagnosis of AD were then calculated for 3 categories of patients: those with no change or a decrease (odds ratio = 1.43), those with an increase ≤5 mm Hg (odds ratio = 1.18), and those with an increase >5 mm Hg (odds ratio = 1.47). The test of homogeneity of the odds ratios across categories indicated no statistically significant differences (p=0.895). The second analysis looked at a predefined limit of change in systolic blood pressure, which was prespecified as a postrandomization value that was ≥180 mm Hg and showed a ≥20 mm Hg increase from baseline. The rofecoxib:placebo hazard ratios for diagnosis of AD were similar in those patients who did not meet the predefined limit of change criteria at any time point during the study (hazard ratio = 1.42 [95% CI: 1.06, 1.92]), compared with those who did meet the criteria (hazard ratio = 1.53 [95% CI: 0.49, 4.81]). In the third analysis, mean arterial blood pressure at all time points in the study was included as a time-varying covariate in the primary model. Mean arterial blood pressure had no effect on conversion to AD in the overall population (hazard ratio = 0.99, [95% CI: 0.98, 1.01], p=0.398) and did not modify the treatment hazard ratio (1.47) compared to the estimate found in the primary analysis (1.46).

5.3.3.2 Relation of AD Diagnosis to Cardiovascular Risk Factor Status

An analysis was performed to examine whether patients at higher cardiovascular risk were more likely to receive an AD diagnosis, and whether cardiovascular risk status modified the treatment hazard ratio. The definition of higher cardiovascular risk was the

same as that used throughout the rofecoxib program. The higher risk subgroup was defined as those with either ≥2 major risk factors for coronary artery disease (current smoker, history of hypertension, history of diabetes, history of hypercholesterolemia) or with a prior history of a cardiovascular thrombotic event. When cardiovascular risk category (higher or lower risk) was included as a covariate in the primary model, it had no statistically significant effect on conversion to AD in the overall population (hazard ratio = 1.13, [95% CI: 0.81, 1.56], p=0.458) and did not modify the treatment hazard ratio (1.46) compared to the estimate found in the primary analysis (1.46).

5.3.4 Non-specific Cognitive Effects and AD Diagnosis

NSAIDs have been reported to have central nervous system (CNS) side effects such as decreased mental acuity and somnolence. These have a low reported incidence but it is conceivable that they might have a disproportionate effect in elderly individuals who are already cognitively compromised, potentially leading to a misdiagnosis of dementia. In order to assess this possibility, the percentages of patients with CNS adverse events were examined. There did not appear to be a clear increase in the percentages of patients with these types of events: % with ≥1 CNS adverse experience = 36.5% for rofecoxib and 38.0% for placebo; % with ≥1 psychiatric adverse event = 21.7% for rofecoxib and 19.4% for placebo; % with somnolence = 2.4% for rofecoxib and 1.6% for placebo; % with confusional state = 2.1% for rofecoxib and 1.4% for placebo. Since it might be difficult to detect a signal of CNS-type adverse experiences in patients who are already cognitively compromised, the assessment was repeated using pooled data for patients aged ≥65 years from non-AD rofecoxib trials (these were typically of much shorter duration than the AD trials). The analysis included 2165 patients on rofecoxib and 967 patients on placebo. As in Protocol 078, there did not appear to be a clear increase in the percentages of patients with CNS adverse events in this pooled dataset: % with at ≥1 CNS adverse experience = 12.3% for rofecoxib and 12.2% for placebo; % with ≥1 psychiatric adverse event = 1.8% for rofecoxib and 1.3% for placebo; % with somnolence = 0.6% for rofecoxib and 0.1% for placebo; % with memory impairment = 0.1% for rofecoxib and 0% for placebo; % with decreased mental acuity = 0.2% for rofecoxib and 0.1% for placebo.

Another approach to investigate this possibility involved examination of cognitive test scores over time in Protocol 078 to see if there was any evidence for an early treatment difference which might be indicative of an acute non-specific cognitive effect of rofecoxib. There was no evidence for an early treatment difference on the MMSE or SRT, those tests which were administered every 4 months (data not shown). As a final approach, cognitive test scores in patients from Protocol 091 who received rofecoxib for 12 months and were then switched to placebo (in a blinded fashion) for an additional 3 months were examined to see if there was any evidence of a “rebound” effect following rofecoxib discontinuation. There was no evidence that cognitive test scores improved on discontinuation of rofecoxib (data not shown).

In summary, the above analyses provided no definitive evidence that non-specific cognitive effects might have contributed to the AD diagnosis, but are insufficient to exclude the possibility.

5.3.5 Replication in an Independent Dataset

Ideally, one would like to compare the results from Protocol 078 with results from a similar study to see if the findings were replicated. In this case, there was no other study of rofecoxib in MCI. However, there were subgroups of patients in Protocols 078 and 091 who had overlapping MMSE scores of 24-26 (approximately a third of patients in each study), indicating broadly similar levels of cognitive function despite the difference in diagnosis. Comparison of these overlapping subgroups was used as the closest approximation available to an independent replication. There was no evidence to suggest differences between treatments on assessments of cognition (ADAS-Cog) in the MMSE 24-26 subgroup in either study (data not shown). In the subgroup analysis from Protocol 078, there was a nominally significant difference between treatments for the CDR-sum of boxes score in favor of placebo (annual slope difference = -0.18 [95% CI: -0.35, -0.01], p=0.039). This finding was not surprising given that the global score on the CDR was the trigger for diagnosing AD. There was no difference between rofecoxib and placebo on the CDR sum-of-boxes score in the subgroup analysis from Protocol 091 (annual slope difference = -0.05 [95% CI: -0.56, 0.45], p=0.837). Thus, there was no evidence of a detrimental effect of rofecoxib in the most directly comparable group of patients available.

5.4 Conclusions

Interpretation of results on the primary endpoint in Protocol 078 is difficult for a number of reasons. Firstly, the results were internally inconsistent; the primary endpoint suggested that rofecoxib might accelerate the rate of conversion from MCI to AD, but rofecoxib did not differ from placebo on secondary endpoints including assessments of cognition, global function, and activities of daily living. Secondly, the results need to be interpreted against the backdrop of high discontinuation rates and lower than expected AD diagnosis rates. There was some evidence that differential discontinuations, as well as imbalances between treatment groups, may have influenced the results.

A number of observations argue against rofecoxib having an effect on the underlying pathophysiology of AD. These include the early onset of the treatment difference and constant hazard rates over time, the reduction in the size of the treatment hazard ratio in patients with the most certain AD diagnosis, and the absence of any treatment effect in the subgroup of patients with overlapping MMSE scores in Protocol 091 (the most directly comparable group of patients available). Alternative hypotheses are that rofecoxib might have indirectly led to an AD diagnosis through cardiovascular effects, or that non-specific cognitive effects of rofecoxib might have resulted in an AD (mis) diagnosis. There was no support for the former hypothesis in a relatively extensive set of exploratory analyses. The more limited exploratory analyses designed to investigate the latter hypothesis provided no definitive evidence that non-specific cognitive effects might have contributed to the AD diagnosis, but are insufficient to exclude the possibility.

In summary, it is difficult to draw any definitive conclusions from Protocol 078. The possibility that rofecoxib could accelerate a diagnosis of AD in MCI patients cannot be totally discounted. For the reasons noted above, it seems unlikely that any treatment difference reflects an effect of rofecoxib on the underlying pathophysiology of AD.

References

1 Reines SA, Block GA, Morris JC, Liu G, Nessly ML, Lines CR, et al. Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. Neurology 2004;62:66-71.

2 Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, et al. Effects of rofecoxib or naproxen vs placebo on alzheimer disease progression: a randomized controlled trial. JAMA 2003;289(21):2819-26.

3 Visser H, Thal L, Ferris S, Kirby L, Yuen E, Assaid C, et al. A randomized, double-blind, placebo-controlled study of rofecoxib in patients with mild cognitive impairment [abstract]. 42nd Annual Meeting of the American College of Neuropsychopharmacology; 2003 Dec 7-11. San Juan, Puerto Rico, 2003.

4 Thal LJ, Ferris SH, Kirby L, Block GA, Lines CR, Yuen E, et al. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. Neuropsychopharmacology 2005, in press.

5 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939-44.