CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-361

STATISTICAL REVIEW(S)

U S Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number	21-361
Drug Name	rifaximin tablets
Indication(s)	Treatment traveler s diarrhea
Applicant	Salix Pharmaceuticals Inc
Date(s)	Stamp date November 26 2003
	PDUFA date May 26 2004
	Review date May 3 2004
Review Priority	Standard Resubmission (6 months)
Biometrics Division	Division of Biometrics III (HFD 725)
Statistical Reviewer	Cheryl Dixon, Ph D
Concurring Reviewers	Karen Higgins, Sc D , Team Leader
Medical Division	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
Clinical Team	Regina Alivisatos, M D , Medical Officer
	Leonard Sacks, M D Team Leader
Project Manager	Andrei Nabakowski

Keywords clinical studies, NDA review traveler s diarrhea

Table of Contents

1. EXECUTIVE SUMMARY

1 1 Conclusions and Recommendations

The clinical efficacy, decreased time to last unformed stool (TLUS), of rifaximin 200 mg po tid for 3 days in the treatment of traveler's diarrhea had been shown in one placebo controlled study (RFID9801- original submission) This resubmission contains a second placebo controlled study (RFID3001) which provides additional data to support this claim *E coli* is the only baseline pathogen with sufficient numbers to determine the clinical efficacy of rifaximin by pathogen The TLUS for subjects with *E coli* as a baseline pathogen was shorter when treated with rifaximin as compared to placebo Sufficient evidence to show that rifaximin is better than placebo microbiologically has not been provided

1 2 Brief Overview of Clinical Studies

This resubmission contains the results of a second Phase 3 randomized, double-blind, placebo controlled study of rifaximin 200 mg po tid for 3 days in the treatment of traveler's diarrhea (Study RFID3001) The study also included a ciprofloxacin treatment arm to provide an active control to validate the study findings Study RFID3001 was conducted at sites in Mexico, Guatemala, Peru, and India The primary efficacy endpoint was TLUS

1 3 Statistical Issues and Findings

The results of the primary analysis of TLUS in Study RFID3001 showed a significant treatment by center interaction Therefore, all discussion of the results from this study must be provided separately for each center TLUS for rifaximin and ciprofloxacin treated patients was shorter than that seen for placebo patients at the Guatemala and Calcutta centers The median TLUS for rifaximin at these centers was approximately 24 hours compared to 42 hours or longer for placebo The results for Guatemala in this study are similar to those seen for Guatemala in study RFID9801 At the Mexico center, the median TLUS for the rifaximin treated group (33 hours) is slightly longer than the median TLUS seen for placebo (27 hours) The median TLUS seen for placebo at this site was shorter than what was seen for placebo at any of the other centers The rifaximin results seen at the Mexico center in this study was similar to what was seen at the Mexico site in the previous study The median TLUS at the Goa site was greater than 70 hours for all three treatment groups Since the positive control arm of ciprofloxacin had a prolonged TLUS as well, something else must have occurred at this center to affect the efficacy results This can not be explained by the data that was collected though

The results for the population of subjects who had a baseline pathogen and for the population of subjects who had *E coli* as a baseline pathogen were similar to those for the overall population

2. INTRODUCTION

2 1 Overview

This submission provides a complete response to an October 25, 2002 approvable letter sent to the Applicant regarding the original rifaximin NDA The Applicant was informed that in order to obtain approval a second adequate and well-controlled clinical trial using the 200 mg po tid regimen that confirmed the clinical efficacy demonstrated in Study RFID9801 should be submitted (Please refer to the original Statistical Review and Evaluation dated September 16, 2002 for a complete discussion of Study RFID9801) The approvable letter stated that the additional trial should demonstrate a clinically meaningful benefit and a statistically significant reduction in the duration of diarrhea between rifaximin and placebo regimens

In order to address these requests, the Applicant has submitted the results of study RFID3001 RFID3001 was entitled "A randomized, double-blind, multi-center, comparative study of rifaximin vs placebo vs ciprofloxacin in the treatment of travelers' diarrhea due to enteropathogenic organisms " This study was designed primarily to demonstrate the efficacy of rifaximin 200 mg tid compared to placebo The ciprofloxacin arm was included to provide an active control to validate the study findings The Division was highly involved with the design of this study

2 2 Data Sources

The data analyzed in this review comes from the Phase 3 study submitted as confirmation of Study RFID9801 submitted in the original submission The RFID3001 study report and the datasets provided in the electronic submission were reviewed These can be found in the electronic submission located at \\Cdsesub1\n21361\N_000\2003-12-09

3 STATISTICAL EVALUATION

3 1 Evaluation of Efficacy

3 1 1 Study Design

Study RFID3001 was a Phase 3 randomized, double-blind, placebo and active controlled trial in travelers affected by acute diarrhea The study was conducted in Mexico (Guadalajara, Cuernavaca, and Puerto Vallarta), Guatemala, India (Calcutta and Goa), and Peru Goa randomized approximately 30% of the subjects, followed by Guatemala (26%) and Calcutta (22%) Subjects were randomized to receive treatment with rifaximin, placebo, or ciprofloxacin in a 2 1 1 ratio Rifaximin subjects received a 200 mg rifaximin tablet tid along with 1 placebo capsule tid Placebo subjects received 2 placebo capsules tid Ciprofloxacin subjects received two 250 mg capsules bid plus a middle dose of 2 placebo

capsules Therapy was taken for 3 days and was to begin no later than 72 hours from the onset of diarrhea

Eligible subjects included adult, non-indigenous travelers who showed evidence of acute diarrhea defined as 3 or more unformed stools during the 24 hours preceding enrollment, accompanied by 1 or more of the following signs and symptoms abdominal pain or cramps, excessive gas/flatulence, nausea, vomiting, fever, fecal urgency, blood and/or mucus in the stool, or tenesmus The total duration of diarrhea was not to have been more than 72 hours The study included 3 clinic visits Visit 1 was the screening visit and beginning of treatment Subjects returned to the clinic 24 hours after the first dose (Visit 2) and again 24 to 48 hours after the last dose of study medication (Visit 3) Stool samples were provided at each of the visits Subjects maintained daily diaries on days 1 to 5 The diaries were to document the date, time, and consistency of stools and to record the symptoms of diarrheal syndrome

Efficacy was assessed by the time to return to normal, formed stools and resolution of symptoms Stools were classified as formed (retained its shape), soft (assumes the shaped of the container and cannot be poured), or watery (can be poured) Both soft and watery stools were considered unformed and abnormal A subject was considered "well" when one of the following conditions was met

- No watery stools and no more than 2 soft stools had been passed in a 24 hour period with no other clinical symptoms except for mild excess gas/flatulence
- No unformed stools had been passed in a 48 hour period and no fever, with or without other clinical symptoms

Time to last unformed stool (TLUS) was defined as the interval from the first dose ending with the last unformed stool passed after which wellness was declared Subjects who had no unformed stools after the start of study medication were defined as having a TLUS of 0 hours Subjects for whom TLUS could not be calculated because they were terminated early due to treatment failure or who completed the study without demonstrating wellness were censored as having a TLUS of 120 hours Subjects who terminated early for reasons other than treatment failure had a censored TLUS at the time of the last available information on unformed stools

TLUS was the primary efficacy endpoint The distribution of TLUS was summarized using Kaplan-Meier estimates The primary efficacy analysis was the comparison of TLUS between rifaximin and placebo using a Cox proportional hazards model with treatment group and center as independent variables A treatment by center term was also incorporated to assess potential treatment by center interactions Centers with 5 or fewer subjects per treatment arm were pooled with geographically related centers to form analysis centers Secondary endpoints included the proportion of subjects with wellness, the proportion of subjects with treatment failure, and the proportion of subjects with microbiologic eradication The treatment groups were compared with respect to these endpoints using the chi-square test Secondary analyses included comparisons of the placebo and ciprofloxacin treatment arms and of the ciprofloxacin and rifaximin treatment arms

A total of 400 subjects were to be enrolled approximately 200 subjects in the rifaximin arm, 100 subjects in the placebo arm, and 100 subjects in the ciprofloxacin arm The sample size

was based on the hazard ratio for comparing TLUS of rifaximin to placebo estimated in study RFID9801 Assuming a similar hazard ratio of 1 78 and TLUS distribution, this study has over 90% power to demonstrate the superiority of rifaximin to placebo

The intent to treat (ITT) population was defined as all subjects randomized to treatment The MITT population was defined as all subjects with a positive pretreatment stool sample and had a post-treatment sample The Applicant also defined efficacy evaluable populations defined as subjects who met inclusion and exclusion criteria, and did not have major protocol violations

Reviewer's Comment *The Division does not usually consider the MITT population defined by the Applicant as an ITT-type population since this population excluded subjects based on post-baseline information Very few subjects were excluded from the MITT population for this reason (2 rifaximin 1 placebo and 6 ciprofloxacin) These exclusions do not affect the results so the Applicant s MITT population will be used throughout this review In addition few subjects were excluded from the EE population Therefore this review will only discuss the ITT and MITT populations*

3 1 2 Patient Demographics

A total of 399 unique patients were randomized to receive study treatment, 197 were randomized to receive rifaximin, 101 to receive placebo, and 101 to receive ciprofloxacin Two subjects were enrolled twice Both subjects received rifaximin twice The data from the second randomizations for these subjects are excluded from the efficacy analyses but are included in the safety analyses A total of 44 patients discontinued the study, 20 (10 2%) from the rifaximin group, 17 (16 8%) from the placebo group, and 7 (6 9%) from the ciprofloxacin group In the rifaximin and placebo groups, the most common reason for discontinuation was lack of efficacy (8 6% and 11 9%, respectively) The most common reason for discontinuation in the ciprofloxacin group was adverse event (3 0%) The MITT population consisted of 128 rifaximin patients, 62 placebo patients, and 58 ciprofloxacin patients

Table 1 summarizes the demographic and baseline characteristics of the ITT population There were no significant differences across treatment groups Just over half of the patients were male The mean age of the patients was 33 years with a range of 18 to 80 years

Table 1
Demographic and Baseline Characteristics (ITT)

	Treatment Group		
	Rifaximin	**Placebo**	**Ciprofloxacin**
# Patients	197	101	101
Gender			
Male	99 (50 3)	56 (55 4)	52 (51 5)
Female	98 (49 7)	45 (44 6)	49 (48 5)
Age mean (SD)	32 5 (13 3)	33 4 (14 1)	34 2 (14 4)
min, max	18, 79	18, 80	18, 72
Race			
White	166 (84 3)	83 (82 2)	80 (79 2)
Black	1 (0 5)	1 (1 0)	3 (3 0)
Hispanic	20 (10 2)	8 (7 9)	12 (11 9)
Asian	7 (3 6)	7 (6 9)	4 (4 0)
Other	3 (1 5)	2 (2 0)	2 (2 0)
Study Site			
Calcutta, India	43 (21 8)	23 (22 8)	23 (22 8)
Goa, India	58 (29 4)	29 (28 7)	30 (29 7)
Antigua Guatemala	51 (25 9)	26 (25 7)	26 (25 7)
Guadalajara Mexico	32 (16 2)	17 (16 8)	16 (15 8)
Cuernavaca Mexico	9 (4 6)	5 (5 0)	5 (5 0)
Puerto Vallarta Mexico	2 (1 0)	1 (1 0)	0
Lima Peru	2 (1 0)	0	1 (1 0)
Baseline Pathogen			
Yes	130 (66 0)	63 (62 4)	64 (63 4)
No	67 (34 0)	38 (37 6)	37 (36 6)

Reviewer's Comment *For the purpose of further analyses study sites with 5 or fewer subjects in any treatment arm will be pooled with the geographically nearest study site to create analysis centers Therefore the 3 Mexico sites will be pooled and treated as one analysis center and the Guatemala and Peru study sites will be pooled and treated as one analysis center*

3 1 3 Efficacy Results

The results of TLUS are presented in Table 2 and Table 3 for the ITT and MITT populations, respectively The results are presented by analysis center because there was a significant treatment by center interaction detected when the Cox proportional hazards model including terms for treatment, analysis center, and treatment by analysis center was fit For the primary comparison, rifaximin and placebo, the p-value for the treatment by center interaction was 0 0809 for the ITT population and 0 0281 for the MITT population

Table 2
Median TLUS by Analysis Center (ITT population)

	Rifaximin	Placebo	Cipro
Calcutta, India	24 5 (n=43)	NC (n=23)	24 1 (n=23)
Goa, India	72 0 (n=58)	69 7 (n=29)	70 5 (n=30)
Guatemala and Peru	23 5 (n=53)	42 4 (n=26)	20 8 (n=27)
Mexico sites	33 0 (n=43)	26 7 (n=23)	15 5 (n=21)

NC=not calculable median TLUS could not be calculated if more than half of the subjects in the group failed to achieve wellness

Table 3
Median TLUS by Analysis Center (MITT population)

	Rifaximin	Placebo	Cipro
Calcutta, India	24 5 (n=29)	NC (n=16)	17 7 (n=17)
Goa India	NC (n=41)	67 5 (n=18)	70 5 (n=20)
Guatemala and Peru	23 8 (n=33)	41 35 (n=16)	24 4 (n=9)
Mexico sites	44 8 (n=25)	22 5 (n=12)	12 3 (n=12)

NC=not calculable median TLUS could not be calculated if more than half of the subjects in the group failed to achieve wellness

As can seen from the above tables, the TLUS patterns seen for the Calcutta and Guatemala analysis centers were similar TLUS for rifaximin and ciprofloxacin treated patients was shorter than that seen for placebo patients at these centers TLUS at the Goa site was high and this holds for all three treatment groups not just placebo At the Mexico analysis center, TLUS for the rifaximin treated group is slightly longer than the TLUS seen for placebo Due to the small sample sizes, further statistical testing was not performed

Reviewer's comment *The Applicant claims that the difference between rifaximin and placebo among analysis centers was quantitative rather than qualitative and caused primarily because of the results seen for the Goa site Therefore, they ignore the significant treatment by center interaction and report overall study results This reviewer does not agree with that statement Therefore study results in this review will be discussed and interpreted separately for each analysis center*

The only pathogen with sufficient numbers to perform an analysis of TLUS by center was diarrheagenic *E coli* These results (Table 4) are similar to those seen for the overall MITT population

Table 4

Median TLUS by Analysis Center for Subjects with *E coli* (MITT population)

	Rifaximin	Placebo	Cipro
Calcutta, India	26 4 (n=23)	NC (n=12)	17 6 (n=14)
Goa, India	47 3 (n=19)	69 7 (n=11)	70 3 (n=16)
Guatemala and Peru	10 2 (n=27)	42 4 (n=13)	24 6 (n=8)
Mexico sites	42 7 (n=17)	5 0 (n=9)	4 5 (n=10)

NC=not calculable median TLUS could not be calculated if more than half of the subjects in the group failed to achieve wellness

Secondary endpoints included the proportion of subjects who had wellness declared and the proportion of subjects who were treatment failures These results are presented in Table 5 for the ITT population The rates of wellness and treatment failure are numerically better for the rifaximin treated patients compared to placebo treated patients at all centers with the exception of Goa At the Goa site, the rates of wellness are not different for any of the treatment groups including ciprofloxacin, the positive control There are also more rifaximin patients at this site with treatment failure as compared to the other patients treated at this site or even other rifaximin patients treated at the remaining sites The results (not shown) for the MITT population are similar

Table 5

Secondary Endpoints (ITT Population)

Center	Endpoint	Rifaximin	Placebo	Cipro
Calcutta India	Wellness	38/43 (88 4)	11/23 (47 8)	21/23 (91 3)
	Treatment Failure	3/43 (7 0)	9/23 (39 1)	0/23 (0 0)
Goa, India	Wellness	30/58 (51 7)	15/29 (51 7)	16/30 (53 3)
	Treatment Failure	15/58 (53 6)	8/29 (27 6)	4/30 (13 3)
Guatemala and Peru	Wellness	47/53 (88 7)	21/26 (80 8)	26/27 (96 3)
	Treatment Failure	6/53 (11 3)	5/26 (19 2)	1/27 (3 7)
Mexico sites	Wellness	36/43 (83 7)	15/23 (65 2)	16/21 (76 2)
	Treatment Failure	5/43 (11 6)	5/23 (21 7)	2/21 (9 5)

Microbiologic eradication rates for subjects who had *E coli* at baseline are presented in Table 6 The overall eradication rates varied for each of the treatment groups depending on the analysis center The rate of microbiological eradication of *E coli* for rifaximin treated subjects varies from at least 67% to 82% Differences between rifaximin and placebo could not be detected This is in part due to the small sample sizes at each center and may also be due to the self limiting nature of the disease

Table 6

Microbiologic Eradication by Analysis Center for Subjects with *E coli* (MITT population)

	Rifaximin	Placebo	Cipro
Calcutta, India	17/23(73 9)	7/12(58 3)	12/14(85 7)
Goa, India	13/19(68 4)	9/11(81 8)	15/16(93 8)
Guatemala and Peru	18/27(66 7)	9/13(69 2)	6/8(75 0)
Mexico sites	14/17(82 4)	5/9(55 6)	10/10(100 0)

3 2 Evaluation of Safety

A total of 53 (26 6%) subjects in the rifaximin group, 25 (25 0%) subjects in the placebo group, and 24 (24 0%) subjects in the ciprofloxacin group experienced at least one adverse event Serious adverse events were reported in 2 subjects (1 rifaximin, 1 placebo) Nine subjects (4 rifaximin, 2 placebo, 3 ciprofloxacin) discontinued study drug due to a treatment-emergent adverse event There were no deaths during the study

For a detailed review of the safety data, please see the medical officer's review

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4 1 Gender, Race and Age

There was no significant difference in TLUS by gender when compared to the overall study population The majority of the subjects in this study were white (82%) and less than the age of 40 (75%) Therefore differences due to race or age cannot be assessed using this data

4 2 Other Special/Subgroup Populations

Fever and blood in the stool are predictors of more severe diarrhea TLUS was analyzed for subjects who had fever and/or blood in the stool at baseline and for those without fever or blood in the stool Samples sizes are too small to allow statistical testing There is, however, a trend that indicates that TLUS is prolonged for subjects who had fever and/or blood in the stool at baseline compared to those who did not have fever or blood in the stool at baseline

5 SUMMARY AND CONCLUSIONS

5 1 Statistical Issues and Collective Evidence

The primary issue regarding the interpretation of the results from this study is the significant treatment by center interaction The Applicant claims that the significant interaction is primarily due to the higher TLUS seen at the Goa site and that the extended TLUS for this site was related to missing diary data from this site As claimed by the Applicant, the missing diary data would then artificially prolong the time Further investigation of the results for this site does not support this claim With the exception of 4 patients (1 rifaximin, 1 ciprofloxacin, and 2 placebo patients) missing diary information is not the correct term Insufficient diary data may be more appropriate The majority of the subjects at the Goa site had diary data through day 3 and those who did not have data through day 3 were already

declared treatment failures Excluding the treatment failures, 12 rifaximin, 9 ciprofloxacin, and 4 placebo patients were considered as not achieving wellness but were also not considered treatment failures because of insufficient diary data past day 3 Even if complete diary data was collected for these patients so that wellness could be assessed, the majority of the rifaximin subjects would have TLUS greater than 60 hours and the ciprofloxacin TLUS would be greater than 48 hours The placebo subjects were most likely treatment failures and would have censored TLUS of 120 hours Thus, Goa would still have prolonged TLUS compared to the rest of the sites The interpretation of the results for this site is affected by something else that is not explained by the data collected The concern caused by this is not as worrisome since this is occurring across all 3 treatment groups, including the positive control arm of ciprofloxacin

The Mexico site also plays a part in the significant treatment by center interaction At this site, the median TLUS for the placebo arm was lower than one might expect This lower median TLUS is due in part to the small sample size and the fact that a few of these subjects had a TLUS of 0 Further investigation of the diary data from this site, shows that at least one of the placebo patients who met the requirements for a TLUS of 0 suffered a relapse just after wellness was claimed If this patient was not considered as having achieved wellness, the median TLUS would be extended and closer to what was observed at the other sites

The remaining centers, Calcutta and Guatemala, have similar TLUS patterns Rifaximin treated subjects have a shorter median TLUS than placebo treated subjects This is true for all subjects, those subjects with a baseline pathogen, and those subjects who have *E coli* as a baseline pathogen In addition, the results seen at Guatemala in this study are consistent with the results seen at Guatemala in study RFID9801 (see statistical review dated September 16, 2002)

5 2 Conclusions and Recommendations

Although study RFID3001 would not be sufficient as a stand alone study because of the significant treatment by center interaction, it provides information which supports the results seen in study RFID9801 that was submitted in the original submission Based on this information, it can be stated that rifaximin is effective clinically in that it reduces the TLUS compared to placebo The only pathogen with sufficient numbers to provide a meaningful analysis by pathogen is *E coli* The TLUS results for those subjects who have *E coli* at baseline are consistent with that seen for the overall population The effect of rifaximin seen clinically, however, has not been shown microbiologically

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

---

/s/

Cheryl Dixon
5/3/04 01 49 30 PM
BIOMETRICS

Karen Higgins
5/3/04 04 29 45 PM
BIOMETRICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDAs	21-361
Name of drug	Lumenax™ (rifaximin) tablets
Applicant	Salix Pharmaceuticals, Inc
Indication	Treatment of patients with traveler s diarrhea caused by the following susceptible organisms *Escherichia coli*
Documents reviewed	\\cdsesub1\n21361\n_000\2001_12_21
Project manager	Diana Willard
Clinical reviewer	Regina Alivisatos, M D
Dates	Received 12/26/01, user fee 10/26/02
Statistical reviewer	Cheryl Dixon, Ph D
Statistics team leader	Karen Higgins, Sc D
Biometrics division director	Mohammad Huque, Ph D
Keywords	NDA review, clinical studies, traveler's diarrhea

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1 1 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

This is the original NDA submission for rifaximin Rifaximin is intended for the treatment of traveler's diarrhea caused by *Escherichia coli* The proposed dosage regimen is one 200 mg tablet three times per day for 3 days

Two randomized, double blind phase 3 studies have been submitted to provide the primary support for the use of rifaximin Study RFID9701 was developed and conducted by Alfa Wassermann, rifaximin s innovator Salix Pharmaceuticals, Inc , the applicant of this NDA, analyzed the data following the submission of a data analysis plan to the Division prior to breaking the study blind This study compared the efficacy and safety of rifaximin at 400 mg BID to a standard regimen of ciprofloxacin Study RFID9801 was developed, conducted, and analyzed solely by Salix Pharmaceuticals, Inc The Division reviewed the protocol before the study was initiated Study RFID9801 was a placebo controlled study of rifaximin at 200 mg TID and 400 mg TID The primary efficacy endpoint in both studies was Time to Last Unformed Stool (TLUS) Secondary endpoints included wellness, treatment failure and microbiologic cure overall and by the various organisms that are causative of diarrheal disease

1 2 PRINCIPAL FINDINGS, CONCLUSIONS, AND RECOMMENDATIONS

The two studies submitted for review show that rifaximin dosage regimens of 200 mg TID and 400 mg TID are superior to placebo and a rifaximin dosage regimen of 400 mg BID is non-inferior to ciprofloxacin with respect to the clinical endpoint of Time to Last Unformed Stool In Study RFID9801, median TLUS was 32 5 hours for rifaximin 200 mg TID and 30 1 hours for rifaximin 400 mg TID compared to 58 6 hours for placebo In Study RFID9701, median TLUS was 25 8 hours for rifaximin 400 mg BID compared to 25 0 hours for ciprofloxacin

There is not sufficient evidence to show that rifaximin, at any dose, is better than placebo microbiologically Overall microbiological cure rates were 68 6% for rifaximin 200 mg TID and 56 7% for rifaximin 400 mg TID compared to 67 2% for placebo

Since only one study has been submitted which studied the proposed dose and due to the minimal amount of available data regarding the microbiological efficacy of rifaximin, it has been suggested to the Applicant that an additional study be performed This study will provide additional clinical support for the proposed rifaximin dose, 200 mg TID, and provide the adequate data needed to assess the microbiological efficacy of rifaximin

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2 1 INTRODUCTION AND BACKGROUND

This is the original NDA submission for rifaximin Rifaximin is intended for the treatment of traveler's diarrhea caused by [redacted] *Escherichia coli* [redacted] The proposed dosage regimen is one 200 mg tablet three times per day for 3 days

Two randomized, double blind, phase 3 studies have been submitted to provide the primary support for the use of rifaximin Study RFID9701 was developed and conducted by Alfa Wassermann, rifaximin s innovator Salix Pharmaceuticals, Inc , the applicant of this NDA, analyzed the data following the submission of a data analysis plan to the Division prior to breaking the study blind This study compared the efficacy and safety of rifaximin at 400 mg BID to a standard regimen of ciprofloxacin Study RFID9801 was developed, conducted, and analyzed solely by Salix Pharmaceuticals, Inc The Division reviewed the protocol before the study was initiated Study RFID9801 was a placebo controlled study of rifaximin at 200 mg TID and 400 mg TID

Reviewer's Comment *Note that the total daily dosage of rifaximin in Study RFID9701 is 800 mg This is higher than the proposed total daily dosage of 600 mg Therefore Study RFID9701 will primarily be used for assessing the safety of rifaximin However efficacy results of RFID9701 will be presented for completeness*

2 2 DATA ANALYZED AND SOURCES

The data analyzed in this review comes from the two randomized, double blind, phase 3 studies submitted as primary support Additional supportive information was provided by a phase 2 dose ranging study This study compared 3 dose regimens of rifaximin to a standard regimen of TMP/SMX (trimethoprime/sulfamethoxazole) for 5 days in the treatment of traveler's diarrhea This study will not be discussed in any detail in this review because the duration of treatment is longer than the proposed duration and the small study size (n=19 per treatment group) The Applicant provided the data from all of these studies in the electronic submission

2 3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

2 3 1 SPONSOR S RESULTS AND CONCLUSIONS

The following is a summary of the Applicant's primary results

Results from the two adequate and well-controlled studies of rifaximin for the treatment of traveler s diarrhea which included three treatment arms of rifaximin, demonstrated that rifaximin is superior to placebo and not inferior to ciprofloxacin for infectious diarrhea Efficacy measurements included the primary parameter TLUS, as well as several clinically meaningful secondary endpoints Rifaximin was effective as measured by several of these secondary endpoints Rifaximin was effective in eradicating each of the major pathogens found in traveler s diarrhea for summer travelers As the 200 mg TID and 400 mg TID dose of rifaximin appeared to be the same as measured by TLUS the lowest effective dose has been chosen (200 mg PO TID)

2 3 2 STATISTICAL METHODOLOGIES

The statistical methodologies used in this review are

- For Time to Last Unformed Stool (TLUS), Kaplan-Meier estimates and Cox proportional hazards models were used Confidence intervals for the hazard ratios were calculated
- For binary endpoints, the chi-square test was used

2 3 3 DETAILED REVIEW OF INDIVIDUAL STUDIES

2 3 3 1 Study RFID9801

Study RFID9801 was a Phase 3, multi-site, multinational, randomized, parallel group, double blind study comparing two dose levels of rifaximin with placebo It was conducted at sites in Mexico, Kenya, and Guatemala

Eligible subjects included adult, nonindigenous travelers affected by acute diarrhea defined by the passage of at least 3 unformed stools in a 24-hour period accompanied by one or more of the following signs and symptoms of enteric infection abdominal pain or cramps, nausea, vomiting, fever, dysentery, fecal urgency, excessive gas/flatulence, or tenesmus Subjects were randomized to receive one of the following treatment regimens

- Placebo two placebo tablets, TID
- 600 mg daily one 200 mg rifaximin tablet + one placebo tablet, TID
- 1200 mg daily two 200 mg rifaximin tablets, TID

Therapy was to begin no later than 72 hours from the onset of diarrhea The study consisted of a pretreatment assessment, three dosing days, and an end-of-therapy evaluation 24 to 48 hours following completion of study treatment Stool samples were taken pre-treatment and following the last dose of study drug Subjects maintained daily diaries on days 1 to 5 The diary cards collected the following information stool occurrence documented by date, time, and classification (formed, soft, watery), presence or absence of blood or mucus in the stool, severity of signs and symptoms of enteric infection during the 24 hour period, adverse events, and concomitant medications Signs

and symptoms of enteric infection were graded as absent (0), mild (1), moderate (2), or severe (3)

Efficacy was assessed by the resolution of enteric symptoms of diarrhea and return to normal, formed stools Stools were classified as formed (retains its shape), soft (assumes the shape of the container and cannot be poured), or watery (can be poured) Both soft and watery stools were considered abnormal and categorized as unformed A subject was considered well when one of the following conditions were met

- A 24-hour period passed during which no symptoms were present except mild excess gas, no fever was present, no watery stools were passed, and no more than two soft stools were passed
- A 48-hour period passed during which no stools or only formed stools were passed and no fever was present, with or without other enteric symptoms

Time to Last Unformed Stool, TLUS, was defined as the interval from the first dose to the time the last unformed stool was passed just prior to wellness being declared Subjects meeting the criteria for wellness immediately after the start of the study were defined to have a TLUS of 0 hours Subjects for whom TLUS could not be calculated due to termination early for treatment failure were assigned a TLUS value censored at 120 hours Subjects for whom TLUS could not be calculated because of early termination for other reasons, or because of study completion without wellness being declared were assigned a censored TLUS at the time of the last available information on unformed stools

TLUS was the primary efficacy endpoint The distribution of TLUS was summarized using Kaplan-Meier estimates Each rifaximin treatment group was compared to the placebo group using a Cox proportional hazards model with treatment group and site as independent variables Comparisons were made at the 0 025 significance level (Bonferoni adjustment for 2 comparisons) Two sided 97 5% confidence intervals for the hazard ratios were calculated Secondary endpoints included the proportion of subjects with wellness, the proportion of subjects with treatment failure, and the proportion of subjects with microbiologic cure Treatment groups were compared with respect to these endpoints using the chi-square test

The protocol planned sample size was 120 subjects per treatment arm The sample size calculation assumed that the best rifaximin response rate within the first 72 hours would be 80% compared to a 50% placebo response rate and that TLUS would have an exponential distribution These assumptions translated to hazard rates of 0 022 for rifaximin and 0 11 for placebo and to median TLUS of 31 hours for rifaximin and 62 hours for placebo Assuming a significance level of 0 025 for comparing each of the rifaximin groups to placebo and 90% power, a sample size of 86 subjects per group would be necessary The sample size of 120 subjects per group was selected to ensure an adequate number of subjects in the efficacy evaluable population and to have enough subjects to satisfy safety requirements for regulatory submission

- Patient Demographics

A total of 380 patients were enrolled in the study, 129 were in the placebo group, 125 in the 200 mg TID group, and 126 in the 400 mg TID group Table 9801-1 summarizes the demographic and baseline characteristics for all enrolled patients There were no statistically significant differences between treatment groups The subjects were approximately evenly divided by gender and were primarily white Mexico, which had 5 participating sites, enrolled the most subjects However, 26% of the subjects were enrolled at the single site from Guatemala All subjects randomized into the study are included in the intent-to treat (ITT) population This reviewer and the clinical reviewer are considering subjects who had a pathogen cultured at baseline a modified ITT-type (MITT-type) population

Reviewer's comment *The Applicant also defined an efficacy evaluable population Few patients were excluded from the efficacy evaluable population and the results are similar to the ITT population Therefore only the ITT results will be presented in this review*

Table 9801-1
Demographic and Baseline Characteristics

	Placebo (n=129)	**Rifaximin 200 TID** (n=125)	**Rifaximin 400 TID** (n=126)
Gender n (%)			
Female	63 (48 4)	57 (45 6)	65 (51 6)
Male	66 (51 2)	68 (54 4)	61 (48 4)
Race			
White	112 (86 8)	104 (83 2)	106 (84 1)
Black	2 (1 6)	1 (0 8)	4 (3 2)
Other	15 (11 6)	20 (16 0)	16 (12 7)
Age* mean (SD)	28 3 (10 4)	29 0 (12 2)	29 0 (11 4)
min, max	16 69	18, 72	18 66
Study Site			
Mexico	66 (51 2)	64 (51 2)	65 (51 6)
Kenya	30 (23 3)	28 (22 4)	27 (21 4)
Guatemala	33 (25 6)	33 (26 4)	34 (27 0)
Baseline Pathogen			
Yes	61 (47 3)	70 (56 0)	60 (47 6)
No	68 (52 7)	55 (44 0)	66 (52 4)

Four subjects in the 200 TID group and two in the 400 TID group did not have a date of birth recorded

All subjects at the Kenya site were white These subjects were slightly older (39 4 years) than the subjects seen at the Mexico (24 7 years) and Guatemala (27 5 years) sites More subjects at the Kenya site (83 5%) had baseline pathogens than did subjects at the Mexico (39 0%) and Guatemala (44 0%) sites All subjects from the Guatemala site were infected with only a single pathogen at baseline and 86 4% of these were ETEC At the Mexico site, 84 2% of the subjects were infected with a single pathogen and the rest had 2 infecting pathogens At the Kenya site, 54 9% of the subjects were infected with a single pathogen and the rest had 2 or more infecting pathogens The Kenyan site had the

majority of the *Cryptosporidia* cases (38 of the 43) which accounted for 53 5% of the subjects at the Kenya site who had a baseline pathogen

- Efficacy Results

Reviewer's Comment *In a submission dated April 22 2002 the Division was informed of a programming error in the TLUS algorithm that was identified by the Applicant in the process of responding to a request made in a FAX dated March 15, 2002 This error affected the TLUS for 6 patients (2 placebo 1 rifaximin 200 mg TID 3 rifaximin 400 mg TID) An additional correction was made to one other patient s (rifaximin 200 mg TID) TLUS to resolve conflicting diary and date/time information These corrections do not change the overall conclusions Therefore all results presented in this review with respect to TLUS are based on this revised information*

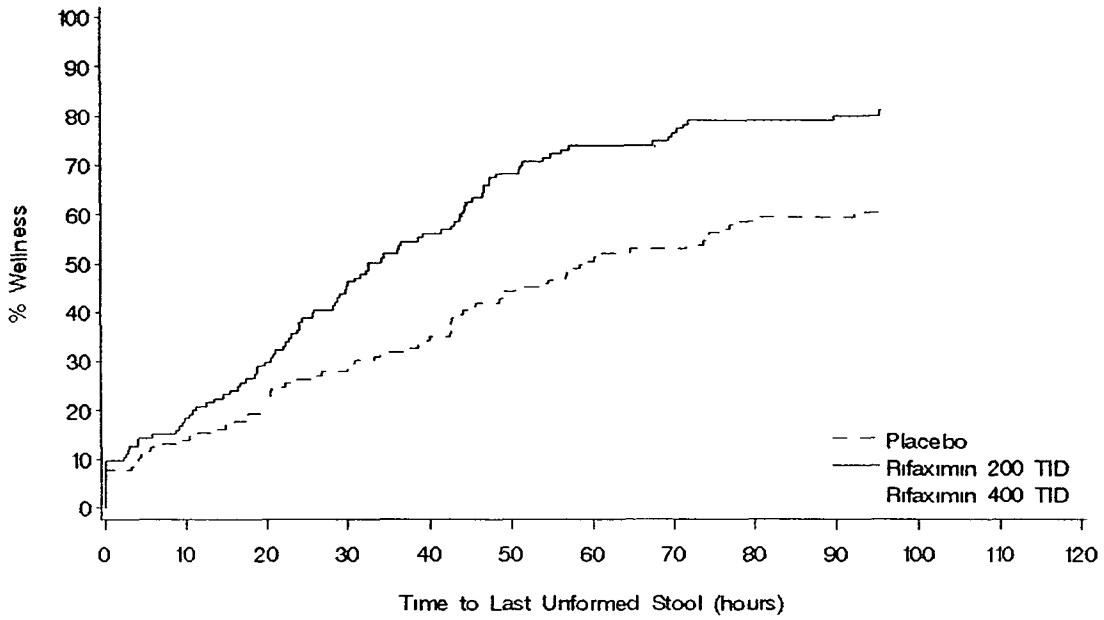
The results of TLUS are presented in Table 9801-2 and Figure 9801-1 Median TLUS was 32 5 hours in the rifaximin 200 mg TID group and 30 1 hours in the rifaximin 400 mg TID group compared to 58 6 hours in the placebo group TLUS was statistically significantly shorter in the rifaximin groups compared to placebo as evidenced by the confidence intervals about the hazard ratios that are completely above one

Table 9801-2
Time to Last Unformed Stool (ITT population)

	Placebo (n=129)	**Rifaximin 200 TID** (n=125)	**Rifaximin 400 TID** (n=126)
Median TLUS (hours)	58 6	32 5	30 1
95% CI	(45 5 79 5)	(28 4 43 4)	(22 7 41 8)
P-value*		0 0002	0 0001
Hazard Ratio		1 78	1 83
97 5% CI		(1 26 2 50)	(1 30, 2 56)

Wald statistic of treatment effect from proportion hazards models with terms for treatment and site

Figure 9801-1
Time to Last Unformed Stool



Censoring patterns are summarized in Table 9801-3 More subjects had a censored TLUS in the placebo group (39 5%) compared to the rifaximin 200 mg TID group (20 8%) and the rifaximin 400 mg TID group (19 0%) This is due to increased rates of early termination (censored TLUS < 120 hours) and failure to achieve cure (censored TLUS=120 hours) in the placebo group compared to treatment with rifaximin Five subjects had a censored TLUS value greater than 120 hours These subjects did not respond to treatment but had continuing records of unformed stools beyond 120 hours

Table 9801-3
Number of Subjects with Censored TLUS (ITT population)

	Placebo (n=129)	**Rifaximin 200 TID** (n=125)	**Rifaximin 400 TID** (n=126)
Censored n(%)	51 (39 5)	26 (20 8)	24 (19 0)
TLUS < 120 hours	28	15	16
TLUS=120 hours	22	8	7
TLUS > 120 hours	1	3	1

TLUS for subjects who had a baseline pathogen (MITT-type population) is presented in Table 9801-4 These results are similar to those seen for the ITT population Treatment with rifaximin leads to statistically significantly shorter TLUS when compared to placebo

Table 9801-4
Time to Last Unformed Stool
Subjects with a Baseline Pathogen (MITT-type population)

	Placebo (n=61)	Rifaximin 200 TID (n=70)	Rifaximin 400 TID (n=60)
Median TLUS (hours)	60 0	30 0	32 9
95% CI	(44 8,)	(23 7 36 3)	(22 7 45 5)
P-value*		0 0002	0 0122
Hazard Ratio		2 21	1 76
97 5% CI		(1 36 3 58)	(1 06 2 92)

* Wald statistic of treatment effect compared to placebo from proportion hazards models with terms for treatment and site

TLUS for ETEC and *Cryptosporidia* is presented in Table 9801-5 Subjects who were infected with ETEC had median TLUS that was similar to the overall MITT-type population Subjects infected with *Cryptosporidia* had longer median TLUS than was seen for the overall MITT-type population Due to the small sample sizes, statistical testing cannot be performed However, there is a trend that treatment with rifaximin leads to shorter TLUS than placebo

Table 9801-5
TLUS by Pathogen (MITT-type population)

	Placebo	Rifaximin 200 TID	Rifaximin 400 TID
ETEC	57 8 (n=54)	28 4 (n=53)	26 8 (n=45)
Cryptosporidia	58 6 (n=11)	39 9 (n=18)	40 4 (n=14)

Table 9801-6 presents the median TLUS by site for the ITT population and the MITT-type population (those with a baseline pathogen) Median TLUS was longer for the Kenyan site and shorter for the Guatemalan site A proportional hazards model including treatment, site, and treatment by site was used to investigate a potential treatment by site interaction No significant interactions were found These quantitative differences could be explained by the fact that all subjects at the Guatemala site only had one infecting pathogen and 45 1% of the Kenya subjects had more than one baseline pathogen which may make them more difficult to treat In addition, 53 5% of the subjects at the Kenya site were infected with *Cryptosporidia* whereas the primary pathogen seen at the Guatemala site was ETEC As seen in Table 9801-5, subjects infected with *Cryptosporidia* had longer median TLUS

Table 9801-6
Median Time to Last Unformed Stool by Site

	Placebo	Rifaximin 200 TID	Rifaximin 400 TID
ITT			
Mexico	57 6	32 5	37 0
Kenya	74 3	42 7	27 2
Guatemala	49 0	28 9	23 2
MITT-type			
Mexico	57 0	22 0	46 1
Kenya		42 7	33 1
Guatemala	56 5	27 2	24 8

= did not attain 50[h] percentile

Secondary endpoints included the proportion of subjects who had wellness declared and the proportion of patients who were treatment failures These results are presented in Table 9801-7 For both endpoints, the comparisons of each rifaximin group versus placebo are highly significant (p=0 001 all comparisons) The rates of wellness are higher and the rates of treatment failure are lower in the rifaximin groups compared to placebo

Table 9801-7
Secondary Endpoints (ITT Population)

	Placebo (n=129)	Rifaximin 200 TID (n=125)	Rifaximin 400 TID (n=126)
Wellness	78 (60 5)	99 (79 2)	102 (81 0)
Treatment Failure	45 (34 9)	20 (16 0)	21 (16 7)

Microbiologic cure rates are presented in Table 9801-8 for subjects who had a baseline pathogen Also included in the table are the microbiological cure rates by individual pathogens It should be noted that a subject could have more than one baseline pathogen The overall microbiological cure rates were 68 6% for rifaximin 200 mg TID, 56 6% for rifaximin 400 mg TID, and 67 2% for placebo The rates were not significantly different across treatment groups (chi-square, p=0 316) The lack of ability for the study to show a difference in microbiological cure rates between rifaximin and placebo could be due to the timing of the post treatment stool sample and the self-limiting nature of the disease The microbiological cure rates by individual pathogen are similar to that seen overall The numbers of individual pathogens are relatively small with the exception of ETEC and *Cryptosporidia*

Table 9801-8
Microbiologic Response
Subjects with a Baseline Pathogen (MITT-type population)

	Placebo (n=61)	Rifaximin 200 TID (n=70)	Rifaximin 400 TID (n=60)
Overall	41 (67 2)	48 (68 6)	34 (56 7)
By Pathogen			
Cryptosporidia	7/11 (63 6)	12/18 (66 7)	5/14 (35 7)
ETEC Heat Labile	14/18 (77 8)	8/12 (66 7)	10/14 (71 4)
ETEC Heat Labile/ Heat Stabile	11/15 (73 3)	16/21 (76 2)	8/11 (72 7)
ETEC Heat Stabile	15 21 (71 4)	14/20 (70 0)	13/20 (65 0)
Giardia Lamblia	3/4 (75 0)	4/6 (66 7)	1/4 (25 0)
Salmonella	2/2 (100 0)	1/2 (50 0)	4/7 (57 1)
Shigella	2/2 (100 0)	3/4 (75 0)	2/3 (66 7)

- Safety Results

A total of 89 (71 8%) rifaximin 200 mg TID patients, 94 (74 6%) rifaximin 400 mg TID patients, and 97 (75 2%) placebo patients reported at least one adverse event The most frequently reported adverse events were gastrointestinal disorders including flatulence, abdominal pain, fecal urgency, nausea, and tenesmus These disorders are related to the disease and worsening of these symptoms was recorded as an adverse event in this study The next most frequently reported adverse event was headache The incidences of these adverse events were similar among treatment groups

Drug related adverse events were reported in 74 (59 7%) rifaximin 200 mg TID patients, 88 (69 8%) rifaximin 400 mg TID patients, and 90 (69 8%) placebo patients One serious adverse event was reported by a patient who received placebo No deaths occurred in this study

For a complete review of the safety data, please refer to the medical officer safety review written by Dr Regina Alivisatos

2 3 3 2 Study RFID9701

Study RFID9701 was a multicenter, double blind, double dummy study comparing rifaximin (400 mg BID) with ciprofloxacin (500 mg BID) It was conducted at sites in Mexico and Jamaica The subjects from Mexico were visiting U S students and faculty members The subjects from Jamaica were international tourists

Eligible subjects included men and non-pregnant women who were at least 18 years of age affected by acute diarrhea defined as the passage of at least 3 unformed stools in a 24-hour period accompanied by one or more of the following signs and symptoms of enteric infection abdominal pain or cramps, nausea, vomiting, fever, dysentery, fecal

urgency, excessive gas/flatulence, tenesmus Subjects were randomized to receive one of the following treatment regimens

- two 200 mg rifaximin tablets + one ciprofloxacin placebo tablet , BID for 3 days
- two rifaximin placebo tablets + one 500 mg ciprofloxacin tablet, BID for 3 days

Therapy was to begin no later than 72 hours from the onset of diarrhea The study consisted of a pretreatment assessment, three dosing days, and an end-of-therapy evaluation between 48 and 72 hours after the last dose of study therapy Stool samples were taken pre-treatment and following the last dose of study drug Subjects maintained daily diaries on days 1 to 5 The diary cards collected the following information the time and form of any stool passed (including the subject's assessment of whether blood or mucus was present), any other symptoms and side effects, and concomitant medication Signs and symptoms of enteric infection were graded as absent (0), mild and tolerable (1), moderate and distressing (2), or severe and incapacitating (3)

Reviewer's Comment *Since ciprofloxacin is recommended as a twice a day regimen rifaximin was also given as a twice a day regimen in order to compare the efficacy of the two products under the same regimen It should be noted that the total daily dose of rifaximin is 800 mg in this study This dose is between the doses studied in Study RFID9801 given in a TID fashion and more than the total dose that is being requested for approval by the Applicant*

Efficacy was assessed by the resolution of enteric symptoms of diarrhea, symptomatically and on the modification of stools Stools were classified as formed (retains its shape), soft (assumes the shape of the container), or watery (can be poured) Both soft and watery stools were considered abnormal and categorized as unformed A subject was considered well when one of the following conditions were met

- The passage of no watery stools and no more than 2 soft stools in a 24 hour interval with no fever and no other clinical symptoms except for mild excess gas/flatulence
- The passage of no unformed stools in a 48 hours interval with no fever (with or without other clinical symptoms)

Time to Last Unformed Stool (TLUS) was defined as the interval beginning with the first dose of medication and ending with the last unformed stool passed, after which wellness was declared Subjects who had no unformed stools after the start of study treatment and met all other criteria for wellness were defined to have a TLUS of 0 hours Subjects for whom TLUS could not be calculated due to termination early for treatment failure were assigned a TLUS value censored at 120 hours Subjects for whom TLUS could not be calculated because of early termination for other reasons, or because of study completion without wellness being declared were assigned a censored TLUS at the time of the last available information on unformed stools

TLUS was the primary efficacy endpoint The distribution of TLUS was summarized using Kaplan-Meier estimates The objective of the analysis of TLUS was to demonstrate that the TLUS for rifaximin was equivalent to that for ciprofloxacin A Cox proportional hazards model with treatment group and site as independent variables using

the procedure described by Com-Nougue et al (*Statistics in Medicine* 12 1353-1364, 1993) establishing equivalence with survival-type data was used for the analysis Based on historical data, the probability of passing the last unformed stool by the end of the first 24 hours was 0 62 If the probability of passing the last unformed stool by the end of the first 24 hours for rifaximin was 0 41 or less, then this was unacceptable An exponential distribution was assumed for TLUS, so these probabilities translated to hazard rates of 0 022 for rifaximin and 0 040 for ciprofloxacin This corresponds to a hazard ratio of 0 55, which corresponds to a value of –0 6 for the coefficient of the treatment term (β_T) in the Cox proportional hazards model The Wald chi-square statistic from the Cox model was used to test if β_T=-0 6 If this hypothesis was rejected, then rifaximin was considered to be equivalent to ciprofloxacin A two-sided 95% confidence interval for the hazard ratio was calculated Secondary endpoints included the proportion of subjects with wellness, the proportion of subjects with treatment failure, and the proportion of subjects with microbiologic cure Treatment groups were compared with respect to these endpoints using the chi-square test

The protocol planned sample size was 88 subjects per treatment group The sample size calculation was based on comparing the treatment groups with respect to the proportion of subjects who passed their last unformed stool by the end of the first 24 hours on study The following were assumed for the samples size calculation a rifaximin response rate of 0 41, a ciprofloxacin response rate of 0 62 a significance level of 0 05, and a power of 0 80

- Patient Demographics

A total of 187 patients were enrolled in the study, 94 were in the ciprofloxacin group, and 93 in the rifaximin 400 mg BID group Table 9701-1 summarizes the demographic and baseline characteristics for all enrolled patients There were no statistically significant differences between treatment groups There were slightly more female subjects and the subjects were primarily white Mexico, which had 5 participating sites, enrolled the most subjects Only 12 patients in each treatment group were from Jamaica All subjects randomized into the study are included in the intent-to treat (ITT) population This reviewer and the clinical reviewer are considering subjects who had a pathogen cultured at baseline a modified ITT-type (MITT-type) population

Reviewer's comment *The Applicant also defined an efficacy evaluable population Few patients were excluded from the efficacy evaluable population and the results are similar to the ITT population Therefore, only the ITT results will be presented in this review*

Table 9701-1
Demographic and Baseline Characteristics

	Ciprofloxacin (n=94)	Rifaximin 400 BID (n=93)
Gender, n (%)		
Female	51 (54 3)	54 (58 1)
Male	43 (45 7)	39 (41 9)
Race		
White	74 (78 7)	76 (81 7)
Black	5 (5 3)	0
Other	15 (16 0)	17 (18 3)
Age mean (SD)	25 6 (9 2)	26 3 (9 5)
min, max	18 59	18 57
Study Site		
Mexico	82 (87 2)	81 (87 1)
Jamaica	12 (12 8)	12 (12 9)
Baseline Pathogen		
Yes	48 (51 1)	46 (49 5)
No	46 (48 9)	47 (50 5)

- Efficacy Results

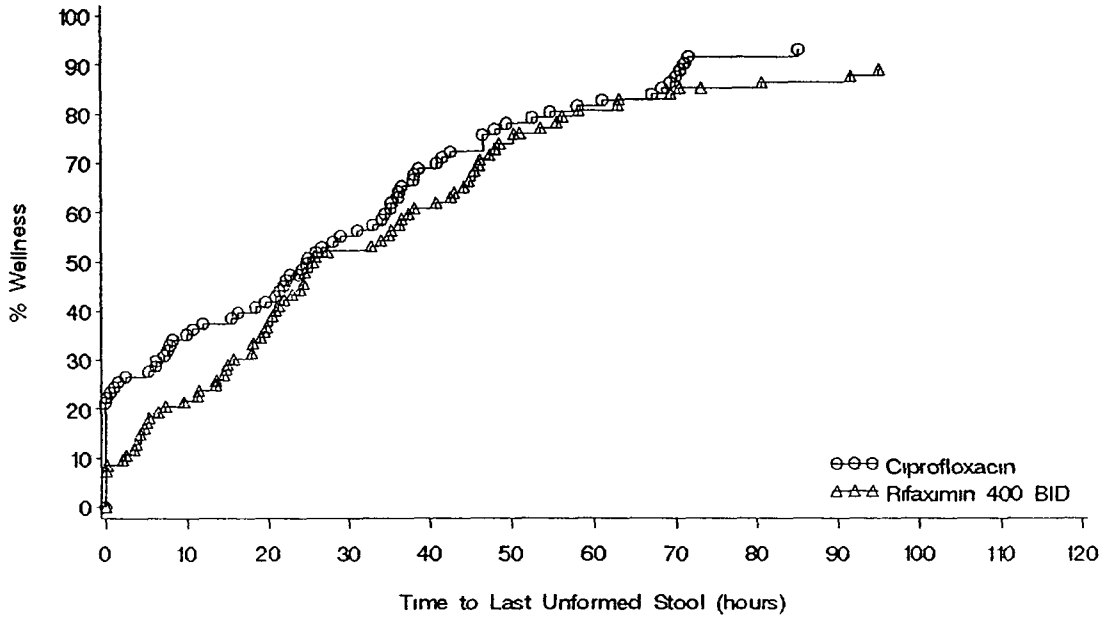
The results of TLUS are presented in Table 9701-2 and Figure 9701-1 Median TLUS was 25 8 hours in the rifaximin 400 mg BID group compared to 25 0 hours in the ciprofloxacin group Since the test of β_T=-0 6 is rejected, rifaximin 400 mg BID and ciprofloxacin are equivalent with respect to TLUS Equivalence with respect to TLUS is also supported by the 95% confidence interval about the hazard ratio The confidence interval contains 1 and the lower bound is greater than 0 55

Table 9701-2
Time to Last Unformed Stool (ITT population)

	Ciprofloxacin (n=94)	Rifaximin 400 BID (n=93)
Median TLUS (hours)	25 0	25 8
95% CI	(18 5 35 2)	(20 9 38 0)
β_T^*		-0 20
P-value		0 0108
Hazard Ratio		0 82
95 0% CI		(0 60 1 11)

Coefficient of the treatment term in the Cox proportional hazards model and corresponding p value of the Wald chi square statistic to test if β_T= 0 6

Figure 9701-1
Time to Last Unformed Stool



Censoring patterns are summarized in Table 9701-3 A similar number of subjects had a censored TLUS in the two treatment groups, 11 7% of the ciprofloxacin subjects were censored and 12 9% of the rifaximin 400 mg BID subjects were censored The ciprofloxacin group had similar numbers of subjects censored due to early termination (censored TLUS < 120 hours) and failure to achieve cure (censored TLUS=120 hours) Whereas, the majority of the rifaximin 400 mg BID subjects were censored due to early termination

Table 9701-3
Number of Subjects with Censored TLUS (ITT population)

	Ciprofloxacin (n=94)	**Rifaximin 400 BID** (n=93)
Censored n(%)	11 (11 7)	12 (12 9)
TLUS < 120 hours	6	10
TLUS=120 hours	5	2

TLUS for subjects who had a baseline pathogen (MITT-type population) is presented in Table 9701-4 The median TLUS for the subjects with a baseline pathogen who were treated rifaximin 400 mg BID is slightly longer (30 7 hours) compared to those with a baseline pathogen treated with ciprofloxacin (25 0 hours) and to the rifaximin 400 mg BID ITT population Equivalence of the treatment groups has not been demonstrated for this population, however, the sample size is small

Table 9701-4
Time to Last Unformed Stool
Subjects with a Baseline Pathogen (MITT-type population)

	Ciprofloxacin (n=48)	**Rifaximin 400 BID** (n=46)
Median TLUS (hours)	25 0	30 7
95% CI	(16 3, 36 2)	(20 9, 44 8)
β_T^*		-0 19
P-value		0 0697
Hazard Ratio		0 82
95 0% CI		(0 53 1 28)

Coefficient of the treatment term in the Cox proportional hazards model and corresponding p value of the Wald chi square statistic to test if $\beta_T = 0$ 6

Secondary endpoints included the proportion of subjects who had wellness declared and the proportion of patients who were treatment failures These results are presented in Table 9701-5 The rate of wellness is slightly better for ciprofloxacin compared to rifaximin but the rate of treatment failure is slightly lower for rifaximin 400 mg BID compared to ciprofloxacin

Table 9701-5
Secondary Endpoints (ITT Population)

	Ciprofloxacin (n=94)	**Rifaximin 400 BID** (n=93)
Wellness	83 (88 3)	81 (87 1)
Treatment Failure	9 (9 7)	5 (5 3)

Microbiologic cure rates are presented in Table 9701-6 for subjects who had a baseline pathogen Also included in the table are the microbiological cure rates by individual pathogens It should be noted that a subject could have more than one baseline pathogen The overall microbiological cure rates were 69 6% for rifaximin 400 mg BID and 85 4% for ciprofloxacin The microbiological cure rates by individual pathogen are similar to that seen overall The numbers of individual pathogens are relatively small with the exception of ETEC

Table 9701-6
Microbiologic Response
Subjects with a Baseline Pathogen (MITT-type population)

	Ciprofloxacin (n=48)	Rifaximin 400 BID (n=46)
Overall	41 (85 4)	32 (69 6)
By Pathogen		
Cryptosporidia	2/2 (100 0)	1/1 (100 0)
ETEC Heat Labile	9/9 (100 0)	5/5 (100 0)
ETEC Heat Labile/ Heat Stabile	7/7 (100 0)	7/10 (70 0)
ETEC Heat Stabile	16/20 (80 0)	14/22 (63 6)
Giardia Lamblia	0/1	-
Salmonella	5/6 (83 3)	2/3 (66 7)
Shigella	5/6 (83 3)	4/6 (66 7)

- Safety Results

A total of 31 (33 3%) subjects in the rifaximin 400 mg BID group and 34 (36 2%) subjects in the ciprofloxacin group had at least one adverse event The most frequently occurring adverse event was headache Drug related adverse events were reported in 10 rifaximin treated patients and 15 ciprofloxacin treated patients There were no serious adverse events

For a complete review of the safety data, please refer to the medical officer safety review written by Dr Regina Alivisatos

2 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

There were no clinically or statistically significant differences in outcome by either age or gender when compared to the overall study population Racial differences were not examined, as the majority of the patients were white

2 5 STATISTICAL AND TECHNICAL ISSUES

There are no additional statistical or technical issues that need to be addressed

2 6 STATISTICAL EVALUATION OF COLLECTIVE EVIDENCE

The following table summarizes the main findings from Studies RFID9801 and RFID9701

	Study RFID9801	Study RFID9701
Basis of Evidence	Primary	Primary (?)
Design	Randomized double-blind controlled	Randomized, double-blind double-dummy, controlled
Daily Rifaximin Dose and Duration	200 TID (600 mg) x 3 days 400 TID (1200 mg) x 3 days	400 BID (800 mg) x 3 days
Control	Placebo	Ciprofloxacin 1000 mg x 3 days
Where Conducted	Mexico Guatemala Kenya	Mexico Jamaica
Assessment	Superiority	Non-Inferiority
Primary Endpoint	Time to Last Unformed Stool	Time to Last Unformed Stool
Secondary Endpoints (major)	Wellness Treatment Failure Microbiologic Cure	Wellness Treatment Failure Microbiologic Cure
Numbers Enrolled		
Rifaximin	125 (200 TID) 126 (400 TID)	93 (400 BID)
Control	129	94
Median Time to Last Unformed Stool (hours)		
Rifaximin	32 5 (200 TID) 30 1 (400 TID)	25 8 (400 BID)
Control	>8 6	25 0
Microbiological Cure Rates		
Rifaximin	68 6% (200 TID) 56 7% (400 TID)	69 6% (400 BID)
Control	67 2%	85 4%

2 7 CONCLUSIONS AND RECOMMENDATIONS

The studies submitted for review show that rifaximin dosage regimens of 200 mg TID and 400 mg TID are superior to placebo and a rifaximin dosage regimen of 400 mg BID is non-inferior to ciprofloxacin with respect to the clinical endpoint of Time to Last Unformed Stool There is not sufficient evidence to show that rifaximin, at any dose, is better than placebo microbiologically

Therefore, it has been suggested to the Applicant that an additional study be performed This study will provide additional clinical support for the proposed rifaximin dose, 200 mg TID, and provide the adequate data needed to assess the microbiological efficacy of rifaximin

Reviewer's Comment *The protocol for the above mention study has been reviewed by the Division and comments were sent to the Applicant*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

---

/s/

Cheryl Dixon
9/16/02 01 11 53 PM
BIOMETRICS

Karen Higgins
9/17/02 09 51 41 AM
BIOMETRICS