Statistical Reviewer Briefing Document for the Advisory Committee

NDA#	**21-042 s-007**
Name of Drug:	Rofecoxib
Applicant:	Merck Research Laboratories
Indication:	Gastrointestinal (GI) Safety Label Change
Documents Reviewed:	Statistical section submitted in June 29, 2000
Medical Reviewer:	Maria Lourdes Villalba, MD
Statistical Reviewer:	Qian Li, Sc.D.
Period of Review:	June-December 2000

I. Introduction:

Rofecoxib was originally submitted as an NDA in November 1998 and approved by the Agency in May 1999 for the relief of sign and symptom of osteo-arthritis (OA) and for the management of acute pain and dysmenorrhea. The current approved maximum dose was 25 mg daily for OA and 50 mg daily for acute pain. The purpose of this supplemental NDA submission was to provide evidence for label revision to remove gastrointestinal (GI) warning section for rofecoxib. A GI outcome study (Protocols 088/089) named VIGOR (Vioxx Gastrointestinal Outcomes Research study) was conducted to support the GI safety claim. The VIGOR trial was a double-blind, randomized, stratified, parallel-group study to compare the occurrence of PUBs (gastroduodenal perforations, gastroduodenal ulcers, or upper gastrointestinal bleeds) between rofecoxib 50 mg daily or naproxen 1000mg per day during chronic treatment for patients with rheumatoid arthritis (RA). This study was divided into two protocols, Protocols 088 and 089. Protocol 088 was a U.S cohort and Protocol 089 an international cohort.

During the VIGOR trial, many serious cardiovascular events were observed. To address the issue of serious cardiovascular events, the sponsor organized a special section in the VIGOR study report to discuss analyses on thrombotic cardiovascular serious adverse events. In addition, clinical trial reports from Protocols 085 and 090, designed to compare the safety and efficacy of rofecoxib 12.5 mg daily vs. nebumetone 1000 mg per day in patients with OA, as well as a 6-week geriatric study (Protocol 58), were submitted to support concomitant use of low-dose aspirin with rofecoxib for cardio-protection.

In this statistical review, analyses on GI safety profile and cardiovascular events between rofecoxib 50 mg daily and naproxen 1000 mg per day treatment groups were reviewed based on the results of the VIGOR study. This statistical review did not cover these additional studies that allowed concomitant use of aspirin for cardiovascular evaluations, as they were short term and low dose studies, and not powered to evaluate the GI and cardiovascular safety of the combination use of rofecoxib and aspirin.

II. Study Design and Statistical Methodology:

The primary object of the VIGOR study was to determine the relative risk of confirmed PUBs in patients with RA taking rofecoxib 50 mg daily compared to patients taking naproxen 1000 mg/day. Patients of age 40 or older, with rheumatoid arthritis which required treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) therapy for at least 1 year were recruited to the studies. Patients who met entry criteria of the study were randomized to rofecoxib, 50 mg daily, or naproxen 500 mg twice daily. Patient allocation was stratified with a prior history of peptic ulcer, upper GI bleeding or perforation versus those who had no prior history. Clinic visits were scheduled at screening, randomization, weeks 6, 17, 35, 52, and every 4 months thereafter until the termination of the study. At the termination, patients were called in for an end-of-study visit and patients were asked to remain off NSAIDs for 14 days. The study was planned to stop when at least 120 confirmed PUBs and a minimum of 40 confirmed complicated PUBs were observed in the study, and minimum duration of treatment was 6 month for the last randomized patient, which ever came last.

The original protocol was designed to stop the trial when 95 confirmed PUBs were observed. In respond to the FDA's emphasis on confirmed complicated PUBs, the VIGOR protocol was amended to observe a minimum of 40 confirmed complicated cases as an additional condition before stopping the trial. During the trial, it was found that only 25-30% of the confirmed cases were complicated. In order to achieve this requirement to observe a minimum of 40 confirmed complicated cases, it was necessary to increase the total confirmed PUBs from 95 to 120. Since the sample size change was not due to the interim result of primary end point, penalty on alpha level was not necessary.

Reviewer's comment on study design:

Rofecoxib has not been approved for rheumatoid arthritis patients. Since RA and OA are two different disease populations, the efficacy effect of rofecoxib is expected be different for the two patient populations. It was not clear if the two patient populations would share the same GI safety profile.

The dosage of rofecoxib used in RA patients in this VIGOR trial was twice of the maximum approved chronic dose for OA patients. It was unavailable at present what would be the effective dose for RA if rofecoxib would be approved for this indication. Therefore, it is too early to conclude what was observed in this VIGOR study represented the worst scenario of rofecoxib in actual use.

Different NSAIDs had different GI safety profile. Therefore using naproxen alone as a NSAID representative may not be appropriate for a claim against a class of drug. However, if there was evidence to show that naproxen was the mildest in GI toxicity in the whole NSAID class, it would be appropriate for rofecoxib to gain the claim against

the class of NSAIDs. However, naproxen has not been shown that it was the mildest among the NSAIDs in GI toxicity.

1. Analysis populations:

Two analysis populations were defined in this study. They were:

All-patient-randomized (APR): the population included all the randomized patients.

Per-protocol population excluded patients who were identified as substantive protocol violation. Substantive protocol violators were defined based on a set of pre-specified criteria.

2. PUBs evaluation:

At each study visit, patients were asked questions concerning the occurrence of PUBs. Suspicious of possible study end point prompted the retrieval of additional information and source documents. Between visits including phone visit, the patients were encouraged to call the study site if a PUB, GI work-up, or other serious adverse experience were occurred. The patients were asked to provide permission to obtain medical records and copies of endoscopy or radiographic reports. An initial end point report form was completed and submitted to an External Coordinating Center. Classification of PUBs was adjudicated by an independent End Point Classification Committee (See medical officer's review for classification).

Primary endpoints:

The primary study end point was defined to be confirmed PUBs by the sponsor. However, the agency placed more emphasis on confirmed and complicated PUBs. The sponsor used this endpoint as a secondary endpoint.

Secondary GI variables specified by the sponsor:

(1) Confirmed and complicated PUBs.
(2) Confirmed and unconfirmed PUBs.
(3) Confirmed and unconfirmed complicated PUBs.
(4) GI related adverse experience.
(5) Any GI bleeding.

3. Other safety evaluations:

Pre-specified safety analyses:

Other than routine safety analyses on adverse events, vital sign and laboratory parameters were tabulated. In addition to the routine safety analyses, the protocol and data analysis plan also specified the following safety parameters for detailed statistical analyses.

(1) Serious clinical adverse experiences (overall)
(2) Drug-related (possibly, probably, definitely) clinical adverse experiences (overall)
(3) Clinical adverse experiences leading to study discontinuation (overall)
(4) Discontinuations due to digestive adverse experiences including abdominal pain
(5) Discontinuations due to edema-related adverse experiences
(6) Discontinuations due to hypertension-related adverse experiences
(7) Discontinuations due to renal-related adverse experiences (clinical and/or laboratory adverse experiences)
(8) Discontinuations due to hepatic-related adverse experiences (clinical and/or laboratory adverse experiences)
(9) Congestive heart failure adverse experiences
(10) Serious laboratory adverse experiences (overall)
(11) Drug-related (possibly, probably, definitely) laboratory adverse experiences (overall)
(12) Laboratory adverse experiences leading to study discontinuation (overall).

Serious cardiovascular adverse events:

In this study, investigator identified cardiovascular events were adjudicated according to Cardiovascular Adjudication Standard Operation Procedures. The primary analysis of the events focused on confirmed thrombotic cardiovascular serious adverse events.

4. Efficacy evaluation:

Rofecoxib has not been approved for the indication of rheumatoid arthritis. Efficacy evaluation in this VIGOR study was not sufficient, as the study design was not oriented to the efficacy evaluation. Nevertheless, the following efficacy endpoints were assessed in this trial:
(1) Patient global assessment of disease activity: a patient global assessment of disease activity on a 5-point Likert scale was administrated at Visit 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 9.0, end-of-study, and discontinuation. The scale is 0=very well, 1=well, 2=fair, 3=poor, 4=very poor.
(2) Investigator global assessment of disease activity: using the same 5-point likert scale as patient global assessment of disease activity.
(3) Discontinuation due to lack of efficacy.
(4) Modified health assessment questionnaire on dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities and recorded at visit 2.0, 3.0, and end-of-study.

5. Statistical Analyses:

The primary GI endpoint, pre-specified safety analysis and serious cardiovascular adverse events were analyzed based on the APR population.

For the primary end point of confirmed PUBs, Cox proportional hazard model was used to compare the relative risk between the two treatment groups. Covariates included in this model were treatment group indicator and stratum of prior history of PUBs.

For other time-to-event end points including various types of PUBs, discontinuations due to lack of efficacy, the pre-specified safety analyses variables, and cardiovascular serious adverse events, similar survival analyses were used to evaluate time to the first event during the study period. Patient's and investigator's global assessments, as well as modified HAQ (US only) were analyzed as the average change from baseline over the treatment period using an analysis of co-variance (ANCOVA) model with factors of treatment, study center, stratum, and baseline value as covariates.

One interim analysis was planned when 60 confirmed PUBs was observed, which was half information time of the total 120 confirmed PUBs. A group sequential stopping rule was used to control the overall type I error rate at 0.05. The corresponding two sided stopping boundaries were 2.753 (α_1=0.0059) and 1.982 (α_2=0.0475) based on an O'brain-Fleming type of α-spending function $\alpha(-4,t)$.

Subgroup analyses:

Prior history of a PUB (yes/no), age (<65 years/≥65 years), gender, race (caucasian/other), study region (U.S./non-U.S.), use of systemic corticosteroids at baseline and H. pylori status at baseline (positive/negative requested by the agency) were evaluated to determine whether or not the effect of rofecoxib compared to naproxen was consistent in the subgroups. For each subgroup variable listed above, a Cox regression model was used for the primary end point and included the treatment, subgroup, and treatment-by-subgroup interaction.

III. Study Results

Three hundred and one sites from United States and other nations screened 9539 patients. Eight thousand and seventy-six patients were enrolled between Jan 14,1999 to March 17, 2000. The median duration of time in the study was 9.0 months ranged from 0.5 month to 13 months. Four thousand and forty-seven patients were randomized to receive rofecoxib, 4029 were randomized to naproxen treatment group. A total of 151 patients were excluded from the per-protocol analysis (73 and 78 patients in the rofecoxib and naproxen treatment groups, respectively).

One thousand and one hundred thirty-one and 1032 patients in the rofecoxib and naproxen groups, respectively, discontinued the study for any reason other than the primary endpoint. The rates of discontinuation were 42.6 and 38.9 per 100 patients years for rofecoxib and naproxen, respectively. The relative risk for rofecoxib vs. naproxen was 1.10 (95% CI: 1.01, 1.19;

p=0.033). This showed rofecoxib treatment group had statistically significantly more patients discontinued study than that in naproxen group for reasons other than the primary endpoint.

Thirty-seven deaths occurred in the VIGOR trial, 22 (0.5%) and 15 (0.4%) in the rofecoxib and naproxen groups, respectively.

Demographic information and baseline disease assessments of RA showed reasonable balances between treatment groups.

Reviewer's comment on discontinuations:

As the withdrawal rate was about 30% in the VIGOR study and there were only about 2% patients developed the GI end point, it was a concern if the relatively high withdrawal rate (compared PUB event rate) could introduce potential bias in analysis results. Patients discontinued the study for reasons other than the study end point formed censoring for the end point PUBs. Some of the censoring such as withdrawal due to patients moved, lost to follow-up and lack of efficacy were unlikely to be informative censoring to PUBs, therefore were not the source of bias. Protocol deviation and withdrew consent can be non-informative censoring if the reason of protocol deviation and the decision of withdrawal consent had nothing to do with the study end point (need further confirmation!!! Waiting for information from the sponsor). Some of those who discontinued the study due to clinical and laboratory adverse events, especially those who discontinued due to GI related adverse events, might be informative censoring to PUBs if the adverse events were the pre-cursor of PUB. In this case, bias could occur. In the VIGOR study, there were 370 (9.2%) patients discontinued study due to adverse reaction in digestive system in naproxen treatment group and 267(6.6%) in rofecoxib group. If the bias exists, the risk of developing PUBs in naproxen treatment group could be under estimated. However, the association of the GI related adverse events to the study end point PUBs was not well understood to medical experts. Therefore, it was difficult to assess any potential bias possibly caused by discontinuation due to GI related adverse events. If the withdrawal mechanism is exactly the same in practice as that was in the VIGOR trial, there was no need to worry about the bias even such a bias exists. However, if the withdrawal pattern is different, we may observe different risks of PUBs in post-marketing data.

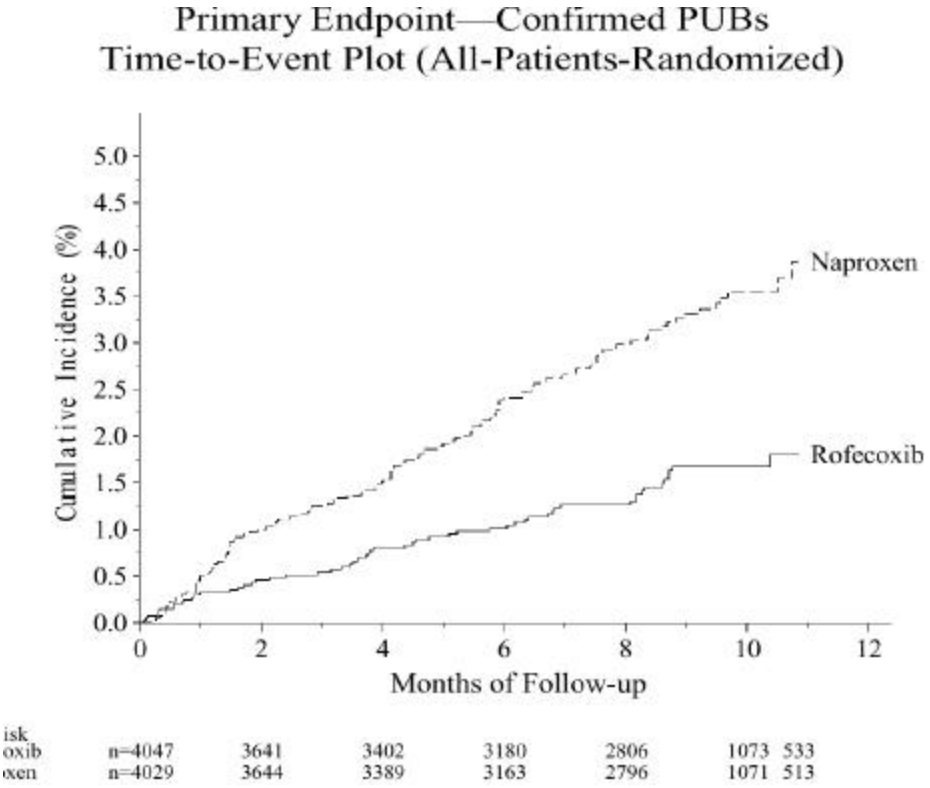
1. GI events:

Sponsor's results of primary endpoint at the end of the study:

A total of 208 patients with potential PUB events were adjudicated. Sixteen events that occurred more than 14 days after discontinuation of study therapy were excluded from the primary analysis. Of the 16 events, six occurred in rofecoxib group and 10 in naproxen group. One hundred and ninety-one patients with PUBs were eligible for the primary analyses: 177

patients had confirmed events, 13 were unconfirmed and 1 was classified as "not an upper GI event". Of the 177 PUB events, 56 occurred in rofecoxib treatment group and 121 in naproxen group. Based on Cox model with a stratification factor (prior history of PUBs) as a covariate, the relative risk of developing confirmed GI PUBs for rofecoxib treatment group vs. naproxen treatment group was 0.46 with 95% CI (0.33, 0.64) and p-value <0.001 (see Table 2). Figure 1 showed the time to event plot for the confirmed PUBs of the two treatment groups.

In the per-protocol analysis, 48 rofecoxib patients and 113 naproxen patients experienced 1 or more confirmed PUBs with rates of 1.80 and 4.25, respectively, per 100 patient-years at risk. The relative risk based on the Cox model was 0.42 (95% CI: 0.30 to 0.59); p<0.001. These results were consistent with the primary analysis.



Sponsor's interim analysis:

Interim analysis was conducted when 66 confirmed PUBs were observed, 20 from rofecoxib treatment group and 46 from the naproxen group. The risk ratio of developing confirmed PUBs for rofecoxib vs. naproxen was 0.44 with p-value 0.002 and 95%CI (0.26, 0.74). The results of interim analysis were consistent with the final result.

Sponsor's secondary GI endpoints at the end of study:

There were 16 rofecoxib patients and 37 naproxen patients that experienced 1 or more confirmed, complicated PUBs with rates of 0.59 and 1.37, respectively, per 100 patient-years at risk. The relative risk from the Cox model stratified by prior history of PUBs was 0.43 (95% CI: 0.24 to 0.78) and p=0.005.

There were 58 rofecoxib patients and 132 naproxen patients that experienced 1 or more confirmed and unconfirmed PUBs with rates of 2.15 and 4.90, respectively, per 100 patient-years at risk. The relative risk from the Cox model stratified by prior history of PUBs and study region was 0.44 (95% CI: 0.32 to 0.60) and p<0.001.

There were 17 rofecoxib patients and 42 naproxen patients that experienced 1 or more confirmed and unconfirmed complicated PUBs with rates of 0.63 and 1.56, respectively, per 100 patient-years at risk. The relative risk from the Cox model stratified by prior history of PUBs was 0.40 (95% CI: 0.23 to 0.71) and p=0.002.

Thirty-one rofecoxib patients and 82 naproxen patients experienced 1 or more GI bleeds with rates of 1.15 and 3.04, respectively, per 100 patient-years at risk. The relative risk from the Cox model stratified by prior history of PUBs was 0.38 (95% CI: 0.25 to 0.57) and p<0.001.

Table 2: Sponsor's analyses on GI end points at the end of study.

Endpoint	Treatment	N	Events	Rates	Relative Risk		
					Estimate	95%CI	p-value
Primary-Confirmed PUBs	rofecoxib naproxen	4047 4029	56 121	2.08 4.49	0.46	(0.33, 0.64)	<0.001
Secondary Endpoints							
Confirmed, complicated PUBs	rofecoxib naproxen	4047 4029	16 37	0.59 1.37	0.43	(0.24, 0.78)	0.005
Comfirmed and unconfirmed PUBs	rofecoxib naproxen	4047 4029	58 132	2.15 4.90	0.44	(0.32,0.60)	<0.001
Confirmed & unconfirmed complicated PUBs	rofecoxib naproxen	4047 4029	17 42	0.63 1.56	0.40	(0.23, 0.71)	0.002
Any GI bleeds	rofecoxib naproxen	4047 4029	31 82	1.15 3.04	0.38	(0.25, 0.57)	<0.001

Subgroup analyses:

In addition to the subgroup analyses specified in DAP, the agency requested some additional subgroup analyses including prior cardiovascular history and baseline NSAID usage on confirmed PUBs, as well as study region effects on confirmed complicated PUBs.

Table 3 listed some of the results from those subgroup analyses that either had statistically significant subgroup effects at level 0.05 or statistically significant subgroup by treatment interactions at level 0.10. P_values for subgroup effects were added by the reviewer.

Table 3: Results of subgroup analyses.

Subgroups:	Treatment	N	Events	Rates	Relative Risk	
					Estimate	95%CI
Prior history of PUBs: p-value for prior history=0.0001, for interaction=0.874						
Prior history of PUBs:	rofecoxib	314	13	6.72	0.44	(0.23, 0.85)
	naproxen	316	29	15.33		
No prior history of PUBs	rofecoxib	3733	43	1.72	0.47	(0.33, 0.67)
	naproxen	3713	92	3.67		
Age: p-values for age=0.0001 , for interaction=0.466						
Non-elderly (<65 years)	rofecoxib	3050	34	1.64	0.52	(0.34, 079)
	naproxen	2959	64	3.15		
Elderly (≥65 years)	rofecoxib	997	22	3.54	0.41	(0.25, 0.67)
	naproxen	1070	57	8.63		
Baseline steroid use: p-values for baseline steroid use=0.0012 , for interaction=0.073						
No baseline steroid use	rofecoxib	1803	24	2.03	0.68	(0.41, 1.15)
	naproxen	1776	35	2.97		
Baseline steroid use	rofecoxib	2244	32	2.11	0.37	(0.25, 0.56)
	naproxen	2253	86	5.67		
H. Pylori: p-values for H.Pylori=0.8800, for interaction=0.043						
Negative H. Pylori	rofecoxib	2244	21	1.43	0.32	(0.19, 0.52)
	naproxen	2260	67	4.51		
Positive H. Pylori	rofecoxib	1740	34	2.87	0.62	(0.40, 0.95)
	naproxen	1712	54	4.62		
Baseline NSAIDs use: p-values for NSAIDs use=0.0011, for interaction=0.645						
No baseline NSAIDs use	rofecoxib	703	14	3.07	0.41	(0.22, 0.76)
	naproxen	688	33	7.59		
Baseline NSAIDs use	rofecoxib	3344	42	1.87	0.48	(0.33, 0.69)
	naproxen	3341	88	3.89		

Reviewer's comment on subgroup analyses:

Subgroup analysis based on prior history of PUBs (yes or no) suggested that there were statistically significantly (p-value=0.0001) increased risk of developing in the subgroup that prior history of PUBs existed compared to the subgroup that had no prior history of PUBs. However, the risk ratios between the two treatment groups were similar in both subgroups. Similar observations were found in subgroups based on baseline NSAIDs use or age groups (<65 years old or ³65 years old).

It made sense that patients with prior history of PUBs or older than 65 years old had higher risk for PUBs, no matter which treatment patients were receiving. However, it

was not clear why the patients who were not NSIADs users at baseline also had relatively higher risk compared with patients who were NSAIDs user at baseline. Even the non-NSAIDs users at baseline who received rofecoxib had risk of PUBs similar to naproxen patients who were NSAIDs user at baseline. One possible reason could be that some of the patients who were not NSAIDs users at baseline might be those who could not tolerate NSAIDs before and at high risk of PUBs.

Statistically significant (p-value=0.073) treatment by baseline steroid use interaction was observed. This was due to the increased risk of developing PUBs in naproxen treatment group in the subgroup that had baseline steroid use. Similarly, statistically significant treatment by baseline H. pylori status interaction was observed (p-value=0.043). This interaction was due to the increased risk of PUBs in rofecoxib treatment group in H. pylori positive subgroup.

Since statistically significant subgroup effects were observed in age groups (<65 years old or ³65 years old), prior history of PUBs, baseline NSAIDs use and baseline steroid use, a proportional hazard model including all the factors as covariates was used to analyze the primary end point. The result of this analysis was similar to the primary analysis with only the stratification factor as the covariate. The treatment difference in risks of developing PUBs observed in this study was very robust.

Reviewer's comments on Study 69 and generalization of the VIGOR results:

Study 69 was submitted in the original rofecoxib NDA to support the claim of GI safety of rofecoxib and was mentioned in this supplemental NDA submission to support the GI sfety claim of rofecoxib. It was of interesting to compare the results between Study 69 and the VIGOR trial.

Study 69 consisted of about 8 phase II/III trials that were different in doses of rofecoxib, study duration, population and NSAID comparators. There were three 6-week studies, two 6-month studies and three studies lasted over one year. The dose ranges of rofecoxib were from 12.5 mg to 50 mg. The NSAIDs comparators used in these trials included nabumetone, ibuprofen, and diclofenac. The observed cumulative incidence rates of PUBs were 1.50 and 2.68 per 100 patient years in combined rofecoxib group and combined NSAIDs group, respectively. Data suggested the occurrences of PUBs in rofecoxib treatment groups were dose dependent and NSAIDs behaved differently in GI reaction. Therefore what we have observed may change if the proportions of different dose levels of rofecoxib were changed. Similar to combined NSAIDs group, if different NSAIDs were used, what we observed may change as well. The duration of the two studies that had 50 mg rofecxib daily was 6 month. The studies lasted a year were rofecoxib 12.5 and 25 mg. The sponsor insisted that survival analysis could take care of problems due to different study duration. This was not true because rofecoxib 50 mg daily carried different risks that rofecoxib 12.5 and 25 mg did. Therefore what we

observed in Study 69 depended on the length of the trials, as well as the proportions of patients in different dose levels of rofecoxib and different NSAIDs. The results obtained in this study can not be interpreted.

If we kept in mind the problems of Study 69 and compare the results with that from the VIGOR trial, it can be seen that the risks for developing PUBs were quite different in either rofecoxib treatment groups or NSAIDs groups between the two studies. One reason to explain the differences could be the difference in study populations, OA patients in Study 69 and RA patients in the VIGOR trial. Another reason, which might be the most important reason, was that the doses of rofecoxib and NSAID comparator were different. This strongly suggested that the occurrence of PUBs was dose dependent in rofecoxib treatment, and the risks for developing PUBs may be different for different NSAIDs. Comparing the risk of rofecoxib 50 mg daily in the VIGOR trial and the risk of combined NSAIDs in Study 69, it can be seen that there were similar risks of PUBs in the two groups (2.08 for rofecoxib in the VIGOR trial and 2.68 for the combined NSAIDs group from Study 69). This suggested that some NSAIDs could have similar risk for PUBs as rofecoxib 50 mg daily. Although future confirmation was needed for the observations, there was no evidence from Study 69 that could lead to the generalization of the results in the VIGOR trial.

2. Safety analysis:

Pre-specified safety variables:

Survival analysis using Cox proportional hazard model with treatment as the covariate was used to analyze the pre-specified adverse experiences. Results that were statistically significant at level 0.1 were listed in Table 4.

Table 4: Results of pre-specified safety analyses.

Type of Adverse Experience	Treatment	N	Events	Rates	Relative Risk		
					Estimate	95%CI	p-value
Serious clinical AEs	rofecoxib	4047	378	14.48	1.21	(1.04,1.40)	0.013
	naproxen	4029	315	11.97			
Discontinued due to GI AEs + abdominal pain	rofecoxib	4047	307	11.47	0.73	(0.63, 0.85)	<0.001
	naproxen	4029	416	15.62			
Discontinued due to edema-related AEs	rofecoxib	4047	25	0.93	1.92	(0.98,3.75)	0.057
	naproxen	4029	13	0.48			
Discontinued due to hypertension-related AEs	rofecoxib	4047	28	1.04	4.67	(1.93, 11.28)	<0.001
	naproxen	4029	6	0.22			
Discontinued due to hepatic disease AEs	rofecoxib	4047	10	0.37	3.33	(0.92, 12.11)	0.067
	naproxen	4029	3	0.11			
CHF AEs	rofecoxib	4047	19	0.70	2.11	(0.96, 4.67)	0.065
	naproxen	4029	9	0.33			
Lab AEs leading to	rofecoxib	4047	22	0.82	1.83	(0.91, 3.71)	0.091

discontinuation	naproxen	4029	12	0.44			

Reviewer's comment on safety analyses:

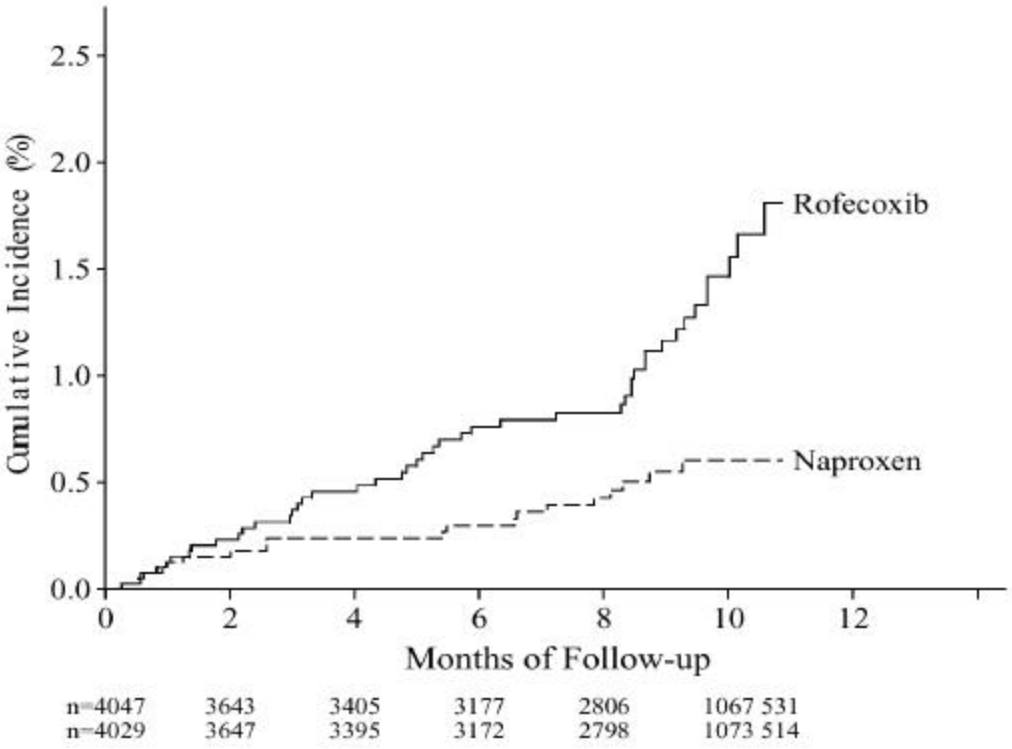
Most clinical trials were not powered to detect safety differences among treatments. It is important to identify those treatment differences so that a comprehensive understanding to treatment procedures could be obtained. Statistically, the p-values were used to identify all the possible safety differences rather than make decisions. Therefore, instead of adjusting multiple tests, significance level 0.1 was used in Table 4 to identify the safety variables that showed possible treatment difference.

As can be seen from the table, rofecoxib treatment group had statistically significantly less patients ($p<0.001$) discontinued due to GI adverse events and abdominal pain than naproxen treatment group. However, compared with naproxen, more patients in rofecoxib treatment group experienced serious clinical adverse events ($p=0.013$); more patients in rofecoxib discontinued due to edema-related adverse events ($p=0.057$); more patients in rofecoxib discontinued due to hypertension-related adverse events ($p<0.001$); more patients in rofecoxib discontinued due to hepatic disease ($p=0.067$); more patients in rofecoxib experienced CHF adverse events ($p=0.065$); and more patients in rofecoxib discontinued due to lab adverse events ($p=0.091$). Based on the pre-specified safety variables, rofecoxib 50 mg daily revealed several undesirable safety issues compared to naproxen in this VIGOR trial.

Cardiovascular events:

Analyses in thrombotic cardiovascular serious adverse events were summarized as follows. Ninety-eight cases (65 from rofecoxib and 33 from naproxen) were sent for adjudication to the vascular endpoint adjudication committee. Forty-six cases from 45 rofecoxib patients and 20 cases from 19 naproxen patients were adjudicated to have thrombotic cardiovascular serious adverse events. The sponsor's analyses were focused on the 66 confirmed cases from the 64 patients. The result of survival analysis on the 64 patients showed that the risk of developing a cardiovascular event in rofecoxib treatment group was 2.37 times of that in naproxen treatment group with p-value 0.0016 and 95% CI (1.39, 4.06). Figure 3 was the survival curves of the two treatment groups for confirmed thrombotic cardiovascular serious adverse events.

in Rheumatoid Arthritis Patients in the VIGOR Study
Time-to-Event Plot (All Patients Randomized)
Updated Application Data



Results from some of the supportive analyses on the thrombotic cardiovascular serious adverse events were also listed in the following:

(1) Subgroup analysis (Aspirin indicated vs. aspirin not indicated): only 321 patients were aspirin indicated patients (170 in rofecoxib and 151 in naproxen). The risk ratio of developing serious cardiovascular events between rofecoxib and naproxen was 4.89 with p-value 0.012 and 95% CI (1.41, 16.88). The risk ratio for aspirin not indicated patients was 1.89 with p-value 0.041 and 95% CI (1.03, 3.45).
(2) Analyses of cardiovascular events in the VIGOR study using endpoint definition standard in large anti-platelet trials: for composite endpoint including cardiovascular death, MI and CVA, 35 events occurred in rofecoxib treatment group and 18 in naproxen group. The risk ratio for such events was 1.96 for rofecoxib vs. naproxen with 95% CI (1.10, 3.45).
(3) Incidence of events judged by investigators to be potential thrombotic cardiovascular serious adverse experiences: As mentioned before, events experienced by 64 patients in rofecoxib and 32 patients in naproxen were eligible for adjudication. The risk ratio of experiencing such events was 2 for rofecoxib vs. naproxen with 95% CI (1.32, 3.03).

Reviewer's comments on cardiovascular serious adverse events:

In addition to the analyses of thrombotic cardiovascular serious adverse events, all the cardiovascular events from the adverse data sets that were serious in investigator's opinion were compared between the two treatment. One hundred and eleven patients in rofecoxib treatment group experienced serious cardiovascular adverse events, while 50 patients in naproxen treatment group experienced such events. Survival analysis showed the risk for serious cardiovascular events in rofecoxib treatment group was 2.22 times of the risk in naproxen treatment group. The p-value obtained from survival analysis was 0.0001.

Based on the sponsor's primary analysis on confirmed thrombotic cardiovascular serious adverse events and other supportive analyses on cardiovascular serious adverse events, there was clear evidence to show that rofecoxib 50 mg daily had increased risk of developing serious cardiovascular adverse events compared to naproxen 1000 mg per day.

3. Efficacy:

The results of this study on the patient and investigator global assessments of disease status and HAQ did not show treatment difference between rofecoxib and naproxen. Analysis on discontinuation due to lack of efficacy yielded p-value 0.769.

Since the VIGOR trial was not designed to evaluate efficacy in treating RA patients, the results of the efficacy analyses could not be used to establish efficacy property of rofecoxib 50 mg daily in comparison to naproxen 1000 mg per day in RA patients.

IV. Conclusion:

The VIGOR trial demonstrated robustly that rofecoxib 50 mg daily treatment statistically significantly reduced risk of developing PUBs compared to naproxen 1000 mg per day treatment in RA patients. The risk of PUBs in rofecoxib treatment group was reduced 0.46 times of that in naproxen treatment group, with 95% CI (0.33, 0.64). The risk of confirmed and complicated PUBs was also reduced 0.43 times with 95% CI (0.24, 0.78). All other secondary GI end points and secondary analyses supported the finding.

The VIGOR trial also revealed some safety concerns for the use of rofecoxib 50 mg daily. For the 12 pre-specified safety analyses, half of them showed statistically significant trend of undesirable safety aspects for rofecoxib 50 mg daily compared to naproxen 1000 mg per day. These undesirable safety aspects included serious clinical adverse events, discontinued due to edema related AEs, discontinued due to hypertension related AEs, discontinuation due to hepatic diseases, CHF AEs, Lab AEs leading to discontinuation. Analyses on confirmed

thrombotic cardiovascular serious adverse events showed rofecoxib 50 mg daily had increased the risk of the event 2.38 times compared with naproxen 1000 mg per day. Analysis on serious cardiovascular adverse events judged by the investigators also showed that rofecoxib 50 mg daily doubled the risk of such events compared to naproxen 1000 mg per day.

As it was discussed before, there were some concerns to the generalization of the results from the VIGOR trial due to the study design. The VIGOR trial used RA patients for whom rofecoxib has not been approved and only one NSAID comparator was used in the VIGOR trial. Since the effective dose of rofecoxib for RA patients was unavailable at present, it was not clear if the safety issue associated with rofecoxib 50 mg daily would be a concern. The comparison of the risks of PUBs with Study 69 did not suggest that the results in VIGOR were generalizable.

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