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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Table of Contents

1 EXECUTIVE SUMMARY 3

1.1 CONCLUSIONS AND RECOMMENDATIONS 3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES 3
1.3 STATISTICAL ISSUES AND FINDINGS 4

2. INTRODUCTION 5

2.1 OVERVIEW 5
2.2 DATA SOURCES 6

3. STATISTICAL EVALUATION 6

3.1 EVALUATION OF EFFICACY 6
3.1.1 Study Objectives (for Protocols 161 and 162) 6
3.1.2 Study Design (for Protocols 161 and 162) 6
3.1.3 Study Procedures (for Protocols 161 and 162) 7
3.1.4 Selection of Study Patients (for Protocols 161 and 162) 8
3.1.5 Efficacy Measures Assessed (for Protocols 161 and 162) 8
3.1.6 Efficacy Parameters (for Protocols 161 and 162) 9
3.1.7 Statistical/ Analytical Methods (for Protocols 161 and 162) 9
3.1.8 Results for Protocol 161 (from Sponsor's Analysis) 10
3.1.9 Reviewer's Analysis 18
3.1.10 Results from Protocol 162 (from Sponsor's Analysis) 21
3.1.11 Reviewer's Analysis *29*
3.2 EVALUATION OF SAFETY 31

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS 31

4.1 GENDER, RACE AND AGE 31
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS 32

5. SUMMARY AND CONCLUSIONS 32

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE 32
5.2 CONCLUSIONS AND RECOMMENDATIONS 33

1 EXECUTIVE SUMMARY

This NDA submitted by Merck Laboratories provided clinical support for the use of refecoxib 25 and 50 mg in the acute treatment of migraine, with or without aura, in adults. The application contained information from two pivotal, multicenter, randomized, placebo-controlled, double-blind trials (Protocols 161 and 162) that were similar in design, as well as an additional trial considered supportive of long term safety that evaluated the use of rofecoxib in the prevention of migraine (Protocol 125). Trial 161 was conducted entirely within the U.S., while Trial 162 was multinational (U.S. plus non-U.S.) and included an active comparator treatment arm and a 3-month extension phase.

The acute phase of each pivotal study utilized rofecoxib doses of 25 and 50 mg and involved treatment of a single migraine attack. The two trials used standard patient-reported diaries and questionnaires for assessing efficacy and safety during and after a migraine attack, and were designed on an outpatient basis without any supervision. The primary assessment of efficacy was based on patients' self-rating of headache severity on a 4-grade scale (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain) immediately to dosing and at 30-minute intervals up to 2 hours after dosing.

1.1 Conclusions and Recommendations

The studies 161 and 162 have demonstrated a statistically significant benefit of rofecoxib 50 mg and 25 mg over placebo in the treatment of acute migraine attack with regard to the primary efficacy parameter and a number of secondary efficacy parameters. Based on the efficacy data I have reviewed for this NDA and the consistency of the efficacy results from the two studies, I conclude that rofecoxib 50 mg and 25 mg are effective in the acute treatment of migraine headache with or without aura in adults. I conclude that rofecoxib is effective as follows:

1. Rofecoxob 50 mg and 25 mg are superior to placebo in providing headache relief at 2 hour post dosing.
2. Rofecoxib 50 mg is superior to placebo in reducing the migraine-associated symptoms of nausea, photophobia, and phonophobia at 2 hour post dosing.
3. Rofecoxib 25 mg is superior to placebo in reducing the migraine-associated symptoms of photophobia and phonophobia at 2 hour post dosing. The effect of rofecoxib 25 mg with regard to symptom of nausea could not be concluded.
4. There were no statistically significant difference in the effectiveness between rofecoxib 50 mg and 25 mg. However, the totality of the data suggested larger benefit of rofecoxib 50 mg than rofecoxib 25 mg.

1.2 Brief Overview of Clinical Studies

The primary objective of the rofecoxib migraine program was to demonstrate the efficacy and safety of rofecoxib 25 mg and 50 mg for the acute treatment of migraine. The clinical program consisted of 2 protocols (Protocols 161 and 162). There were 557 and 783 patients who took study medication in trials 161 and 162, respectively. Both trials had an acute phase during which the efficacy and safety of rofecoxib were evaluated for the acute treatment of a single migraine

attack according to a randomized, placebo-controlled, double-blind, and parallel group design. In addition, Protocol 162 had a 3-month extension phase during which the efficacy, tolerability, and safety of the intermittent use of rofecoxib administration over multiple migraine attacks were assessed.

The two studies were designed similarly. The primary efficacy parameter, the proportion of patients who had pain relief at 2-hour post dose, was common for both studies with same statistical analysis methodology. The two studies also designated same list of secondary efficacy parameters.

Although the acute phase of the two studies were similar in design, compared to Protocol 161, Protocol 162 had additional design features as follows:

- Protocol 162 included an active-comparator arm (ibuprofen 400 mg) in the acute phase.
- Protocol 162 included patients from the United State, as well as patients from the European Union, Asia, and Latin America while Protocol 161 only included U.S. patients.
- Protocol 162 included a 3-month extension.

1.3 Statistical Issues and Findings

The common primary efficacy parameter designated by the two studies was pain relief at 2-hour post dose. Pain relief was defined as headache from moderate/ severe (Grade 2/ 3) pain at baseline to mild or no pain (Grade 1/ 0) at 2 hours after administration of test drug. The two studies also designated a common list of secondary efficacy parameters. Most of those parameters were measured at different time points or they had sub-measures. The total number of secondary efficacy parameters counting multiple time points and sub-measures reached or exceeded 50. No multiplicity adjustment was specified or proposed. The methods the sponsor used to analyze the data also varied from one study to the other for some secondary efficacy parameters.

In reviewing and analyzing the efficacy data regarding the secondary efficacy parameters, I have focused on pain relief and pain freedom within 2 hours of study medication administration and migraine associated symptoms at 2-hour post dose. Since rescue medication was allowed after 2 hours of dosing, pain relief and pain freedom beyond 2-hour post dosing were considered less important, and therefore, those parameters were analyzed but not reported. Secondary efficacy parameters other than the above stated are not reported in this review.

At the 2-hour post dose, the proportions of patients who had pain relief, from Studies 161 and 162, respectively, were 57.8% and 62.2% for rofecoxib 50 mg, 54.0% and 59.4% for rofecoxib 25 mg, compared to 33.1% and 30.5% for patients taking placebo. In both studies, the treatment differences between each of the rofecoxib doses and placebo regarding this primary efficacy parameter were statistically significant ($p<.001$).

Onset of relief was observed from one hour after dosing for rofecoxib 50 mg and 25 mg compared to placebo (35.83% and 33.52% vs. 14.86%, and 34.04% and 31.02% vs. 15.51% for Protocols 161 and 162, respectively). Onset of pain freedom was observed at 2 hour after dosing

for rofecoxib 50 mg and 25 mg compared to placebo (23.53% and 19.32% vs. 7.43%, and 26.60% and 25.13% vs. 5.35% for Protocols 161 and 162, respectively).

Although the difference between the two rofecoxib doses was not statistically significant, the totality of data suggests additional efficacy for the 50 mg compared to the 25 mg dose.

The following table presents a summary of the efficacy results that are discussed in more details later in this review.

Table 1. Summary of Primary and Key Secondary Efficacy Results in Percentage of Patients and p-values for Comparisons to Placebo

	Placebo	Rofecoxib 50 mg	Rofecoxib 25 mg	Ibuprofen 400 mg
Headache Relief at 2 Hour (Primary Efficacy)				
Protocol 161	**33.1%**	**57.8% (p =.0001)**	**54.0% (p=.0002)**	NA
Protocol 162	**30.5%**	**62.2% (p=.0001)**	**59.4% (p=.0001)**	58.2% (p=.0001)
Associated Symptom				
Photophobia				
Protocol 161	70.9%	57.0% (p=.0050)	61.9% (p=.0542)	NA
Protocol 162	65.2%	49.5% (p=.0024)	52.2% (p=.0082)	50.5% (p=.0037)
Phonophobia				
Protocol 161	64.6%	44.6% (p=.0002)	52.3% (p=.0256)	NA
Protocol 162	59.9%	42.6% (p=.0009)	44.9% (p=.0017)	39.4%(.0001)
Nausea				
Protocol 161	41.7%	30.3% (p=.0300)	33.0% (p=.1115)	NA
Protocol 162	41.7%	29.8% (p=.0175)	31.7% (p=.0396)	27,8% (p=.0046)
Secondary Efficacy				
Headache Relief at 1 Hour				
Protocol 161	14.9%	35.8% (p=.0001)	33.5% (p=.0002)	NA
Protocol 162	15.5%	34.0% (p=.0001)	31.0% (p=.0002)	32.5% (p=.0001)
Headache Freedom at 2 Hour				
Protocol 161	7.4%	23.5% (p=.0001)	19.3% (p=.0017)	NA
Protocol 162	5.4%	26.6% (p=.0001)	25.1% (p=.0001)	23.3% (p=.0001)

2. INTRODUCTION

2.1 Overview

The primary objective of the rofecoxib migraine program was to demonstrate the efficacy and safety of rofecoxib 25 mg and 50 mg for the acute treatment of migraine. The clinical program consisted of 2 protocols (Protocol 161 and Protocol 162). Both protocols had an acute phase during which the efficacy and safety of rofecoxib were evaluated for the acute treatment of a single migraine attack according to a randomized, placebo-controlled, double-blind, and parallel group design. In addition, Protocol 162 had a 3-month extension phase during which the efficacy, tolerability, and safety of the intermittent use of rofecoxib administration over multiple migraine attacks were assessed.

The two protocols used standard patient-reported diaries and questionnaires for assessing efficacy and safety during and after a migraine attack, and were designed on an outpatient basis without any supervision. The primary assessment of efficacy was based on patients' self-rating of headache severity on a 4-grade scale (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain) immediately to dosing and at 30-minute intervals up to 2 hours after dosing. The change in patient's headache severity at 3 and 4 hours post-dosing and at 24 hours post-dosing was also rated.

2.2 Data Sources

SAS data files were provided in transport format for the two pivotal studies of Protocols 161 and 162 electronically at \\Cdsesub1\n21647\N_000\2003-05-23\crt\datasets\stat.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The clinical program of rofecoxib consisted of two pivotal studies: Protocols 161 and 162. Both protocols had an acute phase during which the efficacy and safety of rofecoxib were evaluated for the acute treatment of a single migraine attack. The acute phases of the two studies were similar in design and analysis methods with the exception of the following features, which were additions only to the protocol 162:

- Protocol 162 included an active-comparator arm (ibuprofen 400 mg) in the acute phase.
- Protocol 162 included patients from United States, as well as patients from European Union, Asia, and Latin America, while protocol 161 only included U.S. patients.
- Protocol 162 had a 3-month extension phase during which the efficacy, tolerability, and safety of the intermittent use of rofecoxib administration over multiple migraine attacks was assessed.

3.1.1 Study Objectives (for Protocols 161 and 162)

The primary objective of the study was to examine the efficacy, safety, and tolerability of rofecoxib 50 mg compared to placebo for the acute treatment of migraine, with efficacy defined as headache relief (headache from moderate/ severe, Grade 2/ 3, pain at baseline to mild or no pain, Grade 1/ 0) at 2 hours after administration of test drug.

3.1.2 Study Design (for Protocols 161 and 162)

Protocols 161 and 162 were randomized, double- blind, placebo- controlled, double-dummy (triple-dummy for Protocol 162), parallel-group, multicenter studies in outpatients diagnosed with migraine attacks with or without aura. The studies were conducted to assess the efficacy, safety, and tolerability of rofecoxib 50 and 25 mg for the acute treatment of a single migraine attack of moderate (Grade 2) or severe (Grade 3) pain intensity. Protocol 161 included 3 treatment arms of rofecoxib 25 mg and 50 mg and placebo, while protocol 162 had an additional

4th treatment arm of ibuprofen 400 mg as an active comparator. It was planned that each treatment group would enroll about 210 patients to have about 168 treated patients.

3.1.3 Study Procedures (for Protocols 161 and 162)

Prestudy

Outpatients who suffered from migraine with or without aura were medically screened at a prestudy visit. Eligible patients were randomized at the end of the prestudy visit into one of the treatment groups of rofecoxib 50 mg, rofecoxib 25 mg, and placebo (plus ibuprofen 400 mg for protocol 162). Patients were given 3 months to treat a moderate/ severe migraine headache with study drug.

Treatment Day

Upon experiencing a Grade 2 or 3 migraine attack, patients administered test medication if the headache had not started to resolve spontaneously and they had not already taken any prohibited medications. Patients were provided a diary in which to rate headache severity, associated migraine symptoms, and functional disability immediately prior to taking the test medication (0 hour) and then at 0.5, 1, 1.5, 2, 3, and 4 hours post-dose.

Patients who did not obtain pain relief (Grade 1/ 0) at 2 hours after the initial treatment were permitted to take rescue medication at that time and any time thereafter. Patients obtaining relief after their test dose could also treat their moderate/ severe headache recurrence with rescue medication. They recorded in the diary the incidence of, time to, and severity of any moderate/ severe headache recurrence or return to mild/ moderate/ severe headache.

At 24 hours after the test dose, patients completed a 24-Hour Migraine Quality-of-Life Questionnaire. A Migraine Work and Productivity Questionnaire was also completed at the end of the 24-hour treatment period or thereafter, whenever the headache was resolved.

Post-treatment Period

Patients returned to the clinic within 7 days after treatment with study drug, or if they did not treat with study drug within 3 months of randomization. Patients who participated in Protocol 162 were given the option of enrolling in a 3-month extension phase if they had treated a migraine attack with study drug during the acute phase and returned for the acute phase post-treatment visit.

Critical Study Dates:

Protocol 161

First patient in: 24- August- 2001
Last patient out: 29- May- 2002
Frozen file: 20- August- 2002

Protocol 162

First patient in: 04-Sep-2001
Last patient out: 29-May-2002
Frozen file: 06-Dec-2002
Database unblind: 10-Dec-2002

3.1.4 Selection of Study Patients (for Protocols 161 and 162)

Inclusion Criteria

Patients met the following inclusion criteria in order to participate in the study:

1. Patient was at least 18 years of age.
2. Patient had on average >= 1 and <= 8 migraine attacks per month for the 6 months prior to study start, with or without aura.
3. Patient understood the study procedures and agreed to participate in the study by giving written informed consent.

Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria:

1. Patient had difficulty in distinguishing his/ her migraine attacks from tension or interval headaches.
2. If female, patient was pregnant or nursing, or if of childbearing potential and sexually active, not willing to use effective barrier or appropriate oral contraception during the study. Patients who were taking oral contraceptives had done so for <2 months before entering the study.
3. Patient had demonstrated hypersensitivity to or experienced a serious adverse event in response to rofecoxib, or had any contraindication for the use of rofecoxib (e. g., allergic reaction to NSAIDs).
4. Patient had clinical or laboratory evidence of uncontrolled hypertension, or significant pulmonary, renal, hepatic, endocrine, neurologic (apart from migraine), psychiatric or other systemic disease, or any laboratory abnormality that, in the opinion of the investigator, would have confounded the results of the study, posed an additional risk to the patient, or would have interfered with optimal participation in the study.
5. Patient had a history of drug or alcohol abuse within 1 year prior to study start.
6. Patient had received treatment with an investigational device or compound within 30 days of the study start.

3.1.5 Efficacy Measures Assessed (for Protocols 161 and 162)

Efficacy variables were obtained from data recorded by the patient on the migraine diary card during the 24 hours following administration of study drug. Measurements included:

- Rating of Headache Severity: Grade 0 - No pain; Grade 1 - Mild pain; Grade 2 - Moderate pain; Grade 3 - Severe pain;
- Associated Migraine Symptoms: photophobia, phonophobia, nausea, vomiting;
- Rating of Functional Disability: Grade 0 - Normal; Grade 1 - Daily activities mildly impaired; Grade 2 - Daily activities severely impaired; Grade 3 - Unable to carry out daily activities, required bed rest;
- Moderate/ Severe Headache Recurrence: Grade 0/ 1 to 2/ 3;
- Return to Mild/ Moderate/ Severe Headache: Grade 0 to 1/ 2/ 3;
- Twenty- Four- Hour Migraine- Specific Quality of Life Questionnaire;
- Migraine- Specific Work and Productivity Questionnaire.

3.1.6 Efficacy Parameters (for Protocols 161 and 162)

The common primary efficacy endpoint for protocols 161 and 162 was headache relief at 2 hours after study drug administration (headache relief at 2 hours was defined as Grade 2/ 3 at baseline to Grade 1/ 0 at 2 hours). This primary efficacy rating was obtained from data recorded by patients in their migraine diaries.

Secondary efficacy parameters included headache relief and pain freedom at 0.5, 1, 1.5, 2, 3, and 4 hours; 24- hour sustained headache relief; 24-hour sustained pain freedom; associated migraine symptoms at 0.5, 1, 1.5, 2, 3, and 4 hours; need for rescue medication between 2 and 24 hours and functional disability at 0.5, 1, 1.5, 2, 3, and 4 hours.

3.1.7 Statistical/ Analytical Methods (for Protocols 161 and 162)

The all-patients-treated (APT) approach (equivalent to a modified intention-to-treat analysis) was the principal method used in all efficacy analyses. All patients who treated a moderate-to-severe migraine headache and had at least one measurement within 2 hours after the initial dose were included in this analysis population. Missing values after treatment were imputed by carrying forward the preceding value, provided this value was obtained after treatment (Last Observation Carry Forward [LOCF] method). No imputations were made to missing values at baseline or at 0.5-hour post dose.

Logistic Regression Model

The primary efficacy analysis compared the proportion of patients reporting headache relief at 2 hours (primary endpoint) of the rofecoxib 50-mg group to that of the placebo group. Other treatment comparisons were secondary: (1) rofecoxib 25 mg with placebo, and (2) rofecoxib 50 mg with rofecoxib 25 mg. All treatment comparisons were performed in the context of logistic regression models.

The logistic model included terms for treatment, geographic region, and baseline headache severity. The treatment comparisons were performed using pairwise contrasts within this model. In addition, the treatment differences were summarized by the odds ratios derived from this model and the 95% confidence interval.

A step-down closed testing procedure was applied to the tests. The procedure assumed that rofecoxib 50 mg, rofecoxib 25 mg, and placebo were ordered. Practically, the highest dose of rofecoxib (50 mg) was compared with placebo. If the test was significant at 0.05 level, the comparison of next dose of rofecoxib (25 mg) was considered valid at level 0.05.

The consistency of the treatment effect across geographic region and baseline severity was tested using the treatment-by-region interaction and the treatment-by-baseline severity interaction in logistic regression.

Headache relief at time points other than 2 hours post-dose, pain freedom at all time points, sustained pain freedom and sustained headache relief, functional disability (no disability versus other categories), and individual associated migraine symptoms at each time point were analyzed using the same approach as for headache relief at 2 hours.

Multicenter Studies

Trial 161 was conducted at different sites in the United States and trial 162 was conducted at different sites internationally. Because of the large number of sites and the use of logistic regression as a primary analysis method, the sites were combined into regions according to the geographical location of the sites.

For Protocol 161, the geographical regions consisted of Region I: California and Nevada United States; Region II: Midwestern to Western United States; Region III: Southeastern United States; and Region IV: Northeastern United States. For Protocol 162, the geographical regions consisted of Region I: Latin America and Asia; Region II: Europe; Region III: Western/ Midwestern United States; and Region IV: Eastern United States.

3.1.8 Results for Protocol 161 (from Sponsor's Analysis)

3.1.8.1 Accounting for Patients in the Study

Of the 645 patients who were screened, 627 were randomized. Five hundred fifty seven (557) patients took study medication. Of those, 19 patients were excluded from the APT population because they had no diary data. A total of 538 patients were included in the APT population: 187 in rofecoxib 50 mg, 176 in rofecoxib 25 mg, and 175 in placebo.

Table 2 presents the number of patients who were randomized, treated and not treated, and the reasons for discontinuation from the study.

Table 2. Patient Accounting (copied from sponsor's Table 7 of Protocol 161)

	Placebo (N=208)		Rofecoxib 25 mg (N=209)		Rofecoxib 50 mg (N=210)		Total (N=627)	
	n	(%)†	n	(%)†	n	(%)†	n	(%)†
Patients randomized	208		209		210		627	
Patients treated	182		183		192		557	
Patients not treated	26		26		18		70	
Patients 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)
Lost to follow-up	6	(3.3)	6	(3.3)	5	(2.6)	17	(3.1)
Patients not treated	26		26		18		70	
Clinical adverse experience	0		1	(3.8)	0		1	(1.4)
Patient did not have migraine headache‡	8	(30.8)	7	(26.9)	3	(16.7)	18	(25.7)
Patient had migraine headache but did not treat§	10	(38.5)	11	(42.3)	10	(55.6)	31	(44.3)
Patient discontinued for other reason	4	(15.4)	4	(15.4)	1	(5.6)	9	(12.9)
Patient withdrew consent	4	(15.4)	2	(7.7)	4	(22.2)	10	(14.3)
Protocol deviation	0		1	(3.8)	0		1	(1.4)

† For treated patients, the percentage is calculated from all treated patients; for nontreated patients, the percentage is calculated from all nontreated patients.
‡ These patients were not treated with study drug because they did not have a moderate/severe migraine headache within the 3 months of randomization and were thus discontinued from the study.
§ These patients had at least one moderate/severe migraine headache, but were not treated with study drug within 3 months of randomization and were thus discontinued from the study.

Data Source: [4.1; 4.2; 4.7; 4.8]

3.1.8.2 Protocol Deviations

Three patients were identified as protocol violators; all 3 took sumatriptan before the 2- hour assessment. These patients were included in the APT population.

3.1.8.3 Demographic and Other Baseline Characteristics

A total of 557 outpatients from 34 study sites in the United States treated with study drug. Patients were randomly assigned to 1 of 3 treatment groups: placebo (N= 182), rofecoxib 25 mg (N= 183), and rofecoxib 50 mg (N= 192).

Table 3 presents the baseline patient characteristics by treatment group. The sponsor reported that the treatment groups were similar with regard to age and race. The patients' ages ranged from 18 to 70 years with a mean age of 41.3 years. Among the 557 patients, the majority were White (n= 497, 89.2%). There were 497 female patients (89.2%) and 60 male patients (10.8%).

Table 3. Demographic and Baseline Characteristics (copied from sponsor's Table 12 of Protocol 161)

Baseline Patient Characteristics by Treatment Group

	Placebo (N=182)		Rofecoxib 25 mg (N=183)		Rofecoxib 50 mg (N=192)		Total (N=557)	
	n	(%)	n	(%)	n	(%)	n	(%)
Gender								
Female	160	(87.9)	165	(90.2)	172	(89.6)	497	(89.2)
Male	22	(12.1)	18	(9.8)	20	(10.4)	60	(10.8)
Age (Years)								
<18	0		0		0		0	
18 to 29	34	(18.7)	27	(14.8)	41	(21.4)	102	(18.3)
30 to 39	42	(23.1)	45	(24.6)	43	(22.4)	130	(23.3)
40 to 49	61	(33.5)	75	(41.0)	63	(32.8)	199	(35.7)
50 to 59	34	(18.7)	31	(16.9)	36	(18.8)	101	(18.1)
60 to 64	6	(3.3)	2	(1.1)	5	(2.6)	13	(2.3)
≥65	5	(2.7)	3	(1.6)	4	(2.1)	12	(2.2)
Mean	41.9		41.2		40.8		41.3	
SD	11.3		10.2		11.5		11.0	
Median	42.5		42.0		42.5		42.0	
Range	19 to 70		18 to 68		18 to 67		18 to 70	
Racial Origin								
White	163	(89.6)	164	(89.6)	170	(88.5)	497	(89.2)
Black	12	(6.6)	10	(5.5)	15	(7.8)	37	(6.6)
Asian	3	(1.6)	2	(1.1)	1	(0.5)	6	(1.1)
Multiracial	0		2	(1.1)	1	(0.5)	3	(0.5)
Other	4	(2.2)	5	(2.7)	5	(2.6)	14	(2.5)
Baseline Severity								
Moderate	103	(56.6)	127	(69.4)	124	(64.6)	354	(63.6)
Severe	72	(39.6)	49	(26.8)	63	(32.8)	184	(33.0)
Missing	7	(3.8)	7	(3.8)	5	(2.6)	19	(3.4)
Presence of Aura								
Without	143	(78.6)	155	(84.7)	162	(84.4)	460	(82.6)
With	32	(17.6)	22	(12.0)	25	(13.0)	79	(14.2)
Missing	7	(3.8)	6	(3.3)	5	(2.6)	18	(3.2)
Prophylactic Migraine Treatment								
Without	126	(69.2)	118	(64.5)	129	(67.2)	373	(67.0)
With	56	(30.8)	65	(35.5)	63	(32.8)	184	(33.0)
Beta-blockers	24	(13.2)	17	(9.3)	18	(9.4)	59	(10.6)
Calcium channel blockers	12	(6.6)	18	(9.8)	8	(4.2)	38	(6.8)
Selective serotonin reuptake inhibitors	19	(10.4)	24	(13.1)	25	(13.0)	68	(12.2)
Tricyclic antidepressant	18	(9.9)	26	(14.2)	21	(10.9)	65	(11.7)
Valproate	5	(2.7)	2	(1.1)	6	(3.1)	13	(2.3)

3.1.8.4 Efficacy Evaluation and Results

3.1.8.4.1 Analysis of Primary Endpoint

The primary endpoint was headache relief at 2 hours post-dose, with headache relief defined as a reduction of migraine headache severity from Grades 2 or 3 (moderate or severe pain) at baseline to Grade 1 or 0 (mild or no pain) in the setting of a typical migraine attack.

Table 4 displays the summary statistics for the number and percent of patients with a migraine attack reporting headache relief at 2 hours post dose by treatment group. The percentages of patients reporting headache relief 2 hours post dose were 34.3%, 54.0%, and 56.7% in the placebo, rofecoxib 25 mg, and rofecoxib 50 mg treatment groups, respectively.

A significantly higher percentage of migraine patients reported headache relief at 2 hours post-dose in the rofecoxib 50 mg group than in the placebo group ($p< 0.001$): the odds ratio and 95% confidence interval were 2.51 (1.63, 3.86). Also, a significantly higher percentage of migraine patients reported headache relief 2 hours post dose in the rofecoxib 25 mg group than in the placebo group ($p< 0.001$): the odds ratio and 95% confidence interval were 2.21 (1.43, 3.43). Rofecoxib 50 mg was numerically, but not statistically, better than rofecoxib 25 mg ($p= 0.556$) in providing headache relief: the odds ratio and 95% confidence interval were 1.13 (0.75, 1.73).

Table 4. Number (%) of Patients Reporting Headache Relief at 2 Hours Postdose (copied from sponsor's Table 18 of Protocol 161)

Treatment	N	n	%	95% Confidence Interval
Placebo	175	60	34.3	27.3, 41.8
Rofecoxib 25 mg	176	95	54.0	46.3, 61.5
Rofecoxib 50 mg	187	106	56.7	49.3, 63.9
The corresponding p-values and confidence intervals for the various comparisons are presented in Table 19. N = Number of patients with non-missing (or carried-forward) migraine headache severity at 2 hours. n (%) = Number (percent) of patients with headache relief at 2 hours.				

Data Source: [4.3]

Effect of Covariates on the Primary Endpoint

In order to explore the consistency of the treatment effects across the levels of several predefined covariates, treatment-by-covariate interactions were evaluated for the primary efficacy endpoint.

Table 5 presents the number and percent of patients with a migraine attack experiencing headache relief at 2 hours post dose by covariate, as well as the corresponding p-values for the treatment-by-covariate interactions.

Table 5. Number (%) of Patients with Headache Relief at 2 Hours Postdose - Subgroup Analysis (copied from sponsor's Table 20 of Protocol 161)

Subgroup (p-Value)[†]	Placebo (N=175)			Rofecoxib 25 mg (N=176)			Rofecoxib 50 mg (N=187)		
	N	n	%	N	n	%	N	n	%
Gender (p=0.233)									
Male	21	6	28.6	16	4	25.0	19	11	57.9
Female	154	54	35.1	160	91	56.9	168	95	56.5
Age Group (p=0.372)									
<40 years	73	25	34.2	69	43	62.3	81	53	65.4
≥40 years	102	35	34.3	107	52	48.6	106	53	50.0
Race (p=0.870)									
White	157	55	35.0	161	88	54.7	168	95	56.5
Others	18	5	27.8	15	7	46.7	19	11	57.9
Aura (p=0.317)									
Presence	32	12	37.5	22	9	40.9	25	11	44.0
Absence	143	48	33.6	154	86	55.8	162	95	58.6
Concomitant Migraine Prophylactic Treatment (p=0.532)									
With	53	13	24.5	64	32	50.0	62	31	50.0
Without	122	47	38.5	112	63	56.3	125	75	60.0
Prior Response to NSAIDs (p=0.029)									
<50%	105	31	29.5	112	52	46.4	114	68	59.6
≥50%	64	27	42.2	52	38	73.1	58	32	55.2
Use of Oral Contraceptives[‡] (p=0.415)									
Yes	36	12	33.3	35	23	65.7	36	24	66.7
No	118	42	35.6	125	68	54.4	132	71	53.8

Table 5 Continued

	Placebo (N=175)			Rofecoxib 25 mg (N=176)			Rofecoxib 50 mg (N=187)		
Menstrually Associated Migraine Attack[§] (p=0.111)									
Yes	29	10	34.5	42	27	64.3	26	11	42.3
No	70	24	34.3	71	42	59.2	81	54	66.7
Dysmenorrhea[¶] (p=---)									
Presence	3	1	33.3	4	4	100.0	1	0	0.0
Absence	24	7	29.2	38	23	60.5	23	11	47.8
Geographic Region (p=0.058)									
Region I	40	10	25.0	42	23	54.8	45	21	46.7
Region II	42	21	50.0	38	22	57.9	44	29	65.9
Region III	44	8	18.2	46	23	50.0	48	31	64.6
Region IV	49	21	42.9	50	27	54.0	50	25	50.0
Baseline Severity (p=0.142)									
Moderate	103	35	34.0	127	70	55.1	124	79	63.7
Severe	72	25	34.7	49	25	51.0	63	27	42.9

[†] p-Value for subgroup-by-treatment interaction.
[‡] For women only.
[§] For women with recent menses info only.
[¶] For women with menstrually-associated migraine attacks only.
N = Number of patients with nonmissing (or carried-forward) migraine headache severity at 2 hours.
n (%) = Number (percent) of migraine patients with headache relief at 2 hours.
"---" Indicates a case where data were sparse and the model was not fitted.

Data Source: [4.1; 4.3]

The treatment-by-prior response to NSAIDs interaction was significant (p= 0.029). The sponsor reported that further pairwise analysis showed that there was no significant qualitative treatment-by-prior response to NSAIDs interaction (p> 0.100) when comparing each dose of rofecoxib with placebo.

The interaction of treatment by geographical region was significant (p= 0.058). Nevertheless, the percentage of migraine patients with headache relief at 2 hours postdose was higher in the rofecoxib groups than in the placebo group in each geographical region (Table 5).

No other significant treatment-by-covariate interactions were found.

3.1.8.4.2 Analysis of Secondary Endpoints

Headache Relief at 0.5, 1, 1.5, and 2 Hours Postdose

Figure 1 displays the percentage of migraine patients with headache relief at time points within 2 hours of dosing; these percentages are tabulated by baseline headache severity in Table 6.

Figure 1. Percentage of Patients Reporting Headache Relief Within 2 Hours of Dosing (copied from sponsor's Figure 3 of Protocol 161)

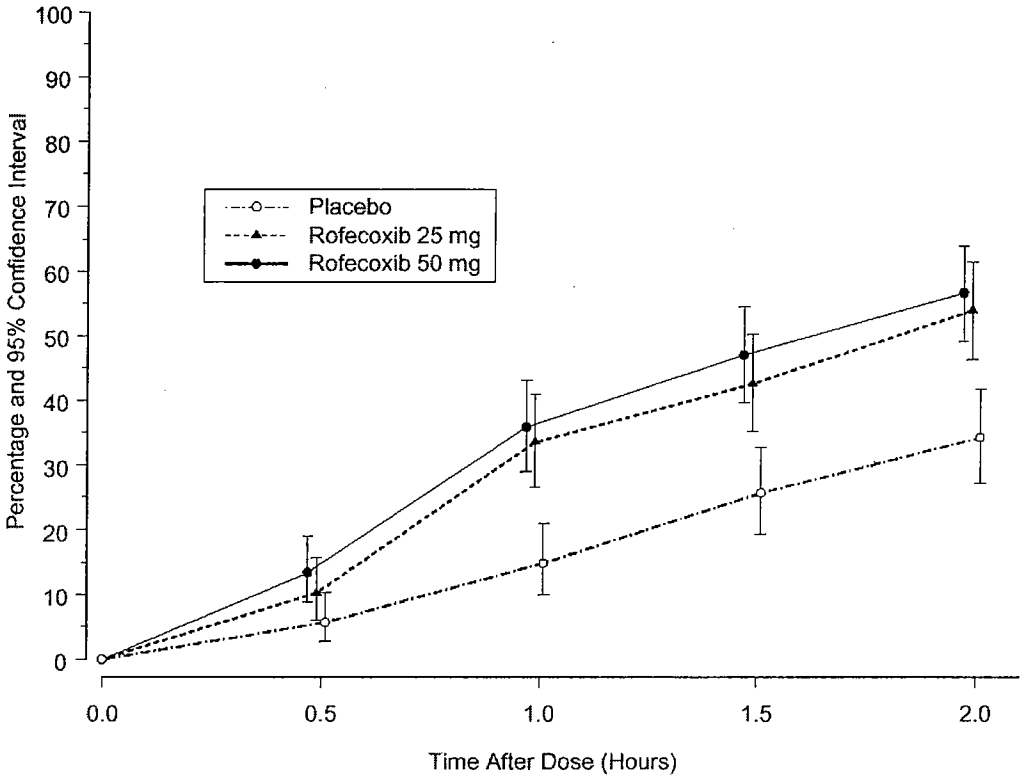

Table 6. Number (%) of Patients reporting Headache Relief at Time Points Within 2 Hours Postdose by Treatment Group and Baseline Severity (copied from sponsor's Table 21 of Protocol 161)

Treatment	Baseline Severity	N	0.5 hr			1.0 hr			1.5 hr			2.0 hr		
			n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Placebo	Moderate	103	10	9.7	4.8, 17.1	17	16.5	9.9, 25.1	27	26.2	18.0, 35.8	35	34.0	24.9, 44.0
	Severe	72	0	0.0	---	9	12.5	5.9, 22.4	18	25.0	15.5, 36.6	25	34.7	23.9, 46.9
	Total	175	10	5.7	2.8, 10.3	26	14.9	9.9, 21.0	45	25.7	19.4, 32.9	60	34.3	27.3, 41.8
Rofecoxib 25 mg	Moderate	127	16	12.6	7.4, 19.7	48	37.8	29.3, 46.8	59	46.5	37.6, 55.5	70	55.1	46.0, 63.9
	Severe	49	2	4.1	0.5, 14.0	11	22.4	11.8, 36.6	16	32.7	19.9, 47.5	25	51.0	36.3, 65.6
	Total	176	18	10.2	6.2, 15.7	59	33.5	26.6, 41.0	75	42.6	35.2, 50.3	95	54.0	46.3, 61.5
Rofecoxib 50 mg	Moderate	124	24	19.4	12.8, 27.4	53	42.7	33.9, 51.9	66	53.2	44.1, 62.2	79	63.7	54.6, 72.2
	Severe	63	1	1.6	0.0, 8.5	14	22.2	12.7, 34.5	22	34.9	23.3, 48.0	27	42.9	30.5, 56.0
	Total	187	25	13.4	8.8, 19.1	67	35.8	29.0, 43.2	88	47.1	39.7, 54.5	106	56.7	49.3, 63.9

N = Number of patients with non-missing (or carried-forward) migraine headache severity evaluation at 2 hours.
n (%) = Number (percent) of migraine patients with headache relief at indicated time points.
CI = Confidence interval.

Data Source: [4.3]

The sponsor reported that rofecoxib 50 mg was significantly superior to placebo in providing headache relief from 0.5 hour onwards ($p= 0.026$ at 0.5 hour, $p< 0.001$ at 1, 1.5, and 2 hours). For rofecoxib 25 mg, this superiority was significant from 1 hour onwards ($p< 0.001$ at 1 and 2 hours, $p= 0.002$ at 1.5 hours).

Rofecoxib 50 mg was numerically better than rofecoxib 25 mg over all time points, but this superiority did not reach statistical significance.

Pain Freedom at 0.5, 1, 1.5, and 2 Hours Postdose

Table 7 presents the percentages of migraine patients reporting pain freedom (moderate or severe migraine headache at baseline improving to no pain) at time points within 2 hours of dosing.

Table 7. Number (%) of Patients Reporting Pain Freedom at Time Points Within 2 Hours Postdose by Treatment Group and Baseline Severity (copied from sponsor's Table 25 of Protocol 161)

Treatment	Baseline Severity	N	0.5 hr			1.0 hr			1.5 hr			2.0 hr		
			n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Placebo	Moderate	103	1	1.0	0.0, 5.3	3	2.9	0.6, 8.3	4	3.9	1.1, 9.6	5	4.9	1.6, 11.0
	Severe	72	0	0.0	---	1	1.4	0.0, 7.5	3	4.2	0.9, 11.7	9	12.5	5.9, 22.4
	Total	175	1	0.6	0.0, 3.1	4	2.3	0.6, 5.7	7	4.0	1.6, 8.1	14	8.0	4.4, 13.1
Rofecoxib 25 mg	Moderate	127	1	0.8	0.0, 4.3	7	5.5	2.2, 11.0	14	11.0	6.2, 17.8	25	19.7	13.2, 27.7
	Severe	49	0	0.0	---	1	2.0	0.1, 10.9	2	4.1	0.5, 14.0	10	20.4	10.2, 34.3
	Total	176	1	0.6	0.0, 3.1	8	4.5	2.0, 8.8	16	9.1	5.3, 14.3	35	19.9	14.3, 26.6
Rofecoxib 50 mg	Moderate	124	1	0.8	0.0, 4.4	5	4.0	1.3, 9.2	22	17.7	11.5, 25.6	35	28.2	20.5, 37.0
	Severe	63	0	0.0	---	0	0.0	---	2	3.2	0.4, 11.0	8	12.7	5.6, 23.5
	Total	187	1	0.5	0.0, 2.9	5	2.7	0.9, 6.1	24	12.8	8.4, 18.5	43	23.0	17.2, 29.7

N = Number of patients with non-missing (or carried-forward) headache severity evaluation at 2 hours.
n (%) = Number (percent) of patients with pain freedom at indicated time points.
CI = Confidence interval.

Data Source: [4.3]

At 2 hours post dose, the percentages of patients reporting pain freedom were 8.0, 19.9, and 23.0% in the placebo, rofecoxib 25 mg, and rofecoxib 50 mg treatment groups, respectively.

The sponsor reported that a higher percentage of patients reported pain freedom 2 hours post dose in the rofecoxib 50 mg group than in the placebo group ($p< 0.001$). Also, a higher percentage of patients reported pain freedom at 2 hours in the rofecoxib 25 mg group than in the placebo group ($p= 0.002$).

Number of Associated Migraine Symptoms at 2 Hours Postdose

Table 8 presents the percentages of patients reporting 0, 1, 2 or 3 associated migraine symptoms (photophobia, phonophobia, nausea) at 2 hours postdose. The percentages of patients with no symptoms of photophobia, phonophobia, or nausea at 2 hours postdose were 18.9, 31.3, and 35.7% in the placebo, rofecoxib 25-mg, and rofecoxib 50-mg treatment groups, respectively.

Table 8. Number (%) of Patients Reporting 0, 1, 2, or 3 Associated Migraine Symptoms (Photophobia, Phonophobia, Nausea) (copied from sponsor's Table 33 of Protocol 161)

		Placebo				Rofecoxib 25 mg				Rofecoxib 50 mg			
Hour	Category	N	n	%	Cum %	N	n	%	Cum %	N	n	%	Cum %
Baseline	No symptom	173	6	3.5	3.5	176	1	0.6	0.6	184	12	6.5	6.5
	1 Symptom		20	11.6	15.0		23	13.1	13.6		27	14.7	21.2
	2 Symptoms		76	43.9	59.0		78	44.3	58.0		70	38.0	59.2
	3 Symptoms		71	41.0	100.0		74	42.0	100.0		75	40.8	100.0
2.0 hr	No symptom	175	33	18.9	18.9	176	55	31.3	31.3	185	66	35.7	35.7
	1 Symptom		27	15.4	34.3		25	14.2	45.5		33	17.8	53.5
	2 Symptoms		62	35.4	69.7		55	31.3	76.7		46	24.9	78.4
	3 Symptoms		53	30.3	100.0		41	23.3	100.0		40	21.6	100.0

N = Number of patients with non-missing (or carried-forward) associated migraine symptoms (photophobia, phonophobia, nausea) information at specified time point.
n (%) = Number (percent) of patients with specified number of associated migraine symptoms (photophobia, phonophobia, nausea) at indicated time points.
Cum % = Cumulative percentage of patients.

Data Source: [4.3]

Summary of Primary and Secondary Efficacy Endpoints

The following table presents the summary of analysis results from primary and secondary efficacy parameters provided by the sponsor. In addition to the results reported above, the table also included results of pain relief and pain freedom at 3 and 4 hours post dose as well as sustained pain relief and sustained pain freedom at 24-hour post dose. These results should be interpreted cautiously since rescue medication was allowed after 2 hours of the administration of the study medication.

Table 9. Summary of Analysis Results of Primary and Secondary Efficacy Parameters (copied from sponsor's Table 77 of Protocol 161)

Endpoint[†]	Placebo (%)	Rofecoxib 25 mg (%)	Rofecoxib 50 mg (%)
Primary Efficacy Endpoint			
Headache Relief at 2 Hours	34.3	54.0***	56.7***
Other Efficacy Endpoints			
Pain Freedom at 2 Hours	8.0	19.9**	23.0***
24-Hour Sustained Headache Relief	17.1	33.5***	37.4***
24-Hour Sustained Headache Pain Freedom	6.3	13.1*	17.6***
Number of Associated Migraine Symptoms (Photophobia, Phonophobia, Nausea) at 2 Hours[‡]			
No symptom	18.9	31.3*	35.7***
1 Symptom	15.4	14.2	17.8
2 Symptoms	35.4	31.3	24.9
3 Symptoms	30.3	23.3	21.6
Associated Migraine Symptoms at 2 Hours			
Photophobia	71.4	61.4*	57.5**
Phonophobia	64.0	52.3*	45.2***
Nausea	41.7	33.0	30.3*
Vomiting	5.7	2.3	1.6
Functional Disability at 2 Hours[‡]			
Normal	12.6	33.5***	29.9***
Mildly Impaired	42.3	42.6	45.5
Severely Impaired	25.7	10.8	10.2
Required Bed Rest	19.4	13.1	14.4
Additional Medication Between 2 to 24 Hours[§]	69.1	56.8*	55.6**

*p≤0.050, **p≤0.010, ***p≤0.001 for the active-placebo pairwise comparison.
[†] Except when otherwise specified, the statistical test compared the proportions between treatment groups.
[‡] The statistical test compared the distribution of proportions between treatment groups.
[§] The statistical test compared the times to intake of additional medication between treatment groups.

Data Source: [4.1; 4.3]

3.1.9 Reviewer's Analysis

I have conducted independent analysis for the primary and secondary efficacy endpoints following the protocol specified statistical methods. The results I have obtained agree with those from the sponsor's analyses except for a few minor differences, which do not affect the significance of the treatment differences or conclusions.

At the 2 hour post dose, the number and percentage of patients who had headache relief were 108 (57.75%), 95 (53.98%), and 58 (33.14%) for treatment groups of rofecoxib 50 mg, rofecoxib 25 mg, and placebo, respectively. The treatment difference between rofecoxib 50 mg and placebo

carries a p-value of .0001, and the difference between rofecoxib 25 mg and placebo has a p-value of .0002. The difference between the two active treatment groups was not significant (p=.5228).

The primary efficacy analysis used logistic regression model with terms of treatment, region, and baseline headache severity. The large diviance value from the model indicated a poor fit of the model. Therefore, Cochran-Mantel-Haenszel (CMH) test was also applied to examine the robustness of the results. The CMH test confirmed that the treatment difference between each of the rofecoxib groups and placebo group was statistically significant with p-values of less than .001.

Effect of Covariates

The effect of baseline severity was found significant in the primary efficacy analysis. Patients with severe headache at the baseline were less likely to get pain relief with the study drug.

The percentage of patients who had pain relief at 2-hour post dose were quite different among the regions (see sponsor's Table 5). The effect of region had a p-value of .058. The relief rate in Region II and IV were much higher than in the other 2 regions for the placebo group. However, it was consistent that in all regions, the relief rates for the active treatment groups were higher than in the placebo group within each region.

Associated Symptoms

The analyses of effect of rofecoxib in associated migraine symptoms were performed separately for each symptom. The following table presents the results.

Table 10. The Number and Percentage of Patients Who Had Symptoms at 2-Hour Post Dose

Symptom	Placebo (N=175)		Rofecoxib 50 mg (N=186)			Rofecoxib 25 mg (N=176)		
	Number	%	Number	%	p-value	Number	%	p-value
Photophobia	124	70.9%	106	57.0%	.0050	109	61.9%	.0542
Phonophobia	113	64.6%	83	44.6%	.0002	92	52.3%	.0256
Nausea	73	41.7%	56	30.3%	.0300	58	33.0%	.1115

The percentages of patients who had symptom of photophobia at 2 hour post dosing were 70.9%, 57.0%, and 61.9% for the treatment of placebo, rofecoxib 50 mg, and rofecoxib 25 mg, respectively. The p-values from the comparisons were .0050 for rofecoxib 50 mg versus placebo and .0542 for rofecoxib 25 mg versus placebo.

The percentages of patients who had symptom of phonophobia at 2 hour post dosing were 64.6%, 44.6%, and 52.3% for the treatment of placebo, rofecoxib 50 mg, and rofecoxib 25 mg, respectively. The comparisons between rofecoxib 50 mg versus placebo and rofecoxib 25 mg versus placebo were both statistically significant with p-values of .0002 and .0256, respectively.

The percentages of patients who had nausea at 2 hour post dosing were 41.7%, 30.3%, and 33.0% for the treatment of rofecoxib 50 mg, rofecoxib 25 mg, and placebo, respectively. The difference between rofecoxib 50 mg and placebo was significant with a p-value of .030. The difference between rofecoxib 25 mg and placebo was not statistically significant (p=.1115).

Since rofecoxib 25 mg was not significantly superior to placebo in symptom of nausea and was marginally insignificant in symptom of photophobia, the analysis was replicated for these two parameters at 1 hour and 1.5 hour post dosing. It was found that for nausea, the p-values between rofecoxib 25 mg and placebo were .0747 at 1-hour post dosing and .1091 at 1.5-hour post dosing. For photophobia, the comparison between rofecoxib 25 mg and placebo reached significance level with a p-value of .0232 at 1.5-hour post dosing.

The analysis of effect of rofecoxib with regard to vomiting was not presented because the incidents of vomiting were too low to warrant a meaningful result.

Secondary Efficacy Endpoints

There are many secondary efficacy endpoints. Since multiplicity adjustment was not pre-specified, all p-values reported by the sponsor are considered nominal p-values.

Most secondary endpoints were related to headache relief or headache freedom at multiple time points. Headache relief or headache freedom after 2 hours of dosing are considered less important since rescue medication was allowed, and their results are not presented.

The data showed that at 1 hour and 1.5 hour post dose, respectively, 35.83% and 47.59% of the patients treated with rofecoxib 50 mg and 33.52% and 42.61% of the patients treated with rofecoxib 25 mg had headache relief, compared to 14.86% and 25.71% of patients treated with placebo (p=.0001 for rofecoxib 50 mg vs. placebo at 1 hour and 1.5 hour post dose; p=.0002 and p=.0017 for rofecoxib 25 mg vs. placebo at 1 hour and 1.5 hour post dose, respectively). One hour post dose appeared to be the time from which the difference in the relief rates between rofecoxib 50 mg and 25 mg groups and placebo group became apart and stayed apart (Figure 1 and Table 6).

At 2 hour post dose, more patients treated with rofecoxib 50 mg (23.53%) and 25 mg (19.32%) had pain freedom than patients treated with placebo (7.43%) (p=.0001 for rofecoxib 50 mg vs placebo and p=.0017 for rofecoxib 25 mg vs. placebo). The difference between rofecoxib 50 mg and 25 mg was not significant (p=.3314).

Reviewer's Efficacy Conclusion

In conclusion, rofecoxib 50 mg and 25 mg are effective in the acute treatment of migraine as measured by pain relief at 1 hour and 2 hour post dosing, pain freedom at 2 hour post dosing, and incidents of migraine associated symptoms of photophobia and phonophobia. Rofecoxib 50 mg is also effective in reliving the symptom of nausea while such effect for rofecoxib 25 mg could not be concluded for this study.

Although the two rofecoxib doses were not significantly different in any of the primary or secondary efficacy parameters, the data suggested that rofecoxib 50 mg has added effectiveness compared to rofecoxib 25 mg.

3.1.10 Results from Protocol 162 (from Sponsor's Analysis)

3.1.10.1 Accounting for Patients in the Study

Table 11 presents the number of patients who were randomized, treated, and not treated, and the reasons for discontinuation from the study.

Table 11. Patient Accounting (copied from sponsor's Table 7 of Protocol 162)

	Placebo (N=238)		Rofecoxib 25 mg (N=237)		Rofecoxib 50 mg (N=239)		Ibuprofen 400 mg (N=243)		Total (N=957)	
	n	(%)†	n	(%)†	n	(%)†	n	(%)†	n	(%)†
Patients randomized	238		237		239		243		957	
Patients treated	194		194		196		199		783	
Patients not treated	44		43		43		44		174	
Patients 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)
Clinical adverse experience	0		0		0		1	(0.5)	1	(0.1)
Lost to follow-up	6	(3.1)	6	(3.1)	7	(3.6)	9	(4.5)	28	(3.6)
Patient withdrew consent	1	(0.5)	0		1	(0.5)	0		2	(0.3)
Other	0		1	(0.5)	0		0		1	(0.1)
Patients not treated	44		43		43		44		174	
Clinical adverse experience	0		0		1	(2.3)	0		1	(0.6)
Patient did not have migraine headache‡	10	(22.7)	17	(39.5)	19	(44.2)	14	(31.8)	60	(34.5)
Patient had migraine headache but did not treat§	25	(56.8)	23	(53.5)	16	(37.2)	22	(50.0)	86	(49.4)
Patient discontinued for other reason	4	(9.1)	2	(4.7)	1	(2.3)	4	(9.1)	11	(6.3)
Patient withdrew consent	4	(9.1)	1	(2.3)	6	(14.0)	4	(9.1)	15	(8.6)
Protocol deviation	1	(2.3)	0		0		0		1	(0.6)

† For treated patients, the percentage is calculated from all treated patients; for non-treated patients, the percentage is calculated from all non-treated patients.
‡ These patients were not treated with study drug because they did not have a moderate/severe migraine headache within the 3 months of randomization and were thus discontinued from the study.
§ These patients had at least one moderate/severe migraine headache, but were not treated with study drug within 3 months of randomization and thus discontinued from the study.

Data Source: [4.1; 4.2; 4.7; 4.8]

Of the 967 patients who were screened, 957 were randomized to the 4 treatment groups. Seven hundred eighty three (783) patients took study medication. Of those, 751 patients completed the study and were included in the APT population: 187 in the placebo group, 187 in the rofecoxib 25 mg group, 188 in the rofecoxib 50 mg group, and 189 in the ibuprofen 400 mg group.

Table 12 presents the baseline patient characteristics by treatment group.

Table 12. Demographic and Baseline Characteristics (copied from sponsor's Table 12 of Protocol 162)

	Placebo (N=194)		Rofecoxib 25 mg (N=194)		Rofecoxib 50 mg (N=196)		Ibuprofen 400 mg (N=199)		Total (N=783)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gender										
Female	169	(87.1)	164	(84.5)	169	(86.2)	173	(86.9)	675	(86.2)
Male	25	(12.9)	30	(15.5)	27	(13.8)	26	(13.1)	108	(13.8)
Age (years)										
<18	0		0		0		0		0	
18 to 29	39	(20.1)	49	(25.3)	50	(25.5)	40	(20.1)	178	(22.7)
30 to 39	56	(28.9)	56	(28.9)	61	(31.1)	49	(24.6)	222	(28.4)
40 to 49	57	(29.4)	52	(26.8)	44	(22.4)	64	(32.2)	217	(27.7)
50 to 59	30	(15.5)	31	(16.0)	30	(15.3)	30	(15.1)	121	(15.5)
60 to 64	9	(4.6)	3	(1.5)	8	(4.1)	9	(4.5)	29	(3.7)
≥65	3	(1.5)	3	(1.5)	3	(1.5)	7	(3.5)	16	(2.0)
Mean	40.4		38.7		38.7		41.3		39.8	
SD	11.5		11.6		11.8		12.0		11.7	
Median	40.0		38.0		38.0		41.0		39.0	
Range	21 to 71		18 to 74		18 to 71		19 to 78		18 to 78	
Racial Origin										
White	151	(77.8)	158	(81.4)	157	(80.1)	160	(80.4)	626	(79.9)
Black	6	(3.1)	3	(1.5)	1	(0.5)	6	(3.0)	16	(2.0)
Asian	9	(4.6)	11	(5.7)	12	(6.1)	13	(6.5)	45	(5.7)
Multiracial	14	(7.2)	10	(5.2)	10	(5.1)	10	(5.0)	44	(5.6)
Other	14	(7.2)	12	(6.2)	16	(8.2)	10	(5.0)	52	(6.6)
Baseline Severity										
Moderate	113	(58.2)	110	(56.7)	114	(58.2)	114	(57.3)	451	(57.6)
Severe	74	(38.1)	77	(39.7)	73	(37.2)	75	(37.7)	299	(38.2)
Missing	7	(3.6)	7	(3.6)	9	(4.6)	10	(5.0)	33	(4.2)
Presence of Aura										
Without	169	(87.1)	167	(86.1)	158	(80.6)	164	(82.4)	658	(84.0)
With	19	(9.8)	21	(10.8)	29	(14.8)	26	(13.1)	95	(12.1)
Missing	6	(3.1)	6	(3.1)	9	(4.6)	9	(4.5)	30	(3.8)
Prophylactic Migraine Treatment										
Without	150	(77.3)	144	(74.2)	154	(78.6)	152	(76.4)	600	(76.6)
With	44	(22.7)	50	(25.8)	42	(21.4)	47	(23.6)	183	(23.4)
Beta-blockers	17	(8.8)	25	(12.9)	17	(8.7)	23	(11.6)	82	(10.5)
Calcium channel blockers	5	(2.6)	1	(0.5)	4	(2.0)	4	(2.0)	14	(1.8)
Selective serotonin reuptake inhibitors	7	(3.6)	15	(7.7)	11	(5.6)	11	(5.5)	44	(5.6)
Tricyclic antidepressant	12	(6.2)	11	(5.7)	12	(6.1)	15	(7.5)	50	(6.4)
Valproate	10	(5.2)	7	(3.6)	7	(3.6)	6	(3.0)	30	(3.8)
% Migraine Response to NSAIDs										
No NSAIDs use	34	(17.5)	31	(16.0)	26	(13.3)	32	(16.1)	123	(15.7)
<50%	79	(40.7)	71	(36.6)	82	(41.8)	79	(39.7)	311	(39.7)
≥50%	72	(37.1)	84	(43.3)	81	(41.3)	85	(42.7)	322	(41.1)
Unknown	9	(4.6)	8	(4.1)	7	(3.6)	3	(1.5)	27	(3.4)

Table 12 continued

	Placebo (N=194)		Rofecoxib 25 mg (N=194)		Rofecoxib 50 mg (N=196)		Ibuprofen 400 mg (N=199)		Total (N=783)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Oral Contraceptive in Women										
N†	169		164		169		173		675	
Without	131	(77.5)	127	(77.4)	131	(77.5)	145	(83.8)	534	(79.1)
With	38	(22.5)	37	(22.6)	38	(22.5)	28	(16.2)	141	(20.9)
SD = Standard deviation. N† = Number of female patients.										

Data Source: [4.1; 4.3]

The sponsor reported that the treatment groups were similar with regard to age and race. The patients' ages ranged from 18 to 78 years with a mean age of 39.8 years. Among the 783 patients, the majority were White (n= 626, 79.9%); 45 patients (5.7%) were Asian; 44 patients (5.6%) were Multiracial; 16 patients (2.0%) were Black; and 52 patients (6.6%) were Other (51 patients were Hispanic American and 1 patient was Native American). There were 675 female patients (86.2%) and 108 male patients (13.8%).

3.1 10.2 Efficacy Evaluation and Results

3.1.10.2.1 Analysis of Primary Efficacy Parameter

The primary endpoint was headache relief at 2 hours post dose with headache relief defined as a reduction of migraine headache severity from Grades 2 or 3 at baseline to Grade 1 or 0.

Table 13 displays the summary statistics for the number and percent of patients with a migraine attack reporting headache relief at 2 hours postdose by treatment group.

Table 13. Number (%) of Patients Reporting Headache Relief at 2 Hours Postdose (copied from sponsor's Table 18 of Protocol 162)

Treatment	N	n	%	95% Confidence Interval
Placebo	187	57	30.5	24.0 , 37.6
Rofecoxib 25 mg	187	111	59.4	51.9 , 66.5
Rofecoxib 50 mg	188	117	62.2	54.9 , 69.2
Ibuprofen 400 mg	189	109	57.7	50.3 , 64.8
N = Number of patients with non-missing (or carried-forward) migraine headache severity at 2 hours. n (%) = Number (percent) of patients with headache relief at 2 hours postdose. The corresponding p-values and confidence intervals for the various comparisons are presented in Table 19.				

Data Source: [4.3]

The percentages of patients reporting headache relief at 2 hours post dose were 30.5%, 59.4%, 62.2%, and 57.7% in the placebo, rofecoxib 25 mg, rofecoxib 50 mg, and ibuprofen 400 mg treatment groups, respectively. The sponsor reported that rofecoxib 50 mg and 25 mg were significantly superior to placebo ($p< 0.001$) in providing headache relief at 2 hours post dose: the odds ratio and 95% confidence interval were 4.02 (2.58,6.26) for Rofecoxib 50 mg versus placebo and 3.67 (2.36,5.70) for Rofecoxib 25 mg versus placebo. The difference in headache relief between the two active treatment groups was not statistically significant ($p=.675$). There was no significant treatment-by-baseline severity interaction ($p= 0.875$) or treatment-by-region interaction ($p= 0.674$).

Effect of Covariates on the Primary Endpoint

In order to explore the consistency of the treatment effects across the levels of several predefined covariates, treatment-by-covariate interactions were evaluated for the primary efficacy endpoint. Table 14 presents the number and percent of patients with a migraine attack experiencing headache relief at 2 hours post dose by covariate, as well as the corresponding p-values for the treatment-by-covariate interactions.

The overall treatment-by-gender interaction was significant ($p= 0.031$). It was mainly caused by high response rate in placebo group and low response rate in rofecoxib groups in men. The results should be interpreted with caution given the small number of patients in the male sub-population (25, 29, 24, and 24 patients in the placebo, rofecoxib 25 mg, rofecoxib 50 mg, and ibuprofen 400 mg treatment groups, respectively).

No other significant treatment-by-covariate interactions were found.

Table 14. Number (%) of Patients with Headache Relief at 2 Hours Postdose - Subgroup Analysis (copied from sponsor's Table 20 of Protocol 162)

	Placebo (N=187)			Rofecoxib 25 mg (N=187)			Rofecoxib 50 mg (N=187)			Ibuprofen 400 mg (N=189)		
Subgroup (p-Value)[1]	N	n	%	N	n	%	N	n	%	N	n	%
Gender (p=0.031)												
Male	25	11	44.0	29	13	44.8	24	13	54.2	24	9	37.5
Female	162	46	28.4	158	98	62.0	164	104	63.4	165	100	60.6
Age group (p=0.704)												
<40 years	91	29	31.9	101	68	67.3	103	67	65.0	84	56	66.7
≥40 years	96	28	29.2	86	43	50.0	85	50	58.8	105	53	50.5
Race (p=0.627)												
White	145	39	26.9	152	83	54.6	150	90	60.0	153	82	53.6
Others	42	18	42.9	35	28	80.0	38	27	71.1	36	27	75.0
Aura (p=0.168)												
Presence	19	7	36.8	21	13	61.9	29	13	44.8	26	14	53.8
Absence	168	50	29.8	166	98	59.0	158	104	65.8	163	95	58.3
Concomitant Migraine Prophylactic Treatment (p=0.513)												
With	43	15	34.9	49	25	51.0	41	25	61.0	46	25	54.3
Without	144	42	29.2	138	86	62.3	147	92	62.6	143	84	58.7

Table 14 continued

Subgroup (p-Value)[1]	Placebo (N=187)			Rofecoxib 25 mg (N=187)			Rofecoxib 50 mg (N=187)			Ibuprofen 400 mg (N=189)		
	N	n	%	N	n	%	N	n	%	N	n	%
Prior Response to NSAIDS (p=0.143)												
<50%	108	28	25.9	98	47	48.0	102	61	59.8	103	48	46.6
≥50%	70	26	37.1	81	59	72.8	79	51	64.6	83	58	69.9
Use of Oral Contraceptives[2] (p=0.186)												
Yes	38	7	18.4	36	25	69.4	37	20	54.1	28	18	64.3
No	124	39	31.5	122	73	59.8	127	84	66.1	137	82	59.9
Menstrually Associated Migraine Attack[4] (p=0.270)												
Yes	47	14	29.8	33	19	57.6	43	27	62.8	36	25	69.4
No	63	20	31.7	74	53	71.6	78	47	60.3	80	49	61.3
Dysmenorrhea[4] (p=0.257)												
Presence	3	0	0.0	3	2	66.7	3	2	66.7	2	2	100.0
Absence	30	10	33.3	23	14	60.9	24	16	66.7	24	15	62.5
Geographic Region (p=0.674)												
Region I	39	17	43.6	37	29	78.4	40	30	75.0	38	28	73.7
Region II	76	17	22.4	80	43	53.8	78	38	48.7	82	40	48.8
Region III	38	13	34.2	37	20	54.1	37	29	78.4	39	22	56.4
Region IV	34	10	29.4	33	19	57.6	33	20	60.6	30	19	63.3

Table 14 continued

Subgroup (p-Value)[1]	Placebo (N=187)			Rofecoxib 25 mg (N=187)			Rofecoxib 50 mg (N=187)			Ibuprofen 400 mg (N=189)		
	N	n	%	N	n	%	N	n	%	N	n	%
Baseline Severity (p=0.875)												
Moderate	113	41	36.3	110	72	65.5	114	78	68.4	114	69	60.5
Severe	74	16	21.6	77	39	50.6	73	38	52.1	75	40	53.3

[1] p-Value for subgroup-by-treatment interaction.
[2] For women only.
[3] For women with recent menses info only.
[4] For women with menstrually associated migraine attacks only.
N = Number of patients with nonmissing (or carried-forward) headache severity at 2 hours.
n (%) = Number (percent) of patients with headache relief at 2 hours.

Data Source: [4.1; 4.3]

3.1.10.2.2 Analyses of Secondary Efficacy Parameters

Headache Relief at 0.5, 1, 1.5, and 2 Hours Postdose

The percentages of patients with headache at time points within 2 hours are presented graphically in Figure 2 and are tabulated by baseline headache severity in Table 15.

The sponsor reported that both rofecoxib 50 mg and rofecoxib 25 mg were significantly superior to placebo in providing headache relief from 0.5 hour onwards ($p= 0.004$ at 0.5 hour and $p= 0.046$ at 0.5 hour, for rofecoxib 50 mg and 25 mg, respectively, and $p < 0.001$ at 1, 1.5, and 2 hours).

Figure 2. Percentage of Patients Reporting Headache Relief Within 2 Hours of Dosing (copied from sponsor's Figure 3 of Protocol 162)

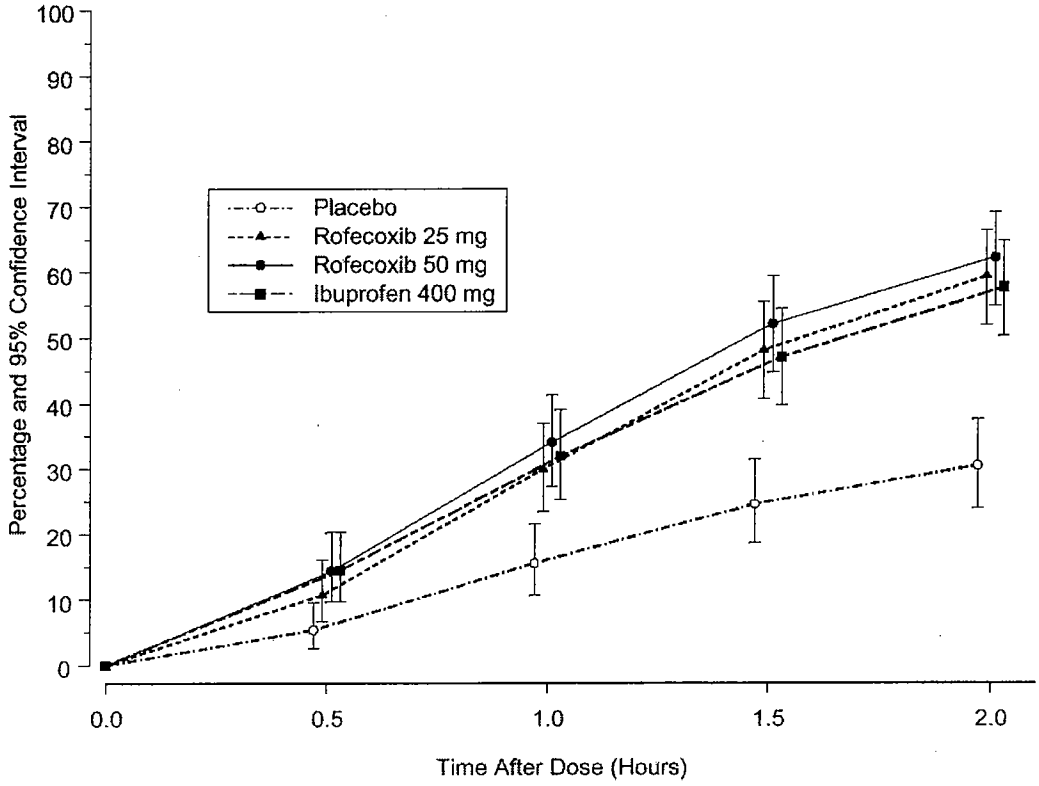

Table 15. Number (%) of Patients Reporting Headache Relief at Time Points Within 2 Hours Postdose by Treatment Group and Baseline Severity (copied from sponsor's Table 21 of Protocol 162)

Treatment	Baseline Severity	N	0.5 hr			1.0 hr			1.5 hr			2.0 hr		
			n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Placebo	Moderate	113	8	7.1	3.1 , 13.5	22	19.5	12.6 , 28.0	35	31.0	22.6 , 40.4	41	36.3	27.4 , 45.9
	Severe	74	2	2.7	0.3 , 9.4	7	9.5	3.9 , 18.5	11	14.9	7.7 , 25.0	16	21.6	12.9 , 32.7
	Total	187	10	5.3	2.6 , 9.6	29	15.5	10.6 , 21.5	46	24.6	18.6 , 31.4	57	30.5	24.0 , 37.6
Rofecoxib 25 mg	Moderate	110	17	15.5	9.3 , 23.6	43	39.1	29.9 , 48.9	62	56.4	46.6 , 65.8	72	65.5	55.8 , 74.3
	Severe	77	3	3.9	0.8 , 11.0	13	16.9	9.3 , 27.1	28	36.4	25.7 , 48.1	39	50.6	39.0 , 62.2
	Total	187	20	10.7	6.7 , 16.0	56	29.9	23.5 , 37.1	90	48.1	40.8 , 55.5	111	59.4	51.9 , 66.5
Rofecoxib 50 mg	Moderate	114	22	19.3	12.5 , 27.7	51	44.7	35.4 , 54.3	67	58.8	49.2 , 67.9	78	68.4	59.1 , 76.8
	Severe	73	5	6.8	2.3 , 15.3	13	17.8	9.8 , 28.5	30	41.1	29.7 , 53.2	38	52.1	40.0 , 63.9
	Total	188	27	14.4	9.7 , 20.2	64	34.0	27.3 , 41.3	98	52.1	44.7 , 59.5	117	62.2	54.9 , 69.2
Ibuprofen 400 mg	Moderate	114	23	20.4	13.4 , 29.0	46	40.4	31.3 , 49.9	58	50.9	41.3 , 60.4	69	60.5	50.9 , 69.6
	Severe	75	4	5.4	1.5 , 13.3	14	18.9	10.7 , 29.7	31	41.3	30.1 , 53.3	40	53.3	41.4 , 64.9
	Total	189	27	14.4	9.7 , 20.3	60	31.9	25.3 , 39.1	89	47.1	39.8 , 54.5	109	57.7	50.3 , 64.8

N = Number of patients with non-missing (or carried-forward) headache severity evaluation at 2 hours.
n (%) = Number (percent) of patients with headache relief at indicated time points.
CI = Confidence interval.
'Total' also includes those patients with missing baseline severity.

Data Source: [4.3]

Pain Freedom at 0.5, 1, 1.5, and 2 Hours Postdose

The percentages of patients reporting pain freedom (moderate or severe headache at baseline improving to no pain) at time points within 2 hours of dosing are presented in Table 16.

At 2 hours post dose, the percentage of patients reporting pain freedom were 5.3%, 26.2%, 26.6%, and 23.8% in the placebo, rofecoxib 25 mg, rofecoxib 50 mg, and ibuprofen 400 mg treatment groups, respectively. The sponsor reported that rofecoxib 50 mg and rofecoxib 25 mg were significantly superior to placebo in providing pain freedom from 1.0 hour post dose onwards (p= 0.034 and 0.003 at 1 and 1.5 hours in rofecoxib 50 mg; and p= 0.015 and 0.003 at 1 and 1.5 hours in rofecoxib 25 mg; and p< 0.001 at 2 hours in both groups).

Table 16. Number (%) of Patients Reporting Pain Freedom at Time Points Within 2 Hours Postdose (copied from sponsor's Table 25 of Protocol 162)

Treatment	Baseline Severity	N	0.5 hr			1.0 hr			1.5 hr			2.0 hr		
			n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Placebo	Moderate	113	0	0.0	---	2	1.8	0.2, 6.2	8	7.1	3.1, 13.5	9	8.0	3.7, 14.6
	Severe	74	0	0.0	---	0	0.0	---	0	0.0	---	1	1.4	0.0, 7.3
	Total	187	0	0.0	---	2	1.1	0.1, 3.8	8	4.3	1.9, 8.3	10	5.3	2.6, 9.6
Rofecoxib 25 mg	Moderate	110	0	0.0	---	7	6.4	2.6, 12.7	16	14.5	8.5, 22.5	31	28.2	20.0, 37.6
	Severe	77	0	0.0	---	5	6.5	2.1, 14.5	9	11.7	5.5, 21.0	18	23.4	14.5, 34.4
	Total	187	0	0.0	---	12	6.4	3.4, 10.9	25	13.4	8.8, 19.1	49	26.2	20.1, 33.1
Rofecoxib 50 mg	Moderate	114	1	0.9	0.0, 4.8	8	7.0	3.1, 13.4	18	15.8	9.6, 23.8	35	30.7	22.4, 40.0
	Severe	73	1	1.4	0.0, 7.4	2	2.7	0.3, 9.5	7	9.6	3.9, 18.8	15	20.5	12.0, 31.6
	Total	188	2	1.1	0.1, 3.8	10	5.3	2.6, 9.6	25	13.3	8.8, 19.0	50	26.6	20.4, 33.5
Ibuprofen 400 mg	Moderate	114	1	0.9	0.0, 4.8	9	7.9	3.7, 14.5	19	16.7	10.3, 24.8	28	24.6	17.0, 33.5
	Severe	75	0	0.0	---	2	2.7	0.3, 9.4	10	13.3	6.6, 23.2	17	22.7	13.8, 33.8
	Total	189	1	0.5	0.0, 2.9	11	5.9	3.0, 10.2	29	15.3	10.5, 21.3	45	23.8	17.9, 30.5

N = Number of patients with non-missing (or carried-forward) headache severity evaluation at 2 hours.
n (%) = Number (percent) of patients with pain freedom at indicated time points.
CI = Confidence interval.
'Total' also includes those patients with missing baseline headache severity.

Data Source: [4.3]

Number of Associated Migraine Symptoms at 2 Hours Postdose

Table 17 presents the percentages of patients reporting 0, 1, 2, or 3 associated migraine symptoms (photophobia, phonophobia, nausea) at 2 hours post-dose. The percentages of patients with no symptoms of photophobia, phonophobia, or nausea at 2 hours postdose were 23.0%, 38.7%, 43.6%, and 39.6% in the placebo, rofecoxib 25 mg, rofecoxib 50 mg, and ibuprofen 400 mg treatment groups, respectively.

Table 17. Number (%) of Patients Reporting 0, 1, 2, or 3 Associated Migraine Symptoms (Photophobia, Phonophobia, Nausea) (copied from sponsor's Table 33)

Hour	Category	Placebo				Rofecoxib 25 mg				Rofecoxib 50 mg				Ibuprofen 400 mg			
		N	n	%	Cum %	N	n	%	Cum %	N	n	%	Cum %	N	n	%	Cum %
Baseline	No symptom	186	8	4.3	4.3	186	6	3.2	3.2	188	9	4.8	4.8	188	13	6.9	6.9
	1 symptom		23	12.4	16.7		37	19.9	23.1		28	14.9	19.7		20	10.6	17.6
	2 symptoms		86	46.2	62.9		73	39.2	62.4		59	31.4	51.1		77	41.0	58.5
	3 symptoms		69	37.1	100.0		70	37.6	100.0		92	48.9	100.0		78	41.5	100.0
2.0 hr	No symptom	187	43	23.0	23.0	186	72	38.7	38.7	188	82	43.6	43.6	187	74	39.6	39.6
	1 symptom		35	18.7	41.7		34	18.3	57.0		25	13.3	56.9		41	21.9	61.5
	2 symptoms		50	26.7	68.4		40	21.5	78.5		39	20.7	77.7		40	21.4	82.9
	3 symptoms		59	31.6	100.0		40	21.5	100.0		42	22.3	100.0		32	17.1	100.0

N = Number of patients with non-missing (or carried-forward) associated migraine symptoms (photophobia, phonophobia, nausea) information at specified time point.
n,% = Number, percent of patients with specified number of associated migraine symptoms (photophobia, phonophobia, nausea) at indicated time points.
Cum % = Cumulative percent of patients.

Data Source: [4.3]

The sponsor reported that rofecoxib 50 mg and rofecoxib 25 mg were significantly superior to placebo ($p< 0.001$ and $p= 0.001$, respectively) in reducing the number of associated migraine symptoms at 2 hours.

Summary of Primary and Secondary Efficacy Endpoints

The results from analyses of primary and secondary efficacy parameters was summarized by the sponsor and presented in Table 18. In addition to the results reported above, the table also included results of pain relief and pain freedom at 3 and 4 hours post dose as well as sustained pain relief and sustained pain freedom at 24-hour post dose. These results should be interpreted cautiously since rescue medication was allowed after 2 hours of the administration of the study medication.

Table 18. Summary of Analysis Results of Primary and Secondary Efficacy Parameters (copied from sponsor's Table 77 of Protocol 162)

Efficacy Endpoints[†]	Placebo (%)	Rofecoxib 25 mg (%)	Rofecoxib 50 mg (%)	Ibuprofen 400 mg (%)
Primary Efficacy Endpoint				
Headache relief at 2 hours	30.5	59.4***	62.2***	57.7***
Secondary Efficacy Endpoints				
Pain freedom at 2 hours	5.3	26.2***	26.6***	23.8***
24-hour sustained headache relief	13.4	39.0***	39.9***	31.2***
24-hour sustained headache pain freedom	2.7	20.3***	18.1***	18.0***
Number of Associated Migraine Symptoms (Photophobia, Phonophobia, Nausea) at 2 Hours [‡]				
No symptom	23.0	38.7***	43.6***	39.6***
1 symptom	18.7	18.3	13.3	21.9
2 symptoms	26.7	21.5	20.7	21.4
3 symptoms	31.6	21.5	22.3	17.1
Associated Migraine Symptoms at 2 Hours				
Photophobia	65.2	51.1**	49.5**	50.0**
Phonophobia	59.4	43.5**	42.6***	38.8***
Nausea	42.2	31.2*	29.8*	27.8**
Vomiting	7.5	2.7*[§]	5.9	1.6*
Functional Disability at 2 Hours [‡]				
Normal	17.1	36.0***	36.2***	39.9***
Mildly impaired	31.0	38.7	39.4	37.2
Severely impaired	26.2	13.4	10.6	13.3
Required bed rest	25.7	11.8	13.8	9.6
Additional medication between 2 to 24 hours[‖]	70.6	44.9***	47.9***	54.5***

* $p \leq 0.050$, ** $p \leq 0.010$, *** $p \leq 0.001$ for the active-placebo pairwise comparison.
† Except where otherwise specified, the statistical test compares the proportions between treatment groups.
‡ The statistical test compares the distribution of proportions between treatment groups.
§ Considered not significant because of stepdown test of doses of rofecoxib.
‖ The statistical test compares the times of intake of additional medication between treatment groups.

Data Source: [4.1; 4.3]

3.1.11 Reviewer's Analysis

I have conducted independent analysis for the primary and secondary efficacy endpoints following the protocol specified statistical methods. The results I have obtained agree with those from the sponsor's analyses except a few minor differences, which do not affect the significance of the treatment differences or conclusions.

At the 2 hour postdose, the number and percentage of patients who had headache relief were 117 (62.63%), 111 (59.36%), 57 (30.48%), and 110 (58.20%) for treatment groups of rofecoxib 50 mg, rofecoxib 25 mg, placebo, and Ibuprofen 400 mg, respectively. The treatment difference between rofecoxib 50 mg and placebo carried a p-value of .0001, and the difference between rofecoxib 25 mg and placebo had a p-value of .0001. The difference between the two active treatment groups was not significant (p=.6725).

The primary efficacy analysis used logistic regression model with terms of treatment, region, and baseline headache severity. Similar to the results from Protocol 161, the large diviance value from the model indicated a poor fit of the model. Therefore, Cochran-Mantel-Haenszel (CMH) test was also applied to examine the robustness of the results under different model assumptions. The CMH test confirmed that the treatment difference between each of the rofecoxib groups and placebo group was statistically significant with p-values of less than .001.

Effect of Covariates

The effect of baseline severity was found significant in the primary efficacy analysis. Patients with severe headache at the baseline were less likely to get pain relief within 2 hours after the administration of the study drug (Table 14).

The percentages of patients who had pain relief at 2-hour post dose were quite different among the regions. However, it was consistent that in all regions, the relief rates were higher in the active treatment groups than in the placebo group within each region (Table 14).

Associated Symptoms

The analyses of effect of rofecoxib in associated symptoms were performed separately for each symptom. The following table presents the details of the results.

Table 19. The Number and Percentage of Patients Who Had Symptoms at 2-Hour Post Dose

Symptom	Placebo (N=187)	Rofecoxib 50 mg (N=188)	Rofecoxib 25 mg (N=186)	Ibuprofen 400 mg (N=188)
Photophobia				
Number (%)	122 (65.2%)	93 (49.5%)	97 (52.2%)	95 (50.5%
p-value		.0024	.0082	.0037
Phonophobia				
Number (%)	112 (59.9%)	80 (42.6%)	82 (44.1%)	74 (39.4%)
p-value		.0009	.0017	.0001
Nausea				
Number (%)	78 (41.7%)	56 (29.8%)	59 (31.7%)	52 (27.8%)
p-value		.0175	.0396	.0046

The percentage of patients who had symptom of photophobia at 2 hour post dosing were 65.2%, 49.5%, and 52.2% for treatment groups of placebo, rofecoxib 50 mg and rofecoxib 25 mg. The treatment effect of rofecoxib 50 mg and 25 mg were both significant with p-values of .0024 and .0082, respectively.

The percentage of patients who had symptom of phonophobia at 2 hour post dosing were 59.9%, 42.6%, and 44.1% for treatment groups of placebo, rofecoxib 50 mg and rofecoxib 25 mg. The treatment effect of rofecoxib 50 mg and 25 mg were both significant with p-values of .0009 and .0017, respectively.

The percentage of patients who had symptom of nausea at 2 hour post dosing were 41.7%, 29.8%, and 31.7% for treatment groups of placebo, rofecoxib 50 mg and rofecoxib 25 mg. The treatment effect of rofecoxib 50 mg and 25 mg were both significant with p-values of .0175 and .0396, respectively.

The analysis of effect of rofecoxib with regard to vomiting is not presented because the incidents of vomiting are too low to warrant a meaningful result.

Secondary Efficacy Endpoints

There are many secondary efficacy endpoints. Since multiplicity adjustment was not specified, all the p-values reported by the sponsor are considered nominal p-values.

Most secondary endpoints are related to headache relief or headache freedom at multiple time points. Headache relief or headache freedom after 2 hours of dosing are considered less important and their results are not presented. This is because rescue medication was allowed after 2 hours of dosing.

The data showed that 34.0% and 30.0% of patients had headache relief at 1 hour postdose with rofecoxib 50 mg and 25 mg, respectively, compared to 15.5% relief rate for patients treated with placebo (Table 1). The comparisons between each of the rofecoxib treatment groups and placebo carried a p-value of less than .001. The data suggested that one hour appeared to be the time from

which the difference in the relief rates between the active treatment groups and placebo group became apart and stayed apart (sponsor's Figure 3).

The data also suggested that at 2 hour post dose, more patients treated with rofecoxib 50 mg or 25 mg had pain freedom than patients treated with placebo: 26.6% and 25.1% for rofecoxib 50 mg and 25 mg, respectively, compared to 5.4% for placebo ($p<.001$ for comparisons of rofecoxib 50 mg vs. placebo and rofecoxib 25 mg vs. placebo) (Table 1).

Reviewer's Efficacy Conclusion

In conclusion, rofecoxib 50 mg and 25 mg are effective in the treatment of acute migraine attack as measured by pain relief at 1 hour and 2 hour post dosing, pain freedom at 2 hour post dosing, and incidents of associated migraine symptoms of photophobia, phobnophobia, and nausea.

Although the two rofecoxib doses were not significantly different in any of the primary or secondary efficacy parameters, the data suggested that rofecoxib 50 mg has added effectiveness as compared to rofecoxib 25 mg.

3.2 Evaluation of Safety

Please refer to Clinical Review by medical officer Dr. Kevin Prohaska for evaluation of safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The following table presents the percentages of patients who had pain relief at 2-hour post-dose by gender, Race, and Age. P-values from the comparisons between each of the active treatment groups versus placebo group are also presented. Readers should be aware that those are nominal p-values without multiplicity adjustment and should be used with cautious, especially for treatment comparisons for Men and Non-White, where sample sizes are small. The age groups are divided in consistence with those from the sponsor.

In both Protocols 161 and 162, the majority of patients were women. Men comprised of 11.6% in Protocol 161 and 15.7% in Protocol 162. The differences between the treatment groups in the 2-hour post-dose pain relief were mainly contributed by women.

In both Protocols 161 and 162, the majority of patients were White. Patients with White race comprised of 90% and 80%, respectively, of the patient population in Protocols 161 and 162.

Treatment effect was found consistent in patients younger than 40 years old and those 40 years old and beyond.

Table 20. Percentage of Patients with Pain Relief at 2-Hour Post Dosing by Gender, Race, and Age

Variable	Placebo	Rofecoxib 50 mg		Rofecoxib 25 mg		Ibuprofen 400 mg	
Protocol	% (n/N)	% (n/N)	p-value	% (n/N)	p-value	% (n/N)	p-value
Gender							
Protocol 161							
Male	28.6 (6/21)	57.9 (11/19)	.1092	25.0 (4/16)	.8873	N/A	
Female	33.8 (52/154)	57.7 (97/168)	.0001	56.9 (91/160)	.0001		
Protocol 162							
Male	44.0 (11/25)	54.2 (13/24)	.5950	44.8 (13/29)	.9100	37.5 (9/24)	.5600
Female	28.4 (46/162)	63.4 (104/164)	.0001	62.0 (98/158)	.0001	61.2 (101/165)	.0001
Race							
Protocol 161							
White	33.1 (52/157)	57.7 (97/168)	.0001	54.7 (88/161)	.0002	N/A	
Non-White	33.3 (6/18)	57.9 (11/19)	.1411	46.7 (7/15)	.4297		
Protocol 162							
White	26.9 (39/145)	60.0 (90/150)	.0001	55.3 (84.152)	.0001	54.3 (83/153)	.0001
Non-White	42.9 (18/42)	71.1 (27/38)	.0292	77.1 (27/35)	.0058	75.0 (27/36)	.0069
Age							
Protocol 161							
< 40 (year)	34.3 (25/73)	66.7 (54/81)	.0001	62.3 (43/69)	.0011	N/A	
>= 40 (year)	32.4 (33/102)	50.9 (54/106)	.0056	48.6 (52/107)	.0145		
Protocol 162							
< 40 (year)	31.9 (29/91)	65.1 (67/103)	.0001	66.3 (67/101)	.0001	66.7 (56/84)	.0001
>= 40 (year)	29.2 (28/96)	58.8 (50/85)	.0001	51.2 (44/86)	.0005	51.4 (54/105)	.0003

4.2 Other Special/Subgroup Populations

No other special/subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The two studies of Protocols 161 and 162 had demonstrated that rofecoxib 50 mg and 25 mg were efficacious based on the protocol specified primary efficacy parameter and corresponding analysis methods. For the secondary efficacy parameters, I have focused analysis on a few key parameters: pain relief and pain freedom within 2 hours of dosing and migraine associated symptoms.

For the secondary parameter of pain freedom at 2-hour post dose, the difference of rofecoxib 25 mg versus placebo met the significance level in study 162. But the same effect could not be concluded in study 161, if multiplicity adjustment was applied (alpha=0.05/total number of secondary parameters). Similarly, rofecoxib 25 mg failed to meet the significance level for

associated symptoms of nausea and photophobia in study 161. In considering the consistency of the collective evidence at different time points and collective evidence across the two studies, I conclude that the two studies have provided sufficient evidence that both rofecoxib 50 mg and 25 mg are effective in providing pain freedom at 2 hour post dosing and in relieving the associated symptoms of photophobia, phonophobia, and nausea.

5.2 Conclusions and Recommendations

The two studies (Protocols 161 and 162) submitted in this NDA have provided quite consistent results of the efficacy of the two doses of rofecoxib. A significantly higher proportion of patients who were treated with rofecoxib 50 mg or 25 mg than patients treated by placebo had reported pain relief at 2-hour post dose. Therefore, I conclude that both rofecoxib 50 mg and 25 mg are efficacious in the treatment of acute migraine with regard to pain relief at 2 hour post dose.

I also conclude that rofecoxib 50 mg and 25 mg are efficacious in the acute treatment of migraine in relieving the pain as soon as one hour post dosing, in providing pain freedom at 2 hour post dosing, and in relieving migraine associated symptoms of photophobia, phonophobia, and nausea. This conclusion was made based on the significance of the treatment difference and the consistency of the results from the two studies.

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