CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-647

MEDICAL REVIEW

Clinical Review Cover Sheet
Original NDA 21-647
Supplement to NDA 21042 and 21052

Sponsor:	**Merck Laboratories**
Drug:	**Vioxx (rofecoxib)**
Proposed Indication:	**Acute Migraine**
Correspondence Date:	**May 27, 2003**
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PDUFA Date	**March 27, 2004**
Division:	**DNDP (HFD-120)**
Reviewer:	**Kevin Prohaska, D.O.**

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Executive Summary Section

Clinical Review for NDA 21647

Executive Summary

1. Background

Merck Research Laboratories has submitted a new drug application (NDA) for the use of Vioxx (rofecoxib 25 and 50 mg tablets ——————— for the treatment of acute migraine with and without an aura in adults. This will be a type 6 NDA application. Although this is a new application to this Division, for administrative purposes the application is considered a supplemental application to NDA 21042 and 21052 according to the sponsor. The NDA is formatted according to the International Conference on Harmonization (ICH) Common Technical document and has been submitted electronically at: (http://edr/loadfile.asp?PATH=FILE://\\CDSESUB1\N21647\N_000\2003-05-23).

Vioxx (rofecoxib) Oral Tablets and Oral solution (25 mg/5 ml) is a COX-2 non-steroidal anti-inflammatory drug (NSAID) already approved in the United States for the following indications:

- For relief of the signs and symptoms of osteoarthritis (12.5 to 25 mg daily).
- For relief of the signs and symptoms of rheumatoid arthritis in adults (25 mg daily).
- For the management of acute pain in adults (50 mg daily, up to 5 days).
- For the treatment of primary dysmenorrhea (50 mg daily, up to 5 days).

A discussion about the present available treatments for acute migraine can be found in section 1.2 of this review. The most common treatment for acute migraine prescribed in the United States are a group of medications collectively known as triptans. All triptan products are associated with cardiovascular adverse events including myocardial infarction and should be given with great care to subjects with multiple risk factors for cardiovascular disease. The sponsors states that approximately 40% of all patients in the United States treat their migraines with non-steroidal anti-inflammatory drugs. Traditional NSAIDs are nonselective inhibitors of cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) and are known to cause significant gastrointestinal complaints such as dyspepsia, gastritis and frank ulceration with bleeding. Rofecoxib is a selective COX-2 inhibitor and has been shown in several studies to have less gastrointestinal adverse events then nonselective NSAIDs. Hence the sponsor believes Vioxx will provide a safer alternative to migraineurs than standard triptan therapy and non-selective NSAIDs.

2. Recommendations

2.1 Recommendation on Approvability

Considering the favorable risk-benefit balance seen with ——rofecoxib 25 mg and 50 mg use in migraine, and based on efficacy and safety data reviewed for this NDA, and from a clinical perspective I recommend approval of Vioxx (rofecoxib) Tablets (25 and 50 mg) , ——————— ——————— for the treatment of acute migraine with and without an aura in adults. A discussion of the efficacy and safety of rofecoxib is briefly described below and elaborated further in this review. Although I recommend approval of rofecoxib in the treatment of migraine

in adults I do not believe accelerated approval or restrictive distribution is warranted. My recommendations for changes to the proposed label are contained in a separate document.

2.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

Phase IV commitments should include a clinical development program to evaluate the safety and efficacy of Vioxx in adolescent patients (12 to 17 years). The sponsor does not provide a pediatric development program for my evaluation. At the time of the pre-NDA meeting (December 4, 2002) the sponsor was informed the Pediatric Final Rule of December 1998 was no longer in effect and as such pediatric studies were not required. However since then the Final Rule has been reinstated and pediatric studies are now required. Given the fact that migraines are extremely rare in children less than 12 years of age the sponsor should be granted a waiver for this age group (if requested) and a deferral for adolescents between the ages of 12 to 17 years of age. The Agency pharmacotoxicology reviewer should be requested to determine whether available preclinical data supports the use of rofecoxib in adolescents. If not then additional preclinical studies may be required.

Other than a pediatric (adolescent) clinical development program, I have no specific recommendations for Phase IV studies or commitments.

3. Summary of Clinical Findings

3.1 Brief Overview of Clinical Program

The following table briefly summarizes the clinical development program for rofecoxib in the treatment of migraine.

Table 1 Clinical Development Program for Vioxx in Migraine

Trial #	Vioxx Dose (mg)	Type of Trial	N	Duration	Comments
Trial 161	25, 50	Single Attack Efficacy	557	Single attack	Conducted in the U.S. only.
Trial 162 (acute)	25, 50	Single Attack Efficacy	783	Single attack	Conducted in 16 countries and included an ibuprofen 400 mg arm.
Trial 162 (extension)	25, 50	Multiple Attack Efficacy	635	3 months (8 attacks/month)	Conducted in 16 countries and included an ibuprofen arm but no placebo arm.
Trial 125	25	Migraine Prophylaxis	264	3 months continuos treatment	Included a placebo and montelukast arm.

My assessment of acute efficacy is primarily based on the review of trial 161 and the acute phase of trial 162. Trial 161 and the acute phase of trial 162 are randomized, placebo controlled, double blinded, parallel, multicenter, single attack trials. The acute phase of trial 162 also included ibuprofen 400 mg as an active comparator however the trial was not designed or powered to demonstrate superiority to ibuprofen. The extension phase of trial 162 was a double blinded, (re)randomized (rofecoxib 25 mg, rofecoxib 50 mg and ibuprofen 400 mg), multiple attack, 3 month trial. The extension phase of trial 162 had no prestated hypotheses and all analyses were considered exploratory by the sponsor. Although this extension phase was a double blind,

randomized study it did not include a placebo arm and was not designed to show superiority over the active comparator (ibuprofen 400 mg) hence its relevance to assessing efficacy is limited. A detailed description of these trials can be found in section 5.1.1 of this review. My assessment of safety is based on all clinical trials conducted in support of this NDA. Additionally I reviewed multiple Agency (HFD-550) safety reviews of the VIGOR trial submitted as a supplement (007) to NDAs 21042 (capsules) and 21052 (oral solution). A complete listing of these reviews can be found in the safety section of this review.

The sponsor has not conducted any study using rofecoxib 25 and 50 mg, for the treatment of migraine, that is longer than 3 months. At the pre-NDA meeting we agreed we would consider the long term safety of rofecoxib in other conditions as supportive data for the approval of rofecoxib 25 and 50 mg in the treatment of acute migraine in lieu of traditional long term migraine safety data. In support of this the sponsor provides long term safety information (up to 1 year) on the daily use of rofecoxib in subjects with osteoarthritis and rheumatoid arthritis as well as the result of a study (protocol 125) that evaluated the long term (3 months) safety and efficacy of rofecoxib 25 mg in the prophylactic treatment of migraine. The following table summarizes the amount of exposure from the long term safety data available for review. As demonstrated in the table the sponsor provides safety information from 284 subjects using rofecoxib 50 mg (highest planned dose) for at least 1 year and 3890 subjects for at least 6 months. The amount of long term exposure greatly exceeds the minimum requirements (300 to 600 for 6 months and at least 100 for 1 year) for migraine NDAs and is acceptable to this reviewer.

Table 2 Long Term Exposure of Vioxx (up to 50 mg).

Patient Population	Number of Patients Exposed to Rofecoxib					
	Rofecoxib 12.5 mg		Rofecoxib 25 mg		Rofecoxib 50 mg	
	≥6 Months	≥1 Year	≥6 Months	≥1 Year	≥6 Months	≥1 Year
Phases IIb and III studies in OA	446	371	663	381	265	63
Phases IIb and III studies in RA[§]	-	-	580	188	444	164
VIGOR[*] study in RA[‡]	-	-	-	-	3181	57
Total	446	371	1243	569	3890	284

[*] VIOXX GI Clinical Outcome Research.
[‡] Only rofecoxib 50 mg was studied.
[§] Only rofecoxib 25 mg and 50 mg studied.

Source: Sponsor table 2.7.4:46, ISS page 134.

As agreed this NDA does not contain any new CMC, pharmacokinetic, pharmacodynamic or pharmacotoxicology studies or data. The sponsor refers the Agency to previous data submitted to NDA 21042 and 21052 for supporting information.

3.2 Efficacy

The primary endpoint for trial 161 and the acute phase of trial 162 was Headache Relief at 2 hours. Headache relief is defined as pain reduction from moderate (2) or severe (3) at baseline going to none (0) or mild (2) at 2 hours. The assessment times for both studies include baseline, then every 30 minutes until 2 hours, then at 3 and 4 hours after dosing. A final assessment was done at 24 hours in both studies. As with most migraine studies rescue medication was prohibited for the first 2 hours after treatment. Secondary endpoints for both trials included the usual evaluation of the incidence of each associated symptom (nausea, photophobia,

phonophobia), pain freedom, use of rescue medication etc. All endpoints were defined in the usual manner.

Both trial 161 and 162 enrolled healthy adult individuals with a history of migraine with and without an aura as defined by the International Headache Society (IHS 1.1 and 1.2). All subjects were expected to have at least a 6 month history of migraine and a frequency no greater than 8 migraine attack per month. Subjects with any significant medical or psychiatric conditions or diseases were excluded. Subjects completing the acute phase of trial 162 were eligible to enter the 3 month extension phase if they continued to meet the original entry criteria.

Dose selection for all migraine trials was based on the clinical and research experience of the dose required to manage acute pain and dysmenorrhea. The initial recommendation for rofecoxib in acute pain is 50 mg with subsequent down-titration as required. The maximum duration of recommended therapy for acute pain and dysmenorrhea is 5 days. The rofecoxib analgesia program previously established 7.5 mg as the no-effect dose, 12.5 mg as the minimal effective dose, 25 mg as an effective dose, and 50 mg as the most effective dose.

The Data Analysis Plans for trial 161 and 162 were supplied to the Agency prior to unblinding. A review of these plans was conducted by myself and the Agency statistician soon after receipt of the submission (serial 035, review in DFS). The method of analysis for each endpoint is briefly summarized in the following table. Missing data was handled using a last-observation carried forward (LOCF) algorithm. All tests were analyzed using a two-sided test with an alpha of 0.05. Treatment groups were compared through a pairwise contrast in the context of regression models using a step down approach starting with rofecoxib 50 mg then rofecoxib 25 mg.

Table 3 Summary of Analysis Plan for Trial 161 and 162 (acute phase).

Endpoint	Statistical Method
Headache Relief at 2 hours (primary)	Logistical Regression model with the following covariates: gender, race, age, aura, prophylactic medication, prior response to NSAIDs, use of oral contraceptives, presence of menses, dysmenorrhea, geographic region, and baseline severity.
Number of Associated Symptoms at 2 hours	Cumulative Logistic Regression
Functional Disability	
Presence of Associated Symptoms	Logistic Regression Model
Headache Relief at various timepoints	
Pain Freedom	
Sustained Headache Relief at 24 hours	
Sustained Pain Freedom at 24 hours	
Presence of Associated Symptoms at various timepoints if present at baseline	
Use of Rescue Medication	Kaplan-Meier Estimate and Cox regression
Headache Recurrence	Descriptive Statistics
Pain Intensity Difference	ANOVA Model
24 Hour QOL Rating	
Time to Headache Relief	Discrete Proportional Hazards Regression

Adapted from sponsor table 2.7.3:3 page 24 ISE.pdf

The following table provides a brief overview of the sponsor efficacy results for the essential endpoints from trial 161 and the acute phase of trial 162. As demonstrated in the table rofecoxib 50 mg and 25 mg had a clear advantage over placebo for pain relief at 2 hours (primary endpoint) as well as most symptoms associated with migraine in both trials. In both trials and for both doses of rofecoxib there was a statistically significant improvement in the proportion of subjects reporting headache relief at 2 hours ($p \leq 0.001$). An average treatment effect of 24.9% for rofecoxib 25 mg and 27.7% for rofecoxib 50 mg is clinically significant in my opinion. Similarly rofecoxib 25 mg and 50 mg demonstrated superior efficacy compared to placebo for the proportion of patients reporting photophobia and phonophobia at 2 hours in both studies ($p \leq 0.036$). The only essential endpoint in doubt is the proportion of subjects on rofecoxib 25 mg reporting nausea at 2 hours in trial 161 ($p=0.111$). Although the sponsor did not win on this endpoint there was a clear numerical benefit for the low dose rofecoxib 25 mg compared to placebo (33.0% vs. 41.7%) in trial 161. Additionally the rofecoxib 50 mg cohort in trial 161 reported significantly less nausea than placebo cohort (30.3% vs. 41.7%, $p \leq 0.001$). In trial 162 both the low dose and high dose rofecoxib cohorts reported significantly less nausea at two hours than subjects taking placebo ($p \leq 0.032$). All together I do not believe the lack of significance in trial 161 for the proportion of patients on rofecoxib 25 mg reporting nausea at 2 hours should hold up the approval of this NDA. In addition to demonstrating benefit for pain relief and the presence of associated symptoms at 2 hours both doses of rofecoxib demonstrated significant improvement in the proportion of subject reporting complete pain relief at 2 hours in both studies ($p \leq 0.002$). This secondary endpoint is presently recommended by the International Headache Society as the preferred primary endpoint for migraine studies.

Table 4 Essential Endpoints from Trial 161 and 162#.

		Rofecoxib 25 mg	Rofecoxib 50 mg	Ibuprofen	Placebo
Primary Endpoint					
Percentage of subjects reporting Headache Relief at 2 hours	Trial 161	54.0%	56.7%	NA	33.7%
	p-value*	**≤0.001**	**≤0.001**		
	Trial 162	59.4%	62.2%	57.7%	29.9%
	p-value*	**≤0.001**	**≤0.001**	≤0.001	
Associated symptoms					
Percentage of subjects reporting nausea at 2 hours	Trial 161	33.0%	30.3%	NA	41.7%
	p-value*	0.111	**0.030**		
	Trial 162	31.2%	29.8%	27.8%	42.2%
	p-value*	**0.023**	**0.013**	**0.001**	
Percentage of subjects reporting photophobia at 2 hours	Trial 161	61.4%	57.5%	NA	71.4%
	p-value*	**0.032**	**0.005**		
	Trial 162	51.1%	49.5%	50.0%	65.2%
	p-value*	**0.004**	**0.002**	**0.003**	
Percentage of subjects reporting phonophobia at 2 hours	Trial 161	52.3%	45.2	NA	64.0%
	p-value*	**0.036**	**≤0.001**		
	Trial 162	43.5%	42.6%	38.8%	59.4%
	p-value*	**0.002**	**0.001**	**≤0.001**	
Noteworthy Secondary Endpoint					
Percentages of subjects reporting Pain Freedom at 2 hours	Trial 161	19.9%	23.0%	NA	8.0%
	p-value*	**0.002**	**≤0.001**		
	Trial 162	26.2%	26.6%	23.8%	5.3%
	p-value*	**≤0.001**	**≤0.001**	**≤0.001**	

*Compared to placebo, # bolded numbers denotes statistical significance.

In addition to the above summary I offer the following statements relative to efficacy:

1. Acute studies

- The two pivotal trials conducted in support of this NDA supplement were adequately designed, conducted, and analyzed. Additionally the level of acute exposure to rofecoxib 25 mg and rofecoxib 50 mg is sufficient.
- Both trial 161 and trial 162 (acute phase) demonstrated efficacy for rofecoxib 50 mg and rofecoxib 25 mg using the pre-stated primary endpoint of Headache Relief at 2 hours compared to placebo ($p \leq 0.001$ both trials). Additionally both trials demonstrated a small numerical difference/dose effect in headache response at 2 hours between rofecoxib 25 mg and rofecoxib 50 mg, favoring rofecoxib 50 mg. This difference did not reach statistical significance.
- Statistically significant headache relief was first observed at 30 minutes with rofecoxib 50 mg and at 1 hour with rofecoxib 25 mg in one study and at 30 minutes with both rofecoxib 25 mg and 50 mg in the other study.
- Following administration of rofecoxib 50 mg, there was a significant decrease incidence of photophobia, phonophobia, and nausea at 2 hours in trial 161 and trial 162 compared to placebo. Following administration of rofecoxib 25 mg there was a significant decrease in photophobia and phonophobia at 2 hours in trial 161 and trial 162 compared to placebo. The proportion of subject reporting nausea at 2 hours following treatment with rofecoxib 25 mg was significantly less than subjects treated with placebo in trial 162 and numerically lower in

trial 161. A slight dose effect favoring rofecoxib 50 mg compared to rofecoxib 25 mg was evident for nausea, photophobia and phonophobia at 2 hours in both studies.

- In general rofecoxib 50 mg was numerically superior to rofecoxib 25 mg on most secondary efficacy measurements during the acute studies including headache response, pain freedom, relief of associated symptoms, and improvement in quality-of-life.
- Rofecoxib was effective as measured by 2 hour headache relief regardless of aura, gender, race, age, presence of menses, or dysmenorrhea. Rofecoxib efficacy was not affected by concomitant use of common prophylactic migraine drugs, oral contraceptives, or previous response to NSAIDs.

2. Long term study and comparison with ibuprofen (phase 2 of trial 162)

- The long term exposure of migraine subjects to rofecoxib 25 mg and 50 mg is limited to 3 months with each cohort treating an average of 2 to 3 migraines per month. I discuss the level of chronic exposure in further detail in the Safety section of this review.
- The long term phase of trial 162 demonstrated consistency of effect for relief at 2 hours in subjects treated with rofecoxib 50 mg and rofecoxib 25 mg. Most endpoints did not demonstrate a significant difference between active cohorts except for the following: rofecoxib 50 mg vs. rofecoxib 25 mg for 2-Hour Headache Relief (p=0.050), rofecoxib 50 mg vs. rofecoxib 25 mg for 24-Hour Sustained Relief (p=0.042), rofecoxib 50 mg vs. ibuprofen 400 mg for 24-Hour Sustained Relief (p=0.001), and rofecoxib 50 mg vs. ibuprofen 400 mg for Use of Rescue Medication between 2 to 24 hours (p=0.003). There was a consistent slight numerical benefit for rofecoxib 50 mg versus rofecoxib 25 mg in all endpoints evaluated. The results of this extension phase adds additional support to the benefit of rofecoxib 50 mg over rofecoxib 25 mg although the study is limited by the lack of a placebo arm and no prestated efficacy hypotheses.
- As previously stated trial 162 includes an ibuprofen arm in the acute and long term extension phases. The sponsor hoped that rofecoxib 25 mg and 50 mg would be superior to ibuprofen for headache recurrence since it has a longer half life. In my opinion trial 162 does not support a conclusion that rofecoxib 25 mg or 50 mg provides any additional significant benefit over ibuprofen. The strongest suggestion of a benefit comes from the comparison of the subset of patients reporting 24 Hour Headache Recurrence where numerically fewer patients reported a headache recurrence following rofecoxib 25 mg (25.2%) or rofecoxib 50 mg (23.9%) compared to ibuprofen 400 mg (33.9%) in the acute phase of trial 162. The sponsor did not perform any statistical analysis of this endpoint. Similar results were seen in the extension phase where fewer patients reported a headache recurrence following rofecoxib 25 mg (19.8%) or rofecoxib 50 mg (16.0%) compared to ibuprofen 400 mg (29.9%). Additionally the efficacy of rofecoxib was numerically better than ibuprofen 400 mg for the percentage of patients with: headache relief at 2 hours, pain freedom at 2 hours, 24-hour sustained headache relief, 24-hour sustained pain freedom, and the need for rescue medication (see acute phase trial 162 for results). I am uncertain what type of claim (if any) the sponsor intends to make of these comparisons in marketing however there are several factors to keep in mind when weighing their validity. First of all despite the sponsor contention that 400 mg is the most effective dose of ibuprofen, most clinicians, including myself, believe that additional efficacy can be achieved with the 600 and 800 mg dose of ibuprofen albeit more adverse events may occur. Secondarily it must be remembered that

study 162 was not powered to determine a difference between rofecoxib and ibuprofen. Thirdly, none of these results have been replicated. And finally, since the long term phase of trial 162 did not include a placebo arm it is not possible to determine whether rofecoxib 25, rofecoxib 50 and ibuprofen 400 mg would perform any better than placebo for these long term endpoints.

In summary subjects treating a migraine attack of moderate to severe intensity with rofecoxib 25 mg and rofecoxib 50 mg reported significantly more relief of pain at 2 hours than subjects taking placebo. The benefit for this endpoint is clear. Relative to the associate symptoms (nausea, photophobia, phonophobia) seen in some migraineurs, rofecoxib 25 mg and rofecoxib 50 mg demonstrated efficacy as seen in the proportion of patients reporting each of these symptoms at 2 hours. For the proportion of patients reporting photophobia and phonophobia at 2 hours, both trial 161 and 162 demonstrated significant efficacy compared to placebo. For the proportion of patients reporting nausea at 2 hour, trial 162 demonstrated significant efficacy for subjects taking the low dose and high dose of rofecoxib compared to subjects taking placebo. Trial 161 however resulted in mixed results with only rofecoxib 50 mg demonstrating significance for this comparison. Rofecoxib 25 mg, however, demonstrated a strong numerical benefit over placebo for nausea at 2 hours and was clearly significant at 3 hours. In conclusion the efficacy results from trial 161 and 162 favors the approval of this NDA.

3.3 Safety

The following table briefly outlines the total number of new patient exposures discussed in my safety review. The design of trial 161 and 162 are discussed above. Trial 125 was a Phase IIa trial that investigated the safety and efficacy of rofecoxib 25 mg or montelukast 20 mg daily compared with placebo in the prophylactic treatment of migraine over a 3 month period. The acute efficacy of rofecoxib was not evaluated in trial 125. As demonstrated in the table approximately 85% to 87% of all subjects are female and the average age was around 40 years in all studies. This is typical of migraine studies which I have reviewed and typical of migraineurs in the general population. Additional discussion about patient demographics can be found in section 5.1.2 of this review.

Table 5 New Exposure Data Contained in this NDA

Trial	Treatment group size	Gender and Age (mean/range)	Comment
161	Placebo =182 Vioxx 25 mg = 183 Vioxx 50 mg = 192	Female 497 Male 60 Age 41.3/(18 to 70 years)	Randomized, double blind, placebo controlled, single migraine study
162 acute phase	Placebo = 194 Vioxx 25 mg = 194 Vioxx 50 mg = 196 Ibuprofen 400 mg = 199	Female 675 Male 108 Age 39.8/(18 to 78 years)	Randomized, double blind, placebo and active controlled, single migraine study
162 extension	Vioxx 25 mg = 268 Vioxx 50 mg = 244 Ibuprofen 400 mg = 123	Female 545 Male 90 Age 40.1/(18 to 78 years)	Re-randomized, double blind, active controlled, 3 month, multiple migraine study
125*	Placebo = 83 Vioxx 25 mg = 89 Montelukast 20 mg = 92	Female 230 Male 38 Age 39.7/(18 to 66 years)	Outpatient, randomized, double blind, placebo controlled study on the prophylactic treatment of migraine (3 month daily use)

*Discussed in further details in section 6.5

In total, 1340 unique individuals participated in trial 161 and 162. The extension phase of trial 162 only included subjects who successfully completed the 1st phase of the trial. Since trial 161 and the acute phase of trial 162 are single-attack studies actual exposure data is straight forward with 377 subjects receiving rofecoxib 25 mg, 388 subjects receiving rofecoxib 50 mg, 376 subjects receiving placebo and 199 subjects receiving ibuprofen 400 mg. The amount of acute exposure is acceptable.

The following table summarizes the exposure statistics from the extension phase of trial 162. Out of the 635 subjects who took study medication in the extension phase of trial 162, 572 (90.1%) completed the study [243 (90.7%) from rofecoxib 25 mg, 218 (89.3%) from rofecoxib 50 mg, and 111 (90.2%) from ibuprofen 400 mg]. Subjects were instructed to treat up to 8 migraines per month over the 3 month period. The range of patients actual days on any treatment was 1 to 31 days. Two hundred subjects took study drug for 1 to 4 days, 197 subjects took study drug for 5 to 8 days, 190 subjects took study drug for 9 to 17 days, 44 subjects took study drug for 18 to 26 days and finally 4 subjects took study drug for 27 to 31 days. On average patients took study drug for 8 days during this extension phase (range 7.7 to 8.5 for 3 treatment groups). This is greater than the 2 migraines/month minimum (i.e. 6 days of treatment for a 3 month study) we require for long term migraine studies. Although patients were instructed to not take more than a single dose of study medication in any 24 hour period, seven patients took more than 50 mg of rofecoxib in a single day (1 patient took 75 mg and 6 patients took 100 mg). Overall the higher doses were well tolerated with only 2 patients reporting an adverse event (both upper respiratory infections occurring 4 to 6 days later). Of the 5088 treated migraine attacks, >97% were treated with a single dose of study medication.

Table 6 Summary of Exposure Date, Extension Phase Trial 162

	Number of Days on Which Patients Took Study Drug						Range of Days† on Drug	Mean Number of Days‡ on Drug
	1 to 4 days†	5 to 8 days†	9 to 17 days†	18 to 26 days†	27 to 31 days†	Number of Patients		
Any group								
Any dosage¶	200	197	190	44	4	635	1 to 31	8.0
Rofecoxib 25 mg								
Any dosage¶	92	82	75	18	1	268	1 to 29	7.7
Once daily	93§	82	74	18	1	268	1 to 29	7.6
Twice daily‖	4	0	0	0	0	4	1 to 2	1.3
Three times daily‖	1	0	0	0	0	1	1 to 1	1.0
Rofecoxib 50 mg								
Any dosage¶	71	73	76	21	3	244	1 to 31	8.5
Once daily	71	73	76	21	3	244	1 to 31	8.5
Twice daily‖	6	0	0	0	0	6	1 to 1	1.0
Ibuprofen 400 mg								
Any dosage¶	37	42	39	5	0	123	1 to 24	7.8
Once daily	37	43§	38	5	0	123	1 to 24	7.7
Twice daily‖	1	0	0	0	0	1	3 to 3	3.0

† Days represent calendar days, not 24-hour periods.
‡ Although some patients may have taken 2 or more different dosages, they have been counted only once in the "any dosage" rows. Therefore, in any given column containing numbers of patients, only the values in the "any dosage" rows will add up to the totals given in the "any group" row.
§ In some columns, there are more patients counted under the "once daily" heading than in the "any dosage" heading. The reason for this is that patients could only be counted once in any "any dosage" row. Some patients who took extra doses of study drug for a certain number of days (e.g., 2 days) were on "any dose" of study drug for a different number of days (e.g., 8 days). These patients would be counted in the "any dosage" row in a separate column.
‖ All patients who dosed more than once daily took the extra doses of study drug at least 2 hours after the initial dose.

Source: Sponsor table 43, study report 162-EXT, page 112.

The sponsor also refers the reviewer to previously submitted long term safety data on the use of rofecoxib in conditions such as osteoarthritis and rheumatoid arthritis. Since much of the long term safety information provided by the sponsor is blended data from subjects taking 12.5 mg and 25 mg daily I chose to focus primarily on the VIGOR study which evaluated the long term safety (up to 1 year) of rofecoxib 50 mg daily in subjects with rheumatoid arthritis. Approximately 3181 subjects took rofecoxib 50 mg daily for 6 months and 440 subjects took rofecoxib 50 mg daily for 11 months (see section 6.5 for additional details). The amount of long term exposure is adequate.

During trial 161 and 162 safety was primarily assessed using patient diaries reviewed at each follow up visit. Follow up visits occurred within 14 days after dosing during trial 161 and the acute phase of trial 162 and at 1 or 2 monthly intervals for the extension phase of trial 162. In trial 161 and the acute phase of trial 162 adverse events were recorded from the start of trial

medication up to 14 days post-treatment. For the extension phase of trial 162 adverse events were recorded through the initiation of trial medication for the first time up to 14 days after treatment of the last migraine recorded. Adverse events were coded using the MedDRA system.

Safety was also assessed in trial 161 and 162 by laboratory tests, physical examinations, and vital signs recordings done at the pretreatment and posttreatment visits. Laboratory analysis included a CBC, a basic Metabolic Chemistry Panel, a Urinalysis and a pregnancy test (if appropriate). Since the post treatment laboratories were done up to 14 days after treatment during the acute phase and longer in the long-term phase of trial 162, their relevance is limited. Objective data such as laboratory values and vitals signs were analyzed for mean changes and the proportion of subjects exceeding predefined limits. Overall, this level of surveillance is typical for what I have seen for migraine studies.

The following safety summary is provided by the sponsor:

Short Term use:

- Both rofecoxib 25 mg and 50 mg were generally well tolerated when used for the acute treatment of migraine.
- In the acute phase studies, the overall incidence of adverse events was either numerically or statistically more frequent in the rofecoxib 50 mg treatment group compared to the other groups. In contrast the opposite was true in the 3 month extension phase of trial 162. No single adverse event accounted for the observed differences among the treatment groups.
- The most common (≥2%) adverse events reported following a single dose of rofecoxib included dizziness, somnolence, nausea, dry mouth, dyspepsia, asthenia, and paresthesia.
- One or more adverse events occurred in 29.4% of patients taking rofecoxib 25 mg, 38.7 % of patients taking rofecoxib 50 mg, 25.8% of patients taking placebo, and 28.1% of patients taking ibuprofen 400 mg.
- The adverse events were mild or moderate in intensity in 88% of patients taking rofecoxib 25 mg, 90% of patients taking rofecoxib 50 mg, 90% of patients taking placebo, and 93% of patients taking ibuprofen 400 mg.
- Overall the nature of the adverse events seen in these trials were comparable for what is already included in the professional label for rofecoxib and consistent with what is known for this class of drugs.
- Subgroup analysis of safety data (short and long term) revealed no difference in incidence rates when looking at age, gender and race.
- The incidence of abnormal laboratory values in the short term studies were low and showed no particular pattern (0.6% for rofecoxib 25 mg, 1.1% for rofecoxib 50 mg, 0.9% for placebo and 0.5% for ibuprofen). None of the abnormal laboratory values were considered drug related.

Long-term use in migraineurs (3 months)

- The discontinuation rate due to adverse events was low during the long term phase of trial 162 (1.9% for rofecoxib 25 mg, 2.5% for rofecoxib 50 mg, and 0% for ibuprofen 400 mg).
- The percentage of patients having one or more adverse events over the 3 month period was 39.2% for rofecoxib 25 mg, 31.6% for rofecoxib 50 mg, and 36.6% for ibuprofen 400 mg.

- The most common adverse events seen during the long term phase of trial 162 were similar to those seen during the acute phase of trail 161 and 162. And the vast majority were mild or moderate, transient and resolved without treatment.
- Nausea, dry mouth, dyspepsia, and dizziness were the most frequently observed adverse events reported in all treatment groups.
- The incidence of abnormal laboratory values in the long term studies were low and showed no particular pattern (1.9% for rofecoxib 25 mg, 2.1% for rofecoxib 50 mg, and 0.8% for ibuprofen). Except for a single case of proteinuria in a patient randomized to rofecoxib 50 mg, none of the abnormal laboratory values were considered drug related.

Long-term safety in non-migraine population (6 months to 1 year)

- The 6-month and 1-year safety data in OA and RA patients demonstrate that continuous, chronic administration of rofecoxib 12.5 mg, 25 mg, and 50 mg is safe and generally well tolerated. In acute pain (5 days of use), rofecoxib 25 and 50 mg were generally well tolerated with 50 mg providing superior efficacy. The data in OA and RA patients with acute pain support the intermittent use of rofecoxib 25 mg and 50 mg in the acute treatment of migraine.
- The incidences of overall and specific clinical adverse experiences in the migraine studies were less than or similar to those found in continuous, chronic dosing of rofecoxib 12.5 and 25 mg in OA and RA patients and in intermittent dosing of rofecoxib 25 mg and 50 mg in primary dysmenorrhea and acute pain.

Overall I concur with the sponsor's bulleted summary itemized above. Rofecoxib 25 mg and rofecoxib 50 mg was well tolerated in the acute studies as well as in the 3 month extension phase of trial 162. Clearly the vast majority (approximately 92%) of adverse events were mild to moderate intensity and self limiting in the subjects that were randomized to rofecoxib. Few adverse events resulted in discontinuation in both the acute studies and the single, 3-month, multiple attack study. Approximately 88% of all patients in the acute phase of trial 162 enrolled into the extension phase and approximately 87% of these patients continued for the entire treatment period.

The more common adverse events ($\geq$ 2%, see Table 39) seen with rofecoxib during the acute studies included dizziness, dry mouth, nausea, somnolence, asthenia, dyspepsia and paresthesia. There was no consistent evidence of a dose effect for most of these complaints with some of them being more frequent in rofecoxib 25 mg than in rofecoxib 50 mg. However in general more adverse events were reported by subjects randomized to rofecoxib 50 mg than subjects randomized to rofecoxib 25 mg. Most of the common adverse events were slightly more common in rofecoxib than in placebo. In the 3-month extension phase of trial 162 the more common adverse events ($\geq$ 2%) seen with rofecoxib included dizziness, vomiting, dry mouth, gastroenteritis, nausea, upper abdominal pain, dyspepsia, pharyngitis, and upper respiratory tract infection. Oddly all of the common adverse events except for gastroenteritis were more common in rofecoxib 25 mg than in rofecoxib 50 mg. No comparison to placebo is possible since there was no placebo cohort in 162 extension.

There were no deaths in subjects treated with rofecoxib in any study. In trial 162 there were two deaths, one in a patient randomized to ibuprofen and the other in a patient that never took her randomized treatment. Neither event was considered related to study medication.

In the acute studies there were only 3 serious adverse events, only one of which was in a subject taking rofecoxib (50 mg, deep vein thrombosis). None of the events were considered related to study medication. In the extension phase of trial 162 there were 5 serious adverse events. Three occurred in the rofecoxib 50 mg cohort (gastroenteritis, menometrorrhagia, low back pain), 1 occurred in the rofecoxib 25 mg cohort (bronchospasm) and the other occurred in the ibuprofen cohort (leg fracture). None of the events were considered related to study medication.

Overall there were no clinically relevant changes in vital signs, laboratory or physical findings in either the acute studies or the 3 month extension study.

The supporting long-term safety information provided by the sponsor is very helpful. Overall the information provided by the sponsor represents approximately 3600 osteoarthritis subjects and approximately 5600 rheumatoid arthritis subjects. The safety data presented by the sponsor was mostly a blended average of incidences for rofecoxib 12.5 mg and 25 mg. For this reason I chose to look further and came across additional long term safety data from the VIGOR study submitted to the Agency and previously reviewed by HFD-550. The reviews located in DFS were very helpful and are briefly discussed in my review. Overall the long term safety seen in the VIGOR study was not unexpected except for the higher incidence of cardiovascular events seen in patients randomized to rofecoxib compared to patients randomized to naproxen. The cumulative rate for serious CV/thrombotic events was 1.8% (n=45) and 0.6% (n=19) in the rofecoxib 50 mg and naproxen groups respectively over the study period. The difference was mainly due to the difference in the number of myocardial infarction; 20 in the rofecoxib 50 mg group and 4 in the naproxen group (crude rate 0.5% and 0.1% respectively, RR=5.0). The reason for this difference is not clear and several theories have been proposed by the sponsor. This issue resulted in considerable discussion within the Agency and the convening of an Advisory Committee meeting. The final decision was the rofecoxib label should describe the cardiovascular/thrombotic events seen in the VIGOR trial. Of course this unexpected findings brings into question whether rofecoxib should be approved for a self-limiting condition such as migraine. Several things must be kept in mind when weighing the relevance of the VIGOR study to the migraine population. Subjects in the VIGOR study were generally older, had multiple chronic medical conditions, and took rofecoxib 50 mg on a continuous daily basis for up to 1 year. The typical migraineur is generally a young (30 to 40's) female with few chronic medical conditions and uses acute treatment intermittently. My clinical opinion is although migraine is a self limiting condition it is associated with considerable disability. Additionally the available migraine therapies do not provide all people with complete relief and many subjects are unable to take or tolerate triptans. As such I think the risk benefit analysis of intermittent use of rofecoxib in the treatment of migraine favors approval. However the daily use of rofecoxib for migraine and/or migraine prophylaxis should be discouraged. Additionally migraine subjects with multiple cardiovascular risk factors should be informed of the potential risks associated with rofecoxib.

In summary I believe the safety and tolerability of rofecoxib in migraine patients is clinically acceptable for intermittent use during an acute migraine attacks with and without an aura.

3.4 Dosing

Other than trial 161 and 162 no other dose finding studies have been conducted. The dose of 25 mg and 50 mg was selected by the sponsor because they represent the doses generally employed clinically to treat acute pain. The results of these two trials indicate that rofecoxib 25 mg and rofecoxib 50 mg are both effective in the treatment of acute migraine. Several questions arise when reviewing these studies. Most obvious is whether a lower dose of rofecoxib, such as 12.5 mg, might be effective. This has not been studied by the sponsor and should be considered although I would be concerned whether a lower treatment effect would be clinically relevant. Another question is whether there are any additional benefits achieved by using a 50 mg dose of rofecoxib over a 25 mg dose. The answer to this question is not so obvious and requires some thought. Throughout my review of the efficacy results I qualified the dose effect seen for each endpoint in both studies. Although none of the endpoints demonstrated a significant difference between rofecoxib 25 mg and rofecoxib 50 mg in the acute studies there was consistent evidence that additional benefit could be achieved by a higher dose of rofecoxib for most endpoints. Likewise during my discussion of safety results I found no clinically relevant difference in the safety profiles of the two doses although intuitively one should expect more adverse events with increasing doses of rofecoxib. The common adverse events seen were generally mild to moderate and self limiting. For this reason I believe it is prudent to approve both rofecoxib 25 mg and rofecoxib 50 mg for the acute treatment of migraine. Clearly the data supports the initial use of rofecoxib 25 mg in the treatment of acute migraine with the rofecoxib 50 mg dose being reserved for subjects who have generally obtained an incomplete response to the lower dose in the past. Chronic use of rofecoxib 50 mg should be avoided. Retreatment with rofecoxib for an incomplete response or recurrence within 24 hours has not been evaluated and is not recommended.

3.5 Special Populations

There is no data on the efficacy and safety of rofecoxib in migraineurs with hepatic or renal impairment. The present label for Vioxx tablets states "*a single-dose pharmacokinetic study in mild (Child-Pugh score ≤6) hepatic insufficiency patients indicated that rofecoxib AUC was similar between these patients and healthy subjects. A pharmacokinetic study in patients with moderate (Child-Pugh score 7-9) hepatic insufficiency indicated that mean rofecoxib plasma concentrations were higher (mean AUC: 55%; mean C_{max}: 53%) relative to healthy subjects.*" Patients with severe hepatic insufficiency have not been studied. Further the label recommends the lowest possible dose of Vioxx should be used in subjects with moderate hepatic insufficiency. Relative to renal insufficiency the label states *"in a study (N=6) of patients with end stage renal disease undergoing dialysis, peak rofecoxib plasma levels and AUC declined 18% and 9%, respectively, when dialysis occurred four hours after dosing. When dialysis occurred 48 hours after dosing, the elimination profile of rofecoxib was unchanged. While renal insufficiency does not influence the pharmacokinetics of rofecoxib, use of VIOXX in advanced renal disease is not recommended."* I agree with the hepatic and renal statements already in the label.

No new reproductive studies were performed in support of this NDA. Eight pregnancies have been reported during the clinical development program for rofecoxib in migraine (see Table 48 for details). A review of each pregnancy does not suggest any obvious signal for concern. Use in pregnancy and during lactation is already described in labeling. The label for rofecoxib includes the statement that "*in late pregnancy rofecoxib should be avoided because it may cause premature closure of the ductus arteriosus*" and is rated Category C (use only if benefit justifies potential risk). A pregnancy registry for rofecoxib is already in place. It is not known whether rofecoxib is excreted in Human breast milk. I agree with the pregnancy statements already in the label.

The following table summarizes the sponsor's subgroup comparison of the proportion of patients reporting 2 Hour Headache Relief for the subgroups age (<40 years/≥40 years), gender (male/female), and race (white/other). Approximately 87% of all participant in trial 161 and 162 were female and 85% were Caucasian. The mean age in the trial 161 was 41.3 years and in trial 162 it was 39.8. Overall only 2.1% of all patients in both trials were 65 years of age or older and no subject was less than 18 years of age hence no valid conclusions about the safety and efficacy of rofecoxib in Geriatric and Pediatric migraineurs can be made. These demographic characteristics are typical of what I have seen in other migraine NDAs.

There was no significant treatment-by-age category interaction in trial 161 (p=0.372), trial 162 acute phase (p=0.704), or the Combined acute phase (p=0.345), indicating that the treatment effects were consistent between age categories. In subjects less than 40 years of age, the percentages of patients who had headache relief at 2 hours postdose were 31.8%, 49.2%, and 53.9% in the placebo, rofecoxib 25-mg, and rofecoxib 50-mg treatment groups, respectively. In subjects ≥40 years of age, the percentages of patients who had headache relief at 2 hours postdose were 32.9%, 65.3%, and 65.2% in the placebo, rofecoxib 25-mg, and rofecoxib 50-mg treatment groups, respectively.

The overall treatment-by-gender interaction was nearly significant in the combined analysis of trial 161 and trial 162 acute (p=0.077). This finding was driven primarily by the results of the gender subgroup analysis of trial 162 where the treatment-by-gender interaction was significant (p=0.031) however in trial 161 it was not significant (p=0.233). Further analysis showed that there were no qualitative interactions when making pairwise comparisons between treatment groups. In women, the percentages of patients who had headache relief at 2 hours postdose were 31.6%, 59.4%, and 59.9% in the placebo, rofecoxib 25-mg, and rofecoxib 50-mg treatment groups, respectively. In men, the percentages of patients who had headache relief at 2 hours postdose were 37.0%, 37.8%, and 55.8% in the placebo, rofecoxib 25-mg, and rofecoxib 50-mg treatment groups, respectively. This would suggest that men require a higher dose of rofecoxib in order to receive benefit however the small number of male patients makes it difficult to draw a conclusion. Overall, the absence of a significant qualitative interaction indicates the superiority of rofecoxib 25 mg and 50 mg over placebo in both women and men and suggests that the interaction observed was a chance finding.

There was no significant treatment-by-race interaction in either trial 161, 162 acute, or the Combined acute phase (p=0.870, p=0.627, and p=0.718, respectively), indicating that the

treatment effects were consistent among races however the small number of non-Caucasian subjects makes it difficult to draw a conclusion.

Table 7 Proportion of Patients Reporting 2-Hour Headache Relief by Subgroup and Treatment, Combined Acute Phase Population.

Subgroup (p-Value)	Placebo Total N=362		Vioxx 25 mg Total N=363		Vioxx 50 mg Total N=374	
	N	n (%)	N	n (%)	N	n (%)
Gender						
Male	46	17 (37.0)	45	17 (37.8)	43	24 (55.8)
Female	316	100 (31.6)	318	189 (59.4)	332	199 (59.9)
Age						
<40 years	164	54 (32.9)	170	111 (65.3)	184	120 (65.2)
≥40 years	198	63 (31.8)	193	95 (49.2)	191	103 (53.9)
Race						
White	302	94 (31.1)	313	171 (54.6)	318	185 (58.2)
Other	60	23 (38.3)	50	35 (70.0)	57	38 (66.7)

Source: Adapted from sponsor table 2.7.3:50, ise.pdf, page 139

As discussed in section 6.4.11 there does not appear to be any clinically relevant differences in the proportion of patients reporting an adverse event or experiencing a serious adverse event between younger and older patients. The nature and character of the adverse events profile was similar between the various demographic groupings.

As discussed earlier the sponsor has not evaluated the safety and efficacy of rofecoxib in adolescent migraineurs. The sponsor should be requested to conduct phase IV studies in this population.

Clinical Review

1. Introduction and Background

Merck Research Laboratories has submitted a new drug application (NDA) for the use of rofecoxib 25 and 50 mg tablets ——————— in the treatment of acute migraine. This will be a type 6 NDA application. Although this is a new application to this Division, for administrative purposes the application is considered a supplemental application to NDA 21042 and 21052 according to the sponsor. The NDA is formatted according to the International Conference on Harmonization Common Technical Document and has been submitted electronically (http://edr/loadfile.asp?PATH=FILE://\\CDSESUB1\N21647\N_000\2003-05-23).

1.1 Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Vioxx (rofecoxib) Oral Tablets and Oral solution (25 mg/5 ml) is a non-steroidal anti-inflammatory drug (NSAID) already approved for the following indications:

- For relief of the signs and symptoms of osteoarthritis (12.5 to 25 mg daily).
- For relief of the signs and symptoms of rheumatoid arthritis in adults (25 mg daily).
- For the management of acute pain in adults (50 mg daily, up to 5 days).
- For the treatment of primary dysmenorrhea (50 mg daily, up to 5 days).

The sponsor seeks Agency approval for the use of rofecoxib 25 mg or 50 mg for the "acute treatment of migraine attacks with or without an aura in adults". Repeat dosing for an incomplete response or recurrence within 24 hours is not recommended.

1.2 State of Armamentarium for Indication(s)

Migraine is a common neurological disorder usually characterized by attacks of moderate to severe pulsating, unilateral, headache often associated with nausea, photophobia, and phonophobia.. In approximately 10 to 20% of migraineurs there is a preceding aura. Each attack can generally last from 4 to 72 hours. The prevalence of migraine has been estimated to be between 3 to 8% of all men and 11 to 18% of all women. In general migraine is more common in women during their reproductive years. It is estimated that one-third of all migraine is disabling enough to require bed rest.

The exact etiology of migraine is not known however it is believed that dilation of cranial blood vessels is a major contributor, possibly in combination with sensitization of trigeminal sensory nerve fibers and/or neurogenic inflammation. Several biochemical pathways are thought to be involved with the manifestations of migraine. Many substances, including serotonin and prostaglandins are believed to play a role in migraine. It is believed prostaglandins may cause migraine by their pro-inflammatory and nociceptive action. Rofecoxib is known to inhibit the production of prostaglandins and has been previously shown to be effective in the treatment of various painful and inflammatory conditions. Other non-selective COX inhibitors have been shown to be effective in the treatment of migraine. The sponsor believes that rofecoxib would

offer the migraineurs effective treatment of migraine without the high incidence of GI symptoms frequently seen with non-selective COX inhibitors.

There are currently 16 approved drug products for treatment of acute migraine. The majority of the prescription products fall within the 5-hydroxytryptamine$_{1B/1D}$ ($5HT_{1B/1D}$) receptor agonist family often referred to as a "triptan". These include Amerge (naratriptan), Axert (almotriptan), Frova (frovatriptan), Imitrex (sumatriptan), Maxalt (rizatriptan), Relpax (elatriptan) and Zomig (zolmitriptan). Many of these triptan products are available in several formulations (see table below). Additionally Advil Migraine Liquidgels (ibuprofen), Motrin Migraine Pain Caplets (ibuprofen) and Excedrin Migraine Caplets/Gelcaps/Tablets (acetaminophen 250 mg, aspirin 250 mg and caffeine 65 mg) are also approved as over-the-counter treatments for the indication of acute migraine. In addition to these products, there are a wide variety of approved treatment options for acute migraine including Bayer Aspirin (OTC-pain of migraine approval only), dihydroergotamines (ex D.H.E.), and isometheptene (Midrin, labeled as "possibly effective in migraine" by the DESI review).

Since all triptan products are associated with cardiovascular adverse events the sponsor has developed Vioxx Migraine as an alternative treatment option to these products. The sponsors states that approximately 40% of all patients in the United States treat their migraines with non-steroidal anti-inflammatory drugs. Traditional NSAIDs are nonselective inhibitors of cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) and are known to cause significant gastrointestinal complaints such as dyspepsia, gastritis and frank ulceration with bleeding. Rofecoxib is a selective COX-2 inhibitor and has been shown in several studies to have less gastrointestinal adverse events then nonselective NSAIDs.

Table 8 Approved Treatments for Migraine Syndrome

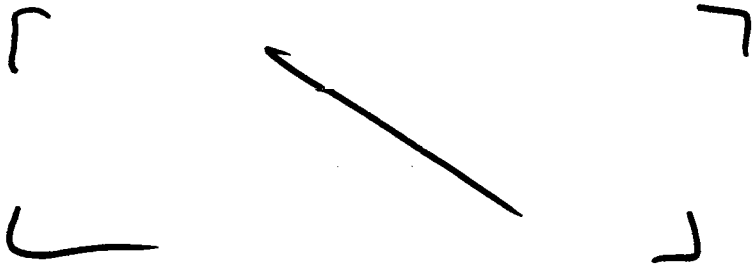
Drug Product	NDA	Sponsor	FDA Approval	Approved Strengths
Imitrex Injection	20-080	Glaxo Wellcome	12/28/1992	6 mg
Imitrex Tablets	20-132	Glaxo Wellcome	6/1/1995	25 and 50 mg
Imitrex Nasal Spray	20-626	Glaxo Wellcome	8/26/1997	5, 10, and 20 mg/spray
Zomig Tablets	20-768	IPR	11/25/1997	2.5 and 5.0 mg
Zomig-ZMT	21-231	Astra Zeneca	2/13/2001	2.5 mg
Amerge Tablets	20-763	Glaxo Wellcome	2/10/1998	1 and 2.5 mg
Maxalt Tablet	20-864	Merck	6/29/1998	5 and 10 mg
Maxalt-MLT Tablets	20-865	Merck	6/29/1998	5 and 10 mg
Axert Tablets	21-001	Pharmacia and Upjohn	5/7/2001	6.25 and 12.5 mg
Relpax Tablets	21-016	Pfizer	12/26/2002	20 and 40 mg
D.H.E. 45 Injectable	05-929	XCEL Pharmaceuticals	4/12/1946	1 mg/ml
Migranal Nasal	20-148	XCEL Pharmaceutical	12/08/1997	0.5 mg/inh
Advil Migraine	20-402	Wyeth	4/20/1995	200 mg
Excedrin Migraine	20-802	Bristol Myers	1/14/1998	Combination product
Frova Tablets	21-006	Elan Pharmaceuticals	11/08/2001	2.5 mg

1.3 Important Milestones in Product Development

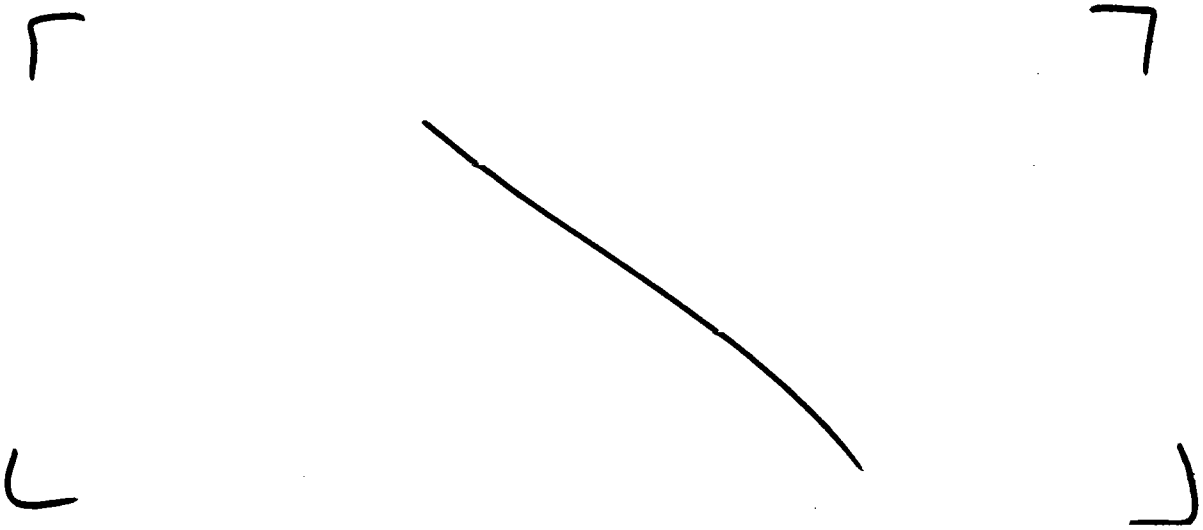
The following milestones occurred during the clinical development program for rofecoxib tablets in the treatment of acute migraine:

- December 21, 2000 IND 61419 c [redacted]

- January 18, 2001
- March 6, 2001
- March 28, 2001
- April 3, 2001
- May 22, 2001



- July 5, 2001 — Sponsor submits protocol 161 and 162 to evaluate the use of rofecoxib alone in the treatment of acute migraine.
- July 25, 2002 — The Data Analysis Plan for study 161 and 162 submitted.
- October 31, 2002 — The Data Analysis Plan for Protocol 162 extension submitted.
- September 30, 2002 — Agency letter issued with comments about the Data Analysis Plan.
- December 4, 2002 — Agency meeting with the sponsor to discuss the pre-NDA package.
- May 27, 2003 — NDA submitted.
- July 8, 2003 — 45 Day Filing Meeting.



At the pre-NDA meeting we reiterated that the long-term safety data from previous rofecoxib NDAs (rheumatoid and osteoarthritis) may suffice for the migraine indication however the sponsor would need to present their case. During this meeting we agreed that the submission did not need to include new "Chemistry, Manufacturing, Control" (CMC) data, Nonclinical Pharmacology and Toxicology data, or Human Pharmacokinetic and Bioavailability data. The sponsor refers the Agency to NDA 21-042 and 21-052 for such details. Additionally we stated that the lack of a pre-specified primary hypothesis in the extension phase of Protocol 162 may preclude the use of this data in labeling.

All protocols and all data analysis plans were submitted to the IND and reviewed by the Agency. All reviews can be found in DFS.

1.4 Other Relevant Information

Background information on rofecoxib can be obtained from NDA 021052 (oral suspension) and 021042 (oral tablets).

Rofecoxib is approved almost world wide (83 countries) for the chronic treatment of osteoarthritis and rheumatoid arthritis, and the acute treatment of general pain and dysmenorrhea. There are no countries where rofecoxib is approved for migraine headaches. As of March 31, 2003, the marketing approval of rofecoxib has not been rejected, suspended, revoked, or withdrawn in any country. To date approximately [redacted] tablets of rofecoxib, representing over 15 million patient-years, have been distributed.

1.5 Important Issues with Pharmacologically Related Agents

Vioxx (rofecoxib) is a non-steroidal anti-inflammatory drug (NSAID) with selective cyclooxygenase 2 (COX-2) inhibitory properties. It was originally approved for marketing in the United States in May of 1999 for the indication of acute pain in adults, dysmenorrhea and the signs and symptoms of osteoarthritis (OA). Since then it has also been approved for rheumatoid arthritis (RA).

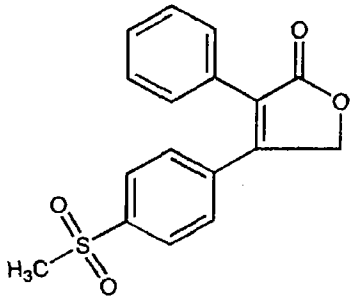
The NSAID class includes a heterogeneous group of drugs with different degrees of selectivity for the COX-1 and COX-2 isoforms. In addition to COX inhibition, NSAIDs may have other non-prostaglandin mediated effects that contribute to their efficacy and toxicity. Celebrex (celecoxib) also claims to be a selective COX-2 inhibitor. This selectivity is thought to provide a larger safety margin for these two products compared to nonselective inhibitors although there is often debate about this in the medical literature. Common adverse events seen with this class of compounds are primarily gastrointestinal in nature and include dyspepsia, gastritis and nausea. Less common but more serious adverse events include gastrointestinal bleeding, peptic ulcer disease, and renal insufficiency resulting in hypertension, electrolyte abnormalities and edema. All of these untoward effects are considered class effects and are included in labeling of all NSAIDs including rofecoxib.

2. Clinically Relevant Findings From Other Disciplines

2.1 Chemistry, Manufacturing and Control Issues

This submission contains no new CMC data. The sponsor directs the Agency reviewers to NDA 21-042 and 21-052 for supporting CMC data. Merck requests a categorical exclusion from the requirements to prepare an Environmental Assessment under 21CFR 25.31(b). The sponsor states the patient use of rofecoxib meets the requirements of a categorical exclusion because the estimated concentration of the active drug substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). I defer to the Chemistry reviewer for the response to this request.

Figure 1 Structural Formula for Rofecoxib



Rofecoxib is described chemically as 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furone. The empirical formula is $C_{17}H_{14}O_4S$. The molecular weight is 314.36. Rofecoxib is a white to off white to yellow powder. It is sparingly soluble in acetone, slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol and particularly insoluble in octanol, and insoluble in water.

A chemistry review completed by Dr. Martha Heimann recommends approval of the NDA from a chemistry perspective. No chemistry related post-approval commitments are required. The chemistry reviewer states the claim for categorical exclusion is appropriate.

2.2 Human Pharmacokinetics and Pharmacodynamics

There is no new pharmacokinetic and pharmacodynamic data in the submission. The sponsor refers the Agency to their original 1998 Marketing Application and its supplements for details.

Rofecoxib tablets is well absorbed orally with a bioavailability of approximately 93%. Rofecoxib is extensively metabolized by the liver with approximately 1% of the dose recovered in the urine unchanged. The main metabolic pathway is reduction to produce *cis*- and *trans*-dihydrorofecoxib (as hydroxy acids). Rofecoxib is not oxidized by the cytochrome P450 enzymes. Elimination occurs almost exclusively through metabolism followed by renal excretion. Steady state concentration of rofecoxib are reached within 4 days after once daily administration of 25 mg, with an accumulation ratio of approximately 1.7, corresponding to an accumulation half life of approximately 17 hours. The plasma clearance is estimated to be approximately 120 mL/min for a 25 mg dose.

2.3 Pharmacotoxicology Issues

No new pharmacotoxicology studies were conducted in support of this NDA. The sponsor refers the Agency to their original 1998 Marketing Application and its supplements for details.

2.4 Statistical Review Issues

I conferred with the Agency statistician (Sharon Yan) several times throughout my review of this NDA. Although her review is not complete at this time she informs me she has completely replicated the sponsor's analysis and agrees with their findings.

3. Description of Clinical Data and Sources

3.1 Overall Data

This application contains information from 2 pivotal, multicenter, placebo controlled, double blind, randomized trials (Protocols 161 and 162). Both studies are of similar design with 161 being conducted in the United States and 162 being conducted in several countries (primarily Europe and the United States). Trial 162 also has an active control arm (ibuprofen 400 mg) and a 3-month extension phase in which re-randomized subjects were to treat up to 8 migraines per month. Additionally the sponsor submits the results from Protocol 125 which provides supportive long-term safety (3-months) information on the use of rofecoxib 25 mg in the prophylactic treatment of migraine. The sponsor states the two pivotal trials demonstrate that rofecoxib 25 and 50 mg is effective in the relief of migraine headache pain and its associated symptoms (nausea, photophobia and phonophobia) at 2 hours compared to placebo. Each trial is described in further details below. Since there are no ongoing clinical trials for this application the sponsor will not be submitting a 4 month safety update. Data was submitted electronically and can be found at \\CDSESUB1\N21647\N_000\2003-05-23.

3.2 Tables Listing the Clinical Trials

The primary objective of the rofecoxib migraine program is to demonstrate the efficacy and safety of rofecoxib 25 and 50 mg for the treatment of acute migraine with and without an aura (International Headache Society classification 1.1 and 1.2) in adults. The clinical program consists of 2 pivotal trials (study 161 and 162) of nearly identical design and a phase IIa trial (study 125) to evaluate the potential use of rofecoxib 25 mg as migraine prophylaxis. Both pivotal trials are randomized, double blind, placebo controlled, parallel group studies during which the efficacy of rofecoxib was evaluated during a single migraine attack. Additionally protocol 162 had a 3-month extension phase during which subjects could treat up to 8 attacks per month and an active comparator arm (ibuprofen 400 mg) during both phases. Trial 125 was a Phase IIa trial that investigated the safety and efficacy of rofecoxib 25 mg or montelukast 20 mg daily compared with placebo in the prophylactic treatment of migraine over a 3 month period.

Table 9 Clinical Development Program for Vioxx in Migraine

Trial #	Vioxx Dose (mg)	Type of Trial	N	Duration	Comments
Trial 161	25, 50	Single Attack Efficacy	557	Single attack	Conducted in the U.S. only.
Trial 162 (acute)	25, 50	Single Attack Efficacy	783	Single attack	Conducted in 16 countries and included an ibuprofen 400 mg arm.
Trial 162 extension	25, 50	Multiple Attack Efficacy	635	3 months (8 attacks/month)	Conducted in 16 countries and included an ibuprofen arm but no placebo arm.
Trial 125	25	Prophylaxis	264	3 months continuos treatment	Included a placebo and montelukast arm.

3.3 Postmarketing Experience

Rofecoxib 12.5 and 25 mg has been approved in the United States since 1999 for several indications (OA, RA, acute pain, and dysmenorrhea). Since then, the marketing experience has

been typical for products in this category. In support of this NDA the sponsor provides a brief summary of post marketing experience with rofecoxib for the indication of migraine (unapproved indication). I summarize their discussion in section 6.5.2.

3.4 Literature Review

The sponsor does not provide a literature review in support of this NDA. I performed a PubMed search using the phrase "Vioxx AND migraine" without any limits and found only three articles. I reviewed each article and found no new or useful information relative to the use of rofecoxib for the indication of migraine with and without an aura (IHS 1.1 and 1.2).

4. Clinical Review Methods

4.1 How the Review was Conducted

The materials reviewed for this NDA review include the data submitted electronically on May 23, 2003. Additionally I reviewed multiple Agency (HFD-550) safety reviews of the VIGOR trial submitted as a supplement (007) to NDAs 21042 (capsules) and 21052 (oral solution). A complete listing of these reviews can be found in the safety section of this review.

The emphasis of this review with respect to efficacy is trial 161 and the acute phase of trial 162. Although the 3 month extension phase of trial 162 was randomized it did not include a placebo arm and was not powered to demonstrate a significant difference between active comparators hence the determination of efficacy is difficult. Additionally the extension phase of trial 162 did not include any prestated hypothesis hence its relevance to an efficacy assessment and labeling is limited.

The emphasis of this review with respect to safety will be on all studies submitted in which subjects took trial medication. This includes trial 161, all of trial 162, and trial 125 (3 month migraine prophylaxis study). Additionally I will briefly summarize the safety findings from the VIGOR trial previously reviewed by the review team in HFD-550. Safety findings from the VIGOR trial are already discussed in labeling. Since no studies are presently ongoing there will be no safety update to this NDA.

4.2 Data Quality and Integrity

Data integrity during the trial was supported by the sponsor's strict policy that allowed only patients to make any entries into the migraine diaries. Standard validated migraine diaries were employed during all trials. After the migraine event the completed diary was reviewed by the patient and the investigator (or representative). Any discrepancies were corrected with the patient present. Any changes to the diary required the patients to initial and date the entry and to verify that it was an accurate record.

4.3 Ethical Standards Statements and Issues

The sponsor states that all studies conducted in support of this application were conducted in accordance with the Good Clinical Practice standards. The sponsor quality assurance audits are stated to meet the standards set in 21 CFR Part 58.

There were no apparent ethical problems during the clinical development program of rofecoxib for the indication of migraine. I have been the primary reviewer for this IND/NDA since its inception and at no time were there any ethical concerns or any other safety issues that might have resulted in a HOLD.

4.4 DSI Audit (by Dr. Ni Aye Khin)

DSI randomly selected for audit one site in Phoenix, Arizona (Dr. Marshall Block, site 001) and one site in Anderson, South Carolina (Dr. Harry Geisberg, site 009) from trial 161. Neither site has been previously inspected by the Agency. The Clinical Inspection Summary from these sites can be found in DFS (1/14/04). In summary the inspection did not find any serious violations at either site and the data was deemed "Acceptable". Minor findings are discussed in the DSI review.

4.5 Evaluation of Financial Disclosure

As required the sponsor submits a completed FDA Form 3454, "Certification: Financial Interests and Arrangements of Clinical Investigators". The sponsor certifies that with respect to all clinical studies submitted in support of this application they have not entered into any financial arrangement with the investigators whereby the value of compensation could be affected by the outcome of this study as defined in 21 CFR 54.2(a). Additionally the sponsor certifies that none of the listed clinical investigators reported any proprietary interest in this product or a significant equity in the sponsor. Finally the sponsor certifies that no listed Investigator was the recipient of significant payments of other sorts as defined in 21CFR.2(f).

5. Integrated Review of Efficacy

The sponsor submits the results of 2 clinical trials (161 and 162) in support of their application. Both trials were randomized, placebo controlled, double blind, parallel, multicenter trials. Trial 161 was conducted entirely in the United States. Trial 162 was multinational with sites in nearly every continent although most subjects enrolled came from Western Europe and the United States. In addition trial 162 also had an active-comparator arm (ibuprofen 400 mg) and a 3 month extension phase during which the safety and efficacy of rofecoxib 25 mg and 50 mg over multiple migraines (up to 8 per month) was assessed. The extension phase of trial 162 was a double blinded, active-controlled, re-randomized (rofecoxib 50 mg, rofecoxib 25, or ibuprofen 400 mg), multiple attacks, 3 month trial. The primary objective of both studies was to determine the safety and efficacy of rofecoxib 25 and 50 mg for the treatment of acute migraine. The primary endpoint for trial 161 and the acute phase of trial 162 was Headache Relief at 2 hours. The extension phase of trial 162 had no prestated hypotheses and all analyses were considered exploratory by the sponsor.

5.1 Detailed Review of Trials by Indication

5.1.1 Detailed Description of Trial 161 and 162 Design

The designs of trial 161 and 162 are in general typical of what I have seen for most migraine studies. Both trials are randomized, double blind, parallel design trials in which subjects were instructed to treat a single migraine of moderate to severe intensity with either rofecoxib 25 mg, rofecoxib 50 mg or placebo. Trial 162 also had a ibuprofen 400 mg parallel arm and a 3-month multiple migraine attack (up to 8 per month) extension. The sponsor included an active

comparator in trial 162 primarily to determine whether rofecoxib provides improved sustained relief compared to ibuprofen. This hypothesis was generated from the finding that the half-life for rofecoxib is 17 hours compared to a much shorter half life for ibuprofen. I will discuss the efficacy findings relative to ibuprofen in each subsection as appropriate however my primary emphasis will be on the comparison of rofecoxib to placebo. The 162 extension phase was designed as a double blind, active control (ibuprofen 400 mg) study in which subject from phase 1 were rerandomized to either rofecoxib 25 mg, rofecoxib 50mg or ibuprofen 400 mg. The primary objective of phase 2 was to assess the long term safety and efficacy in patients treating up to 8 migraines per month.

The following sponsor table outlines the number of subjects in each trial and cohort in the "all-patients treated approach" (APT). The sponsor defines this population as all patients who treated a migraine attack and had a least one efficacy measurement after the initial dose of study medication. This is the typical modified intent to treat population we generally recommend for migraine studies. As demonstrated the number of acute exposures are typical for what we see for migraine NDAs. I discuss long term exposure in the safety section of this review.

Table 10 Summary of Number of Patients in Efficacy Analysis (APT population)

Protocol Number	Placebo	Rofecoxib (mg)		Ibuprofen	All
		25	50	400 mg	Treatments
Phase III—Acute Phase					
Protocol 161	175	176	187	-	538
Protocol 162 Acute Phase	187	187	188	189	751
Combined Acute Phase: Total	***362***	***363***	***375***	***189***	***1289***
Phase III—Extension Phase					
Protocol 162 Extension Phase	-	267	241	120	628

Source: Sponsor table 2.7.3:2, ise.pdf, page 12.

The primary endpoint of both acute studies was Headache Relief at 2 hours. Headache relief is defined as pain reduction from moderate (2) or severe (3) at baseline going to none (0) or mild (2) at 2 hours. The assessment times for both studies included baseline, then every 30 minutes until 2 hours, then at 3 and 4 hours after dosing. A final assessment was done at 24 hours in both studies. As with most migraine studies rescue medication was prohibited for the first 2 hours after treatment. Any subject that took rescue medication prior to 2 hours was treated as a treatment failure in the sponsor's "sensitivity analysis". For the purposes of my assessment I will use the results of the sensitivity analysis to discuss the primary endpoint results since this represents the analysis we generally prefer. The secondary endpoints are discussed below. There was no pre-specified primary hypothesis for the extension phase of trial 162 and all efficacy analysis done by the sponsor were considered exploratory.

Both trial 161 and 162 enrolled healthy adult individuals with a history of migraine with and without an aura as defined by the International Headache Society (IHS 1.1 and 1.2). All subjects were expected to have at least a 6 month history of migraine and a frequency no greater than 8 migraine attack per month. Individuals with more frequent and complicated migraines as well as

significant co-morbid medical conditions were excluded from participation. Subjects completing the acute phase of trial 162 were eligible to enter the 3 month extension phase if they continued to meet the original entry criteria. This type of inclusion and exclusion criteria is typical of what I have seen in most migraine studies.

Dose selection for all migraine trials was based on the clinical and research experience of the dose required to manage acute pain and dysmenorrhea. The initial recommendation for rofecoxib in acute pain is 50 mg with subsequent down-titration as required. The maximum duration of recommended therapy for acute pain and dysmenorrhea is 5 days. The rofecoxib analgesia program previously established 7.5 mg as the no-effect dose, 12.5 mg as the minimal effective dose, 25 mg as an effective dose, and 50 mg as the most effective dose.

The Data Analysis Plans for trial 161 and 162 were supplied to the Agency prior to unblinding. A review of these plans was conducted by myself and the Agency statistician soon after receipt of the submission (serial 035, review in DFS). The method of analysis for each endpoint is briefly summarized in the following table. Missing data was handled using a last-observation carried forward (LOCF) algorithm. All tests were analyzed using a two-sided test with an alpha of 0.05. Since there is only a single primary endpoint no adjustment to the final alpha was required. Treatment groups were compared through a pairwise contrast in the context of regression models using a step down approach starting with rofecoxib 50 mg then rofecoxib 25 mg.

Table 11 Summary of Analysis Plan for Trial 161 and 162 (acute phase).

Endpoint	Statistical Method
Headache Relief at 2 hours (primary)	Logistical Regression model with the following covariates: gender, race, age, aura, prophylactic medication, prior response to NSAIDs, use of oral contraceptives, presence of menses, dysmenorrhea, geographic region, and baseline severity.
Number of Associated Symptoms at 2 hours	Cumulative Logistic Regression
Functional Disability	
Presence of Associated Symptoms	Logistic Regression Model
Headache Relief at various timepoints	
Pain Freedom	
Sustained Headache Relief at 24 hours	
Sustained Pain Freedom at 24 hours	
Presence of Associated Symptoms at various timepoints if present at baseline	
Use of Rescue Medication	Kaplan-Meier Estimate and Cox regression
Headache Recurrence	Descriptive Statistics
Pain Intensity Difference	ANOVA Model
24 Hour QOL Rating	
Time to Headache Relief	Discrete Proportional Hazards Regression

Adapted from sponsor table 2.7.3:3 page 24 ISE.pdf

As is demonstrated in the table above the sponsor does not analyze "time to headache relief" using the Kaplan Meier Survival Method usually requested by this Division for migraine NDAs. This was brought to the sponsor's attention in an Agency letter dated September 30, 2002. In response the sponsor argued that KM analysis was not appropriate for interval censored data and instead argued their plan to use life table estimates for each treatment group was more accurate. I

previously discussed the sponsor's plan with the Agency statistician and she agreed the approach was appropriate.

The sponsor provides separate efficacy analysis for each of their pivotal trials and a combined analysis of trial 161 and the acute phase of trial 162. In this review I will focus on the analysis of each trial separately however since the design and endpoints of trial 161 and the acute phase of 162 are nearly identical I will blend my discussion of both trials during my review of each endpoint. The analysis of the 3 month, multiple-attacks extension phase of trial 162 will be handled separately. Although this extension phase was a double blind, randomized study it did not include a placebo arm and was not designed to show superiority over the active comparator (ibuprofen 400 mg) hence its relevance to assessing efficacy is minimal. The statistical methodology employed by the sponsor to analyze the endpoint in the extension phase of trial 162 are the same methods used in the acute studies. In discussing the results from trial 162 I will primarily focus on the comparison of rofecoxib to placebo however when appropriate I will discuss the comparisons of rofecoxib to ibuprofen.

I reviewed the sample patient reporting diary and found it to be typical of what I have seen in migraine studies and appears sufficient in the details captured.

The following table briefly summarizes the accounting of all patients randomized in trial 161 and 162. As demonstrated in the table there appears to be very little difference in cohort with respect to discontinuation and trial completion. The sponsor counts all patients lost to follow up as discontinued patients. I discuss discontinuation in further detail in section 6.4.3. Of the 557 subjects that completed trial 161, 19 patients did not provide any diary information resulting in 538 subjects for the "all patients treated population" (APT). This includes 17 patients lost to follow up and 2 subjects that returned for follow up but did not provide their diary. All 751 patient completing trial 162 (acute) are included in the APT population. The total APT population includes 1289 subjects; 362 subjects randomized to placebo, 363 subjects randomized to rofecoxib 25 mg, 375 subjects randomized to rofecoxib 50 mg, and 189 subjects randomized to ibuprofen 400 mg. Overall the amount of acute exposure is acceptable however long term exposure in the clinical development program for rofecoxib in migraine does not meet the generally expected minimum level of 300 subjects for 6 months and 100 subjects for 1 year. As previously discussed the sponsor has chosen to rely on previously submitted long term data of the safety of rofecoxib in other clinical conditions as evidence of safety of rofecoxib in migraineurs. This issue is further discussed in section 6.5.

Table 12 Subject Accounting in Trial 161 and 162

	Placebo	Vioxx 25 mg	Vioxx 50 mg	Ibuprofen 400 mg	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Trial 161					
Randomized	208	209	210	NA	627
Treated	182	183	192		557
Completed	176 (96.7)	177 (96.7)	187 (97.4)		540 (96.9)
Discontinued	6 (3.3)	6 (3.3)	5 (2.6)		17 (3.1)
Returned w/o diary	1	1	0		2
"APT" population	175	176	187		538
Not treated	26	26	18		70
Trial 162 acute					
Randomized	238	237	239	243	957
Treated	194	194	196	199	783
Completed	187 (96.4)	187 (96.4)	188 (95.9)	189 (95.0)	751 (95.9)
Discontinued	7 (3.6)	7 (3.6)	8 (4.1)	10 (5.0)	32 (4.1)
Returned w/o diary	0	0	0	0	0
"APT" population	187	187	188	189	751
Not treated	44	43	43	44	174
Trial 162 extension (3 months)					
Randomized	NA	276	260	125	661
Treated		268	244	123	635
Completed		243 (90.7)	218 (89.3)	111 (90.2)	572 (90.1)
Discontinued		25 (9.3)	26 (10.7)	12 (9.8)	63 (9.9)
Returned w/o diary		1	3	3	7
"APT" population		267	241	120	628
Not treated		8	16	2	26

Adapted from sponsor table 2.7.3: 6 ISE page 35 and table 2.7.3:9 ISE page 41, table 9 study report 161, table 9 study report 162

5.1.2 Population Demographics and Baseline Migraine Characteristics

The following table summarizes the demographics and migraine history of subjects participating in trial 161 and the acute phase of trial 162. In total there were 1340 subjects participating in the two acute trials. In general the cohorts in trial 161 and 162 were well balanced for use of migraine prophylaxis, previous response to NSAIDs, and use of oral contraceptives. As can be seen the vast majority of all patients treated were female (87%) and Caucasian (84%). The patients ranged in age between 18 to 78 years with a mean age from both studies of 40.4 years of age. Overall only 2.1% of all patients were 65 years of age or older. This demographic profile is typical of what I have seen in other clinical trials for migraine where most patients are Caucasian females in the their late thirties to early forties.

Since the baseline demographics of subjects enrolled in the extension phase of trial 162 is nearly identical to the characteristics summarized for the acute phase (85.8% female, mean age 40.1 years, 79.8% Caucasian) the data is not duplicated here for simplicity. Overall 635 patients participated in the extension phase of trial 162 (rofecoxib 25 mg 268, rofecoxib 50 mg 244, Ibuprofen 400 mg 123).

In addition to the usual demographics the sponsor also evaluated the cohorts by secondary medical diagnosis. Approximately 93% of all subjects in trial 161 and 162 had a secondary diagnosis at the time of enrollment with the more common co-morbidities being drug

hypersensitivity, depression, tension headaches, and seasonal allergies. Overall each cohort was fairly well balanced for co-morbid conditions. Likewise each cohort was fairly well balanced for prior therapies/medications. The most common prior therapy in each treatment group were sumatriptan (18.0 to 21.8%), ibuprofen (16.2 to 21.0%) and vitamins (8.5 to 13.5%).

In summary the various cohorts in trial 161 and 162 were generally well balanced for their baseline demographics (age, gender, race) as well as co-morbidities and prior medication use.

Table 13 Baseline Demographics for Study 161 and 162.

Trial 161		Placebo (N=182)	Vioxx 25 mg (N=183)	Vioxx 50 mg (N=192)
		n (%)	n (%)	n (%)
Gender:	Female	160 (87.9)	165 (90.2)	172 (89.6)
	Male	22 (12.1)	18 (9.8)	20 (10.4)
Age (years)				
	18 to 29	34 (18.7)	27 (14.8)	41 (21.4)
	30 to 39	42 (23.1)	45 (24.6)	43 (22.4)
	40 to 49	61 (33.5)	75 (41.0)	63 (32.8)
	50 to 59	34 (18.7)	31 (16.9)	36 (18.8)
	60 to 64	6 (3.3)	2 (1.1)	5 (2.6)
	≥ 65	5 (2.7)	3 (1.6)	4 (2.1)
	Mean (SD)	41.9 (11.3)	41.2 (10.2)	40.8 (11.5)
	Range	19 to 70	18 to 68	18 to 67
Race	White	163 (89.6)	164 (89.6)	170 (88.5)
	Black	12 (6.6)	10 (5.5)	15 (7.8)
	Asian	3 (1.6)	2 (1.1)	1 (0.5)
	Multiracial	0 (0.0)	2 (1.1)	1 (0.5)
	Other	4 (2.2)	5 (2.7)	5 (2.6)
Migraine Prophylaxis				
	No	126 (69.2)	118 (64.5)	129 (67.2)
	Yes	56 (30.8)	65 (35.5)	63 (32.8)
Previous response to NSAIDs				
	No NSAIDs used	32 (17.6)	31 (16.9)	38 (19.8)
	< 50% respond	77 (42.3)	85 (46.4)	79 (41.1)
	> 50% respond	67 (36.8)	55 (30.1)	60 (31.3)
	Unknown	6 (3.3)	12 (6.6)	15 (7.8)
Oral Contraceptive in Women				
	No	123 (76.9)	130 (78.8)	135 (78.5)
	Yes	37 (23.1)	35 (21.2)	37 (21.5)

Trial 162		Placebo (N=194)	Vioxx 25 mg (N=194)	Vioxx 50 mg (N=196)	Ibuprofen 400 mg (N=199)
		n (%)	n (%)	n (%)	n (%)
Gender	Female	169 (87.1)	164 (84.5)	169 (86.2)	173 (86.9)
	Male	25 (12.9)	30 (15.5)	27 (13.8)	26 (13.1)
Age (years)					
	18 to 29	39 (20..1)	49 (25.3)	50 (25.5)	40 (20.1)
	30 to 39	56 (28.9)	56 (28.9)	61 (31.1)	49 (24.6)
	40 to 49	57 (29.4)	52 (26.8)	44 (22.4)	64 (32.2)
	50 to 59	30 (15.5)	31 (16.0)	30 (15.3)	30 (15.1)
	60 to 64	9 (4.6)	3 (1.5)	8 (4.1)	9 (4.5)
	≥ 65	3 (1.5)	3 (1.5)	3 (1.5)	7 (3.5)
	Mean (SD)	40.4 (11.5)	38.7 (11.6)	38.7 (11.8)	41.3 (12.0)
	Range	21 to 71	18 to 74	18 to 71	19 to 78
Race	White	151 (77.8)	158 (81.4)	157 (80.1)	160 (80.4)
	Black	6 (3.1)	3 (1.5)	1 (0.5)	6 (3.0)
	Asian	9 (4.6)	11 (5.7)	12 (6.1)	13 (6.5)
	Multiracial	14 (7.2)	10 (5.2)	10 (5.1)	10 (5.0)
	Other	14 97.2)	12 (6.2)	16 (8.2)	10 (5.0)
Migraine Prophylaxis					
	No	150 (77.3)	144 (74.2)	154 (78.6)	152 (76.4)
	Yes	44 (22.7)	50 (25.8)	42 (21.4)	47 (23.6)
Previous response to NSAIDs					
	No NSAIDs used	34 (17.5)	31 (16.0)	26 (13.3)	32 (16.1)
	< 50% respond	79 (40.7)	71 (36.6)	82 (41.8)	79 (39.7)
	> 50% respond	72 (37.1)	84 (43.3)	81 (41.3)	85 (42.7)
	Unknown	9 (4.6)	8 (4.1)	7 (3.6)	3 (1.5)
Oral Contraceptive in Women					
	No	131 (77.5)	127 (77.4)	131 (77.5)	145 (83.8)
	Yes	38 (22.5)	37 (22.6)	38 (22.5)	28 (16.2)

Adapted from sponsor table 12 study report 161 and table 12 study report 162

The following table summarizes the baseline migraine characteristics of treated subjects participating in trial 161 and the acute phase of trial 162. Among the 1340 patients who treated a

migraine attack, 805 subjects reported a migraine headache of moderate pain intensity at baseline (60.1%), 483 patients (36.0%) reported a severe migraine headaches at baseline, and 52 patients (3.9%) were missing baseline data on pain intensity. The majority of patients had migraine headache without aura (83.4%). In general the cohorts were well balanced for pain severity and presence of an aura in both trials.

Table 14 Baseline Migraine Characteristics Trial 161 and 162 (acute phase)

Trial 161				
	Placebo (N=182)	**Vioxx 25 mg (N=183)**	**Vioxx 50 mg (N=192)**	
	n (%)	n (%)	n (%)	
Baseline Severity				
Moderate	103 (56.6)	127 (69.4)	124 (64.6)	
Severe	72 (39.6)	49 (26.8)	63 (32.8)	
Missing	7 (3.8)	7 (3.8)	5 (2.6)	
Aura Presence				
Without	143 (78.6)	155 (84.7)	162 (84.4)	
With	32 (17.6)	22 (12.0)	25 (13.0)	
Missing	7 (3.8)	6 (3.3)	5 (2.6)	
Trial 162				
	Placebo (N=194)	**Vioxx 25 mg (N=194)**	**Vioxx 50 mg (N=196)**	**Ibuprofen 400 mg (N=199)**
	n (%)	n (%)	n (%)	n (%)
Baseline Severity				
Moderate	113 (58.2)	110 (56.7)	114 (58.2)	114 (57.3)
Severe	74 (38.1)	77 (39.7)	73 (37.2)	75 (37.7)
Missing	7 (3.6)	7 (3.6)	9 (4.6)	10 (5.0)
Aura Presence				
Without	169 (87.1)	167 (86.1)	158 (80.6)	164 (82.4)
With	19 (9.8)	21 (10.8)	29 (14.8)	26 (13.1)
Missing	6 (3.1)	6 (3.1)	9 (4.6)	9 (4.5)

Adapted from sponsor table 12 study report 161 and table 12 study report 162

5.1.3 Primary Endpoint: Headache Relief at 2 hours

The primary endpoint for both studies was Headache Relief at 2 hours. Headache relief was defined in the standard manner, i.e., pain intensity of moderate (2) to severe (3) at treatment onset going to mild (1) or none (2) at 2 hours after treatment. Rescue was not permitted for the first 2 hours. This endpoint is often thought of as the standard for migraine studies although the IHS is recently recommending the use of Pain Freedom at 2 hours.

The following table summarizes the sponsor's results of their sensitivity analysis of the primary endpoint. The results are adjusted for 2 patients (both placebo patients) that took rescue medication prior to 2 hours. No subject randomized to rofecoxib took rescue medication prior to 2 hours. As demonstrated at 2 hours the treatment effect of rofecoxib 25 mg relative to placebo was 20 and 29 percentage points in trial 161 and 162 respectively. At 2 hours the treatment effect for rofecoxib 50 mg was 22 and 32 percentage points in trial 161 and 162 respectively. The analysis conducted by the sponsor demonstrates that rofecoxib 25 mg and rofecoxib 50 mg was superior to placebo for headache relief at 2 hours in both trial 161 and the acute phase of trial 162 ($p<0.001$). Additionally both trials demonstrated a small numerical difference in headache response at 2 hours between rofecoxib 25 mg and rofecoxib 50 mg, favoring rofecoxib 50 mg, however this difference did not reach statistical significance.

Results from trial 162 (acute) showed that significantly more patients reported headache relief at 2 hours postdose in the ibuprofen 400-mg group (57.7%, p≤0.001) than in the placebo group (29.9%). This finding adds to the validity of the study since it is known that ibuprofen is effective in migraine. Although there was a slight numerical benefit to rofecoxib 25 mg and rofecoxib 50 mg compared to ibuprofen for headache relief at 2 hours this difference did not reach statistical significance (odds ratio 0.92 and 0.84 respectively).

Table 15 Proportion of Patients Reporting Headache Relief at 2 hours, Trial 161 and 162, APT Population

	Headache Relief n (%)	Odds Ratio (95% Confidence Interval)		
Protocol 161		**Compared to Placebo**	**Compared to Vioxx 25 mg**	**Compared to Vioxx 50 mg**
Placebo (N=175)	59 (33.7)	NA	--	--
Vioxx 25 mg (N=176)	95 (54.0)	2.27 (1.46, 3.51)†	NA	--
Vioxx 50 mg (N=187)	106 (56.7)	2.57 (1.67, 3.96)†	1.14 (0.75, 1.73)	NA
Protocol 162 (acute)				
Placebo (N=187)	56 (29.9)	NA	--	--
Vioxx 25 mg (N=187)	111 (59.4)	3.76 (2.42, 5.86)†	NA	--
Vioxx 50 mg (N=188)	117 (62.2)	4.12 (2.64, 6.43)†	1.10 (0.71, 1.68)	NA
Ibuprofen 400 mg (N=189)	109 (57.7)	3.46 (2.23, 5.36)†	0.92 (0.60, 1.40)	0.84 (0.55, 1.28)

†p≤0.001 based on a pairwise comparison from logistical regression model.
Adapted from sponsor table 2.7.3:49 ise.pdf, page 122

My own analysis of headache response is summarized in the following table. My analysis is crude in that I did not use an LOCF algorithm for missing data elements or adjust for rescue medication use prior to 2 hours. However my results are nearly identical to those of the sponsor and clearly shows efficacy of Vioxx relative to the headache pain of migraine at 2 hours. The Agency statistical review is not complete at this time however the statistician informs me that she has been able to replicate the sponsor's results and agrees with their results.

Table 16 Agency Medical Officer's Analysis of Headache Relief at 2 Hours.

	Headache Relief n (%)	Compared to placebo p-value*
Protocol 161		
Placebo (N=174)	61 (35.1)	NA
Vioxx 25 mg (N=174)	94 (54.0)	≤ 0.0001
Vioxx 50 mg (N=183)	107 (58.5)	≤ 0.0001
Protocol 162 (acute)		
Placebo (N=186)	56 (30.1)	NA
Vioxx 25 mg (N=185)	110 (59.5)	≤ 0.0001
Vioxx 50 mg (N=187)	117 (62.6)	≤ 0.0001
Ibuprofen 400 mg (N=188)	109 (57.9)	≤ 0.0001

*using Pearson Chi Square

In summary both rofecoxib 25 mg and rofecoxib 50 mg are effective in providing headache pain relief by 2 hours in subjects with migraine. Subgroup analysis (gender age, race, country/region, baseline migraine characteristics, and concomitant medication use) did not result in any significant differences in efficacy findings.

5.1.4 Secondary Endpoints

5.1.4.1 Associated Symptoms (Nausea, Photophobia, and Phonophobia)

The associated symptoms of nausea, vomiting, phonophobia and photophobia were assessed as present or absent through hour 4 in the patient diaries. As noted in Table 11 the sponsor analyzed the endpoints of associated symptoms in a variety of ways. As requested by the Division the sponsor analyzed the proportion of patients reporting each of the associated symptoms (individually) at each timepoint. In addition to the method requested by the Division the sponsor also compared the proportion of patients reporting resolution of their baseline symptom at various timepoints and the proportion of patients reporting 1, 2 or 3 of the symptoms at hour two. For simplicity I will focus on the analysis of the proportion of patients reporting each of the associated symptoms up to hour 2 after which rescue medication was permitted if required. Additionally I will not discuss the endpoint vomiting since the proportion of subjects reporting this associated symptom at each timepoint is too low for each cohort to make a meaningful comparisons.

The following table summarizes the analysis of the proportion of patients reporting each of the associated symptoms at various timepoints. As demonstrated in the table a significantly lower proportion of subjects randomized to rofecoxib 25 and 50 mg reported photophobia at two hours (rofecoxib 25 mg 61.4% and 51.1%, rofecoxib 50 mg 57.5% and 49.5%) compared to placebo (71.4% and 65.2%) in both trials ($p \leq 0.05$ and $p \leq 0.001$ trial 161 and 162 respectively). Similar findings were seen for phonophobia. In trial 161, at 2 hours postdose, 52.3%, and 45.2% of the patients had phonophobia in the rofecoxib 25 mg and 50 mg cohorts respectively compared to 64% in the placebo cohort ($p \leq 0.05$). In Protocol 162 (acute), at 2 hours postdose, 43.5% and 42.6% of the patients had phonophobia in the rofecoxib 25 mg and 50 mg cohorts respectively compared to 59.4% in the placebo cohort ($p \leq 0.01$). For both phonophobia and photophobia significance was reached at earlier timepoints in both studies and a fairly consistent, although not statistically significant, dose effect favoring rofecoxib 50 mg was apparent. There was no statistical difference between the two doses of rofecoxib for the proportion of patients reporting photophobia and phonophobia at 2 hours in either study.

In trial 161 a statistically lower proportion of patients randomized to rofecoxib 50 mg reported nausea at 2 hours (30.3%) compared to the proportion of patients randomized to placebo (41.7%, $p \leq 0.05$). This comparison did not reach statistical significance for the comparison between rofecoxib 25 mg and placebo ($p = 0.111$[1]) however there was a strong and consistent numerical trend favoring rofecoxib 25 mg at every timepoint between 30 minutes and 2 hours and the comparison between rofecoxib 25 mg and placebo reached statistical significance at 3 hours (21.0% vs. 33.7%, $p \leq 0.01$). In trial 162 (acute) a statistically lower proportion of patients randomized to both rofecoxib 25 mg and rofecoxib 50 mg reported nausea at 2 hours (31.2% and 29.8%) compared to patients randomized to placebo (42.2%, $p \leq 0.05$). There was no significant difference between rofecoxib 25 mg and rofecoxib 50 mg in the proportion of patients reporting nausea at any timepoint during the first 2 hours.

[1] Source: Sponsor Table 38, Trial 161 Study Report, page 97.

Results from trial 162 (acute) showed that ibuprofen 400 mg was superior to placebo ($p \leq 0.01$) in reducing the proportion of subjects reporting nausea, phonophobia or photophobia at 2 hours compared to placebo. However there was no significant difference for these endpoints when comparing ibuprofen and rofecoxib 25 mg or rofecoxib 50 mg in trial 162.

Table 17 Proportion of Patients Reporting Associated Symptoms, Trial 161 and 162 (acute), APT Population

	t=0.5 hr	t=1.0 hr	t=1.5 hr	t=2.0 hr#	t=3.0 hr	t=4.0 hr
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Photophobia						
Protocol 161						
Placebo (N=175)	158 (90.8)	148 (85.1)	139 (79.9)	125 (71.4)	103 (58.9)	78 (44.6)
Vioxx 25 mg (N=176)	156 (88.6)	141 (80.1)	121 (68.8)*	108 (61.4)*	84 (47.7)*	64 (36.4)
Vioxx 50 mg (N=187)	153 (82.3)	140 (75.3)*	124 (66.7)‡	107 (57.5)‡	86 (46.2)*	64 (34.4)
Protocol 162 (acute)						
Placebo (N=187)	149 (79.7)	137 (73.3)	129 (69.0)	122 (65.2)	96 (51.3)	74 (39.6)
Vioxx 25 mg (N=187)	159 (85.5)	131 (70.4)	113 (60.8)	95 (51.1)‡	75 (40.3)*	63 (33.7)
Vioxx 50 mg (N=188)	144 (76.6)	126 (67.0)	106 (56.4)‡	93 (49.5)‡	74 (39.4)*	61 (32.4)
Ibuprofen 400 mg (N=189)	144 (77.4)	136 (72.7)	116 (61.7)	94 (50.0)‡	70 (37.2)‡	55 (29.3)*
Phonophobia						
Protocol 161						
Placebo (N=175)	135 (77.6)	127 (73.0)	119 (68.4)	112 (64.0)	88 (50.3)	66 (37.7)
Vioxx 25 mg (N=176)	149 (84.7)*	133 (75.6)	113 (64.2)	92 (52.3)*	67 (38.1)*	47 (26.7)*
Vioxx 50 mg (N=187)	132 (71.0)	116 (62.4)	97 (52.2)‡	84 (45.2)†	63 (33.9)‡	46 (24.7)*
Protocol 162 (acute)						
Placebo (N=187)	142 (75.9)	132 (70.6)	121 (64.7)	111 (59.4)	87 (46.5)	69 (36.9)
Vioxx 25 mg (N=187)	137 (73.7)	113 (60.8)*	99 (53.2)*	81 (43.5)‡	62 (33.3)‡	51 (27.3)*
Vioxx 50 mg (N=188)	140 (74.5)	115 (61.2)*	98 (52.1)*	80 (42.6)†	62 (33.0)‡	49 (26.1)*
Ibuprofen 400 mg (N=189)	141 (75.8)	121 (64.7)	100 (53.2)*	73 (38.8)†	53 (28.2)†	46 (24.5)‡
Nausea						
Protocol 161						
Placebo (N=175)	108 (61.7)	97 (55.4)	82 (46.9)	73 (41.7)	59 (33.7)	43 (24.6)
Vioxx 25 mg (N=176)	98 (56.3)	78 (44.6)	64 (36.4)	58 (33.0)£	37 (21.0)‡	29 (16.5)
Vioxx 50 mg (N=187)	93 (50.5)	72 (38.9)‡	60 (32.4)‡	56 (30.3)*	40 (21.6)‡	29 (15.7)*
Protocol 162 (acute)						
Placebo (N=187)	112 (59.9)	103 (55.1)	85 (45.5)	79 (42.2)	63 (33.7)	50 (26.7)
Vioxx 25 mg (N=187)	95 (51.1)	83 (44.6)*	67 (36.0)	58 (31.2)*	40 (21.5)‡	32 (17.1)*
Vioxx 50 mg (N=188)	117 (62.2)	90 (47.9)	75 939.9)	56 (29.8)*	39 (20.7)	26 (13.8)‡
Ibuprofen 400 mg (N=189)	98 (52.7)	76 (40.9)‡	61 (32.6)*	52 (27.8)‡	39 (20.9)‡	33 (17.6)*

Adapted from sponsor table 2.7.3: 23, 2.7.3:31, 2.7.3:25, 2.7.3:32, 2.7.3:27, 2.7.3:33
*$p \leq 0.05$, ‡$p \leq 0.01$, †$p \leq 0.001$ versus placebo
primary endpoint timepoint
£ p=0.111

The following table summarizes my analysis of associated symptoms at 2 and 3 hours. My analysis is crude in that I did not use an LOCF algorithm for missing data elements or adjust for rescue medication use prior to 2 hours. However my results are nearly similar to those obtained by the sponsor. As with the sponsor's results my analysis demonstrates a clear advantage of rofecoxib 25 mg and rofecoxib 50 mg for phonophobia in both trials ($p \leq 0.033$). Likewise my analysis of the proportion of subjects reporting nausea at 2 hours also demonstrated a "win" for rofecoxib 50 mg in both studies ($p \leq 0.027$) and mixed results for rofecoxib 25 mg (p=0.192 trial

161, p=0.014 trial 162). Finally my analysis of the proportion of subjects reporting photophobia at 2 hours showed a clear advantage for rofecoxib 50 mg compared to placebo in both studies ($p \leq 0.004$) and mixed results for rofecoxib 25 mg ($p = 0.071$ trial 161, $p = 0.004$ trial 162).

Table 18 Agency Medical Officer's Analysis of Proportion of Patient Reporting an Associated Symptom

	t=2.0 hours n (%)	p-value vs. placebo*	t=3.0 hours n (%)	p-value vs. placebo*
Protocol 161	**Photophobia**			
Placebo (N=175)	121 (70.3)	NA	100 (58.1)	NA
Vioxx 25 mg (N=176)	107 (61.1)	0.071	82 (47.9)	0.059
Vioxx 50 mg (N=187)	101 (55.5)	0.004	82 (45.0)	0.014
Protocol 162 (acute)				
Placebo (N=187)	122 (65.6)	NA	92 (50.0)	NA
Vioxx 25 mg (N=187)	93 (50.8)	0.004	69 (38.3)	0.025
Vioxx 50 mg (N=188)	93 (49.5)	0.002	71 (39.0)	0.034
Ibuprofen 400 mg (N=189)	92 (49.2)	0.001	67 (36.4)	0.009
Protocol 161	**Phonophobia**			
Placebo (N=175)	110 (64.3)	NA	84 (48.4)	NA
Vioxx 25 mg (N=176)	91 (52.0)	0.020	64 (37.4)	0.033
Vioxx 50 mg (N=187)	78 (42.9)	<0.001	58 (31.9)	0.001
Protocol 162 (acute)				
Placebo (N=187)	112 (60.2)	NA	84 (45.7)	NA
Vioxx 25 mg (N=187)	79 (43.4)	0.001	61 (33.9)	0.022
Vioxx 50 mg (N=188)	80 (42.6)	<0.001	58 (31.7)	0.006
Ibuprofen 400 mg (N=189)	71 (38.0)	<0.001	50 (27.2)	<0.001
Protocol 161	**Nausea**			
Placebo (N=175)	70 (40.7)	NA	55 (32.2)	NA
Vioxx 25 mg (N=176)	59 (33.9)	0.192	36 (21.2)	0.022
Vioxx 50 mg (N=187)	53 (29.4)	0.027	36 (20.1)	0.010
Protocol 162 (acute)				
Placebo (N=187)	78 (41.9)	NA	60 (32.6)	NA
Vioxx 25 mg (N=187)	54 (29.7)	0.014	36 (20.0)	0.006
Vioxx 50 mg (N=188)	54 (29.0)	0.009	36 (19.8)	0.005
Ibuprofen 400 mg (N=189)	50 (27.2)	0.003	39 (21.2)	0.014

*Using Pearson's Chi Square Analysis

Despite the lack of significance for the comparison of the proportion of subjects reporting nausea at 2 hours between rofecoxib 25 mg and placebo in trial 161, relative to this endpoint, I believe both doses should be approved for migraine. In trial 161 there is a clear numerical trend favoring rofecoxib 25 mg at every timepoint in the study for the proportion of subjects reporting nausea. Additionally the comparison of rofecoxib 25 mg to placebo in trial 162 did meet significance at 2 hours. Likewise rofecoxib 50 mg showed statistical significance for this endpoint in both trials. This recommendation is consistent with what I have been told about previous migraine NDA approvals where the lower dose of a test product failed to show efficacy for an associated symptoms but the higher dose did demonstrate efficacy.

In summary both rofecoxib 25 mg and rofecoxib 50 mg is effective in reducing the number of patients reporting nausea, photophobia and phonophobia at 2 hours compared to placebo. Although not presented in my review, the sponsor's analysis of the number of associated symptoms reported (i.e., a tallying of symptoms experienced by a single individual) at 2 hours shows a statistical benefit favoring rofecoxib 25 mg and rofecoxib 50 mg over placebo. Likewise

the sponsor's analysis of the proportion of patients reporting resolution of their baseline symptom (nausea, photophobia and phonophobia) at 2 hours also demonstrates a statistical benefit favoring rofecoxib 25 mg and rofecoxib 50 mg for photophobia and photophobia in both trials. The results for nausea were mixed with trial 162 demonstrating a statistical benefit and trial 161 demonstrating a numerical benefit for subjects reporting resolution of their baseline nausea at 2 hours. The validity of either of these endpoints is debatable however in general I don't believe they are relevant. An analysis of the total number of associated symptoms reported fails to account for the situations where subjects may resolve one associated symptom but then goes on to develop another. For example subjects may have photophobia and phonophobia at baseline (i.e., tally of 2) which quickly resolves but then develops nausea by 2 hours (i.e., tally of 1). This scenario would certainly not be an improvement. Likewise resolution of baseline symptoms sounds great on the first glance however it fails to take into consideration subjects that may develop an associated symptom after the baseline period.

5.1.4.1 Headache Relief at Various Timepoints

The following table demonstrates the sponsor's results for headache response at various timepoints up to 4 hours after administration of study medication. Headache relief is defined in the standard manner, i.e., pain intensity of moderate (2) to severe (3) at treatment onset going to mild (1) or none (2) at 2 hours after treatment. The findings at 2 hours are discussed in section 5.1.3. Rescue medication was not permitted for the first 2 hours. As demonstrated in the table rofecoxib 25 mg was statistically superior to placebo starting at 1 hour in trial 161 ($p \leq 0.01$) and 30 minutes in trial 162 ($p \leq 0.05$). Thereafter rofecoxib 25 mg continued to be superior to placebo through the fourth hour in both trials. Rofecoxib 50 mg was superior to placebo starting at time 30 minutes in both trial 161 ($p \leq 0.05$) and trial 162 ($p \leq 0.01$). Thereafter rofecoxib 50 mg also continued to be superior to placebo through the fourth hour in both trials. There was no significant difference between rofecoxib 25 mg and rofecoxib 50 mg in providing headache relief at any timepoint in either trial. However at each timepoint in both trials, except hour 4 in trial 162, there was a small but consistent numerical difference favoring rofecoxib 50 mg over rofecoxib 25 mg for headache relief. At hour 4 in trial 162, 81.3% of the patients randomized to rofecoxib 25 mg reported headache relief compared to 76.6% of the subjects randomized to rofecoxib 50 mg. The findings past 2 hours may be confounded by use of rescue medication and the natural evolution of migraines to resolve with time. This difference is important relevant to the Agency's decision whether both doses of rofecoxib should be approved. In my opinion this consistent dose effect favors the approval of both doses.

Results from trial 162 (acute) showed that ibuprofen 400 mg was superior to placebo ($p \leq 0.01$) in the proportion of subjects reporting headache relief from 30 minutes onward. At no time point within 4 hours were the differences between either dose of rofecoxib and ibuprofen 400 mg statistically significant.

Table 19 Headache Response at Various Timepoints, Trial 161 and 162, APT Population

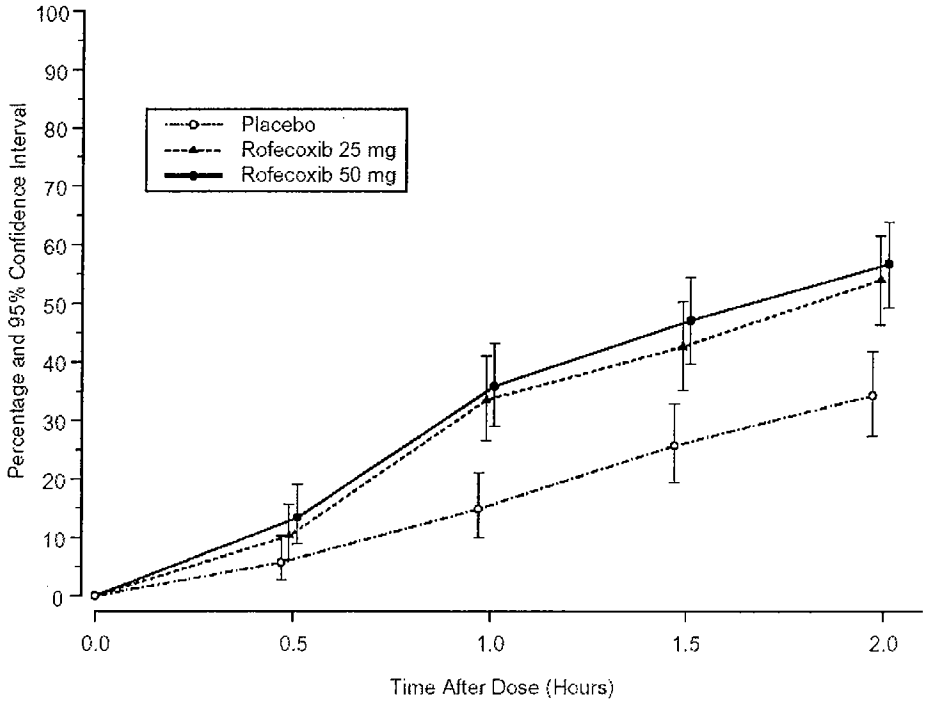
	t=0.5 hr	t=1.0 hr	t=1.5 hr	t=2.0 hr	t=3.0 hr	t=4.0 hr
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Protocol 161						
Placebo (N=175)	10 (5.7)	26 (14.9)	45 (25.7)	60 (34.3)	94 (53.7)	111 (63.4)
Vioxx 25 mg (N=176)	18 (10.2)	59 (33.5)†	75 (42.6)‡	95 (54.0)†	119 (67.6)*	137 (77.8)‡
Vioxx 50 mg (N=187)	25 (13.4)*	67 (35.8)†	88 (47.1)†	106 (56.7)†	137 (73.3)†	153 (81.8)†
Protocol 162 (acute)						
Placebo (N=187)	10 (5.3)	29 (15.5)	46 (24.6)	57 (30.5)	87 (46.5)	109 (58.3)
Vioxx 25 mg (N=187)	20 (10.7)*	56 (29.9)†	90 (48.1)†	111 (59.4)†	132 (70.6)†	152 (81.3)†
Vioxx 50 mg (N=188)	27 (14.4)‡	64 (34.0)†	98 (52.1)†	117 (62.2)†	134 (71.3)†	144 (76.6)†
Ibuprofen 400 mg (N=189)	27 (14.4)‡	60 (31.9)†	89 (47.1)†	109 (57.7)†	138 (73.0)†	140 (74.1)†

*p≤0.05, ‡p≤0.01, †p≤0.001 versus placebo

Adapted from sponsor table 2.7.3:16, page 53 and table 2.7.3:16, page 55, ise.pdf

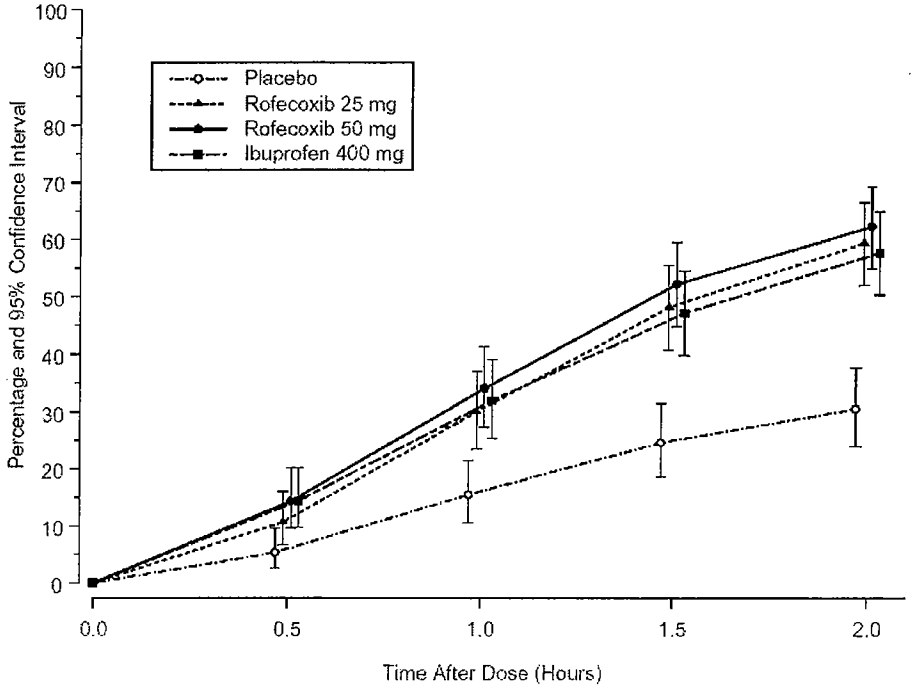
The following two figures visually demonstrates headache response over time as well as the confidence interval (CI) for each analysis. As can be seen there is a clear separation of response lines favoring rofecoxib 25 mg and rofecoxib 50 mg starting at 30 minutes. Additionally a small but consistent dose effect is evident.

Figure 2 Percentage of Subjects Reporting Headache Relief within 2 hours, Trial 161



Source: sponsor figure 2.7.3:1 ise.pdf, page 50.

Figure 3 Percentage of Subjects Reporting Headache Relief within 2 hours, Trial 162



Source: Sponsor figure 2.7.3:2, ise.pdf, page 51

In summary both rofecoxib 25 mg and rofecoxib 50 mg demonstrated superiority over placebo in both trials starting as early as 30 minutes for rofecoxib 50 mg and 30 to 60 minutes for rofecoxib 25 mg. Rofecoxib 50 mg provided a small (but not statistically significant) numerical advantage over rofecoxib 25 mg in the number of patients reporting headache relief up to 3 hours in both trials.

5.1.4.1 Pain Freedom

The following table demonstrates the sponsor's results for the secondary endpoint "Pain Freedom" at various timepoints up to 4 hours after administration of study medication. Although the sponsor defines Pain Freedom as complete alleviation of headache pain (0) without the use of rescue mediation the sponsor did not adjust the results for subjects that may have used rescue medication after hour 2. For this reason I limit my comments to the results from the first 2 hours only. The International Headache Society has recently recommended that studies in acute migraine treatment should consider using Pain Freedom as a primary endpoint so this endpoint will acquire added significance over the next few years.

As demonstrated in the table a significantly higher proportion of subjects randomized to rofecoxib 25 and 50 mg reported Pain Freedom at 2 hours (19.9% and 23.0% respectively) compared to placebo (8.0%) in both trials ($p \leq 0.01$). This comparison reached significance as early as 1 hour in trial 162 ($p \leq 0.05$). I consider the results at 2 hours to be clinically meaningful and consistent with what I have seen in other NDAs for approved migraine treatments. This finding would support approval of rofecoxib if we were to use the IHS recommendation of Pain Freedom as the primary endpoint. As with Headache Relief there appears to be a slight, but not

statistically significant, dose response for Pain Freedom in the comparison between rofecoxib 25 mg and rofecoxib 50 mg at many timepoints however this comparison is not as consistent as it was for Headache Relief.

Results from trial 162 (acute) showed that significantly more patients reported Pain Freedom at 2 hours postdose in the ibuprofen 400-mg group (23.8%, p≤0.001) than in the placebo group (5.3%). Although there was a slight numerical benefit to rofecoxib 25 mg and rofecoxib 50 mg compared to ibuprofen this difference did not reach statistical significance.

Table 20 Pain Freedom at Various Timepoints, Trial 161 and 162, APT Population

	t=0.5 hr	t=1.0 hr	t=1.5 hr	t=2.0 hr	t=3.0 hr#	t=4.0 hr#
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Protocol 161						
Placebo (N=175)	1 (0.6)	4 (2.3)	7 (4.0)	14 (8.0)	33 (18.9)	55 (31.4)
Vioxx 25 mg (N=176)	1 (0.6)	8 (4.5)	16 (9.1)	35 (19.9)‡	58 (33.0)‡	74 (42.0)
Vioxx 50 mg (N=187)	1 (0.5)	5 (2.7)	24 (12.8)‡	43 (23.0)†	62 (33.2)‡	94 (50.3)†
Protocol 162 (acute)						
Placebo (N=187)	0 (0.0)	2 (1.1)	8 (4.3)	10 (5.3)	26 (13.9)	54 (28.9)
Vioxx 25 mg (N=187)	0 (0.0)	12 (6.4)*	25 (13.4)‡	49 (26.2)†	66 (35.3)†	85 (45.5)†
Vioxx 50 mg (N=188)	2 (1.1)	10 (5.3)*	25 (13.3)‡	50 (26.6)†	65 (34.6)†	81 (43.1)‡
Ibuprofen 400 mg (N=189)	1 (0.5)	11 (5.9)*	29 (15.3)†	45 (23.8)†	72 (38.1)†	92 (48.7)†

*p≤0.05, †p≤0.01, ‡p≤0.001 versus placebo
Hour 3 and 4 may include subjects that took rescue medication.
Adapted from sponsor table 2.7.3:17 and 2.7.3:19, ise page 61 and 64.

In summary a significantly higher and clinically relevant proportion of subjects randomized to rofecoxib 25 mg and rofecoxib 50 mg reported complete relief of pain at two hours compared to placebo. Earlier statistically significant responses with rofecoxib in the range 5 to 15% were seen in Trial 162 however the results are not clinically meaningful in my opinion.

5.1.4.1 24-Hour Sustained Headache Relief and Freedom

The following table demonstrates the sponsor's results for the proportion of patients reporting 24 hour Sustained Headache Relief and 24 hour Sustained Pain Freedom. Twenty four hour Sustained Relief is defined as the proportion of patients with moderate to severe pain at baseline, who improve to mild or no pain at two hours postdose, who require no rescue medication, and who do not experience a moderate or severe headache recurrence between 2 to 24 hours post initial dose. Twenty four hour Sustained Pain Freedom is defined as the proportion of patients with moderate to severe pain at baseline, who improve to no pain at 2 hours post dose, who require no rescue medication and who do not experience a mild, moderate or severe headache recurrence 2 and 24 hours post initial dose.

In both trial 161 and 162 the proportion of patients randomized to rofecoxib 25 and 50 mg reporting Sustained Headache Relief at 24 hours was statistically superior to the proportion of patients randomized to placebo (p≤0.001). The proportion of subjects reporting Sustained Headache Relief were 34% and 39% (rofecoxib 25 mg) and 37% and 40% (rofecoxib 50 mg) compared to 13% and 17% (placebo) in trial 161 and 162 respectively. There was no consistent dose effect for this endpoint with 33.5% and 39.0% of the subjects taking rofecoxib 25 mg reporting Sustained Relief compared to 37.4% and 36.4% of subjects taking rofecoxib 50 mg in

trial 161 and 162 respectively. There was no significant difference between rofecoxib 25 mg and rofecoxib 50 mg in the proportion of subjects reporting 24 hour Sustained Headache Relief in either trial.

In both trial 161 and 162 the proportion of patients randomized to rofecoxib 25 and 50 mg reporting Sustained Pain Freedom at 24 hours was statistically superior to the proportion of patients randomized to placebo ($p \leq 0.001$). The proportion of subject reporting Sustained Pain Freedom were 13% to 20% (rofecoxib 25 mg) and 18% (both studies for rofecoxib 50 mg) compared to 3 to 6% (placebo) in trial 161 and 162 respectively. As with 24 hour Sustained Response there was no consistent dose response for this endpoint with 13.1% and 20.3% of the subjects taking rofecoxib 25 mg reporting sustained pain freedom compared to 17.6% and 18.1% of subjects taking rofecoxib 50 mg in trial 161 and 162 respectively. There was no significant difference between rofecoxib 25 mg and rofecoxib 50 mg in the proportion of subjects reporting 24 hour Sustained Pain Freedom in either trial 161 or trial 162.

Results from trial 162 (acute) showed that significantly more patients reported 24-Hour Sustained Headache Relief and Freedom 2 hours postdose in the ibuprofen 400-mg group (31.2% and 18.0% respectively, both $p \leq 0.001$) than in the placebo group (13.4% and 2.7% respectively). Although there was a slight numerical benefit to rofecoxib 25 mg and rofecoxib 50 mg compared to ibuprofen this difference did not reach statistical significance for either endpoint.

Table 21: 24-Hour Pain Freedom and Relief, Trial 161 and 162, APT Population

	24-Hour Sustained Headache Relief		24-Hour Sustained Pain Freedom	
	n (%)	Odds Ratio (95% CI) vs. placebo	n (%)	Odds Ratio (95% CI) vs. placebo
Protocol 161				
Placebo (N=175)	30 (17.1)	NA	11 (6.3)	NA
Vioxx 25 mg (N=176)	59 (33.5)	2.45 (1.47, 4.06)†	23 (13.1)	2.29 (1.07, 4.88)†
Vioxx 50 mg (N=187)	70 (37.4)	2.90 (1.77, 4.75)†	33 (17.6)	3.23 (1.57, 6.65)†
Protocol 162 (acute)				
Placebo (N=187)	25 (13.4)	NA	5 (2.7)	NA
Vioxx 25 mg (N=187)	73 (39.0)	4.35 (2.59, 7.32)†	38 (20.3)	9.54 (3.66, 24.92)†
Vioxx 50 mg (N=188)	75 (36.4)	4.37 (2.60, 7.35)†	34 (18.1)	8.22 (3.13, 21.57)†
Ibuprofen 400 mg (N=189)	59 (31.2)	3.03 (1.79, 5.13)†	34 (18.0)	8.15 (3.10, 21.39)†

*$p \leq 0.05$, †$p \leq 0.01$, ‡$p \leq 0.001$ versus placebo
Adapted from sponsor table 2.7.3:20 and table 2.7.3:21, ise.pdf page 66 and 68.

In summary, both rofecoxib 25 mg and rofecoxib 50 mg provide statistically superior efficacy compared to placebo for both 24 Hour Sustained Headache Relief and 24-Hour Sustained Pain Freedom. However there is no significant difference or consistent dose response between the two doses of rofecoxib for either endpoint.

5.1.4.1 Functional Disability

The following table summarizes the proportion of patients reporting normal activity within the initial 4 hours of treatment in trial 161 and 162 (acute). Functional disability was rated by the patient using a 4 point scale with 0 equal to normal activity, 1 equal to mildly impaired, 2 equal to severely impaired, and 3 equal to unable to carry out daily activities (requires rest). As demonstrated in the table a statistically higher proportion of subjects randomized to rofecoxib 25 mg and rofecoxib 50 mg reported normal activity compared to placebo starting as early as 15 to

30 minutes in trial 161 and 162 respectively. At no time in either trial was there a statistical difference between rofecoxib 25 mg and rofecoxib 50 mg. At 2 hours the treatment effect was clinically significant with approximately 18% to 20% more rofecoxib treated subjects reporting normal activity than placebo treated subjects. Findings after 2 hours may have been confounded by the use of rescue medication. A review of each possible response (normal to bed rest) at 2 hours demonstrates a predictable distribution of responses such that notably more patients randomized to placebo required bed rest or reported "severely impaired" than subjects randomized to rofecoxib 25 or 50 mg[2]. However it is important to note the scale used did not include a response for moderately impaired. It is difficult to determine how this oversight may have affected the results although I would assume it would have skewed the responses towards reports of severe impairment.

There were no significant differences between either rofecoxib dose and ibuprofen 400 mg with regards to functional disability at 2 hours.

Table 22 Proportion of Patients Reporting Normal Activity, Study 161 and 162 (acute)

	t=0.5 hr	t=1.0 hr	t=1.5 hr	t=2.0 hr	t=3.0 hr	t=4.0 hr
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Protocol 161						
Placebo (N=175)	4 (2.3)	10 (5.7)	13 (7.4)	22 (12.6)	48 (27.4)	69 (39.4)
Vioxx 25 mg (N=176)	7 (4.0)	19 (10.8)*	38 (21.6)†	59 (33.5)†	79 (44.9)	100 (56.8)
Vioxx 50 mg (N=187)	12 (6.4)*	27 (14.4)‡	47 (25.1)†	56 (29.9)†	85 (45.5)	114 (61.0)
Protocol 162 (acute)						
Placebo (N=187)	8 (4.3)	14 (7.5)	23 (12.3)	32 (17.1)	47 (25.1)	77 (41.2)
Vioxx 25 mg (N=187)	6 (3.2)	25 (13.4)*	45 (24.2)†	67 (36.0)†	82 (44.1)†	107 (57.2)†
Vioxx 50 mg (N=188)	9 (4.8)	23 (12.2)*	44 (23.4)†	68 (36.2)†	86 (45.7)†	104 (55.3)†
Ibuprofen 400 mg (N=189)	15 (8.1)*	27 (14.4)‡	48 (25.5)†	75 (39.9)†	91 (48.4)†	109 (58.0)†

Adapted from sponsor table 2.7.3:42, ise.pdf, page 99
*p≤0.05, ‡p≤0.01, †p≤0.001 versus placebo

In summary, compared to placebo both rofecoxib 25 mg and rofecoxib 50 mg were effective with regards to improving functional disability at 2 hours postdose.

5.1.4.1 Use of Escape Medication

The following table summarizes the proportion of patients taking additional rescue medication between hour 2 and hour 24 in trial 161 and 162 (acute). As previously stated the use of escape medication was prohibited for the first 2 hours after treatment with study medication. Rescue medication could consist of other analgesics, anti-emetic and/or triptan type products. The proportion of subjects taking rescue medications between 2 and 24 hours in trial 161 were 69.1%, 56.8%, and 55.6% in the placebo, rofecoxib 25-mg, and rofecoxib 50-mg groups respectively. The proportion of subjects taking rescue medications between 2 and 24 hours in trial 162 were 70.6%, 44.9%, and 47.9% in the placebo, rofecoxib 25-mg, and rofecoxib 50-mg groups respectively. Significantly fewer patients reported taking rescue medication in the rofecoxib 50 mg ($p \leq 0.01$ trial 161, $p \leq 0.001$ trial 162) and rofecoxib 25 mg ($p \leq 0.05$ trial 161, $p \leq 0.001$ trial 162) than in the placebo group in both trials. There was no significant difference between rofecoxib 50 mg and 25 mg in respect to the use of rescue medication in either trial.

[2] See sponsor table 2.7.3:41, ise.pdf, page 97 for details

There was no significant difference between the rofecoxib 50-mg (47.9%, p>0.05) and the rofecoxib 25-mg (44.9%, p>0.05) groups compared with ibuprofen 400 mg (54.5%) with regards to time to first intake of additional medication between 2 and 24 hours postdose.

Table 23 Use of Rescue Between 2 to 24 hours, Trial 161 and 162 (acute), APT Population.

	Use of Rescue n (%)	Odds Ratio (95% Confidence Interval)		
Protocol 161		**Compared to Placebo**	**Compared to Vioxx 25 mg**	**Compared to Vioxx 50 mg**
Placebo (N=175)	121 (69.1)	NA		
Vioxx 25 mg (N=176)	100 (56.8)	0.73 (0.56, 0.95)*	NA	
Vioxx 50 mg (N=187)	104 (55.6)	0.71 (0.54, 0.92)‡	0.97 (0.74, 1.27)	NA
Protocol 162 (acute)				
Placebo (N=187)	132 (70.6)	NA		
Vioxx 25 mg (N=187)	84 (44.9)	0.47 (0.36, 0.62)†	NA	
Vioxx 50 mg (N=188)	90 (47.9)	0.50 (0.38, 0.66)†	1.07 (0.79, 1.44)	NA
Ibuprofen 400 mg (N=189)	103 (54.5)	0.58 (0.45, 0.76)†	1.24 (0.93, 1.65)	1.16 (0.88, 1.54)

Adapted from sponsor table 2.7.3:44, ise.pdf, page 106
*p≤0.05, ‡p≤0.01, †p≤0.001 versus placebo

In summary patients treated with rofecoxib 25 and 50 mg had a reduced need for additional migraine medication between 2 to 24 hours after treatment with study medication compared to placebo.

5.1.4.1 Headache Recurrence/Worsening of Headache

The following table summarizes the proportion of patients reporting a Headache Recurrence and Headache Worsening. Headache recurrence is defined as the return of headache pain to moderate or severe intensity between 2 to 24 hours in patients who previously reported headache relief at 2 hours. Worsening of headache is defined as the return of headache to mild, moderate or severe intensity between 2 to 24 hours in patients who were pain free at 2 hours. It is important to remember that these variables only evaluate a subset of patients and does not encompass the entire population. The sponsor did not perform a statistical analysis of these endpoints. However as demonstrated in the table a numerically larger proportion of subjects randomized to placebo reported Headache Recurrence than subjects randomized to rofecoxib 25 mg or rofecoxib 50 mg (31.7%/38.6% vs. 29.5%/25.2% and 15.1%/23.9% respectively in trial 161/trial 162). A dose response favoring the higher dose of rofecoxib was also evident in both studies. However for Headache Worsening the results were not as consistently favorable for rofecoxib. In trial 161 a smaller proportion of subjects randomized to placebo reported headache worsening between 2 to 24 hours than either rofecoxib 25 mg or rofecoxib 50 mg (21.4% vs. 34.3% and 23.3% respectively). Whereas in Trail 162 a higher proportion of subjects randomized to placebo reported headache worsening between 2 to 24 hours compared to either rofecoxib 25 mg or rofecoxib 50 mg (50.0% vs. 22.4% and 30.0% respectively). There was no consistent dose effect for this endpoint.

Table 24 Proportion of Subjects Reporting Headache Worsening and Recurrence

	Headache Recurrence		Headache Worsening	
	N	n (%)	N	n (%)
Protocol 161				
Placebo	60	19 (31.7)	14	3 (21.4)
Vioxx 25 mg	95	28 (29.5)	35	12 (34.3)
Vioxx 50 mg	106	16 (15.1)	43	10 (23.3)
Protocol 162 (acute)				
Placebo	57	22 (38.6)	10	5 (50.0)
Vioxx 25 mg	111	28 (25.2)	49	11 (22.4)
Vioxx 50 mg	117	28 (23.9)	50	15 (30.0)
Ibuprofen 400 mg	109	37 (33.9)	45	10 (22.2)

Modified from sponsor table 2.7.3:45 and 2.7.3:46, ise.pdf page 107 and 109 respectively

In summary, in the subset of patients reporting headache relief at 2 hours, a larger proportion of patients randomized to placebo reported headache recurrence between 2 to 24 hours than subjects randomized to either rofecoxib 25 mg or rofecoxib 50 mg in both trial 161 and 162. Whereas, in the subset of patients reporting pain freedom at 2 hours, there was no consistent findings suggesting benefit for rofecoxib, between trial 161 and 162 in the proportion of patients reporting worsening of their headache.

5.1.4.1 24-Hour Migraine Specific Quality of Life/24-Hour Global Question of Improvement

The 24-hour Migraine-Specific Quality-of-Life Questionnaire is a self administered questionnaire consisting of 5 domains: work functioning, social functioning, energy/vitality, migraine symptoms, and feelings/concerns. Each domain included 3 questions, and each question was answered using a 7-point scale, with 1 indicating maximum impairment of quality of life and 7 indicating no impairment. A higher mean score on a domain corresponds to better quality of life. There was also a question on the overall change in migraine symptoms scored using a 7-point scale, with 0 representing "very much better" and 6 indicating "very much worse". The 24-Hour Global Question of Improvement asked patients to rate their overall satisfaction with the change in migraine symptoms experienced with treatment from "very much worse (-3) to very much better (+3).

The following table summarizes the mean change in the five domains assessed in the 24-Hour Specific Quality of Life questionnaire and the results of the 24-Hour Global Question of Improvement. As demonstrated in the table rofecoxib 50 mg was consistently superior to placebo for each of the 5 domains evaluated in the 24 Hour Specific Quality of Life questionnaire in each trial. In trial 162 rofecoxib 25 mg was consistently superior to placebo for each of the same 5 domains however the results in trial 161 were mixed. The differences between rofecoxib 25 mg and rofecoxib 50 mg did not reach significance in any domain of any study. Both rofecoxib 25 mg and rofecoxib 50 mg was superior to placebo in improving the response to the 24-Hour Global Question of Improvement.

Table 25 Mean Response to 24 Hour Specific QOL Questionnaire by Domain and Global Improvement

	Work Functioning	Social Functioning	Energy - Vitality	Migraine Symptoms	Feeling - Concerns	Global Improvement
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Trail 161						
Placebo N=175	11.47 (0.36)	11.26 (0.37)	10.73 (0.38)	11.98 (0.36)	10.39 (0.36)	1.40 (0.13)
Vioxx 25 mg N=174	12.97 (0.36)‡	12.33 (0.37)	11.97 (0.39)	13.01 (0.34)	11.55 (0.38)	1.88 (0.11)‡
Vioxx 50 mg N=187	13.47 (0.35)†	13.25 (0.36)†	12.34 (0.39)‡	13.68 (0.34)†	12.23 (0.35)†	1.92 (0.10)‡
Trial 162						
Placebo N=186	11.23 (0.36)	11.27 (0.37)	10.63 (0.35)	11.77 (0.32)	10.63 (0.36)	0.95 (0.12)
Vioxx 25 mg N=184	12.40 (0.35)*	12.42 (0.35)*	11.99 (0.37)‡	13.14 (0.33)‡	12.15 (0.35)‡	1.62 (0.11)†
Vioxx 50 mg N=182	12.72 (0.37)‡	12.51 (0.38)*	11.98 (0.39)‡	13.63 (0.34)†	12.16 (0.37)‡	1.55 (0.10)†
Ibuprofen 400 mg N=188	12.48 (0.36)*	12.51 (0.36)*	12.30 (0.37)†	12.80 (0.34)*	11.83 (0.35)*	1.41 (0.11)‡

Adapted from sponsor Appendices 2.7.3:5 and 2.7.3:6, ise.pdf, page 163 and 165.
*$p \leq 0.05$, ‡$p \leq 0.01$, †$p \leq 0.001$ versus placebo

In summary subjects randomized to rofecoxib 25 mg and rofecoxib 50 mg reported better quality of life responses on questionnaires performed at 24 hours.

5.1.4.1 Pain Intensity Difference (PID)

The following table summarizes the mean change in Pain Intensity Difference (PID) for patients in trial 161 and the acute phase of trial 162. Pain Intensity difference is calculated as the baseline pain intensity value (4-point scale) minus the pain intensity value at a specific time. Thus a low PID represents a small reduction in pain intensity over time and a high PID represent a large reduction. Pain intensity difference at 0.5, 1.0, 1.5, 2, 3, and 4 hours after treatment was calculated. As demonstrated in the table rofecoxib 25 mg and rofecoxib 50 mg were superior ($p \leq 0.001$) to placebo in the mean reduction in PID at 2 hours in both trial 161 and 162 (trial 161: 0.56 vs. to 0.86 and 0.98 respectively, trial 162: 0.34 vs. 1.09 and 1.11 respectively). This benefit was seen as early as 30 minutes for rofecoxib 50 mg and 1 hour for rofecoxib 25 mg in both trials. A fairly consistent although not statistically significant dose effect, favoring rofecoxib 50 mg, was seen in both trials for the first 2 hours. Findings after 2 hours may have been confounded by the use of rescue medication.

Table 26 Mean Change in PID, Trial 161 and 162 (acute), APT Population

	t=0.5 hr	t=1.0 hr	t=1.5 hr	t=2.0 hr	t=3.0 hr	t=4.0 hr
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Protocol 161						
Placebo (N=175)	0.11 (0.03)	0.25 (0.05)	0.42 (0.07)	0.56 (0.08)	0.92 (0.09)	1.22 (0.09)
Vioxx 25 mg (N=176)	0.14 (0.04)	0.47 (0.06)†	0.63 (0.07)‡	0.86 (0.08)†	1.19 (0.08)†	1.43 (0.07)‡
Vioxx 50 mg (N=187)	0.20 (0.04)*	0.52 (0.06)†	0.78 (0.06)†	0.98 (0.07)†	1.30 (0.07)†	1.59 (0.07)†
Protocol 162 (acute)						
Placebo (N=187)	0.07 (0.03)	0.25 (0.05)	0.30 (0.06)	0.34 (0.07)	0.74 (0.07)	1.05 (0.08)
Vioxx 25 mg (N=187)	0.13 (0.04)	0.52 (0.06)†	0.83 (0.07)†	1.09 (0.08)†	1.39 (0.07)†	1.63 (0.07)†
Vioxx 50 mg (N=188)	0.21 (0.04)‡	0.53 (0.06)†	0.87 (0.07)†	1.11 (0.08)†	1.33 (0.08)†	1.50 (0.07)†
Ibuprofen 400 mg (N=189)	0.22 (0.04)	0.57 (0.06)†	0.88 (0.07)†	1.11 (0.07)†	1.44 (0.07)†	1.58 (0.07)†

Adapted from sponsor Appendix 2.7.3:3 and 2.7.3:4, ise.pdf, page 161 and 162
Times after 2 hours may have been confounded by the use of rescue medication.
*p≤0.05, †p≤0.01, ‡p≤0.001 versus placebo

In summary rofecoxib 25 mg and rofecoxib 50 mg was consistently superior to placebo in providing a reduction in the mean pain intensity difference starting at 1 hours after treatment.

5.1.4.1 Time to Headache Relief

The following table and figures summarizes the analysis of "time to headache relief" within 2 hours after treatment. The sponsor primary analysis method for this endpoint is by the use of discrete proportion hazards regression model using life table estimates.

As demonstrated in the following table a statistically (p≤0.001) greater proportion of patients randomized to rofecoxib 25 mg and rofecoxib 50 mg reported headache relief within 2 hours compared to placebo in both trial 161 (39.8%, 58.2%, and 61.2%, respectively) and trial 162 (35.8%, 61.3%, 64.9%, respectively). There was no statistical difference between the rofecoxib 25 mg and rofecoxib 50 mg groups in providing earlier time to initial headache relief within 2 hours of dosing in either trial.

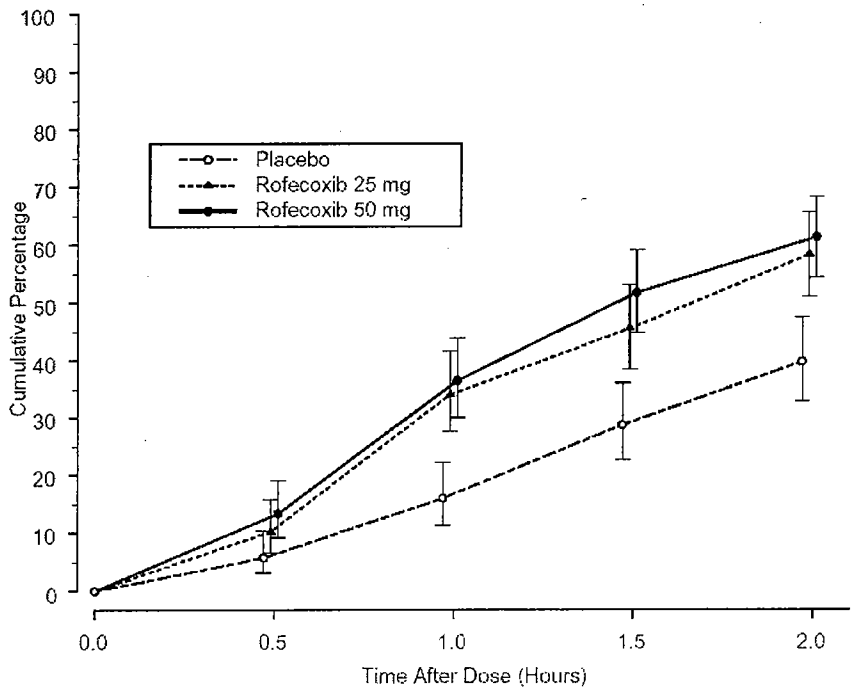
Table 27 Cumulative Percentage of Subjects (Life-Table Estimates) with Headache Relief Within 2 hours

	t=0.5 hr	t=1.0 hr	t=1.5 hr	t=2.0 hr	Hazard Ratio (95% CI)
	n (%)	n (%)	n (%)	n (%)	Compared to Placebo
Protocol 161					
Placebo (N=175)	10 (5.7)	18 (16.0)	22 (28.7)	19 (39.8)	NA
Vioxx 25 mg (N=176)	18 (10.2)	42 (34.1)	20 (45.5)	22 (58.2)	1.70 (1.25, 2.31)†
Vioxx 50 mg (N=187)	25 (13.4)	43 (36.5)	28 (51.7)	17 (61.2)	1.99 (1.47, 2.69)†
Protocol 162 (acute)					
Placebo (N=187)	10 (5.3)	21 (16.6)	22 (28.3)	14 (35.8)	NA
Vioxx 25 mg (N=187)	20 (10.7)	37 (30.5)	35 (49.2)	22 (61.3)	2.22 (1.64, 3.00)†
Vioxx 50 mg (N=188)	27 (14.4)	38 (34.6)	36 (53.7)	21 (64.9)	2.44 (1.81, 3.29)†
Ibuprofen 400 mg (N=189)	27 (14.3)	37 (34.0)	28 (48.9)	26 (62.9)	2.34 (1.73, 3.17)†

Adapted from sponsor table 2.7.3:47, ise.pdf, page 112.
*p≤0.05, †p≤0.01, ‡p≤0.001 versus placebo

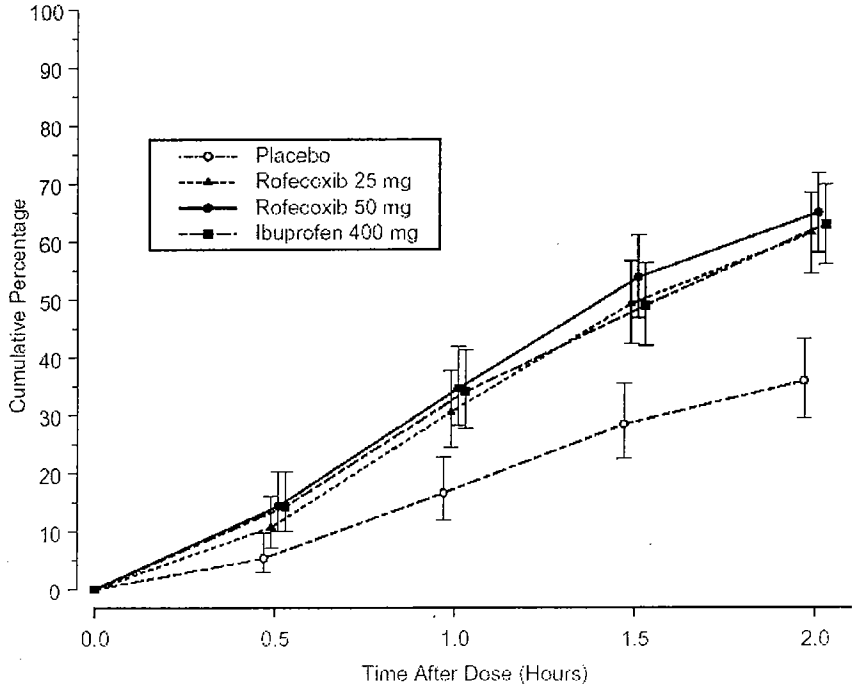
The following 2 figures graphically demonstrates the results of this analysis. As demonstrated in the two figures there is a nice separation of event lines with a significant difference favoring rofecoxib 25 and 50 mg clearly shown at 1 hour for both studies and at 30 minutes for rofecoxib 50 mg in trial 162.

Figure 4 Cumulative Percentage (Life-Table Estimates) of Subjects with 1st Report of Headache Relief Within 2 Hours, Trial 161.



Source: Sponsor Figure 2.7.3:11, ise.pdf, page 114

Figure 5 Cumulative Percentage (Life-Table Estimates) of Subjects with 1st Report of Headache Relief Within 2 Hours, Trial 162 (acute).



Source: Sponsor Figure 2.7.3:12, ise.pdf, page 115

In summary, within 2 hours of dosing, both rofecoxib 50 mg and rofecoxib 25 mg were superior to placebo with respect to the time to initial headache relief.

5.1.4.1 Long-Term (3 months) Efficacy Results (Phase 2, Trial 162)

Trial 162 included a 3-month extension phase in which eligible subjects were re-randomized in a 2:2:1 fashion to either rofecoxib 50 mg, rofecoxib 25 mg or ibuprofen 400 mg respectively. There was no placebo control during this phase. Overall 268 subjects continued on rofecoxib 25 mg, 244 subjects continued on rofecoxib 50 mg and 123 subjects continued on ibuprofen. The mean number of migraines attacks treated per month were 2.6 for rofecoxib 25 mg, 2.9 for rofecoxib 50 mg and 2.6 for ibuprofen 400 mg. There were few withdrawal during the study. I discuss withdrawals and exposure in greater detail in section 6 of this review. There were no prestated hypothesis for this phase of the study hence all analyses are considered exploratory.

The following table summarizes the proportion of patients' attacks with Headache Relief at 2 hours (adjusted for subjects who took rescue medication prior to 2 hours). As demonstrated in the table the comparison of rofecoxib 50 mg to rofecoxib 25 mg just meets the threshold for statistical significance (p=0.050). There was no significant difference between either dose of rofecoxib and ibuprofen for this endpoint. The overall treatment response rates for rofecoxib 25 mg and rofecoxib 50 mg were similar to the response rates seen during trial 161 and the acute phase of trial 162. Specifically, rofecoxib 25 mg and 50 mg, respectively, provided headache relief at 2 hours in 54.0% and 56.7% of patients in trial 161, and 59.4% and 62.2% in trial 162 acute phase. In the trial 162 extension phase, the mean percentages of patients' attacks with headache relief at 2 hours were 61.7% and 65.4% in the rofecoxib 25-mg and rofecoxib 50-mg groups, respectively. The "mean percentages of patients' attacks" were obtained by calculating the percentage of each patient's treated attacks for which the endpoint was achieved. These individual percentages were then averaged to obtain the mean percentages. The sponsor's analysis of covariates failed to demonstrate any significant interactions by gender, age, race, region, previous response to NSAIDs, use of migraine prophylaxis, use of oral contraceptives, or baseline severity.

Table 28 Proportion of Patients' Attacks with Headache Relief at 2 Hours, 162 Extension

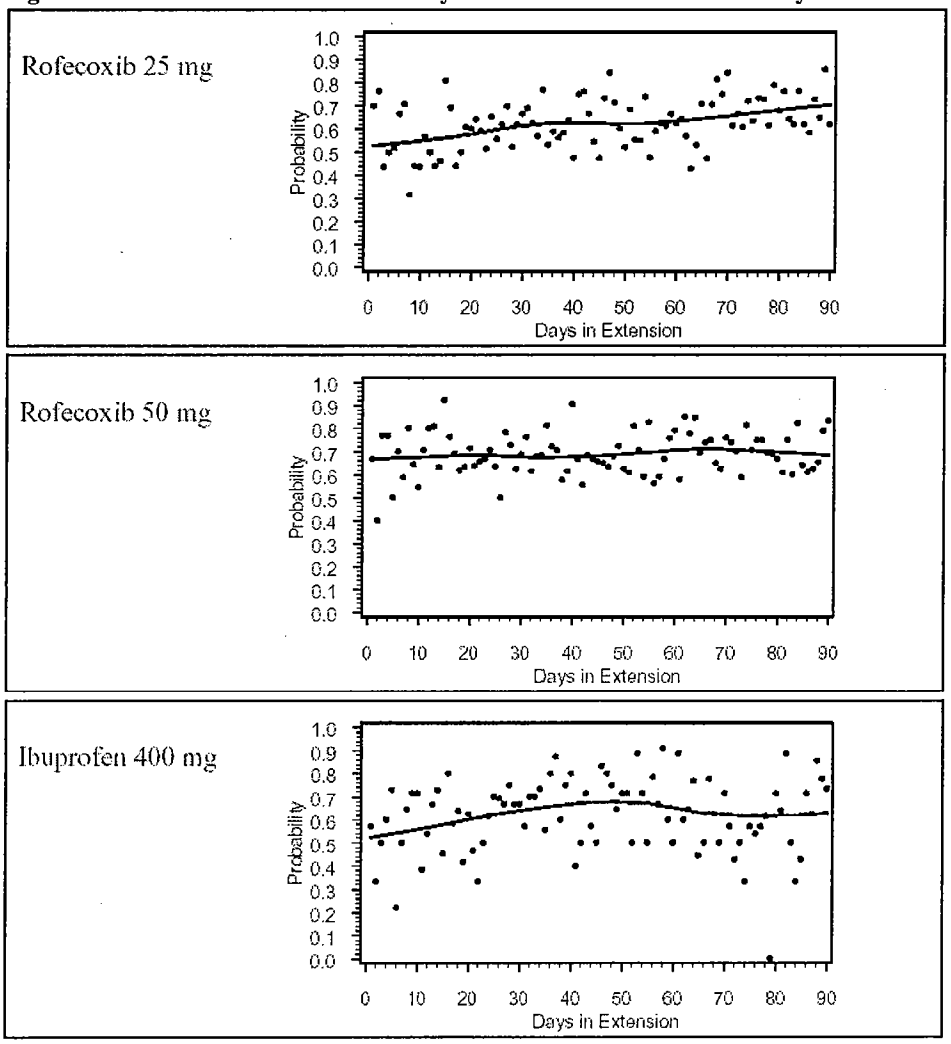
	Rofecoxib 25 mg (N = 267)	Rofecoxib 50 mg (N = 241)	Ibuprofen 400 mg (N = 120)
Mean	61.7	65.4	59.2
Median	66.7	73.7	66.7
Interquartile range	33.3 to 95.5	50.0 to 100.0	30.9 to 93.5
Pairwise Comparison		Statistic	
Rofecoxib 50 mg versus rofecoxib 25 mg		p-value	0.050
		odds ratio (95% CI)	1.44 (1.00 to 2.08)
Rofecoxib 25 mg versus ibuprofen 400 mg		p-value	0.947
		odds ratio (95% CI)	0.98 (0.63 to 1.55)
Rofecoxib 50 mg versus ibuprofen 400 mg		p-value	0.133
		odds ratio (95% CI)	1.42 (0.90 to 2.25)

An odds ratio >1 is in favor of the first treatment group of the corresponding pairwise comparison.
N = Number of patients with non-missing evaluation at 2 hours postdose.
Interquartile range = First quartile - third quartile.
CI = Confidence interval.

Source: Sponsor Table 42, P162x1.pdf, page 109

The sponsor discusses consistency of effect over time by providing the following diagrams of smoothed estimated probability of relief at 2 hours by time (days in extension study up to 90 days). As demonstrated there does not appear to be any diminution of treatment response over time for any of the test products evaluated. There was no statistical difference in overall consistency between any of the cohorts.

Figure 6 Smoothed Estimated Probability of Headache Relief at 2 hours by Time



Source: Sponsor figure 2, P162x1.pdf, page 86

Defined for each of the first 90 days in extension, a dot (•) represents, among all attacks occurring on that day, the percentage of attacks for which headache relief at 2 hours occurred. The line is a smoothed estimate of this percentage over the first 90 days.

The following table briefly summarizes the sponsor analyses of several endpoints. The mean percentages of patients' attacks with Pain Freedom at 2 hours postdose were 27.6%, 30.6%, and 28.0% in the rofecoxib 25-mg, rofecoxib 50-mg, and ibuprofen 400-mg groups, respectively. There were no significant differences between treatment groups ($p>0.050$) in providing Pain Freedom at 2 hours postdose.

The mean percentages of patients' attacks with 24-hour Sustained Headache Relief were 47.8%, 52.0%, and 39.0% in the rofecoxib 25-mg, rofecoxib 50-mg, and ibuprofen 400-mg groups, respectively. The rofecoxib 50-mg group was significantly superior to the rofecoxib 25-mg group (p=0.042) and to the ibuprofen 400-mg group (p=0.001) in providing 24-Hour Sustained Headache Relief. Rofecoxib 25 mg tended to be better than ibuprofen 400 mg, but did not reach statistical significance for this comparison (p=0.066).

The mean percentages of patients' attacks with 24-Hour Sustained Pain Freedom were 24.3%, 26.9%, and 21.8% in the rofecoxib 25-mg, rofecoxib 50-mg, and ibuprofen 400-mg groups, respectively. There were no significant differences between treatment groups (p≥0.134) in providing 24-Hour Sustained Pain Freedom. Rofecoxib 50 mg was numerically but not statistically superior to rofecoxib 25 mg (p=0.134) and ibuprofen 400 mg (p=0.150) in providing 24-Hour Sustained Pain Freedom. Rofecoxib 25 mg was not significantly different from ibuprofen 400 mg (p=0.806)

The mean percentages of patients' attacks requiring rescue medication between 2 and 24 hours postdose were 36.2%, 36.0%, and 47.1% in the rofecoxib 25-mg, rofecoxib 50-mg, and ibuprofen 400-mg groups, respectively. The rofecoxib 25-mg group was not significantly different from the rofecoxib 50-mg group (p=0.477) in reducing the need for rescue medication between 2 and 24 hours postdose. Rofecoxib 25 mg (p=0.015) and rofecoxib 50 mg (p=0.003) were significantly superior to ibuprofen 400 mg for this endpoint.

Table 29 Secondary Endpoint Results, Mean Percentage of Patients Attacks Reporting each Outcome.

	Vioxx 25 mg N=267	Vioxx 50 mg N=241	Ibuprofen 400 mg N=120	Comparison p-values		
				Vioxx 50 vs. Vioxx 25	Vioxx 25 vs. ibuprofen	Vioxx 50 vs. ibuprofen
Pain Freedom at 2 hours	27.6	30.6	28.0	0.127	0.607	0.474
24 hr Sustained Relief	47.8	52.0	39.0	0.042	0.066	0.001
24 hr Sustained Pain Freedom	24.3	26.9	21.8	0.134	0.806	0.150
Use of Rescue 2 to 24 hours	36.2	36.0	47.1	0.477	0.015	0.003
Headache Recurrence	19.8	16.0	29.9			
Headache Worsening	14.4	15.3	25.1			

Source: Sponsor Tables 36 (page 102), 37 (page 104), 38 (page 105), 39 (page 106), 40 (page 107), 41 (page 109), P162x1.pdf

In summary rofecoxib 50 mg was either statistically superior to, or numerically better than rofecoxib 25 mg in all endpoints evaluated. Specifically rofecoxib 50 mg was superior to rofecoxib 25 mg for 24 hour Sustained Headache Relief (p=0.042) and Pain Relief at 2 hour (p=0.050). The sponsor concludes that the long term analyses support the efficacy of rofecoxib 25 and rofecoxib 50 mg in treating migraine and some patients may receive additional benefit from rofecoxib 50 mg as compared to rofecoxib 25 mg. I concur with this statement. Relative to ibuprofen the sponsor concludes that rofecoxib appears to have an efficacy "*at least as good and possibly better*" than ibuprofen 400 mg and rofecoxib 50 mg appears to have a longer duration of

efficacy than ibuprofen 400 mg. The sponsor draws this conclusion primarily from the comparison of rofecoxib 50 mg to ibuprofen 400 mg for the endpoint 24 hour Sustained Headache Relief (p=0.001). The sponsor argues this is a potential advantage for rofecoxib over ibuprofen. I am uncertain what type of claim (if any) the sponsor intends to make of these comparisons in marketing however there are several factors to keep in mind when weighing their validity. First of all despite the sponsor contention that 400 mg is the most effective dose of ibuprofen most clinicians, including myself, believe that additional efficacy can be achieved with the 600 and 800 mg dose of ibuprofen albeit more adverse events may occur. Secondarily it must be remembered that this phase of the study was not powered to determine a difference between rofecoxib and ibuprofen. Thirdly, none of these results have been replicated. And finally, since the long term phase of trial 162 did not include a placebo arm it is not possible to determine whether rofecoxib 25, rofecoxib 50 and ibuprofen 400 mg would perform any better than placebo for these long term endpoints. For these reasons marketing claims against ibuprofen should be carefully evaluated for validity and no comparisons in labeling should be permitted in my opinion.

5.1.5 Trial P125 (Migraine prophylaxis)

Trial P125 was a phase IIa, randomized, placebo-controlled, double-blind, parallel group study to evaluate the safety and efficacy of rofecoxib 25 mg daily for the prophylactic treatment of migraines. Eligible adult subjects underwent a 2-month placebo run-in to determine migraine frequency. Patients with at least 3 migraines in the last month of the placebo run-in were eligible for the 3 month blinded treatment period. Eligible subjects were then randomized to either rofecoxib 25 mg (n=91), montelukast 20 mg (n=93), or placebo (n=84) once daily for 90 days. Breakthrough migraines were treated with rizatriptan 10 mg. The primary efficacy endpoint was the proportion of patients reporting a ≥50% decrease from baseline (month 2) in migraine attack frequency/month (adjusted to 28 days). Secondary endpoints included: (1) the proportion of patients reporting ≥50% decrease from baseline (Month 2) in migraine attack frequency/month (adjusted to 28 days) during Month 5; (2) the change from baseline (Month 2) in mean number of migraine headache days per month (adjusted to 28 days); (3) the change from baseline (Month 2) in average migraine headache severity; (4) the mean rating of physician's global response; and (5) the change from baseline (Month 2) in mean rating of patient's satisfaction. The primary analysis population was based on the modified intention-to-treat approach (MITT) including all patients who took at least one dose of post-randomization treatment and who had a baseline value and at least one postrandomization evaluation.

The following table summarizes the sponsor's analysis of the primary endpoint. As demonstrated in the table the percentage of responders (≥50% reduction) was significantly higher in the rofecoxib 25 mg group than in the placebo group (p=0.024). There was no significant differences between montelukast 20 mg and placebo (p=0.231). The sponsor reports that the proportion of responders was generally smaller than what was expected in all treatment groups. The study was planned on the assumption of 60% response with rofecoxib 25 mg and 35% response with placebo.

Table 30 Proportion of Patients Reporting ≥50% Decrease in Migraine Frequency (Primary Endpoint)

Treatment	N	Number (%) of Patients Reporting ≥ 50% Decrease in Migraine Attack Frequency During Double-Blind Treatment Period	
Rofecoxib 25 mg	72	15 (20.8)	
Montelukast 20 mg	77	10 (13.0)	
Placebo	71	5 (7.0)	
Pairwise Comparison		Odds Ratio (95% CI)	p-value
Rofecoxib 25 mg versus Placebo		3.55 (1.18, 10.7)	0.024
Montelukast 20 mg versus Placebo		2.02 (0.64, 6.40)	0.231
Rofecoxib 25 mg versus Montelukast 20 mg		1.76 (0.71, 4.33)	---
Effect		p-Value	
Treatment		0.072	
Region		0.015	
Treatment-by-Region Interaction		0.870	

Source: sponsor Table 1 (Per Protocol Approach), study report P125, page 837.
Analyzed using Logistic Regression model including terms for treatment and region.

The following table briefly outlines the sponsor's analysis of the secondary endpoints. As demonstrated in the table rofecoxib 25 mg was not statistically superior for any of the secondary endpoints.

Table 31 Selected Secondary Endpoints, Trial 125

		Rofecoxib 25 mg N=84	**Montelukast 20 mg N=91**	**Placebo N=78**
Responders at 5 months n(%)		26 (31.0%)	22 (24.2%)	17 (21.8%)
	p-value	0.176	0.674	
Mean change in number of days with migraine		-1.1	-0.7	-0.5
	p-value	0.211	0.739	
Mean change in severity		-0.0	-0.0	-0.1
	p-value	0.377	0.205	
Mean physician global response		3.0	3.4	3.4
	p-value	0.099	0.897	
Mean change in patient satisfaction		-0.5	-0.2	-0.2
	p-value	0.177	0.917	

Source: Sponsor tables: 21 (page 71), 22 (page 73), 23 (page 73), 24 (page 75), and 25 (page 77) study report p125.pdf.

The sponsor summarizes the study by stating rofecoxib 25 mg may be useful in the prophylactic treatment of migraine. However the overall response rate observed with rofecoxib 25 mg (20.8%) in this study is less than that typically reported for other agents such as beta-blockers (44 to 48%). The sponsor states further data are needed before definitive conclusions can be reached about the efficacy of rofecoxib as a prophylactic treatment for migraine attacks. At this time the sponsor does not seek this indication. These results are briefly presented for completeness only. If the sponsor intends to further pursue this indication then significant discussion and thought must occur about the safety of daily rofecoxib use in a young, mostly female, migraine population. I have significant doubts whether a response rate of 20.8%, representing as little as 1 to 2 fewer migraine per month, clinically justifies the risks associated with daily use of rofecoxib.

5.2 Efficacy Conclusions

5.2.1 Sponsor Efficacy Conclusions

The sponsor summarizes their efficacy results as follows:

Acute Phase

1. *Rofecoxib 50 mg and 25 mg are superior to placebo in providing headache relief at 2 hours.*
2. *Rofecoxib 50 mg and 25 mg are superior to placebo in providing pain freedom at 2 hours, 24-hour sustained headache relief, and 24-hour sustained pain freedom; in reducing the need for additional migraine medication between 2 and 24 hours; and in improving functional disability at 2 hours.*
3. *Rofecoxib 50 mg and 25 mg are superior to placebo in reducing the number of associated migraine symptoms (photophobia, phonophobia, nausea) at 2 hours.*
4. *Rofecoxib 50 mg and 25 mg significantly decreased the incidence of photophobia, phonophobia, and nausea, compared to placebo.*
5. *Rofecoxib 50 mg and 25 mg tend to be better than ibuprofen 400 mg in providing 24-hour sustained headache relief.*
6. *Ibuprofen 400 mg is superior to placebo in providing headache relief at 2 hours.*

Extension Phase

1. *Rofecoxib 25 mg and 50 mg provide consistent efficacy.*
2. *Rofecoxib 50 mg is superior to rofecoxib 25 mg in providing 24-hour sustained headache relief, and possibly headache relief at 2 hours.*
3. *Rofecoxib 50 mg is superior to ibuprofen 400 mg in providing 24-hour sustained headache relief.*
4. *Rofecoxib 25 mg and 50 mg are superior to ibuprofen 400 mg in reducing the need for additional migraine medication between 2 and 24 hours.*

5.2.2 Agency Medical Reviewer Conclusions

The following table provides a brief overview of the sponsor efficacy results for essential the endpoints from trial 161 and 162. As demonstrated in the table rofecoxib had a clear advantage over placebo for pain relief at 2 hours as well as most symptoms associated with migraine. The only essential endpoint in doubt is the proportion of subjects on rofecoxib 25 mg reporting nausea at 2 hours in trial 161 (p=0.111). Although the sponsor did not win on this endpoint there was a clear numerical benefit for the low dose rofecoxib 25 mg compared to placebo (33.0% vs. 41.7%). The rofecoxib 50 mg cohort in trial 161 reported significantly less nausea than placebo. In trial 162 both the low dose and high dose of rofecoxib reported significantly less nausea at two hours than placebo. All together I do not believe the lack of significance in trial 161 for the proportion of patients on rofecoxib 25 mg reporting nausea at 2 hours should hold up the approval of this NDA.

Table 32 Essential Endpoints from Trial 161 and 162.

		Rofecoxib 25 mg	Rofecoxib 50 mg	Ibuprofen	Placebo
Percentage of subjects reporting Headache Relief at 2 hours	Trial 161	54.0%	56.7%	NA	33.7%
	p-value*	**≤0.001#**	**≤0.001**		
	Trial 162	59.4%	62.2%	57.7%	29.9%
	p-value*	**≤0.001**	**≤0.001**	≤0.001	
Percentage of subjects reporting nausea at 2 hours	Trial 161	33.0%	30.3%	NA	41.7%
	p-value*	0.111	**0.030**		
	Trial 162	31.2%	29.8%	27.8%	42.2%
	p-value*	**0.023**	**0.013**	**0.001**	
Percentage of subjects reporting photophobia at 2 hours	Trial 161	61.4%	57.5%	NA	71.4%
	p-value*	**0.032**	**0.005**		
	Trial 162	51.1%	49.5%	50.0%	65.2%
	p-value*	**0.004**	**0.002**	**0.003**	
Percentage of subjects reporting phonophobia at 2 hours	Trial 161	52.3%	45.2	NA	64.0%
	p-value*	**0.036**	**≤0.001**		
	Trial 162	43.5%	42.6%	38.8%	59.4%
	p-value*	**0.002**	**0.001**	**≤0.001**	
Percentages of subjects reporting Pain Freedom at 2 hours	Trial 161	19.9%	23.0%	NA	8.0%
	p-value*	**0.002**	**≤0.001**		
	Trial 162	26.2%	26.6%	23.8%	5.3%
	p-value*	**≤0.001**	**≤0.001**	**≤0.001**	

*Compared to placebo, # bolding denotes statistical significance.

In addition to the above summary table I offer the following statements relative to efficacy:

1. Acute Studies

- The two pivotal trials conducted in support of this NDA supplement were adequately designed, conducted, and analyzed. Additionally the level of acute exposure to rofecoxib 25 mg and rofecoxib 50 mg is sufficient.
- Both trial 161 and trial 162 (acute phase) demonstrated efficacy for rofecoxib 50 mg and rofecoxib 25 mg using the pre-stated primary endpoint of Headache Relief at 2 hours compared to placebo ($p \leq 0.001$ both trials). Additionally both trials demonstrated a small numerical difference/dose effect in headache response at 2 hours between rofecoxib 25 mg and rofecoxib 50 mg, favoring rofecoxib 50 mg. This difference did not reach statistical significance however it supports the approval of both doses of rofecoxib.
- Statistically significant headache relief was first observed at 30 minutes with rofecoxib 50 mg and at 1 hour with rofecoxib 25 mg in one study and at 30 minutes with both rofecoxib 25 mg and 50 mg in the other study.
- Following administration of rofecoxib 50 mg, there was a significant difference in the incidence of photophobia, phonophobia, and nausea at 2 hours in trial 161 and trial 162 compared to placebo. Following administration of rofecoxib 25 mg there was a significant difference in the incidence of photophobia and phonophobia at 2 hours in trial 161 and 162 compared to placebo. The proportion of subject reporting nausea at 2 hours following treatment with rofecoxib 25 mg was significantly less than in subjects treated with placebo in

trial 162 and numerically lower in trial 161. A slight dose effect favoring rofecoxib 50 mg compared to rofecoxib 25 mg was evident for nausea, photophobia and phonophobia at 2 hours in both studies.

- In general rofecoxib 50 mg was numerically superior to rofecoxib 25 mg on most secondary efficacy measurements during the acute studies including headache response, pain freedom, relief of associated symptoms, and improvement in quality-of-life.
- Rofecoxib was effective as measured by 2 hour headache relief regardless of aura, gender, race, age, presence of menses, or dysmenorrhea. Rofecoxib efficacy was not affected by concomitant use of common prophylactic migraine drugs, oral contraceptives, or previous response to NSAIDs.

3. Long Term Study and comparison with ibuprofen

- The long term exposure of migraine subjects to rofecoxib 25 mg and 50 mg is limited to 3 months with each cohort treating an average of 2 to 3 migraines per month. I discuss the level of chronic exposure in further detail in the Safety section of this review.
- The long term phase of trial 162 demonstrated consistency of effect for relief at 2 hours in subjects treated with rofecoxib 50 mg and rofecoxib 25 mg. Most endpoints did not demonstrate a significant difference between active cohorts except for the following: rofecoxib 50 mg vs. rofecoxib 25 mg for 2-Hour Headache Relief (p=0.050), rofecoxib 50 mg vs. rofecoxib 25 mg for 24-Hour Sustained Relief (p=0.042), rofecoxib 50 mg vs. ibuprofen 400 mg for 24-Hour Sustained Relief (p-0.001), and rofecoxib 50 mg vs. ibuprofen 400 mg for Use of Rescue Medication between 2 to 24 hours (p=0.003). However there was a consistent slight numerical benefit for rofecoxib 50 mg versus rofecoxib 25 mg in all endpoints evaluated. The results of this extension phase adds additional support to the benefit of rofecoxib 50 mg over rofecoxib 25 mg although the study is limited by the lack of a placebo arm and no prestated efficacy hypotheses.
- Protocol 162 includes an ibuprofen arm in the acute and long term extension phases. The sponsor hoped that rofecoxib 25 mg and 50 mg would be superior to ibuprofen for headache recurrence since it has a longer half life. In my opinion trial 162 does not support a conclusion that rofecoxib 25 mg or 50 mg provides any additional significant benefit over ibuprofen. The strongest suggestion of a benefit comes from the comparison of the subset of patients reporting 24 Hour Headache Recurrence where numerically fewer patients reported a headache recurrence following rofecoxib 25 mg (25.2%) or rofecoxib 50 mg (23.9%) compared to ibuprofen 400 mg (33.9%) in the acute phase of trial 162. The sponsor did not perform any statistical analysis of this endpoint. Similar results were seen in the extension phase where fewer patients reported a headache recurrence following rofecoxib 25 mg (19.8%) or rofecoxib 50 mg (16.0%) compared to ibuprofen 400 mg (29.9%). Additionally the efficacy of rofecoxib was numerically better than ibuprofen 400 mg for the percentage of patients with: headache relief at 2 hours, pain freedom at 2 hours, 24-hour sustained headache relief, 24-hour sustained pain freedom, and the need for rescue medication (see acute phase trial 162 for results). I am uncertain what type of claim (if any) the sponsor intends to make of these comparisons in marketing however there are several factors to keep in mind when weighing their validity. First of all despite the sponsor contention that 400 mg is the most effective dose of ibuprofen most clinicians, including myself, believe that additional efficacy can be achieved with the 600 and 800 mg dose of ibuprofen albeit more

adverse events may occur. Secondarily it must be remembered that study 162 was not powered to determine a difference between rofecoxib and ibuprofen. Thirdly, none of these results have been replicated. And finally, since the long term phase of trial 162 did not include a placebo arm it is not possible to determine whether rofecoxib 25, rofecoxib 50 and ibuprofen 400 mg would perform any better than placebo for these long term endpoints.

In summary following treatment with rofecoxib 25 mg and rofecoxib 50 mg subjects treating a migraine attack of moderate to severe intensity reported significantly more relief of pain at 2 hours than subjects taking placebo. The benefit for this endpoint is clear. Relative to the associate symptoms (nausea, photophobia, phonophobia) seen in some migraineurs, rofecoxib 25 mg and rofecoxib 50 mg demonstrated efficacy as seen in the proportion of patients reporting each of these symptoms at 2 hours. For the proportion of patients reporting photophobia and phonophobia at 2 hours, both trial 161 and 162 demonstrated significant efficacy compared to placebo. For the proportion of patients reporting nausea at 2 hour, trial 162 demonstrated significant efficacy compared to placebo. Trial 161 however resulted in mixed results with only rofecoxib 50 mg demonstrating significance for this comparison. Rofecoxib 25 mg, however, demonstrated a strong numerical benefit over placebo for nausea at 2 hours and was clearly significant at 3 hours. In conclusion the efficacy results from trial 161 and 162 favor the approval of this NDA.

6. Integrated Review of Safety

In this section of my review I summarize the safety results from the clinical development program for rofecoxib in the treatment of acute migraine. The rofecoxib migraine program includes 2 acute treatment clinical trials, trial 161 and trial 162, and a single migraine prophylaxis trial (trial 125). Both trial 161 and the 1st phase of trial 162 were single attack studies of similar design (double blind, randomized, placebo controlled, parallel studies) hence the safety data from 1st phase of trial 162 will be combined with the safety results from trial 161 (single-attack only study). Trial 162 also included a second phase in which subjects were re-randomized to rofecoxib 25 mg, rofecoxib 50 mg or ibuprofen 400 mg in order to treat up to 8 migraines per month for 3 months. The 3-month safety data from trial 162 will be handled separately and augmented by safety data from trial 125 (described below). The sponsor has not conducted any other long term studies to evaluate the safety of rofecoxib in migraineurs. No clinical pharmacology studies were conducted in support of this NDA.

In lieu of the traditional long term safety studies generally required for a migraine NDA the sponsor submits a brief summary of the previously submitted long-term safety data for rofecoxib in other approved indications (Osteoarthritis, Rheumatoid Arthritis, Acute Pain and Dysmenorrhea) as well as a brief summary of the post-marketing experience of rofecoxib in migraine. I will briefly summarize the sponsor's discussion of the long term safety findings from these sources. In addition to these resources I also reviewed the Agency Review of the VIGOR trial (VIOXX GI Clinical Outcome Research, sNDA 21-042/052 s/007, review dated March 30, 2001) conducted by Maria Villalba M.D. (Medical Officer, HFD 550). The VIGOR trial is a long term (up to 1 year) trial designed to compare the safety of rofecoxib 50 mg compared to naproxen 1000 mg daily in over 8000 subjects with Rheumatoid Arthritis.

During trial 161 and 162 safety was primarily assessed using patient diaries reviewed at each follow up visit. Follow up visits occurred within 14 days after dosing during trial 161 and the acute phase of trial 162 and at 1 or 2 monthly intervals for the extension phase of trial 162. In trial 161 and the acute phase of trial 162 adverse events were recorded from the start of trial medication up to 14 days post-treatment. For the extension phase of trial 162 adverse events were recorded through the initiation of trial medication for the first time up to 14 days after treatment of the last migraine recorded. Adverse events were coded using the MedDRA system. In the adverse events tables, a patient is counted for each adverse event reported, but any patient who reported multiple occurrences of the same adverse experience appears only once for that particular event. Statistical comparisons of incidence rates were compared between cohorts using the Fishers Exact test when appropriate. In addition the 95% confidence interval (CI) is provided using the [redacted] method.

Safety was also assessed in trial 161 and 162 by laboratory tests, physical examinations, and vital signs recordings done at the pretreatment and posttreatment visits. Laboratory analysis included a CBC, a basic Metabolic Chemistry Panel, a Urinalysis and a pregnancy test (if appropriate). Since the post treatment laboratories were done up to 14 days after treatment during the acute phase and longer in the long-term phase of trial 162, their relevance is limited. Objective data such as laboratory values and vitals signs were analyzed for mean changes and the proportion of subjects exceeding predefined limits. Overall, this level of surveillance is typical for what I have seen for migraine studies.

6.1 Description of Patient Exposure

The following table briefly outlines the total number of patients for each cohort from trial 161 and 162. Since trial 161 and the acute phase of trial 162 are nearly identical in design the safety data discussed here will be primarily pooled data for rofecoxib 25 mg, rofecoxib 50 mg and placebo. Trial 162 also contained an ibuprofen 400 mg cohort in the acute and extension phases. The long-term (3 months) safety data from the extension phase of trial 162 will be discussed separately and will be augmented by the safety results from trial 125 and the known long-term safety data from other chronic indications for rofecoxib such as rheumatoid arthritis and osteoarthritis. Trial 125 was a Phase IIa trial that investigated the safety and efficacy of rofecoxib 25 mg or montelukast 20 mg daily compared with placebo in the prophylactic treatment of migraine over a 3 month period. As demonstrated in the table approximately 85 to 87% of all subjects are female and the average age was around 40 years in all studies. This is typical of migraine studies which I have reviewed and typical of migraineurs in the general population. Additional discussion about patient demographics can be found in section 5.1.2.

Table 33 New Exposure Data Contained in this NDA

Trial	Treatment group size	Gender and Age (mean/range)	Comment
161	Placebo =182 Vioxx 25 mg = 183 Vioxx 50 mg = 192	Female 497 Male 60 Age 41.3/(18 to 70 years)	Randomized, double blind, placebo controlled, single migraine study
162 acute phase	Placebo = 194 Vioxx 25 mg = 194 Vioxx 50 mg = 196 Ibuprofen 400 mg = 199	Female 675 Male 108 Age 39.8/(18 to 78 years)	Randomized, double blind, placebo and active controlled, single migraine study.
162 extension	Vioxx 25 mg = 268 Vioxx 50 mg = 244 Ibuprofen 400 mg = 123	Female 545 Male 90 Age 40.1/(18 to 78 years)	Re-randomized, double blind, active controlled, 3 month, multiple migraine study
125*	Placebo = 83 Vioxx 25 mg = 89 Montelukast 20 mg = 92	Female 230 Male 38 Age 39.7/(18 to 66 years)	Outpatient, randomized, double blind, placebo controlled study on the prophylactic treatment of migraine (3 month daily use)

*Discussed in further details in section 6.5

In total, 1340 unique individuals participated in trial 161 and 162. The extension phase of trial 162 only included subjects who successfully completed the 1st phase of the trial. Since trial 161 and the acute phase of trial 162 are single-attack studies actual exposure data is straight forward with 377 subjects receiving rofecoxib 25 mg, 388 subjects receiving rofecoxib 50 mg, 376 subjects receiving placebo and 199 subjects receiving ibuprofen 400 mg.

The following table summarizes the exposure statistics from the extension phase of trial 162. Out of the 635 subjects who took study medication in the extension phase of trial 162, 572 (90.1%) completed the study [243 (90.7%) from rofecoxib 25 mg, 218 (89.3%) from rofecoxib 50 mg, and 111 (90.2%) from ibuprofen 400 mg]. Subjects were instructed to treat up to 8 migraines per month over the 3 month period. The range of patients actual days on any treatment was 1 to 31 days. Two hundred subjects took study drug for 1 to 4 days, 197 subjects took study drug for 5 to 8 days, 190 subjects took study drug for 9 to 17 days, 44 subjects took study drug for 18 to 26 days and finally 4 subjects took study drug for 27 to 31 days. On average patients took study drug for 8 days during this extension phase (range 7.7 to 8.5 for 3 treatment groups). This is greater than the 2 migraines/month minimum (i.e. 6 days of treatment for a 3 month study) we require for long term migraine studies. Although patients were instructed to not take more than a single dose of study medication in any 24 hour period, seven patients took more than 50 mg of rofecoxib in a single day (1 patient took 75 mg and 6 patients took 100 mg). Overall the higher doses were well tolerated with only 2 patients reporting an adverse event (both upper respiratory infections occurring 4 to 6 days later). Of the 5088 treated migraine attacks, >97% were treated with a single dose of study medication.

Table 34 Summary of Exposure Date, Extension Phase Trial 162

	Number of Days on Which Patients Took Study Drug						Range of Days[†] on Drug	Mean Number of Days[†] on Drug
	1 to 4 days[†]	5 to 8 days[†]	9 to 17 days[†]	18 to 26 days[†]	27 to 31 days[†]	Number of Patients		
Any group								
Any dosage[‡]	200	197	190	44	4	635	1 to 31	8.0
Rofecoxib 25 mg								
Any dosage[‡]	92	82	75	18	1	268	1 to 29	7.7
Once daily	93[§]	82	74	18	1	268	1 to 29	7.6
Twice daily[‖]	4	0	0	0	0	4	1 to 2	1.3
Three times daily[‖]	1	0	0	0	0	1	1 to 1	1.0
Rofecoxib 50 mg								
Any dosage[‡]	71	73	76	21	3	244	1 to 31	8.5
Once daily	71	73	76	21	3	244	1 to 31	8.5
Twice daily[‖]	6	0	0	0	0	6	1 to 1	1.0
Ibuprofen 400 mg								
Any dosage[‡]	37	42	39	5	0	123	1 to 24	7.8
Once daily	37	43[§]	38	5	0	123	1 to 24	7.7
Twice daily[‖]	1	0	0	0	0	1	3 to 3	3.0

[†] Days represent calendar days, not 24-hour periods.

[‡] Although some patients may have taken 2 or more different dosages, they have been counted only once in the "any dosage" rows. Therefore, in any given column containing numbers of patients, only the values in the "any dosage" rows will add up to the totals given in the "any group" row.

[§] In some columns, there are more patients counted under the "once daily" heading than in the "any dosage" heading. The reason for this is that patients could only be counted once in any "any dosage" row. Some patients who took extra doses of study drug for a certain number of days (e.g., 2 days) were on "any dose" of study drug for a different number of days (e.g., 8 days). These patients would be counted in the "any dosage" row in a separate column.

[‖] All patients who dosed more than once daily took the extra doses of study drug at least 2 hours after the initial dose.

Source: Sponsor table 43, study report 162-EXT, page 112.

The sponsor also refers the reviewer to previously submitted long term safety data on the use of rofecoxib in conditions such as osteoarthritis and rheumatoid arthritis (generally using 12.5 mg or 25 mg daily). I chose to focus primarily on the VIGOR study which evaluated the long term safety (up to 1 year) of rofecoxib 50 mg in subjects with rheumatoid arthritis. In the VIGOR study approximately 3181 subjects took rofecoxib 50 mg daily for 6 months and 57 subjects took rofecoxib 50 mg daily for 11 months (see section 6.5 for additional details). Overall the long term safety data provided by the sponsor includes 3890 subjects taking rofecoxib 50 mg daily for at least 6 months and 284 subjects taking rofecoxib 50 mg daily for at least 1 year. The amount of long term exposure is acceptable to this reviewer.

The following Agency table summarizes the breakdown of randomized patients from trial 162 by country and treatment. As can be seen the largest proportion of subjects came from the United States or the United Kingdom. The breakdown of participant in the extension phase of trial 162 is similar and is not summarized here. In trial 161 all subjects came from the United States. As can be seen the randomization appears to be fairly well balanced in all countries.

Table 35 National Origin of Subjects by Treatment in Trial 162.

Country (N)	Randomized Treatment			
	Ibuprofen 400 mg	Vioxx 25 mg	Vioxx 50 mg	Placebo
Brazil (20)	5	5	5	5
Columbia (40)	10	10	10	10
Denmark (46)	12	11	12	11
France (15)	6	3	3	3
Germany (49)	13	12	12	12
Italy (16)	4	4	4	4
Netherlands (24)	6	6	6	6
Peru (56)	14	14	14	14
Philippines (28)	7	7	7	7
Portugal (32)	8	8	8	8
Spain (104)	26	26	26	26
Sweden (32)	8	8	8	8
Taiwan (28)	7	7	7	7
United Kingdom (113)	29	27	29	29
United States (344)	86	86	85	87
Venezuela (10)	2	3	3	2

6.2 Adequacy of Safety Testing

The primary database evaluated in the safety review includes all patients who received trial medication in trial 161 and 162. All trials are complete and no further safety updates are planned. The safety surveillance conducted in these trials were previously described and I believe are adequate. In total, 377 unique subjects administered rofecoxib 25 mg and 388 subjects administered rofecoxib 50 mg to treat a single migraine attack in the acute studies. Overall this is adequate acute single attack exposure. In the 3 month multiple attack study (162 extension), 268 subjects administered rofecoxib 25 mg and 244 subjects administered rofecoxib 50 mg to treat multiple migraines. On average subjects in the 3 month study treated between 2 to 3 migraines per month. Additionally 89 subjects administered rofecoxib 25 mg daily for 3 months during trial 125. This level of exposure is adequate for 3 months however in general for migraine NDAs the Agency requires the sponsor to provide a minimum of at least 300 subjects intermittently exposed to study mediation for 6 months and at least 100 subjects intermittently exposed for 1 year.

In lieu of 6 month and 12 month intermittent exposure (at least 2 migraines/month) safety data the sponsor has provided a summary of the safety data from 284 subjects exposed to rofecoxib 50 mg daily for over a year and 3890 subjects exposed for over 6 months in patients with osteoarthritis and rheumatoid arthritis. This very large safety database is certainly large enough to satisfy our minimum threshold for adequate long term exposure however the question remains

whether the information obtained in these patients is relevant to patients with migraine. I discuss this issue in further detail in section 6.5.

6.3 Methods Used to Evaluate Safety in This Review

The primary sources of data for this safety review include the Integrated Summary of Safety (ISS) and the individual study reports for trial 161 and 162 submitted electronically by the sponsor on May 23, 2003 and the SAS transport file datasets for trial 161 and trial 162. Case reports forms (CRFs) and individual narrative summaries for adverse events were consulted as needed. All documents submitted by the sponsor for this NDA are available in the Electronic Document Room (edr) at \\CDSESUB1\N21647\N_000\2003-05-23. Additionally I reviewed the following reviews conducted by Agency staff in the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550) relative to the NDA 21-042 and NDA 21-052, supplement 007 (VIGOR trial):

Reviewer	Comment
Maria Lourdes Villalba M.D.	Medical Officer Safety Review of VIGOR
Lawrence Goldkind M.D.	Medical Officer Briefing Review for Advisory Committee
Shari Targum M.D.	Cardio-Renal Medical Officer Consultative Reviews

6.4 Safety Findings from Trial 161 and 162

6.4.1 Deaths

There were no deaths in trial 161. In trial 162 there were two deaths reported in the single attack phase and no deaths in the extension phase of trial 162. Neither death was considered related to study medication.

A 57 year old female patient (AN 4207) was diagnosed with glioblastoma multiforme soon after enrollment into trial 162. Due to her condition the patient was discontinued from the study and she returned the unused study medication prior to her death. The sponsor/investigator did not create a narrative for this case since the patient did not treat with study medication. From the details provided it is not clear to which cohort this subject was randomized however it is clear that the event was unrelated to study medication.

The other death occurred in a 40 year old female (AN 5040) randomized to ibuprofen 400 mg in trial 162. The patient experienced a fatal case of sepsis 41 days after randomization. The investigator assessed the event as unrelated to study medication. To be clear, the sponsor is not certain whether this patient actually took study medication since the diary is not available and no follow up ever occurred. I reviewed the case narrative for this study and concur with the sponsor's assessment.

6.4.2 Serious Adverse Events

The following table outlines the serious adverse events reported in trial 161 and 162. The percentages of patients with a serious adverse experience were 0.3%, 0.0%, 0.3%, and 0.5% in the placebo, rofecoxib 25-mg, rofecoxib 50-mg, and ibuprofen 400-mg groups, respectively. There were no statistically significant differences between cohorts for serious adverse events reported. None of the events were considered drug related by the sponsor. I reviewed the case reports for each event and agree with the sponsor's characterization of these events.

Table 36 Nonfatal Serious Adverse Events during Trial 161 and 162

Patient ID	Trial/Phase	Drug	Event	Comment
AN 1269	161/acute	Placebo	Intervertebral Disc herniation/Sciatica	Occurred 1 day after treatment.
AN 1307	161/acute	Rofecoxib 50 mg	Deep Vein Thrombosis	Occurred 8 days after treatment. Has a history of prior DVT and had active phlebitis at time of entry.
AN 4001	162/acute	Ibuprofen 400 mg	Leg Fracture	Occurred 1 day after treatment.
AN 5217	162/extension	Rofecoxib 25 mg	Bronchospasm	Occurred 7 days after treatment.
AN 4994	162/extension	Rofecoxib 50 mg	Gastroenteritis	Occurred 2 days after treatment.
AN 4228	162/extension	Rofecoxib 50 mg	Menometrorrhagia	Occurred 3 days after treatment.
AN 5528	162/extension	Rofecoxib 50 mg	Low back pain	Occurred 12 days after treatment.

The following is a brief description of serious adverse events occurring in patients treated with rofecoxib.

- Patient AN 1307 was a 55 year old female who developed a deep vein thrombosis 7 days after taking rofecoxib 50 mg. Her history is interesting in that at entry she was noted to have active phlebitis in the same leg as the DVT and she had a prior history of DVT in the same leg. Despite the medical history and the physical finding at entry the patient was not on anticoagulants or anti-platelets therapy. The DVT was asymptotic and found incidentally during a follow up visit with her primary care doctor for hyperglycemia. The event resolved within 12 days of onset. The event was deemed unrelated to study medication.
- Patient AN 5217 is a 29 year old female who developed acute bronchospasm requiring hospitalization 7 days after taking rofecoxib 25 mg. She was discharged from the hospital 2 days later. The patient continued to treat with study medication without recurrence of bronchospasm.
- Patient AN 4994 is a 46 year old female who developed acute gastroenteritis requiring an emergency room visit (12 hour observation) 2 days after using rofecoxib 50 mg. The patient continued on rofecoxib 50 mg without recurrence however she withdrew consent at the 1 month follow up visit. The sponsor does not state why the patient discontinued however it does not appear to have been due to an adverse event since the subject is not listed in the case reports of subjects discontinued due to an adverse event.
- Patient AN 4228 is a 40 year old female who developed menometrorrhagia requiring hospitalization 3 days after treating a migraine with rofecoxib 50 mg. Although the event was considered unrelated to study drug the decision was made to discontinue the patient from the study.
- Patient AN 5528 is a 28 year old female who developed sudden onset low back pain requiring hospitalization 12 days after taking rofecoxib 50 mg for a migraine. The event occurred immediately after lifting some heavy objects. The patient recovered after 3 days of bed rest and pain medication.

6.4.3 Withdrawals/Discontinuations

During trial 161 and the acute phase of trial 162 none of the patients on placebo, rofecoxib 25 mg and rofecoxib 50 mg discontinued due to adverse events. In trial 161, 17 patients were lost to follow up; 6 patients randomized to placebo, 6 subjects randomized to rofecoxib 25 mg and 5 subjects randomized to rofecoxib 50 mg. In trial 162 (acute phase) 32 subjects discontinued; 1

patient had a clinical adverse experience (randomized to ibuprofen), 28 patients were lost to follow-up, 2 patients withdrew consent, and 1 patient moved out of the area. No patient taking rofecoxib withdrew or discontinued due to an adverse event.

During the extension phase of trial 162, five patient (1.9%) taking rofecoxib 25 mg, six patients (2.5%) taking rofecoxib 50 mg, and no patient taking ibuprofen discontinued due to an adverse event. The following table outlines the withdrawal/due to an adverse event seen during the extension phase of trial 162. As can be seen there does not appear to be a specific category of complaint that resulted in discontinuation. I reviewed the narratives provided and generally agree with the sponsor's characterization of the events.

Table 37 Withdrawal/Discontinuations due to an adverse event during Trial 161 and 162

PID	Trial	Therapy	Event	Comment
AN 5051	162 extension	Vioxx 25 mg	Herpes Simplex	Assessed probably related, see below for details.
AN 5220	162 extension	Vioxx 25 mg	Dizziness	Assessed probably not related, occurred 1 day after treatment
AN 5289	162 extension	Vioxx 25 mg	Complicated migraine	Assessed as definitely not related. See below for details
AN 4275	162 extension	Vioxx 25 mg	Abdominal pain	Assessed as definitely related. See below for details.
AN 4513	162 extension	Vioxx 25 mg	Dyspepsia	Assessed as definitely not related. Occurred 8 days after treatment.
AN 5166	162 extension	Vioxx 50 mg	IVth Nerve Palsy	Assessed as definitely not related. Occurred 1 day after treatment.
AN 5194	162 extension	Vioxx 50 mg	Face swelling/rash	Assessed as possibly related. See below for details
AN 5218	162 extension	Vioxx 50 mg	Tongue disorder	Assessed as possibly related. See below for details
AN 4127	162 extension	Vioxx 50 mg	Dizziness	Assessed as possibly related. See below for details
AN 4133	162 extension	Vioxx 50 mg	Diarrhea	Assessed as probably related. Occurred 1 day after treatment.
AN 4228	162 extension	Vioxx 50 mg	Menometrorrhagia	Occurred 11 days after treatment with ibuprofen. See below for details.

What follows is a brief description of the more interesting/unusual cases.

- Patient AN 5051 was a 27 year old female who developed 2 cold sores diagnosed as herpes simplex 3 days after taking rofecoxib 25 mg. Concomitant medications included nadolol, nortriptyline, paroxetine, cetirizine, sumatriptan, ibuprofen, promethazine, topical benzoyl peroxide, topical sulfacetamide, topical metronidazole, topical tazarotene, riboflavin and magnesium. Oddly the investigator assessed the event as probably related to study drug however the assessment seems odd to me. Certainly I can imagine someone developing aphthous stomatitis from medication but not herpes simplex. It is however possible the stress of a migraine attack or medication may have reactivated quiescent oral herpes. I would not consider this related to study drug. The event is resolved.
- Patient AN 4228 was a 40 year old female who withdrew from the study due to menometrorrhagia. This case is also discussed in the section on serious adverse events. Although the event is listed under the cohort rofecoxib 50 mg of the extension phase of 162

the event actually occurred 11 days after taking ibuprofen 400 mg during the acute phase of trial 162. Prior to the event the patient had been rerandomized to rofecoxib 50 mg however the patient had not yet taken the new randomized mediation when the event started. Given the lack of temporal relationship between the event and treatment it is unlikely they are related. The event is resolved.

- Patient AN5289 was a 34 year old male who developed prolonged auras after taking rofecoxib 25 mg. The subject treated 6 migraines with rofecoxib 25 mg during the extension phase of trial 162. On the day of the first treated attack the patient experienced prolonged auras that lasted from 1 to 24 hours. Prior to the study the patient experienced only brief auras. Concomitant medications included bupropion hydrochloride, rizatriptan benzoate, magnesium, and vitamin supplements. The investigator rated the event as unrelated to study medication. The event is still ongoing.
- Patient AN4275 was a 58 year old female who developed upper mild abdominal pain soon after taking rofecoxib 25 mg. The pain eventually worsened and was rated as severe 2 days later and took nearly 1 month to resolve. Her past medical history was significant for migraine and appendectomy. Concomitant medications included nadolol and rizatriptan. All physical examinations and laboratories tests were normal. The event was considered definitely related to study drug. Gastrointestinal upset is a well known adverse event with NSAIDs. Gastrointestinal pain can also occur from triptans (rizatriptan) although it is not thought to be as common. From what is described it does not sound like the subject developed a frank GI bleed.
- Patient 5194 was a 49 year old female who developed facial swelling on the same day as taking rofecoxib 50 mg. Four days later she also developed a rash on her hands and feet. Both events resolved after 2 to 3 days of topical desoximethasone. The patient's past medical history was significant for migraine, obsessive-compulsive disorder, cardiac murmur, hyperopia, intermittent swollen joints, seasonal allergies, psoriasis, concussion, chronic neck pain, left knee tear, left finger tendon tear, hand and knee tendon repair operations, uterine fibroids, and hysterectomy. Concomitant therapies included citalopram, estradiol, fluticasone propionate with salmeterol xinafoate, and fexofenadine. The investigator assessed the event as possibly related to study medication. Insufficient information is provided in order for me to assess causality or get a clear clinical impression. The rash described does not sound like an allergic rash likewise the localized swelling does not sound like the swelling seen with anaphylaxis or allergies.
- Patient 5218 was a 49 year old female who developed mild swelling of her tongue the day after taking her second dose of rofecoxib 50 mg. The event was treated with diphenhydramine for 2 to 3 days and the event resolved. The patient's past medical history was significant for migraine, hypothyroidism, insomnia, depression, irritable bowel syndrome, allergic rhinitis, penicillin allergy, thyroid cyst excision, nasal polypectomy, carpal tunnel decompression, tonsillectomy, adenoidectomy, and hysterectomy. Concomitant therapies included levothyroxine, buspirone hydrochloride, hyoscyamine sulfate, sumatriptan, valerian, and soy isoflavones. The patients physical examination and laboratory assessments were unremarkable. The event was assessed as possibly related to study medication. From what is described it is possible the patient had a delayed hypersensitivity reaction to rofecoxib.

- Patient 4127 was a 61 year old female that developed moderate dizziness after taking rofecoxib 50 mg. The event occurred 3 times, each after taking rofecoxib, and lasted from 1 to 2 days. The patient's past medical history was significant for migraine, hay fever, and uterine prolapse. Concomitant therapy included sumatriptan succinate. The event was considered possibly related to study medication. Giving the rechallenge experience I concur with the assessment.

6.4.4 Common Adverse Events

The following table summarizes the incidences of patients who reported one or more adverse event by cohort in each study. As can be seen there is relatively little difference between subjects treated with placebo and subjects treated with rofecoxib 25 mg. However subjects treated with rofecoxib 50 mg reported significantly more adverse events than subjects treated with placebo in trial 161 (p=0.001) and the acute phase of trial 162 (p=0.041). Although, during the 3-month extension phase of trial 162 fewer subjects taking rofecoxib 50 mg reported an adverse event then subjects taking rofecoxib 25 mg or ibuprofen 400 mg (31.6% compared to 39.2% and 36.6% respectively). On average 89% of all adverse events reported in the rofecoxib cohorts and placebo were rated as mild to moderate with very little difference between cohorts (89.7% placebo, 88.3% rofecoxib 25 mg, 90.0% rofecoxib 50 mg). These adverse event incidences are similar to those of the combined dysmenorrhea and dental studies (23.4% in rofecoxib 25 mg and 30.6% in rofecoxib 50 mg) and less than those of the combined osteoarthritis studies (52.4% in the rofecoxib 12.5-mg 6-week studies, 56.6% in the rofecoxib 25-mg 6-week studies, and higher in the 6-month and 12-month studies) as indicated in the Original Marketing Application 1998. Intuitively this makes sense given that subjects with osteoarthritis and rheumatoid arthritis take NSAIDs on a daily basis and tend to be older and sicker than the typical subjects in a migraine study.

Table 38 Proportion of Patients Reporting an Adverse Event by Cohort and Study

Trial	Placebo	Vioxx 25 mg	Vioxx 50 mg	Ibuprofen 400 mg
161	23.6%	26.8%	39.6%	NA
162 (acute)	27.8%	32.0%	37.8%	28.1%
162 (ext.)	NA	39.2%	31.6%	36.6%

Source: Adapted from sponsor table 2.7.4:12, ISS page 46.

The following table summarizes the most common adverse events seen during trial 161 and the acute phase of trial 162. As demonstrated, gastrointestinal disorders accounted for the vast majority of events. This is consistent with what is known for rofecoxib and this class of medications in general. The most common adverse events occurring in at least 2% of the patients were dry mouth, dyspepsia, nausea, vomiting, asthenia, feeling hot, dizziness, paresthesia, and somnolence. Rofecoxib 25 mg compares favorably with placebo with only dyspepsia and somnolence appreciably more frequent in rofecoxib 25 mg treated patients than placebo treated patients. However for rofecoxib 50 mg there were consistently more patients complaining about most of these common adverse events compared to placebo and there was a suggestion of a dose effect compared to rofecoxib 25 mg. However despite these numerical differences between cohorts there were no statistical differences between groups for each of these adverse events.

Table 39 AE Incidence (≥2%) in Trial 161 and 162 (acute phase only)

	Placebo (N=376)		Rofecoxib 25 mg (N=377)		Rofecoxib 50 mg (N=388)		Ibuprofen 400 mg (N=199)	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	97	(25.8)	111	(29.4)	150	(38.7)	56	(28.1)
Abdominal pain upper[†]	4	(1.1)	4	(1.1)	7	(1.8)	2	(1.0)
Asthenia	2	(0.5)	5	(1.3)	9	(2.3)	8	(4.0)
Dizziness	16	(4.3)	19	(5.0)	26	(6.7)	10	(5.0)
Dry mouth	22	(5.9)	20	(5.3)	24	(6.2)	12	(6.0)
Dyspepsia	3	(0.8)	10	(2.7)	9	(2.3)	4	(2.0)
Gastroenteritis viral NOS[†]	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	11	(2.9)	9	(2.4)	19	(4.9)	4	(2.0)
Paraesthesia	3	(0.8)	5	(1.3)	9	(2.3)	2	(1.0)
Pharyngitis[†]	0	(0.0)	0	(0.0)	2	(0.5)	0	(0.0)
Somnolence	7	(1.9)	16	(4.2)	12	(3.1)	7	(3.5)
Vomiting NOS[†]	8	(2.1)	3	(0.8)	3	(0.8)	2	(1.0)

[†] Incidences of adverse experiences in the rofecoxib treatment groups were ≥2% in the Extension Phase Population and are shown for comparison purposes of the incidences of specific adverse experiences between the Acute and Extension Phase populations.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
NOS = Not otherwise specified.

Source: Sponsor table 2.7.4:17, ISS page 61.

The following table summarizes the most common adverse events reported during the three month extension phase of trial 162. As demonstrated the incidence rates and nature of complaints are similar to the events reported during the single-attack 161 study and the single-attack phase of trial 162. As with the acute studies the organ system with the highest incidence rate for an adverse event was the gastrointestinal system. There were no significant differences among the rofecoxib 25-mg group (39.2%), the rofecoxib 50-mg group (31.6%), and the ibuprofen group (36.6%) with regard to the percentages of patients with one or more adverse event and there were no predominant adverse experiences that accounted for most of the numerical differences. Unlike the common adverse events seen during the acute studies, there is no suggestion of a dose effect for these adverse events. In fact, in general it appears for most common adverse events more patients in the lower dose rofecoxib cohort complained of the event than subject in the rofecoxib 50 mg cohort. Likewise rofecoxib 50 mg compares well to ibuprofen 400 mg with many adverse events being slightly more common in the ibuprofen cohort than the rofecoxib 50 mg cohort. The most common adverse events (≥1%) on the attack level for subjects using rofecoxib 25 mg was nausea (1.8%), dry mouth (1.3%), dizziness (1.1%) and dyspepsia (1.0%). The most common adverse events (≥1%) on the attack level for subjects using rofecoxib 50 mg was dizziness (1.0%).

Table 40 AE Incidence (≥2%) in Trial 162 (extension phase only), Patient and Attack level*

	Rofecoxib 25 mg (N = 268)			Rofecoxib 50 mg (N = 244)			Ibuprofen 400 mg (N = 123)		
	n	(%)	Mean†	n	(%)	Mean†	n	(%)	Mean†
Patients with one or more adverse experiences	60	(22.4)	8.2	47	(19.3)	6.2	27	(22.0)	4.8
Patients with no adverse experience	208	(77.6)		197	(80.7)		96	(78.0)	
Gastrointestinal Disorders	33	(12.3)	5.0	20	(8.2)	3.2	14	(11.4)	2.8
Dry mouth	8	(3.0)	1.3	5	(2.0)	0.8	5	(4.1)	1.0
Dyspepsia	6	(2.2)	1.0	1	(0.4)	0.3	2	(1.6)	0.5
Nausea	13	(4.9)	1.8	5	(2.0)	0.8	7	(5.7)	1.0
Vomiting NOS	6	(2.2)	0.7	4	(1.6)	0.3	3	(2.4)	0.4
General Disorders and Administration Site Conditions	7	(2.6)	0.7	5	(2.0)	0.4	4	(3.3)	0.8
Infections and Infestations	4	(1.5)	0.1	9	(3.7)	0.6	2	(1.6)	0.1
Nervous System Disorders	21	(7.8)	2.2	14	(5.7)	1.6	7	(5.7)	1.1
Dizziness	10	(3.7)	1.1	8	(3.3)	1.0	7	(5.7)	1.1
Psychiatric Disorders	7	(2.6)	0.7	3	(1.2)	0.2	1	(0.8)	0.1
Skin and Subcutaneous Tissue Disorders	4	(1.5)	0.2	5	(2.0)	0.5	2	(1.6)	0.3

† Mean = Attack-adjusted estimate of the incidence, which is the mean of each patient's percentage of treated attacks that were accompanied by each specific adverse experience within 24 hours of study drug intake.
n (%) = Number (percentage) of patients with each specific adverse experience within 24 hours of study drug intake.
NOS = Not otherwise specified.

Source: Sponsor table 52, study report 162 extension, page 144.
*Mean column represents incidence at the attack level.

When the acute phase and extension phase populations are considered together, there is no consistent pattern for any specific adverse experience. For example, in the majority of adverse events in the acute phase population, the incidences in the rofecoxib groups were similar to those of placebo. The only exceptions were for nausea (rofecoxib 50 mg only), dizziness (rofecoxib 50 mg only), and somnolence (rofecoxib 25 mg only), which were the only specific adverse events in the acute phase population where the incidences were >2 percentage points more frequent in the rofecoxib treatment group compared with the control groups (placebo or ibuprofen). However, the pattern was not the same in the extension phase population.

These long term (3 month) findings are consistent with the experience obtained during previous long term studies outlined in the professional label and discussed in the submission. The migraine-associated adverse events and their incidences were similar to or less than those of the combined Osteoarthritis 6-week to 6-month studies of rofecoxib 12.5 and 25 mg, which included abdominal pain, asthenia/fatigue, dizziness, influenza like disease, lower extremity edema, upper respiratory infection, hypertension, diarrhea, dyspepsia, epigastric discomfort, heartburn, nausea, sinusitis, back pain, headache, bronchitis, and urinary tract infection (all between 2 and 8.5% incidence, see Table 51).

In summary, the adverse events of migraineurs treated intermittently with rofecoxib 25 mg or rofecoxib 50 mg are generally similar to those seen in patients with dysmenorrhea or acute pain treated intermittently with rofecoxib 25 mg or rofecoxib 50 mg, and generally similar or lower than those of Osteoarthritis and Rheumatoid Arthritis patients treated with chronic daily doses of rofecoxib 12.5 or 25 mg. A review of the less common adverse events did not result in any significant findings or patterns suggesting some underlying syndrome such as Steven Johnson's or unusual potential signs for concern.

6.4.5 Adverse Events Incidence Table

The following Agency table summarizes the adverse events reported in trial 161 and the acute phase of trial 162. The sponsor used the MedDRA coding system for coding the verbatim terms

recorded in the case report forms. I reviewed the conversion of terms of all adverse events from the verbatim to the MedDRA coding done by the sponsor and in general agree with the sponsor.

Table 41 Agency AE Incidence (≥ 1%) Table for the Single-Attack Studies

Adverse Event	Vioxx 50 mg N=388 n (%)	Vioxx 25 mg N=377 (%) n (%)	Placebo N=376 n (%)	Ibuprofen 400 mg N=199 n (%)
Dizziness	26 (6.7)	19 (5.0)	17 (4.5)	11 (5.5)
Dry Mouth	24 (6.2)	20 (5.3)	22 (5.9)	12 (6.0)
Nausea	19 (4.9)	11 (2.9)	12 (3.2)	4 (2.0)
Somnolence	12 (3.1)	16 (4.2)	7 (1.9)	8 (4.0)
Asthenia	10 (2.6)	5 (1.3)	2 (0.5)	8 (4.0)
Dyspepsia	9 (2.3)	10 (2.7)	3 (0.8)	5 (2.5)
Paresthesia	9 (2.3)	5 (1.3)	3 (0.8)	2 (1.0)
Abdominal Pain (upper)	7 (1.8)	4 (1.1)	5 (1.3)	4 (2.0)
Nasopharyngitis	7 (1.8)	3 (0.8)	0 (0.0)	5 (2.5)
Back Pain	6 (1.5)	3 (0.8)	1 (0.3)	1 (0.5)
Upper Respiratory Tract Infection	6 (1.5)	5 (1.3)	8 (2.1)	1 (0.5)
Hypoasthesia	5 (1.3)	2 (0.5)	1 (0.3)	0 (0.0)
Insomnia	5 (1.3)	0 (0.0)	2 (0.5)	1 (0.5)
Abdominal pain NOS	4 (1.0)	4 (1.1)	2 (0.5)	3 (1.5)
Fatigue	4 (1.0)	2 (0.5)	1 (0.3)	0 (0.0)
Headache NOS	4 (1.0)	3 (0.8)	2 (0.5)	1 (0.5)
Pharyngitis	4 (1.0)	3 (0.8)	1 (0.3)	1 (0.5)
Sinusitis	4 (1.0)	3 (0.8)	4 (1.1)	2 (1.0)
Tremor	3 (0.8)	5 (1.3)	2 (0.5)	1 (0.5)
Vomiting NOS	3 (0.8)	4 (1.1)	9 (2.4)	3 (1.5)
Diarrhea NOS	2 (0.5)	5 (1.3)	2 (0.5)	5 (2.5)
Rigors	2 (0.5)	3 (0.8)	5 (1.3)	2 (1.0)
Blurred Vision	2 (0.5)	0 (0.0)	5 (1.3)	1 (0.5)
Influenza	1 (0.3)	4 (1.1)	1 (0.3)	0 (0.0)

The following Agency table summarizes the adverse events (≥ **0.3%**) reported within 24 hours of treatment in the extension phase of trial 162. From my calculations I determined 268 subjects using rofecoxib 25 mg treated 2055 migraine attack, 244 subjects using rofecoxib 50 mg treated 2086 attacks and 123 subjects using ibuprofen 400 mg treated 955 attacks. Subjects using rofecoxib 25 mg reported 168 adverse events, subjects using rofecoxib 50 mg reported 105 adverse events and subjects using ibuprofen 400 mg reported 42 adverse events. As demonstrated the type of adverse events seen in this 3 month study were low and are similar in nature to the events seen in the single attack studies. Overall there does not appear to be any clinically significant trends in the nature of adverse events with repeated use of rofecoxib over 3 months. The validity of this information is enhanced by the fact that subject enrolled in this extension phase were rerandomized.

Table 42 Agency AE Incidence (≥0.3%) Table for Multiple-Attack 162 Extension Study for AEs within 24 hours of treatment.

Event	Vioxx 25 mg 2055 attack n (%)	Vioxx 50 mg 2086 attacks n (%)	Ibuprofen 400 mg 955 attack n (%)
Dry mouth	31 (1.5)	20 (1.0)	5 (0.52)
Nausea	29 (1.4)	8 (0.4)	6 (0.63)
Dizziness	17 (0.8)	9 (0.4)	9 (1.0)
Insomnia	13 (0.6)	1 (0.1)	0 (0.0)
Dyspepsia	8 (0.4)	2 (0.1)	2 (0.2)
Abdominal pain upper	6 (0.3)	3 (0.1)	2 (0.2)
Irritability	2 (0.1)	8 (0.4)	0 (0.0)
Paresthesia	5 (0.2)	7 (0.3)	0 (0.0)

6.4.6 Potential Class Effect Concerns

Like the nonselective NSAIDs, use of rofecoxib may be associated with renal-vascular effects such as fluid retention, hypertension, electrolyte abnormalities, renal insufficiency, urolithiasis and edema possibly due to the inhibition of COX-2 in the kidney. Long term administration of NSAIDs have resulted in renal papillary necrosis and other renal injuries often presenting as edema and/or hypertension. These issues have been reviewed in great detail by Dr. Targum (Medical Officer, Cardio-Renal) in her review of the renal safety findings from the VIGOR study (review in DFS). In general these effects are dose related and increase with chronic dosing. Patients at greatest risk for these reactions are those with pre-existing impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. During the trial 161 and 162 two patients reported transient edema (1 rofecoxib 25 acute phase, 1 rofecoxib 50 mg extension phase) and three patients reported hypertension (2 rofecoxib 50 mg acute phase, 1 rofecoxib 50 mg extension phase) while taking rofecoxib. The label for rofecoxib already includes an adequate statement in the warning and precautions section of the professional package insert about these adverse events.

Rofecoxib use may also be associated with NSAID-type GI adverse experiences such as abdominal pain and dyspepsia or more rarely gastrointestinal ulcers, perforations and GI bleeds. This issue has been reviewed in great detail by Dr. Villalba (Medical Officer, Division of Anti-Inflammatory Products) in her review of the general safety findings from the VIGOR trial (review in DFS). These adverse events are also dose-dependent and increase with chronic dosing. However in clinical trials they have generally been less frequent with the selective NSAIDs compared to nonselective NSAIDs and aspirin. In trial 161 and 162 no patient reported a clinically significant GI event such as peptic ulcers or GI bleeding. The label for rofecoxib already includes an adequate statement in the warning and precautions section of the professional package insert about these adverse events.

Overall serious NSAID-class related adverse event are not common but can be potentially fatal. It is believed that individual NSAIDs are associated with different preferential organ toxicity and in particular different degrees of gastrointestinal (GI) toxicity [Fries et al., "The relative toxicity of NSAIDs" *Arthritis Rheum.*, 34 (1991): Henry et al., Variability in risk of GI complications with individual NSAIDs: Results of a collaborative meta-analysis. *BMJ*, 312 (1996)].

6.4.7 Laboratory Findings

The following table outlines the abnormal laboratory findings during trial 161 and 162. Laboratory studies were conducted at screening and follow up visits. Follow up visits could occur up to 14 days after treatment in the single attack studies and up to 1 to 2 months after last treatment in the multiple attack 162 extension study. Hence the usefulness of these studies are limited in evaluating acute changes that may be associated with the use of rofecoxib. The incidence of abnormal laboratory values was captured from the 1268 (94.6%) randomized patients in the acute studies and 627 patients from the 3 month extension study. Of the 1268 patients, 3 (0.9%) patients in the placebo group, 2 (0.6%) patients in the rofecoxib 25-mg group, 4 (1.1%) patients in the rofecoxib 50-mg group, and 1 (0.5%) patient in the ibuprofen 400-mg group had one or more abnormal laboratory value. Of the 627 patients, 5 (1.9%) in the rofecoxib 25-mg group, 5 (2.1%) in the rofecoxib 50-mg group, and 1 (0.8%) in the ibuprofen 400-mg group had one or more abnormal laboratory value. None of the results were considered clinically serious. None of the incidences between cohorts reached the level of statistical significance ($p>0.100$ in single attack studies, >0.050 in 162 extension).

As can be seen in the table there does not appear to be any clinically relevant pattern to the abnormal laboratory findings. The changes over time also failed to demonstrate any significant signals of concern. Overall the incidence of abnormal laboratories were very low.

Table 43 Incidence of Abnormal Laboratories* (post treatment)

	Placebo	Vioxx 25 mg	Vioxx 50 mg	Ibuprofen 400 mg
Single-Attack Studies	(N=376)	(N=377)	(N=388)	(N=199)
≥1 abnormal lab	3 (0.9%)	2 (0.6%)	4 (1.1%)	1 (0.5%)
Blood Chemistry				
Alkaline Phos. ↑	0	0	1 (0.3%)	0
Glucose ↑	0	1 (0.3%)	0	1 (0.5%)
Uric Acid ↑	1 (100%)	0	0	0
Creatinine ↑	1 (0.3%)	0	0	0
CBC				
HGB ↓	0	1 (0.3%)	0	0
WBC ↑	0	0	1 (0.3%)	0
Urinalysis				
Bacteria Present	0	0	1 (100%)	0
Proteinuria Present	1 (0.3%)	0	1 (0.3%)	0
RBC Present	1 (1.1%)	0	0	0
Multiple attack study	NA	(N=268)	(N=244)	(N=123)
≥1 abnormal lab		5 (1.9%)	5 (2.1%)	1 (0.8%)
Blood Chemistry				
Alanine AT ↑	NA	1 (0.4%)	0	1 (0.8%)
Alkaline Phos. ↑		0	0	1 (0.8%)
Aspartate AT ↑		1 (0.4%)	0	1 (0.8%)
Glucose ↑		2 (0.8%)	1 (0.4%)	0
CBC				
Antibody +		0	1 (100%)	0
HCT ↓		0	1 (0.4%)	0
HGB ↓	NA	0	1 (0.4%)	0
Metomyelocyte CT ↑		1 (100%)	0	0
RBC ↑		0	1 (100%)	0
WBC ↑		1 (0.4%)	1 (0.4%)	0
Urinalysis				
Bacteria Present	NA	0	1 (100%)	0
Proteinuria Present		0	2 (0.8%)	0
Sediment Present		0	1 (100%)	0

Adapted from sponsor table 2.7.4:36 (ISS, page 95) and 2.7.4:37 (ISS, page 96).
*Incidence values of 100% occurred only when a single patient was sampled.

The following table outlines the number of patients that exceeded the predefined limits for change in any laboratory value (see Appendix 10.1). As can be seen there were very few patients that exceeded the threshold for an abnormal change from baseline. None of the changes were considered clinically relevant and none were considered by the sponsor to be an adverse event. Likewise there does not appear to be any pattern suggestive of an abnormal signal.

Table 44 Number of Patients Exceeding Predefined Limits of Change in Laboratory Measurements

	Placebo	Vioxx 25 mg	Vioxx 50 mg	Ibuprofen 400 mg
Single-Attack Studies				
CBC				
HCT ↓	5 (1.4%)	5 (1.4%)	6 (1.6%)	2 (1.1%)
HGB ↓	1 (0.3%)	0	0	1 (0.6%)
WBC ↓	0	0	0	0
WBC ↑	0	0	2 (0.5%)	0
Eosinophil ↑	3 (0.9%)	2 (0.6%)	0	1 (0.6%)
Neutrophil ↓	0	0	0	0
Platelet ↓	0	0	0	0
Platelet ↑	0	0	0	0
Chemistry Panel				
Bilirubin ↑	0	0	0	0
Alkaline Phos. ↑	0	0	0	0
Alanine ↑	0	1 (0.3%)	0	0
Aspartate ↑	0	1 (0.3%)	0	0
Creatinine ↑	1 (0.3%)	0	1 (0.3%)	0
Potassium ↓	0	0	0	0
Potassium ↑	0	2 (0.6%)	1 (0.3%)	0
Sodium ↓	0	0	0	0
Sodium ↑	0	0	0	0
Multiple Attack Study				
CBC				
HCT ↓		4 (1.6%)	3 (1.3%)	1 (0.9%)
HGB ↓		0	0	1 (0.9%)
WBC ↓		2 (0.8%)	0	0
WBC ↑	NA	0	0	0
Eosinophil ↑		1 (0.4%)	4 (1.7%)	1 (0.9%)
Neutrophil ↓		0	0	0
Platelet ↓		0	0	0
Platelet ↑		0	0	1 (0.9%)
Chemistry Panel				
Bilirubin ↑		1 (0.4%)	0	1 (0.9%)
Alkaline Phos. ↑		0	0	0
Alanine ↑		0	0	0
Aspartate ↑	NA	1 (0.4%)	0	0
Creatinine ↑		0	0	0
Potassium ↓		0	0	0
Potassium ↑		0	01 (0.4%)	0
Sodium ↓		0	0	0
Sodium ↑		0	0	0

Source: Adapted from sponsor table 2.7.4:40, ise.pdf, page 111-112

6.4.8 Vital Signs

The following table summarizes the mean changes in blood pressure, pulse and weight during trial 161 and 162. As can be seen there were no clinically relevant differences in heart rate, systolic blood pressure or diastolic blood pressure with rofecoxib 25 mg or rofecoxib 50 mg. In trial 161 and the acute phase of trial 162, a single patient on placebo (0.3%) and 2 patients on rofecoxib 50 mg (0.5%) reported elevated blood pressure readings. During the long term extension phase of trial 162 a single patient, randomized to rofecoxib 50 mg, reported increased blood pressure. None of the changes were considered clinically relevant.

Table 45 Change in Vital Signs Between Screening and Follow-up Visit, Trial 161 and 162

Vital Sign	Cohort	Baseline mean (SD)	Treatment mean (SD)	Mean change (SD)
Trial 161 and Acute Phase of Trial 162				
Diastolic BP	Placebo	74.9 (9.5)	74.7 (8.8)	-0.2 (8.0)
	Vioxx 25 mg	74.6 (9.4)	74.5 (9.2)	-0.1 (8.3)
	Vioxx 50 mg	74.3 (9.2)	73.8 (9.3)	-0.5 (8.8)
	Ibuprofen	74.8 (10.4)	74.4 (9.9)	-0.4 (8.5)
Systolic BP	Placebo	117.8 (14.0)	116.6 (13.7)	-1.2 (12.2)
	Vioxx 25 mg	118.4 (14.5)	117.8 (14.7)	-0.7 (11.3)
	Vioxx 50 mg	117.3 (14.6)	116.6 (14.3)	-0.7 (11.9)
	Ibuprofen	120.0 (14.9)	118.7 (15.4)	-1.3 (12.5)
Heart Rate	Placebo	73.1 (9.0)	73.9 (8.8)	0.7 (8.8)
	Vioxx 25 mg	73.3 (10.1)	74.9 (10.0)	1.6 (9.5)
	Vioxx 50 mg	73.7 (9.1)	73.5 (8.8)	-0.2 (8.7)
	Ibuprofen	73.2 (9.8)	73.8 (9.0)	0.6 (9.1)
Weight (kg)	Placebo	71.2 (16.7)	71.3 (16.7)	0.1 (1.4)
	Vioxx 25 mg	74.2 (19.9)	74.4 (20.0)	0.2 (1.4)
	Vioxx 50 mg	71.8 (17.5)	71.9 (17.6)	0.1 (1.7)
	Ibuprofen	69.8 (15.9)	69.8 (15.7)	0.0 (1.6)
Trial 162 Extension				
Diastolic BP	Vioxx 25 mg	74.2 (9.8)	73.7 (9.2)	-0.4 (8.5)
	Vioxx 50 mg	74.1 (9.3)	74.2 (9.4)	0.1 (8.3)
	Ibuprofen	73.4 (10.3)	73.4 (9.0)	0.0 (9.0)
Systolic BP	Vioxx 25 mg	117.1 (14.5)	116.7 (13.0)	-0.3 (12.0)
	Vioxx 50 mg	117.7 (15.5)	116.7 (13.4)	-1.0 (11.3)
	Ibuprofen	115.4 (14.5)	116.0 (12.5)	0.7 (11.7)
Heart Rate	Vioxx 25 mg	74.6 (9.6)	74.4 (8.9)	-0.2 (9.6)
	Vioxx 50 mg	74.8 (9.5)	74.2 (9.6)	-0.6 (9.5)
	Ibuprofen	73.2 (8.0)	75.1 (9.0)	1.8 (9.7)
Weight (kg)	Vioxx 25 mg	70.5 (17.6)	70.6 (17.6)	0.1 (1.9)
	Vioxx 50 mg	71.2 (16.9)	71.1 (16.4)	-0.2 (5.7)
	Ibuprofen	68.5 (15.5)	68.2 (15.6)	-0.2 (2.2)

Source: Adapted from Sponsor Table 2.7.4:42 and 2.7.4:43, ISS page 117 and 119.

The following table summarizes the number of individuals in each cohort that exceeded the predefined limits for change in vital signs. As can be seen few patients met this threshold and there does not appear to be a pattern suggestive of a safety concern.

Table 46 Individual Patients Exceeding Predefined Limits for Change in Vital Signs

Vital sign	Limit of change	Placebo	Vioxx 25 mg	Vioxx 50 mg	Ibuprofen 400 mg
Trial 161 and acute phase Trial 162					
Diastolic BP	≤50 and ≥15 decrease	0	1 (0.3%)	2 (0.5%)	0
	≥105 and ≥15 increase	0	0	4 (1.1%)	1 (0.5%)
Systolic BP	≤90 and ≥20 decrease	1 (0.3%)	4 (1.1%)	3 (0.8%)	2 (1.1%)
	≥180 and ≥20 increase	0	0	0	0
Heart Rate	≤50 and ≥15 decrease	0	0	0	0
	≥120 and ≥15 increase	0	1 (1.3%)	0	0
Trial 162 extension					
Diastolic BP	≤50 and ≥15 decrease	NA	0	0	1 (0.8%)
	≥105 and ≥15 increase		0	0	0
Systolic BP	≤90 and ≥20 decrease		3 (1.1%)	2 (0.8%)	2 (1.7%)
	≥180 and ≥20 increase		0	0	0
Heart Rate	≤50 and ≥15 decrease		1 (0.4%)	1 (0.4%)	0
	≥120 and ≥15 increase		0	0	0

Source: Adapted from Sponsor tables 2.7.4:44 and 2.7.4:45, ISS pages 122 and 124.

6.4.9 Electrocardiogram Findings

No ECG recording were obtained during any of the clinical trials involved with this submission. Previous clinical acute and chronic use safety studies and extensive clinical experience have not demonstrated any alterations in cardiac conduction with rofecoxib use.

6.4.10 Drug-Drug Interaction

No drug interaction studies were conducted in support of this NDA.

It is known that the metabolism of rofecoxib is primarily through cytosolic enzymes with cytochrome 450 system playing a minor role (CYP3A4). Previous drug interaction studies with rofecoxib demonstrated a possible interaction with rifampin, theophylline and warfarin; drug that are rarely used in migraineurs. Drug-interaction studies do not support the potential for clinically important interactions between antacids or cimetidine with rofecoxib. Similar to the experience with other NSAIDs, studies with rofecoxib suggest the potential for interaction with ACE inhibitors. The effects of rofecoxib on the pharmacokinetics and/or pharmacodynamics of ketoconazole, prednisone/prednisolone, oral contraceptives, and digoxin have been studied in vivo and clinically important interactions have not been found. The present label for rofecoxib already reflect these findings.

A subset analysis of adverse events in women using birth control failed to demonstrate any significant difference in the nature and character of adverse events experienced by women in trial 161 and 162. Likewise a subset analysis of adverse events in subjects using migraine prophylaxis also failed to demonstrate any significant difference in the nature and character of adverse events experienced by these subjects in trial 161 and 162.

6.4.11 Drug-Demographic Interactions

The following table summarizes the proportion of patients reporting an adverse event (AE) or a serious adverse event by age, gender and race from trial 161 and the acute phase of trial 162. As can be seen there were no clinically relevant differences in the proportion of patients reporting an adverse event or experiencing a serious adverse event between younger and older patients.

Likewise the nature and character of the adverse events reported in each age group, race category, and gender category and were similar. The results from the extension phase of trial 162 were similar.

Table 47 Proportion of Patients Reporting an AE by Age, Gender and Race, Acute Studies.

		Placebo	Vioxx 25 mg	Vioxx 50 mg	Ibuprofen
Age					
≥1 AE reported	**< 40 years**	50 (29.2%)	58 (32.8%)	80 (41.0%)	29 (32.6%)
	≥ 40 years	47 (22.9%)	53 (26.5%)	70 (36.3%)	27 (24.5%)
Serious AE	**< 40 years**	0	0	0	1(1.1%)
	≥ 40 years	1 (0.5%)	0	1 (0.5%)	0
Gender					
≥1 AE reported	**Male**	15 (31.9%)	14 (29.2%)	18 (38.3%)	4 (15.4%)
	Female	82 (24.9%)	97 (29.5%)	132 (38.7%)	52 (30.1%)
Serious AE	**Male**	0	0	0	0
	Female	1 (0.3%)	0	1 (0.3%)	0
Race					
≥1 AE reported	**White**	73 (23.3%)	93 (28.9%)	127 (38.8%)	45 (28.1%)
Serious AE	**Other**	24 (38.7%)	18 (32.7%)	23 (37.7%)	11 (28.2%)

Adapted from sponsor Appendix 2.7.4:4, 2.7.4:7, 2.7.4:10, ISS pages 143, 149 and 156.

Overall rofecoxib 25 and 50 mg was well tolerated by all age groups, both genders and all races exposed during trial 161 and 162. The adverse events profiles in each subgroup reflects the profile summarized for the entire population. Since the trails submitted under this NDA involved few non-Caucasian individuals I am unable to draw any conclusions about the potential impact of race on the incidence of adverse events. Similarly since trials 161 and 162 included no adolescents and few subjects over 65 years of age I am unable to draw any conclusions about the impact of age on the incidence of adverse events.

6.4.12 Withdrawal Phenomena, Abuse Potential and Overdose

Overdose, drug abuse, withdrawal, or rebound effects have not been seen in any rofecoxib clinical program to date. In clinical studies, single doses up to 1000 mg and multiple doses up to 250 mg per day for 14 days did not result in significant toxicity. During the extension phase of trial 162 there was no overall increase in frequency of attacks during the 3 month period. During the clinical program for rofecoxib in migraine there was no evidence of drug abuse.

The sponsor recommends during an event of suspected overdose with rofecoxib it would be reasonable to remove any unabsorbed material from the gastrointestinal tract, employ clinical monitoring and provide supportive care if required. Rofecoxib is not removed by hemodialysis and it is not known whether rofecoxib is removed by peritoneal dialysis. The label for Vioxx already include appropriate language relative to overdosages of Vioxx.

6.4.13 Human Reproductive Data

No new reproductive studies were performed in support of this NDA. Use in pregnancy and during lactation is already described in labeling. The label for rofecoxib includes the statement that "*in late pregnancy rofecoxib should be avoided because it may cause premature closure of the ductus arteriosus*" and is rated Category C (use only if benefit justifies potential risk). A

pregnancy registry for rofecoxib is already in place. It is not known whether rofecoxib is excreted in Human breast milk.

The following table outlines the pregnancies reported during trial 161 and 162. In total there were 8 pregnancies reported during the trials. As can be seen there does not appear to be any obvious signal for concern.

Table 48 Pregnancies and Outcomes During Vioxx Migraine Program.

PID	Trial/Treatment	Comment
AN 1059	161/Vioxx 25 mg	Did not take study medication. Pregnancy electively terminated
AN 1270	161/Vioxx 25 mg	Did not take study medication. Pregnancy electively terminated
AN 1645	161/Vioxx 25 mg	Took study medication without problems. Completed to term without complications
AN 1542	161/Placebo	Did not take study medication. Completed to term without complications
AN 4779	162 acute/Vioxx 25 mg	Experienced abdominal trauma requiring D&C and termination of pregnancy 2 days prior to dosing with study medication.
AN 5188	162 extension/Vioxx 50 mg	The patient did not treat with study medication and was found to be pregnant on Day 81 of the extension phase. The patient had been randomized to ibuprofen during the acute phase. Outcome information is not available.
AN 5502	162 extension/Vioxx 25 mg	After treating 2 migraine attacks on Day 52 and 58, the patient had a positive pregnancy test on Day 99 follow up visit. Spontaneous abortion occurred on Day 148.
AN 5563	162 extension/Vioxx 25 mg	Patient treated a single migraine with Vioxx (Day 21) and was found to be pregnant on Day 31. The pregnancy went to term without complications

6.4.14 Long-Term Safety Update

All studies are complete and no further safety data is expected.

6.5 Supporting Safety Data

6.5.1 Supporting Long Term Safety Data (non-migraine)

The sponsor has not conducted any study using rofecoxib 25 and 50 mg for the treatment of migraine that is longer than 3 months. At the pre-NDA meeting the sponsor requested that we consider the long term safety of rofecoxib in other conditions as supportive data for the approval of rofecoxib 25 and 50 mg in the treatment of acute migraine. In support of their argument the sponsor provides long term safety information (up to 1 year) on the daily use of rofecoxib in subjects with osteoarthritis and rheumatoid arthritis as well as the result of a study (protocol 125) that evaluated the long term (3 months) safety and efficacy of rofecoxib 25 mg in the prophylactic treatment of migraine. In this section I summarize their discussion and augment it with safety information I was able to obtain from a review of previously completed Agency reviews of the VIGOR study.

The following table summarizes the safety data from protocol 125, a phase IIa trial that investigated the safety and efficacy of daily rofecoxib 25 mg or montelukast 20 mg compared to placebo in the prophylactic treatment of migraine over 3 months. Following a 56 day, single blind, placebo run in period, 91 subjects were randomized to rofecoxib 25 mg, 93 subjects were

randomized to montelukast 20 mg, and 84 patients were randomized to placebo. Patients were treated in a double blind fashion during the active treatment period. The mean number of days on treatment was 79.4 days for rofecoxib 25 mg, 79.5 days for montelukast 20 mg and 80.1 days for placebo.

Table 49 Adverse Events Table for Trial 125

	Rofecoxib 25 mg (N=89)		Montelukast 20 mg (N=92)		Placebo (N=83)	
	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	38	(42.7)	35	(38.0)	34	(41.0)
Patients with no adverse experience	51	(57.3)	57	(62.0)	49	(59.0)
Body as a Whole/Site Unspecified	**14**	**(15.7)**	**17**	**(18.5)**	**15**	**(18.1)**
Asthenia/fatigue	0	(0.0)	1	(1.1)	2	(2.4)
Chest pain	2	(2.2)	0	(0.0)	0	(0.0)
Dizziness	1	(1.1)	3	(3.3)	1	(1.2)
Influenza-like disease	4	(4.5)	1	(1.1)	4	(4.8)
Upper respiratory infection	4	(4.5)	8	(8.7)	7	(8.4)
Cardiovascular System	**4**	**(4.5)**	**1**	**(1.1)**	**1**	**(1.2)**
Hypertension	2	(2.2)	0	(0.0)	1	(1.2)
Digestive System	**11**	**(12.4)**	**11**	**(12.0)**	**8**	**(9.6)**
Acid reflux	0	(0.0)	2	(2.2)	0	(0.0)
Dental pain	1	(1.1)	2	(2.2)	1	(1.2)
Diarrhea	1	(1.1)	2	(2.2)	0	(0.0)
Heartburn	2	(2.2)	0	(0.0)	0	(0.0)
Nausea	4	(4.5)	1	(1.1)	2	(2.4)
Eyes, Ears, Nose, and Throat	**8**	**(9.0)**	**11**	**(12.0)**	**10**	**(12.0)**
Pharyngitis	3	(3.4)	2	(2.2)	3	(3.6)
Sinusitis	5	(5.6)	4	(4.3)	3	(3.6)
Musculoskeletal System	**5**	**(5.6)**	**4**	**(4.3)**	**9**	**(10.8)**
Back Pain	2	(2.2)	1	(1.1)	3	(3.6)
Nervous System	**3**	**(3.4)**	**5**	**(5.4)**	**2**	**(2.4)**
Migraine	1	(1.1)	2	(2.2)	1	(1.2)
Psychiatric Disorder	**1**	**(1.1)**	**3**	**(3.3)**	**4**	**(4.8)**
Respiratory System	**2**	**(2.2)**	**1**	**(1.1)**	**4**	**(4.8)**
Cough	2	(2.2)	0	(0.0)	1	(1.2)
Skin and Skin Appendages	**4**	**(4.5)**	**2**	**(2.2)**	**2**	**(2.4)**
Urogenital System	**4**	**(4.5)**	**1**	**(1.1)**	**2**	**(2.4)**

Source: Sponsor table 38, Study 125 Report, page 102

Overall there were no statistically significant differences between treatment groups in the incidences of adverse events. Specifically, the percentages of patients with one or more clinical adverse event were 42.7%, 38.0%, and 41.0% in the rofecoxib 25-mg, montelukast 20-mg, and placebo groups, respectively. The most common clinical adverse experiences, i.e., those that occurred in at least 3 patients (≥3%) in the rofecoxib group were sinusitis, nausea, upper respiratory tract infection, influenza-like disease and pharyngitis (all incidences ≤5.6%). There were no significant differences between the 3 treatment groups in the incidence of adverse experiences of special interest (i.e., NSAID-type gastrointestinal events and hypertension-related events). No patient randomized to rofecoxib 25 mg discontinued due to an adverse event. Serious adverse events were reported in 3 (3.4%) patients randomized to rofecoxib 25 mg (non-cardiac

chest pain, cervical stenosis, and malignant melanoma) and 1 (1.2%) patient randomized to placebo (labyrinthitis). A review of the cases does not suggest a causal relationship. There were no significant changes in vitals signs or safety laboratories (CBC, Chemistry Panel, Urinalysis). There were no deaths. In summary the safety experience seen during trial 125 is similar to the experience seen during trial 161 and 162. Rofecoxib 25 mg daily for 90 days appears to be well tolerated. This trial is useful relative to understanding the long term safety (3 months) of rofecoxib 25 mg however it does not address the safety of 50 mg over an extended period.

Additional long term safety data can be found in the previous marketing applications submitted to the Agency for the use of rofecoxib in osteoarthritis (rofecoxib 12.5 or 25 mg daily) and rheumatoid arthritis (rofecoxib 25 mg daily) as well as the experienced gained from the VIGOR trial (VIOXX GI Clinical Outcome Research). The VIGOR study was designed to evaluate the comparative GI safety of rofecoxib 50 mg once daily (twice the highest dose recommended for chronic use in OA and RA) versus naproxen 500 mg twice daily (common therapeutic dose). The general safety and tolerability was also studied. VIGOR was a randomized, double-blind study in 8076 patients with rheumatoid arthritis (RA) requiring chronic NSAID therapy. The median duration of therapy was 9 months and the mean age was 58 years. The gastrointestinal, cardiovascular and cerebrovascular findings from the VIGOR trial are outlined in the product label. The safety results from the VIGOR trial was a matter of significant discussion within the Agency due to an unexpected increase in the relative risk for a cardiovascular events in patients randomized to rofecoxib 50 mg (RR=2.37; 95%CI 1.39, 4.06; p=0.0016). There were several Agency reviews done of the study as well as an Advisory Board meeting. The most helpful review in understanding the safety results from this trial was done by Dr. Maria Lourdes Villalba (Medical Reviewer, HFD 550) and can be found in DFS (NDA 21052 S-007, dated June 29, 2000).

The following sponsor table summarizes the long term exposure from previous studies with rofecoxib. As can be seen the total number of patients exposed to rofecoxib 50 mg for 6 months (3890) and 1 year (284) exceeds the minimum generally required by the Agency for a migraine marketing application. Not reflected in this table is the fact that approximately 440 subjects in the VIGOR study was on daily rofecoxib 50 mg for 11 months.

Table 50 Long Term Exposure of Vioxx (up to 50 mg).

	Number of Patients Exposed to Rofecoxib					
	Rofecoxib 12.5 mg		Rofecoxib 25 mg		Rofecoxib 50 mg	
Patient Population	≥6 Months	≥1 Year	≥6 Months	≥1 Year	≥6 Months	≥1 Year
Phases IIb and III studies in OA	446	371	663	381	265	63
Phases IIb and III studies in RA[§]	-	-	580	188	444	164
VIGOR[†] study in RA[‡]	-	-	-	-	3181	57
Total	446	371	1243	569	3890	284

† VIOXX GI Clinical Outcome Research.
‡ Only rofecoxib 50 mg was studied.
§ Only rofecoxib 25 mg and 50 mg studied.

Source: Sponsor table 2.7.4:46, ISS page 134.

Long term daily dosing of rofecoxib 12.5 or 25 mg has been generally well tolerated when used in OA and RA. Adverse experiences with chronic administration of rofecoxib are reported in the product circular. The following adverse events were reported in 6-week to 6-month OA clinical

studies: asthenia/fatigue, dizziness, lower extremity edema, upper respiratory infection, hypertension, dyspepsia, epigastric discomfort, heartburn, nausea, sinusitis, back pain, bronchitis, and urinary tract infection. These occurred in ≥ 2% of patients treated with VIOXX and at an incidence greater than placebo. This adverse experience profile is similar in patients treated with VIOXX for 1 year or longer. In addition, small increases in serum creatinine, systolic blood pressure, fluid retention, and edema have been noted in some patients. Most of these changes have been of limited clinical significance and only rarely resulted in discontinuation of patients from clinical studies. Similar changes have also been reported with nonselective NSAIDs.

Table 51 Incidence of AEs (≥2%) seen in Long-term OA Studies (up to 6 months, doses up to 25 mg)

	Placebo	Rofecoxib 12.5 or 25 mg Daily	Ibuprofen 2400 mg Daily	Diclofenac 150 mg Daily
	(N=783)	(N=2829)	(N=847)	(N=498)
Abdominal pain	4.1	3.4	4.6	5.8
Asthenia/fatigue	1.0	2.2	2.0	2.6
Back pain	1.9	2.5	1.4	2.8
Bronchitis	0.8	2.0	1.4	3.2
Diarrhea	6.8	6.5	7.1	10.6
Dizziness	2.2	3.0	2.7	3.4
Dyspepsia	2.7	3.5	4.7	4.0
Epigastric discomfort	2.8	3.8	9.2	5.4
Headache	7.5	4.7	6.1	8.0
Heartburn	3.6	4.2	5.2	4.6
Hypertension	1.3	3.5	3.0	1.6
Influenza-like disease	3.1	2.9	1.5	3.2
Lower extremity edema	1.1	3.7	3.8	3.4
Nausea	2.9	5.2	7.1	7.4
Sinusitis	2.0	2.7	1.8	2.4
Upper respiratory infection	7.8	8.5	5.8	8.2
Urinary tract infection	2.7	2.8	2.5	3.6

Source: Sponsor table 2.7.4:20, ISS page 64

The adverse event profile of long term daily dosing of rofecoxib 50 mg in OA and RA has been similar to that found with rofecoxib 25 mg daily, except that gastrointestinal symptoms (abdominal pain, epigastric pain, heartburn, nausea, and vomiting), lower extremity edema, and hypertension occurred with increased frequency. The incidences of serious adverse events and discontinuation due to an adverse event for rofecoxib 50 mg daily versus naproxen 1000 mg daily were 9.3% versus 7.8% and 15.9% versus 15.8%, respectively (VIGOR study). Since the use of rofecoxib 50 mg is not associated with greater efficacy compared with rofecoxib 25 mg in OA or RA, and the incidences of various adverse experiences are higher for rofecoxib 50 mg daily than 25 mg daily, chronic use of rofecoxib 50 mg is not recommended. Additional safety information on rofecoxib in rheumatoid arthritis is available in the review done by Dr. Joel Schiffenburger (Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products) found in DFS (sNDA 21042/s012, submission dated 2/28/01).

The following table summarizes the safety experience from the VIGOR study[3]. As can be seen the general safety experience of rofecoxib 50 mg (QD) and naproxen 1000 mg (500 mg BID) were similar however there was a clinically relevant difference in CV adverse events (discussed below). In reviewing these events it is important to keep in mind the demographic differences between patient enrolled in the VIGOR study and typical migraineurs. In the VIGOR study the average age was 58.1 ± 9.5 years with approximately 25% being over 65 years of age, additionally 46% of subjects had a history of cardiac disease and approximately 56% were taking concomitant corticosteroids and methotrexate. In general these patients were older and sicker then your typical patient that participates in migraine studies which tend to be young healthy females specifically selected to not have any cardiac conditions. Additional details can be found in the review done by Dr. Villalba.

Table 52 Overall Safety from VIGOR Study

Event	Vioxx 50 mg N=4047 (%)	Naproxen 1000 mg N=4029 (%)
Deaths	22 (0.5)	15 (0.4)
Serious AEs	378 (9.3)	315 (7.8)
Drop out due to AEs	643 (15.9)	635 (15.8)
Hospitalizations	338 (8.4)	263 (6.6)
Common Adverse Events by body system (≥2 %)		
One or more AE	2872 (71.0)	2824 (70.1)
Body as a whole	1071 (26.5)	1003 (24.9)
Cardiovascular	**590 (14.6)**	**390 (9.7)**
Digestive System	1320 (32.6)	1449 (36.0)
EENT	450 (11.1)	397 (9.9)
Metabolism/Nutrition	128 (3.2)	132 (3.3)
Musculoskeletal System	630 (15.6)	613 (15.2)
Nervous System	456 (11.3)	356 (8.8)
Psychiatric Disorder	108 (2.7)	92 (2.3)
Respiratory system	346 (8.5)	343 (8.5)
Skin and Appendages	508 (12.6)	410 (10.2)
Urogenital System	372 (9.2)	341 (8.5)

Adapted from review done by Dr. Villalba

Overall the long term safety seen in the VIGOR study was not unexpected except for the higher incidence of cardiovascular events seen in patients randomized to rofecoxib compared to patients randomized to naproxen. The cumulative rate for serious CV/thrombotic events was 1.8% (n=45) and 0.6% (n=19) in the rofecoxib 50 mg and naproxen groups respectively over the study period. The difference was mainly due to the difference in the number of myocardial infarction; 20 in the rofecoxib 50 mg group and 4 in the naproxen group (crude rate 0.5% and 0.1% respectively, RR=5.0). The reason for this difference is not clear and several theories have been proposed by the sponsor. This issue resulted in considerable discussion within the Agency and the convening of an Advisory Committee meeting. The final decision was that the rofecoxib label should retain the NSAID class warning about gastrointestinal side effects and the cardiovascular/thrombotic events seen in this trial are discussed in labeling. Of course this unexpected findings brings into question whether rofecoxib should be approved for a self-limiting condition such as migraine.

[3] The following details relative to the VIGOR study are derived from the review done by Dr. Villalba, medical review officer HFD 550. A complete discussion of safety can be found in her review in DFS.

My clinical opinion is although migraine is a self limiting condition it is associated with considerable disability. Additionally the available migraine therapies do not provide all people with complete relief and many subjects are unable to take or tolerate triptans. As such I think the risk benefit analysis of intermittent use of rofecoxib in the treatment of migraine favors approval. However the daily use of rofecoxib for migraine and/or migraine prophylaxis should be discouraged in my opinion.

Recently the sponsor submitted several summaries of recent epidemiological studies to address the unexpected cardiac findings in the VIGOR trial (serial 044, dated May 29, 2003). As is often the case with epidemiological studies there was discordant results. In a case control study Solomon et al[4] estimates the relative risk (95% CI) of myocardial infarction is 1.14 (1.00-1.31) in patients taking rofecoxib compared to patients who did not take NSAIDs. The investigator concludes that concurrent rofecoxib use was associated with an increase adjusted relative risk of acute myocardial infarction compared to celecoxib use and no NSAID use. "Dosages of rofecoxib > 25 mg were associated with the highest risk." A retrospective cohort study by Rahme et al[5]., suggests that patients taking rofecoxib had similar rates of myocardial infarction compared to patients who took the NSAIDs ibuprofen or diclofenac. The author reports based on preliminary estimates, the unadjusted rates for myocardial infarction were 1.1 and 1.0 per 100 patient years for rofecoxib and NSAIDs, respectively. The sponsor admits that both studies are limited by selection bias and potential confounders such as use of aspirin, smoking etc. Neither epidemiological study or past Agency reviewers conclusively have answered the question about myocardial risk and rofecoxib use. As a clinician I have confidence that intermittent use of rofecoxib in migraineurs is most likely safer than chronic daily use in older subjects with arthritis. However despite this I believe it is prudent to recommend initial treatment of migraine with the lower dose of rofecoxib and to limit the monthly use of rofecoxib.

In addition to the long term safety data discussed above the sponsor summarizes the safety data from their short term acute pain (dental) and dysmenorrhea trials of rofecoxib (up to 50 mg for 5 days) in the following table. As can be seen the adverse events profile of rofecoxib 25 or 50 mg acute administration in the dysmenorrhea and analgesia studies was generally similar to or less than that reported for the chronic administration of rofecoxib 12.5 or 25 mg in the osteoarthritis studies.

[4] Unpublished summary under attachment 1 of submission. Study supported by MRL.
[5] Unpublished summary under attachment 2 of submission. Study supported by MRL.

Table 53 Incidence (≥2%) Table from Combined Acute Pain and Dysmenorrhea Studies

	Placebo (N=446)		Rofecoxib 25 mg (N=274)		Rofecoxib 50 mg (N=291)		Rofecoxib 50/25 mg† (N=179)	
	n	%	n	%	n	(%)	n	(%)
Patients with one or more adverse experiences	109	(24.4)	64	(23.4)	89	(30.6)	42	(23.5)
Dizziness	7	(1.6)	3	(1.1)	3	(1.0)	4	(2.2)
Headache	18	(4.0)	6	(2.2)	7	(2.4)	2	(1.1)
Nausea	30	(6.7)	5	(1.8)	18	(6.2)	6	(3.4)
Post-extraction alveolitis‡	19	(4.3)	27	(9.9)	43	(14.8)	0	(0.0)
Vomiting	15	(3.4)	5	(1.8)	10	(3.4)	0	(0.0)

† This group includes patients from the Primary Dysmenorrhea Studies only.
‡ This adverse experience is unique to the Post-Dental Surgery Pain Studies, although Ns may include patients who were not in the Post-Dental Surgery Pain Studies.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Source: Sponsor table 2.7.4:19, ISS page 63.

The sponsor argues that since the long term safety seen in OA and RA were used to support the approval of rofecoxib 50 mg in the acute treatment of pain (for 5 days) then they should be adequate to support the intermittent use of rofecoxib (25 and 50 mg) in the acute treatment of pain. In general I agree with this argument however there are several issues to consider. The first is whether the population are similar enough to permit extrapolation of safety data. The second issue is the language the sponsor proposes in labeling for their dosing regimen.

The usefulness of this additional safety data is dependent upon whether one were to consider the various populations (OA, RA, acute pain etc,) similar to migraineurs. As previously stated migraineurs tend to be adult females, less than 45 years of age, with few to no other medical conditions. This demographic profile is certainly similar to the patients with primary dysmenorrhea and not too unlike patients in the acute pain studies (dental pain) which also tended to be younger adults (male and female) with few to no medical conditions. The more difficult question is whether the long term safety data from studies involving patients with osteoarthritis and rheumatoid arthritis is applicable to patients with migraine. Although the two populations are not similar in many ways I would expect the OA and RA populations to be more prone to adverse events since they tend to be older patients (mean age in VIGOR was 58.1 ± 9.5 years), often with multiple medical problems, on multiple co-medications, and use rofecoxib daily as opposed to young otherwise healthy migraineurs who will use the product intermittently. For these reason I do agree the long term safety data is relevant and should be considered in the Approval of rofecoxib for migraine.

The present label for rofecoxib in acute pain has a clear finite statement relative to the duration of treatment (no longer than 5 days of continuous treatment) whereas the duration of treatment for the indication of migraine in the proposed label is confusing ("daily" but later states daily use of rofecoxib 50 mg is not recommended). I address labeling language in a separate document however I bring the issue up here to make the point that it is not the same for the RA/OA long term safety to support 5 days of rofecoxib 50 mg in acute pain and unlimited daily use of rofecoxib 25 and 50 mg in acute migraine. A limit on the number of days per month an individual can treat with the maximum dose of rofecoxib needs to be considered. This is

especially true since long term uninterrupted daily use of rofecoxib 50 mg has been on rare occasion associated with serious adverse events including myocardial infarction and death. Given that the maximum number of migraine treated in trial 162 extension was 8 per month then I would recommend the regimen be limited to 8 migraine attacks in any given month.

6.5.2 Supporting Post Marketing Safety Information

In support of the NDA the sponsor searched the Worldwide Adverse Experience (WAES) database for spontaneous report for rofecoxib with a reported indication of migraine (a non approved indication) and located 36 reports. Two reports did not include sufficient data to determine the adverse event experienced. Thirty reports contained a total of 69 nonserious adverse events (generally GI in nature) which are already discussed in labeling and four reports were considered serious (see following table).

Table 54 Serious Spontaneous Adverse Events Reports of Vioxx in Migraine

Patient ID	Age/gender	Event	Comment
0205USA02331	12 year old female	Developed meningitis some unstated time after starting Vioxx for migraine. Other details are not provided.	Labeled event
0301USA00847	14 year of female	Developed anaphylaxis some time after starting Vioxx	Labeled event
0205CAN001129	38 year old male	Developed a pituitary abscess and died 3 weeks after starting Vioxx. Autopsy results are pending.	Unlabeled
0210CAN00074	Female	Developed seizure 3 hours after taking Vioxx 50 mg. Rechallenge was positive.	Unlabeled

As demonstrated in the table there does not appear to be any pattern to these event. However the focus of the post marketing search conducted by the sponsor is extremely narrow in that it only looked at reports where rofecoxib was given for the indication of migraine. The sponsor does not provide a discussion on safety reports that may have been reported for rofecoxib in other indications or at high doses.

6.6 Brief Statement of Conclusions

6.6.1 Sponsor Summary

Short Term use:

- Both rofecoxib 25 mg and 50 mg were generally well tolerated when used for the acute treatment of migraine.
- In the acute phase studies, the overall incidence of adverse events was either numerically or statistically more frequent in the rofecoxib 50 mg treatment group compared to the other groups. In contrast the opposite was true in the 3 month extension phase of trial 162. No single adverse event accounted for the observed differences among the treatment groups.
- The most common (≥2%) adverse events reported following a single dose of rofecoxib included dizziness, somnolence, nausea, dry mouth, dyspepsia, asthenia, and paresthesia.
- One or more adverse events occurred in 29.4% of patients taking rofecoxib 25 mg, 38.7 % of patients taking rofecoxib 50 mg, 25.8% of patients taking placebo, and 28.1% of patients taking ibuprofen 400 mg.

- The adverse events were mild or moderate in intensity in 88% of patients taking rofecoxib 25 mg, 90% of patients taking rofecoxib 50 mg, 90% of patients taking placebo, and 93% of patients taking ibuprofen 400 mg.
- Overall the nature of the adverse events seen in these trials were comparable for what is already included in the professional label for rofecoxib and consistent with what is known for this class of drugs.
- Subgroup analysis of safety data (short and long term) revealed no difference in incidence rates when looking at age, gender and race.
- The incidence of abnormal laboratory values in the short term studies were low and showed no particular pattern (0.6% for rofecoxib 25 mg, 1.1% for rofecoxib 50 mg, 0.9% for placebo and 0.5% for ibuprofen). None of the abnormal laboratory values were considered drug related.

Long-term use in migraineurs (3 months)

- The discontinuation rate due to adverse events was low during the long term phase of trial 162 (1.9% for rofecoxib 25 mg, 2.5% for rofecoxib 50 mg, and 0% for ibuprofen 400 mg).
- The percentage of patients having one or more adverse events over the 3 month period was 39.2% for rofecoxib 25 mg, 31.6% for rofecoxib 50 mg, and 36.6% for ibuprofen 400 mg.
- The most common adverse events seen during the long term phase of trial 162 were similar to those seen during the acute phase of trail 161 and 162. And the vast majority were mild or moderate, transient and resolved without treatment.
- Nausea, dry mouth, dyspepsia, and dizziness were the most frequently observed adverse events reported in all treatment groups.
- The incidence of abnormal laboratory values in the long term studies were low and showed no particular pattern (1.9% for rofecoxib 25 mg, 2.1% for rofecoxib 50 mg, and 0.8% for ibuprofen). Except for a single case of proteinuria in a patient randomized to rofecoxib 50 mg, none of the abnormal laboratory values were considered drug related.

Long-term safety in non-migraine population (6 months to 1 year)

- The 6-month and 1-year safety data in OA and RA patients demonstrate that continuous, chronic administration of rofecoxib 12.5 mg, 25 mg, and 50 mg is safe and generally well tolerated. In general, rofecoxib 50 mg was not as well tolerated as rofecoxib 12.5 and 25 mg, and provided no additional difference in chronic use. In acute pain (5 days of use), rofecoxib 25 and 50 mg were generally well tolerated with 50 mg providing superior efficacy. These data in OA and RA patients with acute pain support the intermittent use of rofecoxib 25 mg and 50 mg in the acute treatment of migraine.
- The incidences of overall and specific clinical adverse experiences in the migraine studies were less than or similar to those found in continuous, chronic dosing of rofecoxib 12.5 and 25 mg in OA and RA patients and in intermittent dosing of rofecoxib 25 mg and 50 mg in primary dysmenorrhea and acute pain.

6.6.2 Reviewer summary

Overall I concur with the sponsor's bulleted summary itemized above. Rofecoxib 25 mg and rofecoxib 50 mg was well tolerated in the acute studies as well as in the 3 month extension phase of trial 162. Clearly the vast majority (approximately 92%) of adverse events were mild to

moderate intensity and self limiting in the subjects that were randomized to rofecoxib. Few adverse events resulted in discontinuation in both the acute studies and the single multiple attack study. Approximately 88% of all patients in the acute phase of trial 162 enrolled into the extension phase and approximately 87% of these patients continued for the entire treatment period.

The more common adverse events (≥ 2%) seen with rofecoxib during the acute studies included dizziness, dry mouth, nausea, somnolence, asthenia, dyspepsia and paresthesia. There was no consistent evidence of a dose effect for most of these complaints with some of them being more frequent in rofecoxib 25 mg than in rofecoxib 50 mg. However in general more adverse events were reported by subjects randomized to rofecoxib 50 mg than subjects randomized to rofecoxib 25 mg. Most of the common adverse events were slightly more common in rofecoxib than in placebo. In the 3-month extension phase of trial 162 the more common adverse events (≥ 2%) seen with rofecoxib included dizziness, vomiting, dry mouth, gastroenteritis, nausea, upper abdominal pain, dyspepsia, pharyngitis, and upper respiratory tract infection. Oddly all of the common adverse events except for gastroenteritis were more common in rofecoxib 25 mg than in rofecoxib 50 mg. No comparison to placebo is possible since there was no placebo cohort in 162 extension.

There were no deaths in subjects treated with rofecoxib in any study. In trial 162 there were two deaths, one in a patient randomized to ibuprofen and the other in a patient that never took her randomized treatment. Neither event was considered related to study medication.

In the acute studies there were only 3 serious adverse events, only one of which was in a subject taking rofecoxib. None of the events were considered related to study medication. In the extension phase of trial 162 there were 4 serious adverse events. Three of these events occurred in the rofecoxib 50 mg cohort and the other in the ibuprofen cohort. None of the events were considered related to study medication.

Overall there were no clinically relevant changes in vital signs, laboratory or physical findings in either the acute studies or the 3 month extension study.

The supporting long-term safety information provided by the sponsor is very helpful. Overall the information provided by the sponsor represents approximately 3600 osteoarthritis subjects and approximately 5600 rheumatoid arthritis subjects. The safety data presented by the sponsor was mostly a blended average of incidences for rofecoxib 12.5 mg and 25 mg. For this reason I chose to look further and came across additional long term safety data from the VIGOR study submitted to the Agency and previously reviewed by HFD-550. The reviews located in DFS were very helpful and are briefly summarized earlier in my review. Overall rofecoxib in doses up to 50 mg daily for a year was well tolerated. Surprisingly the VIGOR study did demonstrate a slight increase in cardiovascular events compared to naproxen 1000 mg. This issue has been well debated within the Agency and is discussed in labeling. Of course this unexpected finding brings into question whether rofecoxib should be approved for a self-limiting condition such as migraine. My clinical opinion is although migraine is a self limiting condition it is associated with considerable disability. Additionally the available migraine therapies do not provide all

people with complete relief and many subjects are unable to take or tolerate triptans. As such I think the risk benefit analysis of intermittent use of rofecoxib in the treatment of migraine favors approval. However the daily use of rofecoxib for migraine and/or migraine prophylaxis should be discouraged in my opinion.

In summary I believe the safety and tolerability of rofecoxib in migraine patients is clinically acceptable for intermittent use during an acute migraine attacks with and without an aura.

7. Dosing, Regimen, and Administration Issues

Other than trial 161 and 162 no other dose finding studies have been conducted. The dose of 25 mg and 50 mg was selected by the sponsor because they represent the doses generally employed clinically to treat acute pain. The results of these two trials indicate that rofecoxib 25 mg and rofecoxib 50 mg are both effective in the treatment of acute migraine. Several questions arise when reviewing these studies. Most obvious is whether a lower dose of rofecoxib, such as 12.5 mg, might be effective. This has not been studied by the sponsor and should be considered although I would be concerned whether a lower treatment effect would be clinically relevant. Another question is whether there are any additional benefits achieved by using a 50 mg dose of rofecoxib over a 25 mg dose. The answer to this question is not so obvious and requires some thought. Throughout my review of the efficacy results I qualified the dose effect seen for each endpoint in both studies. Although none of the endpoints demonstrated a significant difference between rofecoxib 25 mg and rofecoxib 50 mg in the acute studies there was consistent evidence that a small additional benefit could be achieved by a higher dose of rofecoxib for most endpoints. Likewise during my discussion of safety results I found no clinically relevant difference in the safety profiles of the two doses although intuitively one should expect more adverse events with increasing doses of rofecoxib. The common adverse events seen were generally mild to moderate and self limiting. For this reason I believe it is prudent to approve both rofecoxib 25 mg and rofecoxib 50 mg for the acute treatment of migraine.

Clearly the data supports the initial use of rofecoxib 25 mg in the treatment of acute migraine with the rofecoxib 50 mg dose being reserved for subjects who have generally obtained an incomplete response to the lower dose in the past. Chronic use of rofecoxib 50 mg should be avoided.

As previously discussed the sponsor did not conduct the usual long term studies generally required for a migraine NDAs. Instead they have chosen to rely on long term safety data of the use of rofecoxib 25 mg and 50 mg in patients with osteoarthritis and rheumatoid arthritis. Overall the long term safety information from this population is reassuring that long term use of rofecoxib is generally safe however there are significant risks such as an increase in cardiovascular, renal, and gastrointestinal events. The presently approved labeling for rofecoxib adequately discusses these risks. However osteoarthritis and rheumatoid arthritis patients are not necessarily the same as migraine patients. Arthritis patients tend to be older with multiple chronic medical conditions and multiple concomitant medications compared to migraineurs. Additionally arthritis is more of a chronic unremitting medical problem requiring daily treatment as oppose to migraine which tend to be more intermittent. All of this would suggest that rofecoxib would be safer in the younger healthier migraine population than in the arthritis

population however migraineurs also tend to have delayed gastric emptying during a migraine attack which theoretically would make them more prone to the local effects of rofecoxib on the gastrointestinal tract. Additionally local gastrointestinal damage from NSAIDs is frequently asymptotic early and repeated insults with local toxicity can result in cumulative damage. Although this has not been seen in trial 161 and 162 this concern makes it prudent to limit the monthly administration of rofecoxib in the setting of a migraine attack. Additionally, the experience from the VIGOR trial demonstrates that there may be a small increase in cardiovascular events in subjects who take rofecoxib 50 mg daily for extended periods. Given that the 3 month long-term study limited the number of treatable attacks to 8 per month I would suggest this be the maximum number of treatments per month approved. Additionally the label should state that daily use of rofecoxib is not recommended in migraineurs.

8. Use in Special Populations

8.1 Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The following table summarizes the sponsor's subgroup comparison of the proportion of patients reporting 2 Hour Headache Relief for the subgroups age (<40 years/≥40 years), gender (male/female), and race (white/other). As previously discussed approximately 87% of all participant in trial 161 and 162 were female and 85% were Caucasian. The mean age in the trial 161 was 41.3 years and in trial 162 it was 39.8. Overall only 2.1% of all patients in both trials were 65 years of age or older hence no valid conclusions about the safety and efficacy of rofecoxib in Geriatric migraineurs can be made. Additionally no adolescent were included in the trial

The overall treatment-by-gender interaction was nearly significant in the combined analysis of trial 161 and trial 162 acute (p=0.077). This finding was driven primarily by the results of the gender subgroup analysis of trial 162 where the treatment-by-gender interaction was significant (p=0.031) however in trial 161 it was not significant (p=0.233). Further analysis showed that there were no qualitative interactions when making pairwise comparisons between treatment groups. In women, the percentages of patients who had headache relief at 2 hours postdose were 31.6%, 59.4%, and 59.9% in the placebo, rofecoxib 25-mg, and rofecoxib 50-mg treatment groups, respectively. In men, the percentages of patients who had headache relief at 2 hours postdose were 37.0%, 37.8%, and 55.8% in the placebo, rofecoxib 25-mg, and rofecoxib 50-mg treatment groups, respectively. This would suggest that men require a higher dose of rofecoxib in order to receive benefit however the small number of male patients makes it difficult to draw a firm conclusion. Overall, the absence of a significant qualitative interaction indicates the superiority of rofecoxib 25 mg and 50 mg over placebo in both women and men and suggests that the interaction observed was a chance finding.

There was no significant treatment-by-age category interaction in trial 161 (p=0.372), trial 162 acute phase (p=0.704), or the Combined acute phase (p=0.345), indicating that the treatment effects were consistent between age categories. In subjects less than 40 years of age, the percentages of patients who had headache relief at 2 hours postdose were 31.8%, 49.2%, and 53.9% in the placebo, rofecoxib 25-mg, and rofecoxib 50-mg treatment groups, respectively. In subjects ≥40 years of age, the percentages of patients who had headache relief at 2 hours

postdose were 32.9%, 65.3%, and 65.2% in the placebo, rofecoxib 25-mg, and rofecoxib 50-mg treatment groups, respectively.

There was no significant treatment-by-race interaction in either trial 161, 162 acute, or the Combined acute phase (p=0.870, p=0.627, and p=0.718, respectively), indicating that the treatment effects were consistent among races however the small number of non-Caucasian subjects makes it difficult to draw a conclusion.

Table 55 Proportion of Patients Reporting 2-Hour Headache Relief by Subgroup and Treatment, Combined Acute Phase Population.

Subgroup (p-Value)*	Placebo Total N=362		Vioxx 25 mg Total N=363		Vioxx 50 mg Total N=374	
	N	n (%)	N	n (%)	N	n (%)
Gender (p=0.233, p=0.031, p=0.077)						
Male	46	17 (37.0)	45	17 (37.8)	43	24 (55.8)
Female	316	100 (31.6)	318	189 (59.4)	332	199 (59.9)
Age Group (p=0.372, p=0.704, p=0.345)						
<40 years	164	54 (32.9)	170	111 (65.3)	184	120 (65.2)
≥40 years	198	63 (31.8)	193	95 (49.2)	191	103 (53.9)
Race (p=0.870, p=0.627, p=0.718)						
White	302	94 (31.1)	313	171 (54.6)	318	185 (58.2)
Other	60	23 (38.3)	50	35 (70.0)	57	38 (66.7)
Aura (p=0.317, p=0.168, p=0.064)						
Present	51	19 (37.3)	43	22 (51.2)	54	24 (44.4)
Absent	311	98 (31.5)	320	184 (57.5)	320	199 (62.2)
Baseline Severity (p=0.142, p=0.875, p=0.408)						
Moderate	216	76 (35.2)	237	142 (59.9)	238	157 (66.0)
Severe	146	41 (28.1)	126	64 (50.8)	136	65 (47.8)

Source: Adapted from sponsor table 2.7.3:50, ise.pdf, page 139
*p-value for subgroup by treatment interaction in protocol 161, 162 and in the combined analysis.

As discussed in section 6.4.11 there does not appear to be any clinically relevant differences in the proportion of patients reporting an adverse event or experiencing a serious adverse event between younger and older patients. The nature and character of the adverse events profile was similar between the various demographic groupings.

8.2 Evaluation of Pediatric Program

The sponsor does not provide a pediatric development program for my evaluation. During the pre-NDA meeting (December 4, 2002) the sponsor was reminded that the Pediatric Final Rule of December 1998 was no longer in effect and as such pediatric studies were not required. At that time we informed the sponsor that if the Final Rule is reinstated as previously written we would most likely grant a deferral of the pediatric/adolescent studies but not a waiver. As predicted the pediatric rule has been reinstated. The sponsor should be granted a deferral for pediatric studies. A pediatric program should be part of the phase IV commitments.

9. Conclusions and Recommendations

9.1 Conclusions

Overall the clinical development program for the use of rofecoxib in the treatment of acute migraine with and without an aura is acceptable. The two trials convincingly demonstrate that

rofecoxib 25 mg and rofecoxib 50 mg is effective in the treatment of migraine. Additionally the safety seen during these trials as well as the previous well known experience with rofecoxib in previous clinical trials and clinical use support the safe intermittent use of rofecoxib in migraineurs. The new safety data presented by the sponsor includes over 1000 migraine patients treating approximately 4000 attacks. Prior clinical trials included the short term and long term use of rofecoxib in patients with osteoarthritis, rheumatoid arthritis, acute pain and dysmenorrhea. Many of these older studies included patients much older and generally sicker than the typical patient with migraine who tends to be female in their reproductive years in otherwise general good health. As such the old safety information is informative and useful and in my opinion is sufficient in lieu of additional long term safety studies in migraine patients.

The sponsor states the overall 2 hour headache response seen with rofecoxib (between 54 and 62%) is at the lower range seen in most triptan studies (on average 60 to 65%). Although firm comparisons between rofecoxib and triptans can not be made from the data presented here it does appear that the results are within the expected range seen during a typical triptan trial.

As I outlined above, the safety and tolerability of rofecoxib 25 mg and rofecoxib 50 mg appears to be acceptable for approval in migraine patients. The character of adverse complaints reported in trial 161 and 162 is consistent with what is already discussed in labeling.

Based on the data presented in this submission rofecoxib 25 mg will be an effective and safe treatment option for most subjects with migraine. The 50 mg dose of rofecoxib may provide additional benefit to migraineurs as evidenced by the numerical superiority to rofecoxib 25 mg in almost all endpoints analyzed. The proposed label recommends a starting dose of rofecoxib 25 mg and mentions some patients may receive additional benefit from 50 mg. Chronic daily use of rofecoxib 50 mg is not recommended. Rofecoxib will provide an alternative treatment option and should, in my opinion, be approved.

In conclussion:

- The risk benefit analysis of rofecoxib 25 and 50 mg favors the approval of rofecoxib for the treatment of migraine.
- The efficacy and safety compares favorably to other migraine products already approved for use in the United States.

9.2 Recommendations

From a clinical perspective I recommend the approval of rofecoxib 25 mg and rofecoxib 50 mg for the acute treatment of migraine with and without aura. Phase IV commitments should include the development of a clinical program to evaluate the safety and efficacy of rofecoxib in the treatment of migraines in adolescent patients. In order to facilitate team input my review of the proposed label can be found in a separate document.

10. Appendix

10.1 Predefined Limits for Change in Laboratory Values

Predefined Limit of Change	
Laboratory Parameter	Limit
Hematocrit (%)	$\leq 0.949^{*}$ LLN, $0.941^{\#}$ LLN
Hemoglobin (gm/dL)	$\leq 0.905^{*}$ LLN, $0.819^{\#}$ LLN
WBC count (10^3/microL)	≤ 0.642 LLN and ≥ 1.490 ULN
Eosinophil count (10^3/microL)	≥ 1.470 ULN
Neutrophil count (10^3/microL)	≤ 0.370 LLN
Platelet count (10^3/microL)	≤ 0.577 LLN and ≥ 1.777 ULN
Total serum bilirubin (mg/dL)	≥ 1.667 ULN
Serum alkaline phosphatase (IU/L)	≥ 3 ULN
Serum alanine aminotransferase	≥ 3 ULN
Serum aspartate aminotransferase	≥ 3 ULN
Serum creatinine	≥ 1.429 ULN
Serum Potassium	≤ 0.882 LLN and ≥ 1.111 ULN
Serum sodium	≤ 0.947 LLN and ≥ 1.054 ULN

*For Males, # For Females
ULN = upper limits of normal for laboratory
LLN = lower limits of normal for laboratory

10.2 List of Tables and Figures

List of Tables

List of Figures

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