VI.C.(4) Patient Accountability

A total of 824 patients were screened for entry into the study of whom 102 were screening failures and were not exposed to study medication. This left 722 patient who were randomized to receive study medication (361 to each treatment arm).

Of the 722 patients randomized, 570 were evaluable for efficacy for the intent-to-treat analysis by the applicant (284 in the rifampin combination arm and 286 in the rifapentine combination arm). Thus, 152 patients who were exposed to study drug were not evaluable for the applicant's intent-to-treat analysis. Reasons that these patients were not evaluable are delineated below:

Table C-4. Summary of Reasons Exposed Patients Not Evaluable for Efficacy in the Controlled Clinical Study (Protocol 000473PR0008)

Reasons [1]	*Rifampin Combination (N=361)*	*Rifapentine Combination (N=361)*	*Total (N=722)*
Negative culture at baseline N(%)	56 (15.5)	59 (16.3)	115 (15.9)
No baseline sputum (not done/missing) N(%)	2 (0.6)	0 (0.0)	2 (0.3)
Baseline isolate resistant to study medication N(%)	14 (3.9)	11 (3.0)	25 (3.5)
Pregnancy N(%)	3 (0.8)	3 (0.8)	6 (0.8)
Other N(%)	3 (0.8)	4 (1.1)	7 (1.0)
Total N(%)	77 (21.3)	75 (20.8)	152 (21.1)

[1] A patient may have had more than one reason for not being evaluable for efficacy; therefore, the sum of patient counts over columns may not equal the total count.

Appendix C.2.6.2, Listing 3: Reasons Exposed Patients Not Evaluable for Efficacy in Controlled Clinical Study 000473PR0008

At FDA request, the applicant also provided the reasons for "Other" in this table. The three rifampin combination patients who had "Other" as a reason included:

- patient 0022-0227 who had elevated liver enzymes at baseline
- patient 0035-0005 who had hepatomegaly and liver damage at baseline (and who later died 17 days after receiving a single dose of study medication)
- patient 0047-0035 who died after 4 doses of study medication of a pulmonary embolism.

The three rifapentine combination patients who had "Other" as a reason included:

- patient 0031-0005 who moved to another area and was unable to participate in the trial. Due to a medication error this patient did not receive rifapentine, but did receive 13 doses of isoniazid, pyrazinamide, and ethambutol.
- patient 0032-0006 who had elevated hepatic enzymes at baseline.
- patient 0046-0607 who stopped the study after one dose of study medications due to a rash related to pyrazinamide.

In addition, FDA requested the applicant provide a brief summary of the six patients who were pregnant and were excluded from the primary ITT efficacy analysis. See pregnancy section, VII.J. for further discussion of these patients.

Medical Officer Comment:
The reasons that patients were not considered evaluable for efficacy were relatively balanced between treatment arms. Slightly over two thirds of the patients who were considered non-evaluable had negative cultures at baseline as the reason, while the second most common reason was that the baseline isolate was resistant to one or more study medications.

It is reasonable to exclude patients with negative or missing cultures at baseline or with resistant isolates at baseline from the ITT efficacy analyses. A reliable outcome measure in these patients is impossible to ascertain since it is uncertain they had TB at study initiation, or they had infections which may not have responded to the study drugs due to baseline resistance. However, pregnant patients and those patients in the "other" category should, arguably, be included in an intent-to-treat analysis. FDA therefore performed some efficacy analyses which included these subjects.

A little over one third of the 570 patients who were considered for the applicant's intent-to-treat analysis of efficacy had major protocol violations. Two hundred and fourteen of the 570 ITT patients had major protocol violations, which led to a "protocol correct" population of 356. A summary of the major protocol violations for the 570 ITT patients follows:

Table C-5. Summary of Major Protocol Violations (Intent-to-Treat Patients) in the Controlled Clinical Study (Protocol 000473PR0008)			
Major Protocol Violation [1]	*Rifampin Combination (N=284) N(%)*	*Rifapentine Combination (N=286) N(%)*	*Total (N=570) N(%)*
Entrance criteria not met	2 (0.7)	1 (0.3)	3 (0.5)
Prohibited concomitant medications	4 (1.4)	5 (1.7)	9 (1.6)
Prohibited pretreatment medication/therapy	3 (1.1)	6 (2.1)	9 (1.6)
Greater than 14 days without study medication	22 (7.7)	24 (8.4)	46 (8.1)
Insufficient duration of exposure	79 (27.8)	78 (27.3)	157 (27.5)
Missing visit/missing primary evaluation	2 (0.7)	4 (1.4)	6 (1.1)
Lost to follow-up	39 (13.7)	42 (14.7)	81 (14.2)
Noncompliance with study procedures	6 (2.1)	7 (2.4)	13 (2.3)
HIV+	9 (3.2)	3 (1.0)	12 (2.1)
Interfering concomitant disease/medical condition	10 (3.5)	3 (1.0)	13 (2.3)
Other	9 (3.2)	2 (0.7)	11 (1.9)
Total	120 (42.3)	116 (40.6)	236 (41.4)
[1] A patient may have had more than one major protocol violation; therefore, the sum of patient counts over rows may not equal the total count.			
Appendix C.2.6.2, Listing 4: Major Protocol Violations for Intent-to-Treat Patients in Controlled Clinical Study 000473PR0008			

Medical Officer Comment:
Approximately 40% of the patients in each treatment arm had at least one major protocol violation. The most frequent reasons were lost to follow-up or inadequate study drug exposure. This review will focus primarily on the ITT analysis of efficacy. Some analyses of the protocol correct patient population will, however, be provided for additional perspective.

VI.D. Primary Efficacy Outcome: Applicant's Analyses

This submission included interim efficacy results based on data collected through November 8, 1996 from a clinical trial (Protocol 0047PR0008) for the treatment of tuberculosis. To better understand the incidence of relapse, the applicant with prior FDA agreement, submitted a clinical update on March 4, 1998 which summarized follow-up data through a July 1997 cut-off date. By this date, all of the patients would have been treated and followed to the 6 month post therapy visit.

The following sections summarizes the applicant's primary efficacy analyses, both "intent-to-treat" and "protocol correct", from the ongoing 0008 study database through July 8, 1997.

The applicant summarized preliminary conclusions from the study as follows:

- The treatment success rate at the end of 6 months follow-up for rifapentine, when used in combination with other standard antitubercular drugs, was equivalent to that of rifampin, the primary comparator agent, for treatment of patients with pulmonary tuberculosis. This equivalence was maintainded across several analyses, which differed in the manner by which the data from patients without 6 months of follow-up were handled.

- Efficacy of rifapentine combination therapy was demonstrated when the drug was used twice weekly in the Intensive Phase and once weekly in the Continuation Phase. The treatment effect of rifapentine combination therapy appeared to be consistent in different subgroups of patients defined by age, gender, baseline weight, race and region.

- Rates of "treatment nonsuccess" (treatment failures+relapses+dropouts) supported equivalent efficacy for the rifampin combination group and the rifapentine combination group. While there were more treatment failures in rifampin combination patients, and more relapses in the rifapentine combination group, the overall number of "treatment nonsuccess" was nearly the same in both treatment groups.

- Several factors, primarily a low number of Intensive Phase isoniazid, pyrazinamide and ethambutol doses and subsequent failure to convert sputum after 2 months of treatment, appear to have played a role in the higher relapse rate in rifapentine combination patients.

Each of these conclusions are examined further below.

It should be remembered that for purposes of these analyses the applicant counted missing sputum results as positive for M. tuberculosis, which reflects the least favorable possible efficacy outcome.

Medical Officer Comment:
The least favorable analysis would have been to count missing sputum cultures as positive for the rifapentine arm and negative for the rifampin arm. The applicant's analysis does not discriminate between all patients that lack sputum cultures at each visit and patients who were truly cured and not able to produce sputum at those visits, and who where continued to be followed in the clinic. The latter would be counted as failures by the applicant. The FDA counted the latter group as successes.

VI.D.(1) Sputum Conversion at the End of Treatment
In the following table the "Intent-to-Treat" results are displayed. The sustained success rates at the end of 6 months of follow-up for rifampin combination and rifapentine combination group were 71.1% (202/284) and 70.3% (201/286), respectively.

Treatment Success for Intent-To-Treat Patients
(missing results assumed sputum positive): Percentages and 95% Confidence Intervals
Study 0008.

Time Period During Trial	Rifampin Combo (N=284)	Rifapentine Combo (N=286)	Treatment Difference
End of Intensive Phase	79.2% (225/284) (74.5%, 83.9%)	74.8% (214/286) (69.8%, 79.9%)	4.4% (-2.5%, 11.3%)
End of Continuation Phase	81.7% (232/284) (77.2%, 86.2%)	88.1% (252/286) (84.4%, 91.9%)	-6.4% (-12.3%, -0.6%)
End of 6 Month Follow-Up	71.1% (202/284) (65.9%, 76.4%)	70.3% (201/286) (65%, 75.6%)	0.8% (-6.6%, 8.3%)
End of 12 Month Follow-Up	47.2% (134/284) (41.4%, 53%)	34.4% (124/286) (37.6%, 49.1%)	3.8% (-4.3%, 12%)

NDA submission; SC-V8-p1.

Medical Officer Comment:
It is of interest to note that the sputum conversion rate at the end of 2 months is lower in the rifapentine arm than the rifampin arm. In addition, at the end of the continuation phase the rate of sputum conversion is higher in the rifapentine arm. Finally the denominator for the end of 12-month follow up is not the total enrolled, since only about two-thirds of the patients had reached the 12 month follow-up period.

An additional analysis was performed by the applicant for a smaller, selected group of "protocol correct patients". The results are presented in the following table. As noted above, this analysis excludes many patients who withdrew early or were lost to follow-up.

Treatment Success for Protocol Correct Patients
(missing results assumed sputum positive): Percentages and 95% Confidence Intervals
Study 0008.

Time Period During Trial	Rifampin Combo (N=164)	Rifapentine Combo (N=170)	Treatment Difference
End of Intensive Phase	85.4% (140/164) (80%, 90.8%)	79.4% (135/170) (73.3%, 85.5%)	6% (-2.2%, 14.1%)
End of Continuation Phase	97.6% (160/164) (95.2%, 99.9%)	99.4% (169/170) (98.3%, 100.6%)	-1.9% (-4.5%, -0.8%)
End of 6 Month Follow-Up	89% (146/164) (84.2%, 93.8%)	86.5% (147/170) (81.3%, 91.6%)	2.6% (-4.5%, 9.6%)
End of 12 Month Follow-Up	61% (100/164) (53.5%, 68.4%)	56.5% (96/170) (49%, 63.9%)	4.5% (-6%, 15.1%)

NDA reference, SC-V8-p1

Medical Officer Comment:
The qualitative pattern seen in this analysis is similar to the "intent-to-treat" analysis. Rifapentine has a lower sputum conversion rate at the end of two months and a higher sputum conversion rate at the end of therapy. Again, the sustained sputum conversion is lower at the end of 6 month follow up in the rifapentine arm.

There was no statistically significant treatment difference between treatment arms in the rates of conversion overtime based upon the log-rank test. The time to conversion in the "Intent-to-Treat Patient" (ie, patients with at least two consecutive sputum cultures negative for M. tuberculosis without recurrence of a positive sputum culture by the end of active treatment) censored those patients who did not convert or were lost to follow-up at the time of analysis.

VI.D.(2) Treatment Nonsuccess

Treatment non-successes in the intent to treat population included patients classified as treatment failures, relapses or dropouts. The applicant noted that 74 patients were classified as nonsuccesses in the rifampin combination group and 82 were classified as nonsuccess in the rifapentine arm. The most frequent reasons were patient elected to discontinue (34 on rifampin vs 32 on rifapentine) or relapse (11 on rifampin vs 27 on rifapentine).

Medical Officer Comment:
Since the number of discontinuation and loss to follow-up is large relative to the relapse rate, including all these events in the nonsuccess (failure) category makes the two treatment arms appear similar. FDA felt it was important to consider relapse rates as a separate measure of failure. The lack of information on outcome for those who discontinued or were lost to follow-up may also have an influence on the true relapse rate..

VI.D.(3) Relapse Rates in Converters During the Follow-Up Period

Patients who converted their sputum by the end of treatment (2 consecutive negative sputum cultures), were followed for relapse. Relapse rates by period of occurrence during the study are listed below.

Cumulative Relapse Rate for Intent to Treat Patients in Study 0008

Interval from Last Dose of Study Drug to Relapse	Rifampin Combination (N= 232)	Rifapentine Combination (N=252)	Total (N= 484)
3 months	5 (2.2%)	17 (6.7%)	22 (4.5%)
6 months	10 (4.3%)	22 (8.7%)	32 (6.6%)
12 months	11 (4.7%)	27 (10.7%)	38 (7.9%)

NDA Table 8-64, S8-V1.127-p38

Overall relapse rates were 4.7% (11/232) for rifampin and 10.7% (27/252) for rifapentine in the intent to treat analysis.

Medical Officer Comment:
As stated earlier, expected relapse rates in the design of this study were The relapse rates were higher than expected for both arms. There was a 2 times greater risk of relapse in the rifapentine arm which was statistically significant. The applicant performs several exploratory analysis in order to explain this difference. It is of interest to note that while virtually all of relapses occurred by 6 months in the rifampin arm one-quarter of the rifapentine relapses occurred after 6 months.

VI.D.(4) Exploratory Analysis Regarding Relapse Differences
In order to further explore potential reasons for the higher relapse rate in the rifapentine combination group, the applicant retrospectively compared demographic, disease and treatment factors for patients who relapsed.

Medical Officer Comment:
These analyses should we weighed carefully since they were post-hoc and include a small number of events (relapses) upon which multiple analyses were conducted. Review of these analyses may be viewed as exploratory and hypothesis generating.

Plasma pharmacokinetics of rifapentine did not appear to be a predictor of relapses in this study. Clearance values between the patients who were successfully treated (2.34± 0.63 L/h) and those who relapsed (2.38 ± 0.58 L/h) were similar.

Of the demographic and baseline characteristics, the gender analysis demonstrated a greater preponderance of male patients, which was greater among relapsed patients than among non-relapsed patients: 86.8% (33/38) vs 75.6% (337/446).

Of interest is a sub-analysis regarding relapse rate and the demographic silicosis/mineworker. The applicant explored the possible relationship and did not find any. Of the 94 patients who came from mining sites, 3 (3.2%) relapsed, while 35 of the 390 (9%) who did not come from mining sites relapsed.

The applicant analyzed baseline chest x-rays as an indication of severity of disease and possible predictor of relapse. The results are shown below.

Summary of Sit-Read Chest X-Ray Findings at Baseline for Intent-to-Treat Patins in Follow-up in Study 0008

	Not Relapsed		**Relapsed**	
Results	Rifampin Combo (N=221)	Rifapentine Combo (N=225)	Rifampin Combo (N=11)	Rifapentine Combo (N=27)
Abnormal	221 (100.0)	225 (100.0)	11 (100.0)	27 (100.0)
Cavities	157 (71.0)	158 (70.2)	9 (81.8)	24 (88.9)
Bilateral	127 (57.5)	136 (60.4)	7 (63.6)	22 (81.5)

NDA reference SC-V10-p247.

Relapsed patients from both treatment groups had higher incidences of cavitary disease than nonrelapsed patients: 81.8% (9/11) vs 71.0% (157/231), respectively , for rifampin combination patients; 88.9% (24/27) vs 70.2% (158/225), respectively, for rifapentine combination patients. The previously noted difference between the two treatment groups with respect to the incidence of bilateral disease was maintained in the group of relapsed patients. The applicant states that these results further support the contention that patients who relapsed had more severe disease than those who did not, and also support the suggestion that rifapentine relapsers may have had more severe disease than rifampin relapsers.

Medical Officer Comment:
It is important to note that the majority of patients in both groups had bilateral disease at baseline. While this may be a predictor of relapse it is neither sensitive nor specific. In support of this, 82.5% of the rifapentine patients who relapsed had bilateral chest disease at baseline (considerably more than the 64% overall). However, 60.4% of the rifampin patients who relapsed had bilateral chest disease which is quite comparable to the incidence of this finding at baseline of 57.4%. Thus, it is not entirely clear that the presence of bilateral infiltrates on chest radiograph truly predicts a worse outcome. If it did, this should be true in the rifampin arm as well as in the rifapentine arm.

Two factors which were reported by the applicant to be clearly associated with relapse were failure to convert sputum by 2 months on therapy (end of intensive phase) or lack of compliance with the companion drugs during the first two months of therapy. These factors are described below.

Relapse Status Versus Conversion by 2 Months for Intent-to-Treat Patients in Follow-up in Study 0008

	Time to Conversion ≤ 2 Months		**Time to Conversion > 2 Months**	
	Not Relapsed	Relapsed	Not Relapsed	Relapsed
Rifampin Combination	176/184 (95.7%)	8/184 (4.3%)	45/48 (93.8%)	3/48 (6.3%)
Rifapentine Combination	176/187 (94.1%)	11/187 (5.9%)	49/65 (75.4%)	16/65 (24.6%)

NOTE: The denominators presented here include intent to treat patients who completed 6 months of active treatment with negative sputum cultures and entered follow-up.
NDA reference; SC-V10-p270

As is demonstrated above, a greater percentage of patients who did not convert at the end of 2 months relapsed.

Medical Officer Comment:
It should be noted that this is a risk factor for both rifampin and rifapentine patients, and is neither a sensitive nor specific predictor. It should be noted that the applicant has chosen a subset of patients from the intent to treat population to include in this table. For this reason the denominators do not match the previous table. FDA analysis will address these rates without excluding non-adherent patients (see Section VI. E.).

VI.D.(5) Study Drug Adherence and Outcome

The applicant explored the effect of adherence to study medication schedule on outcome in two ways: 1.) protocol defined; 2.) post-hoc by companion drugs during intensive phase. Both of these analysis are reviewed below. The applicant notes that the more meaningful analysis may be the second.

a. Protocol Defined Adherence and Outcome

1). Adherence During Intensive Phase of Study Drug Therapy

The applicant calculated study drug adherence for the intent to treat population based on the following definitions.

Intensive phase/Rifampin Arm: These subjects had to receive at least 45 of the 60 daily doses of study drug. When patient self-administration was possible with expected patient adherence, DOT was required for at least 40 days. Additionally, to be considered adherent, patients must not have discontinued any of the study drugs for more than 14 consecutive days.

Intensive phase/Rifapentine Arm: These subjects had to receive all 17 doses of rifapentine by DOT during the Intensive phase. Additionally, to be considered adherent, patients must not have discontinued any of the study drugs for more than 14 consecutive days.

Results of the applicant's assessment of patient adherence during the intensive phase regimen showed a difference between treatment arms. Non-adherence rates in the rifampin arm were 8.7% (23/263) compared to a rate of 12.6% (30/239) in the rifapentine arm.

Medical Officer Comment:

The applicant's analysis reveals a significantly higher rate of noncompliance in the rifapentine treatment arm during intensive phase therapy. The applicant later links the higher rate of non-adherence in the rifapentine arm during intensive therapy as a possible explanation for the higher rate of relapse in this arm. Some of the difference in adherence, however, may reflect a bias in the way that non-adherence was defined for each treatment arm. Essentially, perfect adherence (17 of 17 doses) was required for the rifapentine treatment arm compared to 75% adherence (45 of 60 doses) for the rifampin arm.

FDA asked the applicant to recalculate non-adherence using the following definition:

Intensive Phase/Rifampin Arm: (60 total doses of INH/R/PZA/EMB):

A patient would be considered non-adherent if:

1. They missed 7 or more consecutive days of ANY DRUG in this regimen (or a combination of drugs or the entire regimen) AND/OR
2. They missed a total of 20 or more days of ANY DRUG in this regimen (or a combination of drugs, or the entire regimen).

*Note: when patient self-administration was possible with expected patient adherence, DOT was required for at least 40 days.

Intensive Phase/Rifapentine Arm: (60 doses of INH/PZA/EMB and 17 doses of Rpt):
A patient would be considered non-adherent if:

1. They missed 7 or more consecutive days of INH, PZA, or EMB in this regimen (or any combination of these drugs AND/OR
2. They missed a total of 20 days or more of INH, PZA, or EMB in this regime (or any combination of these drugs AND/OR
3. They missed more than 1 full week of rifapentine AND/OR
4. They missed four or more total doses of rifapentine.

*Note: when patient self-administration was possible with expected patient adherence, DOT was required for at least 40 days.

Using the revised FDA definition, analyses revealed that non-adherence during the intensive phase of therapy in the rifampin arm was 26.6% compared to a rate of 23.6% in the rifapentine arm.

Medical Officer Comment:
Using the FDA definition, there were comparable rates of non-adherence in both the rifampin and rifapentine arms during intensive phase therapy. The FDA definition required that all patients take essentially the same amount if INH, PZA, or EMB, and that a patient not miss more than a week of consecutive rifampin or rifapentine doses. In this regard, the definition was balanced for both treatment arms. In addition, the FDA required that patients take a total of at least 40 of their 60 rifampin doses (67%) and 13 of their 17 rifapentine doses (76.5%). The FDA definition (like that of the applicant) also was somewhat more strict in defining adherence for rifapentine versus rifampin. Nonetheless, the FDA definition showed comparable rates of non-adherence in each treatment arm during intensive phase therapy. Finally, it should be noted that there is more room for error, missing doses, in the rifampin regimen, given the greater number of doses required.

2.) Adherence During the Continuation Phase of Therapy
To be considered adherent during the continuation phase of therapy, the applicant required rifampin patients to receive at least 32 doses by DOT. Rifapentine combination patients were required to receive at least 16 doses by DOT. The requirement that patient must not have discontinued any study drug for more than 14 consecutive days also applied to the continuation phase. Results of the applicant's analysis revealed comparable rates of non-adherence: 12.6% in the rifampin arm versus 10.7% in the rifapentine arm.

FDA again requested that the applicant reanalyze non-adherence during the continuation phase of therapy using the following definition:

Treatment Arm A (Rifampin Regimen): INH and Rifampin taken twice a week (32 doses total).

1. Any patient who missed > 4 consecutive doses (i.e. > 14 consecutive days) of INH and/or Rifampin AND/OR
2. Any patient who missed 8 or more of the 32 required doses (i.e. ≥25% of required doses) of INH and/or Rifampin.

Treatment Arm B (Rifapentine Regimen): INH and Rifapentine taken once a week (16 doses total).

1. Any patient who missed > 2 consecutive doses (i.e. > 14 consecutive days) of INH and/or Rifapentine AND/OR
2. Any patient who missed 4 or more of the required 16 required doses (i.e. ≥ 25% of required doses) of INH and/or Rifapentine.

Using the revised FDA definition, these analyses revealed a non-adherence rate during the continuation phase of therapy of 6.8% versus 7.5% for rifampin and rifapentine patients, respectively.

b. Adherence During the Intensive Phase for Companion Medications and Outcome; Post-Hoc Analysis

In this analysis the applicant divided patients from the intent-to-treat population into four dosing groups: a "high" dosing group (INH/PZA > 47 doses, EMB > 41 doses); two "moderate" dosing groups (INH/PZA ≥ 47 doses, EMB < 41 doses; or INH/PZA ≤ 47doses, EMB > 41 doses); and one "low" dosing group (INH/PZA ≤ 47 doses, EMB ≤ 41 doses). It is of interest to note that the there was equally good compliance for the rifampin and rifapentine doses, therefore only the companion medications are considered in this analysis.

For both the rifampin and rifapentine combination groups the number of patients who relapsed increased as the number non-rifamycin doses in the Intensive Phase decreased, with the lowest relapse (< 2.0%) in the high dosing group and the highest relapse in the low dosing group. In the moderate dosing groups, relapse rates were approximately 4-6%. The relapse rates were similar between the two treatment groups for both the high and moderated dosing groups, but the rifapentine relapse rate more than tripled when compared to the rifampin rate in the low dosing group. Thus, the rifapentine combination group appeared to be more sensitive to relapse with a regimen containing a lower number of non-rifamycin Intensive Phase doses.

Relapse Rates by Number of Intensive Phase Isoniazid. Pyrazinamide, and Ethambutol Doses for Intent-to-Treat Patients Who Entered Follow-Up.

Rifampin Combo	Rifapentine Combo	Rifampin Combo	Rifapentine Combo
INH/PZA≤ 47, EMB ≤ 41		**INH/PZA> 47, EMB ≤ 41**	
7.1% (5/70)	22.6% (19/84)	4.2% (2/48)	6.4% (3/47)
INH/PZA≤ 47, EMB ≥41		**INH/PZA> 47, EMB > 41**	
5.2% (3/58)	5.6% (4/71)	1.8% (1/56)	2.0% (1/50)

Note: Denominators used are for the INH and EMB dose categories.
NDA sumission, 4/15/98, vol 1, table 20.

The applicant noted that the rifamycin dosing was comparable in both treatment groups during the intensive phase.

Medical Officer Comment:
This analysis is of interest, and points out the difficulty with the rifapentine regimen. In this non-blinded study, patients were encouraged not to miss doses of experimental agents, perhaps a greater emphasis was placed upon the twice weekly dosing of rifapentine during the early phase of treatment. There is some concern regarding the attribution of outcome to study drug adherence; e.g. was it the disease that made the patients less compliant or the study medication?

VI.E. FDA Efficacy Analyses

(Note: all text in this section represents medical officer commentary except where indicated.)

VI.E.(1) FDA Comments Regarding Study Design and Analysis Issues

In Study 0008, inclusion and exclusion criteria prohibited patients with HIV/AIDS, pregnant women, patients with negative baseline sputum cultures, and cultures revealing organisms resistant to study drugs. Patients were excluded from the FDA analysis if they did not begin study drug or did not meet the above characteristics. Since tubercule bacilli may take up to a month and a half to be detected in cultures, some patients would have been treated upon suspicion of disease, but not have had a positive baseline sputum culture result reported to the study site for most of the induction phase. In addition, concern that HIV/AIDS patients may be at greater risk for the development of rifampin resistant isolates, indicates that this group of patients should be considered separately. These exclusion criteria were developed before the data were publicly presented at the Annual AIDS Meeting (1998) by the Centers for Disease Control and Prevention Study.

The following table outlines the patients excluded from analysis by the FDA and constitute the basis upon which FDA analysis are conducted.

FDA: Eligible Patients Receiving Treatment

	Rifampin	Rifapentine
Randomized	361	361
Excluded by Applicant	77	75
Baseline negative culture	56	59
Baseline culture missing	2	0
Baseline isolate resistant	14	11
Pregnancy/Other	6*	7
Excluded by FDA	14	7
HIV positive	9	4
Baseline isolate resistant	6*	3
FDA-modified ITT	270	279

*Subcategories not mutually exclusive
FDA Analysis

The outcomes of patients who were inadvertently maintained in study with HIV are outlined above. Only 4 patients in the rifapentine arm were HIV positive. Outcomes of these patients included one who converted and did not relapse in the follow-up period, two who converted at the end of treatment but were lost to follow-up and one who relapsed. The patient who relapsed did so with a rifamycin sensitive isolate. There are two few HIV patients in the rifapentine arm to comment on the efficacy in this subgroup.

HIV Positive Patient Outcomes

	Rifampin N=9	Rifapentine N=4
Withdrew Early	1	0
-Conversion, NO relapse	8	1
Converted in the continuation phase then lost to follow-up	0	2
RELAPSES	0	1

FDA Analysis

Endpoints:

Whether the rifapentine therapeutic regimen is adequate therapy for tuberculosis may be assessed in part by demonstrating the ability of the therapy to convert the sputum during treatment and, most importantly, by comparable, low-level, relapse rates in the follow-up period. Two years of follow-up after treatment is completed is the standard, however, in this application, the most complete follow-up is through 6 months, though the great majority of patients had the opportunity for one year of follow-up. It was agreed that the 6 month data would be acceptable for review based upon the accelerated approval regulations.

Endpoints of interest in this study include sputum culture status at the end of induction (60 days) and continuation (180 day) therapy, as well as 6-month post-treatment relapse rates and later relapses.

VI.E.(2) Data analysis issues

The data base from this clinical trial raised many challenges in its interpretation. These included the use of multiple culture media, two sputum samples for many of the study visits, missing data, and inability to induce sputum from patients who appeared to be clinically cured. In an effort to address these issues, the applicant has performed an initial analysis, followed by several sensitivity analyses.

While these analysis are appropriate, the FDA chose to handle the data slightly differently, based upon its interpretation of the protocol specified endpoints, and in an attempt not to penalize the applicant for patients who converted and could not produce sputum, even upon induction. Treatment "non-successes" were defined by the applicant as including treatment failures + relapses + dropouts. Since there were a large numbers of patients in the dropout category, this may tend to obscure the relapse outcome, we focused upon the conversion

rates and relapse rates. Additionally, information regarding the FDA handling of the data will be presented at the advisory committee.

VI.E.(3) FDA Comments Regarding Efficacy Endpoint Evaluation

a. Results:

Note: Unless otherwise specified the rates stated below are based upon the FDA analysis of the data and differ slightly from the applicant's numbers. In addition, for complete details regarding FDA analysis please refer to biostatistical review of Dr. Hammerstrom.

The most important conclusions from this study are the following:

1. There is essential equivalence for conversion rates at the end of therapy between the rifampin and rifapentine 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.

FDA: Outcomes During Treatment Periods

	Rifampin	Rifapentine
FDA: Modified ITT	270	279
Reached End of 180 days Rx	232	249
Lost to follow-up early	38 (14%)	30 (11%)
Did Not Convert (Treatment Failure)	9 (3.3%)	4 (1.4%)
CONVERTED	223 (83%)	245 (88%)

FDA analysis

The sputum conversion rates were 83% on rifampin and 88% on rifapentine, where conversion was defined as having at least two successive negative cultures, which are sustained by the end of treatment at day 180. An additional 5.6% of rifampin subjects and 4.3% of rifapentine subjects converted before end of treatment but were lost to follow-up before reaching end of treatment (see table below). Kaplan-Meier plots showed no difference between the arms with respect to time to conversion.

Sputum Status Among Patients Lost to Follow-Up During Treatment Phase

	Rifampin N=270	Rifapentine N=279
Lost to Follow-up Early	38	30
Last 2 visits negative	15	12
Last visit negative	8	9
Last visit positive	15	9

FDA analysis

2. There is a statistically significant difference between the treatment arms for relapse (at any time during follow-up) 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 relapsing following conversion is 2.15, with a 95% confidence interval of 1.09 to 4.25. The interval excludes one so the relative risk is statistically significantly greater than one.

Outcome of Converters During Follow-up Phase

	Rifampin	Rifapentine
CONVERTED	223	245
NO relapse	212 (95%)	219 (89%)
Relapse	11 (5%)	26 (11%)

- FDA analysis

If one compares the two arms with respect to difference in relapse rates (rather than the relative risk), one obtains an observed difference in rates of 6% with a 95% confidence interval for the difference of 2-10% (i.e. rifapentine was worse than rifampin).

3. Analyses of time to relapse do not suggest that this observed difference is an artifact of interim analysis. It is important to compare the additional relapses at 12 months between both treatment groups. While the majority of relapses occurred by six months in the rifampin arm, approximately one-quarter of the rifapentine relapses occurred between 6 and 12 months.

The observed relapses for the two arms were distributed as follows:

Follow-up	rifampin	rifapentine
3 months	5	10
6 months	5	9
12 months	1	7

Kaplan-Meier plots also show divergence of the probability of relapse between the two arms as duration of follow-up increases.

The duration of follow-up by converters during the follow-up phase is displayed in the following table.

Duration of follow up completed among converters

	Rifampin	Rifapentine
Followed < 6 months	24	28
Followed to 6 months	62	65
Followed to 12 months	126	126

FDA analysis

4. Analyses of baseline covariates that mark severity of disease (e.g. chest x-ray) show that the elevated risk of relapse with rifapentine is found at all levels of the covariate. The overall relative risk of 2.15 does not appear to be an artifact of sample imbalance.

Risk of Relapse by baseline chest x-ray†

	RIFAMPIN	RIFAPENTINE	Relative Risk
TOTAL	5.0% (11/221)	12.0% (27/225)	2.41
No Cavitation	3.1% (2/64)	4.5% (3/67)	1.43
Cavitation			
Unilateral	6.7% (2/30)	9.1% (2/22)	1.36
Bilateral	5.5% (7/127)	16.2% (22/136)	2.93

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

5. Analyses stratified by results at the end of the intensive treatment phase (day 60 of treatment), varying the definitions of outcome according to sputum status, shows the relative risk of relapse for rifapentine to rifampin is about 2 for each group among early converters vs late converters (< 60 days vs > 60 days) . However, Subjects with poor results at the end of the intensive phase are at higher risk of relapse, regardless of which treatment arm they are in.

Sensitivity analysis of relapse rates conditioned by sputum results

	RELAPSES		Difference Rifapen - Rif (C.I.)	Relative Risk (C.I.)
	Rifampin	Rifapentine		
CONVERTED at 60 days	5% (8/171)	7% (13/178)	3% (-2,7%)	1.57 (.66,3.67)
FAILED to Convert at 60 Days	6% (3/52)	19% (13/67)	7% (5,22%)	3.36 (1.01,1.19)
Two Negatives by Day 60	2% (2/89)	7% (6/90)	4% (0,9%)	2.97 (.62,14.31
Did not have 2 neg by Day 60	7% (9/134)	13% (20/155)	6% (0,12%)	1.92 (.91,4.08)
Negative Sputum Day 60	4% (8/188)	9% (17/194)	5% (0,9%)	2.06 (.60,7.07)
Positive Sputum Day 60	9% (3/35)	18% (9/51)	9% (-3,21%)	2.06 (.91,4.66)

*CI's are computed at 95%
FDA analysis

6. Analyses of relapse rates stratified by compliance with the other drugs in the regimen do not suggest that relapse is an artifact of lower compliance on rifapentine.

RISK OF RELAPSE ACCORDING TO INH, PZA, EMB COMPLIANCE†

	RIFAMPIN	RIFAPENTINE	Relative Risk
TOTAL	5.0% (11/221)	12.0% (27/225)	2.41
INH<48,EMB<42	7.1% (5/70)	22.6% (19/84)	3.17
INH<48,EMB>41	5.2% (3/58)	5.6% (4/71)	1.09
INH>47,EMB<42	4.2% (2/48)	6.4% (3/47)	1.53
INH>47,EMB>41	1.8% (1/56)	2.0% (1/50)	1.12

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

The above 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, 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. The relative risk was never below one in any category.
One should keep in mind that compliance is not a baseline characteristic, but rather is part of the response to the drug, in that case, however, it may be partly a response to study design.

Medical Officer Comment :
In general, the conclusions are not qualitatively different from the applicants results: similar conversion rates between the two treatment arms, and a greater risk for relapse at 6 months in the rifapentine arm.

Regarding exploratory analysis of increased risk of relapse in the rifapentine arm, there appears to be an increase in risk of about 2 times that in the rifampin arm. From our analysis, it is uncertain how sputum status at 60 days or bilateral caviation on CXR at baseline can be utilized by the clinician to direct the selection of patients at risk for relapse.

VI.E.(4) Rifamycin Resistance Issues

There were only two patients from whom rifampin-resistant M.Tb was isolated in a follow-up sputum culture. One was on the rifampin treatment arm and currently no RFLP (restriction fragment length polymorphism) is available in order to determine if this was the original isolate which developed resistance or a new infection. The other isolate was from a patient in the rifapentine arm. The RFLP was available and was reported to be different from the baseline isolate; hence, it is assumed that this was a new infection and not the development of a resistant isolate. It appears that resistance to rifampin did not develop during this study. Statements regarding the development of rifapentine resistance cannot be made since the break-points for resistance have not been established. In general, cross-resistance between rifampin and rifapentine is expected.

VI.F. Efficacy Summary

For the treatment of pulmonary tuberculosis, rifapentine appears to be comparable regarding conversion rates (at or before the end of treatment), however, greater risk of relapse in the rifapentine treated group was seen at 6 months follow-up. Rifampin resistance was not seen to develop among the patients followed in this study. Additional discussion regarding relapse rates and recommendations for the use of rifapentine in the induction and continuation phase, as well as comments from the committee regarding recommended populations or potential restrictions for the use of rifapentine was sought from the Advisory Committee Meeting, held May 5, 1998.

VII. Safety Review

VII.A. Study Drug Exposure

A total of 722 patients (361 per arm) were exposed to study medication. This group of patients makes up the safety database for the controlled clinical trial. Study drug exposure was also reviewed in Section VI.C.(3). of this NDA review and is based upon the safety data presented in the original application through November 8, 1997.
The applicant did provide a safety update including additional safety data through July 1997.

Medical Officer Comment:
Overall, the safety update changed the percentages reported below very little. The safety conclusions remain unchanged. For purposes of labeling, the treatment-related adverse events are updated in this review, the remainder of the information reported here reflects the original application.

VII.B. Adverse Events

Adverse events during the intensive phase of therapy were balanced between treatment arms. 85.4% of rifampin and 87.8% of rifapentine patients experienced one or more adverse events during this phase. The most frequently reported events were as follows:

All Adverse Events During Intensive Treatment Phase

Adverse Event	Rifampin Arm (n=361)	Rifapentine Arm (n=361)
Hyperuricemia	23.0%	31.9%
Overdose	7.8%	13.6%
Anemia	11.4%	11.4%
Pyuria	15.5%	10.8%
Hematuria	10.5%	10.8%
Lymphopenia	10.2%	10.5%
Proteinuria	14.7%	10.0%

NDA Table 41, S8-V1.68-p110

Medical Officer Comment:
The higher incidence of hyperuricemia during intensive phase therapy in the rifapentine arm is notable. Hyperuricemia is generally attributed to either pyrazinamide or ethambutol, and each of these drugs were dosed identically during the intensive phase of therapy in each treatment arm. It is possible that rifapentine may result in some sort of metabolic interaction with either pyrazinamide or ethambutol to result in this finding.

Importantly, the hyperuricemia resolved after the intensive phase of therapy in both treatment arms, and the incidence of clinically significant findings related to hyperuricemia (such as arthralgia or arthritis) were balanced between treatment arms during both treatment phases. Arthralgia was noted in 3.6% of patients in each arm, and arthritis in 1.4%of rifampin and 1.1% of rifapentine patients.

A more complete discussion of the overdose category follows in Section VII.B.(5.).

Adverse events during the continuation phase of therapy were also comparable between treatment arms. 69.7% of rifampin and 73.2% of rifapentine patients experienced one or more adverse events during this treatment phase. The most frequently reported adverse events (events which occurred in > 5% of patients in either treatment arm) during the continuation phase and during 3 months of follow-up are listed below:

All Adverse Events During Continuation Treatment Phase & 3 Months Follow-Up

Adverse Event	Rifampin Arm (n=304)	Rifapentine Arm (n=317)
Pyuria	11.8%	14.8%
Hematuria	8.9%	10.1%
UTI	3.3%	7.3%
Hyperkalemia	6.9%	6.3%
Neutropenia	7.9%	8.5%
Influenza Infection	3.9%	6.9%

NDA Table 41, S8-V1.68-p110

Adverse events during the continuation phase of therapy were less common than during the intensive phase. Pyuria and UTI were somewhat more common in the rifapentine arm, as were influenza infections.

The two body systems with the greatest discrepancy of total adverse events between treatment arms were the Body as a Whole-General, and the Respiratory System. Overall, 29.9% of rifampin versus 39.1% of rifapentine patients experienced Body as a Whole adverse events, however this discrepancy was largely due to a higher incidence of overdosage in the rifapentine arm. These overdosages were not associated with any related adverse event usually, and therefore were well-tolerated; most were due to errors in the calculations of the body weight-based doses of the non-rifamycin class study drugs. Respiratory system adverse events occurred overall in 22.4% of rifampin versus 28.0% of rifapentine patients. This difference was most marked during the intensive phase of therapy when 13.0% of rifampin versus 19.7% of rifapentine subjects complained of respiratory system events. This difference did not reflect any specific event, but rather the overall spectrum of respiratory complaints.

Medical Officer Comment:
While subtle, it is possible that the difference in respiratory system complaints between treatment arms may reflect a somewhat reduced efficacy of the rifapentine regimen, particularly during the intensive phase of therapy. Rifapentine dosed twice weekly during the intensive phase of therapy may not reduce respiratory complaints as well as the rifampin regimen dosed daily.

VII.B.(1) Treatment Related Adverse Events

Approximately half of the adverse events experienced by patients in each treatment arm were possibly, probably, or definitely attributed to study drugs. During the intensive phase 42.1% or rifampin and 46.0% of rifapentine patients experience treatment related adverse events. Those events reported in more than 5% of patients in either treatment arm are summarized in the following table:

Treatment Related Adverse Events During Intensive Treatment Phase (Hepatobiliary Events Broken Down Specifically)

Adverse Event	Rifampin Arm (n=361)	Rifapentine Arm (n=361)
Hyperuricemia	13.9%	19.9%
Rash	5.8%	2.5%
Hepatobiliary	6.1%	5.0%
-increased ALT	4.4%	3.6%
-increase AST	4.2%	3.6%
-bilirubinemia	0.6%	0.6%
-hepatomegaly	0.3%	0
-liver tenderness	0.3%	0
-jaundice	0	0.3%

NDA Table 42, S8-V1.68-p126 (original NDA)

Other than hyperuricemia, the most common treatment related adverse events during the intensive phase of treatment were more frequent in the rifampin arm than rifapentine arm. Hyperuricemia was already discussed in detail in this review in section VII.B. Hepatobiliary events were balanced between treatment arms.

During the continuation phase, treatment-related adverse events occurred in only 15.1% of rifampin and 16.1% of the rifapentine patients. The most common system organ class reported was hematologic (5.6% and 5.7% of rifampin and rifapentine patients, respectively), renal and urinary (2.6% and 5.0% of rifampin and rifapentine patients, respectively), and hepatobiliary (3.3% and 2.5% of rifampin and rifapentine patients, respectively). Thus. there were no imbalances or concerning findings regarding the treatment-related adverse events which occurred during the continuation phase.

The applicant submitted an integrated safety update along with the efficacy supplement in March of 1998. The treatment-related adverse events occurring in > 1% of patients in the 0008 study are displayed below.

Table 2-3. Treatment–Related Adverse Events Occurring in ≥1% of the Patients in Study 0008						
	Intensive Phase [1]		*Continuation Phase* [2]		*Total*	
Preferred Term	*Rifapentine Combination (N=361) N (%)*	*Rifampin Combination (N=361) N (%)*	*Rifapentine Combination (N=321) N (%)*	*Rifampin Combination (N=306) N (%)*	*Rifapentine Combination (N=361) N (%)*	*Rifampin Combination (N=361) N (%)*
Hyperuricemia	77 (21.3)	55 (15.2)	0	0	77 (21.3)	55 (15.2)
ALT increased	14 (3.9)	17 (4.7)	5 (1.6)	7 (2.3)	19 (5.3)	24 (6.6)
AST increased	12 (3.3)	16 (4.4)	5 (1.6)	7 (2.3)	16 (4.4)	23 (6.4)
Neutropenia	7 (1.9)	9 (2.5)	12 (3.7)	9 (2.9)	18 (5.0)	18 (5.0)
Pyuria	12 (3.3)	10 (2.8)	6 (1.9)	2 (0.7)	15 (4.2)	12 (3.3)
Proteinuria	15 (4.2)	10 (2.8)	2 (0.6)	1 (0.3)	17 (4.7)	11 (3.0)
Hematuria	10 (2.8)	11 (3.0)	4 (1.2)	3 (1.0)	13 (3.6)	14 (3.9)
Lymphopenia	14 (3.9)	13 (3.6)	3 (0.9)	1 (0.3)	16 (4.4)	14 (3.9)
Urinary casts	11 (3.0)	3 (0.8)	4 (1.2)	0	14 (3.9)	3 (0.8)
Rash	9 (2.5)	20 (5.5)	4 (1.2)	3 (1.0)	13 (3.6)	22 (6.1)
Pruritus	8 (2.2)	15 (4.2)	1 (0.3)	1 (0.3)	9 (2.5)	16 (4.4)
Acne	5 (1.4)	3 (0.8)	2 (0.6)	1 (0.3)	7 (1.9)	4 (1.1)
Anorexia	6 (1.7)	8 (2.2)	3 (0.9)	4 (1.3)	8 (2.2)	10 (2.8)
Anemia	7 (1.9)	9 (2.5)	2 (0.6)	1 (0.3)	9 (2.5)	10 (2.8)
Leukopenia	4 (1.1)	4 (1.1)	3 (0.9)	5 (1.6)	7 (1.9)	8 (2.2)
Arthralgia	9 (2.5)	7 (1.9)	0	0	9 (2.5)	7 (1.9)
Pain	7 (1.9)	5 (1.4)	0	1 (0.3)	7 (1.9)	6 (1.7)
Nausea	7 (1.9)	2 (0.6)	0	1 (0.3)	7 (1.9)	3 (0.8)
Vomiting	4 (1.1)	6 (1.7)	1 (0.3)	1 (0.3)	5 (1.4)	7 (1.9)
Headache	3 (0.8)	4 (1.1)	1 (0.3)	3 (1.0)	4 (1.1)	7 (1.9)
Dyspepsia	3 (0.8)	5 (1.4)	2 (0.6)	3 (1.0)	4 (1.1)	8 (2.2)
Hypertension	3 (0.8)	0 (0.0)	1 (0.3)	1 (0.3)	4 (1.1)	1 (0.3)
Dizziness	4 (1.1)	0	0	1 (0.3)	4 (1.1)	1 (0.3)
Thrombocytosis	4 (1.1)	2 (0.6)	0	0	4 (1.1)	2 (0.6)
Diarrhea	4 (1.1)	0	0	0	4 (1.1)	0
Rash maculopapular	4 (1.1)	3 (0.8)	0	0	4 (1.1)	3 (0.8)
Hemoptysis	2 (0.6)	0	2 (0.6)	0	4 (1.1)	0
Note: ≥1% refers to rifapentine in the TOTAL column.						
Note: A patient may have experienced the same adverse event more than once during the course of the study, therefore, patient counts across the columns may not equal the patient counts in the TOTAL column.						
1 Intensive Phase consisted of therapy with either rifapentine or rifampin combined with isoniazid, pyrazinamide, and ethambutol administered daily (rifapentine twice weekly) for 60 days.						
2 Continuation Phase consisted of therapy with either rifapentine or rifampin combined with isoniazid for 120 days. Rifapentine patients were dosed once weekly; rifampin patients were dosed twice weekly. Events recorded in this phase includes those reported up to 3 months after Continuation Phase therapy was completed.						

Medical Officer Comment:

The treatment-related adverse events frequencies, as reported in the safety update, have changed slightly since the original submission. However, the overall conclusions, such as a greater incidence of hyperuricemia in the rifapentine arm, remain the same. It was recommended that this table be placed in the label, as it represents events possibly, probably or definitely related to the drug regimens.

VII.B.(2) Treatment Related Adverse Events By Severity

The majority of treatment related adverse events in both treatment arms during both the intensive and continuation phases of therapy were graded as mild or moderate in severity, and the relative frequency was balanced between treatment arms. Only 5.0 and 3.9% of adverse events during the intensive phase were considered severe in the rifampin and rifapentine arms, respectively. During the continuation phase of therapy, less than 1% of adverse events in each treatment arm were considered severe.

For hyperuricemia events (all of which occurred during intensive phase therapy) the severity assessment in each treatment arm was:

mild: 10.2% of rifampin patients versus 15.8% of rifapentine patients
moderate: 1.1% of rifampin patients versus 2.8% of rifapentine patients
severe: 2.5% of rifampin patients versus 1.4% of rifapentine patients

Medical Officer Comment:

The severity breakdown of the hyperuricemia cases was comparable between treatment arms, although hyperuricemia occurred more commonly in the rifapentine arm.

For hepatobiliary events that occurred during intensive phase therapy, the severity assessment in each treatment arm was:

mild: 4.2% of rifampin patients versus 2.8% of rifapentine patients
moderate: 1.9% of rifampin patients versus 1.9% of rifapentine patients
severe: 0.6% of rifampin versus 0.3% of rifapentine patients

Medical Officer Comment:

The severity breakdown of hepatobiliary events which occurred during intensive therapy was comparable between treatment arms.

VII.B.(3) Adverse Events by Gender, Age, and Race

The majority (77%) of the safety evaluable patients in the study were male. The overall frequency of adverse events for males was somewhat higher in the rifapentine arm (46.9%) than the rifampin arm (41.8%). In females, however, the overall frequency of adverse events was more common in the rifampin arm (63.4%) than in the rifapentine arm (56.2%). Overall, adverse events occurred with greater frequency in female subjects, and were primarily driven by higher frequencies of renal/urinary, and hepatobiliary system events, as well as dermatologic events.

In the rifampin arm, rash was approximately three times more common in female patients whereas the incidence of rash by gender in the rifapentine arm was approximately the same for each gender. Hematuria occurred in 1.5% of males versus 10.8% of females in the rifampin arm, and it occurred in 2.1% of males versus 9.6% of females in the rifapentine arm. Increases in ALT occurred approximately three times more commonly in female patients in each treatment arm, however increases in AST were only slightly more common in females as compared to males within each treatment arm. Nausea, vomiting, and

anorexia were also somewhat more common in females than in males within each treatment arm.

Medical Officer Comment:
It appears that females may be more sensitive than males to rifampin regarding the incidence of rash. Females also appeared to be more inclined than males to develop hematuria when receiving either rifampin or rifapentine. Approximately three times as many females as males in either treatment arm developed increases in ALT, although the same effect did not occur for AST enzymes. Finally, nausea and vomiting and anorexia were somewhat more common in females in each arm.

The overall incidence of treatment-related adverse events by age-group revealed no particular predisposition for older patients (age $\geq$ 35) versus younger patients (age < 35) to have adverse events. For hepatic and biliary events in particular, however, there was a tendency the older subjects in each arm to have more frequent events. Hepatobiliary events, for example, occurred in 5.1 and 4.3%, respectively of rifampin and rifapentine patients who were younger, but occurred in 11.3 and 8.6%, respectively of rifampin and rifapentine patients who were older. General "Body as a whole" complaints (encompassing pain, fatigue, asthenia, and edema) were also approximately three times more common in older patients. Finally, musculoskeletal complaints were also somewhat more common in older subjects.

Medical Officer Comment:
Hepatobiliary adverse events were more common in older subjects, but this predisposition is well-recognized with tuberculosis treatment regimens. General "body as a whole" and "musculoskeletal" complaints were also somewhat more common in the elderly, as might be anticipated.

The incidence of treatment-related adverse events by race is difficult to assess due to the small numbers of Caucasian and Asian/Oriental patients who were enrolled in this study. Thus, no analyses of adverse events broken down by race were performed. A summary of adverse events experienced by the small number of Caucasian subjects is, however, provided in section VII.H. of this NDA review.

VII.B.(4) Deaths

There were 12 deaths (six in each arm) reported in the database which extended through November of 1996. None of the deaths were attributed directly to study drug by the primary investigators. A summary of deaths in the rifampin arm follows:

Deaths in the Rifampin Combination Arm

Patient	Days on Study Drugs	Cause of Death	Other Information
#0021-0005: 48 year old male with negative TB culture at baseline	123 days Continuation	Died of "sudden death" while on a bus. Cause of death unknown.	Patient missed 20 of 60 doses during the intensive phase of therapy.
#0022-0301: 27 year old male with positive TB cultures and a newly determined HIV seropositive status	29 days Intensive	Died of AIDS.	Patient compliant with study drug doses for the short duration he was in the study.
#0047-0011: 23 year old male with positive TB culture at baseline	66 days Continuation	Died of a pulmonary embolus.	Patient had extensive tuberculosis noted and was culture + on day 30, and was too weak and ill to submit a culture on day 60
#0047-0035: 43 year old male with positive TB culture at baseline	4 days Intensive	Died of a pulmonary embolus	
#0035-0005: 39 year old male with positive TB culture at baseline	1 day Intensive	Died of cardiac failure with probable liver disease	Hepatomegaly was noted 5 days prior to death and prior to treatment.
#0032-0002: 65 year old male with positive TB culture at baseline	19 days Intensive	Died due to progression of TB.	

NDA Table 54, S8-V1.68-p172

Six rifampin patients died while receiving study drug therapy: one without definitive tuberculosis, and five with tuberculosis. Two patients died very early on in the study (on day 1 and day 4, respectively), and it is difficult to attribute their deaths to either study drug toxicity or study drug failure, per se. A third patient died of progressive AIDS, and it appeared unlikely that study drug toxicity or failure played a role in his death. Two of the remaining 3 patients died of progressive tuberculosis (one of a pulmonary embolus), and did not appear to respond well to study drugs; one of these died after 19 days of therapy, and the other after receiving 66 days of therapy. The final patient died of sudden death and had negative TB cultures at baseline. In summary, therefore, two rifampin subjects had little response to therapy and appeared to die from progression of tuberculosis. There was no

clear evidence of study drug toxicity or study drug regimen failure for the remaining 4 deaths which occurred while patients were receiving the rifampin combination regimen.

The following table summarizes the six deaths in the rifapentine combination arm:

Deaths in the Rifapentine Combination Arm

Patient	Days on Study Drugs	Cause of Death	Other Information
#0030-0205: 20 year old male with positive TB culture at baseline	173 days Follow-up	Stab wound secondary to assault.	Patient compliant with therapy and was culture negative from day 120 to day 180.
#0033-0040: 50 year old male with negative TB culture at baseline	113 days Continuation	Suspected lung cancer with left apical lung mass. Biopsy via bronchoscopy negative, however.	Patient treated with palliative radiation therapy with no response and died after 108 days of treatment.
#0039-0004: 24 year old male with positive TB culture at baseline	8 days Intensive	Gunshot wound	
#0052-0002: 49 year old male with positive TB culture at baseline	20 days Intensive	Lung cancer-small cell with metastases to bone.	
#0021-0001: 61 year old male with positive TB culture at baseline	189 days Follow-up	Natural causes	Patient successfully completed therapy and was due for 6 month follow-up
#0022-0302: 44 year old male with positive TB culture at baseline	6 months into Follow-up	Lung cancer	Patient had study drugs discontinued after 59 days of treatment due to hepatitis.

NDA Table 54, S8-V1.68-p172

Two of the rifapentine subjects who died were murdered, and therefore study drug toxicity or failure appeared unlikely in these cases. Two other patients had underlying lung cancer (one case documented, one case highly suspected) and study drug failure or toxicity also appeared unlikely. One patient successfully completed therapy and was due for his 6-month follow-up appointment when he died of "natural causes." This case also does not reflect any striking evidence of an association to the rifapentine combination regimen. The most notable case, however, was the 45 year-old male who relapsed with tuberculosis and died 3 months after completing the rifapentine combination regimen.

Medical Officer Comment:

Two rifampin patients died of progressive tuberculosis and were treatment failures while one rifapentine patient suffered a TB relapse and died. Thus, deaths related to failure of the study drug regimen were rare, and were balanced between arms. None of the patient deaths appeared to be directly attributable to study drug toxicity.

VII.B.(5) Serious Adverse Events

During the study, 17.5% of rifampin patients and 24.1% of rifapentine patients reported one or more serious adverse events.

The following two tables summarize serious adverse events: the first table relates to all events, and the second to treatment related adverse events.

Incidence of All Serious Adverse Events

Serious Adverse Event	Intensive Phase		Continuation Phase and 3 months Follow-up	
	Rifampin Combination (n=361)	Rifapentine Combination (n=361)	Rifampin Combination (n=304)	Rifapentine Combination (n=317)
Death	4 (1.1%)	2 (0.6%)	2 (0.7%)	4 (1.3%)
Immediate Risk of Death	1 (0.3%)	0	0	0
Hospitalization	16 (4.4%)	7 (2.9%)	12 (3.9%)	16 (5%)
Cancer	3 (0.8%)	1 (0.3%)	0	1(0.3%)
Overdose	28 (7.8%)	54 (15%)	8 (2.6%)	14 (4.4%)
Patient Total	44 (12.2%)	60 (16.6%)	20 (6.6%)	31 (9.8%)

NDA Table 43, S8-V1.68-p134

The most common adverse event in either treatment arm was overdose. Overall, 99/722 (13.7%) of patients in the study received an overdose of study medication. Overdoses generally involved too frequent administration. For example, patients received daily doses instead of the two doses per week which was scheduled for rifapentine patients during the intensive phase, or they received daily doses instead of the one to two doses per week scheduled for patients during the continuation phase. Another common cause of overdose was incorrect weight-based doses of study drugs. It is important to note, however, that only seven of the overdosed patients had any additional adverse event associated with the actual overdose. A summary of these 7 patients follows:

Overdosed Patients with Associated Adverse Events

Patient #	Treatment	Overdose (Date Onset)	Associated Adverse Event (Date of Onset)
0028-0007	Rifampin	R/PZA x 4 doses* (12May95) R/PZA/EMB x 3 doses* (22May95)	Arthralgia/myalgia (12May95)
0030-0005	Rifampin	RPT/INH x 28 doses* (31Oct95)	Anorexia (26Dec95)
0022-0018	Rifapentine	PZA x 33 doses* EMB x 34 doses* (13 Sept95)	Hyperuricemia (13Sept95)
0030-0013	Rifapentine	PZA/EMB x 5 doses* (17Oct 95)	Hematuria (15Nov95)
0030-0224	Rifapentine	PZA x 34 doses* EMB x 32 doses* (22Mar96)	Neutropenia (4Apr96) Arthritis (16May96)
0036-0001	Rifapentine	RPT x 6 doses (600mg/day) 6 consecutive daily doses (2Jun95)	ALT increased Hyperglycemia (15June95) (Pt diabetic)
0047-0003	Rifapentine	PRT x 20 doses (600 mg/day) 20 consecutive daily doses (27Sep95)	Puritus (9Oct95)

Section C.3.17.3, Listing 7 of NDA.
*Patients weighed < 50 kg, but inadvertently received higher dosage fro patients who weighed ≥ 50 kg.

There were a total of 34 overdosed patients in the rifampin combination group compared with 65 in the rifapentine group. (These numbers differ somewhat from the total number of patients in the above table because some patients overdosed both during the intensive and continuation phase of therapy.) Of the 34 overdosed rifampin subjects: 30 received an overdose of rifampin, 22 of pyrazinamide, 18 of ethambutol, and 14 of isoniazid. Of the 65 patients who received an overdose of study medication in the rifapentine combination group, there were 32 who received an overdose of rifapentine, 21 of pyrazinamide, 11 of ethambutol, and 26 of isoniazid; in addition, two of the rifapentine patients who were classified as "overdoses" inadvertently received a dose of rifampin instead of rifapentine.

Medical Officer Comment:
Although overdoses were more common in the rifapentine treatment arm, the large majority of these overdoses were clinically benign. The difference in overdoses between treatment arms was most marked during the intensive phase of therapy, in which rifapentine was dosed twice weekly with other study medications being dosed daily. This confusing regimen is probably not ideal, and offers no benefit to reduce DOT visits.

Although overdoses were more common overall in the rifapentine arm, the actual number of rifampin versus rifapentine drug overdoses was balanced between treatment arms.

Incidence of Treatment Related Serious Adverse Events

Treatment Related Serious Adverse Event	Intensive Phase		Continuation Phase	
	Rifampin Combination (n=361)	Rifapentine Combination (n=361)	Rifampin Combination (n=304)	Rifapentine Combination (n=317)
Immediate Risk of Death	1	0	0	0
*Hospitalization	3	2	1	0
Overdose	1	5	1	0
Patient Total	4	7	2	0

*This category includes only those hospitalizations that were considered severe adverse events. For a discussion of all hospitalizations, the reader is referred to section XX of this NDA review.

NDA Table 44, S8-V1.68-p135

Serious adverse events which were considered to be treatment related occurred in 6 rifampin and 7 rifapentine patients overall for an overall incidence of less than 2% per arm. Immediate risk of death was seen in one patient on the rifampin arm, who developed renal failure. The causes of hospitalization in the 3 rifampin arm patients were peripheral neuropathy due to INH, thrombocytopenia and deep venous thrombosis. The causes of hospitalization in the 2 rifapentine arm patients included erosive gastritis and increased LFT's with bronchial carcinoma. Specific adverse events associated with overdoses were reviewed in the previous table.

VII.B.(6) Discontinuation of Study Drug Due to Adverse Events

A total of 16 (4.4%) rifampin and eight (2.2%) rifapentine patients discontinued the study drugs during the study secondary to the occurrence of an adverse event. Of the sixteen rifampin subjects, 12 discontinued during the intensive phase and 4 discontinued during the continuation phase. Of the 8 rifapentine subjects, four discontinued during the intensive phase, one discontinued during the continuation phase, and the remaining four discontinued after treatment had been stopped per protocol (during follow-up).

Reasons for study drug discontinuation during intensive phase therapy for the four rifapentine subjects are summarized below:

Pt 0039-0004: 24 year old black male who suffered a gunshot wound to the head and died after receiving 8 days of study drug medicine.

Patient 0046-0216: 44 year old black male who discontinued study drugs after 59 days of therapy. Patient had hepatitis with liver enzymes Investigator felt the

hepatitis was possibly related to study drugs. The event did not resolve; follow-up is ongoing.

Patient 0046-0607: 33 year old multiracial male with a severe urticarial rash after 1 day of therapy. Investigator felt the rash was probably related to pyrazinamide. The rash resolved within 1 week with no sequelae.

Patient 0052-0002: 49 year old white male who discontinued study drugs after 18 days of therapy due to nausea and vomiting. The investigator definitely related these symptoms to ethambutol and isoniazid. The patient ultimately died 11 days after the last dose of study drug due to metastatic small cell lung cancer.

One rifapentine patient had to discontinue study drug therapy during the continuation phase. This patient is described below:

Pt 0036-0004: 63 year old white male who discontinued study drugs after 47 days of therapy. Patient had erosive gastritis and esophagitis with bleeding, and also had acute pancreatitis by CT scan. The investigator felt that the gastritis and esophagitis were definitely related to study medications, primarily to ethambutol and isoniazid. The event resolved without sequelae, and the patient was later retreated with isoniazid and rifampin.

Medical Officer Comment:
Twelve rifampin versus 4 rifapentine subjects discontinued during the intensive phase of therapy due to an adverse event. Four rifampin versus 1 rifapentine subject discontinued the study during the continuation phase of therapy due to an adverse event. This data suggests that the rifapentine regimen appears to be tolerated at least as well as the rifampin regimen regarding the need to discontinue study drugs due to an adverse event.

There were only 12 Caucasian patients enrolled in the trial in the rifapentine arm, yet two of these patients (#0052-0002 and # 0036-0004) developed serious adverse events and discontinued study drug therapy during the intensive phase of therapy. FDA therefore requested the applicant provide a summary of serious adverse events experienced by Caucasian subjects as follows in section VII.H. of this safety review.

VII.C. Adverse Events Noted in Caucasians

Seventeen Caucasian subjects were enrolled in the rifampin arm and 12 were enrolled in the rifapentine arm. A brief summary of adverse events noted in these patients follows:

Of the 17 rifampin patients, there were 3 patients who had notable adverse events: a 35 year old female who had liver toxicity attributed to INH or rifampin after 17 days of study drug therapy (event resolved after study drugs discontinued with no sequelae), a 38 year old female hospitalized for alcoholic gastritis who nonetheless successfully completed study drug therapy, and a 56 year old female had adenocarcinoma of the lung diagnosed after 11 doses of study medication. Of these events, the only event with likely attribution to study drug was the liver toxicity.

Of the 12 rifapentine subjects, there were 5 patients who had notable adverse events. A description of each patient follows:

#0036-0001: 74 year old female diabetic hospitalized due to bladder prolapse, increased WBC in the urine, and proteinuria. This was assessed as not related to study drugs and the event resolved without sequelae. Additionally this patient was inadvertently given 6 consecutive daily doses of rifapentine at the start of treatment. Eight days after the last consecutive dose, her glucose was elevated
The increased ALT was attributed to the rifapentine overdose. Both events have since resolved without sequelae.

#0036-0004: 63 year old male with prior history of peptic ulcer disease and esophagitis who had nausea, vomiting and was hospitalized after 47 days of study drug therapy with upper gastrointestinal bleeding. Non-serious event included nausea and vomiting, hyperuricemia and elevated AST levels. The patient was diagnosed with erosive esophagitis and chronic gastritis with probably acute on chronic pancreatitis. The patient was discontinued from the study but later was retreated with isoniazid and rifampin. The event resolved with no sequelae.

#0039-0009: 36 year old female treated with 45 doses of DOT during intensive phase and all 16 required doses of isoniazid and rifampin by DOT during the continuation phase. It was noted that the patient was under-dosed with isoniazid at 600 mg for continuation doses 12 to 16 while her weight was $\geq$ 50kg. The patient had a positive culture for TB at her 3 month follow-up visit and was diagnosed a TB relapse with the same TB isolate identified by RFLP. New treatment was begun with INH/R/EMB/PZA. No serious adverse events were reported for this patient while on initial study drug therapy.

#0042-0007: 42 year old male who relapsed with the same TB isolate 3 months after completing tuberculosis therapy. He was noted to receive only 42 of the required 45 DOT doses during intensive phase therapy with a low dose of pyrazinamide given for his weight. He received all 16 doses of study drugs by DOT during the continuation phase, however he was noted to often exceed 7 days between dosing. Once relapse was determined the patient was started on INH/R/EMB/PZA /ofloxacin and streptomycin.

#0052-0002: 49 year old male who had study therapy discontinued after 19 days due to nausea and vomiting. Patient also complained of cough, loss of appetite and weight loss. The patient was eventually diagnosed with metastatic small cell cancer of the lung, and died 11 days after his last dose of study drug therapy.

Medical Officer Comment:
Of the 12 Caucasian patients enrolled in the rifapentine arm, five had adverse events or relapses which were of concern. Of the remaining 7 patients, only two were definitively cured while two discontinued the study during the continuation phase and three either had no baseline isolate or a resistant isolate and were excluded from the study. This very limited data, therefore, is not optimistic regarding the safety and efficacy of the rifapentine regimen in Caucasians. Notably, however, there are no known biological reasons why the outcome of

Caucasian patients with tuberculosis should differ overall from the largely black population enrolled in this study.

VII.D. Hospitalizations

A total of 55 patients (29 rifampin and 26 rifapentine) were hospitalized during the study. While relapses were balanced between treatment arms, it is nonetheless notable that six of the 26 rifapentine subjects were hospitalized for relapse of their tuberculosis.

VII.E. Pregnancy

Six patients in each treatment arm reported pregnancy through the November 8, 1996 data cutoff. In the rifampin combination arm, three patients tested positive for pregnancy during the continuation phase and three during follow-up. Three of these patients had normal deliveries, while the outcomes of the other three pregnancies were unknown. In the rifapentine combination arm, the outcomes of pregnant patients are summarized below:

Patient 0051-0002: (North America site): had a positive serum pregnancy test at baseline and received 4 days of intensive treatment (including one dose of 600 mg rifapentine) before she discontinued treatment. The patient subsequently had an elective abortion.

Patient 0048-0013: (South African site): was discontinued after 42 days of intensive phase therapy due to a positive pregnancy test. She had taken 10 doses of 600 mg rifapentine during that time. She had a first trimester spontaneous abortion 7 days after the last dose of study medication (9 days after her last dose of rifapentine). This resulted in hospitalization, and was recorded as a severe adverse event. The patient had a history of alcohol abuse as well.

Patient 0051-0005 (North America site): was discontinued during the continuation phase of therapy after 85 days of treatment due to a positive pregnancy test. She had received 22 doses of 600 mg rifapentine. The patient had a first trimester spontaneous abortion 16 days after the last dose. The investigator noted that the miscarriage was due to HIV infection.

Patient 0046-0014: (South African site): had a positive pregnancy test during follow-up phase. She had a normal delivery 229 days after completing the study drug regimen.

0039-0003: (North America site): was 5 months pregnant at her 12-month follow-up visit. She subsequently had a normal delivery.

0029-0002: (South African site): was pregnant during the follow-up phase, and outcome is unknown at this time.

Medical Officer Comment:

Of the 6 pregnant rifapentine subjects, 3 became pregnant during actual study drug therapy and three became pregnant during follow-up. While the outcome of the follow-up pregnancies was generally good, the fetuses were very unlikely to have been exposed to study drugs. All three of the pregnancies which occurred during study drug therapy, however, resulted in loss of the fetus: one patient had an elective abortion, and two patients

had spontaneous abortions. The two spontaneous abortions were both in the first trimester, and occurred after 42 and 22 days of study drug therapy, respectively. Extensive experience with isoniazid in pregnancy has been reported. Even though it crosses the placenta, it is not teratogenic when given during the first 4 months of gestation. Ethambutol also appears safe during pregnancy; in 650 cases in which pregnant women were treated with ethambutol, there was no evidence of fetal malformations. The primary drug of concern for pregnant women is rifampin. The action of rifampin to inhibit DNA-dependent RNA polymerases combined with its ability to cross the placenta has created concern. However, only 3% of 446 fetuses exposed in utero to rifampin had abnormalities, compared to 2% for ethambutol and 1% for isoniazid. There are virtually no data on the effects of pyrazinamide on pregnancy. The finding of two spontaneous abortions in the rifapentine arm is very concerning, since rifapentine acts through a mechanism similar to rifampin, and may also theoretically predispose to fetal loss/damage. Confounding factors include co-morbid conditions of alcohol abuse and HIV. In addition it was noted by the applicant that the spontaneous abortion rate among these patients is 20%. The rifapentine label will contain some description of the pregnancy experience as noted in the pivotal trial.

VII.F. Clinical Laboratory Evaluations

Clinical laboratory tests including hematology, chemistry, and urinalysis were performed at baseline, on study days 15, 30, end of intensive phase, day 120, and at the end of continuation phase. They were also obtained within 30 days of the 3 month follow-up visit to monitor post-treatment change. Additional testing was performed at the investigator's discretion.

VII.F.(1) Hematology

On average, patients' hemoglobin levels increased by approximately from baseline to the end of intensive therapy in each treatment arm. White blood cell counts tended to decrease by approximate and platelet counts tended to decrease by approximate in each treatment arm. All of these effects can be explained as part of the bone marrow's response to the effective treatment of the acute infectious disease.

Six rifampin patients and 7 rifapentine patients had low WBC outlier values at the end of the intensive phase of therapy. At the end of the continuation phase of therapy there were 9 rifampin and 8 rifapentine patients who had low WBC outlier values. Finally, at 3-month follow-up there were 5 rifampin and 4 rifapentine patients with low WBC outlier values. Thus, the number of patients who had low WBC counts while on therapy or after receiving therapy were quite balanced between treatment arms.

Two patients were discontinued from the study due, in part, to their hematologic laboratory parameters. The first patient (0024-0064 on rifampin) discontinued to acute hemolytic anemia with renal failure. The patient entered the study with a normal hemoglobin of This even was considered severe in nature, and was possibly related to study drugs. The second patient (0046-0216 on rifapentine) discontinued due to thrombocytopenia in conjunction with elevated liver enzymes. This patient entered the study with a platelet count This event was also considered severe in intensity and possibly related to study drugs.

Medical Officer Comment:
Hematologic toxicity, when it occurred, was balanced between treatment arms. Only two subjects had to discontinue therapy due to the occurrence of hematologic toxicity and again this represented one patient from each arm. There does not appear to be any potential for rifapentine to have any greater potential for hematologic toxicity.

VII.F.(2) Liver Function

At the end of intensive phase therapy, AST was elevated and identified as an outlier in 10 of 351 rifampin subjects compared to 8 of 352 rifapentine subjects, while ALT was elevated in 8 of 351 rifampin subjects versus 10 of 352 rifapentine subjects. During continuation phase, increases in AST were noted in 7 of 292 rifampin and 6 of 299 rifapentine patients, while ALT increases were noted in 6 of 292 rifampin and 6 of 299 rifapentine patients. Thus, the number of subjects per arm with significant liver enzyme elevations during treatment was balanced.

Three patients discontinued the study due to liver function abnormalities. These 3 subjects were:

Patient 0036-0007 (Rifampin arm): entered the study with an
At day 15 these enzymes had increased to an
. This event was considered severe and probably related to isoniazid or rifampin. Medications were stopped 2 days prior to the laboratory values due to flu-like symptoms, and the patient was subsequently permanently withdrawn from the study. The event resolved with no sequelae.

Patient 0054-0009 (Rifampin arm): entered the study with an
At day 30, patient had
Repeat values the following day were similarly quite elevated. The AST and ALT changes were definitely related to isoniazid and an elevated bilirubin of 44 umol/L was attributed to rifampin. The patient was discontinued from the study and the event resolved with the exception of a slightly elevated bilirubin with no sequelae.

Patient 0046-0216: (Rifapentine arm): entered the study with and

Bilirubin increased from
The patient was discontinued from the study due to the event. The event had not resolved and follow-up was ongoing.

Medical Officer Comment:
The incidence and severity of liver toxicity was balanced between treatment arms. The rifapentine regimen, therefore, appeared no more toxic than the rifampin regimen regarding hepatotoxicity.

VII.F.(3) Renal function

The number of patients with high applicant-defined outlier values was low (≤ 1.4%) for both treatment arms with no trends identified.

One patient (#0024-0064) discontinued the study due to hemolytic anemia and renal failure. This patient entered the study with a BUN and a creatinine of At day 15, the BUN The event was considered severe, and possibly related to study drugs. The patient was withdrawn from the study. The event resolved with no sequelae. Retreatment information is not available.

The most marked changes in urinalysis were noted at the end of the intensive phase therapy. During this time frame, there were 7.2% of rifampin and 6.0% of rifapentine subjects who had an increase in urine RBC outlier values. In addition, there were 10.1% of rifampin and 7.4% of rifapentine subjects who had high urine WBC values during this time.

Data at the end of the combination phase showed that fewer (although still comparable) percentages of patients in each treatment arm had urine RBC or WBC outlier values.

Even after being off treatment for 3 months, high urine RBC outlier values were noted for 5.8% and 5.6% of rifampin and rifapentine patients, respectively. The number of high WBC outlier values in each arm at 3 months follow-up included 10.1% of rifampin patients and 6.8% of rifapentine patients.

The relative percentage of patients with urine protein outlier values was 10.1% for rifampin versus 6.8% of rifapentine subjects at the end of intensive phase therapy. At the end of continuation phase therapy, 7.2% of rifampin and 4.7% of rifapentine patients had urine protein outlier values. Finally, at 3-month follow-up, 7.5% of rifampin and 5.0% of rifapentine patients had urine protein outlier values.

Medical Officer Comment:

There was no evidence of significant renal disease either by BUN and creatinine values or by urinalysis results during the study. While approximately 7 to 10% of patients had outlier values on their urinalysis, this often was true even during 3 month follow-up, when study drug attribution is difficult to support.

VII.G. Safety Summary

In general, the adverse events noted during the pivotal trial were balanced between treatment arms. Hyperuricemia occurred only during the intensive treatment phase, and was somewhat more common in the rifapentine arm (31.9%) than in the rifampin arm (23.0%). Notably, however, the cases of hyperuricemia were rarely associated with clinically significant findings such as arthralgia (noted in 3.6% of subjects in each treatment arm) and arthritis (noted in 1.4% of rifampin and 1.1% of rifapentine subjects. Thus, regarding overall adverse events, the rifapentine regimen appears safe when compared to the rifampin regimen.

It was notable that respiratory system adverse events occurred more commonly in the rifapentine arm during the intensive phase of therapy: 19.7% of rifapentine subjects versus 13.0% of rifampin subjects. This finding does not reflect a specific event, but rather the overall spectrum of respiratory complaints. It is possible that this finding, while not a major safety concern, could reflect that rifapentine dosed only twice weekly during the intensive phase of therapy may not reduce respiratory complaints as well as rifampin dosed daily.

An analysis of adverse events by gender revealed that females overall had a greater frequency of adverse events. Females appeared more sensitive to develop a rash while on rifampin, and were more inclined to develop hematuria regardless of treatment arm. In addition, almost three times as many females as males in either treatment arm developed increases in ALT (although, somewhat surprisingly, this effect was not noted with AST). In addition, nausea, vomiting, and anorexia were all more common in females regardless of treatment arm. If approved, product labeling for rifapentine should describe that hematuria, increases in ALT, and nausea, vomiting and anorexia occurred somewhat more commonly in females versus males.

Analyses of adverse events by race could not be performed due to the limited number of Caucasian or Asian subjects enrolled. A review of 12 Caucasian subjects enrolled in the rifapentine arm, however, revealed that five of these patients had adverse events or relapses which were notable, only two were definitively cured, two discontinued the study during the continuation phase, and three subjects had a negative or resistant baseline TB culture. While the data is extremely limited, therefore, it is recommended that post-marketing surveillance by the applicant focus on the outcome of patients broken down by race.

Deaths were equally balanced between treatment arms with six deaths in each arm. There was rarely any clear evidence of study drug toxicity or study drug failure as the cause of death. Serious adverse events other than death were relatively uncommon with the exception of study drug overdose. Overdosages were not uncommon (being the most common severe adverse in either treatment arm). However, it was rare for these overdoses to be clinically significant. The only remaining serious adverse events included hospitalization and cancer which occurred in $\leq$ 5% of patients in either arm, overall. Study drug discontinuation was relatively uncommon in each treatment arm: 16 rifampin and 8 rifapentine subjects required discontinuation of their study drugs. Based on this data, the rifapentine regimen appeared to be at least as well tolerated as the rifampin regimen.

Pregnancy occurred in six patients in the rifapentine treatment arm. Of these 6 patients, three became pregnant during actual study drug therapy, with all three pregnancies resulting in fetal loss: one elective abortion and two spontaneous abortions. This data, while limited, should be provided in the product label since there is a plausible biologic mechanism by which rifapentine might cause this finding. Rifamycins, in general, act by inhibiting DNA-dependent RNA polymerase and are able to cross the placenta. The fetus might therefore be readily exposed and potentially harmed by this therapy if exposed early on in development.

Finally, while liver toxicity rarely occurred with rifapentine, this was also seen in the rifampin treatment arm as well. Renal function was also rarely affected by the study drug

regimens. Hematologic toxicity was also rare, with only one patient in each arm discontinuing the study due to abnormalities. Thus, the rifapentine regimen appeared comparable to the rifampin regimen regarding these various laboratory parameters.

In conclusion, the safety of rifapentine itself is difficult to ascertain since the study drugs were administered as a regimen. Overall, however, the rifapentine regimen appeared to be comparable to the rifampin regimen regarding adverse events of clinical significance.

VII. Anti-Viral Advisory Committee Hearing: May 5, 1998
Treatment of Pulmonary Tuberculosis.
(http://www.fda.gov/ohrms/dockets/ac/98/transcript/3415t2.pdf)

Hoechst Marion Roussel, Inc. submitted New Drug Application 21-024 for rifapentine to the FDA December, 1997. This submission included interim efficacy results based on data collected through November 8, 1996 from a clinical trial (Protocol 0047PR0008) for the treatment of tuberculosis. To better understand the incidence of relapse, the applicant with prior FDA agreement, submitted a clinical update on March 4, 1998 which summarized follow-up data through a July 1997 cut-off date. By this date, all of the patients would have been treated and followed to the 6 month post therapy visit.

Rifapentine was given orphan drug status for the treatment of tuberculosis in June of 1995. The current submission is based upon the accelerated approval regulations (21CRF 314 subpart H). In this case, the 6 month relapse rate is being used as a surrogate for the 2 year relapse rate.

During the advisory committee meeting a closed session was held, during which CDC made a presentation to the advisory committee, the topic of which is confidential.

The committee voted to recommend approval of rifapentine for the treatment of pulmonary tuberculosis, with only one dissenting vote. The committee was concerned that rifapentine be used with extreme caution, if at all in HIV positive patients. This was due to both the information from a study presented by the CDC where rifamycin resistance developed in the HIV-positive patients, and the potential for rifapentine to significantly reduce the AUC (area under the curve) of the protease inhibitor, Indinavir. It was felt that experts in the field of HIV and TB may need to utilize the agent, and given current knowledge of pharmacokinetics and the management of TB, more frequent dosing in the intensive phase may prevent resistance. This was speculation not based upon clinical study information. In addition, it was felt that in HIV-infected patients, the continuation phase should be biweekly, until further studies can future clarify these issues.

In general the committee believed that rifampin and rifapentine would be comparable agents, however, currently the optimal therapeutic regimen has not been determined for rifapentine. It was pointed out that clinicians utilize rifampin differently than they did 25 years ago when it was approved.

Finally, although the adherence to companion drugs was an issue of interest to the committee, there was speculation regarding other reasons for the higher relapse rates in the rifapentine group. These include the dosing of INH during the continuation phase and the difference in pharmacokinetic profile, ie. the longer half-life of rifapentine would essentially place the patient on mono-therapy with rifapentine for a period of time each week. However, neither INH nor rifampin resistance was seen in the submitted study.

It was recommended not to restrict the use of rifapentine to specialty groups, but that clear explanation of study dosing and results be placed in the label for the clinician to use in decision making.

The committee recommended further studies, including the completion of the US CDC Study 22, which utilizes rifapentine in the last 4 months of therapy at a weekly dose with INH, and standard rifampin therapy in the first two months of intensive therapy. Many of the group felt that perhaps the optimal use would be 6 months of thrice weekly therapy, however, no data exist upon which to base that recommendation. The committee recommended further study into these types of regimens.

IX. Overall Summary of Efficacy and Safety

The efficacy of rifapentine was demonstrated in a single, open-label, randomized, active controlled trial. The rifapentine regimen was similar to the rifampin regimen in converting sputum cultures to negative at the end of treatment (6 months). However, there were approximately twice as many relapses in the rifapentine arm than the rifampin arm 6 months after treatment. Exploratory analysis by the applicant suggested one possible reason for the higher relapse rate. Compliance with the companion drugs in the rifapentine arm was a risk factor for relapse. While this may explain some of the difference additional factors which were unable to be tested in this study may have had an influence on the higher relapse rate. It was felt by many on the advisory committee that a thrice weekly dose of rifapentine may be the optimal dose, however, there is not data available upon which to make this recommendation. Thus, the importance of adherence to the regimen is stressed in the label. The development of resistance to rifampin was not seen in the pivotal clinical trial.

The safety profile was similar to that of rifampin with one exception. There was a greater rate of hyperuricemia in during the first two months of therapy (intensive phase) for the rifapentine arm compared to the rifampin arm.

Six pregnancies occurred on the rifapentine arm; two had normal deliveries, two had first trimester spontaneous abortions, one had an elective abortion and one patient was lost to follow-up. Of the two patients who spontaneously aborted, co-morbid conditions of ethanol abuse in one and HIV infection in the other were noted.

Finally, experience in the treatment of TB in the context of HIV infection was discussed. Limited data are available for the use of rifapentine in HIV positive patients. The CDC

study demonstrated a possible risk for the development of rifapentine resistant TB isolates. Drug-drug interaction studies with Crixivan demonstrated an effect similar to that of rifampin, that is, significant decrease in AUC of Crixivan. It was recommended that this information be placed in the label and further studies be considered in HIV positive patients. Extreme caution should be taken if rifapentine is administered to HIV positive patients.

X. Label:

Please refer to the finalized negotiated label contained in the approval packet. Labeling concerns involved the following issues:

1. Clearly stated primary efficacy outcomes: comparable conversion rates with greater relapse rates at 6 month follow-up for rifapentine.

2. Potential drug-drug interactions, especially with protease inhibitors. The concomitant use of rifampin with protease inhibitors is contraindicated. The advisory committee did not recommend an absolute contraindication, but rather strong wording describing the interaction for practitioners in the label.

3. Inclusion of information regarding HIV positive patients and the development of rifapentine resistance in the CDC study.

4. Clear use instructions especially in the first two months of therapy: companion medications are given DAILY while rifapentine is given twice per week.

5. Increased absorption of rifapentine with food.

6. Information regarding human pregnancy outcomes was described in the label.

It is recommended that Rifapentine (Priftin®) be approved for the treatment of pulmonary tuberculosis.

CC: ORM-590 Division Files
NDA 21-024 File
Concurrences:
Officer Director ODE IV: Murphy, D. /S/
Division Director ORM-590: Goldberger, M.
Team Leader: Cavaillé-Coll, M. /S/ 4.24.98

Appendix I: References

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APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 21-024
HFD-590/DivDir/Goldberger
HFD-590/DepDivDir/Albrecht
HFD-590/MOTL/Cavaillé-Coll
HFD-590/MO/Korvick
HFD-590/Chem/SmithJ
HFD-590/Micro/Gosey
HFD-590/Pharm/McMaster
HFD-880/Biopharm/Kumi
HFD-725/Stat/Hammerstrom
HFD-590/ CSO/Atkins
HFD-880/Biopharm/Davit

APPEARS THIS WAY
ON ORIGINAL