

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-361

MEDICAL REVIEW(S)

Team leader's review

NDA 21-361

Applicant Salix Pharmaceuticals

Address 3600 West Bayshore Road
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Drug Name Rifaximin

Proprietary Name XIFAXAN™

Pharmacologic Category Rifamycin

Chemical Name (2S, 16Z, 18E, 20S, 21S, 22R, 23R, 24R, 25S, 26S, 27S, 28E)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca(1,11,13)trienimino)benzofuro(4,5-e)pyrido(1,2-a)benzimidazole 1,15(2H)-dione 25 acetate

Molecular formula C₄₃H₅₁N₃O₁₁

Molecular weight 785.89

Dosage Form Tablets

Route of Administration Oral

Strengths 200 mg tablets

Applicant's Proposed Indication Rifaximin tablets are indicated for the treatment of patients (≥ 12 years of age) with traveler's diarrhea caused by the following susceptible organisms

Escherichia coli

Recommendations on approval

Approval is recommended for rifaximin in the treatment of traveler s diarrhea due to *E coli*
 The indicated dosage regimen is one 200mg tablet, taken three times a day for 3 days in patients ≥ 12 years of age

The recommended labeling for indications and usage is as follows

XIFAXAN™ Tablets are indicated for the treatment of patients (≥ 12 years of age) with travelers diarrhea caused by noninvasive strains of *Escherichia coli* (see **Microbiology, WARNINGS, and CLINICAL STUDIES**)

XIFAXAN™ Tablets should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*

Labeled warnings should include the following

- Rifaximin is not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*
- Rifaximin is not effective in cases of travelers diarrhea due to *Campylobacter jejuni*
- The effectiveness of rifaximin in travelers diarrhea caused by *Shigella spp* and *Salmonella spp* has not been proven
- Rifaximin should not be used in patients where *Campylobacter jejuni*, *Shigella spp* or *Salmonella spp* may be suspected as causative pathogens
- Rifaximin should be discontinued if diarrhea symptoms get worse or persist more than 24-48 hours and alternative antibiotic therapy should be considered

Background

Rifaximin is a minimally absorbed rifamycin that was originally submitted for the treatment of traveler s diarrhea on 12/21/2002. This submission incorporated three clinical studies (RFID 9801, 9701 and 9601). These studies investigated doses of rifaximin ranging from 200mg tid for 3 days to 600mg tid for 5 days. The applicant proposed a 200mg tid dose for 3 days. Only one of the three studies (9801) employed this dosing regimen. The results of this study were regarded as pivotal whereas the results from the other two clinical studies (using higher doses or longer durations of therapy) provided supportive safety data.

The findings of study RFID9801 according to the primary endpoint (the time to last unformed stool) and according to clinical cure in the intent-to-treat population are tabulated below

	Placebo n=129	Rifaximin 200mg TID n=125	Rifaximin 400mg TID n=126
TLUS (hours) Kaplan Meier Estimates			
Median TLUS	58.6	32.5	30.1
95% CI of median TLUS	(45.5, 79.5)	(28.4, 43.4)	(22.7, 41.8)
P Value (Wald statistic)		0.0002	0.0001
97.5% CI for Hazard ratio		(1.26, 2.50)	(1.3, 2.56)

Clinical cure	60.5% (78/129)	79.2% (99/125)	-
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In this study, the commoner pathogens (those isolated in at least two patients in at least one study arm) were analyzed for rates of eradication, 24 to 48 hours after completion of treatment as shown below

	Placebo % eradicated	Rifaximin 200mg TID	Rifaximin 400mg TID
<i>E coli</i>	40/54 (74%)	38/54 (70%)	27/41 (66%)
<i>S sonnei</i>	2/2 (100%)	2/2 (100%)	1/1 (100%)
<i>S flexneri</i>	0	1/2 (50%)	0/1
<i>Salmonella group C1</i>	1/1 (100%)	1/2 (50%)	3/4 (75%)
<i>Salmonella group C2</i>	1/1 (100%)	0	1/3 (33%)
<i>C jejuni</i>	0/1	1/2 (50%)	0
<i>E histolytica</i>	1/1 (100%)	1/1 (100%)	2/3 (67%)
<i>G lamblia</i>	3/4 (75%)	4/6 (67%)	1/3 (33%)
<i>Cryptosporidium parvum</i>	7/11 (64%)	12/18 (67%)	4/14 (29%)
Total	59/79 (75%)	61/88 (69%)	43/75 (57%)

Eradication rates were similar for both rifaximin arms and placebo although the number of isolates for most given organisms was small

The application received an approvable action and the following deficiencies were to be addressed

- 1) A second adequate and well-controlled clinical study was required to confirm the clinical efficacy demonstrated in the first study. This study was to include efficacy data from patients with diarrhea who demonstrated a clinically meaningful benefit was to be demonstrated for rifaximin with a statistically significant reduction in the duration of diarrhea when rifaximin was compared with placebo.
- 2) The abovementioned study was to include a sufficient number of isolates so that a significant difference could be demonstrated both in the eradication rates and the corresponding clinical responses, when rifaximin was compared to placebo.
- 3) A pharmacokinetic study was needed to assess systemic absorption.
- 4) Information was requested to characterize drug-drug interactions between rifaximin and other CYP 3A4 substrates.
- 5) Three CMC requirements included documentation of drug product lots used in phase 3 studies, identification of degradants, and additional stability data.

Clinical study (RFID3001) included in the resubmission

In addressing requirements 1 and 2 the applicant conducted a randomized, double-blind, three arm study comparing rifaximin (200mg tid for 3 days) with placebo (negative control) and with ciprofloxacin (positive control). The study included 399 patients in the intent-to-treat population, accrued from several centers around the world, in India (Calcutta and Goa), Guatemala, Peru and Mexico. The primary endpoint of the study was the time from initiation of therapy to last unformed stool (in hours). A second dichotomous endpoint was whether the patient was clinically cured, (wellness) 4-5 days after initiation of therapy.

Problems in the conduct and analysis of the study (RFID3001)

The pooled analysis of all study sites in RFID3001 was complicated by a significant center effect. The Goa site failed to demonstrate efficacy of the positive control (cipro arm) and the Mexican site demonstrated a treatment effect in the negative control (placebo arm) weakening the conclusions to be drawn from these two sites (see table below)

An additional pooled analysis was performed excluding patients from these sites. The results were also examined individually by study site.

Pooled results showing reduced duration of illness in study RFID 3001

The results (where all sites were included) showed a statistically significant reduction in the time to last unformed stool (TLUS) among the ITT population, from a median of 65.5 hours in the placebo arm to 23.85 hours in the rifaximin arm. The strength of this conclusion was weakened by inability to evaluate two sites (Goa and Mexico (see above)). However, a second analysis excluding these 2 sites, confirmed the efficacy of rifaximin (median TLUS rifaximin 23.85hrs, placebo 65.5hrs, cipro 49hrs). The study satisfied the requirement to support the clinical efficacy demonstrated in the first study (study RFID9801 in the original submission) where the respective TLUS were 58.6 hours for placebo and 32.5 hours for rifaximin.

These findings were supported by a second analysis of clinical cure (wellness) where 76.6% of rifaximin treated patients in study RFID3001 were well (no diarrhea or fever) by day 4-5 as compared with 61.4% of placebo treated patients.

[The previously submitted study 9801 provided similar results where 79.2% (99/125) of rifaximin treated patients were well (no diarrhea or fever) by day 4-5 as compared with 60.5% (78/129) of placebo-treated patients.]

The results are shown in the table below which further details the results by study site.

Median TLUS ITT Population

Median TLUS in Hours (Kaplan-Meier Estimates)	Treatment Group		
	Rifaximin	Placebo	Cipro
All Centers study RFID9801	(N = 125) 32.5	(N = 129) 58.6	NA
All Centers study RFID3001	(N=197) 32.0	(N=101) 65.5	(N=101) 28.8
TLUS by Center RFID3001			
Calcutta, India (#100)	(N=43) 24.5	(N=23) NC	(N=23) 24.1
Goa, India (#101)	(N=58) 72.0	(N=29) 69.7	(N=30) 70.5
Antigua, Guatemala (#107) & Lima, Peru (#269)	(N=53) 23.5	(N=26) 42.4	(N=27) 20.8
Guadalajara, Mexico (#200), Cuernavaca, Mexico (#242) & Puerto Vallarta Mexico (#249)	(N=43) 33.0	(N=23) 26.7	(N=21) 15.5

Microbiological results

Pathogens were identified in 248 (62%) of the 399 patients enrolled in study RFID3001. The pathogens most frequently identified were *E coli* (151), *Campylobacter* (44), *Shigella* (18), *Salmonella* (7) and other agents (21).

Efficacy for organisms present in 10 or more cases (study 3001)

	Eradication rates (total # isolates)		
	Rifaximin	Placebo	Cipro
<i>E coli</i>	74.7% (83)	69.8% (43)	95.6% (45)

Campylobacter	36% (25)	40% (10)	66.7% (9)
Shigella	90.9% (11)	60% (5)	100% (2)
Clinical cure rates (total # isolates)			
	Rifaximin	Placebo	Cipro
E coli	89% (73)	74% (38)	83% (40)
Campylobacter	24% (25)	30% (10)	44% (9)
Shigella	100% (11)	60% (5)	100% (2)
Median TLUS (from table A32)			
	Rifaximin	Placebo	Cipro
E coli (only)	23.9 hours (64)	26.7 hours (33)	23.4 hours (36)
Campylobacter (only)	>120 hours (13)	>120 hours (4)	55.5 to 120 hours (2)
Shigella (only)	42.6 (7)	31.8 to >120 (2)	15.6 (1)

In patients with diarrhea due to *Campylobacter*, rifaximin was numerically less effective than placebo both in eradicating the organism and in curing the clinical symptoms

In patients with diarrhea due to *E coli* rifaximin was numerically more effective than placebo, both in eradicating the organism and in curing the clinical symptoms

In the case of *E coli* infections, spontaneous resolution of symptoms and spontaneous eradication of the organism was frequent. Hence the benefit of rifaximin treatment in *E coli* infection appears limited

In patients with diarrhea due to *Shigella* species rifaximin was numerically more effective than placebo in eradication of the organism. Adequate comparative data were unavailable to determine whether rifaximin hastened clinical recovery compared to placebo

Shigella sonnei

The table below indicates the pooled cure and eradication rates for all *S sonnei* isolates identified in both studies 9801 and 3001 as well as a single patient treated with the recommended dose in one of the non-pivotal studies (RFID9601)

Evaluable patients with only <i>S sonnei</i> as a baseline pathogen		
Clinical cure	Eradicated	Total
7 (100%)	7 (100%)	7
Evaluable patients with multiple pathogens at baseline including <i>S sonnei</i>		
Clinical cure	Eradicated	Total
4 (100%)	3 (75%)	4

Only 7 patients were identified with *S sonnei* as the sole pathogen. This number of isolates was too small to allow a conclusion of efficacy against this pathogen

Shigella flexneri

Pooled cure and eradication rates for patients in RFID 9801 and RFID3001 with isolates of *S flexneri* are shown below

Evaluable patients with only <i>S flexneri</i> as a baseline pathogen		
Clinical cure	Eradicated	Total
2/2	2/2	2

Evaluable patients with multiple pathogens at baseline including <i>S flexneri</i>		
Clinical cure	Eradicated	Total
2/2	1/2	2

The applicant performed a separate pharmacokinetic study of the efficacy of Rifaximin in 15 healthy volunteers experimentally infected with *S flexneri*. Thirteen of the fifteen volunteers developed diarrhea or dysentery and were treated with rifaximin (200mg tid for 3 days). The study was designed to examine the pharmacokinetics of rifaximin in patients with colonic inflammation, and not to test antimicrobial efficacy. Ultimately all 13 were given rescue therapy with ciprofloxacin for reasons of clinical or microbiological failure. In most cases rescue therapy was administered early, before allowing an adequate time interval to test the efficacy of rifaximin. In the light of these data and in the absence of an adequate number of clinical isolates in the clinical studies, the efficacy of rifaximin in patients with diarrhea due to *Shigella flexneri* has not been shown.

Subgroup analysis (RFID 3001)

Results for selected subgroups of patients in this study were analyzed as shown below.

TLUS (hours) results for clinical subgroups in study 3001 (n)

	Rifaximin	Placebo	Cipro
Fever at baseline	>120 (25)	51.1 (12)	23.4 (14)
Blood in stool at baseline	63.5 (42)	69.7 (25)	55.5 (18)
Fecal leukocytes at baseline	29 (91)	72 (45)	23.4 (38)
Inflammatory/invasive pathogens at baseline	>120 (46)	67.5 (19)	65 (13)
<i>E coli</i> (only)	23.9 (74)	38 (38)	23.4 (46)
<i>Campylobacter</i> (only)	>120 (13)	>120 (4)	55.5 to 120 (2)
<i>Shigella</i> (only)	42.6 (7)	31.8 to >120 (2)	15.6 (1)
Subjects negative for baseline pathogens	23.5 (67)	71.6 (38)	29.7 (37)

Rifaximin was not effective in subjects with fever, blood in stool, or inflammatory/invasive pathogens at baseline.

With the exception of infections due to *E coli*, efficacy was not statistically different from placebo in patients with a specific pathogen.

Notably, rifaximin was effective in shortening the TLUS in subjects negative for baseline pathogens (A proportion of such subjects might have had *E coli* infections that were not identified on culture).

The study was not statistically powered to measure efficacy in the subgroups shown above.

Integrated assessment of efficacy

A total of 653 subjects participated in the 2 pivotal studies (RFID 9801 and 3001) supporting this application.

Of these, 318 received rifaximin at the proposed dose of 200mg tid for 3 days.

Gender: Forty-eight percent of the rifaximin treated patients were women.

Race: Eighty-four percent were white; the remaining 16 percent were predominantly Asian or Hispanic. Only 2 patients among the 318 rifaximin treated patients in these studies were recorded as black.

Age The studies included adults ranging in age from 18 to 79 with a mean for the 2 studies of 32 years and 29 years respectively. Nine subjects were 65 years of age. Pediatric patients were not studied.

Both pivotal studies (RFID 9801 and 3001) showed that rifaximin was superior to placebo in reducing the time to last unformed stool, and in producing a clinical cure 24-48 hours after completion of therapy in a diverse population of subjects with traveler's diarrhea. Efficacy was confirmed for infections caused by *E. coli* but not by any other organism.

Safety

A total of 593 subjects received rifaximin at doses between 600mg and 1800mg per day. Three hundred and twenty received 200mg tid for three days. Flatulence was reported in 11.3% and headache in 9.7%. The frequency of adverse events occurring in 2% of subjects in clinical trials is shown below.

All Adverse Events With an Incidence ≥2% Among Patients Receiving XIFAXAN™ Tablets, 600 mg/day, in Placebo-Controlled Studies		
MedDRA Preferred Term	Number (%) of Patients	
	XIFAXAN™ Tablets, 600 mg/day (N = 320)	Placebo N = 228
Flatulence	36 (11.3%)	45 (19.7%)
Headache	31 (9.7%)	21 (9.2%)
Abdominal Pain NOS	23 (7.2%)	23 (10.1%)
Rectal Tenesmus	23 (7.2%)	20 (8.8%)
Defecation Urgency	19 (5.9%)	21 (9.2%)
Nausea	17 (5.3%)	19 (8.3%)
Constipation	12 (3.8%)	8 (3.5%)
Pyrexia	10 (3.1%)	10 (4.4%)
Vomiting NOS	7 (2.2%)	4 (1.8%)

Adverse event rates for rifaximin were similar to (and in most categories, lower than) those for placebo. Most of these adverse event reports represented symptoms of the underlying disease and did not appear specifically drug-related.

Foreign post marketing reports Since the product was launched in Italy in 1987 and subsequently in 14 other countries, only 11 patient reports of adverse events were submitted. These included 5 cases of urticaria. The remaining cases included single occurrences of agitation, syncope, headache, nausea, oesophageal pain, and limb edema.

Conclusions

The applicant provided results of 2 adequate and well-controlled studies each of which showed that rifaximin was superior to placebo in reducing the time to last unformed stool, and in producing a clinical cure 24-48 hours after completion of therapy in a diverse population of subjects with traveler's diarrhea.

In the present submission (study RFID3001), rifaximin shows a moderate ability to shorten the duration of diarrhea, supporting the results in the original submission. Rifaximin is not shown to be efficacious in patients with blood in the stool, or fever, or with cultures positive for one of several recognized diarrheagenic pathogens, including *Campylobacter* and *Salmonella*.

Microbiological efficacy has only been demonstrated in infections with *E. coli* where spontaneous resolution is frequent. The drug is not effective in cases of *Campylobacter* infection and efficacy has not been demonstrated against other enteric pathogens.

Rifaximin was shown to be effective in patients without an identifiable baseline pathogen.

Pooled eradication rates for invasive pathogens (*Campylobacter*, *Salmonella* and *Shigella*) are identical for rifaximin and placebo (55.6%) and higher for cipro (76.9%). This is consistent with the expected

performance of a non-systemic agent, hence rifaximin should not be used in patients with invasive pathogens

Rifaximin is minimally absorbed (approximately 0.4%) and does not present any safety concerns. Flatulence and headache are the most commonly associated adverse events.

While the safety profile of rifaximin is favorable, its efficacy is limited to patients without invasive pathogens, generally those presenting with milder illness without blood in the stool or fever. Approved labeling indicates the types of patient where empirical use of rifaximin is not appropriate.

Other regulatory requirements

There are no outstanding issues in the approval of this application.

The antibiotic labeling rule was not applied, as rifaximin is not significantly absorbed (approximately 0.4%) and does not function as a systemic antibiotic.

- Biopharmaceutical requirements included a pharmacokinetic study to assess systemic absorption and submission of information characterizing drug-drug interactions between rifaximin and other CYP 3A4 substrates. These were satisfactorily addressed (see biopharmaceutics review by Dr. D. Chilukuri).
- Three CMC requirements included documentation of drug product lots used in phase 3 studies, identification of degradants, and additional stability data. These were satisfactorily addressed (see CMC review by Dr. R. Sood).
- The pre-approval safety meeting with the office of drug safety for this new chemical entity was waived, based on the minimal systemic absorption of the drug and the absence of any safety signals despite substantial human exposure.

Pediatric requirements

Pediatric studies in children >3 and <12 years of age have been deferred for 5 years until they can effectively be completed.

Pediatric studies in children between the ages of 0 and 3 years have been waived since the etiology of diarrhea differs from that in older children, being predominantly due to viral infections.

A pediatric written request was issued on 4/15/03 requesting two studies, one to examine the pharmacokinetics and safety of rifaximin at 1mg/kg and 3mg/kg tid over 3 days in children with acute diarrhea between 3 and 12 years of age, and the second to examine the safety and efficacy of rifaximin at 1mg/kg and 3mg/kg tid over 3 days in children with acute diarrhea between 3 and 16 years of age.

Phase 4 studies

There are no phase 4 requirements other than the pediatric studies described above.

Leonard Sacks
Acting medical team leader

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/s/

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**MOR of NDA 21-361
Resubmission
Rifaximin
Traveler's Diarrhea**

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EXECUTIVE SUMMARY for NDA 21-361 resubmission
XIFAXAN™
(Rifaximin, formerly known as LUMENAX)

Applicant's Proposed Indication XIFAXAN™ Tablets are indicated for the treatment of patients (≥ 12 years of age) with traveler's diarrhea caused by

Escherichia coli

Background

Salix Pharmaceuticals resubmitted a new drug application (NDA) 21-361 for the use of rifaximin tablets in the treatment of traveler's diarrhea. The proposed dosing schedule is a 200 mg tablet TID for 3 days (600 mg QD). NDA 21-361 was originally submitted on December 21, 2001. On October 25, 2002 at the conclusion of the review cycle, an "approvable" letter was issued. The applicant was informed that in order to obtain an approval a second adequate and well-controlled Phase III trial of rifaximin in the treatment of traveler's diarrhea at the proposed dose of 200 mg PO TID should be submitted. This trial was to confirm the results of trial RFID9801 and was required to show a clinically meaningful benefit and a statistically significant reduction in the duration of diarrhea between rifaximin and placebo regimens.

1 Clinical and microbiologic efficacy results were required to be similar between the ITT and MITT population. The applicant was also requested to submit additional pharmacokinetic data pertaining to the level of systemic absorption of rifaximin in subjects with traveler's diarrhea as well as information characterizing pharmacokinetic drug-drug interactions between rifaximin and other CYP3A4 substrates.

Clinical Studies

Pertinent to this resubmission, the applicant submitted the results of a second Phase III, randomized, double-blinded placebo-controlled trial (RFID3001) of rifaximin 200 mg PO TID for 3 days in the treatment of traveler's diarrhea for review. Additionally, the applicant provided an integrated summary of efficacy wherein the results of study RFID3001 as well the previously reviewed trials (RFID9801 and RFID9701) are combined. RFID9801 was conducted by the applicant Salix under FDA guidance and was a Phase III, randomized, placebo-controlled study designed to support a claim of efficacy for rifaximin in the treatment of traveler's diarrhea (EOP meeting for IND 52,980, September 21, 1998). RFID9701, a Phase III study comparing rifaximin to ciprofloxacin, was developed and conducted by Alfa Wassermann and then transferred to Salix for analysis. Of note, the rifaximin dose in study RFID9701 was 400 mg PO BID.

Both study RFID 9801 and RFID3001 were Phase 3, randomized, multicenter, double-blind studies of 3-day treatment regimens of rifaximin in adult subjects with travelers' diarrhea.

RFID3001 compared rifaximin (200 mg TID) with placebo and ciprofloxacin (500 mg BID), RFID9801 compared 2 doses of rifaximin (200 mg TID, 400 mg TID) with placebo,

Eligible subjects showed evidence of acute diarrhea, defined as 3 or more unformed stools during the 24 hours preceding enrollment, accompanied by one or more of the following signs and symptoms: abdominal pain or cramps, excessive gas/flatulence, nausea, vomiting, fever ($\geq 100^{\circ}\text{F}$ or $\geq 37.8^{\circ}\text{C}$), fecal urgency, tenesmus, or dysentery (passage of bloody stool), total duration of diarrhea was to be no more than 72 hours. A pretreatment stool was collected from all subjects, verified as “unformed” and tested for the presence of enteropathogens. Subjects ≥ 18 years of age were enrolled at sites in Mexico, Guatemala, Peru, Jamaica, India, and Kenya.

In both trials, stool specimens for identification of enteric pathogens were collected before treatment and 1 to 3 days following the end of treatment. In study RFID3001, an attempt was also made to collect specimens after 24 hours of treatment in order to further assess the microbiologic activity of rifaximin. The subjects maintained daily diary cards for recording the time and form (formed, soft, or watery) of all stools passed and the presence or absence of clinical signs and symptoms (nausea, vomiting, abdominal pain/cramps, excess gas/flatulence, fecal urgency, tenesmus, and fever). The primary efficacy variable in each study was time-to-last-unformed-stool (TLUS), other efficacy variables included improvement in diarrheal syndrome, the number of unformed stools passed per time interval, the number of subjects achieving wellness (clinical cure), at the TOC visit 24- 48 hours after the last dose, the number of subjects who were treatment failures, improvement in clinical symptoms, and microbiological eradication/persistence of pretreatment pathogens.

With regards to the primary efficacy parameter TLUS in the ITT population, similar results were obtained between the studies indicating consistency in the ability of rifaximin to decrease morbidity in subjects suffering from traveler’s diarrhea.

Median TLUS ITT Population

Median TLUS in Hours (Kaplan-Meier Estimates)	Treatment Group		
	Rifaximin	Placebo	Cipro
All Centers study RFID9801	(N = 125) 32.5	(N = 129) 58.6	NA
All Centers study RFID3001	(N=197) 32.0	(N=101) 65.5	(N=101) 28.8
TLUS by Center RFID3001			
Calcutta, India (#100)	(N=43) 24.5	(N=23) NC	(N=23) 24.1
Goa, India (#101)	(N=58) 72.0	(N=29) 69.7	(N=30) 70.5
Antigua, Guatemala (#107) & Lima, Peru (#269)	(N=53) 23.5	(N=26) 42.4	(N=27) 20.8
Guadalajara Mexico (#200), Cuernavaca Mexico (#242) & Puerto Vallarta Mexico (#249)	(N=43) 33.0	(N=23) 26.7	(N=21) 15.5

Specifically, in study RFID9801 median TLUS was 32.5 hours in the rifaximin 200 mg TID group, and 58.6 hours in the placebo group.

In study RID 3001, the median TLUS in the rifaximin ITT population, (32.0 hours) was less than that in the placebo group (65.5 hours) and the median TLUS in the ciprofloxacin group was 28.8 hours. However, the acceptability of the pooled results was called into question because of significant treatment-by-center interactions necessitating that results be reported by center. These interactions were caused by the failure of the positive control at the Goa center and the failure of the negative control at the Mexican site. When TLUS was assessed for only those sites where the study was performed in an acceptable manner rifaximin was found to be effective at shortening the duration of diarrhea relative to placebo. The relative risk (rifaximin/placebo) for TLUS for Calcutta and Guatemala/Peru was 2.17 (95% CI=1.44-3.27, P=0.0002).

Median TLUS by Analysis Center excluding Goa and Mexico ITT Population RFID3001

Median TLUS in Hours (Kaplan-Meier Estimates)	Treatment Group		
	Rifaximin	Placebo	Cipro
Calcutta/Guatemala/Peru	(N= 96) 23.85	(N=49) 65.5	(N= 50) 23.60

The MO assessed TLUS for the MITT populations in both studies. The MITT population was that subset of the ITT population that had a pathogen cultured from stool at baseline.

Median TLUS in Hours/MITT

Median TLUS in Hours/MITT	Treatment Group		
	Rifaximin	Placebo	Ciprofloxacin
All Centers/RFID9801	(N = 70) 30 0	N = 61 59 8	NA
All Centers/RFID3001	(N = 128) 40 3	(N=62) 48 3	(N=58) 28 3
TLUS by Center RFID3001			
Calcutta, India (#100)	(N = 29) 24 5	(N = 16) NC	(N = 17) 17 7
Goa, India (#101)	(N = 41) NC	(N = 18) 67 5	(N = 20) 70 5
Antigua, Guatemala (#107) & Lima, Peru (#269)	(N = 33) 23 8	(N = 16) 41 4	(N = 9) 24 4
Guadalajara Mexico (#200) Cuernavaca Mexico (#242) & Puerto Vallarta Mexico (#249)	(N = 25) 44 8	(N = 12) 22 5	(N =12) 12 4

In study RFID9801 the TLUS for the rifaximin 200 mg TID MITT population was 30 hours as compared to 59 8 hours for the placebo MITT population

The median TLUS in study RFID3001 was 8 hours lower for the rifaximin-treated subjects (40 3 hours) as compared to placebo (48 3 hours) Additionally, the median TLUS was much lower on the ciprofloxacin arm (28 3 hours) as compared to the rifaximin Because of the aforementioned by center treatment interactions, results were also assessed by center and excluding the centers where the study was performed inappropriately As in the ITT analysis, when TLUS was assessed for only those sites where the study was performed in an acceptable manner rifaximin was found to be effective at shortening the duration of diarrhea relative to placebo

Median TLUS by Analysis Center excluding Goa and Mexico MITT Population RFID3001

Median TLUS in Hours (Kaplan-Meier Estimates)	Treatment Group		
	Rifaximin	Placebo	Cipro
Calcutta/Guatemala/Peru	(N = 62) 23 95	(N =32) 61 90	(N = 26) 20 55

The Median TLUS was calculated by the applicant for a number of subgroups of the ITT population in study RFID3001 including subjects with

- fecal leukocyte-positive illness,
- fecal leukocyte-negative illness,
- inflammatory/invasive pathogens,
- diarrheagenic *E coli* without evidence of inflammatory/invasive pathogens,
- other agents without evidence of inflammatory/invasive pathogens

- diarrheagenic *E coli*,
- agent-specific illness,
- agent-negative illness

As the Agency disputed the acceptability of the pooled results from this study these analyses were not utilized to determine approvability although information from these analyses was utilized to formulate labeling recommendations

Analyses of wellness and treatment failure were performed by both the Applicant and the Agency for both studies in both the ITT and MITT populations. These assessments were performed at the TOC visit approximately 24 – 48 hours after the last dose of study medication. Wellness or clinical cure was assessed at the post-treatment visit and was defined as follows:

1. No unformed stools within a 48-hour period with no fever (with or without other clinical symptoms), or
2. No watery stools and no more than 2 soft stools within a 24-hour period with no fever and no other clinical symptoms except for mild excess gas/flatulence

It was the MO's determination that this analysis provided a more accurate assessment of the efficacy of rifaximin as compared to TLUS or to microbiologic eradication rates as this drug does not appear to perform as a conventional antimicrobial in eradicating possible pathogenic organisms.

In study RFID9801 99/125 (79.2%) of rifaximin-treated ITT subjects achieved wellness as compared to 78/129 (60.5%) of placebo-treated subjects. Similar results were obtained for the MITT population. In study RFID3001, 76.6% rifaximin-treated subjects were classified as clinical cures as compared to 61.4% of placebo recipients. Of note, in study RFID3001, the treatment failure rate with rifaximin was slightly more than double that observed with ciprofloxacin (14.7% vs 6.9%, respectively). A by-center breakdown of the results revealed continuing issues with the Goa site whereas the results of the Mexican centers were more consistent with those of the other sites, lending weight to the argument that the median TLUS value is not the only, and perhaps not always the ideal, statistic to use to assess efficacy. While the median TLUS at Mexican centers for the ITT population was larger for rifaximin (median=33.0h) than for placebo (median=26.7h), a greater percentage of rifaximin subjects achieved wellness (N=36/43, 83.7%) than did placebo subjects (N=15/23, 65.2%) suggesting that early during therapy, placebo subjects achieved wellness faster than rifaximin subjects, but did not continue to improve throughout the treatment and follow-up period. On the other hand, rifaximin subjects were somewhat delayed in initial response, but continued to achieve wellness after the initial placebo response had begun to cease.

Wellness-ITT RFID9801 and RFID3001

	Rifaximin	Placebo	Cipro
Overall RFID9801	99/125 (79.2%)	78/129 (60.5%)	N/A
Overall RFID3001	151/197 (76.6%)	62/101 (61.4%)	79/101 (78.2%)
By Center RFID3001			
Calcutta, India	38/43 (88.4%)	11/23 (47.8%)	21/23 (91.3%)
Goa, India	30/58 (51.7%)	15/29 (51.7%)	16/30 (53.3%)
Guatemala and Peru	47/53 (88.7%)	21/26 (80.8%)	26/27 (96.3%)
Mexico sites	36/43 (83.7%)	15/23 (65.2%)	16/21 (76.2%)

The Agency requested that the applicant provide analyses of TLUS, wellness and microbiologic eradication for subjects with fever and/or blood in the stool for subjects in study RFID3001. In both the ITT and MITT populations, it was clear that the presence or absence of fever at baseline played a major role in efficacy with fewer rifaximin and placebo-treated subjects with fever becoming well when this parameter was present. TLUS was either not calculable in this group because of the large number of patients with censored data (i.e. failures) or it was prolonged. Only those subjects treated with ciprofloxacin had lower TLUS and increased percentages of subjects cured. Similar results were not seen for the presence or absence of blood in the stool at baseline in the ITT population but the presence or absence of blood at baseline had a clear effect on efficacy in the MITT population again with similar TLUS and clinical cure rates in the rifaximin and placebo-treated populations. Similar analyses were not performed for study RFID9801 where fewer subjects had fever and/or blood in the stool at baseline.

TLUS, Wellness and Microbiologic Eradication Rates in Subjects with Fever and Blood in the Stool at Baseline Study RFID3001

Group	Rifaximin	Placebo	Ciprofloxacin
Fever at Baseline			
TLUS	NC	51.1	23.4
Wellness	12/25 (48%)	8/12 (66.7%)	12/14 (85.7%)
Eradication	14/25 (56%)	6/12 (50%)	12/14 (85.7%)
Blood at Baseline			
TLUS	63.5	69.7	55.5
Wellness	24/42 (57.1%)	14/25 (56%)	13/18 (72.2%)
Eradication	26/42 (61.9%)	12/25 (48%)	13/18 (72.2%)
Fever and Blood at Baseline			
TLUS	NC	NC	36.5
Wellness	6/14 (42.9%)	3/7 (42.9%)	7/8 (87.5%)
Eradication	8/14 (57.1%)	3/7 (42.9%)	7/8 (87.5%)

Although minor differences existed between the 2 studies regarding overall pathogen eradication rates, the results of both studies confirmed that rifaximin did not have superior microbiologic activity to that of placebo versus any pathogen.

In RFID9801 both rifaximin and placebo demonstrated a similar level of overall pathogen eradication in the MITT population. Additionally, the specific pathogen identification rates were similar between the rifaximin 200 mg TID and placebo groups.

In RFID 3001 overall eradication rates were again similar between the rifaximin and placebo arms at visit 2 and although in the MITT population at the TOC visit that occurred 24 – 48 hours after the last dose, a slightly greater proportion of subjects in the rifaximin group than in the placebo group had an overall microbiological response of eradication (61.6% vs 51.7%) these results were not significant and again raised concerns about the true microbiologic activity of rifaximin. Results obtained on the ciprofloxacin arm were numerically superior to those obtained on the placebo or rifaximin treatment arms. A by center and by pathogen breakdown of the results also did not reveal a significant difference between rifaximin and placebo at any level.

**Microbiologic Eradication rate by Pathogen TOC Visit (24 – 48 hours post-treatment)
Study RFID3001**

Genus (Species)	Number (%) of MITT/MEE Subjects		
	Rifaximin (N=125)	Placebo (N=62)	Ciprofloxacin (N=58)
<i>Aeromonas (hydrophila)</i>	2/3 (66.7%)	1/1 (100%)	1/1 (100%)
<i>Campylobacter (jejuni)</i>	9/25 (36.0%)	4/10 (40.0%)	6/9 (66.7%)
<i>Plesiomonas sp</i>	3/3 (100%)	-	-
<i>Plesiomonas shigelloides</i>	1/1 (100%)	1/2 (50.0%)	-
<i>Salmonella Group B</i>	1/3 (33.3%)	-	-
<i>Salmonella Group C1</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Salmonella Group C2</i>	-	-	1/1 (100%)
<i>Shigella boydu</i>	1/1 (100%)	-	-
<i>Shigella flexneri</i>	2/2 (100%)	2/4 (50.0%)	1/1 (100%)
<i>Shigella sonnei</i>	7/8 (87.5%)	1/1 (100%)	1/1 (100%)
<i>Vibrio cholerae</i>	2/2 (100%)	-	-
<i>Providencia</i>	1/1 (100%)	-	1/1 (100%)
Diarrheagenic <i>E coli</i>	62/83 (74.7%)	30/43 (69.8%)	43/45 (95.6%)
<i>Cryptosporidium parvum</i>	2/6 (33.3%)	1/4 (25.0%)	2/6 (33.3%)
<i>Entamoeba histolytica</i>	1/3 (33.0%)	-	-
<i>Giardia lamblia</i>	6/15 (40.0%)	2/8 (25.0%)	3/5 (60.0%)

**Microbiologic Eradication rate by Pathogen TOC Visit (24 – 48 hours post-treatment)
Study RFID9801**

Pathogen	RFID 9801 Rifaximin 200 mg TID		RFID9801 Placebo	
	No	No Eradicated (%)	No	No Eradicated (%)
<i>Escherichia coli</i>	60	45/60 (75%)	54	40/54 (74%)
<i>Shigella sonnei</i>	3	3/3 (100%)	2	2/2 (100%)
<i>Shigella flexneri</i>	2	1/2 (50%)	0	0
<i>Salmonella</i> Group C1	3	2/3 (67%)	1	1/1 (100%)
<i>Salmonella</i> Group C2	0	0	1	1/1 (100%)
<i>Campylobacter jejuni</i>	4	3/4 (75%)	1	0/1
<i>Cryptosporidium parvum</i>	18	12/18 (67%)	1	1/1 (100%)

Analyses of TLUS were performed for MITT subjects with *Escherichia coli*. The goal of these analyses was to enable appropriate labeling recommendations.

Median TLUS for MITT Subjects with *Escherichia coli*

Median TLUS in Hours/MITT	Treatment Group		
	Rifaximin	Placebo	Ciprofloxacin
Study RFID9801	N = 125	N = 129	NA
<i>Escherichia coli</i> only	N = 53 28.4	N = 54 57.8	
Study RFID3001	Rifaximin (N=128)	Placebo (N=62)	Ciprofloxacin (N=58)
<i>Escherichia coli</i> only	N = 64 23.9	N = 33 26.7	(N= 36) 23.4

In study RFID9801, subjects who were infected with ETEC had median TLUS that was similar to the overall MITT-type population and there appeared to be a trend that treatment with rifaximin leads to shorter TLUS than placebo in this subgroup.

In study RFID3001 there were similar TLUS results for the rifaximin and placebo-treated subjects with *Escherichia coli*.

An attempt was made to calculate median TLUS for those subjects with *Shigella* spp and *Campylobacter* spp isolated in baseline stool culture however, the numbers of isolates were small and in subjects with these isolates as sole pathogens, the numbers became even smaller. Specifically, of 18 total patients with *Shigella* spp (not speciated), 10 had this isolate as a sole pathogen. 7 of these subjects were treated with rifaximin and had a median TLUS of 42.6 hours, 2 were treated with placebo and one had a median TLUS of 31.8 hours while the other failed (TLUS > 120 hours), and one was treated with ciprofloxacin. That patient had a TLUS of 120 hours. Of the 7 rifaximin-treated subjects with *Shigella* spp as their sole pathogen, 5 had *Shigella sonnei*. The median TLUS in this very small subgroup was 30.6 hours and the mean was 34 hours. No placebo-treated subjects had *Shigella sonnei* isolated in the stool and only one ciprofloxacin-treated subject had this pathogen. That subject had a TLUS of 120 hours. The MO

concluded that there was not enough information available regarding the efficacy of rifaximin versus this pathogen to justify inclusion in the Indication section of the labeling

Of 44 patients with *Campylobacter* spp 23 had *Campylobacter* spp as the sole pathogen 17 of these subjects were treated with rifaximin with the following outcomes 9 failures, 4 well at — hours, and 4 censored at 25 2, 58 1, 70 1, and 71 hours Of 4 placebo-treated subjects, 3 failed and one was cured with TLUS of — hours and of 2 ciprofloxacin-treated subjects, 1 failed and 1 had a TLUS of — hours

Overall, it appeared as if rifaximin was effective in reducing the TLUS in subjects in subjects with agent-negative disease or in those with *Escherichia coli* isolated from pretreatment stool culture These results were confirmed in two Phase III clinical trials Rifaximin did not appear to be effective in subjects with inflammatory/invasive pathogens including *Campylobacter jejuni*, *Salmonella* spp and *Shigella* spp Regarding *Shigella sonnei*, — the median TLUS for *Shigella* spp (7 subjects) was 42 6 hours as compared to 24 hours in rifaximin-treated subjects with diarrheagenic *E coli* Additionally microbiologic efficacy was shown in only 7 subjects with this organism as a sole causative pathogen Regarding *Escherichia coli*, a requested pathogen for which there was adequate data, the data were encouraging In study RFID9801, TLUS in the subset of subjects with this pathogen was less in rifaximin-treated subjects as compared to placebo A similar trend was seen in study RFID3001 when subjects with *Escherichia coli* only were assessed Finally, as in the first review cycle, eradication rates were similar between the rifaximin and placebo treatment arms indicating that rifaximin does not appear to cause clinical improvement directly via microbiologic eradication

To conclude, patients with fever and/or bloody diarrhea, *Campylobacter jejuni*, *Shigella* spp or *Salmonella* spp should not take rifaximin

Safety Conclusions

Five hundred ninety three subjects were exposed to rifaximin doses of 600 mg/day, 800 mg/day, 1200 mg/day, or 1800 mg/day in the traveler's diarrhea studies Three hundred twenty of these subjects received the requested dose and duration of treatment of 200 mg TID

Among the 320 subjects who received rifaximin 600 mg/day the most commonly experienced adverse events were flatulence (11 3%) and headache (9 7%)

A comparison of adverse event data presented in the original NDA to combined data presented in the safety update showed no differences in the specific types of events reported The incidence rates of the events were higher in the original NDA compared with the safety update apparently due to the differences in adverse event reporting among the studies

When presented by individual study, the incidences of adverse events noted among subjects treated with the rifaximin 600 mg/day dose were generally comparable to those observed among subjects treated with placebo or ciprofloxacin

No subjects died during the Phase 2/3 studies. One (0.2%) rifaximin-treated subject experienced a serious adverse event (dysentery NOS) and 3 (0.5%) rifaximin-treated subjects prematurely discontinued treatment due to adverse events (nasal passage irritation and weight decreased, dysentery NOS, nausea, taste loss, and anorexia).

No clinically important changes in WBC counts, hemoglobin, or platelet counts were observed following treatment with rifaximin.

Special Populations

Efficacy

The sample size was too small to allow for the observation of differences in the efficacy rates with respect to race, gender, age, or ethnic group.

Recommendations

The MO concluded that

In two double-blind placebo-controlled randomized studies that utilized the proposed rifaximin dose of 200 mg PO TID for three days, rifaximin decreased the time to last unformed stool as compared to placebo primarily in subjects with agent-negative disease or in those with *Escherichia coli* isolated from pretreatment stool culture. A similar effect was not seen in subjects who had inflammatory/invasive pathogens isolated from the stool.

The MO is recommending that rifaximin be approved in the treatment of traveler's diarrhea caused by *Escherichia coli*. Efficacy was not shown in subjects with inflammatory or invasive pathogens or more serious disease and rifaximin should not be considered approvable for the treatment of subjects with dysentery (bloody stools) or with fever > 101. Rifaximin was proven ineffective in subjects with *Campylobacter* and *Salmonella*. Inconclusive evidence was provided regarding the efficacy of rifaximin in subjects with *Shigella sonnei*. Rifaximin should also not be used in subjects with clinical evidence of dehydration. If no symptomatic improvement is apparent within 48 hours, consideration should be given to modification of the treatment regimen.

**Medical Officer's Clinical Review of NDA 21-361
XIFAXAN™ (rifaximin LUMENAX)**

Applicant's Proposed Indication XIFAXAN™ Tablets are indicated for the treatment of patients (≥ 12 years of age) with traveler's diarrhea caused by

Escherichia coli (ε —

I Introduction and Background

A Applicant, Drug Established and Proposed Trade Names, Drug Class, Applicant's Proposed Indication(s), Dose, Regimens, Age Groups

Applicant Salix Pharmaceuticals

Address 3600 West Bayshore Road
Suite 205
Palo Alto, CA 94303

Date of Submission November 25, 2003

CDER Stamp date November 26, 2003

Date Submission received by reviewer December 3, 2003

Date Review Completed May 20, 2004

Drug Name Rifaximin

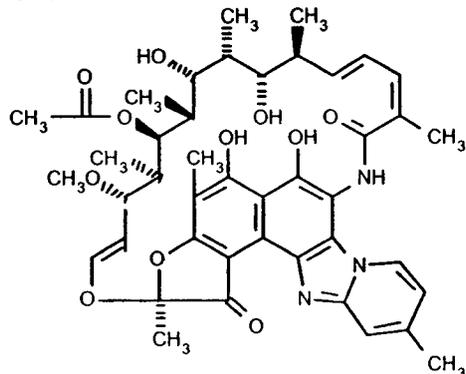
Proprietary Name XIFAXAN™

Pharmacologic Category Rifamycin

Chemical Name (2S, 16Z, 18E, 20S, 21S, 22R, 23R, 24R, 25S, 26S, 27S, 28E)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca(1,11,13)trienimino)benzofuro(4,5-e)pyrido(1,2,-a)benzimidazole-1-15(2H)-dione,25-acetate

Molecular formula C₄₃H₅₁N₃O₁₁

Molecular weight 785.89

Chemical structure**Dosage Form** Tablets**Route of Administration** Oral**Strengths** 200 mg tablets**Proposed Indications and Usage**

'XIFAXAN™ Tablets are indicated for the treatment of patients (≥ 12 years of age) with traveler's diarrhea caused by

Escherichia coli

Related INDs IND

IND 52,980 (Salix,

IND

IND

Materials Reviewed

NDA volumes 1 - 34

CDROM with WORD documents submitted 12/5/2003

CDROM copy of Esub submitted 12/9/03

TLUS Table for MITT Population submitted 12/10/2003

CDROM with Appendices submitted 12/12/2003

CDROM with CRFs submitted 12/23/03

Email Responses to Agency requests 1/9/04, 1/11/04, 1/12/04, 1/15/04, 1/16/04, 1/22/04, 2/6/04

Abbreviations

CRF = Case Report Form
 RIF= Rifaximin
 CIP = Ciprofloxacin
 TMP/SMX = Trimethoprim sulfamethaxazole
 PL= Placebo
 CRF = Case Report Form
 AE = Adverse Event
 EOT = End of Therapy
 ITT = Intent to Treat
 EP = Evaluable Population
 MITT = Modified Intent to Treat
 ETEC = Enterotoxigenic *Escherichia coli*
 TLUS = Time to Last Unformed Stool
 ID = Infectious Diarrhea
 HE= Hepatic encephalopathy
 LT = Shiga-like heat labile toxin
 ST = heat stable toxin

Note on fonts This review is written in Times New Roman 12 Arial is used for direct quotes from the applicant's submission

B State of Armamentarium for Indication(s)
 (Literature Review Please see original MOR dated 10/10/2002)

C Important Milestones in Product Development
 (Please see original MOR dated 10/10/2002)

Pertinent to the current resubmission, Salix Pharmaceuticals resubmitted a new drug application (NDA) 21-361 for the use of rifaximin tablets in the treatment of traveler's diarrhea. The proposed dosing schedule is a 200 mg tablet TID for 3 days (600 mg QD). NDA 21-361 was originally submitted on December 21, 2001. On October 25, 2002 at the conclusion of the review cycle, an "approvable" letter was issued. The applicant was informed that in order to obtain an approval a second adequate and well-controlled Phase III trial of rifaximin in the treatment of traveler's diarrhea at the proposed dose of 200 mg PO TID should be submitted. This trial was to confirm the results of trial RFID9801 and was required to show a clinically meaningful benefit and a statistically significant reduction in the duration of diarrhea between rifaximin and placebo regimens.

Clinical and microbiologic efficacy results were required to be similar between the ITT and MITT population. The applicant was also requested to submit additional pharmacokinetic data pertaining to the level of systemic absorption of rifaximin in subjects with traveler's diarrhea as well as information characterizing pharmacokinetic drug-drug interactions between rifaximin and other CYP3A4 substrates.



Antimicrobial Agents Approved for Infectious Diarrhea

(Excerpts from approved labels)

Cipro® (ciprofloxacin) Oral Suspension, Cipro® Tablets

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella boydii**, *Shigella dysenteriae*, *Shigella flexneri* or *Shigella sonnei** when antibacterial therapy is indicated

Typhoid Fever (Enteric Fever) caused by *Salmonella typhi*

NOTE The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated

*Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients

Infectious Diarrhea Mild/Moderate/Severe 500-mg q 12 h 5 to 7 Days

Typhoid Fever Mild/Moderate 500-mg q 12 h 10 Days

Furoxone (furazolidone) Liquid and Tablets (AP 1958, 1961)

Indicated in the specific and symptomatic treatment of bacterial or protozoal diarrhea and enteritis caused by susceptible organisms. Furoxone products are well tolerated, and have a very low incidence of adverse reactions.

ACTION

Furoxone has a broad antibacterial spectrum covering the majority of gastrointestinal tract pathogens including *Escherichia coli*, staphylococci, *Salmonella*, *Shigella*, *Proteus*, *Aerobacter aerogenes*, *Vibrio cholerae* and *Giardia lamblia*. Its bactericidal activity is based upon its interference with several bacterial enzyme systems, this antimicrobial action minimizes the development of resistant organisms. It neither significantly alters the normal bowel flora nor results in fungal overgrowth. The brown color found in the urine with adequate dosage is of no clinical significance.

Bactrim Pediatric suspension, Tablets, DS Tablets

Shigellosis For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated
Travelers' Diarrhea in Adults For the treatment of travelers' diarrhea due to

susceptible strains of enterotoxigenic *E coli*

Septra® Suspension, Tablets, DS Tablets

Travelers' Diarrhea in Adults For the treatment of travelers' diarrhea due to susceptible strains of enterotoxigenic *E coli* Shigellosis For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated

Prior FDA Reviews and Guidances

(Please see original MOR dates 10/10/2002)

C Other Relevant Information

(See MOR 10/22/2002)

The product was first approved in 1985 in Italy as 200-mg tablets and as an oral granulates for suspension, 2 g/100 mL upon reconstitution Alfa Wassermann, its licensee, holds marketing authorizations for rifaximin in a number of other countries Argentina, Bulgaria, Colombia, The Czech Republic, Hungary, Mexico, Pakistan, Romania, Spain, Venezuela, and Vietnam

Since the first approval of rifaximin in 1985, no marketing authorizations have been rejected for safety reasons and no drug suspensions or distribution restrictions have occurred

untoward, serious, or unexpected adverse events associated with the use of the drug In neither case were any

II Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

(Please see original MOR dated 10/10/2002)

Pertinent to this submission, the applicant submitted

III Description of Clinical Data and Sources

A Overall Data

Pertinent to this resubmission, the applicant submitted the results of a second Phase III, randomized, double-blinded placebo-controlled trial (RFID3001) of rifaximin 200 mg PO TID for 3 days in the treatment of traveler's diarrhea for review Additionally, the applicant provided an integrated summary of efficacy wherein the results of study RFID3001 as well the previously reviewed trials (RFID9801 and RFID9701) are combined RFID9801 was conducted by the

applicant Salix under FDA guidance and was a Phase III, randomized, placebo-controlled study designed to support a claim of efficacy for rifaximin in the treatment of traveler's diarrhea (EOP meeting for IND 52,980, September 21, 1998) RFID9701, a Phase III study comparing rifaximin to ciprofloxacin, was developed and conducted by Alfa Wassermann and then transferred to Salix for analysis. Of note, the rifaximin dose in study RFID9701 was 400 mg PO BID.

**APPEARS THIS WAY
ON ORIGINAL**

B Table Listing the Clinical Trials**Table 1**

Study	Study Design	Sponsor	Rifaximin Regimen	Comp	Patients Enrolled	ITT Population ¹	Microbiologic al Population ²
RFID9801	Randomized DB PC	Salix	200 mg TID x 3 d 400 mg TID x 3 d	Placebo	Total 380 Rifaximin 200 mg TID (n=125) 400 mg TID (n=126) Placebo (n=129)	Total 380 Rifaximin 200 mg TID (n=125) 400 mg TID (n=126) Placebo (n=129)	218/380 (57%)
RFID9701	Randomized DB AC	Alfa Wass Spain	400 mg BID x 3 d	Cipro	Total 187 Rifaximin (n=93) Ciprofloxacin (n=94)	Total 187 Rifaximin (n=93) Ciprofloxacin (n=94)	87/187 (47%)
RFID9601	Randomized DB Phase II	Alfa Wass Spain	200 mg TID x 5 d 400 mg TID x 5 d 600 mg TID x 5 d	TMP/SMX	Total 76 Rifaximin 200 mg TID (n=19) 400 mg TID (n=19) 600 mg TID (n=19) TMP/SMX (n=19)	Total 72 Rifaximin 200 mg TID (n=18) 400 mg TID (n=18) 600 mg TID (n=19) TMP/SMX (n=17)	27/72 (38%)
RFID3001*	Randomized DB, PC AC	Salix	200 mg TID x 3 d	Placebo Cipro			

Patients were all travelers with infectious diarrhea

* Reviewed in current MOR

¹ For studies RFID9801 and RFID9701, the ITT population was defined as all patients who were randomized to treatment, and for study RFID9601, the ITT population was defined as all patients who were randomized, took at least two days of study medication, and completed two or more daily diaries

² Microbiologically evaluable patients were patients who had a pathogen identified in their baseline stool sample and provided a post treatment stool sample

Postmarketing Experience

Since the initial product launch in Italy, 1987 and followed by subsequent approvals in additional 14 countries there have been 19 spontaneous AEs reported from 11 patients. Of these events, the most frequently reported was urticaria (N=5) and there were two related events reported, pruritus (N=1) and allergic dermatitis (N=1). One case of urticaria was listed as ‘serious’, the other cases were listed as ‘non-serious’. Abdominal pain was reported on two separate occasions, and the remaining AEs were reported once: agitation, syncope, headache, nausea, esophageal pain, edema (limb). The ‘‘Observed During Clinical Practice’’ section of the applicant’s proposed

product labeling contains a statement to reflect the AEs in these reports including allergic dermatitis, rash, and urticaria

IV Clinical Review Methods

A How the Review was conducted including overview of materials reviewed and methods used to evaluate data quality and integrity

In order to assess the overall data quality and integrity of the datasets, the MO reviewed a random sample of the CRFS from each of the pivotal and supportive studies. Twenty percent of the CRFs were reviewed and cross-checked with the CRTs (JMP datasets) to ensure accurate transcription of the data.

Subsequent to the review of the CRFs, the MO reviewed study 3001 as well as the integrated summaries of efficacy and safety provided by the applicant.

B Were Trials Conducted in Accordance with Accepted Ethical Standards

It appeared as if all trials were conducted ethically and after IRB approval. In all CRFs reviewed, the consent forms were signed.

C Evaluation of Financial Disclosure

There was no conflict of interest with regards to the indications under review,

V Integrated Review of Efficacy

A Brief Statement of Conclusions of data reviewed for the original submission

In the original submission, conclusions regarding the effectiveness and safety of rifaximin in the treatment of traveler's diarrhea were drawn from 3 studies. Two studies, (RFID9801 and RFID9701) were phase III, multicenter, randomized, double blind, controlled studies. Study RFID9801 was conducted in subjects traveling in Mexico, Guatemala, and Kenya and compared two doses of rifaximin, 200 mg or 400 mg TID (600 mg/day or 1200 mg/day, respectively) to placebo. Study RFID9701 was conducted in Mexico and Jamaica and compared rifaximin, 400 mg BID (800 mg/day), with ciprofloxacin, 500 mg twice daily (1000 mg/day). Subjects in both studies received study medication for 3 days. An additional randomized, double blind, dose-ranging phase II study (RFID9601) conducted in Mexico was considered supportive of efficacy. This study compared three doses of rifaximin, 200 mg, 400 mg, or 600 mg TID for 5 days to a TMP/SMX (trimethoprim/sulfamethaxazole) regimen of 160/800 mg twice daily for 5 days.

Both Phase III studies (RFID9801 and RFID9701) were designed and conducted in accordance with the General Guidelines for the Evaluation of New Anti-Infective Drugs for the Treatment of Acute Infectious Diarrhea (Clin Inf Dis 1992, 15 [Suppl 1] S228-235) and were comparable in terms of study population, methodology, and safety and efficacy endpoints. In each study, study medication was taken for three days with one to 2 days of additional observation after the end of

treatment Study RFID9801 compared rifaximin to placebo and was designed as a superiority study, while RFID9701 compared rifaximin to ciprofloxacin and was designed as a non-inferiority study

Only study RFID9801 was considered pivotal by the FDA review team. Study RFID9701 was considered supportive because the doses utilized in that trial were higher than the proposed 200 TID dose and the dosing interval was BID as opposed to TID. In view of this, the MO will only present data from study RFID9801 in this summary. For further details of the previously reviewed studies RFID9701 and 9601, Please see the original MOR.

The primary efficacy endpoint of study RFID9801 was the time to last unformed stool (TLUS) defined as the interval beginning with the first dose of study drug and ending with the last unformed stool passed, after which wellness (clinical cure) was declared.

In the applicant's analysis, TLUS was analyzed for the intent-to treat (ITT) population whereas the FDA performed this analysis on a modified intent-to-treat (MITT) population from all 3 studies consisting of subjects who had a pathogen isolated at baseline.

The results of the primary efficacy analysis of study RFID9801 demonstrated that rifaximin was superior to placebo in the treatment of diarrhea in travelers ($p = 0.0001$ for the rifaximin 200 mg PO TID versus placebo group and $p = 0.0001$ for the rifaximin 400 mg PO TID for 3 days versus placebo group). Median TLUS was significantly shorter in both rifaximin groups compared to placebo, 32.5 hours in the rifaximin 200 mg PO TID group, 32.9 hours in the 400 mg PO TID group, and 60.0 hours in the placebo group.

The TLUS values obtained for the FDA MITT population were consistent with those obtained for the ITT population in study RFID9801.

Table 2
Dose Regimen and Median TLUS for RFID9801 (ITT)

Study	Total Daily Dose	Schedule	Median TLUS (hours)	Median TLUS FDA MITT
RFID9801	600 mg/day	TID	32.5	30
RFID9801	1200 mg/day	TID	32.9	32.8
RFID9801	Placebo	TID	60.0	59.3

The MO performed an analysis on patients with leukocytes in the stool after determining that this patient subgroup is representative of subjects with dysentery. There were 20 subjects with leukocytes in the stool (20/129, 15%). Of these, 14 (70%) were determined to be cures and 6 (30%) to be failures. The TLUS for this group was 45.07 as compared to the median TLUS for all 200 mg TID subjects of 32 hours. For those subjects receiving the 400 mg TID dose, 17 (15%) had leukocytes in the stool and 15 (88%) were determined to be cures with a median TLUS of 36.6 as compared to 32.9 for all 400 mg TID subjects. Twenty-three placebo patients had leukocytes in the stool and 11 were cures. The applicant could not provide a median TLUS for this group. The MO determined that the applicant did not provide an adequate sample size in order to accurately assess rifaximin effectiveness in subjects with dysentery.

The pathogen identification rate was similar between the rifaximin and control groups and was consistent (50%) with the published literature. The organisms identified at baseline were consistent with those known to cause infectious diarrhea in travelers. In the rifaximin treatment groups, the most common pathogen identified was *Escherichia coli*, followed by Cryptosporidia. *Shigella*, *Salmonella*, and *Campylobacter* were found in very few patients.

Pathogen eradication rates assessed at the TOC visit (24 – 48 hours after the last dose) for patients stratified by rifaximin dose are shown below.

Table 3
Pathogen eradication rates/RFID9801

Pathogen	RFID 9801 Rifaximin 200 mg TID		RFID 9801 Rifaximin 400 mg TID		RFID9801 Placebo	
	No	No Eradicated (%)	No	No Eradicated (%)	No	No Eradicated (%)
<i>Escherichia coli</i>	60	45/60 (75%)	49	32/49 (65%)	54	40/54 (74%)
<i>Shigella sonnei</i>	3	3/3 (100%)	1	1/1 (100%)	2	2/2 (100%)
<i>Shigella flexneri</i>	2	1/2 (50%)	1	0/1	0	0
<i>Salmonella</i> Group C1	3	2/3 (67%)	4	3/4 (75%)	1	1/1 (100%)
<i>Salmonella</i> Group C2	0	0	4	2/4 (50%)	1	1/1 (100%)
<i>Campylobacter jejuni</i>	4	3/4 (75%)	0	0	1	0/1
<i>Cryptosporidium parvum</i>	18	12/18 (67%)	15	5/15 (33%)	1	1/1 (100%)

For rifaximin patients with ETEC, eradication rates of 75%, and 65%, were seen with total daily doses of 600 mg, and 1200 mg. Relatively consistent eradication rates across all rifaximin doses for ETEC subtypes were observed. Of note were the very similar eradication rates between the placebo arm and the rifaximin treatment arms.

The safety of rifaximin was evaluated from safety data available on 504 patients who received at least one dose of rifaximin \geq 600 mg per day and 294 patients who received at least one dose of control. 400/ 504 rifaximin patients received rifaximin in one of the three ID studies (RFID9801, RFID9701, and RFID9601) and 104 patients received rifaximin for the treatment of hepatic encephalopathy (HE) in two HE studies (RFHE 9702 and RFHE9701).

Additionally, the applicant provided unverifiable safety data from another 1,647 patients treated with rifaximin in other published and unpublished studies, of whom 412 were treated for infectious diarrhea. Rifaximin is approved for commercial use in Italy and in a number of other countries worldwide, safety data from foreign post-marketing were also provided.

The safety profile of rifaximin in RFID9801 and RFID9701 was comparable to the control arms in each study (i.e. placebo and ciprofloxacin respectively).

When adverse event data were pooled for the three infectious diarrhea studies (RFID9801, RFID9701 and RFID9601), there was no difference in the adverse event rate for infectious diarrhea rifaximin patients compared to infectious diarrhea control patients (NOTE: the control group was comprised of subjects receiving placebo, ciprofloxacin, and

trimethoprim/sulfamethaxazole) The incidence of fatigue was higher for the ID rifaximin group than for the infectious diarrhea composite control group (infectious diarrhea rifaximin rate = 3%, infectious diarrhea composite control rate = 0.4%) There were no associated symptoms such as lethargy, anemia or other CNS events indicating that this may be a chance finding rather than a clinically significant pattern

AEs reported for 2% or more of the infectious diarrhea rifaximin and infectious diarrhea composite control patients, respectively, were flatulence (18%, 17% per group respectively), abdominal pain (13%, 10%), headache (13%, 10%), nausea (11%, 9.1%), fecal incontinence (9%, 8%), tenesmus (9%, 8%), constipation (5%, 4%), pyrexia (4%, 5%), fatigue (3%, 0.4%), vomiting (3%, 3%), nasopharyngitis (2%, 0.4%), and dizziness (excluding vertigo) (2%, 4%)

Adverse events reported for $\geq 1\%$ and $< 2\%$ of the infectious diarrhea rifaximin or infectious diarrhea composite control patients, respectively, were weakness (2%, 2% per group respectively), AST increase (1%, 2%), sore throat (1%, 0%), and diarrhea (1%, 3%),

Severe adverse events reported in 1% or more of rifaximin infectious diarrhea patients were abdominal pain (14 or 4%), nausea (12 or 3%), fecal incontinence (9 or 2%), flatulence (9 or 2%), vomiting (7 or 2%), tenesmus (5 or 1%), and headache (4 or 1%) Severe adverse events reported in 1% or more of composite control infectious diarrhea patients were similar to those reported with rifaximin

No rifaximin infectious diarrhea patients experienced a serious adverse event (SAE) One composite control infectious diarrhea patient who received placebo in RFID9801 experienced serious diarrhea that was considered possibly related to treatment Placebo treatment was stopped and this patient was withdrawn from the study due to lack of efficacy and an antibiotic was started

A small number of infectious diarrhea rifaximin and composite control patients had substantially abnormal laboratory values There were no treatment group differences for any of the blood chemistry or hematology parameters in infectious diarrhea patients None of the substantially abnormal clinical laboratory values in infectious diarrhea patients were associated with an adverse event

Within the much sicker hepatic encephalopathy (HE) population, nausea and hepatic encephalopathy were the only adverse events reported at an incidence $\geq 5\%$ The majority of adverse events reported by rifaximin HE patients were associated with complications of hepatic encephalopathy

Five percent (8/157) of the HE patients died on study Five of the deaths occurred in the group receiving rifaximin (5/104, 5%) and 3 occurred in the control, lactitol, group (3/53, 6%) The cause of death was considered unrelated to study treatment for all 8 patients Eight percent (13/157) of the HE patients experienced a serious adverse event on study 9 patients (9/104, 9%) were in the rifaximin group and 3 (3/53, 6%) were in the control group All but one of the serious adverse events was judged by the investigator as not related to study treatment One serious adverse event in a rifaximin HE patient (ascites requiring hospitalization) with an onset 2

days after starting rifaximin treatment was considered possibly related to treatment by the investigator

Since the product launch in Italy (1987), followed by approvals and release in an additional 14 countries, there have been 19 spontaneous adverse events reported from 11 patients. Of these events, the most frequently reported was urticaria (n=5) followed by the related events of pruritus (n=1) and allergic dermatitis (n=1). One case of urticaria was listed as "serious", the other cases were listed as "non-serious". Abdominal pain was reported on two separate occasions, and the remaining adverse events were reported once, agitation, syncope, headache, nausea, esophageal pain, edema (limb)

In summary, the applicant was able to show in study RFID9801 that rifaximin at a dose of 200 mg PO TID for 3 days was effective in decreasing the TLUS (primary efficacy parameter) as compared to placebo. This decrease was statistically significant. The applicant was unable to show adequate microbiologic efficacy given the similar pathogen eradication rates between the placebo arm and the rifaximin treatment arms. Based on these results the applicant was informed that in order to obtain an approval a second adequate and well-controlled Phase III trial of rifaximin in the treatment of traveler's diarrhea at the proposed dose of 200 mg PO TID should be submitted. This trial was to confirm the results of trial RFID9801 and was required to show a clinically meaningful benefit and a statistically significant reduction in the duration of diarrhea between rifaximin and placebo regimens.

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Clinical and microbiologic efficacy results were required to be similar between the ITT and MITT population

B Summary of Conclusion of MOR of study RFID3001

The results of this study support the following conclusions regarding rifaximin 600 mg daily for 3 days versus placebo in the treatment of travelers' diarrhea

Rifaximin reduced the duration of diarrhea (TLUS) compared to placebo in both the ITT and MITT populations. The median TLUS in the rifaximin ITT population, (32.0 hours) was less than that in the placebo group (65.5 hours) and the median TLUS in the ciprofloxacin group was 28.8 hours. However, the acceptability of the pooled results was called into question because of significant treatment-by-center interactions necessitating that results be reported by center. These interactions were caused by the failure of the positive control at the Goa center and the failure of the negative control at the Mexican site. When TLUS was assessed for only those sites where the study was performed in an acceptable manner rifaximin was found to be effective at shortening the duration of diarrhea relative to placebo (TLUS 23.85 hours rifaximin versus 65.6 hours placebo). The relative risk (rifaximin/placebo) for TLUS for Calcutta and Guatemala/Peru was 2.17 (95% CI=1.44-3.27, P=0.0002).

The MO assessed TLUS for the MITT populations in both studies. The MITT population was that subset of the ITT population that had a pathogen cultured from stool at baseline.

The median TLUS in study RFID3001 was 8 hours lower for the rifaximin-treated subjects (40.3 hours) as compared to placebo (48.3 hours). Additionally, the median TLUS was much lower on the ciprofloxacin arm (28.3 hours) as compared to the rifaximin. Because of the aforementioned by center treatment interactions, results were also assessed by center and excluding the centers where the study was performed inappropriately. As in the ITT analysis, when TLUS was assessed for only those sites where the study was performed in an acceptable manner, rifaximin was found to be effective at shortening the duration of diarrhea relative to placebo (rifaximin 23.95 hours versus 61.9 hours placebo).

Because of the differences in TLUS between the centers, the data were reanalyzed for the MITT population excluding subjects with specific pathogens as a greater number of subjects had pathogens including invasive pathogens in that study.

Analyses of TLUS were performed for MITT subjects with *Escherichia coli* only and for subjects with all pathogens except *Campylobacter*.

Of note were the very similar TLUS results for the rifaximin and placebo-treated subjects with *Escherichia coli* only indicating that independent of treatment, improvement would occur for this subgroup.

The TLUS for the MITT population of study RFID3001 excluding subjects with *Campylobacter* in the stool revealed that TLUS for the rifaximin-treated population from all centers was 26.4 hours as compared to 42.4 hours for the placebo-treated subjects and 23.7 hours for the ciprofloxacin-treated subjects. At centers such as Goa where *Campylobacter* was prevalent, TLUS was much more prolonged for the rifaximin-treated subset.

The Median TLUS was calculated by the applicant for a number of subgroups of the ITT population in study RFID3001 including subjects with

- fecal leukocyte-positive illness,
- fecal leukocyte-negative illness,
- inflammatory/invasive pathogens,
- diarrheagenic *E. coli* without evidence of inflammatory/invasive pathogens,
- other agents without evidence of inflammatory/invasive pathogens
- diarrheagenic *E. coli*,
- agent-specific illness,
- agent-negative illness

As the Agency disputed the acceptability of the pooled results from this study, these analyses were not utilized to determine approvability, although information from these analyses was utilized to formulate labeling recommendations.

Analyses of wellness and treatment failure were performed by both the Applicant and the Agency for both studies in both the ITT and MITT populations. These assessments were performed at the TOC visit approximately 24 – 48 hours after the last dose of study medication. Wellness or clinical cure was assessed at the post-treatment visit and was defined as follows:

- 3 No unformed stools within a 48-hour period with no fever (with or without other clinical symptoms), or
- 4 No watery stools and no more than 2 soft stools within a 24 hour period with no fever and no other clinical symptoms except for mild excess gas/flatulence

It was the MO's determination that this analysis provided a more accurate assessment of the efficacy of rifaximin as compared to TLUS or to microbiologic eradication rates as this drug does not appear to perform as a conventional antimicrobial in eradicating possible pathogenic organisms

In study RFID3001, 76.6% rifaximin-treated subjects were classified as clinical cures as compared to 61.4% of placebo recipients. Of note the treatment failure rate with rifaximin was slightly more than double that observed with ciprofloxacin (14.7% vs 6.9%, respectively). A by center breakdown of the results revealed continuing issues with the Goa site whereas the results of the Mexican centers were more consistent with those of the other sites lending weight to the argument that the median TLUS value is not the only, and perhaps not always the ideal, statistic to use to assess efficacy. While the median TLUS at Mexican centers for the ITT population was larger for rifaximin (median=33.0h) than for placebo (median=26.7h), a greater percentage of rifaximin subjects achieved wellness (N=36/43, 83.7%) than did placebo subjects (N=15/23, 65.2%) suggesting that early during therapy, placebo subjects achieved wellness faster than rifaximin subjects, but did not continue to improve throughout the treatment and follow-up period. On the other hand, rifaximin subjects were somewhat delayed in initial response, but continued to achieve wellness after the initial placebo response had begun to cease.

Table 4
Wellness-ITT RFID9801 and RFID3001

	Rifaximin	Placebo	Cipro
Overall RFID9801	99/125 (79.2%)	78/129 (60.5%)	N/A
Overall RFID3001	151/197 (76.6%)	62/101 (61.4%)	79/101 (78.2%)
By Center RFID3001			
Calcutta, India	38/43 (88.4%)	11/23 (47.8%)	21/23 (91.3%)
Goa, India	30/58 (51.7%)	15/29 (51.7%)	16/30 (53.3%)
Guatemala and Peru	47/53 (88.7%)	21/26 (80.8%)	26/27 (96.3%)
Mexico sites	36/43 (83.7%)	15/23 (65.2%)	16/21 (76.2%)

The Agency requested that the applicant provide analyses of TLUS, wellness and microbiologic eradication for subjects with fever and/or blood in the stool for subjects in study RFID3001. In both the ITT and MITT populations, it was clear that the presence or absence of fever at baseline played a major role in efficacy with fewer rifaximin and placebo-treated subjects with fever becoming well when this parameter was present. TLUS was either not calculable in this group because of the large number of patients with censored data (i.e. failures) or it was prolonged. Only those subjects treated with ciprofloxacin had lower TLUS and increased percentages of

subjects cured. Similar results were not seen for the presence or absence of blood in the stool at baseline in the ITT population but the presence or absence of blood at baseline had a clear effect on efficacy in the MITT population again with similar TLUS and clinical cure rates in the rifaximin and placebo-treated populations. Similar analyses were not performed for study RFID9801 where fewer subjects had fever and/or blood in the stool at baseline.

Table 5
TLUS, Wellness and Microbiologic Eradication Rates in Subjects with Fever and Blood in the Stool at Baseline Study RFID3001

Group	Rifaximin	Placebo	Ciprofloxacin
Fever at Baseline			
TLUS	NC	51.1	23.4
Wellness	12/25 (48%)	8/12 (66.7%)	12/14 (85.7%)
Eradication	14/25 (56%)	6/12 (50%)	12/14 (85.7%)
Blood at Baseline			
TLUS	63.5	69.7	55.5
Wellness	24/42 (57.1%)	14/25 (56%)	13/18 (72.2%)
Eradication	26/42 (61.9%)	12/25 (48%)	13/18 (72.2%)
Fever and Blood at Baseline			
TLUS	NC	NC	36.5
Wellness	6/14 (42.9%)	3/7 (42.9%)	7/8 (87.5%)
Eradication	8/14 (57.1%)	3/7 (42.9%)	7/8 (87.5%)

Although minor differences existed between the 2 studies regarding overall pathogen eradication rates, the results of both studies confirmed that rifaximin did not have superior microbiologic activity to that of placebo versus any pathogen.

Eradication rates were similar between the rifaximin and placebo arms at visit 2 (24 hours after the first dose) and although in the MITT population at the TOC visit, 24 – 48 hours after the last dose), a slightly greater proportion of subjects in the rifaximin group than in the placebo group had an overall microbiological response of eradication (61.6% vs 51.7%) these results were not significant and again raised concerns about the true microbiologic activity of rifaximin. Results obtained on the ciprofloxacin arm were numerically superior to those obtained on the placebo or rifaximin treatment arms. A by center and by pathogen breakdown of the results also did not reveal a significant difference between rifaximin and placebo at any level.

Overall, it appeared as if rifaximin was effective in reducing the TLUS in subjects with agent-negative disease or in those with *Escherichia coli* isolated from pretreatment stool culture. These results were confirmed in two Phase III clinical trials. Rifaximin did not appear to be effective in subjects with inflammatory/invasive pathogens including *Campylobacter jejuni*, *Salmonella* spp and *Shigella* spp. Regarding *Shigella sonnei*, the median TLUS for *Shigella* spp (7 subjects) was 42.6 hours as compared to 24 hours in rifaximin-treated subjects with diarrheagenic *E. coli*. Additionally, microbiologic efficacy was shown in only 7 subjects with this organism as a sole causative pathogen. Regarding *Escherichia coli*, a requested pathogen for which there was adequate data, the data were encouraging. In study RFID9801, TLUS in the subset of subjects with this pathogen was less in rifaximin-treated subjects as

compared to placebo. A similar trend was seen in study RFID3001 when subjects with *Escherichia coli* only were assessed. Finally, as in the first review cycle, eradication rates were similar between the rifaximin and placebo treatment arms indicating that rifaximin does not appear to cause clinical improvement directly via microbiologic eradication.

To conclude, patients with fever and/or bloody diarrhea, *Campylobacter jejuni*, *Shigella* spp or *Salmonella* spp should not take rifaximin.

C Integrated Summary of Efficacy

The applicant included data from the following clinical studies in the efficacy update:

- 1 Study RFID3001: A Randomized, Double-Blind, Multi-Center, Comparative Study of Rifaximin Vs Placebo Vs Ciprofloxacin (Cipro®) in the Treatment of Travelers' Diarrhea Due to Enteropathogenic Organisms
- 2 Study RFID9801: A Randomized, Double-Blind, Parallel, Comparative, Placebo-Controlled Study of Rifaximin at 600 mg/day (200 mg, TID) and 1200 mg/day (400 mg, TID) in the Treatment of Bacterial Infectious Diarrhea in Travelers
- 3 Study RFID9701: Double-Blind Randomized Trial Comparing Rifaximin to a Standard Regimen of Ciprofloxacin in the Treatment of Travelers' Diarrhea

Both study RFID3001 and study RFID9801 were randomized controlled trials that assessed the requested rifaximin dose of 200 mg TID for 3 days in the treatment of travelers' diarrhea. Study RFID9701 evaluated a different dose of rifaximin (400 mg BID for 3 days). Studies RFID9801 and RFID9701 were submitted in the original NDA and reviewed during the first cycle.

In addition to a juxtaposition of the results from the 2 Phase III trials (9801 and 3001), the applicant provided a summary of pooled efficacy results across all 3 clinical trials. The rationale for this was to allow an assessment of rifaximin efficacy at the individual pathogen level by combining specific pathogen results from the 3 trials.

Medical Officer's Comment: The MO elected to assess only those studies that utilized the requested rifaximin dose. Study RFID 9701 was reviewed during the first cycle. The dose utilized in that trial (400 mg PO BID) was higher than the requested dose. For further details please see the original MOR.

The primary efficacy endpoint in both studies RFID3001 and 9801 was time to last unformed stool (TLUS). This endpoint was calculated from data contained on the daily diary cards. Subjects who terminated the study early due to treatment failure were noted as having a censored TLUS as of 120 hours. Subjects who terminated the study early due to other reasons (e.g., adverse event, subject request, intercurrent illness) or because they completed the study without achieving a clinical cure were noted as having a censored TLUS as of the time of the last available information on unformed stools.

Secondary efficacy endpoints were also analyzed for each study and include improvement of diarrheal syndrome, number of unformed stools passed per time interval, number of subjects with wellness (clinical cure), number of subjects who failed treatment, persistence of clinical symptoms, and number of subjects with microbiologic cure

Four data sets were analyzed for efficacy

- **Intent-to-treat (ITT) population** All subjects who were randomized to treatment. Protocol violators and subject dropouts were considered part of the ITT population and were included in the efficacy analyses
- **Efficacy-evaluable (EE) population** All subjects who met the inclusion/exclusion criteria, took at least 2 days of study medications as prescribed, completed the daily diaries for at least 2 days, and did not take any prohibited medications that could have impacted efficacy assessments
- **Modified intent-to-treat population (MITT)** The subset of the ITT population whose stool specimens at pretreatment were positive for pathogens and who had a culture performed on a posttreatment stool specimen
- **Modified efficacy-evaluable (MEE) population**, Subjects with positive pretreatment stool samples and a posttreatment sample (positive or negative), who met the inclusion/exclusion criteria, took at least 2 days of study medications as prescribed, and did not take any prohibited medications that could have impacted microbiological outcome

Overview Both RFID 9801 and RFID3001 were Phase 3, randomized, multicenter, double-blind studies of 3-day treatment regimens of rifaximin in adult subjects with travelers' diarrhea. RFID3001 compared rifaximin (200 mg TID) with placebo and ciprofloxacin (500 mg BID), RFID9801 compared 2 doses of rifaximin (200 mg TID, 400 mg TID) with placebo,

Eligible subjects showed evidence of acute diarrhea, defined as 3 or more unformed stools during the 24 hours preceding enrollment, accompanied by one or more of the following signs and symptoms: abdominal pain or cramps, excessive gas/flatulence, nausea, vomiting, fever ($\geq 100^{\circ}\text{F}$ or $\geq 37.8^{\circ}\text{C}$), fecal urgency, tenesmus, or dysentery (passage of bloody stool), total duration of diarrhea was to be no more than 72 hours. A pretreatment stool was collected from all subjects, verified as "unformed" and tested for the presence of enteropathogens. Subjects ≥ 18 years of age were enrolled at sites in Mexico, Guatemala, Peru, Jamaica, India, and Kenya.

In the 3 trials, stool specimens for identification of enteric pathogens were collected before treatment and 1 to 3 days following the end of treatment. In study RFID3001, an attempt was also made to collect specimens after 24 hours of treatment in order to further assess the microbiologic activity of rifaximin. The subjects maintained daily diary cards for recording the time and form (formed, soft, or watery) of all stools passed and the presence or absence of clinical signs and symptoms (nausea, vomiting, abdominal pain/cramps, excess gas/flatulence, fecal urgency, tenesmus, and fever). The primary efficacy variable in each study was TLUS,

other efficacy variables included improvement in diarrheal syndrome, the number of unformed stools passed per time interval, the number of subjects achieving wellness (clinical cure), the number of subjects who were treatment failures, improvement in clinical symptoms, and microbiological eradication/persistence of pretreatment pathogens

Table 6
Summary of Study Characteristics

Study	RFID3001	RFID9801
Phase of Development/ Study Design	Phase 3/ Parallel groups, double-blind, placebo- and active control	Phase 3/ Parallel groups, double-blind, placebo-control
Sponsor	Salix Pharmaceuticals, Inc	Salix Pharmaceuticals Inc
Population	Travelers' diarrhea	Travelers diarrhea
Study Sites	7 sites in Mexico, Guatemala, India, and Peru	3 sites in Mexico, Kenya and Guatemala
Days of Dosing	3 days	3 days
Doses of Rifaximin	200 mg TID	200 mg TID 400 mg TID
No Subjects Enrolled	399	380
No Subjects w/ Rifaximin	200 mg TID (n=197)	200 mg TID (n=125) ^a 400 mg TID (n=126)
No Subjects by Country	Mexico 87 Guatemala 103 India 206 Peru 3	Mexico 195 Kenya 85 Guatemala 100
No Subjects w/ Control	Placebo (N=101) Ciprofloxacin 500 mg BID (N=101)	Placebo (N=129) ^b
Primary Efficacy Endpoint	TLUS	TLUS
Other Efficacy Variables	Improvement in diarrheal syndrome, # of unformed stools passed per time interval, wellness (clinical cure), treatment failure, clinical symptoms, microbiologic cure	Improvement in diarrheal syndrome, # of unformed stools passed per time interval, wellness (clinical cure), treatment failure, dysentery clinical symptoms, microbiologic cure

Demographic and Baseline Characteristics

Demographic characteristics were similar across the groups in both studies. The mean age was slightly higher in RFID3001 than in RFID9801. The proportion of males was higher than females in the placebo group in RFID3001 and in the rifaximin group in RFID9801. The majority of subjects in both studies were Caucasian.

Table 7
Subject Demographics (ITT Population) RFID3001 and RFID9801

Demographics	RFID3001			RFID9801	
	Rifaximin 600 mg/day (N=197)	Placebo (N=101)	Ciprofloxacin (N=101)	Rifaximin 600 mg/day (N=125)	Placebo (N=129)
Age (years)					
N	197	101	101	121 ^a	129
Mean \pm SD/SEM ^b	32.5 \pm 13.33	33.4 \pm 14.09	34.2 \pm 14.36	29.0 \pm 1.1	28.3 \pm 0.9
Range	18 – 79	18 – 80	18 – 72	18 – 72	16 – 69
Sex [No. (%) of Subjects]					
Male	99 (50.3)	56 (55.4)	52 (51.5)	68 (54.4)	66 (51.2)
Female	98 (49.7)	45 (44.6)	49 (48.5)	57 (45.6)	63 (48.8)
Race [No. (%) of Subjects]					
White	166 (84.3)	83 (82.2)	80 (79.2)	104 (83.2)	112 (86.8)
Black	1 (0.5)	1 (1.0)	3 (3.0)	1 (0.8)	2 (1.6)
Hispanic	20 (10.2)	8 (7.9)	12 (11.9)	NA	NA
Asian	7 (3.6)	7 (6.9)	4 (4.0)	NA	NA
Other	3 (1.5)	2 (2.0)	2 (2.0)	20 (16.0) ^c	15 (11.6) ^c

Reference RFID3001 In-text Table 13 (from Table 14.1.6)

RFID9801 In-text Table 10 (from Table 14.1.4a)

^a Date of birth was not recorded for 4 rifaximin subjects

^b SD = standard deviation, in RFID3001, SEM = standard error of the mean, in RFID9801

^c In RFID9801, race was categorized as white, black or other, other included Hispanic and Asian

The applicant separated the subjects in both studies into 4 mutually exclusive categories of baseline pathogens (inflammatory/invasive pathogens (with or without evidence of other pathogens), diarrheagenic *E. coli* without evidence of inflammatory/invasive pathogens, other agents without evidence of inflammatory/invasive pathogens or diarrheagenic *E. coli*, and no pathogens) in order to evaluate treatment effects in a group of subjects with uncomplicated *E. coli* (one that did not contain invasive pathogens) versus those who had invasive pathogens.

Medical Officer's Comment The separation of the subjects into the 4 categories was done in a post-hoc fashion. As can be seen in the following table provided by the applicant, there were substantial differences between the populations of the 2 studies suggesting that the RFID3001 population had more severe illness. A greater proportion of subjects in study RFID3001 had blood in the stool at baseline (30.8% overall in RFID3001, 12.2% overall in RFID9801), mean number of unformed stools in the 24 hours before randomization was higher in RFID3001 (7.1 stools) than in RFID9801 (6.1 stools), a higher proportion of subjects in RFID3001 than in RFID9801 had agent-specific illness (64.4% and 54.2% respectively) while more than double the proportion of subjects in RFID3001 (43.6%) as in RFID9801 (17.5%) had fecal leukocyte-positive illness.

In both studies, the most common pathogens identified in each treatment group were diarrheagenic *E. coli* (39.6% overall in RFID3001, 43.7% overall in RFID9801). However, the incidence of inflammatory/invasive pathogens in RFID3001 (19.5%) was more than double the incidence in RFID9801 (9.4% overall). The proportion of subjects with inflammatory/invasive pathogens in the rifaximin group in RFID3001 was almost double the proportion in the ciprofloxacin group (23.4% versus 12.9%).

Table 8
Baseline Disease Characteristics RFID3001 and RFID9801 (ITT Population)

Disease Characteristic	RFID3001			RFID9801	
	Rifaximin 600 mg/day (N=197)	Placebo (N=101)	Ciprofloxacin (N=101)	Rifaximin 600 mg/day (N=125)	Placebo (N=129)
No Unformed Stools (24-hrs Before Randomization)				(N=119)	(N=121)
Mean ± SD/SEM	7.3 ± 4.61	6.9 ± 4.58	6.9 ± 3.88	6.1 ± 0.3	6.1 ± 0.3
Median	6.0	6.0	6.0	5.0	5.0
Range	3 – 30	3 – 30	3 – 29	3 – 20	3 – 25
No (%) Subjects with Pretreatment Symptoms					
Abdominal pain/cramps	186 (94.4)	92 (91.1)	96 (95.0)	108 (86.4)	118 (91.5)
Exc. gas/flatulence	100 (50.8)	50 (49.5)	49 (48.5)	96 (76.8)	103 (79.8)
Nausea	119 (60.4)	59 (58.4)	59 (58.4)	74 (59.2)	72 (55.8)
Vomiting	38 (19.3)	19 (18.8)	17 (16.8)	20 (16.0)	12 (9.3)
Fever	39 (19.8)	16 (15.8)	20 (19.8)	26 (20.8)	32 (24.8)
Fecal urgency	136 (69.0)	71 (70.3)	67 (66.3)	108 (86.4)	111 (86.0)
Blood/mucus in stool	33 (16.8)	15 (14.9)	11 (10.9)	2 (1.6)	3 (2.3)
Tenesmus	53 (26.9)	25 (24.8)	27 (26.7)	43 (34.4)	46 (35.7)
No (%) Subjects with Fecal Leukocyte-Positive/-Negative Illness				(N=117)	(N=123)
Positive illness	91 (46.2)	45 (44.6)	38 (37.6)	19 (16.2)	23 (18.7)
Negative illness	106 (53.8)	56 (55.4)	63 (62.4)	98 (83.8)	100 (81.3)
No (%) Subjects with Agent-Specific/Agent-Negative Illness				(N=117)	(N=123)
Agent-specific illness	130 (66.0)	63 (62.4)	64 (63.4)	69 (59.0)	61 (49.6)
Bacterial	121 (61.4)	57 (56.4)	59 (58.4)		
Parasitic	23 (11.7)	12 (11.9)	11 (10.9)		
Agent-negative illness	67 (34.0)	38 (37.6)	37 (36.6)	48 (41.0)	62 (50.4)
No (%) Subjects by Baseline Pathogens					
Inflammatory/invasive	46 (23.4)	19 (18.8)	13 (12.9)	12 (9.6)	12 (9.3)
Diarrheagenic <i>E. coli</i>	74 (37.6)	38 (37.6)	46 (45.5)	56 (44.8)	55 (42.6)
Other agents	10 (5.1)	6 (5.9)	5 (5.0)	8 (6.4)	5 (3.9)
No pathogens	67 (34.0)	38 (37.6)	37 (36.6)	49 (39.2)	57 (44.2)
No (%) Subjects w/ Blood in Stool at Baseline	64 (32.5)	34 (33.7)	25 (24.8)	11 (8.8)	20 (15.5)

Three hundred and ninety nine subjects were randomized to receive rifaximin 600 mg/day (197), placebo (101), or ciprofloxacin (101) in RFID3001 (India, Mexico,

Guatemala) and 254 subjects were randomized to receive treatment with rifaximin 600 mg/day (125) or placebo (129) in RFID9801 (Mexico, Guatemala, and Kenya) A total of 322 subjects were randomized to receive the requested rifaximin dose of 200 mg TID A large number of subjects in each treatment group completed their respective study, with greater proportions of rifaximin and ciprofloxacin subjects than placebo subjects completing each study

Medical Officer's comment *Lack of efficacy/treatment failure was the most common reason for early withdrawal in both studies This occurred primarily among placebo subjects but also among rifaximin-treated subjects In study 3001 where a more ill population was enrolled the percentage of rifaximin-treated subjects who withdrew due to lack of efficacy was higher than in study RFID 9801 One subject who discontinued due to an AE in study 3001 was suffering from dysentery*

Table 9
Subject Disposition for RFID3001 and RFID9801

Disposition	RFID3001			RFID9801	
	Rifaximin 600 mg/day	Placebo	Ciprofloxacin	Rifaximin 600 mg/day	Placebo
Randomized Subjects	197	101	101	125	129
	Number (%) of Subjects				
Completed study	177 (89.8)	84 (83.2)	94 (93.1)	115 (92.0)	110 (85.3)
Early withdrawals	20 (10.2)	17 (16.8)	7 (6.9)	10 (8.0)	19 (14.7) ^a
Lack of efficacy / treatment failure	17 (8.6)	12 (11.9)	2 (2.0)	4 (3.2)	10 (7.8)
Noncompliance	0	0	0	3 (2.4)	0
Adverse event	2 (1.0)	1 (1.0)	3 (3.0)	1 (0.8)	0
Subject request to withdraw	1 (0.5)	0	1 (1.0)	0	0
Lost to follow-up	0	1 (1.0)	0	0	1 (0.8)
Other / Administrative	0	3 (3.0)	1 (1.0)	2 (1.6)	0
Included in ITT Population	197	101	101	125	129
Included in EE Population	186	91	94	116	119
Included in MITT Population	128	62	58	65	55
Included in MEE Population	125	62	55	64	49

^a Although 19 subjects prematurely discontinued the study, 8 of these subjects had completed study drug use prior to termination, reasons for withdrawal are presented for the 11 subjects who prematurely discontinued study drug

Most of the rifaximin subjects in study RFID3001 who discontinued due to lack of efficacy were culture-positive at baseline for inflammatory/invasive pathogens (12/17, 70.6%), primarily *C. jejuni* as compared to 2/2, 100% in the ciprofloxacin treatment group who prematurely discontinued due to lack of efficacy and who were culture-positive for *C. jejuni*. Among placebo-treated subjects who prematurely discontinued

due to lack of efficacy, no specific trend was apparent for pathogens identified at baseline

Table 10
Subjects Who Discontinued Study Drug In RFID3001 Due to Lack of Efficacy

Center #- Subject #	Age (yrs)/ Sex	Pathogens Isolated at Baseline	# Unformed Stools at Baseline	Fever and/or Blood in Stool at Baseline?
Subjects in the Rifaximin Group in RFID3001				
101-0444	56/F	<i>Campylobacter</i>	10	No
101-0464	52/F	<i>Campylobacter</i>	9	Yes
101-0473	44/F	--	6	No
101 0485	73/M	<i>Giardia</i> ETEC ST/LT	10	Yes
101-0492	32/F	<i>Campylobacter</i>	4	No
101-0516	45/F	<i>Salmonella Aeromonas</i> EAEC	8	Yes
101-0525	67/M	<i>Campylobacter</i>	5	No
101-0534	42/F	<i>Campylobacter Plesiomonas</i> , EAEC	12	Yes
101 0535	31/F	<i>Giardia Campylobacter</i>	8	No
101 0669	39/M	<i>Salmonella Campylobacter Plesiomonas</i> , ETEC ST/LT	12	Yes
107 0051	22/F	<i>Campylobacter</i>	3	Yes
107 0070	41/M	-	3	Yes
107-0093	25/M	--	12	Yes
200 0253	22/M	-	10	Yes
200 0265	58/M	<i>Campylobacter</i>	6	Yes
200 0269	24/M	<i>Campylobacter</i>	3	Yes
200-0270	23/F	<i>Campylobacter</i> , ETEC ST	4	No
Subjects in the Placebo Group in RFID3001				
100-0392	23/M	<i>Giardia</i> , ETEC ST/LT, EAEC	3	No
100-0550	35/M	<i>Giardia Entamoeba</i>	3	No
100-0559	26/F	<i>Shigella</i> , ETEC LT	10	Yes
100-0573	24/F	ETEC ST/LT	3	Yes
101-0436	57/M	--	5	No
101-0489	48/F	<i>Giardia Cryptosporidium Campylobacter</i>	20	Yes
101-0664	67/F	ETEC ST	12	No
107-0079	22/M	--	4	No
200-0202	24/F	<i>Cryptosporidium</i>	4	No
200-0244	27/F	--	6	No
200-0252	23/M	--	10	No
200-0260	25/M	<i>Campylobacter</i>	16	Yes
Subjects in the Ciprofloxacin Group in RFID3001				
101 0461	29/F	<i>Campylobacter</i>	10	Yes
107-0103	36/M	<i>Campylobacter</i> , EAEC	4	No

Reference Table 10 in CSR for RFID3001

In study RFID9801, 4/125 (3.2%) rifaximin-treated subjects discontinued treatment due to lack of efficacy compared with 10/110 (9.1%) placebo-treated subjects. Of the subjects who prematurely discontinued due to lack of efficacy in RFID9801, only 1 of 4 subjects in the rifaximin group and 2 of 18 subjects in the placebo group were culture-positive at baseline for inflammatory/invasive pathogens (*C. jejuni* in 2 subjects and *Shigella* in 1 subject).

Table 11
Subjects Who Discontinued Study Drug in RFID9801 Due to Lack of Efficacy

Subject #	Pathogens Isolated at Baseline	≥8 Unformed Stools at Baseline	Fever and/or Blood in Stool at Baseline?
Subjects in the Rifaximin 600 mg/day Group in RFID9801			
01052	ETEC ST/LT	No	Present
01077	--	No	Present
01150	--	Yes	Present
02095	<i>Campylobacter</i> ETEC LT	No	Present
Subjects in the Placebo Group in RFID9801			
01030	--	No	Not Present
01062	--	No	Not Present
01080	--	No	Present
01083	<i>Shigella</i> , ETEC ST	Yes	Present
01085	--	No	Not Present
01092	-	Yes	Present
01099	--	No	Not Present
01103	ETEC LT	No	Present
01116	-	Yes	Present
01129	--	No	Present
01148	ETEC ST/LT	No	Not Present
01177	ETEC ST	No	Not Present
01178	--	Yes	Not Present
02006	<i>Cryptosporidium</i> ETEC LT	No	Not Present
02030	<i>Cryptosporidium</i>	No	Present
02083	<i>Cryptosporidium</i> <i>Campylobacter</i> ETEC ST	Yes	Present
02089	<i>Cryptosporidium</i> , ETEC LT	No	Not Present
02094	ETEC LT	No	Not Present

Reference Efficacy Update Table 17

Primary Efficacy Parameter TLUS

ITT Population

NOTE all p values are per the applicant

In both studies, TLUS was shorter in the rifaximin group as compared to the placebo group. As per the applicant, "the median TLUS in the rifaximin group was approximately one-half that observed in the placebo group, with statistically significant differences between the groups"

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Table 12
Distribution of Time to Last Unformed Stool (TLUS) RFID3001 and RFID9801
(ITT Population/Applicant's Analysis)

TLUS	RFID3001			RFID9801	
	Rifaximin 600 mg/day (N=197)	Placebo (N=101)	Ciprofloxacin (N=101)	Rifaximin 600 mg/day (N=125)	Placebo (N=129)
Median TLUS (hours)	32.0	65.5	28.8	32.5	58.6
95% CI of median TLUS	24.3 – 44.9	40.2 – 83.5	23.6 – 48.0	28.4 – 43.4	45.5 – 79.5
Cox Model	0.0014*	0.0003*	<0.0001*	0.0002	
Risk ratio	(Rif/Pbo) 1.6275	(Cipro/Pbo) 1.8887	(Rif/Cipro) 0.8782	(Rif/Pbo) 1.78	
95% CI of risk ratio (2-sided or 1-sided)	1.2071 – 2.1943	1.3437 – 2.6548	0.6683	1.32 – 2.39	

Agency Analyses

In study RFID9801 median TLUS was 32.5 hours in the rifaximin 200 mg TID group and 58.6 hours in the placebo group. The Agency independently assessed the TLUS on the MITT population and found that the results were consistent with those of the ITT population. It was concluded that treatment with rifaximin led to statistically significantly shorter TLUS when compared to placebo.

Table 13
Time to Last Unformed Stool
Subjects with a Baseline Pathogen (MITT-type population) RFID9801

	Placebo (n=61)	Rifaximin 200 TID (n=70)
Median TLUS (hours)	60.0	30.0
95% CI	(44.8,)	(23.7, 36.3)
P-value*	0.0002	
Hazard Ratio	2.21	
97.5% CI	(1.36, 3.58)	

Analyses of median TLUS by site for the ITT population and the MITT-type populations (those with a baseline pathogen) revealed that 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. Subjects infected with Cryptosporidia had longer median TLUS.

Table 14
Median Time to Last Unformed Stool by Site RFID9801

	Placebo	Rifaximin 200 TID
ITT		
Mexico	57.6	32.5
Kenya	74.3	42.7
Guatemala	49.0	28.9
MITT-type		
Mexico	57.0	22.0
Kenya		42.7
Guatemala	56.5	27.2

TLUS for ETEC and Cryptosporidia is presented in the following table. 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 was a trend that treatment with rifaximin leads to shorter TLUS than placebo.

Table 15
TLUS by Pathogen (MITT-type population) RFID9801

	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)

In RFID3001, the median TLUS in the rifaximin ITT population, (32.0 hours) was less than that in the placebo group (65.5 hours) and the median TLUS in the ciprofloxacin group was 28.8 hours.

The TLUS values at Center #101 (Goa, India) were much higher in the rifaximin and ciprofloxacin groups (and similar to those obtained on the placebo arm) compared with the other sites. According to the applicant, this difference was related to the substantial amount of missing diary data from Center #101 and an analysis of the TLUS without that center was performed. As per the applicant, no statistically significant treatment-by-center interaction was observed in the analysis of TLUS when this center was excluded. (See Appendix A for further details).

However, in addition to the Goa results, the MO was concerned with the inconsistent results obtained between the remaining centers. Specifically, at the Mexican sites, there was very little difference between TLUS for subjects on the rifaximin and placebo treatments arms, whereas at the Guatemalan site, the results were as expected. Finally, results were not obtained for a large number of placebo recipients at the Calcutta site, leading to the exclusion of at least 1/3 of the placebo recipients from the calculation of the primary efficacy parameter.