

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21024

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#: 21-024/S-000
APPLICANT: Hoechst Marion Roussel
NAME OF DRUG: Priftin[®] (Rifapentine)
INDICATION: Treatment of Pulmonary Tuberculosis
TYPE OF REVIEW: Clinical
DOCUMENTS REVIEWED: Volume 1.1, 1.69, 1.127
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STATISTICAL REVIEW AND EVALUATION

NDA#:

21-024

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1. Background

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1.1 Objectives in Trials

The applicant submitted one randomized, open label, active controlled clinical trial, trial 08. The primary objective of this study was to determine if rifapentine is effective in the treatment of pulmonary tuberculosis as measured by percent of subjects who either never became sputum negative while on treatment or relapsed to sputum positive state during 6 months of treatment and and 24 months of follow-up post treatment. Accelerated approval, the subject of this review was based on 6 months post treatment follow-up. Secondary endpoints were the percent of subjects who became sputum negative during the intensive phase of the treatment and time to sputum conversion from positive to negative during this phase of treatment.

1.2 Summary of Study Design

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Trial 08 was an open label, randomized, two-arm parallel, rifampin-controlled trial conducted at 20 centers in South Africa and 10 centers in North America. The trial population was patients ≥ 18 years old with a presumed diagnosis of previously untreated pulmonary tuberculosis, later confirmed by a sputum culture positive for Mycobacterium tuberculosis.

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The trial was divided into three phases: 60 days of active treatment, intensive phase; 120 days of active treatment, continuation phase; and 6 months of follow-up. During the intensive phase, all subjects received isoniazid 300 mg/day, pyrazinamide 1500 or 2000 mg/day, ethambutol 800 or 1200 mg/day, pyridoxine 50 mg/day, and the randomized drug: either the control rifampin at 450 or 600 mg/day or the test rifapentine at 600 mg twice/week. During the continuation phase, all subjects received isoniazid 600 or 900 mg twice/week, pyridoxine 50 mg twice/week and the randomized drug: either the control rifampin at 450 or 600 mg twice/week or the test rifapentine at 600 mg once/week. In all cases, where two doses of a drug were possible, the lower (higher) dose was given to subjects weighing <50 kg (≥ 50 kg).

Patients were randomly assigned to the rifampin or the rifapentine arm in a 1:1 ratio. Randomization was stratified by center.

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1.3 Patient Accounting and Baseline Characteristics

722 patients were randomized, 361 to each arm. Of these 722, 570 were considered to be ITT patients because they also had at least one post-baseline efficacy measurement. Most of the exclusions were for negative or drug resistant baseline cultures. See table 1.3 A. Of the 570 patients in the (modified) ITT analysis, 284 were assigned to rifampin and 286 to rifapentine. The largest center had 76 patients (13% of the patients in the modified ITT population). The 15 smallest centers had fewer than 10 patients each and held among them 12% of the modified ITT population.

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TABLE 1.3 A
MODIFIED ITT SUBSET, TRIAL 08

	Rifampin	Rifapentine
Randomized	361	361
Baseline Culture Negative	56	59
Baseline Culture Missing	2	0
Baseline Isolate Resistant to Study Medication	14	11
Pregnancy	3	4
Otherwise Not ITT	3	3
Used in ITT Analysis	284	286

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The study populations in the two arms were male and predominately Black, with mean ages of 37 years. The underlying risk factors for TB were similarly distributed between arms, with unemployed for at least one year, living communally, and consuming alcohol at a rate ≥ 1 drink/day. Clinical signs and symptoms were also similarly distributed and all but one subject had abnormal baseline chest x-rays.

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Table 1.3 B gives the completion status for the modified ITT subset by arm.

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TABLE 1.3 B
TREATMENT COMPLETION, TRIAL 08

	Rifampin	Rifapentine
Modified ITT	284	286
Withdrew Intensive Phase	21	15
Adverse Event	4	2
Patient Choice	12	7
Other	5	6
Completed Intensive Phase	263	271
Withdrew Continuation Phase	26	18
Adverse Event	3	1
Patient Choice	13	13
Therapeutic Failure	2	0
Other	8	4
Completed Continuation	237	253
Withdrew Follow-up Phase	24	44
Adverse Event	0	3
Patient Choice	0	2
Therapeutic Failure	5	13
Other	0	1
Lost During Follow-up	19	25

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1.4 Summary of Methods of Assessment

Sputum specimens for smear/culture were collected from patients at screening (day 0), on day 1 prior to first study drug administration, on day 2, for two consecutive days beginning on days 14, 30, 60, 90, 120, 150, and 180, and once each at the ends of months 3, 6, 12, 18, and 24 after the 180 days of treatment.

The primary efficacy endpoint for this accelerated approval review was treatment outcome at the end of 12 months (6 months of active treatment + 6 months of follow-up). This was a binary variable with success defined as achieving a negative sputum culture during active treatment and sustaining it to the end of 5-7 months of follow-up. (A margin of ± 1 month was allowed in the timing of the 6 month follow-up culture.) Non-successes occurred in three ways. 'Treatment failures' still had positive sputum cultures at the end of active treatment. 'Relapses' had negative sputum cultures at the end of active treatment but had either one follow-up culture with at least 10 colonies or two follow-up cultures with 1-9 colonies. Patients who withdrew for

any reason were the other non-successes. Missing cultures were considered negative if the preceding and succeeding cultures were negative.

This endpoint is a surrogate marker for the endpoint of interest. The final endpoint is proportion converted during treatment and still negative after two years of follow-up. The current analysis is in support of an accelerated approval. The final analysis of the data from this trial will use the results at the end of two years follow-up.

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The primary analysis for accelerated approval counted all patients without 6-months of follow-up data as non-successes. Three supplemental analyses treated 1) only observed treatment failures and relapses as non-successes and all others as successes, 2) lost to follow-up without observed treatment failure or relapse as missing, and 3) only administratively censored patients as missing with all others as non-successes. Administratively censored patients are those who were still sputum negative and still being observed as scheduled at the time of the interim analysis.

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Other secondary endpoints were 1) treatment success at the end of the intensive phase, 2) treatment success by the end of the continuation phase, 3) times to conversion of sputum from positive to negative, and 4) percent of relapses.

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1.5 Summary of Statistical Analysis

Analyses were modified intent-to-treat (ITT) analyses, using all patients who received at least one dose of study medication, had a positive culture at baseline, had non-resistant organisms at baseline, and had at least one valid post-baseline measurement. As table 1.3 A shows 72 out of 78 rifampin subjects and 70 out of 77 rifapentine subjects were dropped from the modified ITT analysis for negative or resistant baseline cultures.

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The applicant considered clinical equivalence on the primary endpoint of success rate and on the secondary endpoints of success with modified definitions to be no more than 10% worse than rifampin with two-sided 95% confidence. Large sample

approximations to the binomial distribution were used for the confidence intervals.

Time to sputum conversion was analyzed by the Kaplan-Meier curve and the log-rank test, treating both administratively censored patients and lost-to-follow-up patients as censored. Recall that this variable is a waiting time until to success, not a waiting time until failure.

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Subgroup analyses were conducted by separate binomial tests within each category. The subgroups analyzed were 1) above or below 35 years age, 2) gender, 3) continent, 4) above or below 50 kg in weight, and 5) race.

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2. Summary of Applicant's Results

2.1 Efficacy

Table 2.1 A shows the success rates at the end of the first six months of follow-up for each arm together with the 95% confidence interval for rifapentine success rate minus rifampin success rate. Higher values for this difference and its confidence limits indicate better performance for rifapentine. The primary and three supplemental definitions of success and non-success are included.

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TABLE 2.1 A
SIX MONTH FOLLOW-UP SUCCESS RATES BY ARM
(95% CONFIDENCE LIMITS FOR DIFFERENCE)

Definition of Success or Failure	Rifampim	Rifapentine	Rifapentine - Rifampin
LTFU = Failure	106/284 = 37%	115/286 = 40%	2.9% (-5.1%, 10.9%)
LTFU = Success	273/284 = 96%	269/286 = 94%	-2.1% (-5.6%, 1.5%)
LTFU = Missing	106/117 = 91%	115/132 = 87%	-3.5% (-11.3%, 4.3%)
AdCen = Missing	106/162 = 65%	115/170 = 68%	2.2% (-7.9%, 12.4%)

LTFU = Lost to Follow-up,
AdCen = Administratively Censored

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The applicant briefly noted that there was a higher relapse rate on rifapentine but did not comment in their submission on the statistical significance or clinical importance of this issue. Their comparison of relapse rates is given in table 2.1 B.

TABLE 2.1 B
RELAPSE COUNTS BY ARM & LENGTH OF FOLLOW-UP

Duration of Follow-Up	Rufampin N = 234	Rifapentine N = 251
3 Months	5	14
6 Months	1	2
12 Months	0	1

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3. Summary of Applicant's Conclusions

The applicant considered rifapentine 600 mg twice/week for 3 months followed by 600 mg once/week for another 3 months to have demonstrated clinical equivalence to rifampin 450 or 600 mg daily for 3 months and twice/week for another 3 months in achieving and sustaining TB negative sputum cultures for up to a year after start of treatment.

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Subsequent to their submission, the applicant also asserted that the increased relapse rate with rifapentine was partly due to confounding with differential levels of compliance with the non-rifamycin drugs in the regimen.

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4. Statistical Reviewer's Comments and Analyses

There are two issues of concern with respect to this NDA. The first is whether the conclusion of comparable conversion rates is sensitive to missing data. The second is the extent to which the arms differ in relapse rates. In more detail, there are issues as to relapse rates over different periods of follow-up and as to differences in relapse rates among different strata of covariates. This review will address these two main issues.

4.1 Differences between FDA and Applicant Populations

The FDA clinical reviewers recommended using a slightly smaller set of subjects than did the applicant. In their judgment, certain patients should have been excluded on the grounds of violation of inclusion-exclusion criteria. Table 4.1 A gives the counts of these extra exclusions with the reasons for exclusion.

TABLE 4.1 A
EXCLUSION OF RANDOMIZED PATIENTS

	RIFAMPIN	RIFAPENTINE
Randomized	361	361
Excluded by Applicant [†]	77	75
Excluded by FDA	14	7
HIV Positive	8	4
Resistant at Baseline	5	3
Both	1	0
In FDA Modified ITT	270	279

[†] See Table 1.3 A

4.2 Comparison of Conversion Rates

Using the FDA's modified ITT population, the distribution of subjects with respect to their status at the end of treatment is given in table 4.2 A. The times of loss for the 38 subjects who did not complete treatment were mostly early and similar in the two arms.

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TABLE 4.2 A
 PATIENT STATUS AT END OF TREATMENT

	RIFAMPIN	RIFAPENTINE
Modified ITT	270	279
Dropped Trtment Early	38	30
Last Visit Positive	15	9
Last Visit Negative	8	9
Last 2 Visits Negative	15	12
Finished Treatment	232	249
Did Not Convert	9	4
Converted	223	245

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Simple comparisons of the conversion rates are given in table 4.2 B. This table gives the number converted and the number not converted by end of treatment under 5 sets of assumptions about the subjects lost to follow-up (LTFU). These subjects are, successively, 1) excluded from analysis, 2) counted as not converted in both arms, 3) counted as converted in both arms if the last culture was negative and as not converted in both arms if the last culture was positive, 4) counted as not converted in the rifapentine arm but counted as converted if the last culture was negative in the rifampin arm, and 5) counted as not converted in the rifapentine and as converted in the rifampin arm. For each method, the table gives the number converted and not converted on rifampin and rifapentine, the conversion rates and their 95% confidence intervals on each arm, and the difference in conversion rates, for rifapentine - rifampin with 95% confidence intervals.

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One can see from this table that conversions slightly favor rifapentine, with 95% lower confidence limits of 0 to -1% if lost to follow-up are treated the same way on both arms (methods 1-3 above). Even assuming that the lost to follow-up convert only on rifampin, the 95% lower confidence bounds is -8% if lost subjects convert only if their last culture is negative and they were on rifampin. A large, unfavorable difference of -13% (lower confidence limit) is obtained only by assuming that all losses to follow-up on rifampin, even those with last culture positive, convert and none of the losses on rifapentine convert.

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TABLE 4.2 B
CONVERSION RATES AND CONFIDENCE LIMITS

HOW LTFU HANDLED	RIFAMPIN			RIFAPENTINE			DIFFERENCE
	CONV	NOT	RATE	CONV	NOT	RATE	
LTFU DROPPED	223	9	96%	245	4	98%	2%
			(94%, 99%)			(97%, 100%)	(-1%, 5%)
LTFU = FAIL	223	47	83%	245	34	88%	5%
			(78%, 87%)			(84%, 92%)	(-1%, 11%)
LTFU POS=FAIL	246	24	91%	266	13	95%	4%
			(88%, 95%)			(93%, 98%)	(0%, 8%)
RM LTFU POS & RP LTFU=FAIL	246	24	91%	245	34	88%	-3%
			(88%, 95%)			(84, 92%)	(-8%, 2%)
RP LTFU=FAIL	261	9	97%	245	34	88%	-9%
			(95%, 99%)			(84%, 92%)	(-13%, -4%)

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Figures 4.2 i and ii show the pattern of times to conversion. Figure 4.2 i shows the Kaplan-Meier curves for time to conversion for each arm. The right pair of curves treats subjects lost to follow-up in the same way on both arms. Specifically, subjects are considered censored at the time of the last visit if the last culture is the first negative, as converting if the last two cultures are negative, and as not converted at day 180 if the last culture is positive.

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The left pair of curves gives a sensitivity analysis for the possible effect of loss to follow-up. In the left pair of curves, all loss to follow-up on rifapentine is treated as not converted at day 180; loss to follow-up on rifampin is treated as censored if the last culture is positive and as converting if the last culture is negative. Thus, subjects lost to follow-up on rifapentine are treated as having longer times to conversion in the left panel than in the right panel; subjects lost to follow-up on rifampin are treated as having shorter times to conversion in the left panel than in the right panel.

Figure 4.2 ii shows the 95% (non-simultaneous) confidence limits for the difference between rifapentine and rifampin. The right and left pairs of curves correspond to the right and left pairs in figure 4.2 i.

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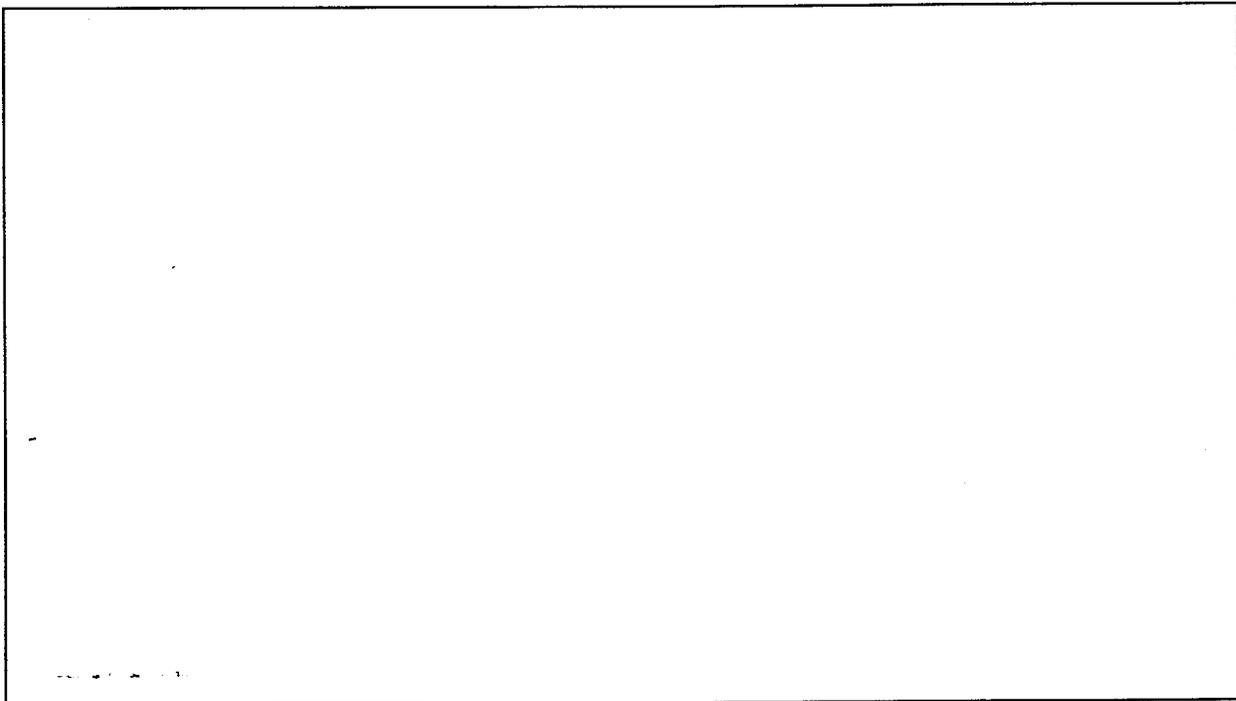


Figure 4.2 i

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One can see that the left panel of these figures show the same pattern as table 4.2 B: rifapentine, is with 95% confidence, no more than about 10% worse than rifampin with respect to percent converted, even at the lowest spot on the curve and is slightly superior to rifampin at day 180. The sensitivity analysis in the right panels also concurs with table 4.2 B. If all the lost to follow-up with last negative cultures converted on rifampin and none of them converted on rifapentine, rifapentine might credibly be as much as about 15-20% worse than rifampin at the worst point and as much as 10% worse at day 180. It should be emphasized that these limits reflect worst case scenarios.

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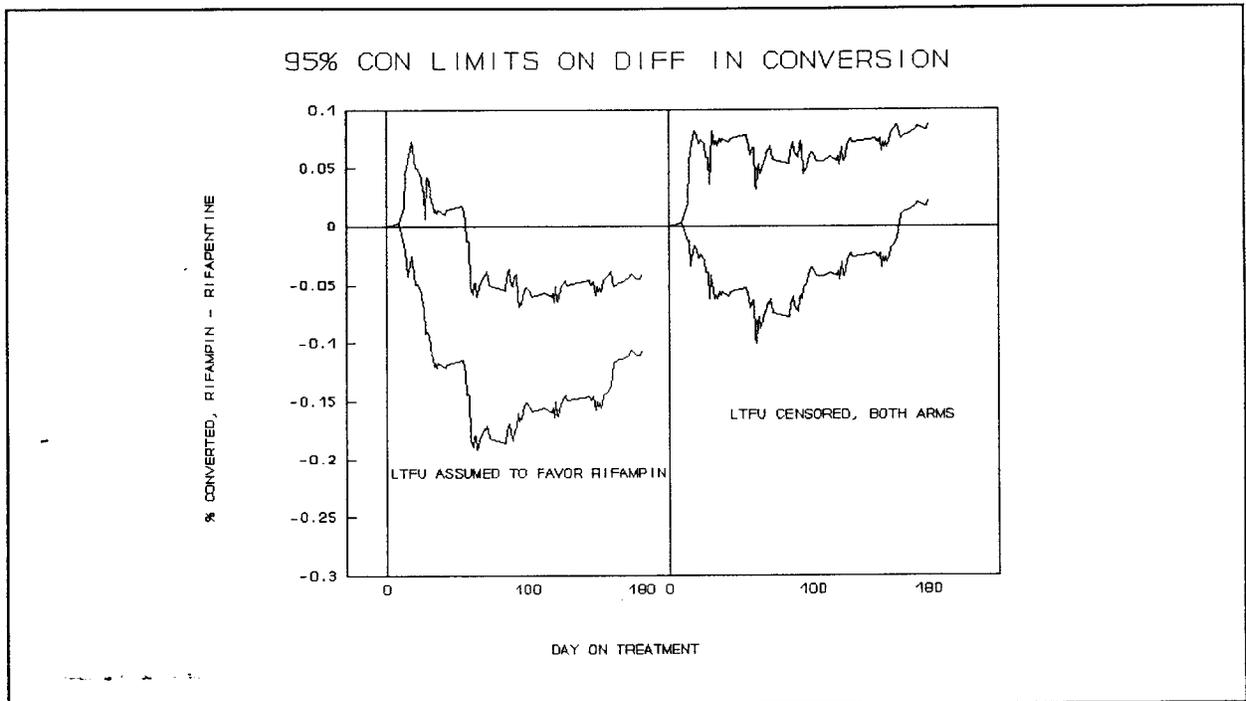


Figure 4.2 ii

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Finally, the FDA reviewer did an analysis to compare conversion rates using an analysis stratified by center, to reflect the stratification of the randomization by center. The weighted average of the center differences, weighted inversely to center variances was 1% with a 95% confidence interval for the difference of -5% to 6%. These results are essentially the same as those computed ignoring center.

4.3 Relapse Rates

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The applicant's analysis do show a higher rate of relapse on rifapentine than on rifampin. The next three sections of this review will focus on confidence intervals for the difference in rates of relapse, comparison of the times from end of treatment to relapse, and possible associations between relapse rate and other covariates. It should be noted that this review will use all available follow-up, not just the first 6 months of follow-up.

The occurrence of a relapse requires that positive cultures be found after the end of treatment. There are some instances where subjects had positive cultures after end of treatment but were not considered to have relapsed by the applicant. The final negative or positive determination of a single monthly visit was actually based on the combination of two LJ Slant cultures, two agar cultures, and two Bactec measurements, one of each taken on each of two (nearly) successive days. Any positive finding could also be assessed as TB or other organism. The applicant regarded any positive finding of TB on any one of the six cultures at a visit as making that visit positive during the treatment phase. However, positive cultures after the treatment phase were coded as positive visits only if there were either two positive cultures or one positive culture with a CFU count ≥ 10 . Any positive Bactec measurement was considered to have a CFU count < 10 .

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The FDA clinical and microbiological reviewers agreed with the applicant that TB testing produces scattered false positive results. Using their advice, the FDA statistical reviewer conducted sensitivity analyses using the following variations on the applicant's algorithm. Version 1 required either two positive TB cultures or one positive TB culture with a CFU count ≥ 10 to get a positive coding for a visit. Version 2 required one positive TB culture to get a positive coding for a visit. In both of these versions, visits before and after end of treatment were treated equally. Version 3 was slightly stricter than version 2 with respect to positive events after the end of treatment. In version 3, a single positive TB culture with CFU count < 10 resulted in a positive coding for the visit unless there were two days subsequently with all cultures negative and no subsequent visits with any positive cultures. These two days did not need to be for different visits. They could be the cultures on successive days for the same visit.

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In all three versions, if a subject came in for a visit and was unable to produce sputum, then all cultures for that day were counted as negative. The FDA clinical reviewer regarded inability to produce sputum as evidence of absence of TB. This was also different from the applicant's algorithm, which treated such a visit as having missing data.

The results of these analyses on the data subsequent to the FDA exclusions documented in section 4.1 above are given in table 4.3 A.

TABLE 4.3 A
COMPARISON OF RELAPSE RATES
ACROSS ARMS AND ACROSS ALGORITHMS

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Positive Cultures Counted	# Convert Rm	# Relapsed Rifap	Rate Relapsed & 95% Con Limits Rifam	Rate Relapsed & 95% Con Limits Rifap	Relative Risk & 95% Confid Limits	Difference & 95% Confid Limits
ANY TB	220	241	6%	15%	2.28	8%
-	14	35	(3%, 10%)	(11%, 18%)	(1.26, 4.13)	(4%, 13%)
TB >= 10	222	244	5%	11%	2.15	6%
-	11	26	(2%, 8%)	(8%, 13%)	(1.09, 4.25)	(2%, 10%)
ANY CONFIRMED TB	223	245	5%	11%	2.15	6%
-	11	26	(2%, 8%)	(8%, 13%)	(1.09, 4.25)	(2%, 10%)

This table shows that the presence and magnitude of the excess relapse rate with rifapentine is not sensitive to the particular method of treating post-treatment positives. Regardless of how positive results with CFU counts < 10 are treated, the observed relapse rate is at least 6% higher on rifapentine. With 95% confidence, one can only rule out relapse rates as much as 10% higher. In terms of relative risk, the observed relative risk of relapse is more than two times higher or rifapentine and, with 95% confidence, one cannot rule out relative risks as much as four times higher.

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One might observe that the analyses presented in table 4.3 A are not true ITT analyses since they are proportions conditional on having converted by end of treatment and are thus computed on a treatment emergent subset. This analysis can, however, be regarded as an ITT analysis if one considers that there are three possible outcomes: 1) cured (= converted and still negative at 2 years follow-up), 2) not converted, and 3) converted but relapsed. The FDA clinical reviewers regard outcome 3 as worse than outcome 2. Table 4.3 B contains rates, differences in rates, and confidence intervals for relapse as a percent of all ITT subjects. One should note that the results are not much different from those in table 4.3 A.

TABLE 4.3 B
ITT ANALYSIS OF RELAPSE

Positive Cultures Counted ANY TB	# in ITT	# Relapsed	Rate Relapsed & 95% Con Limits	Rifam Rifap	Rifap	Difference & 95% Confid Limits
	256	244	5%	13%	7%	
	14	35	(3%, 8%)	(9%, 16%)	(3%, 12%)	
ANY CONFIRMED TB	259	253	4%	9%	5%	
	11	26	(2%, 6%)	(6%, 13%)	(1%, 9%)	

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4.4 Time Until Relapse

Since this NDA is based on a surrogate marker, 6 months follow-up, one might be concerned that the apparent increased relapsed rate may be partly an artifact of incomplete follow-up. To examine the pattern of relapse rates over different durations of follow-up, one may examine table 4.4 A, which shows the relapse counts in three windows of duration of follow-up. This table shows no evidence that the risk of relapse on rifapentine is diminishing with longer follow-up.

TABLE 4.4 A
TIME TO RELAPSE
Number Relapsed

Post Treatment Peiod	Rifampin	Rifapentine
0-3 Months	5	10
4-7 Months	5	9
≥ 8 Months	1	7

The FDA reviewer also plotted Kaplan-Meier curves for time to relapse, measured from end of treatment, for the subset of subjects who converted. Figure 4.4 i shows the Kaplan-Meier curves for the two arms; figure 4.4 ii shows the 95% confidence limits for the difference in relapse rates.

In each figure, there are three panels. The right panel shows results from the algorithm that counts any TB culture as positive, regardless of CFU count. The center panel shows results when only CFU counts ≥ 10 are counted as positive. The left panel shows the results when any TB culture is positive,

provided a single culture with CFU count < 10 is not followed by at least two negative cultures.

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One can see, first, the observed differences in the relapse rate are statistically significant, with the rifapentine relapse being, with 95% confidence, between 2 and 15% higher than the rifampin rate. One can also see that the rates continue to diverge as far as subjects were followed. (In fact, plots of the confidence bands for the log hazard ratio show no evidence that the hazard ratio for risk of relapse is not constant. This plot is not included in the review.) Finally, one can see that the three ways of treating positive cultures with low CFU count make little difference to the conclusions.

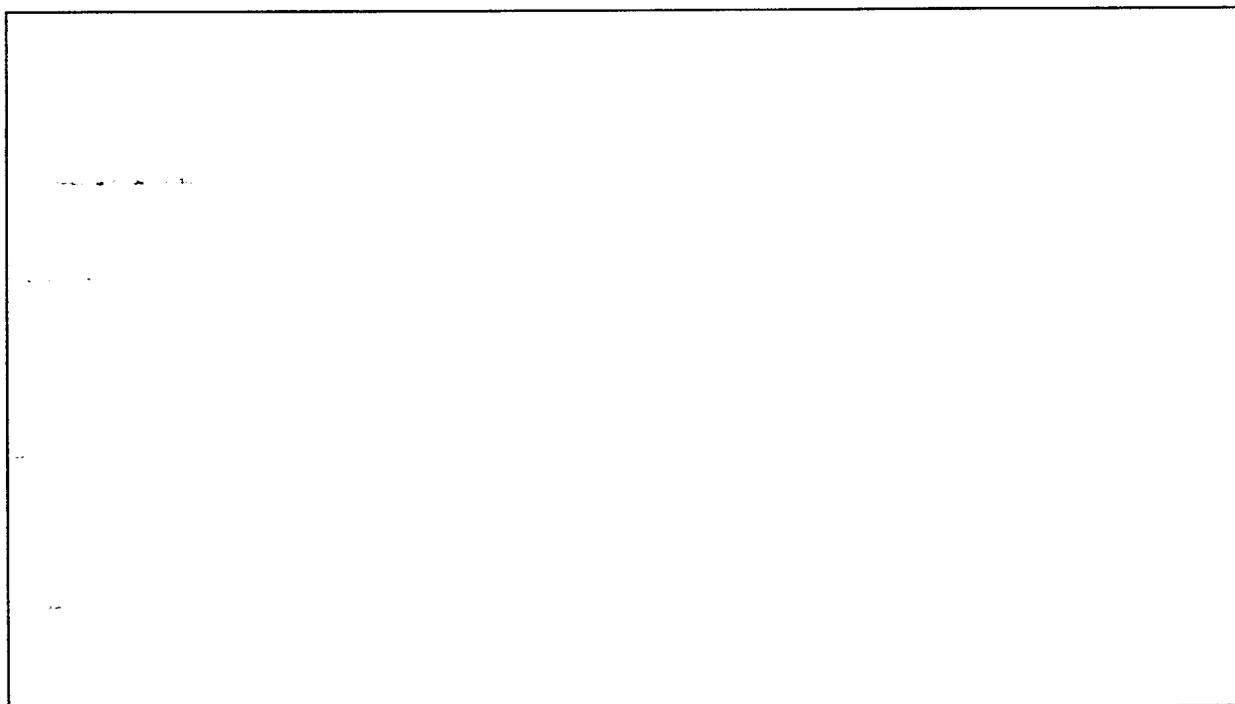


Figure 4.4 i

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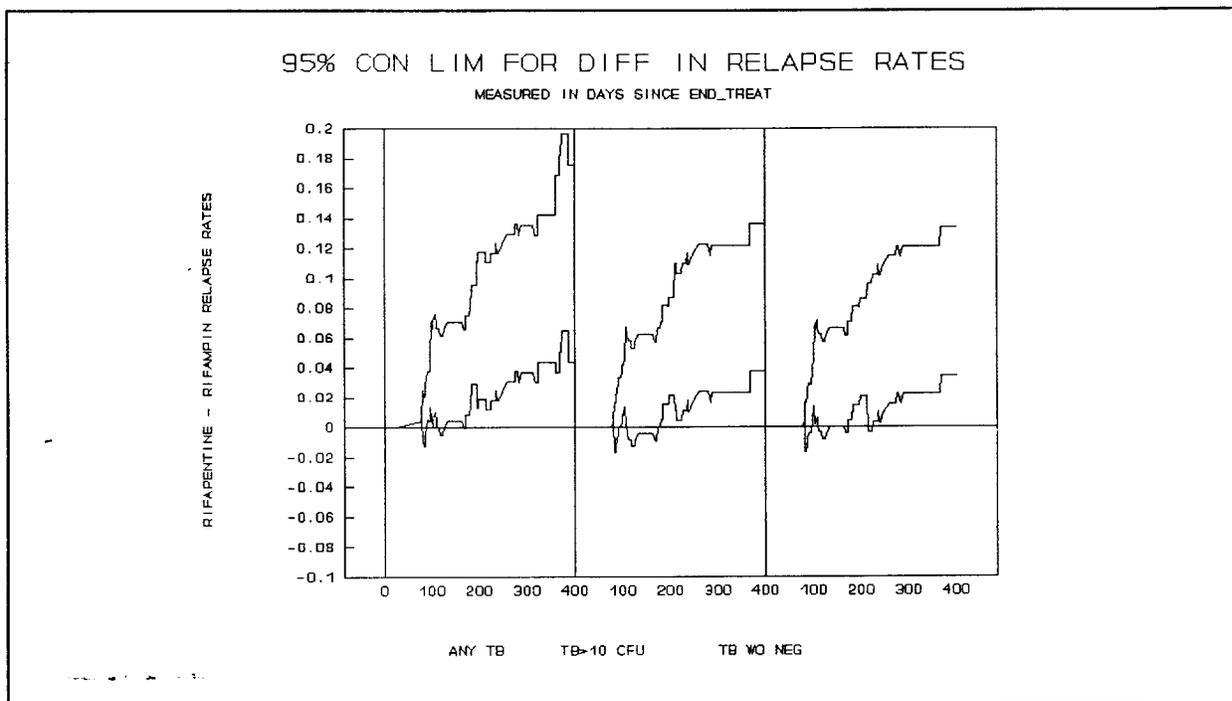


Figure 4.4 ii

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4.5 Relapse Rates Stratified by Covariates

The FDA reviewer examined the differences in relapse rate among subsets of subjects defined by several different baseline covariates: gender, age, race, country, center, and baseline chest X-ray. Table 4.5 A gives the relapse rates and the confidence limits around the difference in rates for the two most interesting stratifications.

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One can see that males had higher relapse rates than females and that males constituted a larger fraction of the rifapentine population. However, the difference in rates between the arms is the same in both genders so the observed difference in the overall sample is not explicable as confounding with gender. One can also see that site 22 (which was also the largest site) had a much large difference in relapse rates than all the other sites combined. However, all sites were equally represented on both arms so the observed difference in relapse rates in the whole sample is not explicable as confounding with site.

Finally, one can see that the size of the treatment effect does increase with severity of baseline chest X-ray. The largest effect is seen with bilateral cavitation. The two arms are balanced with respect to this covariate so the observed difference in relapse rates in the whole sample is not explicable as confounding with baseline chest X-ray. However, the FDA clinical reviewers have observed that the "No cavitation" and "Unilateral cavitation" subgroups may be more representative of the US tuberculosis population.

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TABLE 4.5 A
RELAPSE RATES BY BASELINE COVARIATES

Subgroup	Rates (N)		Difference in Rates with 95% Con. Limits
	Rifampin	Rifapentine	
Female	3% (66)	8% (49)	5% (-1%, 11%)
Male	6% (157)	11% (196)	5% (1%, 10%)
All sites but 22	5% (191)	8% (215)	3% (-1%, 7%)
Site 22	6% (32)	20% (30)	24% (12%, 36%)
No Cavitation in Baseline Chest X-ray†	3% (64)	4% (67)	1% (-5%, 8%)
Unilateral Cavitation	7% (30)	9% (22)	2% (-13%, 17%)
Bilateral Cavitation	6% (127)	16% (136)	11% (3%, 18%)

† Chest X-ray results use applicant's counts, which are slightly different from FDA's.

Breslow-Day tests for differences in treatment effects among the different strata were statistically insignificant for all three covariates: gender, site, and baseline chest X-ray.

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None of the other baseline covariates examined produced differences between the strata as large as for these covariates. Therefore details of analyses stratified by the other baseline covariates are not reproduced here.

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The FDA reviewer also examined the interaction of treatment with two treatment emergent covariates: 1) response by end of the intensive phase (day 60) and 2) compliance with other drugs in the regimen. Response at day 60 was stratified in three different ways. First, subjects were classified as converted or not at day 60. This classification had the drawback of using knowledge that the subjects would not have later positive cultures, knowledge not available when the subject first reached day 60. Second, subjects were classified as having had at least two negative cultures (the criterion for conversion) by day 60. This classification had the drawback of being quite strict since the first negative culture must occur by day 30. Third, subjects were classified as positive or negative at their day 60 culture.

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The results from these three ways of stratifying are given in table 4.5 B. These analyses do not show that the relative risk of relapse changes according to whether or not the subject has converted during the intensive phase of treatment. Subjects with poor results at the end of the intensive phase are at higher risk of relapse, regardless of which arm they are in. However, regardless of how well they were doing at the end of day 60, subjects on rifapentine were at consistently higher risk of relapse than were subjects on rifampin with the same culture results at day 60. On an absolute difference scale, the excess risk of rifapentine compared to rifampin was larger in the subgroups with poorer performance by day 60 (14% vs 3%, 6% vs 4%, or 9% vs 4%, depending on the stratification). On a ratio scale, however, the relative risk of rifapentine to rifampin is about 2 both among early converters and late converters. There is no consistent pattern as to whether the relative risk is higher or lower with late converters.

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TABLE 4.5 B
RELAPSE RATES BY RESPONSE AT DAY 60

Subgroup	Rates (N)		Difference in Rates with 95% Con. Limits	Relative Risk
	Rifampin	Rifapentine		
Converted by Day 60	5% (171)	7% (177)	3% (-2%, 8%)	1.57
Not Converted by Day 60	6% (51)	19% (67)	14% (2%, 25%)	3.30
Two Negatives by Day 60	2% (89)	7% (89)	4% (-2%, 11%)	3.00
Fewer than 2 Negatives by Day 60	7% (133)	13% (155)	6% (-1%, 13%)	1.91
Negative at Day 60	4% (187)	9% (193)	5% (0%, 9%)	2.06
Positive at Day 60	9% (35)	18% (51)	9% (-5%, 23%)	2.06

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Subjects were classified in a two-by-two table with respect to compliance with non-rifamycin drugs:

- 1) fewer than 48 doses of isoniazid and pyrazinamide (INH) plus fewer than 42 doses of ethambutol (EMB),
- 2) fewer than 48 doses of isoniazid and pyrazinamide plus at least 42 doses of ethambutol,
- 3) at least 48 doses of isoniazid and pyrazinamide plus fewer than 42 doses of ethambutol,
- 4) at least 48 doses of isoniazid and pyrazinamide plus at least 42 doses of ethambutol.

The results using this four-way classification are given in table 4.5 C.

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TABLE 4.5 C †
RELAPSE RATES BY COMPLIANCE WITH OTHER DRUGS

Subgroup	Rates (N)		Difference in Rates with 95% Con. Limits	Relative Risk
	Rifampin	Rifapentine		
INH doses <48, EMB doses < 42	7% (70)	23% (84)	15% (5%, 26%)	3.17
INH doses <48, EMB doses ≥ 42	5% (58)	6% (71)	0% (-7%, 8%)	1.09
INH doses ≥48, EMB doses < 42	4% (48)	6% (47)	2% (-7%, 11%)	1.53
INH doses ≥48, EMB doses ≥ 42	2% (56)	2% (50)	0% (-5%, 5%)	1.12

† table uses sponsor's counts, which are slightly different from FDA's.

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This table does not suggest that relapse is an artifact of lower compliance on rifapentine. The table does show that the relative risk is highest in the sub-group with poor compliance on both INH and EMB and that rifapentine subjects out-numbered rifampin subjects in that arm 84 to 70. However, the relative risk was never below one in any category and in the group with the lowest relative risk (poor INH compliance, good EMB compliance, relative risk = 1.09), rifapentine subjects outnumbered subjects 71 to 58. If one were to argue that bad luck had put too many rifapentine subjects in the category with worst relative risk, one must also concede that good luck has put

too many rifapentine subjects in the category with the best relative risk.

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All of these points, of course, ignore the fundamental point that compliance is not a baseline characteristic but rather is part of the response to the drug. In fact, in this study the most credible interpretation of the observed differential compliance is that it was caused by the fact that rifapentine was taken less frequently than the companion drugs.

5. Statistical Reviewer's Summary

The two most important conclusions from this study are the following:

1. The cure rates are comparable between the rifampin (83%) and rifapentine (88%) arms. This conclusion of equivalence is robust to different ways of coding the results for subjects lost to follow-up before the end of treatment and across different ways of sub-dividing the population on the basis of baseline covariates.

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2. There is a statistically difference between the arms in the chance of a relapse among the subset of converters. The risk is 5% for rifampin (95% confidence limits 2-8%) and 11% for rifapentine (95% confidence limits 8-13%). The relative risk of later relapsing, given conversion is 2.2, with a 95% confidence interval of 1.1 to 4.3. This observed difference does not seem to be an artifact of analysis with incomplete follow-up or of confounding with baseline covariates. There is some evidence to suggest it may result from poorer compliance with companion drugs caused by the difference in schedules among the drugs. There is also some evidence that is of smaller magnitude in subjects with less serious baseline disease, as indicated by chest X-ray.

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Rifapentine appears to be an effective drug in producing conversion to TB negative sputum when used in combination therapy. It is less effective than rifampin in preventing later relapse.

/S/

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

Concur: Dr. Flyer

/S/ 7/27/94

cc:

Archival NDA #21-024

HFD-590

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