

Investigator-Initiated Studies of Rifaximin

There are 2 ongoing investigator-initiated studies of rifaximin

Fourteen subjects have been randomized and enrollment is currently ongoing

Two hundred twenty-three subjects have been randomized in the study and enrollment is complete, however, data analyses are currently ongoing. No deaths, serious adverse events, or discontinuations due to adverse events have been reported in either investigator-initiated study.

Adverse events Reported in the Literature

The applicant identified 3 new clinical and nonclinical non-review publications that contained safety data pertaining to rifaximin. No new adverse events, including a change in incidence, were identified in these 5 publications.

Summaries of the safety data reported in the 3 publications are provided below.

- In a study by Mas et al, a total of 103 subjects with grade I-III HE were randomized to receive rifaximin 1200 mg/day (n=50) or lactitol 60 g/day (n=53) for 5 to 10 days. Two subjects in each treatment group prematurely discontinued due to intolerability. Two rifaximin- and 1 lactitol-treated subject reported mild diarrhea, 1 rifaximin-treated subject reported abdominal pain, and 1 lactitol-treated subject experienced vomiting. These events were considered study drug-related, all other events were considered unrelated to treatment. Three subjects (1 rifaximin and 2 lactitol) died within 28 days of the last dose of study drug (1 due to biliary sepsis and 2 due to bleeding esophageal varices). None of the deaths were considered related to study drug. Tolerability, as assessed by laboratory tests, was good in both groups. No statistically significant differences between the treatment groups in laboratory variables at the end of treatment were observed, except for potassium levels. A greater percentage of subjects in the rifaximin group had potassium values outside the normal range compared to the lactitol group (24.3% vs 7.5% [p=0.0419]).
- In a study by Tursi et al, 218 subjects with diverticulitis were randomized to receive rifaximin 400 mg BID plus mesalazine 800 mg TID for 7 days followed by rifaximin 400 mg BID plus mesalazine 800 mg BID for 7 days/month (n=109) or rifaximin 400 mg BID for 7 days followed by rifaximin 400 mg BID for 7 days/month (n=109) for 12 months. Two subjects died during the study (1 in the rifaximin/mesalazine group due to stroke and 1 in the rifaximin group due to myocardial infarction). Reported AEs were transient urticaria (1 subject in the

rifaximin group) and epigastric pain (9 subjects in the rifaximin/mesalazine group), probably related to rifaximin and mesalazine, respectively

- In a study by Cuoco et al , 21 diabetic subjects who underwent a lactulose H₂-breath test because of gastrointestinal complaints were treated with rifaximin 1200 mg daily for 10 days⁵ No adverse events were reported either during or after therapy

Spontaneous, Postmarketing Surveillance Summary

During the overall post-marketing period (June 1987 to September 2003), a total of 25 events were reported for 16 patients The most common types of events reported during the post-marketing surveillance period were associated with skin and subcutaneous tissue disorders These specific types of events included urticaria (6 patients), generalized urticaria (2 patients), rash generalized (2 patients), angioneurotic edema (2 patients), rash erythematous (1 patient), rash morbilliform (1 patient), dermatitis allergic (1 patient), and pruritus (1 patient) Three of the patients were judged to have serious adverse events (angioneurotic edema, urticaria, and rash erythematous) and 3 had unexpected adverse events (diarrhea with abdominal pain, peripheral edema, and syncope)

Marketing applications for rifaximin, filed by

neither case were any untoward, serious, or unexpected adverse events associated with the applications

In

D Adequacy of Safety Testing

The MO determined that the applicant submitted an adequate safety database to allow for an accurate safety assessment of rifaximin

VII Dosing, Regimen, and Administration Issues

The requested dosing regimen of 200 mg orally TID for 9 doses (3 days) has been determined to be safe and there are no pending issues

VIII Use in Special Populations

A Evaluation of Sponsor’s Gender Effects Analyses and Adequacy of Investigation

Adverse Events by Gender

Of the 320 subjects that received the 200 mg TID dose, 167 (52%) were males and 48% were female Of the 228 placebo recipients, 53% were males and 47% were females

A greater number of female subjects in both the rifaximin (48.4% versus 40.7%) and placebo (57.9% versus 49.6%) groups experienced adverse events compared with male subjects. Female subjects treated with rifaximin had greater incidences of gastrointestinal disorders, and specific adverse events of constipation and rectal tenesmus compared with male subjects. Male subjects treated with rifaximin had greater incidences of nausea and pyrexia compared with female subjects. Similar differences were seen in placebo-treated subjects.

B Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Subjects \geq 65 years of age

Seven hundred thirty patients in the original safety database were \leq 64 years old and 61 $>$ 65 years old. Of the 61 patients $>$ 65 years old, 34 received rifaximin and 27 received a control. With the exception of urinary frequency observed in one patient $>$ 64 years of age and no patients \leq 64 years of age there were no differences in adverse events observed for rifaximin ID or HE patients \leq 64 years old compared to those $>$ 64 years old.

Additionally, safety data in elderly patients were available from two publications, one in infectious diarrhea, and the other in inflammatory bowel disease. The infectious diarrhea study was conducted only in elderly patients and the inflammatory bowel disease study allowed patients of other ages to participate but included elderly patients. For further details on these studies, please see original MOR. The MO concluded at that time that the number of subjects \geq 65 years of age in the database was too small to allow for adequate conclusions to be drawn.

There were 9/316 rifaximin-treated subjects (2.8%) and 4/228 (1.8%) placebo-treated subjects aged \geq 65 years from the 2 ID studies where rifaximin was given at the 200 mg TID dose. Three rifaximin and 2 placebo subjects reported AEs including constipation, flatulence, nausea, and urinary frequency. Again, no meaningful comparisons could be made between the age groups due to the small number of subjects who were \geq 65 years of age.

Adverse Events by Race

The majority of the subjects in both the rifaximin (269/320, 84.1%) and placebo (193/228, 84.6%) treatment groups were white. The numbers of subjects experiencing specific adverse events were similar between white and non-white subjects in the rifaximin group. The most notable difference in adverse event rates with respect to race was for the incidence of headache. In the rifaximin group, a slightly greater proportion of non-white subjects experienced headache (13.7%) compared to white subjects (8.9%). Conversely, a greater proportion of white subjects experienced headache (9.8%) compared to non-white subjects (5.7%) in the placebo group.

Pediatric Subjects (Copied from Original MOR)

Safety data in pediatric patients are available from six studies in patients with infectious diarrhea. Abbreviated reports are available for four pediatric infectious diarrhea studies and synopses only for the other 2 studies

One hundred fifteen pediatric patients, 1 month to 13 years of age, received treatment with rifaximin for 3 to 7 days. Children >5 years old received rifaximin tablets at doses ranging from 200 mg to 600 mg TID or QID and children ≤5 years received rifaximin as an oral suspension at doses ranging from 10 to 40 mg/kg BID to QID. In some studies, the oral suspension was administered to all pediatric patients, regardless of age. Three of the 115 patients reported an AE. Worsening of nausea and vomiting was reported by one patient and vomiting was reported by two patients. Two of the three patients discontinued treatment because of the adverse event, worsening of nausea and vomiting, and vomiting. Severity and relationship to treatment were not reported in either study. No significant changes in hematological or chemistry parameters were observed in pediatric patients following rifaximin treatment.

Medical Officer's Comment *The information pertaining to pediatric patients is not verifiable and thus is inadequate to allow for an approval in those patients < 12 years of age*

IX Conclusions and Recommendations

A Conclusions

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.

The safety profile of rifaximin in the three controlled ID studies in the safety database indicate that rifaximin is safe for use in patients with infectious diarrhea. The incidence of drug-related adverse events in these studies was low. These events were mild, self-limited and occurred with a frequency similar to the placebo and the approved comparator, ciprofloxacin. The most commonly reported adverse events were gastrointestinal in nature and were symptoms typically associated with the disease under study, e.g., abdominal pain, fecal incontinence, flatulence, nausea, and tenesmus, which occurred in $\geq 5\%$ of patients. No serious adverse events with rifaximin use and no deaths were reported in the ID trials.

B Recommendations

The MO recommends that rifaximin be approved in the treatment of traveler's diarrhea caused by *Escherichia coli* at a dose 200 mg PO TID for 3 days.

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Concurrence only
HFD-590/DIVDir/AlbrechtR

5/10/04

4 Draft Labeling Page(s) Withheld

APPENDIX A**Study RFXID 3001**

Title A randomized, double-blind, multicenter, comparative study of rifaximin 600 mg a day (200 mg TID) vs placebo vs ciprofloxacin in the treatment of traveler's diarrhea due to enteropathogenic organisms

Study dates July 10, 2002 – May 14, 2003

Principal Investigators, Sites and Patient Numbers**Table A1**

S Chatterjee, MD	Wellesley Medicentre	Calcutta, India (#100)	Rifaximin 43 (21.8%) Ciprofloxacin 23 (22.8%) Placebo 23 (22.8%)
D Motghare, MD	Goa Medical College	Goa, India (#101)	Rifaximin 58 (29.4%) Ciprofloxacin 30(29.7%) Placebo 29 (28.7%)
E Asturias MD	Johns Hopkins Vaccine testing Unit	Antigua, Guatemala (#107)	Rifaximin 51 (25.9%) Ciprofloxacin 26 (25.7%) Placebo 26 (25.7%)
F M Sandoval	Instituto de Ciencias Biologicas	Guadalajara, Mexico (#200)	Rifaximin 32 (16.2%) Ciprofloxacin 16 (15.8%) Placebo 17 (16.8%)
J Belkind-Gerson	Paseo de Tabacines 430	Cuernavaca, Mexico (#242)	Rifaximin 9 (4.6%) Ciprofloxacin 5 (5%) Placebo 5 (5%)
A Rios Ramirez	San Javier Marina Hospital	Puerto Vallarta, Mexico (# 249)	Rifaximin 2 (1%) Ciprofloxacin 0 Placebo 1 (1%)
E Gotuzzo	Hospital Nacional Cayetano Heredia	Lima, Peru (#269)	Rifaximin 2 (1%) Ciprofloxacin 1 (1%) Placebo 0

Medical Officer's Comment It appeared that the patients were primarily derived from the 2 Indian sites and the Guatemalan site with few patients from Mexico and Peru

Study Summary

A phase III, randomized (1:1:1), double-blind, multicenter placebo and active controlled with ciprofloxacin study in adult travelers suffering from acute infectious diarrhea in Mexico, Peru, India and Guatemala. Patients began treatment within 72 hours of onset of diarrhea. The duration of the study was 4 – 5 days including 3 days of treatment followed by a visit to the treatment center 24 hours after the first dose and again for a post treatment evaluation 24 to 48 hours after the last dose.

The study consisted of a pretreatment / baseline visit (informed consent, history, physical, laboratory, randomization, and receipt of drug and diary), self-administered treatment with rifaximin, placebo or ciprofloxacin on days 1 – 3, a visit to the treatment center 24 hours after the first dose and a final clinical evaluation and collection of patient diary cards on day 4 or 5 of the study

Patients satisfying all the entry criteria at the initial visit were randomly assigned in a 2:1:1 ratio (RIF:PL:CIPRO) to receive one of the following oral treatments for 3 consecutive days

- Rifaximin 600 mg/day delivered as 200 mg PO TID with one placebo capsule TID
- 2 placebo capsules PO TID
- Ciprofloxacin 1000 mgm/day delivered as 500 mg BID plus a middle dose of 2 placebo capsules

Stool specimens for quantification and identification of enteric pathogens and classification of ETEC were collected prior to the first dose, at 24 hours after the first dose, and at 48 to 72 hours after the last dose of study drug was administered. Patients maintained daily diary cards for recording the time and form (formed, soft, watery) of all stools passed, the time and date of study drug administration, the presence or absence of enteric signs and symptoms (abdominal pain/cramps, excessive gas/flatulence, nausea, vomiting, fever, fecal urgency, blood and/or mucus, tenesmus), adverse events, and use of concomitant medications. At follow-up, stool samples were analyzed for evidence of dysentery, i.e., presence of gross blood. Safety was evaluated by monitoring the occurrence of adverse events, both reported and observed, vital signs, and by conducting routine clinical laboratory tests (hematology, chemistry, and urinalysis) and physical examinations. Stool was cultured at a local lab for *Shigella*, *Salmonella*, *Campylobacter jejuni*, *Aeromonas*, *Vibrio*, *Plesiomonas*, *Escherichia coli* and *Yersinia enterocolitica*. Protozoa were identified by an ELISA at a central laboratory in — All specimens were initially assessed at a local lab and then shipped to the — for pathogen verification, speciation and MIC testing

The study was double-blinded (both investigator and subject were blinded)

The primary objective of the study was to compare the safety and efficacy of rifaximin 200 mg TID (600 mg/day) to placebo in the treatment of infectious diarrhea in travelers. The TID rifaximin regimen was shown to be safe and effective in the reduction of the TLUS in study RFID9801. Ciprofloxacin is approved for the treatment of infectious diarrhea at a dose of 1000 mg/day.

Eligible for inclusion were male and female adult travelers at least 18 years of age with acute diarrhea defined as at least 3 unformed stools within the 24 hours preceding

randomization accompanied by at least one of the following signs and symptoms of enteric infection abdominal pain or cramps, nausea, vomiting, fever (≥ 100 °F or 37.8 °C), blood or mucus in the stool, fecal urgency, excessive gas/flatulence, or tenesmus

Patients were excluded from participation in the study for any of the following reasons

- 1 or more symptoms of moderate to severe dehydration,
- Acute diarrhea for more than 72 hours prior to randomization,
- Moderate to severe dehydration,
- Active, uncontrolled or clinically significant heart, lung, kidney, gastrointestinal tract (other than travelers diarrhea) and/or central nervous system disorders,
- Use of any antimicrobial agent with expected activity against enteric pathogens within 7 days preceding randomization,
- Use of symptomatic anti-diarrheal compound within 8 hours preceding randomization,
- Use of any NSAID or fever-reducing agent within 2 hours prior to randomization,
- Pregnant or breast feeding (females only),
- Inability or unwillingness to use adequate contraception (sexually active males and females),
- Hypersensitivity to any of the treatment drugs,
- Previous treatment with rifaximin, or participation in another clinical study within the last 30 days

Concomitant medication for the treatment of pre-existing conditions other than diarrhea was allowed during the study as were antimalarials Antimotility agents as well as other antidiarrheal agents, acetaminophen, NSAIDs, probiotics, antacids, antimicrobial agents or theophylline were not allowed

Subjects whose symptoms did not improve after 24 hours of study treatment, could have received a rescue regimen of azithromycin 500 mg QD for 1 – 3 days All subjects were counseled to increase their fluid intake

Efficacy analyses were performed using the intent-to-treat (ITT) population defined as all patients who were randomized to treatment (primary population for analysis) Protocol violators and patient dropouts were considered part of the ITT population and were included in the efficacy analyses Primary and secondary analyses were also performed on the EE population (Efficacy Evaluable) defined as subjects who met the inclusion/exclusion criteria, who took at least 2 days of treatment, who kept the diary for at least 2 days, and who did not take any of the prohibited medications

Microbiological analyses were performed on the MITT population, subset of the ITT population from whose stool specimens at pre-treatment were positive for pathogens and who had a culture performed on post-treatment stool specimens (independent of results) Microbiological analyses were also performed on the MEE population, a subset of the EE population that met similar microbiologic criteria as the MITT population

The primary efficacy endpoint 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. TLUS was determined from the data collected from the following time intervals: 0–24 hours, 24–48 hours, 48–72 hours, 72–96 hours, 96–120 hours. Patients who met the criteria for clinical cure (defined below in secondary efficacy variables) immediately after the start of the study and prior to passing any unformed stools were defined as having a TLUS of 0 hours. Patients who terminated the study early due to treatment failure were noted as having a censored TLUS of 120 hours. Patients who terminated the study early due to other reasons (AE, patient 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 variables included

- Improvement of Diarrheal Syndrome: reduction of 50% or more in the number of unformed stools (watery or soft) passed during a 24-hour interval compared to the number of stools passed during the 24 hours immediately preceding enrollment in the study
- Number of Unformed Stools Passed per Time Interval of Interest – the number of unformed stools (soft or watery) passed during the intervals 0–24 hours, 24–48 hours, 48–72 hours, 72–96 hours, and 96–120 hours, and the number of unformed stools passed during the 120 hours after the first dose of study medication after the first dose of study medication
- The proportion of patients achieving wellness (clinical cure), where wellness 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
- The proportion of patients who failed treatment where treatment failure was defined as
 - 1 Clinical deterioration or worsening of clinical symptoms after at least 24 hours of therapy, or
 - 2 Subject too ill to continue in a placebo-controlled study, or
 - 3 Illness continuing after 120 hours
- The proportion of subjects with improvement in clinical signs and symptoms of diarrhea

(nausea, vomiting, fever, abdominal pain/cramps, excess gas/flatulence, tenesmus, urgency, blood or mucus in the stool)

NOTE Wellness, failure and improvement were assessed at the TOC visit 24 – 48 hours after the last dose

- The proportion of subjects with microbiologic eradication or persistence

TLUS was also assessed in the following subgroups (NOTE these subgroups were not prespecified in the original protocol For further details see MO Comment below)

- Subjects with fecal leucocyte positive illness
- Subjects with fecal leucocyte negative illness
- Subjects with culture positive invasive diarrhea (cultures positive for *Salmonella*, *Shigella*, invasive *Escherichia coli*, or *Campylobacter*)
- Subjects with other non-invasive pathogens
- Subjects with agent-specific illness
- Subjects with agent-negative illness

Statistics

RFID3001 was designed to show the superiority of rifaximin versus placebo at the 95% CI (two-sided) A secondary endpoint was the demonstration of non-inferiority between rifaximin and ciprofloxacin at the 97.5% CI level (one-sided)

The comparison of TLUS was performed using the Cox proportional hazards model (Wald statistic), with a 2-sided test at a significance level of 0.05 for rifaximin versus placebo (primary efficacy endpoint) and for Cipro versus placebo, or a 1-sided test at a significance level of 0.025 for rifaximin versus Cipro (secondary efficacy endpoint) Other secondary efficacy endpoints were compared using repeated measures ANOVA (number of unformed stools passed per time intervals of interest) or Cochran-Mantel-Haenszel (CMH) test stratified by center (all other secondary endpoints)

Amendments

The protocol was amended three times (4/17/02, 5/29/02 and 4/15/03)

The initial amendment included the addition of a 24 hours stool specimen for culture, changes to the statistical analysis and revised microbiology procedures for stool specimens

Amendment 2 modified the concomitant medications to exclude NSAIDs or acetaminophen and amendment 3 added sites, modified that the duration of diarrhea could be no more than 72 hours, and updated the statistics section with regards to the analysis populations

Medical Officer's comment

The statistical analysis plan was modified twice and the MO defers to the statistician for final comments Of note was the addition of the categories (agent-specific disease etc) to

the subgroups for analysis. These changes were made on 10/2/03 and were not previously discussed with the Agency

Additionally, after the database was locked and preliminary analyses were performed, it was noted that there was failure of the positive control at site 101 (Goa India). Specifically, all treatments at that site had the same TLUS of approximately 70 hours. It was also noted that AE reporting was extremely low. An audit revealed insufficient diary data from that center on all treatment arms (see page 114 for further details). The database was reopened to adding AE data but efficacy data was not modified from that center. The applicant performed additional modifications to the data from other centers that appeared to have no effect on the primary efficacy parameter. The MO defers to the agency statistician for final comments on the acceptability of these modifications.

Patient Disposition and Evaluability/Demographics

399 patients were enrolled in the study at centers located in Mexico, Guatemala, Peru, and India, 197 (49.3%) in the rifaximin 200 mg TID group, 101 (25.3%) in the placebo group, and 101 (25.3%) in the ciprofloxacin group. Two subjects were enrolled twice, both to rifaximin twice. The second randomization of both was excluded from the efficacy analysis although included in the safety assessments (rifaximin safety N = 199).

Eighty-nine of 399 subjects (22.3%) were enrolled at the Calcutta India site (Site 100), (43, 23, and 23 in the rifaximin, placebo, and ciprofloxacin groups, respectively), 117 (29.3%) were enrolled at the Goa, India site (101) (58, 29, and 30 respectively), 103 were enrolled in Guatemala site 107 (51, 26, and 26 respectively), 65 (16.2%) were enrolled in Guadalajara Mexico, 19 (4.8%) in Cuernavaca and 3 (0.7%) each in Puerto Vallarta, and Lima, Peru.

Table A2
Patients by site

Site	Rifaximin	Placebo	Ciprofloxacin
	197 (100%)	101 (100%)	101 (100%)
Calcutta, India (#100)	43 (21.8)	23 (22.8)	23 (22.3)
Goa, India (#101)	58 (29.4)	29 (29.7)	30 (29.7)
Antigua, Guatemala (#107)	51 (25.9)	26 (25.7)	26 (25.7)
Guadalajara, Mexico (#200)	32 (16.2)	17 (16.8)	16 (15.8)
Cuernavaca, Mexico (#242)	9 (4.6)	5 (5)	5 (5)
Puerto Vallarta, Mexico (#249)	2 (1)	1 (1)	0
Lima, Peru (#269)	2 (1)	0	1 (1)

Eighty-nine percent (355/399) of the patients completed the study (177 (89.8%) rifaximin, 84 (83.2%) placebo, and 94 (93.1%) ciprofloxacin).

44 patients (11%) terminated early, 31 (7.8%) for treatment failure (17 (8.6%) rifaximin, 12 (11.9%) placebo, and 2 (2%) ciprofloxacin). Two rifaximin, 1 placebo, and 2 ciprofloxacin subjects terminated early due to an AE.

Table A3
Disposition of Patients – RFID3001

Disposition	Number (%) of Subjects		
	Rifaximin	Placebo	Ciprofloxacin
Enrolled (Randomized/ITT)	197 (100%)	101 (100%)	101 (100%)
Completed Study	177 (89.8)	84 (83.2)	94 (93.1)
Terminated Study	20 (10.2)	17 (16.8)	7 (6.9)
Reason for Early Termination			
Treatment Failure	17 (8.6)	12 (11.9)	2 (2)
Patient request	1 (0.5)	0	1 (1)
Adverse Event*	2 (1)	1 (1)	3 (3)
Lost to Follow-up	0	1 (1)	0
Other / Administrative	0	3 (3)	1 (1)

*protocol violation (1 placebo, 1 Cipro), non-compliance (1 placebo), withdrawal of consent (1 placebo)

Protocol Violations

There were 32 patients with protocol violations (8%) across the treatment groups (15 (7.6%) rifaximin, 10 (9.9%) placebo, and 7 (6.9%) ciprofloxacin). The most common violation was “took a prohibited medication” and this occurred in 26 patients (14 (7.1%) rifaximin, 7 (6.9%) placebo, and 5 (5%) ciprofloxacin). The most common prohibited medications were NSAIDs or acetaminophen taken for pain or headache.

Note: Three rifaximin patients, 2 placebo and 1 ciprofloxacin patients received antimicrobial treatment for worsening diarrhea and were appropriately classified as failures in the analyses of wellness.

Table A4
Protocol Violations – RFID3001

Violation*	Number (%) of Subjects		
	Rifaximin 197 (100%)	Placebo 101 (100%)	Ciprofloxacin 101 (100%)
Inclusion/Exclusion Criteria Not Met	2 (1)	3 (3)	2 (2)
Medication likely affecting efficacy*	14 (7.1)	7 (6.9)	5 (5)
Failed to complete 2 days diary	0	1 (1)	1 (1)

*Patients may be counted in more than one category

Populations

Twenty-eight patients (28, 7.0%) were excluded from the efficacy evaluable population (11 rifaximin, 10 placebo, and 7 ciprofloxacin). One hundred fifty-one (151, 37.8%) subjects were excluded from the MITT analysis, most of whom (142 subjects) were excluded because they did not have pretreatment samples positive for a causative pathogen. One hundred fifty-seven (157, 39.3%) subjects were excluded from the MEE analysis. The proportion of subjects excluded from these analyses (EE, MITT, and MEE) was similar among the treatment groups.

**Table A5
Populations**

	Number (%) of Subjects		
	Rifaximin	Placebo	Ciprofloxacin
ITT	197 (100%)	101 (100%)	101 (100%)
Efficacy Evaluable	186 (94.4)	91 (90.1)	94 (93.1)
Inclusion/Exclusion Criteria Not Met	0	0	1 (1)
Failed to complete diary for 2 days	3 (1.5)	7 (6.9)	3 (3)
Failed to take ≥ 2 days medication	4 (2)	3 (3)	2 (2)
Received prohibited medications	4 (2)	2 (2)	3 (3)
MITT Population	128 (65)	62 (61.4)	58 (57.4)
Negative pretreatment sample	67 (34)	38 (37.6)	37 (36.6)
No post-treatment sample	2 (1)	1 (1)	6 (5.9)
MEE Population	125 (63.5)	62 (61.4)	55 (54.5)
Not in MITT	69 (35)	39 (38.6)	43 (42.6)
Did not take ≥ 2 days study medication	4 (2)	3 (3)	2 (2)
Received prohibited medications	2 (1)	0	2 (2)
Inclusion/Exclusion Criteria Not Met	0	0	1 (1)
Safety**	199 (100%)	100 (100%)	100 (100%)

* Patients may be counted in more than one category

**The Safety population was defined as all subjects that were randomized to treatment, received at least one dose of study medication, and provided at least 1 post-baseline safety assessment. There was one placebo subject (101-0477) and one Cipro subject (242-0353) that were randomized, received study medication, but did not provide post-baseline safety data. Thus, per definition (as outlined in the protocol and statistical analysis plan), these two subjects were excluded from the Safety Population (i.e., Table 12 lists 101 placebo and Cipro ITT subjects, but only 100 each are included in their respective Safety populations).

Medical Officer's Comment: The MO determined that the MITT population consisting of those patients who had a baseline pathogen would be an important population on which to perform the analyses as they had documented evidence of an invasive bacterial process. As the MITT and MEE populations were very similar in number, the MO elected to report results only for the MITT population.

Demographics

Demographic characteristics for age, gender, and race were comparable between the treatment groups. The mean age of the ITT population was 33.2 years and age ranged from 18 to 80 years. The majority of subjects were white (82.5%), 51.9% of the subjects were males and 48.1% were females. Mean weight was 70.39 kg and weight ranged from 40 to 124 kg.

Demographic characteristics of the ITT population were generally similar across the treatment sites. Four sites (#100, #200, #242, #249) had a higher proportion of females than males. Mean age was higher at Center #101 (47.1 years) and Center #249 (44.3 years) compared with mean age at the other centers (range 23.3 to 29.0 years). The majority of subjects at Center #200 were Hispanic (56.9%) whereas most subjects were white at the other sites (range 84.2% to 100%).

The EE population included 186 of the 197 ITT rifaximin subjects, 91 of the 101 ITT placebo subjects, and 94 of the 101 ITT Cipro subjects. Thus, subject demographics for the EE population were similar to those for the ITT population.

Table A6
Demographics

Demographic Characteristic	Rifaximin (N=197)	Placebo (N=101)	Cipro (N=101)
Age (Years)			
Mean ± SD	32.5 ± 13.33	33.4 ± 14.09	34.2 ± 14.36
Median	27.0	27.0	28.0
Range	18 – 79	18 – 80	18 – 72
Sex, n (%)			
Male	99 (50.3%)	56 (55.4%)	52 (51.5%)
Female	98 (49.7%)	45 (44.6%)	49 (48.5%)
Race			
White	166 (84.3%)	83 (82.2%)	80 (79.2%)
Black	1 (0.5%)	1 (1.0%)	3 (3.0%)
Hispanic	20 (10.2%)	8 (7.9%)	12 (11.9%)
Asian	7 (3.6%)	7 (6.9%)	4 (4.0%)
Other	3 (1.5%)	2 (2.0%)	2 (2.0%)

Disease Characteristics

64.4% of patients had at least one enteric pathogen in the pretreatment stool sample. The most common pathogens identified in each treatment group were diarrheagenic *Escherichia coli* (37.6% rifaximin, 37.6% placebo, and 45.5% ciprofloxacin), followed by inflammatory/invasive pathogens (23.4% rifaximin, 18.8% placebo, and 12.9% ciprofloxacin). It was noted that the proportion of subjects with inflammatory/invasive pathogens in the rifaximin group was greater than the proportion in the ciprofloxacin group.

Duration of pretreatment illness was similar amongst the treatment arms and the median ranged from 30 – 32 hours. During the course of the review the MO requested that the applicant respond to the following question:

Question *Was information collected on how many hours subjects had symptoms/diarrhea (duration of illness) prior to beginning treatment? If so, can this information be presented for the MITT population by center and treatment arm? [1/21/04 4:51 PM]*

Applicant Response

In Study RFID3001, the entry criteria specified that only subjects with acute diarrhea for no more than 72 hours could be enrolled. In protocol Amendment 003, dated April 15, 2003, it was clarified that the duration of pre-study acute diarrhea could be no more than 72 hours, but that the enteric symptoms which accompany diarrhea could have been present for longer than 72 hours. The protocol, however, did not require collection of information regarding the duration of specific pre-study signs and symptoms.

Number of unformed stools was also similar between treatment arms and ranged from 3-3 to 30, with a median number of 6 unformed stools in each treatment group in the 24 hours preceding enrollment.

Abdominal pain/cramps were the most common symptoms noted at baseline, reported in (93.7%), 68.7% had fecal urgency, 59.4% had nausea, and 49.9% had excessive gas/flatulence. Based on the presence of gross blood in the pretreatment stool samples, patients with dysentery appeared to account for approximately 1/3 of the subjects (64 rifaximin, 34 placebo, and 25 ciprofloxacin).

Table A7
Disease Characteristics at Baseline (ITT Population) – RFID3001

Disease Characteristic	Rifaximin (N=197)	Placebo (N=101)	Ciprofloxacin (N=101)
No (%) Subjects with Fecal Leukocyte-Positive/-Negative Illness			
Positive Illness	91 (46.2%)	45 (44.6%)	38 (37.6%)
Negative Illness	106 (53.8%)	56 (55.4%)	63 (62.4%)
No (%) Subjects with Agent-Specific/Agent-Negative Illness			
Agent-specific illness	130 (66.0%)	63 (62.4%)	64 (63.4%)
Bacterial	121 (61.4%)	57 (56.4%)	59 (58.4%)
Parasitic	23 (11.7%)	12 (11.9%)	11 (10.9%)
No Unformed Stools in the 24-hour Period Before Randomization			
Mean ± SD	7.3 ± 4.61	6.9 ± 4.58	6.9 ± 3.88
Median	6.0	6.0	6.0
Range	3 – 30	3 – 30	3 – 29
No (%) Subjects with Pretreatment Clinical Symptoms			
Abdominal pain or cramps	186 (94.4%)	92 (91.1%)	96 (95.0%)
Excessive gas/flatulence	100 (50.8%)	50 (49.5%)	49 (48.5%)
Nausea	119 (60.4%)	59 (58.4%)	59 (58.4%)
Vomiting	38 (19.3%)	19 (18.8%)	17 (16.8%)
Fever (≥100°F or ≥37.8°C)	39 (19.8%)	16 (15.8%)	20 (19.8%)
Fecal urgency	136 (69.0%)	71 (70.3%)	67 (66.3%)
Blood and/or mucus in stool	33 (16.8%)	15 (14.9%)	11 (10.9%)
No (%) Subjects with Blood in the Stool at Baseline	64 (32.5%)	34 (33.7%)	25 (24.8%)

Medical Officer's Comment Despite relative consistency in the total numbers of patients per treatment arm with agent-specific disease (bacterial) the MO noted that the proportion of subjects with inflammatory/invasive pathogens in the rifaximin group was greater than the proportion in the ciprofloxacin group. There was also a higher proportion of rifaximin-treated subjects with blood in the stool and/or fecal leukocyte positive stool indicating a population with potentially more severe and/or invasive disease as compared to the placebo and ciprofloxacin arms. It was also noted that there was variability with regards to baseline pathogens between treatment sites with a greater number of subjects with *Escherichia coli* at the Guatemala site as compared to Goa or Calcutta where there were more patients with invasive pathogens.

Pre-treatment and Concomitant Medications

Fifty three percent of rifaximin recipients (100/197) compared to 46% of placebo recipients (46/101) and 47% of ciprofloxacin recipients (47/101) received a concomitant medication. Most commonly, patients received antimalarials for prophylaxis as allowed by the protocol (46 (23.1%) rifaximin, 21 (21.0%) placebo, and 26 (26.0%) ciprofloxacin).

Small numbers of patients took analgesics (4 (2.0%) rifaximin, 3 (3%) placebo, and 2 (2%) ciprofloxacin) or antidiarrheal agents (2 (1%) rifaximin, 4 (4%) placebo, and 1 (1%) ciprofloxacin).

Medical Officer's Comment Azithromycin was administered as rescue medication in 4 (2%) rifaximin, 4 (4%) placebo and 0 ciprofloxacin patients.

A review of the line listings did not reveal the use of other antimicrobials as rescue medication or for other infections.

Treatment Compliance

Treatment compliance was measured by recording the number of doses of study medication taken during the study. The majority (84.5%) of subjects made at least one entry on the diary card on 4 or 5 days. Almost 93% of the subjects were at least 70% compliant with the treatment regimen, with compliance ranging from 89% to 95%.

Primary Efficacy Endpoint Time to Last Unformed Stool (TLUS)

ITT population

As per the applicant, "The median TLUS in the rifaximin group (32.0 hours) was less than half that in the placebo group (65.5 hours, $p=0.0014$). The risk ratio from the Cox model without interaction was greater than 1 (1.6275), indicating greater improvement in the rifaximin group versus the placebo group. The 95% confidence interval for the risk ratio comparing rifaximin to placebo was (1.2071 - 2.1943), indicating a significantly shorter time to wellness in the rifaximin group versus the placebo group."

"The median TLUS in the ciprofloxacin group (28.8 hours) was less than half that in the placebo group (65.5 hours, $p=0.0003$). The risk ratio from the Cox model without interaction was greater than 1 (1.8887), indicating greater improvement in the ciprofloxacin group versus the placebo group. The 95% confidence interval for the risk ratio comparing ciprofloxacin to placebo was (1.3437 - 2.6548), indicating a significantly shorter time to wellness in the ciprofloxacin group versus the placebo group."

Table A8
Time to Last Unformed Stool ITT Population

	Treatment Group		
	Rifaximin (N=197)	Placebo (N=101)	Ciprofloxacin (N=101)
TLUS in Hours (Kaplan-Meier Estimates)			
Median TLUS	32 0	65 5	28 8
95% Confidence Interval of Median TLUS	24 3 – 44 9	40 2 – 83 5	23 6 – 48 0
N (%) Censored	46 (23 4%)	39 (38 6%)	22 (21 8%)
Treatment Effect (Cox Model w/out interaction) ^a	Rifaximin/Placebo		Cipro/Placebo
Regression coefficient	0 4871		0 6359
Standard Error	0 1525		0 1737
P-value	0 0014*		0 0003*
Risk Ratio	1 6275		1 8887
95% CI of Risk Ratio (2-sided)	1 2071 – 2 1943		1 3437 – 2 6548
Treatment Effect (Cox Model w/ interaction) ^b	Rifaximin/Placebo		Cipro/Placebo
Regression coefficient	0 4835		0 6237
Standard Error	0 1549		0 1762
P-value	0 0018*		0 0004*
Risk Ratio	1 6218		1 8658
95% CI of Risk Ratio (2-sided)	1 1971 – 2 1971		1 3210 – 2 6355
P-value for treatment-by-center interaction	0 0809 ^c *		0 0761 ^c *

^a Cox proportional hazards model included terms for treatment effect and analysis center effect, with a 2-sided test using a significance level of 0 05

^b Cox proportional hazards model included terms for treatment effect analysis center effect and treatment by-center effect, with a 2 sided test using a significance level of 0 05 The effect of treatment was averaged over analysis centers (with equal weights), such that analysis center and the interaction between treatment and analysis center were taken into account

^c Treatment-by-center interactions were considered statistically significant at the 0 10 level

* Statistically significant difference between treatment groups

Medical Officer's Comment *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 Similar results were obtained for the EE population*

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

However in addition to the failure of the positive control at the Goa site the MO was concerned with the failure of the negative control at the Mexican site The FDA put the following questions to the applicant

Question *Does Salix have an explanation for the Mexican centers results as compared to the other sites? [1/21/04 4 51 PM]*

Question *Could you also provide a formal explanation about the results of the Goa site (as well as Mexico) We are concerned with the qualitative differences between centers We understand the initial explanations but cannot understand why the results do not make sense as you can see in the attached tables [1/21/04 5 20 PM]*

The applicant's responses were very similar to the FDA conclusions are included below
 "It is our conclusion that the Goa data are explained primarily by relatively poor diary completion at that center, leading to longer TLUS among all treatment groups (our TLUS algorithm equated missing diary data with lack of wellness) It is also possible that mediocre study conduct in general at Goa further contributed to disappointing treatment effects, not only for rifaximin, but also for Cipro (comparing Cipro to rifaximin, RR=1.05, 95% CI=0.52-2.13) While the TLUS data at Goa suggest at most a very weak treatment effect, any differences among the 3 non-Goa analysis centers are quantitative (a range of responsiveness, from weak to strong) rather than qualitative (differences in direction of treatment effect among centers)"

"When TLUS comparing rifaximin and placebo is summarized for the MITT population for a variety of pathogen subgroups among the 4 analysis centers, other factors (besides missing data at Goa) contribute to apparent differences among analysis centers By focusing on the MITT population the sample size is reduced by more than 1/3, as those without a pathogen identified at baseline are excluded Additionally, some of the pathogen subgroups have fairly small denominators, leading to greater variability in TLUS among the analysis centers (see related response to question from 21 Jan 2004, 5 35pm)

Finally, the median value is not the only, and perhaps not always the ideal, statistic to summarize TLUS While the median TLUS at Mexican centers for the ITT population was larger for rifaximin (median=33.0h) than for placebo (median=26.7h), in fact (new Table 14.2.14.1) a greater percentage of rifaximin subjects achieved wellness (N=36/43, 83.7%) than did placebo subjects (N=15/23, 65.2%) This suggests that early during therapy, placebo subjects achieved wellness faster than rifaximin subjects, but did not continue to improve throughout the treatment and followup 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"

The FDA statistician's interpretation of the by-center interaction analysis differed from that of the applicant and it was concluded that these differences could not be ignored as they were qualitative (differences in opposing directions) as opposed to merely quantitative These by center/treatment interactions led the Agency to the conclusion that the results from the 4 centers could not be pooled but rather that each center had to be reported separately

Table A9
Median TLUS by Analysis Center ITT Population

Median TLUS in Hours (Kaplan-Meier Estimates)	Treatment Group		
	Rifaximin	Placebo	Cipro
All Centers	(N=197) 32.0	(N=101) 65.5	(N=101) 28.8
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) 41.4	(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

* Statistically significant interaction between treatment and analysis center

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

A review of the subjects at the Goa site, revealed that with the exception of 4 Goa patients (1 rifaximin, 1 ciprofloxacin and 2 placebo) the use of the term missing data was inaccurate. There was insufficient data on a majority of subjects at that site. Specifically, the majority of the subjects had diary data through day 3 and the subjects who did not have data through day 3 were already declared treatment failures. So excluding the treatment failures, 12 rifaximin, 9 ciprofloxacin, and 4 placebo subjects were considered as not achieving wellness but were also not considered treatment failures because of insufficient diary data past day 3. Of these subjects

Rifaximin- 12 subjects

- 3 were probably failures
- 3 had soft stools but still had other symptoms through day 3. There was no information on the type of stools on days 4 and 5. These patients could go either way but wellness wouldn't be declared before 60 hours in any of them
- 6 were probably well. 4 of the 6 would not have had wellness declared before 70 hours though

Ciprofloxacin - 9 subjects

- 1 was probably a failure
- 1 had soft stools but still had other symptoms though day 3. There was no information on the type of stools on days 4 and 5
- 7 were probably well. 5 of the 7 would not have had wellness declared before 48 hours though

Placebo- 4 subjects

- 3 were probably failures

- 1 was probably well at about 48 hours

Based on the above, the Agency did not agree with the Applicant's argument that TLUS at the Goa site was artificially prolonged because of the missing diary information. Even if there was complete diary information on these subjects, the majority of the rifaximin TLUS's would be > 60 hours and the ciprofloxacin TLUS's would be greater than 48 hours. Thus, Goa would still have prolonged TLUS compared to the rest of the sites. To conclude, there appeared to be unexplained problems at this site, giving further credence to the Agency position that pooled efficacy results were inaccurate and that results had to be assessed by center.

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.

Table A10
Median TLUS by Analysis Center
MITT Population

Median TLUS in Hours/MITT	Treatment Group		
	Rifaximin (N=128)	Placebo (N=62)	Ciprofloxacin (N=58)
All Centers/	40.3	48.3	28.3
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

Because of the differences in TLUS between the centers, the data were reanalyzed for the MITT population excluding subjects with specific pathogens. The goal of these analyses was to enable appropriate labeling recommendations.

Analyses of TLUS were performed for MITT subjects with *Escherichia coli*

Table A11
Median TLUS for MITT by specific pathogens

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

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 15.6 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 — hours.

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.

Additional Analyses supplied by the sponsor

TLUS when Goa and Mexican sites were excluded

As per the applicant, rifaximin was highly effective at shortening the duration of diarrhea when Goa and Mexico were excluded. The relative risk (rifaximin/placebo) for TLUS for Calcutta and Guatemala/Peru was 2.17 (95% CI=1.44-3.27, P=0.0002), indicating a very effective response to rifaximin relative to placebo when Goa and Mexico were excluded.

Table A12
Median TLUS by Analysis Center excluding Goa and Mexico ITT Population

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

Table A13

Median TLUS by Analysis Center excluding Goa and Mexico MITT Population

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

Subgroup analyses

The Median TLUS was calculated by the applicant for a number of subgroups of the ITT population 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

Medical Officer's Comment *As the Agency disputed the acceptability of the pooled results from study RFID3001 these analyses were not utilized to determined approvability although information from these analyses was utilized to formulate labeling recommendations*

As per the applicant, in study RFID3001, median TLUS was shorter in the rifaximin group compared to the placebo group for all subgroups except that of subjects with inflammatory/invasive pathogens where more than half of the rifaximin-treated subjects (N = 46) failed and in the very small subgroup of subjects with other agents where 3/6 placebo patients and 3/5 ciprofloxacin-treated patients failed and the TLUS could not be calculated. The results were statistically significant in favor of rifaximin in subjects with fecal leukocyte-positive illness (p=0.0011), subjects with diarrheagenic *E coli* but without evidence of inflammatory/invasive pathogens (p=0.0476), and subjects with agent-negative illness (p=0.0024). Of note however was the small and not significant difference between TLUS for rifaximin-treated subjects versus placebo in subjects with agent-specific disease (rifaximin 40.3 hours versus placebo 48.8)

Table A14
Subgroup Analysis for Time to Last Unformed Stool ITT Population

Time to Last Unformed Stool (hours)	Treatment Group			P-value ^a Rifaximin vs Placebo
	Rifaximin (N=197)	Placebo (N=101)	Ciprofloxacin (N=101)	
Subjects with Fecal Leukocyte-Positive Illness	(N=91)	(N=45)	(N=38)	0.0011*
Median TLUS ^b	29.0	72.0	23.4	
95% Confidence Interval of Median TLUS	24.0 – 46.0	36.6 – NC	15.5 – 31.3	
N (%) Censored	15 (16.5%)	21 (46.7%)	2 (5.3%)	
Subjects with Fecal Leukocyte-Negative Illness	(N=106)	(N=56)	(N=63)	0.2809
Median TLUS ^b	35.8	48.3	44.1	
95% Confidence Interval of Median TLUS	23.8 – 48.0	25.6 – 71.6	24.1 – 70.3	
N (%) Censored	31 (29.2%)	18 (32.1%)	20 (31.7%)	
Subjects with Inflammatory/Invasive Pathogens	(N=46)	(N=19)	(N=13)	0.9741
Median TLUS ^b	NC	67.5	65.0	
95% Confidence Interval of Median TLUS	47.3 – NC	36.6 – NC	24.4 – NC	
N (%) Censored	24 (52.2%)	10 (52.6%)	5 (38.5%)	
Subjects with Diarrheagenic <i>E. coli</i> (no evidence of inflammatory/invasive pathogens)	(N=74)	(N=38)	(N=46)	0.0476*
Median TLUS ^b	24.0	38.0	23.4	
95% Confidence Interval of Median TLUS	10.2 – 35.3	22.8 – 65.5	7.5 – 45.8	
N (%) Censored	8 (10.8%)	10 (26.3%)	7 (15.2%)	
Subjects with Other Agents (no evidence of inflam / invasive pathogens or diarrheagenic <i>E. coli</i>)	(N=10)	(N=6)	(N=5)	0.3644
Median TLUS ^b	65.3	NC	NC	
95% Confidence Interval of Median TLUS	24.4 – NC	68.8 – NC	30.8 – NC	
N (%) Censored	3 (30.0%)	3 (50.0%)	3 (60.0%)	
Subjects with Agent-Specific Illness	(N=130)	(N=63)	(N=64)	0.1436
Median TLUS ^b	40.3	48.8	28.3	
95% Confidence Interval of Median TLUS	24.5 – 48.0	32.2 – 72.0	17.7 – 55.1	
N (%) Censored	35 (26.9%)	23 (36.5%)	15 (23.4%)	
Subjects with Agent-Negative Illness	(N=67)	(N=38)	(N=37)	0.0024*
Median TLUS ^b	23.5	71.6	29.7	
95% Confidence Interval of Median TLUS	17.3 – 44.1	34.1 – NC	20.8 – 44.1	
N (%) Censored	11 (16.4%)	16 (42.1%)	7 (18.9%)	

^a P-value is 2-sided and calculated using a log-rank test

^b Estimated using the Kaplan-Meier method

* Statistically significant difference between rifaximin and placebo

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

inflam = inflammatory

Assessment of Failures

The applicant assessed subjects who prematurely discontinued the study due to lack of efficacy and found that the majority of the subjects in the rifaximin treatment group who prematurely discontinued due to lack of efficacy were culture-positive at baseline for inflammatory/invasive pathogens (12/17, 70.6%), primarily *Campylobacter jejuni*. Two subjects (2/2, 100%) in the ciprofloxacin treatment group who prematurely discontinued due to lack of efficacy were culture-positive for *Campylobacter jejuni*. Among placebo-treated subjects who prematurely discontinued due to lack of efficacy, no specific trend was apparent for pathogens identified at baseline.

Overall, *Campylobacter jejuni* was isolated in 25 of the 197 (12.7%) subjects in the rifaximin treatment group and in 9 of the 101 (8.9%) subjects in the ciprofloxacin treatment group. Eleven of the 25 (44.0%) rifaximin-treated subjects who were culture-positive for *Campylobacter jejuni* at baseline prematurely discontinued the study due to lack of efficacy. Two of the 9 (22.2%) ciprofloxacin-treated subjects who were culture-positive for *Campylobacter jejuni* at baseline prematurely discontinued the study due to lack of efficacy.

Of the 17 rifaximin-treated subjects who discontinued study drug due to lack of efficacy, 11 (64.7%) had fever and/or blood in the stool at baseline, indicating more severe illness. The proportions of subjects who discontinued study drug due to lack of efficacy and who had fever and/or blood in the stool at baseline were lower in the placebo (4/12, 33.3%) and ciprofloxacin (1/2, 50.0%) groups. Eleven subjects exhibiting fever and/or blood in the stool also exhibited a high frequency of diarrhea (range 8 – 20 unformed stools at baseline), indicating a dysentery-like disease in these subjects. Of the 11 subjects with fever and/or blood in the stool and high stool frequency, 8 were culture-positive for invasive pathogens (*Campylobacter jejuni*, *Shigella* spp, and *Salmonella* spp), 2 had no identified pathogen, and 1 had a parasite (*Giardia*). 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 A15
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%)

Secondary Efficacy Endpoints

NOTE The Applicant performed a number of secondary endpoint analyses that are not included in this review as the Agency disputed the validity of the pooled analyses. For wellness and treatment failure, the Agency performed by center analyses that can be found in the appropriate section.

FDA Analysis of wellness

76.6% rifaximin-treated subjects were classified as clinical cures as compared to 61.4% of placebo recipients. 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 A16
Wellness-ITT RFID3001

	Rifaximin	Placebo	Cipro
Overall	151/197 (76.6)	62/101 (61.4)	79/101 (78.2)
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)

Table A17
Wellness-MITT RFID3001

	Rifaximin	Placebo	Cipro
Overall	94/128 (73.4)	40/62 (64.5)	43/58 (74.1)
Calcutta, India	25/29 (86.2)	7/16 (43.8)	16/17 (94.1)
Goa, India	18/41 (43.9)	10/18 (55.6)	10/20 (50.0)
Guatemala and Peru	30/33 (90.9)	14/16 (87.5)	8/9 (88.9)
Mexico sites	21/25 (84.0)	9/12 (75.0)	9/12 (75.0)

Medical Officer's Comment *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 18
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%)

Microbiologic Efficacy

Overall microbiological eradication was defined as a negative posttreatment culture result for all pathogens identified at pretreatment. Microbiological results were determined on Day 2 (Visit 2) and Day 4 (Visit 3).

Medical Officer's Comment: Although the data from visit 2 is shown below, it should be noted that a number of patients did not provide samples at that visit, decreasing the value of the analyses. Overall eradication rates were similar between the rifaximin and placebo arms at visit 2. At Visit 3, a slightly greater proportion of subjects in the rifaximin MITT group than in the placebo group had an overall microbiological response of eradication (61.6% vs 51.7%). As per the applicant, "there was a statistically significant difference in overall microbiological response was observed between the ciprofloxacin and placebo groups, with a greater proportion of subjects in the ciprofloxacin group demonstrating eradication (80.7% vs 51.7%, p=0.0008)."

Table A19

Microbiological Eradication Rate at Visit 2 (24 hours after first dose)					
	Number (%) of MITT Subjects			P-value^a	
	Rifaximin (N=128)	Placebo (N=62)	Ciprofloxacin (N=58)	Rifaximin/ Placebo	Cipro/ Placebo
Overall response				0.7242	0.0036
Eradication	51 (45.9%)	23 (42.6%)	32 (71.1%)		
Persistence	60 (54.1%)	31 (57.4%)	13 (28.9%)		
Not tested	17	8	13		
Microbiological Eradication Rate at Visit 3 (24 – 48 hours after last dose)					
	Number (%) of MITT Subjects			P-value^a	
	Rifaximin (N=128)	Placebo (N=62)	Ciprofloxacin (N=58)	Rifaximin/ Placebo	Cipro/ Placebo
Overall response				0.1952	0.0008
Eradication	77 (61.6%)	31 (51.7%)	46 (80.7%)		
Persistence	48 (38.4%)	29 (48.3%)	11 (19.3%)		
Not tested	3	2	1		

Medical Officer's Comments Overall microbiological eradication rates were also assessed by center. There was a lack of consistency between centers with regards to rifaximin and placebo arms. Ciprofloxacin rates were generally higher than those on both comparator arms.

Table A20

Proportion of Subjects with Overall Microbiological Response of Eradication at TOC visit (24 – 48 hours after last dose) by Center MITT Population

Microbiological Eradication^a	Treatment Group		
	Rifaximin	Placebo	Ciprofloxacin
Calcutta, India (#100)	19/29 (65.5%)	6/15 (40.0%)	13/17 (76.5%)
Goa, India (#101)	20/39 (51.3%)	11/17 (64.7%)	17/19 (89.5%)
Antigua, Guatemala (#107)	21/31 (67.7%)	10/16 (62.5%)	7/9 (77.8%)
Guadalajara, Mexico (#200)	14/21 (66.7%)	2/8 (25.0%)	7/10 (70.0%)
Cuernavaca, Mexico (#242)	2/4 (50.0%)	2/4 (50.0%)	2/2 (100%)
Puerto Vallarta, Mexico (#249)	NA	NA	NA
Lima, Peru (#269)	1/1 (100%)	0/0	0/0

Reference: Table 14.2.42 and Listing 16.2.13

^a Pathogens that were not tested were excluded from the calculations.

NA = not applicable; none of the subjects in Center #249 were included in the MEE population.

By pathogen eradication rates at visits 2 and 3 are presented below. Of note, where an isolate was not recultured, the MO modified the denominator to reflect the true number of isolates that were cultured.

Rates for *Campylobacter jejuni* were lower in the rifaximin-treated subjects than the placebo or ciprofloxacin subjects. For isolates of *Salmonella* spp. and *Shigella* spp. there were not enough data to make comparisons between treatment arms. For *Escherichia*

coli at both visits 2 and 3, ciprofloxacin arm rates were higher than those seen on the placebo or rifaximin arms. In general, the data fail to show a true difference between the antimicrobial activity of rifaximin and that of placebo

Table A21
Microbiologic Eradication rate by Pathogen at 24 hours after the first dose (visit 2)
and TOC visit 3(24 – 48 hours after last dose)

Genus (Species)	Number (%) of MITT/MEE Subjects					
	Rifaximin (N=125)		Placebo (N=62)		Ciprofloxacin (N=58)	
	Visit 2	Visit 3	Visit 2	Visit 3	Visit 2	Visit 3
<i>Aeromonas (hydrophila)</i>	1/3 (33.3%)	2/3 (66.7%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Campylobacter (jejuni)</i>	1/17 (5.9%)	9/25 (36.0%)	2/9 (22.2%)	4/10 (40.0%)	4/8 (50%)	6/9 (66.7%)
<i>Plesiomonas sp</i>	1/2 (50%)	3/3 (100%)	0	0	0	0
<i>Plesiomonas shigelloides</i>	2/3 (66.7%)	1/1(100%)	1/2 (50.0%)	1/2 (50.0%)	0	0
<i>Salmonella Group B</i>	1/3 (33.3%)	1/3 (33.3%)	0	0	0	0
<i>Salmonella Group C1</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Salmonella Group C2</i>	0	0	0	0	1/1 (100%)	1/1 (100%)
<i>Shigella boydu</i>	1/1 (100%)	1/1 (100%)	0	0	0	0
<i>Shigella flexneri</i>	2/2 (100%)	2/2 (100%)	2/4 (50.0%)	2/4 (50.0%)	1/1 (100%)	1/1 (100%)
<i>Shigella sonnei</i>	4/7 (57.1%)	7/8 (87.5%)	0/1	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Vibrio cholerae</i>	2/2 (100%)	2/2 (100%)	0	0	0	0
<i>Providencia</i>	1/1 (100%)	1/1 (100%)	0	0	0	1/1 (100%)
Diarrheagenic <i>E coli</i>	46/78 (59%)	62/83 (74.7%)	23/38 (60.5%)	30/43 (69.8%)	29/32 (90.6%)	43/45 (95.6%)
<i>E coli</i> [EAEC]	17/24 (70.8%)	24/27 (88.9%)	14/21 (82.4%)	17/20 (85.0%)	10/11 (90.9%)	16/17 (94.1%)
<i>E coli</i> [ETEC-LT]	19/33 (57.6%)	24/34 (70.6%)	8/11 (72.7%)	10/13 (76.9%)	9/9 (100%)	12/13 (92.3%)
<i>E coli</i> [ETEC-ST]	6/10 (60%)	8/12 (66.7%)	3/6 (50%)	4/6 (66.7%)	2/3 (66.7%)	4/4 (100%)
<i>E coli</i> [ETEC-ST/LT]	16/24 (66.7%)	19/24 (79.2%)	3/9 (33.3%)	5/10 (50.0%)	10/10 (100%)	15/15 (100%)
<i>Cryptosporidium parvum</i>	2/6 (33.3%)	2/6 (33.3%)	0/4	1/4 (25.0%)	2/6 (33.3%)	2/6 (33.3%)
<i>Entamoeba histolytica</i>	0/2	1/3 (33.0%)	1/1 (100%)	0	0	0
<i>Giardia lamblia</i>	3/12 (25%)	6/15 (40.0%)	1/6 (16.7%)	2/8 (25.0%)	2/4 (50%)	3/5 (60.0%)

In order to further assess the microbiologic activity of rifaximin the MO elected to assess the microbiologic eradication rates by center and by pathogen, as can be seen below it was again unclear if rifaximin has any microbiologic efficacy given the similarity of the results between rifaximin and placebo at centers

Table A22

n/N = n of isolates eradicated/number tested	MITT Subjects									
	100/Calcutta		101/Goa		107/Antigua		200/Guadalajara		242/Cuernavaca	
	Rifaximin N = 29	Placebo N = 16	Rifaximin N = 41	Placebo N = 18	Rifaximin N = 32	Placebo N = 16	Rifaximin N = 21	Placebo N = 18	Rifaximin N = 4	Placebo N = 14
All	19/29 (66%)	6/15 (40%)	20/39 (51%)	11/17 (65%)	21/31 (68%)	10/16 (63%)	14/21(67%)	2/8(25%)	2/4 (50%)	2/4 (50%)
<i>Aeromonas (hydrophila)</i>	1/1(100%)	-	1/2 (50%)	1/1(100%)	-	-	-	-	-	-
<i>Campylobacter (jejuni)</i>	2/2(100%)	1/2 (50%)	5/15(33%)	3/4 (75%)	1/4 (25%)	0/1(0%)	¼ (25%)	0/1(0%)	-	0/2 (0%)
<i>Plesiomonas sp</i>	-	-	3/3(100%)	-	-	-	-	-	-	-
<i>Plesiomonas shigelloides</i>	-	-	2/2 (100%)	0/1 (0%)	-	1/1(100%)	-	-	-	-
<i>Salmonella Group B</i>	-	-	1/3 (33%)	-	-	-	-	-	-	-
<i>Salmonella Group C1</i>	-	-	1/1(100%)	-	-	1/1(100%)	-	-	-	-
<i>Salmonella Group C2</i>	-	-	-	-	-	-	-	-	-	-
<i>Shigella boydii</i>	-	-	-	-	1/1(100%)	-	-	-	-	-
<i>Shigella flexneri</i>	-	-	1/1(100%)	2/3 (67%)	1/1(100%)	0/1 (0%)	-	-	-	-
<i>Shigella sonnei</i>	2/2(100%)	1/1(100%)	0/1(0%)	-	2/2(100%)	-	3/3 (100%)	-	-	-
<i>Vibrio cholerae</i>	2/2(100%)	-	-	-	-	-	-	-	-	-
<i>Providencia</i>	-	-	-	-	-	-	1/1 (100%)	-	-	-
rrheagenic <i>E coli</i>	17/23 (74%)	7/12 (58%)	13/17 (76%)	9/10 (90%)	18/26 (69%)	9/12(75%)	12/14(86%)	2/6(33%)	2/3 (67%)	3/3(100%)
<i>E coli</i> [EAEC]	9/9(100%)	¾ (75%)	1/2 (50%)	5/5 (100%)	7/9 (78%)	7/7 (100%)	7/7(100%)	1/3 (33%)	-	1/1(100%)
<i>E coli</i> [ETEC-LT]	10/12 (80%)	¾ (75%)	5/7 (71%)	¾ (75%)	4/10(40%)	2/2(100%)	4/4(100%)	0/1(0%)	1/1(100%)	2/2(100%)
<i>E. coli</i> [ETEC-ST]	1/3 (33%)	1/1(100%)	1/1(100%)	1/1(100%)	5/5(100%)	1/2 (50%)	1/2 (50%)	1/2 (50%)	0/1 (0%)	-
<i>E coli</i> [ETEC-ST/LT]	2/4(50%)	2/5(40%)	7/8 (88%)	1/1(100%)	6/7 (86%)	2/4(50%)	¾ (75%)	-	1/1(100%)	-

Center 269, Lima had no bacterial pathogens

Center 249 Puerto Vallarta, had no subjects with bacterial pathogens that were evaluated post-treatment

If a subject had an isolate not tested for microbiologic outcome it was considered not evaluable by the MO

Correlation of Microbiology and Clinical Results

The majority of subjects who achieved wellness had an overall microbiological response of eradication at Visit 3. As per the applicant, "Among subjects achieving wellness, no statistically significant treatment difference was observed between the rifaximin and placebo groups in the proportions of subjects with a microbiological response of eradication. A greater proportion of subjects in the ciprofloxacin group than in the placebo group achieved wellness and demonstrated eradication (p=0.0741)"

Table A23
Microbiological Eradication and Wellness at TOC Visit (24 – 48 hours post-treatment) MITT Population

	Number (%) of Subjects			P-value ^a	
	Rifaximin (N=128)	Placebo (N=62)	Ciprofloxacin (N=58)	Rifaximin Placebo	Cipro Placebo
Wellness and Microbiological Response				0.5573	0.0741+
Wellness and eradication	64 (70.3%)	26 (65.0%)	36 (83.7%)		
Wellness and persistence	27 (29.7%)	14 (35.0%)	7 (16.3%)		

Reference: Table 14.2.43 and Listings 16.2.13 and 16.2.17

^a Based on 2-sided CMH test adjusted for center

⁺ P value between 0.05 and 0.10

In the analysis of wellness and microbiological eradication by individual pathogen, on the rifaximin arm the proportion of subjects with wellness and eradication was lower for subjects with *Campylobacter jejuni* (25 isolated, 6 cured, eradication in 1, persistence in 4, not tested in 1), and for the those with *Shigella sonnei* (8 subjects, 8 well, 4 eradicated, 3 persistent, 1 not tested) as compared to the ciprofloxacin arm where there was rare persistence associated with wellness. Similarly for subjects with *Escherichia coli*, the proportion of subjects with wellness and eradication on the rifaximin arm (52.8%) was similar that of the placebo arm (48.4%) as compared to the ciprofloxacin arm (57.9%). The proportion of subjects with wellness and persistence for each arm was 38.9%, 35.5%, and 7.9%.

Breakthrough or new infections

The most common newly isolated pathogen in both the rifaximin and placebo groups was enterotoxigenic ST/LT *E. coli*. The most common newly isolated pathogen in the ciprofloxacin group was enterotoxigenic ST *E. coli*.

Table A24
Newly Isolated Pathogens at TOC Visit (24 – 48 hours post-treatment) MITT Population

	Number of Newly Isolated Pathogens		
	Rifaximin (N=128)	Placebo (N=62)	Ciprofloxacin (N=58)
No Posttreatment Pathogen at Visit 3	68 (53.1%)	24 (38.7%)	41 (70.7%)
Newly Isolated Pathogen at Visit 3	18 (14.1%)	11 (17.7%)	9 (15.5%)
<i>Campylobacter jejuni</i>	1	1	0
<i>Plesiomonas</i> sp	2	0	0
<i>Salmonella</i> Group C2	1	0	0
<i>Pseudomonas</i>	1	0	0
<i>E. coli</i> (enterotoxigenic LT)	2	1	0
<i>E. coli</i> (enterotoxigenic ST)	2	1	6
<i>E. coli</i> (enterotoxigenic ST/LT)	7	6	2
<i>Cryptosporidium parvum</i>	2	1	0
<i>Entamoeba histolytica</i>	2	1	0
<i>Giardia lamblia</i>	2	1	1

Reference Table 14.2.46 and Listings 16.2.11 and 16.2.12

Clinical and Microbiological Outcome by Baseline Pathogen Category

Among subjects with diarrheagenic *E. coli* (without evidence of inflammatory/invasive pathogens) and in those subjects where no pathogen was identified, median TLUS and the proportion of subjects achieving wellness were similar for the rifaximin and ciprofloxacin groups, microbiological eradication in the rifaximin group was higher than in the placebo group but not as high as in the ciprofloxacin group. Across treatment groups, subjects with inflammatory/invasive pathogens and subjects with other agents had prolonged median TLUS, and lower proportions of these subjects demonstrated clinical wellness and microbiological eradication. Rifaximin was not effective against *Campylobacter jejuni* and *Salmonella* spp. Although both clinical and microbiological efficacy was noted against *Shigella* spp., median TLUS for *Shigella* spp. was almost double that for rifaximin against diarrheagenic *E. coli* and higher than the TLUS seen on the placebo arm although the numbers of placebo- and ciprofloxacin-treated subjects with *Shigella* spp. were too small to allow for valid conclusions.

Table A25
Clinical and Microbiological Outcome by Baseline Pathogen Category MITT
Population TOC Visit (24 – 48 hours post-treatment)

Pathogen Category^a Pathogen	Rifaximin (N=128)	Placebo (N=62)	Ciprofloxacin (N=58)
Median TLUS (hours)			
Any Pathogen	40.3 [N=128]	48.3 [N=62]	28.3 [N=58]
Inflammatory/Invasive Pathogens	NC [N=45]	67.5 [N=18]	65.0 [N=13]
<i>Campylobacter jejuni</i>	NC [N=25]	NC [N=10]	71.4 [N=9]
<i>Salmonella</i>	NC [N=4]	58.3 [N=1]	13.1 [N=2]
<i>Shigella</i>	44.8 [N=11]	31.8 [N=5]	16.6 [N=2]
Diarrheogenic <i>E coli</i>	24.0 [N=73]	38.0 [N=38]	23.4 [N=40]
EAEC	24.1 [N=24]	23.9 [N=16]	23.7 [N=15]
ETEC-LT	26.4 [N=29]	38.0 [N=10]	23.4 [N=11]
ETEC-ST	6.0 [N=11]	68.4 [N=7]	0.0 [N=4]
ETEC-ST/LT	24.1 [N=21]	NC [N=10]	24.8 [N=13]
Other Agents	65.3 [N=10]	NC [N=6]	NC [N=5]
No Pathogens (ITT Population)	23.5 [N=69]	71.6 [N=39]	29.7 [N=43]
Clinical Wellness			
Any Pathogen	94/128 (73.4%)	40/62 (64.5%)	43/58 (74.1%)
Inflammatory/Invasive Pathogens	22/45 (48.9%)	9/18 (50.0%)	8/13 (61.5%)
<i>Campylobacter jejuni</i>	6/25 (24.0%)	3/10 (30.0%)	4/9 (44.4%)
<i>Salmonella</i>	0/4 (0.0%)	1/1 (100%)	2/2 (100%)
<i>Shigella</i>	11/11 (100%)	3/5 (60.0%)	2/2 (100%)
Diarrheogenic <i>E coli</i>	65/73 (89.0%)	28/38 (73.7%)	33/40 (82.5%)
EAEC	22/24 (91.7%)	12/16 (75.0%)	12/15 (80.0%)
ETEC-LT	25/29 (86.2%)	8/10 (80.0%)	9/11 (81.8%)
ETEC-ST	11/11 (100%)	4/7 (57.1%)	4/4 (100%)
ETEC-ST/LT	17/21 (81.0%)	5/10 (50.0%)	11/13 (84.6%)
Other Agents	7/10 (70.0%)	3/6 (50.0%)	2/5 (40.0%)
No Pathogens (ITT Population)	57/69 (82.6%)	22/39 (56.4%)	36/43 (83.7%)
Microbiological Eradication			
Any Pathogen	77/128 (60.2%)	31/62 (50.0%)	46/58 (79.3%)
Inflammatory/Invasive Pathogens	25/45 (55.6%)	10/18 (55.6%)	10/13 (76.9%)
<i>Campylobacter jejuni</i>	9/25 (36.0%)	4/10 (40.0%)	6/9 (66.7%)
<i>Salmonella</i>	2/4 (50.0%)	1/1 (100%)	2/2 (100%)
<i>Shigella</i>	10/11 (90.9%)	3/5 (60.0%)	2/2 (100%)
Diarrheogenic <i>E coli</i>	56/73 (76.7%)	24/38 (63.2%)	37/40 (92.5%)
EAEC	21/24 (87.5%)	12/16 (75.0%)	14/15 (93.3%)
ETEC-LT	20/29 (69.0%)	8/10 (80.0%)	9/11 (81.8%)
ETEC-ST	8/11 (72.7%)	4/7 (57.1%)	4/4 (100%)
ETEC-ST/LT	18/21 (85.7%)	5/10 (50.0%)	13/13 (100%)
Other Agents	4/10 (40.0%)	0/6 (0.0%)	2/5 (40.0%)

Reference Tables 14.2.79 and 14.2.80 and Listings 16.2.13, 16.2.14, 16.2.16, and 16.2.17

^a Subgroups are mutually exclusive. Diarrheogenic *E coli* subgroup excludes subjects with inflammatory/invasive pathogens. Other agents subgroup excludes subjects with diarrheogenic *E coli* and inflammatory/invasive pathogens.

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

Conclusions from study 3001

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. There appeared to be significant treatment-by-center interactions in this study, putting into question the validity of the pooled results and necessitating that all results be reported by center. These interactions were caused by the failure of the positive control at the Goa site and the failure of the negative control at the Mexican site.

In the MITT population the median TLUS in was approximately 8 hours less for the rifaximin-treated subjects (40.3 hours) as compared to placebo (48.3 hours). Again, the median TLUS was lower on the ciprofloxacin arm (28.3 hours) as compared to the rifaximin. As in the ITT analysis, due to the treatment-by-center interaction, the pooled results were not considered valid and the by-center results revealed concerns with the Goa and Mexican sites.

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, for subjects with *Escherichia coli* and one other pathogen, for subjects with other pathogens other than *Escherichia coli* 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 in subjects with *Campylobacter* in the stool for the rifaximin-treated population was not calculable due to high number of failures.

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

The Agency disputed the acceptability of the pooled results from this study. As per the applicant, median TLUS was shorter in the rifaximin group compared to the placebo group for all subgroups except that of subjects with inflammatory/invasive pathogens where more than half of the rifaximin-treated subjects (N = 46) failed and in the very small subgroup of subjects with other agents where 3/6 placebo patients and 3/5 ciprofloxacin-treated patients failed and the TLUS could not be calculated. The results were statistically significant in favor of rifaximin in subjects with fecal leukocyte-positive illness, subjects with diarrheagenic *E. coli* but without evidence of inflammatory/invasive pathogens, and subjects with agent-negative illness.

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.

Analyses of wellness and treatment failure were performed by the Agency by center for both the ITT and MITT populations. A larger number of rifaximin-treated subjects were classified as clinical cures as compared to placebo in both studies. Of note, the treatment failure rate with rifaximin was slightly more than double that observed with ciprofloxacin (14.7% vs 6.9%, respectively). Similar results were obtained for the MITT.

In study RFID 3001 overall eradication rates were again similar between the rifaximin and placebo arms at visit 2 and although in the MITT population at Visit 3, 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.

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 15.6 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 — hours.

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 without inflammatory/invasive pathogens. These results were confirmed in two Phase III clinical trials. Rifaximin did not appear to be effective in subjects with inflammatory/invasive pathogens. Amongst the pathogens categorized as inflammatory/invasive were *Campylobacter jejuni*, *Salmonella* spp. and *Shigella*. Rifaximin demonstrated inadequate clinical and microbiologic efficacy against *Campylobacter jejuni* and *Salmonella* spp. in RFID3001. Regarding *Shigella sonnei* — the median TLUS for *Shigella* spp. (all 18 subjects) was 45.7 hours as compared to 24 hours in rifaximin-treated subjects with diarrheagenic *E. coli*. Microbiologic efficacy was similar across treatment arms in both studies although there were too few isolates of *Shigella sonnei* on the other treatment arms to allow for valid comparisons. Regarding *Escherichia coli*, a requested pathogen for which there was adequate data, the data are conflicting. In study RFID9801, TLUS in the subset of subjects with this pathogen was less in rifaximin-treated subjects as compared to placebo. This trend was not seen in study RFID3001 when subjects with *Escherichia coli* only were assessed. Additionally, as in the first review cycle, eradication rates were similar between the rifaximin and placebo treatment arms. These factors combined led the MO to NOT recommend an approval for rifaximin versus any specific pathogen.

To conclude, patients with fever or bloody diarrhea, *Campylobacter* or *Salmonella* should not take rifaximin.

SAFETY EVALUATION

Safety Population

Two subjects were enrolled twice into RFID3001. Subject #100-0386 was initially randomized to rifaximin and was later re-randomized as Subject #100-0429 to rifaximin. Subject #100-0390 was initially randomized to rifaximin and was later re-randomized as

Subject #100-0425 to rifaximin. For the safety analyses, the second randomizations of these subjects (#100-0429 and #100-0425) were treated as separate subjects. Thus, the safety population includes a total of 199 subjects assigned to rifaximin. One placebo subject and 1 ciprofloxacin subject did not have any post-baseline safety data, these 2 subjects were excluded from the safety population.

The extent of exposure to study drug is summarized below. Across the treatment groups, the mean number of days on study drug was 3.6 and exposure ranged from 1 to 5 days.

Table A26
Extent of Exposure to Study Drug – Safety Population

Exposure	Rifaximin (N=199)	Placebo (N=100)	Ciprofloxacin (N=100)
Number of Days on Study Drug ^a			
Mean ± SD	3.7 ± 0.68	3.6 ± 0.73	3.7 ± 0.58
Median	4.0	4.0	4.0
Minimum – maximum	1 – 5	1 – 4	1 – 5
No. (%) Subjects on Study Medication			
1 day	4 (2.0%)	2 (2.0%)	1 (1.0%)
2 days	10 (5.0%)	8 (8.0%)	2 (2.0%)
3 days	38 (19.1%)	21 (21.0%)	26 (26.0%)
4 days	146 (73.4%)	69 (69.0%)	70 (70.0%)
5 days	1 (0.5%)	0	1 (1.0%)

Reference: Table 14.3.1 and Listing 16.2.8

^a Days on study drug were based on date (calendar days) rather than 24-hour time intervals shown on the diary cards.

Adverse Events

Adverse events were reported in 53/199 (26.6%) rifaximin-treated subjects, 25/100 (25%) of placebo-treated subjects, and 24/100 (24%) of ciprofloxacin-treated subjects. Rates of adverse events were generally similar among the treatment groups. Study drug-related adverse events were reported in 21/199 (10.6%) of subjects in the rifaximin group, 10/100 (10.0%) of subjects in the placebo group, and 14/100 (14.0%) of subjects in the ciprofloxacin group. Serious adverse events were reported in 1 rifaximin (dysentery NOS) and 1 placebo (respiratory tract infection NOS and dehydration) subject. A total of 9 subjects had adverse events that led to discontinuation of study drug, including 4 subjects in the rifaximin group (vomiting NOS, respiratory tract infection NOS, dehydration, dysentery NOS, and nasal passage irritation), 2 subjects in the placebo group (respiratory tract infection NOS and dehydration, diarrhea aggravated), and 3 subjects in the ciprofloxacin group (vomiting NOS, constipation, and malaria NOS).

Table A27
Brief Overview of Adverse Events Safety Population

	Rifaximin (N=199)	Placebo (N=100)	Ciprofloxacin (N=100)
Adverse Events [N (%)]			
All Adverse Events	53 (26.6%)	25 (25.0%)	24 (24.0%)
Study Drug-Related Adverse Events	21 (10.6%)	10 (10.0%)	14 (14.0%)
No (%)Subjects Reporting Adverse Events by Maximum Intensity			
Mild	17 (8.5%)	10 (10.0%)	12 (12.0%)
Moderate	25 (12.6%)	6 (6.0%)	6 (6.0%)
Severe	5 (2.5%)	3 (3.0%)	3 (3.0%)
Not Recorded	6 (3.0%)	6 (6.0%)	3 (3.0%)
Serious Adverse Events [N (%)]	1 (0.5%)	1 (1.0%)	0
Early Terminations Due to AEs [N (%)]	4 (2.0%)	2 (2.0%)	3 (3.0%)
Deaths	0	0	0

Reference Tables 14.3.2, 14.3.8, and 14.3.10 and Listings 16.2.3, 16.2.19, 16.2.21 and 16.2.22

Adverse events reported by $\geq 1\%$ of subjects in a treatment group are presented below

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Table A28
Frequently Reported ($\geq 1\%$ of Subjects in a Treatment Group)
Treatment-Emergent Adverse Events Safety Population

MedDRA System Organ Class Preferred Term of Frequently Reported AE^a	Rifaximin (N=199)	Placebo (N=100)	Ciprofloxacin (N=100)
No (%) Subjects Reporting Adverse Events	53 (26.6%)	25 (25.0%)	24 (24.0%)
Gastrointestinal Disorders	20 (10.1%)	12 (12.0%)	14 (14.0%)
Constipation	8 (4.0%)	5 (5.0%)	8 (8.0%)
Flatulence	4 (2.0%)	3 (3.0%)	2 (2.0%)
Rectal tenesmus	4 (2.0%)	1 (1.0%)	1 (1.0%)
GI Motility disorder	3 (1.5%)	1 (1.0%)	1 (1.0%)
Vomiting NOS (Not Otherwise Specified)	2 (1.0%)	1 (1.0%)	2 (2.0%)
Nausea	1 (0.5%)	1 (1.0%)	2 (2.0%)
Fecal Abnormality	3 (1.5%)	0 (0%)	0 (0%)
Abdominal Pain	2 (1.0%)	0 (0%)	0 (0%)
Abdominal distension	0 (0%)	0 (0%)	1 (1.0%)
Diarrhea aggravated	0 (0%)	1 (1.0%)	0 (0%)
Diarrhea NOS	0 (0%)	1 (1.0%)	0 (0%)
Dry Mouth	0 (0%)	1 (1.0%)	0 (0%)
Hyperacidity	0 (0%)	1 (1.0%)	0 (0%)
Inguinal Hernia	1 (0.5%)	0 (0%)	0 (0%)
Dry Lip	0 (0%)	0 (0%)	1 (1.0%)
Nervous System Disorders	21 (10.6%)	11 (11.0%)	5 (5.0%)
Headache	16 (8.0%)	9 (9.0%)	5 (5.0%)
Dizziness	2 (1.0%)	2 (2.0%)	2 (2.0%)
Migraine NOS	2 (1.0%)	0 (0%)	0 (0%)
Dysgeusia	0 (0%)	1 (1.0%)	0 (0%)
Tremor	0 (0%)	1 (1.0%)	0 (0%)
Blood and Lymphatic System Disorders	2 (1.0%)	0 (0%)	1 (1.0%)
Lymphocytosis	2 (1.0%)	0 (0%)	1 (1.0%)
Neutropenia	2 (1.0%)	0 (0%)	0 (0%)
Ear and Labyrinth System Disorders	3 (1.5%)	0 (0%)	0 (0%)
Tinnitus	2 (1.0%)	0 (0%)	0 (0%)
Eye Disorders	0 (0%)	0 (0%)	2 (2.0%)
Asthenopia	0 (0%)	0 (0%)	1 (1.0%)
Conjunctivitis	0 (0%)	0 (0%)	1 (1.0%)
General Disorders	5 (2.5%)	3 (3.0%)	2 (2.0%)
Pyrexia	2 (1.0%)	1 (1.0%)	1 (1.0%)
Asthenia	0 (0%)	1 (1.0%)	0 (0%)
Fatigue	1 (0.5%)	1 (1.0%)	0 (0%)
Thirst	1 (0.5%)	1 (1.0%)	0 (0%)

Infections and Infestations	3 (1 5%)	2 (2 0%)	2 (2 0%)
Respiratory Tract	1 (0 5%)	1 (1 0%)	0 (0%)
URI	1 (0 5%)	1 (1 0%)	0 (0%)
Dysentery	1 (0 5%)	0 (0%)	0 (0%)
Malaria	0 (0%)	0 (0%)	0 (0%)
Varicella	0 (0%)	0 (0%)	1 (1 0%)
Investigations	2 (1 0%)	0 (0%)	1 (1 0%)
Decreased RBC	0 (0%)	0 (0%)	1 (1 0%)
Metabolism and Nutritional Disorders	1 (0 5%)	1 (1 0%)	0 (0%)
Dehydration	1 (0 5%)	1 (1 0%)	0 (0%)
Musculoskeletal/Connective Tissue Disorders	4 (2 0%)	1 (1 0%)	1 (1 0%)
Arthralgia	2 (1 0%)	0 (0%)	0 (0%)
Back Pain	0 (0%)	0 (0%)	1 (1 0%)
Tendonitis	0 (0%)	1 (1 0%)	0 (0%)
Renal and Urinary Disorders	3 (1 5%)	0 (0%)	0 (0%)
Respiratory/Thoracic/Mediastinal Disorders	7 (3 5%)	4 (4 0%)	1 (1 0%)
Nasopharyngitis	2 (1 0%)	0 (0%)	0 (0%)
Pharyngitis	2 (1 0%)	0 (0%)	0 (0%)
Rhinitis NOS	1 (0 5%)	1 (1 0%)	0 (0%)
Wheezing	0 (0%)	1 (1 0%)	1 (1 0%)
Cough	0 (0%)	1 (1 0%)	0 (0%)
Throat Irritation	0 (0%)	1 (1 0%)	0 (0%)
Skin and SQ Disorders	2 (1 0%)	0 (0%)	1 (1 0%)
Pruritus	0 (0%)	0 (0%)	1 (1 0%)

Reference Table 14.3.4 and Listing 16.2.19

No major differences were observed among treatment groups in the incidence of treatment-emergent adverse events by system organ class. The most common adverse events overall were headache (7.5%) and constipation (5.3%). Headache was reported by a higher proportion of placebo subjects (9.0%) than rifaximin (8.0%) or ciprofloxacin (5.0%) subjects. Constipation was reported by a higher proportion of ciprofloxacin subjects (8.0%) than rifaximin (4.0%) or placebo (5.0%) subjects. As expected, AEs from the GI tract were most common.

Severity

Adverse events rated as severe were reported for 5/199 (2.5%) in the rifaximin group, 3/100 (3.0%) in the placebo group, and 3/100 (3.0%) in the ciprofloxacin group

Table A29**Incidence of Severe Adverse Events - Safety Population**

MedDRA System Organ Class Preferred Term of Severe AEs	Rifaximin (N=199)	Placebo (N=100)	Ciprofloxacin (N=100)
No. (%) Subjects Reporting Severe AEs	5 (2.5%)	3 (3.0%)	3 (3.0%)
Gastrointestinal Disorders			
Constipation	0	0	1 (1.0%)
General Disorders and Administration Site Conditions			
Fatigue	0	1 (1.0%)	0
Pyrexia	0	1 (1.0%)	0
Infections and Infestations			
Dysentery NOS	1 (0.5%)	0	0
Malaria NOS	0	0	1 (1.0%)
Respiratory tract infection NOS	0	1 (1.0%)	0
Musculoskeletal and Connective Tissue Disorders			
Tendonitis	0	1 (1.0%)	0
Nervous System Disorders			
Headache	1 (0.5%)	0	1 (1.0%)
Migraine NOS	1 (0.5%)	0	0
Renal and Urinary Disorders			
Dysuria	1 (0.5%)	0	0
Respiratory, Thoracic and Mediastinal Disorders			
Rhinorrhea	1 (0.5%)	0	0

Reference: Table 14.3.6 and Listing 16.2.19

NOS = not otherwise specified

Relationship to Study Medication

AEs considered to be related to study drug were reported for 21/199 (10.6%) of rifaximin subjects, 10/100 (10.0%) of placebo subjects, and 14/100 (14.0%) of ciprofloxacin subjects. Constipation and headache were the most frequently reported study drug-related adverse events. Severe drug-related adverse events were reported for 1 rifaximin subject (migraine NOS) and 1 ciprofloxacin subject (constipation).

Table A30
Incidence of Drug-Related Adverse Events by Severity Safety Population

MedDRA System Organ Class	Rifaximin (N=199)	Placebo (N=100)	Cipro (N=100)
Preferred Term of Drug-Related AE	N (%)	N (%)	N (%)
Any Adverse Event	21 (10.6%)	10 (10%)	14 (14%)
Blood and Lymphatic System Disorders			
Lymphocytosis	2 (1.0%)	0	1 (1.0%)
Neutropenia	2 (1.0%)	0	0
Monocytosis	1 (0.5%)	0	0
Gastrointestinal Disorders			
Constipation	7 (3.5%)	3 (3.0%)	7 (7.0%)
Flatulence	1 (0.5%)	2 (2.0%)	0
Vomiting NOS	0	1 (1.0%)	1 (1.0%)
Abdominal distension	0	0	1 (1.0%)
Nausea	1 (0.5%)	1 (1.0%)	1 (1.0%)
Faecal abnormality NOS	1 (0.5%)	0	0
Dry mouth	0	1 (1.0%)	0
Hyperacidity	0	1 (1.0%)	0
General Disorders and Administration Site Conditions			
Asthenia	0	0	1 (1.0%)
Pyrexia	0	0	1 (1.0%)
Investigations			
Blood urine present	1 (0.5%)	0	0
Red blood cell count decreased	0	0	1 (1.0%)
Nervous System Disorders			
Headache	7 (3.5%)	3 (3.0%)	2 (2.0%)
Dizziness	1 (0.5%)	0	1 (1.0%)
Abnormal dreams	1 (0.5%)	0	0
Migraine NOS	2 (1.0%)	0	0
Dysgeusia	0	1 (1.0%)	0
Respiratory, Thoracic and Mediastinal Disorders			
Throat irritation	0	1 (1.0%)	0

Reference: Table 14.3.7 and Listing 16.2.19

NOS = not otherwise specified

* Includes events rated as severe by the Investigator and events for which severity was unknown

Deaths

No deaths occurred during the study or within the follow-up period for any subject

Serious Adverse Events

Two (0.5%) subjects (1 rifaximin, 1 placebo) experienced 3 serious adverse events. Both discontinued treatment due to these events.

Table A31
Summary of Treatment-Emergent Serious Adverse Events

MedDRA Preferred Term	Number (%) of Subjects		
	Rifaximin (N=199)	Placebo (N=100)	Ciprofloxacin (N=100)
No. (%) of subjects with serious adverse events	1 (0.5%)	1 (1.0%)	0
Dysentery NOS	1 (0.5%)	0	0
Respiratory tract infection NOS	0	1 (1.0%)	0
Dehydration	0	1 (1.0%)	0

Reference: Table 14.3.10 and Listing 16.2.21

NOS = not otherwise specified

Table A32
Subjects with Serious Adverse Events

Center #- Subject #	Age (yrs)/ Sex	Day ^a of Onset	Day ^a of Resolution	System Organ Class	MedDRA Preferred Term	Reason Serious
Subjects in the Rifaximin Group						
#249-0281	58/M	2	3	Infections and Infestations	Dysentery NOS	HOSP
Subjects in the Placebo Group						
#101-0450	31/M	2	3	Infections and Infestations	Respiratory tract infection NOS	HOSP
		2	2	Metabolism and Nutrition Disorders	Dehydration	HOSP

Discontinuations Due to Adverse Events

Nine (2.3%) subjects (4 (2%) rifaximin, 2 (2%) placebo, 3 (3%) ciprofloxacin) prematurely discontinued study drug due to 1 or more treatment-emergent adverse events. The discontinuation page of the CRF for 3 of these subjects (2 rifaximin, 1 placebo) indicated lack of efficacy as the primary reason for study drug discontinuation. Two subjects, both in the ciprofloxacin group, discontinued due to events considered to be study drug-related.

Table A33
Subjects Who Discontinued Study Drug due to Adverse Events

Center #- Subject #	Age (yrs) / Sex	Day ^a of Onset	Day ^a of Resolution	System Organ Class	MedDRA Preferred Term	Maximum Intensity
Subjects in the Rifaximin Group						
#101-0516 ^b	45/F	2	2	Gastrointestinal Disorders	Vomiting NOS	N/A
#101-0534 ^b	42/F	2	Unknown	Metabolism and Nutrition Disorders	Dehydration	Moderate
		2	4	Infections and Infestations	Respiratory tract infection NOS	Mild
#107-0062	30/M	1	3	Respiratory, Thoracic and Mediastinal Disorders	Nasal passage irritation	Mild
#249-0281	58/M	2	3	Infections and Infestations	Dysentery NOS	Severe
Subjects in the Placebo Group						
#101-0450	31/M	2	3	Infections and Infestations	Respiratory tract infection NOS	Severe
		2	2	Metabolism and Nutrition Disorders	Dehydration	Mild
#107 0079 ^b	22/M	4	5	Gastrointestinal Disorders	Diarrhea aggravated	Moderate
Subjects in the Ciprofloxacin Group						
#100-0391	25/F	2	Unknown	Gastrointestinal Disorders	Constipation ^c	Severe
#100 0398	19/F	2	4	Infections and Infestations	Malaria NOS	Severe
#200-0291	23/M	1	1	Gastrointestinal Disorders	Vomiting NOS ^c	Moderate

Laboratory

Minor mean increases and decreases from pretreatment in hematology and urinalysis parameters were observed in all treatment groups. None of these changes were considered to be clinically meaningful.

The most common shifts across the 3 treatment groups were to lymphocytosis, low hematocrit, low RBC count, and low monocytes.

All but 1 subject had urinalysis values that were within the normal range at pretreatment and at the end of treatment, 1 rifaximin subject with normal urine pH at pretreatment had a low value at the end of treatment.

Laboratory abnormalities judged to be clinically significant were reported as adverse events. Subject #242-0346 in the rifaximin group, a 19-year-old white female, had blood in her urine on Study Day 4. This adverse event was considered related to study drug, no action was taken and the adverse event was not resolved at the end of the study.

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Regina Alivisatos
5/20/04 08 07 59 AM
MEDICAL OFFICER

Leonard Sacks
5/24/04 09 06 14 AM
MEDICAL OFFICER

**EXECUTIVE SUMMARY for NDA 21-361
LUMENAX™ (rifaximin)**

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

Escherichia coli

Background

Salix Pharmaceuticals submitted 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).

The indication as it appears in the proposed label is as follows:

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

Escherichia coli

Clinical Studies

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.