

APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety

APPROVe was designed to evaluate the efficacy of rofecoxib 25 mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. As previously reported in the 156-week base study, there was an increased relative risk for confirmed thrombotic cardiovascular events beginning after 18 months of treatment in the patients taking rofecoxib compared to those taking placebo. The APPROVe protocol called for a one-year off-drug extension to address recurrence of polyps, confirmed thrombotic cardiovascular events and mortality. This report will provide data on confirmed thrombotic cardiovascular events and mortality from the off-drug extension. Recurrence of polyps will be addressed in a separate report.

Confirmed Thrombotic Cardiovascular Events and Mortality

Statistical Approach to the Data

The primary analysis for the on-drug base study included data for all 2587[†] patients through day 14 post-discontinuation of study therapy.

The primary analysis for the off-drug extension used an intention to treat (ITT) approach to data analysis and thus included data both on study therapy and post-discontinuation.

The secondary analysis for the off-drug extension considered only the data from each patient's off-drug period (that is, data starting on day 15 post-discontinuation of study therapy) and did not consider events during the on-drug period.

Additional analyses evaluated data from the off-drug period for subgroups of patients who had different lengths of on-drug exposure before discontinuing from the base study. These analyses explored the relative risks of events after stopping therapy in patients with up to 6 months, 18 months, and approximately 3 years on-drug experience.

Three approaches were taken to the primary and secondary analyses based on different censoring rules. There were 2 prespecified rules: 1) data censored at Week 210, the time at which a patient would have finished the base study plus one year follow-up, and 2) data censored at an October 31, 2005 cut-off date, which would represent an approximately 1- year follow-up after the last patient's final visit in the base study. This provided data in some patients out as far as week 299. A third approach included all information before and after the October 31, 2005 analysis cut-off date that was available in-house as of March 15, 2006[‡]. This provided data in some patients out as far as week 306.

[†]One patient, AN 91495, previously thought to have been randomized to rofecoxib 50 mg, had in fact been randomized to placebo. This patient discontinued therapy after 37 days without having had an AE and without colonoscopy.

[‡] Follow-up data remain outstanding from 1 investigator site that had randomized 17 patients.

The primary endpoint was confirmed thrombotic cardiovascular events. The Anti-Platelet Trialists' Collaboration (APTC) endpoint was secondary.

In general, the results using the 3 censoring approaches were similar. The report will focus on confirmed thrombotic cardiovascular event data through Week 210 and highlight differences using the other approaches and other endpoints.

ITT Analysis, Confirmed Thrombotic Cardiovascular Events

Among the 2,587 patients enrolled in the APPROVe study, confirmed thrombotic cardiovascular event data for the period beginning on day 15 after discontinuation of study therapy were available for 2,178.

The APPROVe off-drug extension provided additional data to what had been obtained in the base study. A total of 74[§] patients had confirmed thrombotic cardiovascular events in the base study. There were 39 additional patients with a first confirmed thrombotic cardiovascular event in data through week 210 and a further 9 patients with a first confirmed thrombotic cardiovascular event in data through October 31, 2005. There were 5 additional patients with first confirmed thrombotic cardiovascular events after the October 31, 2005 cut-off date.

The relative risk of patients having confirmed thrombotic cardiovascular events in the 156-week on-drug base study was 1.92 (95% CI 1.19, 3.11, p=0.008). The difference remained significant after including data from the off-drug follow-up period. In the ITT analysis through week 210 the relative risk was 1.74 (95% CI 1.19, 2.55, p=0.004).

In the 156-week on-drug base study, the relative risk of patients having confirmed thrombotic cardiovascular events was not constant over time: 1.18 (95% CI 0.64, 2.15) for the first 18 months and 4.45 (95% CI 1.77, 13.32) for the period beyond month 18. In the ITT analysis up to Week 210, the relative risk of confirmed thrombotic cardiovascular events for the first 18 months was 1.27 (95% CI 0.71, 2.25). The relative risk beyond month 18 was 2.22 (95% CI 1.32, 3.73). In comparing these datasets, the relative risks for the first 18 months are similar. However, in the period beyond month 18, the relative risk for rofecoxib compared to placebo in the ITT analysis of 210-week data is approximately half what had been observed in the on-drug analysis of the 156-week data.

Between-group differences in myocardial infarction were observed both in the base study and in ITT analyses of the base study plus off-drug follow-up data. In the ITT analysis up to Week 210, there were 31 patients with myocardial infarction in the rofecoxib group and 15 in the placebo group (p=0.017). Between-group differences in ischemic cerebrovascular accidents were observed in the ITT analyses. In the ITT analysis up to Week 210, there were 17 patients with ischemic cerebrovascular accidents in the rofecoxib group and 6 in the placebo group (p=0.024).

[§] MRL learned of thrombotic events in 2 patients in the study subsequent to finalization of the APPROVe clinical study report on 15-Mar-2005. AN 91133, rofecoxib group, had confirmed myocardial infarction on relday 684. AN 90052, placebo group, had confirmed peripheral artery occlusion on relday 784.

Off-Drug Extension data, Confirmed Thrombotic Cardiovascular Events

The off-drug extension secondary analyses considered only the data from each patient's off-drug period (that is, data starting on day 15 post-discontinuation of study therapy) whether or not the patient had an event in the on-drug period. This was considered a conservative approach to the analysis. There were 44 patients with confirmed thrombotic cardiovascular events in patients with follow-up data through week 210. Of these, 5 had a first confirmed thrombotic cardiovascular event in the base study (4 in the rofecoxib group and 1 in the placebo group). There were an additional 9 patients with confirmed thrombotic cardiovascular events in patients with follow-up data through October 31, 2005.

There were 28 patients through week 210 with confirmed thrombotic cardiovascular events in the group previously on rofecoxib compared to 16 in the group previously on placebo, a difference that was not statistically significant (relative risk 1.64, 95% CI 0.89, 3.04, $p=0.115$).

The numeric difference between groups in confirmed thrombotic cardiovascular events observed during the off-drug period was mainly due to patients who experienced a confirmed ischemic cerebrovascular accident. In data through week 210, there were 7 patients in the group previously on rofecoxib and 0 in the group previously on placebo with confirmed ischemic cerebrovascular accident ($p=0.022$). In data through October 31, 2005, there was 1 additional patient in the group previously on rofecoxib and 0 in the group previously on placebo with confirmed ischemic cerebrovascular accident ($p=0.010$); in data beyond the October 31, 2005 cut-off date, there were 2 additional patients in the group previously on placebo with confirmed ischemic cerebrovascular accident. Including all available data, there were a total of 8 patients in the group previously on rofecoxib and 2 in the group previously on placebo with confirmed ischemic cerebrovascular accident ($p=0.134$).

Analyses of off-drug data in patients with different duration of treatment in the base study

An analysis of the off-drug extension was performed for those patients who completed the on-drug base study^{**}. This analysis thus explored the relative risks of events after stopping therapy in patients with the longest on-drug experience.

Among the 2,587 patients enrolled in the APPROVe study there were 1857 patients who completed the on-drug base study. Off-drug extension data were available for 1721 (93%) patients. There were 15 patients through week 210 with confirmed thrombotic cardiovascular events in the group previously on rofecoxib compared to 9 in the group previously on placebo (RR=1.85, 95% CI 0.81, 4.22, $p=0.146$). This is notably less than the relative risk for patients in the on-drug base study during the interval from month 19 through 36 (RR=4.45, 95% CI 1.77, 13.32).

Analyses for the off-drug extension were also performed for those patients who completed: 1) 6 months or less of the on-drug base study, and 2) 18 months or less of the on-drug base study. These analyses thus explored the relative risks of events after stopping therapy in patients with shorter on-drug experience.

^{**} Patients were considered to have completed the base study if they were on drug for at least 150 weeks.

Off-drug extension data were available for 99 patients in the rofecoxib group who completed 6 months or less of the on-drug base study and 53 patients in the placebo group. There were 6 patients through week 210 with confirmed thrombotic cardiovascular events in the group previously on rofecoxib compared to 3 in the group previously on placebo (RR=1.10, 95% CI 0.23, 6.77).

Off-drug extension data were available for 174 patients in the rofecoxib group who completed 18 months or less of the on-drug base study and 118 patients in the placebo group. There were 8 patients through week 210 with confirmed thrombotic cardiovascular events in the group previously on rofecoxib compared to 5 in the group previously on placebo (RR=1.04, 95% CI 0.34, 3.19).

Mortality

Among the 2,587 patients enrolled in the APPROVe study, mortality data for the period beginning on day 15 after discontinuation of study therapy were available for 2,448. Mortality rates were similar between groups in all analyses performed.

Conclusions

- For the first 18 months, the relative risk of confirmed thrombotic cardiovascular events for rofecoxib compared to placebo in the ITT analysis was similar to that observed in the on-drug base study.
- Beyond 18 months, the relative risk of confirmed thrombotic cardiovascular events for rofecoxib compared to placebo in the ITT analysis was approximately half of that observed in the on-drug base study. This lowering of the relative risk was mostly due to the off-drug follow-up data observed during the period beyond month 36 and to the off-drug follow-up data in patients who prematurely discontinued study therapy.
- There was no statistically significant increased relative risk of confirmed thrombotic cardiovascular events for rofecoxib compared to placebo in off-drug follow-up data in all patients regardless of when they discontinued therapy as well as in those who completed 150 weeks of on-drug treatment in the base study. In these analyses, data are insufficient to conclude that there was an increased relative risk following discontinuation of therapy.
- Mortality was similar between groups.