Comparability to comparator NSAIDs (ibuprofen, diclofenac, nabumetone).

a) Ibuprofen.
In two six-week pivotal trials rofecoxib at the doses of 12.5 and 25 mg QD was **statistically and clinically comparable to ibuprofen** in most efficacy endpoints.

b) Diclofenac.
Two one-year trials showed that rofecoxib 12.5 and 25 mg QD was **clinically comparable to diclofenac 50 mg TID** for up to 6 months. Rofecoxib was consistently statistically different from diclofenac (in favor of diclofenac) in all primary efficacy endpoints (except the 25 mg dose for WOMAC Pain Walking on Flat surface in one of the studies). These differences however, were within the range of clinical comparability as defined by the applicant. During the second six month of the one-year studies, concomitant analgesic medication was allowed without restriction for the treatment of OA, therefore, definitive conclusions regarding efficacy should not be drawn.

b) Nabumetone.
Study 058 (rofecoxib and nabumetone in the elderly) showed that **rofecoxib was statistically and clinically comparable to nabumetone** in all efficacy endpoints. However, neither rofecoxib nor nabumetone seemed to show a clinically important difference with placebo. If we were to use the criteria of clinical comparability as defined by the applicant, both rofecoxib and nabumetone would be in the range of clinical comparability to placebo for most efficacy endpoints. The apparent failure of the active treatments is probably due to the fact that this was a "non-flare" study and patients started with a lower degree of disability and pain.

Table 6 summarizes efficacy results for the rofecoxib OA clinical program.

Table 6. Efficacy Results. Phase II and Phase III base studies. Statistical Comparison of Least Square Mean Changes from baseline for primary efficacy endpoints.

Duration	Study #	n	Treatment	PRIMARY EFFICACY ENDPOINTS		
				WOMAC Pain Walking on Flat Surface	Patient Global Assessment of Response to Therapy	Investigator Global Assessment of Disease Status
6 week Phase II studies	010	219	**Placebo, Rfx 25 mg QD Rfx 50 mg QD**	†	†	†
	029	672	**Placebo, Rfx 5, 12.5, 25 and 50 mg QD**	Rfx 5, 12.5, 25 and 50 mg, all **SSD** and clinically different from placebo. Rfx 12.5 **no SSD** vs. 25 mg. Rfx 50 **SSD** vs. 5, 12,5 and 25		
6 week Phase III studies	033*	736	**Placebo, Rfx 12.5 mg QD Rfx 25 mg QD Ibu 2400 mg/d**	Rfx 12.5 and 25 mg and ibu , all **SSD** and clinically different from placebo Rfx 12.5 **no SSD** from 25 Rfx 12.5 and 25 **no SSD** from ibu		
	040*	809		Same as study 033.	Similar to 033 but Rfx 25 mg **SSD** vs. ibu #	Similar to 033 but Rfx 12.5 mg **SSD** vs. ibu #
	058 (elderly)	341	**Placebo, Rfx 12.5 mg QD Rfx 25 mg QD Nabu 1500 mg/d**	¶	¶	¶
6 month # Phase III lies	034*	693	**Rfx 12.5 Rfx 25 mg QD Diclo 150 mg/d**	Rfx 12.5 **no SSD** vs.25 Rfx 25 **no SSD** vs. diclo Rfx 12.5 **SSD** vs. diclo ‡	Rfx 12.5 **no SSD** vs. 25 Rofecoxib 12.5 and 25 both **SSD** vs. diclo ‡	
	035*	784		Rfx 12.5 **no SSD** vs.25 Rfx 25 **SSD** vs. diclo ‡ Rfx 12.5 **SSD** vs. diclo ‡	Rfx 12.5 **no SSD** vs. 25 Rfx 25 **no SSD** vs. diclo Rfx 12.5 **SSD** vs. diclo ‡	Rfx 12.5 **no SSD** vs. 25 Rfx 12.5 and 25 both **SSD** vs. diclo ‡

* Pivotal trials. n: number of patients randomized. Rfx: rofecoxib. Ibu: ibuprofen. Diclo: diclofenac. Nabu: nabumetone. SSD: statistically significant difference ($p < 0.05$).

† For Study 010 the primary endpoints were WOMAC Pain Subscale and Patient Global Assessment of Arthritic Pain. For both endpoints rofecoxib was superior to placebo and there was no SSD between the 25 and 125 mg doses.

¶ For study 058 the single primary endpoint was Patient Global Assessment of Disease Status. For this and other efficacy endpoints, rofecoxib 12.5 and 25 mg and nabumetone, were SSD vs. placebo.

\# For study 034 and 035 only 12 week results are included in the table.

\# Difference in favor of rofecoxib. ‡ Difference in favor of diclofenac. Although the differences were statistically significant, they were within the bounds of clinical comparability pre-defined by the applicant (± 10 mm in a 100 mm VAS and ± 0.5 point in a 0 to 4 point Likert scale).

1.2. DOSE SELECTION

The selection of 12.5 and 25 mg/day for phase III OA trials was based on efficacy and safety considerations from two Phase II studies and one extension:

- Study 010
- Study 029
- An integrated analysis of both studies
- Analysis of the effect of dose escalation in extension study 029-10.

> ***Reviewer's note: the dose range selected for phase III trials in OA is particularly relevant in this case because there is also a need to prove that, at the most efficacious dose, the drug still has its COX-2 selective properties without a significant increase in adverse events.***

The applicant states that on the bases of efficacy and safety analyses, the 12.5 and 25 mg doses of rofecoxib administered once daily were associated with the optimal benefit/risk relationship. The applicant also states that "the dose-response relationship was relatively shallow".

> ***The data reviewed in this NDA confirms that rofecoxib doses of 12.5 and 25 mg QD give the optimal risk/benefit ratio. It also indicates a clear dose-response relationship in terms of efficacy and adverse events. In the six-week dose ranging study (029) the 50 mg/d dose was more efficacious than the 25 mg/d dose with minimal increase in toxicity (mostly fluid retention and edema). However, in six-month studies the 50 mg dose was associated with a numerically higher incidence of hypertension, fluid retention, edema, renal-related laboratory abnormalities and GI adverse events compared to the 12.5 and 25 mg QD doses. (See safety review).***

Study 010. Phase II, six-week pilot study of rofecoxib in OA

1) Design: multi-center, randomized, double-blind, parallel, placebo-controlled study in 219 patients with OA of the *knee only*.

2) Treatment: Placebo, rofecoxib 25 mg and 125 mg QD.

3) Entry criteria:

Because of the difference in primary end points, the entry criteria were a little different:
Patient Assessment of Arthritic Pain had to be less than 80 mm (100-mm VAS) at pre-study visit.
The "flare" criteria at Visit 2 were:
a- Minimum 40 mm on patient-reported Pain (VAS); and
b- Increase 15 mm on patient-reported Pain (VAS) compared with pre-study baseline.

4) Demographics: the reader is referred to general study characteristics and Appendix 2.

5) Efficacy end points:

This study had only two primary endpoints: Patient Assessment of Arthritic Pain and WOMAC Pain Subscale. The three primary efficacy endpoints used in pivotal trials (WOMAC Walking on Flat Surface, Investigator Global Assessment of Disease Status and Patient Global of Response to Therapy) were measured but considered secondary endpoints.

6) Results:

6.1 - Randomization and accounting (Table 7)

Table 7. Study 010. Patient randomization and accounting.

Patients randomized / evaluable	Placebo 72/72	Rofecoxib 25mg 73/73	Rofecoxib 125 mg 74/72
Discontinued (% of randomized patients)	43.0 %	12.3 %	22.9 %
Lack of efficacy	29.6	5.6 *	1.4 *
Adverse events	8.5	5.6	15.1

* $p<0.001$ vs. placebo.

Discontinuation due to lack of efficacy was significantly higher in the placebo group. The incidence of adverse events was higher (but did not reach statistical significance) in the rofecoxib 125 mg QD group. Relevant adverse events in rofecoxib 125 mg QD were fluid retention and edema. Four patients discontinued from the 125 mg dose due to edema related adverse events and two due to GI related adverse events, one of them, a GI bleed (see Safety review).

6.2 - Efficacy analysis. (Table 8, Appendix 5)

Both 25 and 125 mg/day doses were statistically different from placebo for all endpoints ($p< 0.001$). This differences were greater than 19 mm for endpoints using a 0 to 100 VAS and greater than 1.0 for endpoints using a 0 to 4 Likert scale therefore they were likely to be clinically meaningful. There was **no statistically significant difference between the two rofecoxib doses.**

Table 8. Study 010. Least Square Mean difference from baseline averaged over 6 weeks.

Efficacy end point	Placebo (n=72)	Rfx 25 mg QD (n=73)	Rfx 125 mg QD (n=72)
Primary			
Pt Assessment of Arthritic Pain [1]	-15.2*	-35.8	-38.3
WOMAC Pain Subscale [1]	-7.1*	-26.1	-28.2
Secondary			
WOMAC Pain Walking on flat [1]	-7.0*	-26.0	-29.0
Patient Global of Response to Therapy [2]	-1.3*	-2. 6	-2.8
Investigator Global of Disease Status [2]	-0.5 *	-1.5	-1.6

[1] 0 to 100 mm VAS. [2] 0 to 4 Likert scale. * Comparison between placebo and rofecoxib doses $p<0.001$.

There was no apparent advantage in efficacy between rofecoxib 25 and 125 mg QD.

Study 029. Phase II, six-week dose ranging study of rofecoxib in patients with OA.

1. Design: multi-center, US, randomized, double-blind, parallel, placebo-controlled study in 672 patients with OA of the knee or hip.

2. Treatment: Placebo, rofecoxib 5, 12.5, 25 and 50 mg QD.

3. Entry criteria: see general description.

4. Demographics: see general study characteristics (Appendix 2)

5. Efficacy end points: the reader is referred to Table 4.

6. Results:

6.1 - Randomization and accounting (Table 9)

Table 9. Study 029. Patient randomization and accounting

Patients randomized / evaluable for ITT	**Placebo 145/139**	**5 mg/d 149/147**	**12.5mg/d 144/143**	**25mg/d 137/135**	**50mg/d 97/97**
Discontinued (% of randomized patients)	23.4	16.8	15.3	10.2	12.4
Lack of efficacy	19.3	10.1*	8.3*	4.4**	3.1**
Adverse events	1.4	4.0	3.5	5.1	5.2

*p < 0.05 vs. placebo. **p< 0.001 vs. placebo.

The number of patients who discontinued due to lack of efficacy in the placebo group was statistically significantly different than the rofecoxib groups. Discontinuations due to lack of efficacy were evenly distributed among different doses. The incidence of adverse events was numerically higher in the active treatments compared to placebo but the difference was not statistically significant. It is important to note that this was a six-week study and that the incidence of adverse events with rofecoxib 50 mg was not significantly higher than with the 25 mg dose. However, in longer studies the 50 mg dose showed an increased incidence of adverse events. (For complete table of accounting, Appendix A.6.1)

6.2 - Efficacy analysis (Table 10, Appendix.6.2 and 6.3)

All doses of rofecoxib showed statistically significant difference with placebo (p<0.001) for all primary and secondary efficacy endpoints. Rofecoxib 25 mg/day was no different from the 12.5 mg/day dose but **the 50 mg dose showed a statistically significant difference when compared to 25 mg in all thee primary endpoints and most secondary endpoints.**

Table 10. Study 029. Analysis of primary end points. LS Mean change from baseline over the 6 week period .

Endpoint	Placebo (139)	5 mg (147)	12.5mg (143)	25mg (135)	50mg (97).
Primary					
WOMAC Pain Walking in flat surface (VAS 0 to 100 mm)	−17.5	-31.5	-31.8	-33.0	- 41.1 * [a]
Pt Global Response to Therapy (Likert 0 to 4)	-1.2	-2.0	-2.2	- 2.3	-2.6 * [b]
Investigator Global of Disease Status (Likert 0 to 4)	-0.7	-1.2	-1.4	-1.4	-1.7 * [c]

* Statistically significant difference between 50 and 25 mg QD. a. p=0.008; b. p=0.039; c. p=0.006. Data from NDA Table 23 study 029.

For most secondary end points (WOMAC Physical Function Subscale, Stiffness Subscale, Investigator Global of Disease Status, Discontinuation due to lack of efficacy), and other endpoints (Pain Subscales, Total Score Average and Subscale Average) rofecoxib 50 mg QD was statistically significant different from rofecoxib 12.5 and 25 mg QD. Of note, there was no statistically significant difference between rofecoxib 12.5 and 25 or even between 5 and 25 mg QD for the same endpoints. (Appendices 6.4).

Reviewer's comment: In summary, rofecoxib at the dose of 50 mg QD showed a consistent statistically significant difference in LS Mean changes from baseline when compared to the 25 mg dose for all primary endpoints and most secondary endpoints. The differences between 50 and 25 mg QD were numerically greater than the differences between the 25 and 12.5 mg dose and between the 12.5 and 5 mg dose.

<u>**010 and 029** integrated analysis</u>

To combine the results of these two studies the applicant performed a sophisticated "pre-specified integrated analysis" and generated "a best fitted curve" (Appendix 7.1).

The "pre-specified integrated analysis" will not be described in this clinical review. See Statistical review for more details.

These trials were different regarding size, doses studied and patient population. If they were to be combined, they should have been weighted differently. The FDA statistical reviewers consider that the integrated analysis performed by the applicant is not appropriate.

The applicant also conducted a different kind of combined analysis, looking at the percentage of patients with good or excellent responses in both studies. In study 029, rofecoxib 50 mg QD showed a higher percentage of patients with good or excellent responses than the 25 mg QD group. However, in study 010, patients in both the 25 mg group and the placebo group had better responses than in study 029 (Table 11).

Table 11. Percent of patients with good/excellent response in studies 029 and 010.

Assessment by:	Study 029					Study 010		
	Placebo	5 mg	12.5 mg	25 mg	50 mg	Placebo	25 mg	125 mg
Investigator	22	44	55	59	75	33	78	80
Patient	21	45	55	58	67	30	72	84

Data from reference 324 of the NDA.

Reviewer's comment: There is no obvious explanation as to why the 25 mg dose was more effective in study 010. Study 010 was just a pilot, exploratory study with small number of patients. We tend to give more relevance to study 029 because it was a larger study. (For comparison see Appendix A.7.2). One additional confounding factor is the use of different formulations. Study 010 used formulation A (a 25 % formulation). Study 029 used formulation B. (None of them were the formulation to be marketed, formulation C). However, all formulations seemed to have similar steady state concentration and it is unlikely that this is the explanation for the different results.

Study 029-10, Six-month extension to study 029.

1. Design: multi-center, US, randomized, double-blind, parallel, placebo and active-comparator controlled study in 467 patients with OA of the knee or hip. (Appendix 7.3)

2. Treatment: rofecoxib 12.5, 25 and 50 mg QD and diclofenac 50 mg TID.

3. Entry criteria:

Only patients who qualified at visit 5 of the base study were evaluated to be randomized for the extension. Patients who had been randomized to placebo or 5 mg in the Base Study were randomly allocated to 12.5 (25%) or 25 mg (25%) Rofecoxib-966 or 150 mg diclofenac (50%) in the Extension. Fifty percent of patients allocated to 12.5 mg in the Base Study remained on the same therapy in the Extension. The remaining 50% underwent dose escalation to 25 mg. In an analogous manner, 50% of patients treated with 25 mg in the Base Study remained on 25 mg, while the remaining 50% underwent dose escalation to 50 mg. All of the Extension patients treated with 50 mg in the Base Study remained on 50 mg.

4. Demographics: see general study characteristics Appendix.2

5) Efficacy end points:

Same efficacy end points were measured, but for this study, Patient Global Assessment of Response to Therapy was considered secondary, and Patient Global of Disease Status was considered a primary end point. Similar to study 029, WOMAC Pain Walking on Flat surface and Investigator Global Assessment of Disease Activity were the other two primary endpoints.

Patients were then seen following 8, 16, and 24 weeks of the Extension therapy (Treatment Weeks 14, 22, and 30). Patients who completed 24 weeks of Extension therapy without clinically significant drug-related toxicity were eligible to continue in an additional Extension protocol (029-20).

6) Results

Reviewer's comment: One of the objectives of this study was to determine the effect of dose escalation measured by the extent of a double-blind increase in the dose of study medication on clinical efficacy endpoints. Only 467 out of the 672 patients who originally entered study 029 were enrolled into the extension. This was a crossover study with eleven possible combinations of sequences and a small number of patients in each group, making the results very difficult to interpret.

6.1. - Randomization (Table 12) For complete randomization and accounting see Appendix 7.4)

Table 12. Number of patients randomized to each sequence in study 029-10

	Treatment (Base/extension)	N
"LOW"	Placebo/12.5 mg	23
	Placebo/25 mg	19
	Placebo/Diclofenac	47
	5 mg/12.5 mg	31
	5 mg/25 mg	26
	5 mg/Diclofenac	43
"HIGH"	12.5 mg/12.5 mg	48
	12.5 mg/25 mg	50
	25 mg/25 mg	51
	25 mg/50 mg	50
	50 mg/50 mg	50

6.2 - Efficacy analysis

Analysis of primary endpoints after 2 weeks of extension therapy (week 6 to week 8) showed that patients who underwent dose escalation from placebo or rofecoxib 5 mg in the base study, to rofecoxib 12.5 mg or diclofenac in the extension study, and those who went from rofecoxib 12.5 in the base study to 25 mg QD in the extension, had slight additional improvements. Patients who underwent dose escalation from 25 to 50 mg did not seem to show additional improvement.

> ***Reviewer's comment: It is not surprising that LS Mean changes from week 6 to 8 were smaller in patients who had already received 25 mg of rofecoxib for six weeks, because they had entered the extension study with lower scores of pain and disability than patients who had received placebo, 5 and 12.5 mg doses.***

When analyzing LS Mean changes from the original baseline (week 0) averaged over the complete 6-month period in those patients who continued on the treatment that they had been originally randomized to there was a trend in favor of the 50 mg dose.

Table 13. Study 029-10. Primary end points. LS Mean changes from baseline averaged over 30 weeks.

	Rofecoxib 12.5 mg/d	Rofecoxib 25 mg/d	Rofecoxib 50 mg/d
WOMAC pain walking on flat surface [1]	-34.7	-35.6	-37.3
Patient global of disease Status [1]	-27.2	-29.3	-32.7
Investigator Global of disease status [2]	-1.6	-1.5	-1.8

[1]: 0 to 100 mm VAS. [2]: 1 to 4 Likert scale. From NDA Study report for 029-10.

The differences between 50 and 25 mg QD are not statistically significant but they are numerically greater than the differences between 12.5 and 25 QD for each primary endpoint. (Appendix.7).

As noted above, the small number of patients and the crossover design complicate all interpretations from this study. Even safety data from this study was not presented integrated to rest of the NDA safety data, but only individually.

Reviewer's comment: In summary, regarding dose effect of rofecoxib in OA, there is evidence that rofecoxib 50 mg QD is statistically more efficacious than the 12.5 and the 25 mg QD.

These data have not been replicated. As described below, six-month endoscopic studies (044 and 045) measured only one efficacy endpoint. Safety data from these studies, suggest that there may be some limitations to the chronic use of rofecoxib at doses ≥ 50 mg/d. If that were not the case, higher doses should have been explored to prove that rofecoxib, at the most effective dose, was still superior to non-selective NSAIDS regarding GI adverse events.

1.3. INDIVIDUAL STUDY RESULTS

- Six-week pivotal studies: 033 and 040

Study 033 6-week study in patients with OA.

1. Design: multi-center US, randomized, double-blind, parallel, placebo and active comparator controlled study in 736 patients with OA of the knee or hip.
2. Treatment: Placebo, rofecoxib 12.5 or 25 mg QD and ibuprofen 800 mg TID.
3. Entry criteria: see general entry criteria.
4. Demographics: see Appendix 2.
5. Efficacy endpoints: see Table 4.
6. Results.

6.1 - Patient randomization and accounting

Table 14. Study 033. Patient randomization and accounting for the analysis

	Placebo	Rofecoxib 12.5mg/d	Rofecoxib 25mg/d	Ibuprofen 800 mg TID
Patients randomized / evaluable for ITT	69/68	219/217	227/222	221/218
Discontinued study (% of patients randomized)	27.5*	15.1	11.9	14.5
Lack of efficacy	18.8 *	7.8	4.0	8.6
Adverse events	5.8	5.5	6.6	4.1
Patient withdrew consent	2.9	0.5	0.9	0.9

* $p < 0.05$ from active treatments.

The number of patients who discontinued due to lack of efficacy in the placebo group was higher and statistically significantly different from all other treatment groups. The incidence of discontinuation due to adverse events was evenly distributed among groups.

6.2 - Analysis of efficacy endpoints:

For all measured end points (primary, secondary and "other"): rofecoxib 12.5 mg/d, Rofecoxib 25 mg/d and ibuprofen were statistically different (SSD) from placebo ($P<0.001$). Ibuprofen showed no SSD from rofecoxib 12.5 and 25mg; 12.5 mg showed no SSD from rofecoxib 25 mg (For LS Mean changes from baseline see Table 5 and Appendix A.8).

Study 040. Six week study in patients with OA

1) Design: multi-center non-US, randomized, double-blind, parallel, placebo and active comparator controlled study in 809 patients with OA of the knee or hip.

2) Treatment: Placebo, rofecoxib 12.5 or 25 mg QD, or ibuprofen 800 mg TID.

3) Entry criteria: see general entry criteria, page 5.

4) Demographics: see general study characteristics and Appendix A2

5) Efficacy endpoints: (see table 4)

6) Results.

6.1- Patient randomization and accounting (for complete table see Appendix 9)

Table 15. Study 040. Patient randomization and accounting

Patients randomized / evaluable	Placebo 74 /74	Rofecoxib 12.5 mg 244 /242	Rofecoxib 25 mg 242 / 235	Ibuprofen 800 mg TID 249 /245
Discontinued study (% of patients randomized)	16.2	11.1	10.3	14.5
Lack of efficacy	12.12	3.3*	2.9*	3.6*
Adverse events	1.4**	4.9	3.7**	8.4
Patient withdrew consent	1.4	1.6	2.1	1.6

• $p<0.05$ vs. placebo. ** $p<0.05$ vs. ibuprofen.

The number of patients who discontinued due to lack of efficacy in the placebo group was higher and statistically significantly different from all other treatment groups. The incidence of discontinuation due to adverse events was statistically higher in the ibuprofen group when compared to placebo and rofecoxib 25 mg group.

> ***Reviewer's comment: A relatively large number of patients were excluded from the ITT analysis because of missing data regarding primary endpoints. Of a total of 809 randomized patients, 8 lacked data on WOMAC Pain Walking on flat surface; 13 lacked data on Patient Global Assessment of Response to therapy and 7 lacked data on Investigator Global of Disease status.***

6.2 - Efficacy analysis

All active treatments were statistically different from placebo. See Table 4 for summary of results. Table 5 shows LS Mean changes from baseline. (For more detailed information, Appendix 9.2 to 9.5).

Of note, for Patient Global Assessment of Response to Therapy, there was a statistically significant difference between rofecoxib 25 mg and ibuprofen, in favor of rofecoxib; for Investigator Global Assessment of Disease Status there was a statistically significant difference between rofecoxib 12.5 and ibuprofen, in favor of rofecoxib. These differences were within the limits of clinical comparability predefined by the applicant (±10 mm on the pain VAS and ±0.5 on the Likert scale).

IN SUMMARY, in STUDY 033 and 040, daily doses of rofecoxib 12.5 and 25 mg after six weeks of treatment were consistently different from placebo. The 12.5 and 25 mg/day doses were COMPARABLE to the effect of ibuprofen when using pre-specified criteria of clinical comparability as defined by the applicant.

Analysis of the change in the slope from week 2 to 6 suggested that maximum efficacy was achieved within 2 weeks and maintained thorough the 6 weeks study period.

- 034 and 035: One-year pivotal studies in OA: (first 6 months)

1) Design: **034** (multinational) and **035** (US) were multi-center, double-blind, randomized, parallel, one-year active-comparator controlled studies in patients with OA of the knee or hip.

2) Treatment: Rofecoxib 12.5 or 25 mg QD, or diclofenac 50 mg TID (No placebo).

3) Entry criteria: see general entry criteria. Of note, during the second six months of the one year studies, patients were allowed to take concomitant medications.

4) Demographics: see general study characteristics and Appendix 2.

5) Efficacy endpoints: see Table 4. Efficacy assessments were done at 2, 4, 8, 12, 26, 39 and 52 weeks.

Reviewer's comment: Data from these studies were originally presented separately up to 6 months and pooled for analysis over the 12 month period.

Results:
Study 034

Table 16. Study 034. Patient randomization and accounting (6-month analysis)

Patients randomized/ evaluable	Rofecoxib 12.5mg/d 231 / 223	Rofecoxib 25mg/d 232/226	Diclofenac 50mg TID 230 / 226
Discontinued (percentage of patients randomized)	26.6	21.1	24.3
Lack of efficacy	9.5	8.2	5.6
Adverse events	7.7*	6.4*	13.9
Patient withdrew consent	3.4	1.3	1.7
Protocol deviation	3.4	2.6	0.9

- $p<0.05$ vs. diclofenac.

The number of patient discontinuations was evenly distributed (somewhat lower in rofecoxib 25 mg QD but not statistically significant). The number of patients who discontinued due to adverse events was lower in the rofecoxib groups than in the diclofenac group. This difference was statistically significant. The rate of discontinuation due to lack of efficacy was higher in the rofecoxib groups than in the diclofenac group, but not statistically different.

Reviewer's comment: Although discontinuation due to consent withdrawal is usually a negligible cause of discontinuation, it seems to be a little high in this protocol. Discontinuation due to withdrawal of consent, appears to be a surrogate for lack of efficacy or for toxicity to this reviewer, since patients who think that the drug is working would never want to stop the treatment. The % of deviation from protocol also seems higher compared to other studies.

Efficacy analysis

Table 17. Rofecoxib efficacy in study 034. Analysis of primary endpoints after 12 and 26 weeks.

	WOMAC Pain Walking		Investigator Global DS.		Patient Global Response	
	12 weeks	26 weeks	12 weeks	26 weeks	12 weeks	26 weeks
Rfx 12.5 mg	-30.2*	-31.1	-2.2*	-2.2*	-1.4*	-1.4*
Rfx 25 mg	-32.5	-33.1	-2.2*	-2.2*	-1.5*	-1.5*
Diclofenac 150 mg	-35.4	-35.3	-2.4	-2.4	-1.6	-1.6

Statistical comparison to diclofenac $p< 0.05$.

Analysis after 12 weeks (Table 17, Appendix 10.1)

The primary analysis of efficacy, based on the assessment of primary efficacy endpoints averaged over 12 weeks showed that:

- Rofecoxib 12.5 mg QD was not statistically different from rofecoxib 25 QD.
- Rofecoxib 12.5 mg QD was consistently statistically different from diclofenac (in favor of diclofenac) in all primary endpoints.
- Rofecoxib 25 mg/day was statistically different from diclofenac (in favor of diclofenac) in Patient Global assessment of Response to Therapy, Investigator Global of Disease Status (two out of three primary endpoints) and Patient Global of Disease Status (a secondary endpoint in this study). The differences, however, were within the range of clinical comparability pre-defined by the applicant.

Table 18. 034. Statistical comparison of LS Mean changes from baseline over a 12-week period (ITT).

Efficacy end point	12.5 vs 25	12.5 vs diclo	25 vs diclo
WOMAC walking on flat *	No SSD	SSD	No SSD
Pt Global of response to therapy * Investigator Global of disease status* Pt Global of disease status	"	"	SSD
WOMAC Physical Function , Pain Stiffness Total Score Average Subscale Average	"	"	No SSD

* Primary endpoints. LS Mean Changes in secondary endpoints were in a similar direction than for primary endpoints. (For details see Appendix A.10.2)

Analysis after 26 weeks (secondary analysis)

Statistical comparisons of LS Mean changes from baseline averaged over the 6-month period showed very similar results to the 12 week analyses, except that in addition to the 12.5 mg dose, the 25 mg dose was also statistically significant different from diclofenac (in favor of diclofenac) for two out of three primary endpoints. Again, the differences were within the range of clinical comparability (Appendix 10.3 and 10.4)

Reviewer's comment: It is not surprising that the changes from baseline after 26 weeks are very similar to the ones after 12 weeks, because there were no efficacy assessments between week 12 and 26, and as mentioned earlier, the major contribution to the average value is given by the frequent visits at the beginning of the study.