Table II-2: 95% CI including drop out due erosion as end points.

Cumulative Ulcer rate (95%)	Study 44	Study 45
Placebo Rofecoxib 25 mg Rofecoxib 50 mg Ibuprofen	9.92 (4.12, 15.73) 4.10 (1.12, 7.07) 7.31 (3.31, 11.30) 27.69 (20.43, 34.95)	5.10 (0.75, 9.46) 5.83 (2.31, 9.34) 10.01 (5.49, 14.54) 33.74 (26.55, 40.94)
Difference (95% CI)		
Rofecoxib 25 mg – Placebo Rofecoxib 50 mg – Placebo Rofecoxib 25 mg – Ibuprofen Rofecoxib 50 mg – Ibuprofen	-5.83 (-12.35, 0.70) -2.62 (-9.66, 4.43) -23.59 (-31.43, -15.75) -20.38 (-28.66, -12.10)	0.73 (-4.87, 6.32) 4.91 (-1.37, 11.19) -27.91 (-35.92, -19.91) -23.73 (-32.23, -15.23)

4. There was an imbalance in number of patients who were excluded from the ITT population among treatment group in Study 44. Pearson chi-square test yielded a p-value 0.02. A sensitivity analysis was done to include those patients, the result was similar to the ITT analysis. There was a similar observation in Study 45 as well. The reason that the results were not changed much was that the majority of drop outs were occurred at earlier time.

5. In analyzing the study by treatment interaction, the sponsor and the reviewer had two different results. The sponsor showed a p-value of 0.26 in a study by treatment interaction analysis. Whereas the analysis by the reviewer yielded p-values 0.09 and 0.08 for Rofecoxib 25 and 50 mg versus placebo respectively. The sponsor and the reviewer used the same COX's proportional hazard model. The sponsor used the likelihood ratio test which was a combined test (combining three study by treatment interactions: Rofecoxib 25 mg versus placebo, Rofecoxib 50 mg versus placebo and Ibuprofen versus placebo), while the reviewer used Wald test on each of the three study by treatment interactions. The reviewer believes the Wald test on each individual study by treatment interaction was more appropriate for three reasons: there was no intuitive interpretation for the combined test when correlation existed; research has shown that the individual test can be more powerful than combined test; and the test results were consistent with the data observed (see Table II-2). As it can be seen from the table, the difference of ulcer rates in placebo treatment between the two studies was the largest among the four treatment groups studied (4.82% in placebo, -1.19% in Rofecoxib 25 mg group, -1.51% in Rofecoxib 50 mg group, and -1.49% in Ibuprofen); and the comparison of placebo vs. Rofecoxib was in two directions between the two studies. Those differences resulted in statistically significant (significant level at 0.1) study by treatment interaction. In conclusion, facing such strong interaction, the common treatment effect was no longer of any meaning. Therefore, the combined result in study report 44c was no longer meaningful.

In conclusion, no consistent evidence supports the claim that the ulcer rate in either Rofecoxib dose group was similar to that in placebo group.

Study 69:

Study 69 was a prospective, combined analysis to compare the incidence of upper-GI events between patients treated with Rofecoxib (12.5, 25, and 50 mg, combined treatment groups) and those treated with NSAID comparators (Ibuprofen, Diclofenac, and nabumetone, combined treatment groups). Eight studies (and blinded extensions) including all major Phase IIb-III osteoarthritis studies were analyzed. The duration of treatment in the studies ranged from 6 weeks to 24 months. Investigators identified PUB events and provided clinical documentation to corroborate each report. An independent, blinded expert Case Review Committee reviewed the clinical data and used prospectively developed definitions to adjudicate whether the PUB was "confirmed" and whether it was "clinically complicated." The committee was blinded to protocol and treatment information.

The discussion on the end points was complicated, for detailed discussion, please refer to Dr. Goldkind's review. The primary end point was the confirmed PUBs. Other end points included confirmed and complicated PUBs, NASIDS type GI events, the incidence of discontinuation.

Time to the occurrence of the first PUB was compared between treatment groups up to 12 months. Survival analysis was used as the primary analysis. Logrank test and Cox's proportional hazard model were used for the analysis.

Sponsor's Results:

The primary analysis on the confirmed PUBs done by sponsor showed that the cumulative incidence up to 12 months of confirmed upper-GI PUBs in patients treated with Rofecoxib (12.5, 25, and 50 mg combined) was significantly lower than that in patients treated with NSAID patients. The overall relative risk across the 12-month treatment period for patients treated with Rofecoxib versus NSAIDs was 0.45 (95% CI 0.25, 0.81; p=0.006 by log rank test).

The analysis for the confirmed and complicated PUBs showed the overall relative risk over the 12-month treatment period for patients treated with Rofecoxib versus NSAIDs was 0.51 (95% CI 0.16, 1.69), which covered 1.

The cumulative incidence of discontinuation due to GI AE in patients treated with Rofecoxib was significantly lower than that in patients treated with NSAIDs over 12 months (rate difference -2.14%, 95% CI -4.36, 0.09). The overall relative risk across the 12-month treatment period was 0.70 (95% CI 0.52, 0.94; p=0.016 by log rank test).

The cumulative incidence of NSAID-type GI AEs was numerically lower with Rofecoxib than NSAID up to Month 6, after which the incidence rates converged. The difference in cumulative incidence curves over 12 months between Rofecoxib and NSAID was not statistically significant (p=0.065, log rank test).

Requested by FDA, an analysis by treatment groups at different time intervals was also provided by sponsor. The count of patients and confirmed PUBs were summarized in Table II-3 by treatment and time intervals. The cumulative incidence rates using survival analyses by treatment groups at different time intervals were also listed in Table II-4. As it can be seen, the risk sets at varies time points were reduced non-proportionally among treatment groups. Further discussion was made in reviewer's comments.

Table II-3: Confirmed PUBs count by treatment and by time interval

Treatment	Baseline		Week 6		Week 12		Month 6		Year 1		Wk86
	Pat #	Event	Pat #	Event	Pat #	Event	Pat #	Event	Pat #	Event	Pat #
Placebo	514	1	419	2	295	1	0	0	0	0	0
Rof 12.5 mg	1209	0	1007	3	548	1	428	1	250	0	6
Rof 25 mg	1603	0	1383	0	866	3	453	2	267	0	13
Rof 50 mg	545	4	480	2	402	5	94	2	63	0	5
Diclofenac	590	0	538	1	494	2	412	2	238	0	1
Ibuprofen	847	10	673	2	222	5	2	0	0	0	0
Nabumeton	127	0	103	0	41	0	1	0	0	0	0

Table II-4: Cumulative PUBs rate

Treatment	N	Cumulative Incidence (%) with 95% CI			
		6 Weeks	12 Weeks	6 Months	1 Year
Placebo	514	0.22 (0.00,0.65)	0.88 (0.00,1.89)	--	--
Rof 12.5 mg	1209	0.00 (0.00,0.00)	0.51 (0.00,1.09)	0.70 (0.02,1.39)	0.98 (0.11,1.85)
Rof 25 mg	1603	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.39 (0.00,0.82)	0.87 (0.07,1.67)
Rof 50 mg	545	0.76 (0.02,1.51)	1.22 (0.25,2.20)	2.52 (1.03,4.01)	5.31 (1.24,9.37)
Diclofenac	590	0.00 (0.00,0.00)	0.19 (0.00,0.57)	0.64 (0.00,1.37)	1.15 (0.14,2.17)
Ibuprofen	847	1.25 (0.00,0.00)	2.06 (0.71,3.41)	16.2 (0.00,38.2)	--
Nabumetone	127	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.00 (0.00,0.00)	--

Reviewer's comments and analyses:

Interpreting the sponsor's results of Study 69 can be misleading because this study combined 8 individual studies which differed in many aspects; study duration was different, doses of Rofecoxib were different, comparator NSAIDS were different, diagnostic surveillance methods for the end point were different, and patient withdrawal criteria were different. As it can be seen from Dr. Glodkind's review, as well as Table II-3 and II-4, data suggested that there were dose related PUB's rate in Rofecoxib treatment groups, and among the NSAIDS used, the PUB's rates were inconsistent. The study variations, mingled with dose related PUB's rates in Rofecoxib treatment groups and specific NSAID related PUB's realted, make it impossible to generalize and interpret the study results.

1. Combing dose groups:

Without a good understanding of the dose-PUBs relationship in Rofecoxib, it is questionable if the study results can be generalized to any combined population. In the

combined Rofecoxib treatment group, 36% in Rofecoxib 12.5 mg group, 48% in Rofecoxib 25 mg group, and 16% in Rofecoxib 50 mg. In the combined NSAIDS treatment group, there are 54% from Ibuprofen treatment, 38% from Diclofenac, and 8% from Nabumetone.

The combined analysis compared the average risks between the two combined treatment groups. When the risk of developing PUBS depended on dose levels of Rofecoxib or specific NSAID (which was what data has suggested), the average risk depended on the proportion of patient's exposure to certain dose level or specific NSAID. Therefore, the analysis based on the specific combined treatment group can not be generalized to any combined population.

2. Study duration:

Study duration varied from 6 weeks to one year. The differences in study duration introduced another level of difficulty in interpreting study results. There were two primary reasons. 1) Different dose levels of Rofecoxib and different NSAIDS were studied among the individual studies; and 2) the risks of developing PUBS were different for different dose level of Rofecoxib and different NSAIDS. The average risk of a combined treatment group depended on not only the proportion of treatment exposure, but also the duration of a treatment cohort in study. Therefore, because study duration differences, the risk analyzed was different from the one representing the study popuplation.

3. Withdrawal due to non-clinical ulcer:

Among the 8 studies, Studies 44 and 45 were endoscopic surveillance studies. An important feature of the two studies that differed from the rest of the 6 studies was the systematic patient withdrawal from the studies once gastric and/or doudenal ulcers (≥3 mm) were identified by endoscopic surveillance. About 38% and 30% patients withdrew because of the endoscopy identified ulcers in Ibuprofen group in Study 45 and 44 respectively, comparing less than 9% in Rofecoxib group in both studies. The majority non-clinical ulcers were identified in Week 6, 12, and 24, and the studies were terminated at Week 24.

It is no doubt that patients withdrawn due to non-clinical ulcer were in high risk to develop PUBs. However, it is not thoughtful to conclude that the analysis was biased against Rofecoxib simply because more patients withdrew due to non-clinical ulcer in Ibuprofen treatment group. Since the study terminated at Week 24, the direction of bias depended on how many non-clinical became PUBs at Week 24. If very few endoscopy identified ulcers would develop into PUBs at Week 24, the majority of the patients would remain in risk set if they were not removed from the studies. Because there was a large proportion of patient withdrawal due to endoscopy identified ulcer in Ibuprofen group, the risk set became smaller and therefore the PUBs rate could be artificially inflated.

It is certain that withdrawal due to non-clinical ulcer results in bias in the analysis, however, the direction of bias is debatable. This will not be clear unless more information available regarding the timing and rate of PUBs in the subset of patients who have non-clinical ulcers.

III.   Dose-response studies:

An issue arose in reviewing dose-response treatment effect of Rofecoxib. In an integrated analysis, a pilot study (Study 10) and a dose range study (Study 29) was combined to evaluate the dose-response relationship. The integrated analysis indicated that there was a shallow dose response curve from dose 5 to 125 mg and a limited incremental benefit associated with increasing doses above 25 mg. Partially based on this analysis, 25 mg was selected as the optimal study dose for the OA patients. However, the results of Study 29 alone did not support the conclusion of the integrated analysis. It showed a steep dose-response relationship. Especially at 50 mg of Rofecoxib, the therapeutic effect was statistically significant higher than that of Rofecoxib 12.5 and 25 mg.

If 50 mg of Rofecoxib indeed had better therapeutic effect, patients may pursue 50 mg. However, there was not enough safety information on 50 mg of Rofecoxib. The consequence of using 50 mg of Rofecoxib caused concerns.

Studies 10 and 29:
Study 10 was a multicenter double-blind placebo-controlled 6 week pilot study to evaluate safety and tolerability and preliminarily assess clinical efficacy of Rofecoxib in patients with osteoarthritis of knee. Two doses of Rofecoxib were studied 25 and 125 mg daily. The efficacy result was summarized in Table III-1.

From Table III-1, it can be seen that both Rofecoxib treatment groups demonstrated statistically as well as clinically significant improvement over placebo. However, the therapeutic effect between the two Rofecoxib treatment groups did not show large difference. The difference between 25 and 125 mg for the three primary variables were -2.99 (-9.59, 3.62) for pain walk on a flat surface, -0.19 (-0.50, 0.13) for patient global assessment of response to therapy, and -0.06 (-0.32, 0.20) for investigator global assessment of disease status.

Patient accounting information showed that patient withdrawal due to adverse event in 25 and 125 mg were 5.6% and 13.7% respectively. The higher percentage withdrawal due to adverse event may impair the treatment effect in higher dose of Rofecoxib. Since Study 10 had only two Rofecoxib dose groups, 25 and 125 mg, there was no information available in the big dose gap between 25 and 125 mg.

Table III-1: Study results from Study 10.

Protocol	Baseline Mean	Treatment Period Mean	LS Mean[†] Difference From Baseline (95% CI)	LS Mean[†] Difference From Placebo (95% CI)
Pain Walking on a Flat Surface (WOMAC) (0- to 100-mm VAS)				
Placebo (n=70)	57.97	51.41	-6.95 (-11.71, -2.20)	N/A
MK-0966 25 mg (n=73)	63.38	34.83	-25.97 (-30.62, -21.31)	-19.01 (-25.71, -12.32)
MK-0966 125 mg (n=74)	58.32	29.57	-28.95 (-33.58, -24.33)	-22.00 (-28.64, -15.36)
Patient Global Assessment of Response to Therapy (0- to 4-Point Likert Scale)				
Placebo (n=70)	N/A	-1.36	-1.33 (-1.56, -1.11)	N/A
MK-0966 25 mg (n=73)	N/A	-2.63	-2.63 (-2.85, -2.41)	-1.29 (-1.61, -0.98)
MK-0966 125 mg (n=70)	N/A	-2.82	-2.81 (-3.04, -2.59)	-1.48 (-1.81, -1.16)
Investigator Global Assessment of Disease Status (0- to 4-Point Likert Scale)				
Placebo (n=69)	2.74	2.21	-0.54 (-0.72, -0.36)	N/A
MK-0966 25 mg (n=70)	2.80	1.28	-1.51 (-1.69, -1.33)	-0.97 (-1.23, -0.71)
MK-0966 125 mg (n=70)	2.77	1.20	-1.57 (-1.75, -1.39)	-1.03 (-1.29, -0.77)

$p < 0.001$ LS mean difference from placebo for both MK-0966 treatment groups.
[†] Decreasing values represent improvement.

Study 29 was a multicenter double-blind placebo-controlled dose-ranging 6 week study to assess safety and further define the clinically effective dose range of Rofecoxib in patients with osreoarthritis of the knee or Hip. Four Rofecoxib doses were studied, 5 mg, 12.5 mg, 25 mg and 50 mg. Efficacy result are summarized in Table III-2.

Compared with placebo (Table III-2), all Rofecoxib groups in Study 29 demonstrated a significant improvement in the three primary endpoints and all the other secondary endpoints. In terms of the comparison among Rofecoxib treatment groups, 50 mg daily demonstrated consistently statistically as well as clinically superior efficacy to the lower dose group. For the endpoint of pain walking on a flat surface, the 50 mg dose demonstrated a significantly greater improvement compared with 5, 12.5, and 25 mg ($p < 0.008$). For patient global assessment of response to therapy, the 50 mg dose also demonstrated significantly greater improvement compared with 5, 12.5 and 25 mg dose ($p < 0.001$, $p = 0.021$ and 0.039, respectively). For investigator global assessment of disease status, the 50-mg dose again demonstrated significantly greater improvement compared with 5, 12.5, and 25 mg ($p < 0.006$). All the 95% CIs exceeded the comparability range for the three primary endpoints. The majority of the secondary end points in 50 mg group also demonstrated statistically significantly superiority to the rest of the Rofecoxib doses.

Table III-2: Study results from Study 29.

Treatment Group	N	Pain Walking on a Flat Surface (WOMAC) (0- to 100-mm VAS)	Patient Global Assessment of Response to Therapy (0 to 4 Likert Scale)	Investigator Global Assessment of Disease Status (0 to 4 Likert Scale)
Placebo	145	17.5	1.22	0.71
5 mg	149	32.5*	1.98*	1.19*
12.5 mg	144	31.8*	2.24*,**	1.37*
25 mg	137	33.0*	2.27*,**	1.36*
50 mg	97	41.1**	2.41**	1.68**
Pooled SD		(22.6)	(1.07)	(0.86)
* p<0.05 vs. 50 mg.				
** p<0.05 vs. 5 mg.				
All doses of MK-0966 were significantly (p<0.05) decreased vs. treatment placebo.				

Combining two study's results:

Studies 10 and 29 were two similarly designed studies. However, some differences existed in demographic information between the two studies. For examples, ARA score was slightly higher in Study 10 than in Study 29; there was a larger sample size in Study 29 than that in Study 10.

The sponsor's integrated analysis:

A non-linear three parameter logistic model was fitted for the least square means difference from placebo obtained from the two studies. The three parameter model was
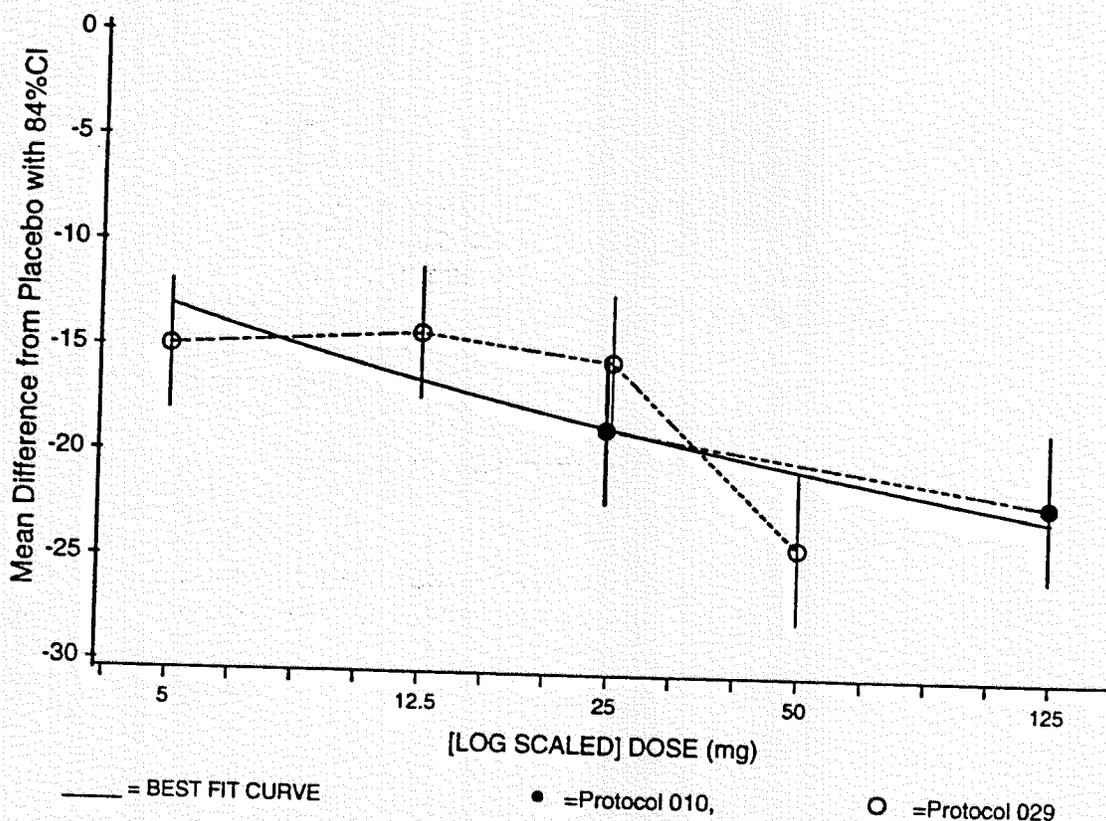
$$y = \frac{a}{1 + (\frac{x}{c})^b}$$

where y=response variable (Lsmean difference from placebo)
       x=log(dose)
       a,b,c=model parameters to be fitted.
The result of fitting this model for the primary end point pain walking on flat surface was shown in the following graph.

= BEST FIT CURVE   ● =Protocol 010,   O =Protocol 029

Reviewer's comments:

1. Studies 10 and 29 presented inconsistent results. The treatment effect of 25 mg of Rofecoxib in Study 10 was higher than that in Study 29. The results in Study 29 were consistent with the results in the two short term studies (Studies 33 and 40), which were Phase III 6 week placebo controlled efficacy studies, in two doses of Rofecoxib, 12.5 and 25 mg. This suggested simple combination of the two studies (Studies 10 and 29) was inappropriate and using Study 29 alone might be proper to assess the dose-response relationship.

2. The three parameter logistic model was not prespecifed. There was no biological and scientific rational as why the parametric model was chosen. The combined analysis had only 6 data points at 5 different doses, 5, 12.5, 25, 50, and 125 mg. Mathematically, any non-linear model that has less than 5 parameters can be fitted uniquely by either least square or maximum likelihood methods. The reviewer had fitted several different models which resulted in different conclusions.

Conclusion:

Rofecoxib doses 12.5 and 25 mg have shown superior therapeutic effect on the treatment of OA patients over placebo for 6 week studies, as well as therapeutic effect comparable to Ibuprofen (6 week studies) and Diclofenac (6 month studies). In the two endoscopy

studies, Ibuprofen had statistically significantly higher endoscopy identified ulcer rates over Rofecoxib 25 and 50 mg dose groups. However, it is not appropriate to claim that the ulcer rates of Rofecoxib were similar to placebo. Cautious should be exercised in interpreting the results from Study 69.

/S/

Qian Li, Sc.D
Mathematical Statistician

Concur:

/S/   5/19/99

Stan Lin, Ph.D
Team Leader

/S/   5/19/99

Mo Huque, Ph.D
Division Director

CC:
HFD-550/Div File
HFD-550/PM/SCook
HFD-550/MO/MLVillalba
HFD-550/MO/LGoldkind
HFD-550/MO/Jhyde
HFD-725/Div File
HFD-725/Mhuque
HFD-725/SLin
HFD-725/Qli

APPEARS THIS WAY
ON ORIGINAL

STATISTICAL REVIEW AND EVALUATION
(Clinical: Analgesia)

NDA #:   21-042/Drug Class 1P

APPLICANT: Merck Research Laboratories

NAME OF DRUG: VIOXX™ (Rofecoxib) Tablets

DOCUMENTS REVIEWED: Documents and Data Components on Electronic Submission.

REVIEWING MEDICAL OFFICER: Mordechai Averbuch, M.D. (HFD-550)

INDICATIONS: Relief of pain and treatment of primary dysmenorrhea.

I.   Summary Findings

Merck has submitted the following analgesic studies as pivotal for the evaluation of Rofecoxib for pain relief:

Post-Dental Surgery Pain Studies: 066, 071
Primary Dysmenorrhea Studies: 055, 056
Post-Orthopedic Surgery Pain Study: 072.

1. Post-Dental Surgery Pain studies confirmed the statistical effectiveness of a single Rofecoxib 50 mg dose for pain relief. The analgesic effect of a single Rofecoxib 50 mg dose was similar to 400 mg of ibuprofen in these studies.
2. Primary Dysmenorrhea studies confirmed the statistical effectiveness of a Rofecoxib 50 mg dose for pain relief. The analgesic effect of a single Rofecoxib 50 mg dose was similar to 550 mg of naproxen sodium in these studies after 2 hours post-dose.
3. Post-Orthopedic Surgery Pain study confirmed the statistical effectiveness of a Rofecoxib 50 mg dose for pain relief. The analgesic effect of Rofecoxib 50 mg daily dose was similar to 550 mg of naproxen sodium in this study.
4. In Post-Dental Surgery Pain studies, the persistency of the analgesic effect of Rofecoxib 50 mg daily dose up to 24 hours is questionable as there are not many patients left in the studies at 24 hours. This result is purely analysis-driven. Thus, a claim of persistent analgesic effect of 50 mg of Rofecoxib up to 24 hours is not justified.
5. In Primary Dysmenorrhea studies, there were significant carryover effects for several endpoints. But, the impact of these significant carryover effects was negligible on the overall results of these studies.

II.   Background Information

Studies

Post-Dental Surgery Pain Studies: 066, 071

The purpose of the Post-Dental Surgery Pain Studies was to demonstrate single dose efficacy of Rofecoxib in a standard single dose analgesic model. Both the studies were parallel group, randomized, double-blind, placebo- and active comparator-controlled trials and thus provided the evidence of efficacy relative to both placebo and the active comparator. The study 066 used 50 mg Rofecoxib dose whereas the study 071 used 50, 100 and 200 mg Rofecoxib doses. The two studies used ibuprofen 400 mg as the active comparator.

Upon development of moderate to severe postsurgical pain, patients consumed a single dose of study medication. Over the ensuing 24 hours, patients completed the following measures of efficacy: (1) Patients completed a diary at various prespecified timepoints in which they rated pain relief, pain intensity, an overall assessment of the study therapy and the time that rescue medication was taken. (2) Patients clicked off 2 stopwatches—one when they achieved perceptible pain relief and a second when they achieved meaningful pain relief.

Primary Dysmenorrhea Studies: 055, 056

The purpose of the Primary Dysmenorrhea Studies was to demonstrate analgesic efficacy of Rofecoxib in a second analgesic model. Both the studies were crossover, randomized, double-blind, multiple-dose, placebo- and active comparator-controlled trials and thus provided the evidence of efficacy relative to both placebo and the active comparator. Both studies included an initial dose of 50 mg Rofecoxib. The two studies used naproxen sodium 550 mg as the active comparator.

Patients were provided study medication to take upon development of moderate to severe cramping pain due to dysmenorrhea. Over the ensuing 12 hours, patients completed a diary identical to that described for the Post-Dental Surgery Pain Studies.

Post-Orthopedic Surgery Pain Study: 072

The purpose of the Post-Orthopedic Surgery Pain Study was to demonstrate both single- and multiple-dose analgesic efficacy of Rofecoxib in a third analgesic model of more prolonged pain. This study was a parallel group, randomized, double-blind, placebo- and active comparator-controlled trial and thus provided the evidence of efficacy relative to both placebo and the active comparator. This study used naproxen sodium 550 mg as the active

comparator. This study was designed to demonstrate the efficacy of Rofecoxib for up to 5 days for the treatment of acute pain.

Patients met the selection criteria at the screening visit. Patients then underwent a major orthopedic surgical procedure (total knee replacement, total hip replacement, or fracture repair with open reduction and internal fixation). Postoperatively, patients were treated with narcotics for up to 72 hours. Upon discontinuation of narcotic medication, patients who developed moderate to severe postsurgical pain consumed the first dose of study medication. Over the ensuing 12 hours, patients completed a diary and clicked off 2 stopwatches identical to that described for the Post-Dental Surgery Pain Studies. Over the ensuing 5 days, patients received a dose of study medication each morning and completed additional measures of analgesic efficacy: (1) a record of the date, time, and number of tablets of supplemental analgesic medication consumed each day, (2) a global assessment of study medication each day, and (3) a pain intensity rating at three specified time points each day.

Endpoints

This NDA submission included four sets of efficacy endpoints to assess the efficacy of Rofecoxib as an analgesic medication:

1. **Endpoints Assessing Overall Analgesic Efficacy:**
   Total Pain Relief (TOPAR),
   Sum of Pain Intensity Differences (SPID),
   Patient's Global Evaluation of Study Medication,
   Average Supplemental Rescue Medication Use over Days 2 to 5,
   Patient's Global Evaluation Score averaged over Days 2 to 5,
   Pain Intensity Averaged over Days 2 to 5.
2. **Endpoints Assessing Onset of Analgesia Activity:**
   Time to Confirmed Perceptible (or Meaningful) Pain Relief
   (Stop Watch), Time to Pain Intensity Difference (PID) ≥ 1.
3. **Endpoints Assessing Peak Analgesic Activity:**
   Peak Pain Relief, Peak PID.
4. **Endpoints Assessing Duration of Analgesic Activity:**
   Percent of Patients Who took Rescue Medication within a specified time post-dose, Time to Rescue Medication,
   Mean of the sum of the Pain Relief Score plus PID Score (PRID) at the 24-hour post-dose time-point,
   Time and Amount of Supplemental Analgesic for Post-Orthopedic Surgery Pain Study.

Please note that the Division advocates the following primary efficacy endpoints: PR, PI, PID and PRID.

III. Statistical Approach to Efficacy Analysis (ITT with LOCF)

An intent-to-treat (ITT) analysis was performed and considered the primary efficacy analysis. Intent-to-treat dataset contained all those patients who took study medication, recorded a baseline pain intensity score, and recorded at least one pain evaluation postdose. Missing pain relief and pain intensity scores were estimated by last observation carried forward approach (LOCF). In this approach, the missing pain scores after a patient took rescue medication were estimated by using the score recorded just prior to patient remedication.

The sponsor's primary endpoint was the overall analgesic effect to 8 hours as measured by Total Pain Relief at 8 hours (TOPAR8). At various prespecified times postdose, patients rated their Pain Relief and these ratings were assigned numeric values (0=none, 1=a little, 2=some, 3=a lot, 4=complete). TOPAR8 was derived from the Pain Relief Scores. This was calculated by multiplying the Pain Relief score at each time point by the duration (in hours) since the preceding time point and summing these values up to 8 hours. Thus, TOPAR8 is the area under the Pain Relief versus Time curve to 8 hours (0-32 Scale).

Please recall that the Division advocates the following primary efficacy endpoints: PR, PI, PID and PRID and not TOPAR8. So, this review will basically be based on these endpoints only.

For each study, treatment effects on PR, PI, PID, PRID, and TOPAR8 (sponsor's primary endpoint) were assessed using an ANOVA model. For the Post-Dental Surgery Pain Studies, this model included treatment group and baseline Pain Intensity score as factors. For the Primary Dysmenorrhea Studies, the ANOVA model included treatment, baseline Pain Intensity, sequence, patient within sequence, period and carryover effects as factors. For the Post-Orthopedic Surgery Pain Study, the ANOVA model included treatment, baseline Pain Intensity, type of surgical procedure and study center as factors.

Treatment effects were estimated by using the Least Square (LS) means and the between treatment differences in LS means (with 95% CI) derived from the ANOVA model.

The time to confirmed perceptible or meaningful pain relief (stopwatch) and Time to Requiring Rescue Medication were analyzed by using the Cox Proportional Hazards Regression model. The respective statistical models for the Post-Dental Surgery Pain, Primary Dysmenorrhea and Post-Orthopedic Surgery Pain Studies included the same factors as described above in the ANOVA model.

These primary analyses were parametric. Parametric model assumptions were assessed through residual analysis.