

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-024/S-005**

**STATISTICAL REVIEW(S)**

HFD-590  
Willard

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**STATISTICAL REVIEW AND EVALUATION**

**NDA#:** 21-024, SE7-005

**Name of Drug:** PRIFTIN® tablets (rifapentine)

**Applicant:** Hoechst Marion Roussel

**Indication(s):** treatment of pulmonary tuberculosis

**Documents Reviewed:** Volume 1, dated Dec. 17, 1999

**Review Type:** Clinical data

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**I. INTRODUCTION**

NDA 21-024, submitted for the use of Priftin (rifapentine) tablets in the treatment of pulmonary tuberculosis, was approved under Accelerated Approval Regulations (21 CFR 314.510) on June 22, 1998. This approval was based on the results from ongoing Study 008, entitled "Efficacy and Safety of Rifapentine Combination Therapy Compared to Standard Therapy in the Treatment of Previously Untreated Pulmonary Tuberculosis". Six month follow-up data from this study was used as a surrogate for the 2 year follow-up generally accepted as evidence of efficacy in the treatment of pulmonary tuberculosis. As part of the accelerated approval, Hoechst Marion Roussel was required to submit Study 008 upon completion. This supplemental NDA contains the final results (2 year follow-up) from Study 008.

In general, results from the final report for Study 008 are similar to those seen in the interim study report submitted with NDA 21-024. There is a higher percentage of patients who were lost to follow-up in the final report, however, which increases the uncertainty associated with the results.

Section II summarizes the results from the final clinical report for Study 008. Section III provides conclusions.

**II. STUDY 008 (FINAL CLINICAL REPORT)**

Study 008 was a Phase III, open-label, randomized, multicenter study of rifapentine combination therapy versus rifampin combination therapy. A total of 722 patients were randomized to study drug, 361 to each treatment arm. Patients were treated for 6 months (60 days of "intensive phase" therapy followed by 120 days of "continuation phase" therapy) and then followed for two years. For the original NDA, 6 month relapse

rates were of primary interest. In this submission, 2 year relapse rates are of primary interest.

Among patients who converted, six month relapse rates (from the sponsor's analysis in the original NDA) were higher on the rifapentine arm, 6.4% (16/251) versus 2.6% (6/234). This difference is marginally statistically significant ( $p=0.05$  using Fisher's exact test). The 95% confidence interval for the difference in relapse rates, rifapentine minus rifampin, is (-0.2%, 7.9%) using the normal approximation to the binomial distribution with a continuity correction. The odds ratio corresponding to this difference is 2.59, with an asymptotic, corrected 95% confidence interval of (0.97, 5.76), suggesting that the odds of relapsing for patients who receive rifapentine are approximately 2 ½ times the odds for those receiving rifampin (an odds ratio of 1 implies no treatment difference).

The advisory committee that was convened to discuss the original NDA felt that rifapentine should be approved even in light of these results. One reason was that the two drug regimens were similar in converting sputum cultures to negative at the end of treatment (6 months). Another reason was that during the intensive phase of treatment (when rifapentine was administered twice weekly, while rifampin and all companion medications were administered daily), the rate of noncompliance with companion medications was somewhat higher for the rifapentine regimen than for the rifampin regimen. Noncompliance with companion medications was found to be a risk factor for relapse (note that this was an exploratory analysis). The approved label stressed the importance of taking all companion medications.

In the original NDA submission, there was also a significant difference between treatments when relapse at any time during follow-up was considered. These rates, which are in the current label, were 10% (25/249) for rifapentine and 5% (11/229) for rifampin ( $p=0.037$  using Fisher's exact test). The 95% confidence interval for the difference in relapse rates, rifapentine minus rifampin, is (0.2%, 10.3%) using the normal approximation to the binomial distribution with a continuity correction. The odds ratio corresponding to this difference is 2.21, with an asymptotic, corrected 95% confidence interval of (1.04, 4.00). Note that these rates assume that patients who were lost to follow-up did not relapse. Nine percent (23/249) of rifapentine patients and 6% (13/229) of rifampin patients were lost to follow-up at the time of this analysis.

The results in the current submission (i.e., from the final study report) are given in Table 1.

**Table 1. Clinical Outcome in Study 008\***

	Rifapentine Combination	Rifampin Combination
<b>Status at End of Treatment</b>		
Converted	87% (248/286)	80% (226/283)
Not Converted	1% (4/286)	3% (8/283)
Lost to Follow-up	12% (34/286)	17% (49/283)
<b>Status through 24 Month Follow-up</b>		
Relapsed	12% (29/248)	7% (15/226)
Sputum Negative	57% (142/248)	64% (145/226)
Lost to Follow-up	31% (77/248)	29% (66/226)

\*All data for patients with confirmed susceptible pulmonary tuberculosis.

Conversion rates were higher for rifapentine patients, but relapse rates were also higher for rifapentine patients. If we exclude patients who were lost to follow-up, the relapse rates are 17% (29/171) for rifapentine patients and 9% (15/160) for rifampin patients ( $p=0.052$  using Fisher's exact test; 95% confidence interval for the difference in rates, rifapentine minus rifampin, of (-0.2%, 15.4%) using the normal approximation to the binomial distribution incorporating the continuity correction). The odds ratio corresponding to this difference is 1.97, with an asymptotic, corrected 95% confidence interval of (1.00, 3.17). If we assume that patients who were lost to follow-up relapsed, the relapse rates are 43% (106/248) for rifapentine patients and 36% (81/226) for rifampin patients ( $p=0.13$  using Fisher's exact test; 95% confidence interval for the difference in rates, rifapentine minus rifampin, of (-2.3%, 16.1%) using the normal approximation to the binomial distribution incorporating the continuity correction). The odds ratio corresponding to this difference is 1.34, with an asymptotic, corrected 95% confidence interval of (0.95, 1.49). Finally, if we assume that patients who were lost to follow-up did not relapse, relapse rates are 12% (29/248) for rifapentine patients and 7% (15/226) for rifampin patients ( $p=0.08$  using Fisher's exact test; 95% confidence interval for the difference in rates, rifapentine minus rifampin, of (-0.5%, 10.6%) using the normal approximation to the binomial distribution incorporating the continuity correction). The odds ratio corresponding to this difference is 1.86, with an asymptotic, corrected 95% confidence interval of (0.96, 3.12).

Excluding patients who were lost to follow-up, relapse rates are approximately double on the rifapentine arm (17% versus 9%). The absolute difference and odds ratio are smaller using the two other estimation techniques discussed above as both impute the same type of response for a patient, regardless of which treatment they received. Generally, relapse rates appear to be higher on the rifapentine arm. There is a substantial amount of missing data, however, which weakens any conclusions that can be drawn from this study. Approximately a third of all patients who converted were lost to follow-up.

### III. CONCLUSIONS (Which May be Conveyed to the Applicant)

The applicant submitted the final report for Study 008, as they were required to do under their accelerated approval for NDA 21-024. In general, results were similar to those seen at the time of the original NDA submission, when Study 008 was ongoing. In the final report, conversion rates are somewhat higher among rifapentine patients. Relapse rates also tend to be higher among rifapentine patients, however (approximately double those of rifampin patients).

The high rate of patients who were lost to follow-up is somewhat concerning. Approximately a third of all patients who converted were lost to follow-up. It might be in the patients' best interest to add a statement to the proposed label cautioning that relapse rates could actually be much higher than they appear due to the fact that we don't know what happened to almost a third of the patients who converted.

**RECOMMENDED REGULATORY ACTION:**

The data provided by the applicant in this submission support continued approval of NDA 21-024, as the final results submitted with this supplemental NDA are similar to those seen at the time of the original submission. Due to the large amount of missing data in this final report, however, appropriate cautionary statements should be added to the label to advise patients that relapse rates could actually be much higher than they appear.

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7/24/00

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