The events in one lactitol patient (035) were considered possibly related to treatment Events in the other patients were considered not related to study drug Two of the rifaximin patients described above had fatal events (031 and 093),

Table 57
HE Patients Who Withdrew Due to an Adverse Event

Study ID Patient ID (Treatment)	Adverse Event with Severity	Relationship	Outcome
RFHE9701 035 (Lactitol)	Moderate epigastralgia Moderate pirosis	Possible Possible	Recovered
RFHE9701 084 (Lactitol)	Moderate worsening of HE	Unrelated	Recovered
RFHE9701 150 (Lactitol)	Moderate urinary infection	Unrelated	Recovered
RFHE9701 010 (Rifaximin)	Mild high digestive bleeding Severe portal gastropathy hypertension	Unrelated Unrelated	Recovered with treatment
RFHE9701 031 (Rifaximin)	Severe hematemesis by variceal bleeding Moderate pain in LUQ of abdomen	Unrelated Unrelated	Died
RFHE9701 093 (Rifaximin)	Severe gastro-intestinal hemorrhage Severe septic shock	Unrelated Unrelated	Died
RFHE9701 104 (Rifaximin)	Moderate worsening of HE grade	Unrelated	No information provided

Serious AEs

None of the rifaximin ID patients experienced a serious adverse event (SAE) One control ID patient (1/241, 0 4%) who received placebo in RFID9801 experienced serious diarrhea that was considered possibly related to treatment Placebo treatment was stopped and this patient was withdrawn from the study due to lack of efficacy and an antibiotic was started,

Thirteen (8 3%) of 157 HE patients (9/104, 8 7% rifaximin, 4/53, 7 5% control) experienced an SAE on study

Table 58
Serious Adverse Events in HE Patients

Adverse Event	Rifaximin (N=104)	Control (N=53)
No of Patients with Serious AEs	8 (7 7%)	4 (7 5%)
Gastrointestinal hemorrhage	3 (2 9%)	1 (1 9%)
Acute renal failure	2 (1 9%)	0
Ascites	1 (1 0%)	0
Coagulation disorder	1 (1 0%)	0
Hepatic encephalopathy	1 (1 0%)	1 (1 9%)
Hepatic failure	1 (1 0%)	0
Portal hypertension	1 (1 0%)	0
Sepsis	1 (1 0%)	0
Septic Shock	1 (1 0%)	0
Bacterial peritonitis	0	1 (1 9%)
Multi-organ failure	0	1 (1 9%)

One of these serious adverse event reports was considered treatment-related, patient 033 who developed ascites in RFHE9702

Six of the 9 HE patients with SAEs discontinued early from study because of an adverse event (3 rifaximin patients (010, 093, and 104), lack of efficacy (1 rifaximin patient (028) and 1 control patient (011), and other (1 rifaximin patient 068), Six of the HE patients with SAEs died, three rifaximin patients (028, 031 and 093) and three control patients (011, 091, and 096)

Serious adverse event reports for rifaximin HE patients were not related to the presence or absence of baseline hepatic impairment Of the 3 rifaximin HE patients with renal impairment, 1 reported hepatic failure versus none of the 100 rifaximin HE patients without renal impairment

Narratives taken from the studies where serious adverse events were reported are provided in appendix 1 to the MOR

Other AEs

One significant adverse event in rifaximin ID patients in RFID9601 was not captured in the safety database An unidentified 21-year old female in the high dose rifaximin group (600 mg TID) in RFID9601 experienced a severe allergic reaction 3 days after completing therapy She experienced an episode of itching and skin burning while running, and then developed generalized urticaria and angioedema (swollen lips) Her systolic blood pressure was also low She was treated with benadryl, epinephrine and corticosteroids The events, all considered unrelated to study treatment, resolved NOTE No further information was available

AEs by age

With the exception of urinary frequency, observed in one patient >64 years of age and no patients ≤64 years of age (p= 0152), there were no statistically significant differences in adverse events observed for rifaximin ID patients ≤64 years old (N = 388) compared to those >64 years (N = 6) old. There were no statistically significant differences in adverse events observed for rifaximin HE patients ≤64 years old (N = 76) compared to those >64 years old (N = 28)

MO Comment *The number of ID patients > 64 years is too small to be able to make any valid comments*

AEs by gender

AEs were more frequent in females (137 events /205 female ID subjects than males (106 evnts/195 male ID subjects) Accounting for the difference were primarily headache and tenesmus Headache was reported by 37/205 (18%) females and 13/195 (7%) males and tenesmus by 23/205 (11%) females and 11/195 (6%) males (p= 0007, and p= 0498, respectively)

Other GI events such as flatulence (females 42/205 (21%), males 28/195 (14%), p = 0 1155) and nausea (females 26/205 (13%), males 17/195 (9%), p = 0 25), were numerically more frequent in females than in males but did not reach statistical significance Similarly, fatigue was reported in 9/205 (4%) of females and 4/195 (2%) of males, p = 0 26

AEs by race

Vomiting and headache were higher in rifaximin ID non-white patients (N = 68) than white patients (N = 332) Vomiting occurred in 5 (7%) of non-white patients and 7 (2%) of white patients and headache occurred in 14 (21%) of non-white patients and 36 (11%) of white patients Asthenia and chest pain were reported in 1/332 (0 3%) white subjects each and in 2/68 (2 9%) of non- white subjects

Weakness

A detailed analysis of subjects complaining of weakness, fatigue, tiredness, feeling run down, or malaise revealed that from study 9601, there were 10 rifaximin 400 mg TID subjects, one 600 mg TID subjects, three 200 mg TID subjects, and 2 TMP/SMX subjects with these complaints From study 9701 there were 3 ciprofloxacin and 4 rifaximin 400 mg BID subjects and from study 9801, there were 6 rifaximin 400 mg TID subjects, 3 placebo subjects and 3 rifaximin 200 mg TID subjects with these complaints It appeared therefore as if the 400 mg TID was more frequently associated with fatigue although the significance of this finding is unclear given the nature of the disease process under treatment For a detailed listing of these subjects, see Appendix 1

Labs

Blood chemistry (serum creatinine, AST, ALT, and total bilirubin) and hematology (white blood cell count, hemoglobin, and platelets) parameters were evaluated in the 5 ISS studies

For the ID population, shift tables for blood chemistry and hematology parameters showed no statistically significant differences between rifaximin and the control groups Most of the ID patients had both normal baseline and post-treatment laboratory values Changes in laboratory parameters listed as adverse events for ID rifaximin patients were elevations of AST (1%), hematuria present (0 5%), and glycosuria present (0 3%),

A detailed listing of ID patients who developed abnormal LFTs during the study revealed that 4 placebo and 4 rifaximin 200 TID patients developed increased aspartate aminotransferase during the study (up to 2 – 3 x ULN) Two of the placebo subjects also had increased ALT For a detailed listing of these subjects see appendix 1

For the HE population, AST, ALT, and total bilirubin levels tended to be high at baseline and remain high post-treatment No statistically significant differences were observed between rifaximin and the control (lactitol) group for any clinical laboratory parameter Changes in laboratory parameters listed as adverse events for HE rifaximin patients were one report of hypokalemia (1 0%),

Table 59
Summary of Substantially Abnormal Clinical Laboratory Values in ID Patients (Corrected for Baseline Abnormalities)

Laboratory Assay	Rifaximin Post-Treatment		Control Post-Treatment		P-Value[c]
	n/N	%	n/N	%	
Chemistry[a]					
AST	6/334	1 8%	3/194	1 5%	0 9084
ALT	5/223	2 2%	1/124	0 8%	0 6750
Bilirubin	0/221	0 0%	0/133	0 0%	1 0000
Creatinine	0/337	0 0%	1/196	0 5%	0 1819
Hematology[b]					
WBC	2/327	0 6%	1/191	0 5%	0 9128
Hemoglobin	0/322	0 0%	0/189	0 0%	1 0000
Platelets	2/324	0 6%	1/193	0 5%	0 6988

[a] Abnormal chemistry parameters are defined as ≥2 x the upper limit of normal
[b] Abnormal hematology parameters are defined as <75% of the lower limit of normal
[c] Two-sample Wilcoxon Test comparing changes for patients with complete data
Notes Control = placebo treated patients (RFID9801), ciprofloxacin treated patients (RFID9701), and TMP/SMX treated patients (RFID9601)

Conclusions

Rifaximin doses of 200 mg TID to 600 mg TID were well tolerated in infectious diarrhea (ID) patients with 95% (381/400) of rifaximin ID patients completing the treatment schedule of 3 to 5 days A similar proportion of patients treated with control completed treatment Overall, of the 1% (8/798) of ID patients in the ISS database who withdrew from study because of an adverse event, only one was from the rifaximin group

The overall incidence of AEs reported by ID patients was similar in the rifaximin and control groups, fatigue was the only adverse event that was significantly more frequent in the rifaximin treated patients (3% vs 0 4 % control (p= 0227) The clinical relevance of this finding is unclear given the dehydrating nature of the disease under study

The most frequently reported AEs were gastrointestinal in nature and were symptoms of the underlying disease (e g , abdominal pain, fecal incontinence, flatulence, nausea and tenesmus)

No deaths (0/641) occurred in any of the ID studies and one of the 641 ID patients (0 2%) reported a serious adverse event on study The serious adverse event occurred a placebo patient who had severe worsening of diarrhea The investigator considered the event as possibly related to study treatment

No treatment group differences were observed in clinical laboratory results A small proportion of ID rifaximin patients had clinical laboratory changes listed as an adverse event elevations of AST (1%), glycosuria present (0 3%), and hematuria present (0 5%)

Of note, in a much sicker HE population 95% (99/104) of patients completed up to a 7-day treatment period The incidence of withdrawals due to an adverse event in the HE studies was 4% (4/104) in the rifaximin group and 6% (3/54) in the control group Nausea and hepatic encephalopathy were the only adverse events reported at an incidence ≥5% in hepatic encephalopathy patients

Five percent (8/157) of the HE patients died on study Five of the deaths occurred in the group receiving rifaximin (5/104, 5%) and 3 occurred in the control group (3/53, 6%) The cause of death was considered unrelated to study treatment for all 8 patients Thirteen of one hundred fifty-seven (8%) HE patients experienced a serious adverse event on study Nine patients (9/104, 9%) were in the rifaximin group and 3 (3/53, 6%) were in the control group All but one of the serious adverse events were judged by the investigator as not related to study treatment One serious adverse event in a rifaximin HE patient (ascites requiring hospitalization) 2 days after starting rifaximin treatment was considered possibly related to treatment by the investigator

No treatment group differences were observed in clinical laboratory results One (1 0%) HE rifaximin patient had a clinical laboratory change listed as an adverse event (hypokalemia)

Additional Safety Information

Published and Unpublished studies

The applicant submitted additional safety information from 1,647 patients treated in other Alfa-Wasserman published and unpublished studies (N = 57) As per the applicant, "No new serious or new severe adverse events were found in these published and unpublished studies that were not already reported in the ISS database"

Four hundred twelve of the 1,647 patients treated with rifaximin had infectious diarrhea, 369 had hepatic encephalopathy and/or liver cirrhosis, 364 had surgical procedures, 359 had diverticulitis, 73 had inflammatory bowel disease, and 70 had intestinal infections Of the 412 rifaximin ID patients, 115 were pediatric patients treated with rifaximin, and 63 were elderly patients

Exposure to rifaximin varied with the greatest exposure to rifaximin reported in patients treated for hepatic encephalopathy diverticular disease, and inflammatory bowel disease 553/1647 (34%) were exposed to rifaximin for ≤ 5 days, 387 (23%) received rifaximin for >5 to ≤ 10 days, 346 (21%) received rifaximin for >10 to ≤ 21 days and 361 (22%) of were exposed to long-term therapy with rifaximin (> 1 to 12 months)

Of the 412 infectious diarrhea subjects, 234 were adults given oral rifaximin at doses ranging from 400 to 1200 mg/day for 2 to 7 days One hundred fifteen pediatric patients were treated for 3 to 7 days at doses ranging from 200 mg/day to 600 mg/day or as calculated by body weight from 14 mg/kg PO BID to 40 mg/kg PO QID 63 elderly subject received 600 mg rifaximin/day (200 mg PO TID) for 7 days, and HIV-infected patients were given rifaximin at doses as high as 1200 to 1800 mg/day (400 mg PO TID to 600 mg PO TID) for 7 to 14 days

Indication	Range of Daily Dose	Duration	No of Pts	No of Pubs
Infectious Diarrhea			412	19
Adults	400 – 1800 mg	2 – 14 days	234	12
Pediatrics	300 – 600 mg or 14 – 40 mg/kg/day	3 – 7 days	115	6
Elderly	600 mg	7 days	63	1

There were 37/1647 (2%) discontinuations Reasons for discontinuation included 9 patient deaths, 13 lost to follow up, 5 adverse events (worsening nausea and vomiting, vomiting, nausea, dyspepsia, and bleeding of the esophageal varices), 3 concomitant diseases, 2 acute diverticulitis, 2 repeat surgery, 1 patient with diverticulitis who was hospitalized for complications not related to disease, 1 patient for a disease complication

(recto-vaginal fistula), and 1 unknown reason Two of the patients who withdrew early were pediatric patients One of these patients was withdrawn on the second day of treatment because of worsening clinical symptoms and another patient was withdrawn on the third day of treatment because of significant vomiting

Three percent (52/1,647) patients had AEs Nausea was the most frequently reported adverse event (23, 1%) followed by flatulence (5), bowel movements alterations (4), epigastric pain (4), nausea and vomiting (3), stomatitis (3), abdominal pain (2), weight loss (2), vomiting (2) and single reports of a urticaria-like rash, nausea and gastric heaviness, dyspepsia, and bleeding of the esophageal varices Most adverse events or side effects were reported in patients undergoing surgical procedures (22), followed by patients with hepatic encephalopathy (15), other infections (11), or infectious diarrhea (3)

Some changes in hematology and clinical chemistry parameters were reported in the Alfa-Wassermann studies Slightly more changes in laboratory parameters were reported with the use of rifaximin in surgical procedures, which included increases in leukocytes and erythrocyte sedimentation rate, and decreases in total bilirubin, erythrocytes, hematocrit, and hemoglobin Changes in mean arterial blood pressure and heart rate that were not clinically significant were also reported after rifaximin treatment in patients undergoing surgical procedures In one infectious diarrhea study, a decrease in aspartate transaminase was reported after treatment with rifaximin In hepatic encephalopathy increases in sodium and albumin, and decreases in bilirubin were observed after rifaximin treatment, and, in other infections, decreases in leukocytes was reported after treatment due to regression of intestinal infection

None of the adverse events reported in Alfa Wassermann-sponsored publications or unpublished abbreviated study reports were considered serious by the investigators

Significant Safety Findings in Rifaximin-treated Patients							
Indication	**Range of Daily Dose (Duration)**	**No of Pubs./Pts**	**SAEs**	**Withdrawals**	**Deaths**	**AEs**	**Lab Changes**
Infectious Diarrhea		**19 / 412**					
Adults	400 – 1800 mg (2 – 14 days)	12 / 234	NR	NR	NR	1 (urticaria-like rash)	↓ AST, BUN, ↑ potassium
Pediatrics	200 – 600 mg OR 14 – 40 mg/kg/d (3 – 7 days)	6 / 115	NR	2 (1 vomiting, 1 worsening N/V	NR	3 vomiting, 2, worsening of nausea and vomiting)	NR
Elderly	600 mg (7 days)	1 / 63	NR	NR	NR	NR	NR

Medical Officer's Comment *Although of interest, the information provided from the published and unpublished studies cannot be verified Additionally, the number of reported AEs seems relatively low compared to that seen in the submitted trials*

Phase I studies

A total of 53 (46 male, 7 female) adult healthy volunteers, 18 to 45 years of age, were enrolled into the four Phase 1 studies in normal subjects Fifty-two received rifaximin 1 subject discontinued prior to dosing for reasons other than safety All 52 subjects completed the studies All subjects received doses that ranged from 50 mg to 400 mg, 400 mg BID, or 400 mg QID over the course of 1 day

Thirteen of the 52 subjects (25%) reported an AE These were

- Feeling more tired than usual (n=3)
- Headache (n=3)
- Abdominal pain, back pain, common sold symptoms including dizziness and headache, cough, diarrhea, dermatitis, dry skin, feces hard, fullness in head, itchy back, paresthesia slight rash (each at n=1)

Two events were considered severe by subjects, one report of feeling more tired than usual at a dose of 50 mg and 1 episode of dizziness at 200 mg

Abdominal pain, diarrhea, feces, and paresthesia were considered treatment-related All other events were considered not related, however, causality was not assigned in one study

Medical Officer's comment The value of this data is also limited by the short duration of dosing the low doses in most subjects and the lack of attribution in at least 1 study However fatigue and headache as well as GI complaints appear to be associated with rifaximin

Non-Salix/Alfa Wasserman Sponsored studies

The applicant identified an additional 10 clinical and nonclinical publications Only 3 of these included any safety information No new adverse events were identified
The studies pertained primarily to subjects with HE (N = 87) or diverticular disease (N = 968) Rifaximin doses ranged from 400 mg TID for 14 days in the HE study to 400 mg BID for 7 days every month x 12 months in the second study

In the HE study, 31 subjects with HE and 56 with diverticulitis were treated with rifaximin Eight percent (7/87) of patients reported an AE with one of the 7 patients reporting 2 AEs nausea (4), abdominal pain (1), dyspepsia (1), and urticaria (2) All of these were of mild or moderate severity and were considered treatment-related Two patients were withdrawn from the study (1 case of nausea and urticaria in a 58-year old male patient with hepatic encephalopathy, and 1 case of urticaria in a 66-year old female patient with diverticulitis of the colon) Another 2 patients, both female with

diverticulitis of the colon) had the dose of rifaximin reduced (1 case of nausea and 1 case of dyspepsia)

In the second study of 968 patients with uncomplicated symptomatic diverticular disease 595 patients received fiber supplementation with rifaximin 400 mg BID for 7 days every month, and 373 patients received the fiber supplement alone Patients were evaluated at 4 month intervals for 12 months At the 12-month visit, 904 patients (558 in the fiber + rifaximin group, 346 in the fiber alone group) were available for evaluation Thirty-seven patients (6 2%) in the fiber + rifaximin group and 27 (7 2%) in the fiber group had withdrawn from the study Reasons for withdrawal in the fiber + rifaximin group were lost to follow-up (16, 2 7%), nausea, headache, or asthenia (10, 1 7%), diverticulitis complications (8, 1 3%), required coronary by-pass (1, 0 2%), and 2 (0 3%) deaths from causes unrelated to diverticular disease Reasons for withdrawal in the fiber group alone were diverticulitis complications (12, 3 2%), lost to follow-up (9, 2 4%), nausea, headache, or asthenia (5, 1 3%), or required surgery for calculous cholecystitis (1, 0 3%)

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 applicant requested an approval for the dose of 200 mg TID in the treatment of traveler's diarrhea One hundred sixty-one subjects were studied using this dose Therefore it is strongly suggested that additional efficacy data be collected at the proposed dose prior to the issuance of an approval

VIII Use in Special Populations

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

Rifaximin was adequately assessed in both males and females with approximately 48% of the population studied being female

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

Pediatric Subjects

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

Subjects ≥ 65 years of age

Seven hundred thirty patients in the safety database were ≤ 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 ≤ 64 years of age there were no differences in adverse events observed for rifaximin ID or HE patients ≤ 64 years old compared to those > 64 years old

Additionally, safety data in elderly patients are 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

The ID study was a double-blind, placebo-controlled, randomized trial conducted in Italy 63 elderly patients with infectious diarrhea were treated with rifaximin 200 mg TID for 7 days Eight of 63 patients with *Salmonella* received treatment, after bacterial eradication, for up to 15 days to prevent re-infection Of the 63 patients treated with rifaximin, 38 were male and 25 were female The mean age was 72 years Patients were not allowed to receive other antibiotics or drugs capable of modifying intestinal mobility on study No restrictions were made on other medications and all patients were suitably rehydrated No AEs attributed to rifaximin were reported during the study No significant changes in clinical laboratory parameters, including liver and kidney functions, were observed from baseline to the end of treatment

Rifaximin was also well-tolerated in an open-label study that included 10 elderly patients with inflammatory bowel disease (acute enterocolitis, ischemic colitis, and small intestine contamination) In this study, rifaximin 400 mg BID was prepared as a suspension and administered via a nasogastric tube Of the 10 patients, three were male and seven were

female The mean age was 72 5 years No adverse events and no clinically significant laboratory changes were observed on study

Medical Officer's Comment *As noted previously, the number of subjects ≥ 65 years of age in the database was too small to allow for adequate conclusions to be drawn*

IX Conclusions and Recommendations

A Conclusions

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 BID (1000 mg/day) Subjects in both studies received study medication for 3 days An additional randomized, double blind, dose-ranging study (RFID9601) conducted in Mexico is considered supportive of efficacy This study compared three doses of rifaximin, 200 mg, 400 mg, or 600 mg TID for 5 days to a standard trimethoprim/sulfamethoxazole (TMP/SMX) regimen of 160/800 mg twice daily for 5 days

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

The primary efficacy endpoint for the three infectious diarrhea studies (RFID9801, RFID9701 and RFID9601) was the time to last unformed stool (TLUS) defined as the interval beginning with the first dose of study drug and ending with the last unformed stool passed, after which wellness (clinical cure) was declared

In two of the three ID studies, TLUS was analyzed for the intent-to treat (ITT) population (RFID9801 and RFID9701) In study RFID9601, TLUS was analyzed for patients who took at least 2 days of study medication and completed two or more daily diaries The MO also performed this analysis on a modified intent-to treat (MITT) population consisting of subjects who had a pathogen isolated at baseline

In RFID9801, results of the primary efficacy analysis demonstrated that rifaximin is superior to placebo in the treatment of diarrhea in travelers (p = 0 0001 for the rifaximin 200 mg TID versus placebo group and p = 0 0001 for the rifaximin 400 mg TID versus placebo group) Median TLUS was significantly shorter in both rifaximin groups compared to placebo, 32 5 hours in the rifaximin 200 mg TID group, 32 9 hours in the 400 mg TID group, and 60 0 hours in the placebo group

Improvement in diarrheal syndrome occurred when there was a reduction of 50% or more in the number of unformed stools passed during a 24-hour period compared with the number of stools passed during the 24-hour period immediately preceding enrollment in the study Significant improvements in diarrheal syndrome were seen during the 24–48 hour (p = 0 007) and 48–72 hour (p = 0 008) intervals compared to placebo In the 400 mg TID rifaximin group, the rate of improvement was also higher than for placebo during these intervals but the differences were not statistically significant (p > 0 025)

The mean number of unformed stools decreased during each time interval, with the mean number consistently lower in both rifaximin groups compared to the placebo group

In RFID9701, results of the primary efficacy analysis demonstrated that rifaximin is equivalent to ciprofloxacin in the time to last unformed stool Median TLUS was 25 7 hours (95% CI, 20 9–38 0) for the rifaximin group, and 25 0 hours (95% CI, 18 5–35 2) for the ciprofloxacin group

Improvement in diarrheal syndrome was comparable between the rifaximin and ciprofloxacin treatment groups, occurring in approximately 60% of patients from both treatment groups over the 0–24 hour time period and in over 80% of patients over the 24–48 time period

In RFID9601, the median TLUS for the rifaximin groups was 35 0 hours (26 3 hours [200 mg TID], 40 5 hours [400 mg TID], 35 0 hours [600 mg TID]) and 47 0 hours for the TMP/SMX group After 24 hours of treatment, 51% of patients treated with rifaximin (56% [200 mg TID], 44% [400 mg TID], 53% [600 mg TID] and 65% treated with TMP/SMX had an improvement in the diarrheal syndrome After 48 hours of treatment, 84% of patients treated with rifaximin (83% [200 mg TID], 78% [400 mg TID], 89% [600 mg TID] and 76% treated with TMP/SMX had an improvement

In a group of patients from RFID9801, RFID9701 or RFID9601 presenting with any sign or symptom of dysentery, the median TLUS for rifaximin-treated patients was 40 0 hours, placebo treated patients 70 5 hours, TMP/SMX treated patients 84 0 hours while the median TLUS for the ciprofloxacin treated patients was 33 0 hours The median TLUS for the rifaximin treated patients with dysentery did not differ significantly from the TLUS for all patients regardless of presenting symptoms (40 0 versus 35 0 hours)

The pathogen identification rate was similar between the rifaximin and control groups and was consistent (50%) with the published literature The organisms identified at

baseline were consistent with those known to cause infectious diarrhea in travelers In the rifaximin treatment groups, the most common pathogen identified was *Escherichia coli*, followed by *Cryptosporidium parvum* *Shigella* spp , *Salmonella* spp , and *Campylobacter* spp were found in very few patients

Of note was the high incidence of *Cryptosporidium parvum* despite the published incidence of < 1%

Pathogen eradication rates for patients in the clinical trials, stratified by rifaximin dose, are shown below

Pathogen	RFID 9801 Rifaximin 200 mg TID		RFID9701 Rifaximin 400 mg BID		RFID 9801 Rifaximin 400 mg TID		RFID9601 Rifaximin 600 mg TID	
	No	No Eradicated (%)	No	No Eradicated (%)	No	No Eradicated (%)	No	No Eradicated (%)
Escherichia coli	60	45/60 (75%)	37	24/37 (65%)	49	32/49 (65%)	2	2/2 (100%)
Shigella sonnei	3	3/3 (100%)	5	3/5 (60%)	1	1/1 (100%)	1	0/1
Shigella flexneri	2	½ (50%)	1	1/1 (100%)	1	0/1	0	0
Salmonella Group C1	3	2/3 (67%)	2	½ (50%)	4	3/4 (75%)	1	0/1
Salmonella Group C2	0	0	1	1/1 (100%)	4	2/4 (50%)	0	0
Campylobacter jejuni	4	3/4 (75%)	2	2/2 (100%)	0	0	0	0
Crytosporidium parvum	18	12/18 (67%)	1	1/1 (100%)	15	5/15 (33%)	0	0
Giardia lamblia	5	4/5 (80%)	0	0	0	0	0	0
Entamoeba histolytica	1	1/1 (100%)	0	0	0	0	0	0
Vibrio fluvialis	1	1/1 (100%)	0	0	0	0	0	0
Aeromonas hydrophila	0	0	0	0	1	1/1 (100%)	0	0
Plesiomonas shigelloides	0	0	0	0	1	1/1 (100%)	0	0
Vibrio parahemolyticus	0	0	0	0	1	1/1 (100%)	0	0

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Pathogen	RFID9801 Placebo		RFID9701 Ciprofloxacin 500 mg BID		RFID9601 TMP/SMX BID	
	No	No Eradicated (%)	No	No Eradicated (%)	No	No Eradicated (%)
Escherichia coli	54	40/54 (74%)	36	30/36 (83%)	6	6/6 (100%)
Shigella sonnei	2	2/2 (100%)	1	1/1 (100%)	0	0
Shigella flexneri	0	0	5	4/5 (80%)	0	0
Salmonella Group C1	1	1/1 (100%)	3	2/3 (67%)	1	1/1 (100%)
Salmonella Group C2	1	1/1 (100%)	2	2/2 (100%)	0	0
Campylobacter jejuni	1	0/1	0	0	0	0
Campylobacter coli	1	1/1 (100%)	0	0	0	0
Crytosporidium parvum	11	7/11 (64%)	2	½ (50%)	0	0
Aeromonas sobria	1	1/1 (100%)	0	0	0	0

For rifaximin patients with ETEC, eradication rates of 75%, 70%, 65%, and 100% were seen with total daily doses of 600 mg, 800 mg, 1200 mg, and 1800mg respectively Relatively consistent eradication rates across all rifaximin doses for ETEC subtypes were observed Of note were the very similar eradication rates between the placebo arm and the rifaximin treatment arms as well as the numerically lower eradication rates seen between both the placebo arm and the rifaximin arms compared to ciprofloxacin and TMP/SMX (NOTE The reader is cautioned that these are cross-study comparisons)

The applicant states that the similar eradication rates in conjunction with the improved TLUS in the rifaximin subjects as well as the fact that only 60% of subjects had an identifiable pathogen, indicate that clinical efficacy is more important than microbiologic in this population Additionally, the applicant pointed out that the levels of rifaximin achieved in the GI tract are very high and exceed all reported MICs NOTE There is a lack of understanding of the relationship between stool levels and antimicrobial activity

Regarding the 200 mg TID dose, it appeared that this dose produced similar symptomatic improvement as higher rifaximin doses Eradication rates for ETEC were similar with 200 mg TID, 400 mg BID, or 400 mg TID doses of rifaximin Eradication of ETEC did not correlate with clinical improvement Thus, in placebo patients, where eradication rates of ETEC were high, the eradication rates, but not improvement in clinical symptoms, were similar to patients treated with rifaximin, ciprofloxacin, and TMP/SMX This argument supports the use of the 200 mg TID dose as the minimum effective dose as well as justifies the pooling of organisms across doses

Although the MO can accept this argument for the selected dosage, this argument cannot support the extrapolation of microbiologic efficacy across doses from higher to lower Further the similar microbiologic efficacy between placebo and rifaximin but not between placebo and ciprofloxacin or TMP/SMX, generates doubts regarding the true antimicrobial activity of this compound

further assessment of the *Cryptosporidia* isolates revealed that only 6 of the 18 isolates on the 600 mg arm were sole pathogens All 6 were eradicated but 2 of the 6 were found to have breakthrough or new infections with ETEC LT

A search of the PUBMED database identify only one paper relating to the role of *cryptosporidium* in traveler's diarrhea (G Diridl, E Wallis, D Wolf, Management of Patients with Traveler's Diarrhea, Acta Med Austriaca, 19 58-60, 1992) In this study, *cryptosporidium* was determined to rarely be a causative organism for traveler's diarrhea

The MO concluded that

In the single pivotal study that utilized the proposed rifaximin dose of 200 mg PO TID for three days, rifaximin shortened the time to last unformed stool as compared to placebo No conclusion regarding microbiologic efficacy can be drawn at this time

Safety

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

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

The safety profile of rifaximin in RFID9801 and RFID9701 was comparable to the control arms in each study

When adverse event data were pooled for the three ID studies (RFID9801, RFID9701 and RFID9601), there was no difference in the adverse event rate for ID rifaximin patients compared to ID control patients The incidence of fatigue was higher for the ID rifaximin group than for the ID control group (ID rifaximin rate = 3%, ID control rate = 0 4%,) There were no associated symptoms such as lethargy, anemia or other CNS events indicating that this may be a chance finding rather than a clinically significant pattern

AEs reported for 2% or more of the ID rifaximin and ID control patients, respectively, were flatulence (18%, 17%), abdominal pain (13%, 10%), headache (13%, 10%), nausea (11%, 9 1%), fecal incontinence (9%, 8%), tenesmus (9%, 8%), constipation (5%, 4%), pyrexia (4%, 5%), fatigue (3%, 0 4%), vomiting (3%, 3%), nasopharyngitis (2%, 0 4%), and dizziness (exc vertigo) (2%, 4%)

Adverse events reported for ≥ 1% and < 2% of the ID rifaximin or ID control patients, respectively, were weakness (2%, 2%), AST increase (1%, 2%), sore throat (1%, 0%), and diarrhea (1%, 3%),

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

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

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

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

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

hospitalization) 2 days after starting rifaximin treatment was considered possibly related to treatment by the investigator

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

Conclusions

In conclusion, the applicant submitted two controlled studies of rifaximin for the treatment of traveler's diarrhea Only one of studies utilized the proposed dose of 200 mg PO TID or 600 mg as total daily dose

In study RFID9801, results of the primary efficacy analysis demonstrated that rifaximin was superior to placebo in the treatment of diarrhea in travelers (p = 0 0001 for the rifaximin 200 mg TID versus placebo group and p = 0 0001 for the rifaximin 400 mg TID versus placebo group) Median TLUS was significantly shorter in both rifaximin groups compared to placebo, 32 5 hours in the rifaximin 200 mg TID group, 32 9 hours in the 400 mg TID group, and 60 0 hours in the placebo group

In RFID9701, results of the primary efficacy analysis demonstrated that rifaximin was equivalent to ciprofloxacin in the time to last unformed stool Median TLUS was 25 7 hours (95% CI, 20 9–38 0) for the rifaximin group, and 25 0 hours (95% CI, 18 5–35 2) for the ciprofloxacin group It should be noted that the rifaximin dose used in this study was 400 g BID, a different dose than the applicant's proposed dose of 200 mg TID

For rifaximin patients with ETEC, eradication rates of 75%, 70%, 65%, and 100% were seen with daily doses of 600 mg, 800 mg, 1200 mg, and 1800mg respectively Of note were the very similar eradication rates between the placebo arm and the rifaximin treatment arms as well as the numerically lower eradication rates seen between both the placebo arm and the rifaximin arms compared to ciprofloxacin and TMP/SMX These results raised concerns about the true antimicrobial profile of 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 ≥ 5% of patients No serious adverse events with rifaximin use and no deaths were reported in the ID trials

The benefits of Rifaximin include

- Local action at the site of infection, the gastrointestinal tract
- Minimal absorption
- A treatment course of 3 days duration
- Reduction in TLUS compared to placebo
- No specific dosing adjustments for the elderly, renally or hepatically impaired population since the systemic exposure to the intact drug is such a small fraction of the administered dose

The risks of rifaximin include

- A pattern of adverse events similar to placebo
- The potential for certain adverse events, such as abdominal pain and headache, which were reported at a higher incidence on rifaximin as compared with placebo, these events could potentially manifest in a larger percentage following marketing launch
- Due to poor absorption, rifaximin would not be expected to provide adequate systemic antimicrobial treatment in subjects with diarrhea due to invasive pathogens
- Based on foreign post-marketing data, there is the potential for mild hypersensitivity reactions based on a small number of reports of allergic dermatitis and urticaria, which have been reported in Italy
- The lack of clear antimicrobial activity

B Recommendations

The MO recommends that rifaximin be considered approvable in the treatment of traveler's diarrhea at a dose 200 mg PO TID for 3 days

The issuance of an approval is dependent upon the submission and review of a second well controlled clinical trial at the proposed dose of 200 mg TID that confirms the efficacy of this trial and that provides additional microbiology data demonstrating a clear difference in effectiveness between rifaximin and placebo

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Concurrence only
HFD-590/DIVDir/AlbrechtR

Cc
Orig NDA 21-361
HFD-590
HFD-590/MTL/CoxE
HFD-590/CSO/WillardD
HFD-590/Micro/Dionne
HFD-590/TLMicro/Bala
HFD-725/Biostat/HigginsK
HFD-725/DixonC
HFD-520/Biopharm/DavitB
10/16/02

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[ii] Ericsson CD, Johnson PC, DuPont HL, et al Ciprofloxacin or Trimethoprim-Sulfamethaxazole as Initial Therapy for Traveler's Diarrhea A Placebo-Controlled Randomized Trial *Annals of Internal Medicine* 1987, 106 216-220
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APPENDIX 1

Table A Patients with Serious Adverse Events

Study ID Patient ID (Treatment)	Serious Adverse Event (Verbatim Term)	Treatment Relationship (Related/Not Related)	Study Disposition
RFID9801			
Patient 2094 (Placebo)	Diarrhea nos (worsening of diarrhea)	Not related	W/D for LOE
RFHE9701			
Patient 011[a] (Lactitol 6000 mg)	Hepatic Encephalopathy (Death due to worsening HF)	Not related	W/D for LOE
Patient 055 (Lactitol 6000 mg)	Gastrointestinal hemorrhage nos (Variceal bleeding [esophagus])	Not related	Completed
Patient 091[a] (Lactitol 6000 mg)	Multi-organ failure (Death due to multi-organ system failure)	Not related	Completed
Patient 096[a] (Lactitol 6000 mg)	Peritonitis bacterial nos (Spontaneous bacterial peritonitis)	Not related	Completed
Patient 010 (Rifaximin 1200 mg)	Gastrointestinal hemorrhage nos (High digestive bleeding)	Not related	W/D for AE
	Portal hypertension (Portal gastropathy hypertension)	Not related	
Patient 028[a] (Rifaximin 1200 mg)	Hepatic failure (Death due to liver failure)	Not related	W/D for LOE
Patient 031[a] (Rifaximin 1200 mg)	Hematemesis by variceal bleeding	Not related	W/D for AE
Patient 068 (Rifaximin 1200 mg)	Sepsis nos (Biliary sepsis)	Not related	W/D for Other Reason
Patient 093[a] (Rifaximin 1200 mg)	Gastrointestinal hemorrhage nos (gastrointestinal hemorrhage)	Not related	W/D for AE
	Septic shock (Septic shock)	Not related	
Patient 104 (Rifaximin 1200 mg)	Hepatic Encephalopathy (Worsening of HE grade)	Not related	W/D for AE
RFHE9702			
Patient 033 (Rifaximin 600 mg)	Ascites	Possibly related	Completed
Patient 016[a] (Rifaximin 2400 mg)	Acute renal failure	Not related	Completed
	Disseminated intravascular coagulation	Not related	
	Intra-abdominal bleed	Not related	
Patient 017[a] (Rifaximin 1200 mg)	Evidence of renal failure	Not related	Completed
	Sepsis	Not related	

[a] Patients who died within 30 days of last dose of study medication

List of Rifaximin Patients that Discontinued from the Infectious Diarrhea Studies

Study Number	Treatment	Pt. No	Reason for Discontinuation
RFID9601	Rifaximin 1200mg	050	Other reasons
RFID9701	Rifaximin 800mg	050	Lost to follow-up
RFID9801	Rifaximin 1200mg	1034	Lack of efficacy
RFID9801	Rifaximin 1200mg	1046	Lack of efficacy
RFID9801	Rifaximin 1200mg	1073	Lack of efficacy
RFID9801	Rifaximin 1200mg	1113	Lack of efficacy
RFID9801	Rifaximin 1200mg	1127	Lack of efficacy
RFID9801	Rifaximin 1200mg	1130	Lack of efficacy
RFID9801	Rifaximin 1200mg	2027	Lack of efficacy
RFID9601	Rifaximin 600mg	046	Other reasons
RFID9801	Rifaximin 600mg	1008	Other reasons
RFID9801	Rifaximin 600mg	1017	Other reasons
RFID9801	Rifaximin 600mg	1052	Lack of efficacy
RFID9801	Rifaximin 600mg	1077	Lack of efficacy
RFID9801	Rifaximin 600mg	1078	Other reasons
RFID9801	Rifaximin 600mg	1090	Other reasons
RFID9801	Rifaximin 600mg	1150	Lack of efficacy
RFID9801	Rifaximin 600mg	2095	Lack of efficacy
RFID9801	Rifaximin 600mg	2103	AE

List of Control Patients that Discontinued from the Infectious Diarrhea Studies

Study Number	Treatment	Pt. No	Reason for Discontinuation
RFID9601	TMP/SMX	023	Lost to follow-up
RFID9601	TMP/SMX	039	Lost to follow-up
RFID9701	Cipro 1000mg	081	Unknown reasons
RFID9801	Placebo	1030	Lack of efficacy
RFID9801	Placebo	1062	Lack of efficacy
RFID9801	Placebo	1080	Lack of efficacy
RFID9801	Placebo	1083	Lack of efficacy
RFID9801	Placebo	1085	Lack of efficacy
RFID9801	Placebo	1092	Lack of efficacy
RFID9801	Placebo	1099	Lack of efficacy
RFID9801	Placebo	1103	Lack of efficacy
RFID9801	Placebo	1116	Lack of efficacy
RFID9801	Placebo	1129	Lack of efficacy
RFID9801	Placebo	1148	Lack of efficacy
RFID9801	Placebo	1177	Lack of efficacy
RFID9801	Placebo	1178	Lack of efficacy
RFID9801	Placebo	2006	Lack of efficacy
RFID9801	Placebo	2030	Lack of efficacy
RFID9801	Placebo	2033	Lost to follow-up
RFID9801	Placebo	2083	Lack of efficacy
RFID9801	Placebo	2089	Lack of efficacy

Study Number	Treatment	Pt. No	Reason for Discontinuation
RFID9801	Placebo	2094	Lack of efficacy

Table 2 Patients Reporting Adverse Events Associated with Abnormal Liver Function Test

Study	Patient	Treatment	Preferred Term	Lab Parameter	Lab Data (U/L)	
					Day 1	Day 4
RFID9801	1041	Placebo	Aspartate aminotransferase increased	SGOT	17	80
RFID9801	1075	Placebo	Aspartate aminotransferase increased	SGOT	25	103
RFID9801	1114	Placebo	Aspartate aminotransferase increased	SGOT	13	57
RFID9801	2004	Placebo	Aspartate aminotransferase increased	SGOT	19 3	39 6
RFID9801	1031	Rifaximin 600 mg/day	Aspartate aminotransferase increased	SGOT	30	116
RFID9801	1131	Rifaximin 600 mg/day	Aspartate aminotransferase increased	SGOT	28	85
RFID9801	1169	Rifaximin 600 mg/day	Aspartate aminotransferase increased	SGOT	28	76
RFID9801	2026	Rifaximin 600 mg/day	Aspartate aminotransferase increased	SGOT	19 8	71 7
RFID9801	1041	Placebo	Alanine aminotransferase increased	SGPT	27	120
RFID9801	1114	Placebo	Alanine aminotransferase increased	SGPT	15	85

Table 3 Patients with Adverse Events Related to, but Not Limited To, Fatigue, Weakness, Tiredness

Study	Patient	Treatment	Preferred Term	Verbatim Term
RFID9601	012	Rifaximin 1200 mg/day	Fatigue	Fatigue
RFID9601	018	Rifaximin 1200 mg/day	Fatigue	Feels dehydrated, run down
RFID9601	034	Rifaximin 1200 mg/day	Fatigue	Tired achey, sad
RFID9601	044	Rifaximin 1200 mg/day	Weakness	"Shaky"
RFID9601	047	Rifaximin 1200 mg/day	Fatigue	Fatigue "feel tired"
RFID9601	053	Rifaximin 1200 mg/day	Fatigue	Fatigue
RFID9601	053	Rifaximin 1200 mg/day	Weakness	Weak lightheaded
RFID9601	060	Rifaximin 1200 mg/day	Fatigue	Tired, weak, headache

Study	Patient	Treatment	Preferred Term	Verbatim Term
RFID9601	060	Rifaximin 1200 mg/day	Weakness	Tired weak headache
RFID9601	076	Rifaximin 1200 mg/day	Fatigue	Tired
RFID9601	009	Rifaximin 1800 mg/day	Fatigue	Fatigue
RFID9601	014	Rifaximin 600 mg/day	Fatigue	Tired
RFID9601	075	Rifaximin 600 mg/day	Fatigue	Tired
RFID9601	075	Rifaximin 600 mg/day	Weakness	Weak
RFID9601	029	TMP/SMX	Weakness	Light-headed, weak
RFID9601	052	TMP/SMX	Fatigue	Tired, low energy short of breath
RFID9701	096	Ciprofloxacin 1000 mg/day	Malaise	General malaise
RFID9701	096	Ciprofloxacin 1000 mg/day	Myasthenic syndrome	Weakness
RFID9701	102	Ciprofloxacin 1000 mg/day	Asthenia	Very tired
RFID9701	089	Rifaximin 800 mg/day	Asthenia	Fatigue
RFID9701	101	Rifaximin 800 mg/day	Myasthenic syndrome	Weakness
RFID9701	186	Rifaximin 800 mg/day	Asthenia	Tiredness
RFID9701	200	Rifaximin 800 mg/day	Asthenia	Fatigue
RFID9801	1135	Placebo	Weakness	Weakness
RFID9801	2089	Placebo	Weakness	Weakness
RFID9801	3021	Placebo	Weakness	Weak
RFID9801	1005	Rifaximin 1200 mg/day	Fatigue	Very tired
RFID9801	1007	Rifaximin 1200 mg/day	Fatigue	Exhaustion
RFID9801	1093	Rifaximin 1200 mg/day	Muscle weakness NOS	Muscle weakness
RFID9801	1125	Rifaximin 1200 mg/day	Fatigue	Tiredness
RFID9801	1127	Rifaximin 1200 mg/day	Fatigue	Fatigue
RFID9801	3017	Rifaximin 1200 mg/day	Weakness	Weakness
RFID9801	1006	Rifaximin 600 mg/day	Weakness	Weakness
RFID9801	2028	Rifaximin 600 mg/day	Malaise	Continuing illness
RFID9801	3022	Rifaximin 600 mg/day	Weakness	Weak

Death summaries

Patient #28 63 year old Caucasian male who entered the study with a diagnosis of cirrhosis due to alcohol and recurrent hepatic encephalopathy, grade 3 He had a history of gastric cancer 9 years prior to study enrollment and heart failure with onset of one month prior to study enrollment Physical examination showed jaundice as the only reported abnormality The patient received only one day of study medication **(rifaximin 1200 mg/day)** and was removed from the study because of worsening of disease to grade 4 hepatic encephalopathy on study day 2, one day prior to death The cause of death was reported as hepatic failure that the investigator assessed as being unlikely related to study medication No concomitant medications were recorded The randomization code was broken for this patient by the investigator

Patient #31 50 year old Caucasian male who entered the study with a diagnosis of acute hepatic encephalopathy secondary to alcoholic cirrhosis He had a prior history remarkable for advanced hepatic cirrhosis, hepatomegaly was noted on physical examination Baseline laboratory evaluations revealed a hematocrit of 25%, hemoglobin of 9 g/dL and a total bilirubin of 10 7 mg/dL After receiving **rifaximin 1200 mg/day** for eight days the patient developed variceal bleeding with subsequent hematemesis The

patient was discontinued from the study the following day, after the ninth day of study drug The condition developed into hepatic and renal failure which led to the patient's death The investigator considered the events as not related to study drug

Patient #93 61 year old Caucasian male who entered the study with a diagnosis of acute hepatic encephalopathy with gastrointestinal hemorrhage, due to alcoholic cirrhosis Upon study entry, baseline laboratory values were remarkable for a hematocrit of 29% and a BUN of 60 mg/dL After two days **of rifaximin 1200 mg/day**, the patient was withdrawn from the study due to worsening hepatic encephalopathy and gastrointestinal hemorrhage The patient subsequently developed septic shock and died one day after discontinuing study drug The investigator considered the events as not related to study drug

Patient #11 64 year old Caucasian male who entered the study with a diagnosis of recurrent hepatic encephalopathy due to cirrhosis secondary to hepatitis C infection The patient also had a medical history of IDDM and idiopathic pulmonary hypertension Baseline laboratory values were remarkable for a creatinine of 2 6 mg/dL and serum potassium of 5 6 indicating functional renal failure After five days of **lactitol 6000 mg/day**, the patient was withdrawn from the study due to worsening hepatic encephalopathy Nine days after discontinuing study medication, the patient died from complications of hepatic cirrhosis and gastrointestinal bleeding The investigator considered the events as not related to study drug

Patient #91 41 year old Caucasian male who entered the study with a diagnosis of advanced liver cirrhosis and bilateral pneumonia that precipitated the onset of hepatic encephalopathy Physical examination upon study entry was significant for ascites The patient completed the study, however 19 days after study completion, the patient's pneumonia worsened and he subsequently died from the development of multi-organ failure The investigator considered the events as not related to study drug **(lactitol 6000 mg/day)**

Patient #96 63 year old Caucasian male patient who entered the study with a diagnosis of recurrent hepatic encephalopathy Physical exam was remarkable for the presence of ascites, jaundice and splenomegaly After five days of treatment with **lactitol 6000 mg/day**, the patient developed bacterial peritonitis and was withdrawn from further treatment on the study The patient died three days later from multi-organ failure subsequent to the advanced liver disease and bacterial peritonitis The investigator considered the events as not related to study drug, and considered the patient to have completed the study

Patient #16 55-year old female who had received **rifaximin 2400 mg/day** for 7 days, died of intra-abdominal bleeding 2 days after completing study One day after completing study, she had undergone embolization of the right liver lobe but remained critically ill and died early the next morning Primary cause of death was determined to be hepatocellular carcinoma and the investigator judged this as "definitely not" related to treatment

Patient #17 58-year old female who had received **rifaximin 1200 mg/day** for 8 days, died 4 days after completing the study as a result of acute renal failure, sepsis, pulmonary edema and decompensated liver disease The investigator judged these events as "definitely not" related to treatment During the study, the investigator had noted some evidence of the onset of renal failure This was attributed to sepsis caused by a spontaneous bacterial peritonitis She received diuretics and antibiotics

TABLE 18
Summary of Microbiological Results Study RFID9601

Subject No	Treatment	Pathogen	Microbiological Outcome	TMP Susceptibility	Rifaximin MIC (µg/mL)	
					Pretreatment	Posttreatment
5	Rifaximin-M	*Crytosporidium parvum*	Cure	****	Not done	Not done
8	Rifaximin-L	ETEC LT	Cure	Resistant	6 25	- -
11	Rifaximin L	ETEC ST/LT	Cure	Susceptible	12 5	--
13	TMP/SMX	ETEC ST/LT	Cure	Resistant	<0 098	---
15	Rifaximin-M	ETEC ST/LT	Failure	Susceptible	6 25	6 25
17	Rifaximin-L	*Shigella sonnei*	Cure	Susceptible	<0 098	--
19	Rifaximin-H	*Shigella sonnei*	Failure	Susceptible	<0 098	<0 098
27	Rifaximin-L	*Campylobacter jejuni*	Cure	****	12 5	---
		ETEC LT	Cure	Susceptible	25 0	---
30	Rifaximin-L	*Salmonella* Group C1	Cure	Susceptible	50 0	---
31	Rifaximin-M	ETEC ST	Cure	Resistant	25 0	---
35	Rifaximin-H	ETEC LT	Cure	Resistant	12 5	---
36	TMP/SMX	ETEC LT	Cure	Resistant	12 5	---
42	TMP/SMX	ETEC ST	Cure	Susceptible	12 5	
43	Rifaximin L	ETEC LT	Cure	Resistant	6 25	---
44	Rifaximin-M	*Salmonella* Group C2	Cure	Susceptible	12 5	---
45	TMP/SMX	*Salmonella* Group C1	Cure	Susceptible	12 5	---
52	TMP/SMX	ETEC ST/LT	Cure	Resistant	<0 098	---
55	TMP/SMX	ETEC LT	Cure	Resistant	25 0	-
56	Rifaximin-L	ETEC ST	Cure	Susceptible	12 5	---
57	Rifaximin-H	ETEC ST/LT	Cure	Resistant	3 125	---
61	TMP/SMX	ETEC ST/LT	Cure	Resistant	6 25	---
64	Rifaximin-H	*Salmonella* Group C1	Failure	Susceptible	6 25	6 25
65	Rifaximin L	ETEC ST	Cure	Susceptible	25 0	---
75	Rifaximin-L	*Campylobacter jejuni*	Cure	****	25 0	---
76	Rifaximin M	ETEC ST/LT	Failure	Susceptible	25 0	25 0
78	Rifaximin L	ETEC ST/LT	Cure	Resistant	6 25	--

ETEC = enterotoxigenic *Escherichia coli* LT = heat-labile ST = heat-stable
Rifaximin L = 200 mg rifaximin tid Rifaximin-M = 400 mg rifaximin tid, Rifaximin-H = 600 mg rifaximin tid
TMP/SMX = trimethoprim/sulfamethoxazole

TABLE 19
Microbiological Cure Rate by Pathogen (Study RFID9601)

	200 mg tid Rifaximin	400 mg tid Rifaximin	600 mg tid Rifaximin	TMP/SMX

Pathogen	No	No Eradicated (%)	No	No Eradicated (%)	No	No Eradicated (%)	No	No Eradicated (%)
Escherichia coli	7	7/7 (100 0%)	3	1/3 (33 3%)	2	2/2 (100 0%)	6	6/6 (100 0%)
Shigella sonnei	1	1/1 (100 0%)	0	---	1	0/1 (00 0%)	0	---
Salmonella Group C1	1	1/1 (100 0%)	0	---	1	0/1 (00 0%)	1	1/1 (100 0%)
Salmonella Group C2	0	--	1	1/1 (100 0%)	0	--	0	---
Campylobacter jejuni	2	2/2 (100 0%)	0	---	0	---	0	---
Crytosporidium parvum	0	---	1	1/1 (100 0%)	0	---	0	---
TOTAL	11	11/11 (100%)	5	3/5 (60%)	4	2/4 (50%)	7	7/7 (100%)

TABLE 22--Bacteriological Response for ITT Population (Study RFID9701)

Subject No	Treatment	Pathogen	Microbiological Outcome	Rifaximin MIC (μg/mL)	
				Pretreatment	Posttreatment
6	Ciprofloxacin	ETEC LT	Cure	16	----
12	Ciprofloxacin	ETEC LT	Cure	16	----
13	Ciprofloxacin	*Shigella flexneri*	Cure	16	---
22	Ciprofloxacin	ETEC ST	Cure	16	
25	Ciprofloxacin	ETEC ST	Cure	64	
26	Ciprofloxacin	ETEC LT	Cure	16	
27	Ciprofloxacin	ETEC ST/LT	Cure	16	---
32	Ciprofloxacin	ETEC ST	Cure	32	--
36	Ciprofloxacin	ETEC ST/LT	Cure	8	---
49	Ciprofloxacin	*Salmonella* species	Cure	Not done	----
		ETEC ST		32	- -
52	Ciprofloxacin	*Salmonella* Group C1	Cure	32	---
54	Ciprofloxacin	*Shigella flexneri*	Cure	32	-- -
62	Ciprofloxacin	ETEC ST/LT	Cure	8	----
65	Ciprofloxacin	*Shigella flexneri*	No Post	16	----
69	Ciprofloxacin	ETEC ST	Cure	16	---
70	Ciprofloxacin	*Shigella flexneri*	Cure	32	----
72	Ciprofloxacin	ETEC LT	Cure	16	----
73	Ciprofloxacin	*Shigella flexneri*	Cure	8	----
81	Ciprofloxacin	ETEC ST/LT	No Post	32	----
87	Ciprofloxacin	ETEC ST	Cure	16	----
91	Ciprofloxacin	ETEC ST	Cure	16	---
94	Ciprofloxacin	ETEC ST	Failure	32	32
116	Ciprofloxacin	ETEC ST/LT	Cure	32	----
117	Ciprofloxacin	ETEC ST	Cure	16	----
118	Ciprofloxacin	ETEC LT	Cure	32	----
120	Ciprofloxacin	ETEC ST	Cure	8	-- -
133	Ciprofloxacin	ETEC LT	Cure	64	----
135	Ciprofloxacin	ETEC ST/LT	Cure	64	---
140	Ciprofloxacin	ETEC ST	Cure	64	----
181	Ciprofloxacin	ETEC ST	Cure	32	----
182	Ciprofloxacin	ETEC ST	Cure	64	--
183	Ciprofloxacin	ETEC ST	Failure	16	16
184	Ciprofloxacin	*Salmonella* Group C1	Cure	64	---
		ETEC ST/LT		16	- -
190	Ciprofloxacin	ETEC ST/LT	Cure	16	----
191	Ciprofloxacin	*Crytosporidium parvum*	Failure	Not done	----
		ETEC ST		16	--
192	Ciprofloxacin	ETEC ST	Failure	16	0 25
193	Ciprofloxacin	*Salmonella* Group C2	Cure	16	---
198	Ciprofloxacin	*Giardia Lamblia*	Failure	Not done	---
201	Ciprofloxacin	ETEC ST	Cure	128	-
202	Ciprofloxacin	*Crytosporidium parvum*	Cure	Not done	----
203	Ciprofloxacin	*Salmonella* Group C2	Cure	32	-

212	Ciprofloxacin	ETEC ST/LT	Cure	32	----
216	Ciprofloxacin	*Shigella sonnei*	Cure	64	----
217	Ciprofloxacin	ETEC ST	Cure	64	----
141	Ciprofloxacin	*Salmonella* Group C1	No Post	32	----
147	Ciprofloxacin	ETEC ST	No Post	32	----
156	Ciprofloxacin	ETEC LT	Cure	16	----
163	Ciprofloxacin	ETEC LT	Cure	32	----

ETEC = enterotoxigenic *Escherichia coli*; LT = heat-labile, ST = heat-stable

No Post = No post-treatment culture test available

TABLE 23-Bacteriological Response for ITT Population (Study RFID9701)

Subject No	Treatment	Pathogen	Microbiological Outcome	Rifaximin MIC (µg/mL)	
				Pretreatment	Posttreatment
4	Rifaximin	ETEC ST/LT	Cure	32	----
15	Rifaximin	ETEC ST/LT	Cure	32	----
21	Rifaximin	ETEC ST/LT	Failure	8	---
23	Rifaximin	ETEC LT	Cure	2	----
24	Rifaximin	ETEC ST	Cure	32	----
30	Rifaximin	*Shigella flexneri*	Cure	64	----
45	Rifaximin	ETEC ST/LT	Cure	64	----
55	Rifaximin	*Crytosporidium parvum*	Cure	Not done	----
		ETEC ST/LT		128	---
57	Rifaximin	ETEC ST	Cure	2	-
58	Rifaximin	ETEC ST/LT	Cure	32	
59	Rifaximin	ETEC ST	Cure	16	--
64	Rifaximin	ETEC ST	Cure	8	---
66	Rifaximin	*Salmonella* Group C1	Cure	16	----
77	Rifaximin	ETEC LT	Cure	32	
79	Rifaximin	ETEC ST	Cure	2	- -
85	Rifaximin	ETEC LT	Cure	16	- -
86	Rifaximin	ETEC ST/LT	No Post	16	- -
95	Rifaximin	ETEC ST	Failure	32	32
99	Rifaximin	ETEC ST	Cure	32	---
100	Rifaximin	*Shigella sonnei*	Cure	16	- -
104	Rifaximin	ETEC ST	No Post	16	-- -
112	Rifaximin	ETEC ST/LT	Cure	4	- -
114	Rifaximin	ETEC ST	Cure	1	-
119	Rifaximin	*Campylobacter jejuni*	Cure	32	-
121	Rifaximin	*Shigella sonnei*	No Post	32	-
		ETEC ST		16	---
132	Rifaximin	ETEC ST	Cure	0 5	-- -
134	Rifaximin	*Shigella sonnei*	Cure	32	----
137	Rifaximin	ETEC ST	Failure	32	16
139	Rifaximin	ETEC ST	Cure	0 5	----
185	Rifaximin	ETEC ST	Failure	16	16
187	Rifaximin	*Salmonella* Group C2	Cure	16	----
189	Rifaximin	ETEC ST/LT	Cure	32	----
194	Rifaximin	ETEC ST	Failure	16	16
196	Rifaximin	ETEC ST	Failure	16	16
199	Rifaximin	ETEC ST	Cure	32	----
200	Rifaximin	ETEC ST	Cure	2	----
207	Rifaximin	ETEC ST	Cure	4	----
208	Rifaximin	*Shigella sonnei*	Cure	64	---
		ETEC LT		8	----
209	Rifaximin	ETEC ST/LT	Failure	16	8
210	Rifaximin	*Campylobacter jejuni*	Cure	32	---
		ETEC ST		16	- -
146	Rifaximin	*Salmonella* Group C1	No Post	32	----
162	Rifaximin	ETEC ST	No Post	32	----
164	Rifaximin	*Entamoeba histolytica*	No Post	Not done	----

ETEC = enterotoxigenic *Escherichia coli*, LT = heat-labile, ST = heat-stable
No Post = No post treatment culture test available

Table 54
Summary of Adverse Events Reported by ≥1% of HE Patients

Adverse Event	Rıfaxımın (N=104)	Control (N=53)
No of Patıents wıth AEs	32 (30 8%)	15 (28 3%)
Hepatıc encephalopathy	6 (5 8%)	3 (5 7%)
Nausea	6 (5 8%)	0
Dıarrhea nos	5 (4 8%)	1 (1 9%)
Gastrointestınal hemorrhage	4 (3 8%)	1 (1 9%)
Vomıtıng NOS	3 (2 9%)	2 (3 8%)
Anemıa	2 (1 9%)	0
Coagulatıon Abnormalıty	1 (1%)	0
Edema	1 (1%)	0
Abdomınal Paın NOS	1 (1%)	0
Abdomınal Paın Upper	1 (1%)	1 (1 9%)
Ascıtes	2 (1 9%)	0
Melena	1 (1%)	0
Perıtonıtıs	0	1 (1 9%)
Multıorgan Faılure	0	1 (1 9%)
Pyrexıa	2 (1 9%)	1 (1 9%)
Hepatıc Faılure	1 (1%)	0
Portal Hypertensıon	1 (1%)	0
Bronchopneumonıa	1 (1%)	0
Genıtal candıdıasıs	1 (1%)	0
Infectıon NOS	0	1 (1 9%)
Perıtonıtıs Bacterıal	0	1 (1 9%)
Pneumonıa	0	1 (1 9%)
Sepsıs	1 (1%)	0
Septıc Shock	1 (1%)	0
UTI	2 (1 9%)	1 (1 9%)
Aggressıon	1 (1%)	0
Endoscopy	1 (1%)	0
Paracentesıs abn	1 (1%)	0
Weıght Gaın	1 (1%)	0
Hyperkalemıa	0	1 (1 9%)
Hypokalemıa	1 (1%)	0
Muscle Cramps	1 (1%)	0
Grand Mal Seızure	1 (1%)	0
ARF	2 (1 9%)	1 (1 9%)
Penıle Dısorder	1 (1%)	0
Pleural Effusıon	1 (1%)	0
Respıratory dısorder	1 (1%)	0
Respıratory Tract Hemorraghe	1 (1%)	0
Dermatıtıs	1 (1%)	0
Prurıtus	1 (1%)	0
Hypertensıon NOS	0	1 (1 9%)

[a] Fisher Exact Test
Notes Control = lactitol treated patients (RFHE9701)

Adverse Events by Dose in HE Studies

The proportion of HE rifaximin patients who reported one or more adverse events was also statistically significant among the HE rifaximin dose groups (p=0 0126), however, there was no trend toward higher adverse event rates with a higher dose The rates for HE rifaximin dose groups were as follows 56% (10/18) for rifaximin 600 mg/day, 22% (15/69) for rifaximin 1200 mg/day, 41% (7/17) for rifaximin 2400 mg/day

The incidence of severe adverse events in rifaximin HE patients also did not appear to be dose-related between rifaximin 600 mg/day (2, 11%), 1200 mg/day doses (8, 12%), and 2400 mg/day (3, 18%),

Table 55
AEs by dose

AEs	Rifaximin ID 600 mg/day (N= 143)	Rifaximin HE 600 mg/day (N= 18)	Rifaximin ID 800 mg/day (N=93)	Rifaximin ID 1200 mg/day (N=145)	Rifaximin HE 1200 mg/day (N=69)	Rifaximin ID 1800 mg/day (N=19)	Rifaximin HE 2400 mg/day (N=17)
# Patients with Any AE	100 (70%)	10 (56%)	31 (33%)	104 (71%)	15 (22%)	8 (42%)	7 (41%)
# of AEs	194	26	47	220	20	14	15
Blood and Lymphatic System							
All	-	**2 (11%)**	-	-	-	-	**1 (6%)**
Anemia	-	2 (11%)	-	-	-	-	-
Coagulation Disorder	-	-	-	-	-	-	1 (6%)
Cardiac							
All	-	**1 (6%)**	1 (1%)	-	-	-	-
Edema	-	1 (6%)	-	-	-	-	-
Palpitations	-	-	1 (1%)	-	-	-	-
Ear and Labyrinth							
All	2 (1 4%)	-	1 (1%)	-	-	-	-
Earache	1 (0 7%)	-	-	-	-	-	-
Motion sickness	1 (0 7%)	-	-	-	-	-	-
Vertigo	-	-	1 (1%)	-	-	-	-
GI disorders							
All	**81 (57%)**	**5 (28%)**	**8 (9%)**	**85 (58%)**	**6 (9%)**	**4 (21%)**	**5 (29%)**
Abdominal distension	1 (0 7%)	-	-	2 (1 4%)	-	-	-
Abdominal Pain	21 (15%)	-	1 (1%)	29 (20%)	-	-	-
Upper Abd Pain	-	-	-	1 (0 7%)	-	1 (5%)	-
Ascites	-	2 (11%)	-	-	-	-	-
Constipation	9 (6%)	-	6 (7%)	3 (2%)	-	1 (5%)	-
Urgency	-	-	-	-	-	1 (5 %)	-
Diarrhea	2 (1 4%)	2 (11%)	-	2 (1 4%)	2 (3%)	-	1 (6%)

Dry Throat	1 (0 7%)	-	-	-	-	-	-
Dyspepsia	-	-	-	2 (1 4%)	-	-	-
Fecal abn	1 (0 7%)	-	-	1 (0 7%)	-	-	-
Fecal Inc	16 (11%)	-	-	21 (15%)	-	-	-
Flatulence	32 (22%)	-	1 (1%)	37 (26%)	-	-	-
GI Hemorraghe	-	-	-	-	3 (4%)	-	1 (6%)
Gingival Disorder	1 (0 7%)	-	-	-	-	-	-
Dry Lip	1 (0 7%)	-	-	-	-	-	-
Melena	-	-	-	-	-	-	1 (6%)
Nausea	18 (13%)	2 (11%)	-	23 (16%)	-	2 (11%)	4 (24%)
Proctalgia	-	-	-	1 (0 7%)	-	-	-
Sore Throat	2 (1 4%)	-	-	2 (1 4%)	-	-	-
Tenesmus	19 (13%)	-	-	15 (10%)	-	-	-
Vomiting	5 (4%)	1 (6%)	1 (1%)	5 (4%)	1 (1%)	1 (5%)	1 (6%)
General							
All	**15 (11%)**	1 (6%)	**5 (5%)**	**22 (15%)**	1 (1%)	1 (5%)	-
Hangover	1 (0 7%)	-	-	-	-	-	-
Asthenia	-	-	3 (3%)	-	-	-	-
Chest Pain	2 (1 4%)	-	-	1 (0 7%)	-	-	-
Fatigue	2 (1 4%)	-	-	10 (7%)	-	1 (5%)	-
Flu	-	-	1 (1%)	1 (0 7%)	-	-	-
Malaise	1 (0 7%)	-	-	-	-	-	-
Pain	1 (0 7%)	-	-	1 (0 7%)	-	-	-
Pyrexia	9 (6%)	1 (6%)	-	7 (5%)	1 (1%)	-	-
Rigors	-	-	1 (1%)	1 (0 7%)	-	-	-
Weakness	3 (2%)	-	-	4 (3%)	-	-	-
-Hepatobiliary							
All	-	-	-	-	2 (3%)	-	-
Hepatic Failure	-	-	-	-	1 (1%)	-	-
Portal Hypertension	-	-	-	-	1 (1%)	-	-
Immune system							
All	**4 (3%)**	1 (6%)	**5 (5%)**	**3 (2%)**	**3 (4%)**	**4 (21%)**	**2 (12%)**
Broncho pneumonia	-		-	-	1 (1%)	-	-
Genital Candidiasis	-	1 (6%)	-	-	-	-	-
HSV	-	-	1 (1%)	-	-	-	-
Infection	-	1 (6%)	-	-	-	-	-
Nasopharyngitis	3 (2%)	-	-	2 (1%)	-	3 (16%)	-
Pharyngitis	-	-	3 (3%)	-	-	-	-
Sepsis	-	-	-	-	1 (1%)	-	-
Septic Shock	-	-	-	-	1 (1%)	-	-
Sinusitis	-	-	-	1 (0 7%)	-	-	-
URI	1 (0 7%)	-	-	-	-	1 (5%)	-
UTI	-	-	-	-	-	-	2 (12%)
Viral Infection	-	-	2 (2 2%)	-	-	-	-
Trauma							
All	2 (1 4%)	-	-	1 (0 7%)	-	-	-
Bite	-	-	-	1 (0 7%)	-	-	-
Sunburn	2 (1 4%)	-	-	-	-	-	-
Laboratory							

All	**7 (5%)**	**3 (17%)**	-	**2 (1%)**	-	-	-
Increased AST	**4 (3%)**	-	-	-	-	-	-
Heme + Stool	1 (0 7%)	-	-	-	-	-	-
Hypertension	-	-	-	1 (0 7%)	-	-	-
Endoscopy	-	1 (6%)	-	-	-	-	-
Glycosuria	-	-	-	1 (0 7%)	-	-	-
Hematuria	**2 (1 4%)**	-	-	-	-	-	-
Paracentesis	-	1 (6%)	-	-	-	-	-
Weight Gain	-	1 (6%)	-	-	-	-	-
Metabolism and Nutritional							
All	**2 (1 4%)**	1 (6%)	1 (1%)	**2 (1%)**	-	-	-
Anorexia	1 (0 7%)	-	1 (1%)	-		-	-
Decreased Appetite	-	-	-	1 (0 7%)	-	-	-
Dehydration	1 (0 7%)	-	-	-	-	-	-
Hypokalemia	-	1 (6%)	-	1 (0 7%)	-	-	-
Musculoskeletal and Connective Tissue Disorders							
All	**2 (1 4%)**	1 (6%)	**3 (3%)**	**4 (3%)**	-	-	-
Back Pain	-	-	1 (1%)	1 (0 7%)	-	-	-
Muscle Cramps	-	1 (6%)	-	1 (0 7%)	-	-	-
Muscle twitches	-	-	-	1 (0 7%)	-		-
Muscle weakness	-	-	-	1 (0 7%)	-	-	-
Myalgia	2 (1 4%)	-	1 (1%)	-	-	-	-
Neck Pain	-	-	1 (1%)	-	-	-	-
Neck stiffness	-	-	-	1 (0 7%)	-	-	-
CNS disorders							
All	**18 (13%)**	2 (11%)	**16 (17%)**	**29 (20%)**	**4 (6%)**	1 (5%)	1 (6%)
Dizziness	1 (0 7%)	-	2 (2%)	5 (3%)	-	-	-
Grand Mail Seizure	-	1 (6%)	-	-	-	-	-
Headache	16 (11%)	-	**10 (11%)**	23 (16%)	-	1 (5%)	-
Hepatic Encephalopathy	-	1 (6%)	-	-	4 (5%)	-	1 (6%)
Insomnia	-	-	1 (1%)	-	-	-	-
Migraine	1 (0 7%)	-	1 (1%)	1 (0 7%)	-	-	-
Myasthenia	-	-	1 (1%)	-	-	-	-
Paresthesia	-	-	-	1 (0 7%)	-	-	-
Somnolence	-	-	2 (2%)	-	-	-	-
Taste Loss	1 (0 7%)	-	-	-	-	-	-
Psychiatric Disorders							
All	-	-	-	-	**1 (1%)**	-	-
Aggression	-	-	-	-	**1 (1%)**	-	-
Renal and UT Disorders							
All	**2 (1 4%)**	-	-	-	**1 (1%)**	-	1 (6%)
Polyuria	1 (0 7%)	-	-	-	-	-	-
ARF	-		-	-	**1 (1%)**	-	1 (6%)
Frequency	1 (0 7%)	-	-	-	-	-	-
Reproductive							
All	-	-	-	2 (1%)	**1 (1%)**	-	-
Dysmenorrhea	-	-	-	1 (0 7%)	-	-	-
Irregularity	-	-	-	1 (0 7%)	-	-	-

Penile Disorder	-	-	-	-	1 (1%)	-	-
Respiratory Tract Disorders							
All	**2 (1 4%)**	2 (11%)	-	1 (0 7%)	-	1 (5%)	-
Cough	-	-	-	-	-	1 (5%)	-
Dyspnea	1 (0 7%)	-	-	-	-	-	-
Nasal Congestion	-	-	-	1 (0 7%)	-	-	-
Pleural Effusion	-	1 (6%)	-	-	-	-	-
Respiratory disorder	-	1 (6%)	-	-	-	-	-
RT Hemorraghe	-	1 (6%)	-	-	-	-	-
Allergic Rhinitis	-	-	-	-	-	1 (5%)	-
Rhinorrhea	1 (0 7%)	-	-	-		-	-
Skin and ST Disorders							
All	1 (0 7%)	-	**2 (2%)**	-	-	-	**2 (12%)**
Clamminess	1 (0 7%)	-	-	-	-	-	-
Dermatitis	-	-	-	1 (0 7%)	-	-	1 (6%)
Pruritus	-	-	-	-	-	-	1 (6%)
Macular Rash		-	-	1 (0 7%)		-	
Maculopapular Rash	-	-	1 (1%)	-	-	-	-
Increased Sweating	-	-	1 (1%)	-	-	-	-
Vascular Disorders							
All	1 (0 7%)	-	-	1 (0 7%)	-	-	-
Hot flushes	1 (0 7%)	-	-	1 (0 7%)	-	-	-

TABLE 27

Bacteriological Response for Placebo ITT Population (Study RFID9801)

Subject No	Treatment	Pathogen	Microbiological Outcome	Rifaximin MIC (μg/mL)	
				Pretreatment	Posttreatment
1033	Placebo	ETEC ST	Cure	32	----
1035	Placebo	*Salmonella* Group C1	Cure	32	----
		ETEC ST/LT	Cure	8	----
1040	Placebo	ETEC ST	No Post	16	----
1044	Placebo	ETEC ST/LT	Cure	8	----
1051	Placebo	ETEC ST	Cure	64	----
1061	Placebo	ETEC ST/LT	Cure	64	----
1069	Placebo	ETEC ST/LT	Cure	4	----
1070	Placebo	ETEC LT	Cure	2	----
1074	Placebo	*Giardia lambila*	Cure	Not done	----
		ETEC ST	Cure	126	---
1075	Placebo	ETEC ST	Cure	256	----
1083	Placebo	*Shigella sonnei*	Cure	32	---
		ETEC ST	Cure	16	----
1106	Placebo	ETEC LT	Cure	128	--
1132	Placebo	*Salmonella* Group C2	Cure	16	--
		ETEC ST/LT	Failure	16	32
1147	Placebo	ETEC ST	Cure	256	----
1148	Placebo	ETEC ST/LT	Cure	32	----
1152	Placebo	ETEC ST/LT	Cure	8	-
1153	Placebo	ETEC ST	Cure	32	----
1162	Placebo	ETEC ST	Cure	8	---
1165	Placebo	ETEC ST	Cure	64	-
1173	Placebo	ETEC LT	Cure	16	-- -
1177	Placebo	ETEC ST	No Post	32	- --

2004	Placebo	*Giardia lambila*	Cure	Not done	----
		Shigella sonnei	Cure	64	----
		ETEC LT	Cure	64	----
2006	Placebo	ETEC LT	Cure	16	----
2007	Placebo	*Giardia lambila*	Cure	Not done	----
		Crytosporidium parvum	Cure	Note done	----
		ETEC ST/LT	Cure	32	----
2008	Placebo	*Crytosporidium parvum*	Failure	Not done	Not done
		ETEC ST	Cure	16	----
2021	Placebo	ETEC LT	Cure	32	----
		Aeromonas sobria	Cure	8	----
2024	Placebo	*Crytosporidium parvum*	Cure	Not done	----
		ETEC ST	Failure	64	64
2025	Placebo	*Giardia lambila*	No Post	Not done	- -
2030	Placebo	*Crytosporidium parvum*	Cure	Not done	----
2032	Placebo	ETEC ST/LT	Cure	16	----
2033	Placebo	ETEC LT	No Post	16	-- -

ETEC = enterotoxigenic *Escherichia coli* LT = heat-labile ST = heat-stable

No Post = No post treatment culture test available

TABLE 27 (Continued)
Bacteriological Response for Placebo ITT Population (Study RFID9801)

Subject No	Treatment	Pathogen	Microbiological Outcome	Rifaximin MIC (µg/mL)	
				Pretreatment	Posttreatment
2037	Placebo	ETEC ST	Cure	32	----
		Entamoeba histolytica	Cure	Not done	----
2072	Placebo	ETEC ST/LT	Failure	128	128
		Plesiomonas shigelloides	Cure	8	----
2076	Placebo	ETEC ST/LT	Failure	4	4
2083	Placebo	ETEC ST	Failure	16	16
		Crytosporidium parvum	Cure	Not done	----
2086	Placebo	ETEC LT	No Post	64	----
2089	Placebo	ETEC LT	Cure	32	- -
		Crytosporidium parvum	Cure	Not done	- --
2094	Placebo	ETEC LT	Failure	32	32
2096	Placebo	*Crytosporidium parvum*	No Post	Not done	----
2098	Placebo	ETEC LT	Cure	64	----
2100	Placebo	*Crytosporidium parvum*	Cure	Not done	---
		ETEC ST	No Post	64	----
2104	Placebo	*Crytosporidium parvum*	Cure	Not done	
		ETEC ST	Cure	4	-
2107	Placebo	*Crytosporidium parvum*	Failure	Not done	Not done
		Campylobacter coli	Cure	64	---
2110	Placebo	*Crytosporidium parvum*	Failure	Not done	Not done
2112	Placebo	ETEC ST/LT	Cure	8	-
2117	Placebo	*Vibrio parahemolyticus*	Cure	32	- -
3006	Placebo	ETEC ST/LT	Failure	128	128
3023	Placebo	ETEC LT	Failure	32	32
3028	Placebo	ETEC ST	Cure	16	
3036	Placebo	ETEC ST	Failure	4	4
3037	Placebo	ETEC ST	Cure	32	---
3038	Placebo	ETEC ST	Cure	64	---
3044	Placebo	ETEC LT	Cure	32	----
3070	Placebo	ETEC LT	Cure	64	----
3074	Placebo	*Campylobacter jejuni*	Failure	Not done	Not done
3084	Placebo	ETEC ST/LT	Cure	32	----
3091	Placebo	ETEC ST/LT	Cure	32	----
3095	Placebo	ETEC ST	Cure	64	----
3097	Placebo	ETEC LT	Cure	16	----
3108	Placebo	ETEC ST	Cure	32	----
3110	Placebo	ETEC LT	Cure	64	-- -

ETEC = enterotoxigenic *Escherichia coli*; LT = heat-labile, ST = heat-stable
No Post = No post-treatment culture test available

TABLE 28

Bacteriological Response for Rifaximin-600 mg ITT Population (Study RFID9801)

Subject No	Treatment	Pathogen	Microbiological Outcome	Rifaximin MIC (µg/mL)	
				Pretreatment	Posttreatment
1001	Rifaximin 600 mg	ETEC ST	Cure	Not done	----
1006	Rifaximin 600 mg	*Shigella sonnei*	Cure	16	---
1020	Rifaximin 600 mg	ETEC ST	Cure	16	----
1025	Rifaximin 600 mg	ETEC ST/LT	Cure	2	----
1031	Rifaximin 600 mg	*Crytosporidium parvum*	No Post	Not done	----
		ETEC LT	No Post	16	----
1036	Rifaximin 600 mg	ETEC ST	Cure	8	----
1042	Rifaximin 600 mg	ETEC ST/LT	Cure	32	----
1045	Rifaximin 600 mg	ETEC ST	Cure	16	- -
1052	Rifaximin 600 mg	ETEC ST/LT	No Post	32	- --
1056	Rifaximin 600 mg	*Crytosporidium parvum*	Cure	Not done	- -
		ETEC LT	Cure	32	----
1057	Rifaximin 600 mg	ETEC LT	Cure	16	---
1065	Rifaximin 600 mg	ETEC LT/ST	Cure	32	----
1079	Rifaximin 600 mg	ETEC ST	Cure	8	----
1087	Rifaximin 600 mg	*Shigella sonnei*	Cure	32	---
		ETEC LT	Cure	8	-- -
1097	Rifaximin 600 mg	*Salmonella* Group C1	Failure	32	8
1098	Rifaximin 600 mg	*Salmonella* Group C1	Cure	32	----
1118	Rifaximin 600 mg	ETEC LT	Cure	16	---
1128	Rifaximin 600 mg	ETEC ST	Cure	16	----
1131	Rifaximin 600 mg	ETEC ST/LT	Cure	32	----
1138	Rifaximin 600 mg	ETEC ST	Cure	128	----
1149	Rifaximin 600 mg	ETEC ST	Cure	32	----
1151	Rifaximin 600 mg	ETEC ST/LT	Cure	64	-- -
1161	Rifaximin 600 mg	ETEC ST/LT	Cure	32	--
1166	Rifaximin 600 mg	*Crytosporidium parvum*	Failure	Not done	Not done
		ETEC ST/LT	Cure	0 5	----
1169	Rifaximin 600 mg	ETEC ST	Failure	32	8
1180	Rifaximin 600 mg	ETEC LT	Cure	16	----
2001	Rifaximin 600 mg	*Crytosporidium parvum*	Cure	Not done	----
		ETEC ST/LT	Cure	32	----
2010	Rifaximin 600 mg	ETEC ST	Failure	16	32
2012	Rifaximin 600 mg	*Crytosporidium parvum*	Cure	Not done	----
2015	Rifaximin 600 mg	*Crytosporidium parvum*	Cure	Not done	----
		ETEC ST/LT	Cure	512	----
		Vibrio fluvialis	Cure	16	----
2023	Rifaximin 600 mg	*Crytosporidium parvum*	Failure	Not done	Not done
		ETEC ST	Cure	4	----
2026	Rifaximin 600 mg	*Crytosporidium parvum*	Cure	Not done	----
		Shigella flexneri	Cure	32	----
		ETEC ST/LT	Cure	32	----

ETEC = enterotoxigenic *Escherichia coli*, LT = heat-labile ST = heat-stable

No Post = No post treatment culture test available

TABLE 28 (Continued)

Bacteriological Response for Rifaximin-600 mg ITT Population (Study RFID9801)

Subject No	Treatment	Pathogen	Microbiological Outcome	Rifaximin MIC (µg/mL)	
				Pretreatment	Posttreatment
2028	Rifaximin 600 mg	*Crytosporidium parvum*	Failure	Not done	Not done
		ETEC ST/LT	Failure	128	128
2034	Rifaximin 600 mg	*Giardia lambila*	Failure	Not done	Not done
2035	Rifaximin 600 mg	ETEC ST	Cure	32	----
2039	Rifaximin 600 mg	*Crytosporidium parvum*	Cure	Not done	----
2071	Rifaximin 600 mg	ETEC ST/LT	Cure	16	----
2075	Rifaximin 600 mg	*Crytosporidium parvum*	Cure	Not done	----
		ETEC ST	Cure	32	----
2078	Rifaximin 600 mg	ETEC ST/LT	No Post	128	
		Giardia lambila	No Post	Not done	
2082	Rifaximin 600 mg	ETEC ST	Cure	64	
2084	Rifaximin 600 mg	ETEC ST/LT	No Post	64	--
2087	Rifaximin 600 mg	ETEC LT	Missing	64	---
2090	Rifaximin 600 mg	*Crytosporidium parvum*	Cure	Not done	---
2093	Rifaximin 600 mg	*Crytosporidium parvum*	Cure	Not done	--
		Entamoeba histolytica	Cure	Not done	
2095	Rifaximin 600 mg	*Campylobacter jejuni*	Failure	16	64
		ETEC LT	Cure	64	--
2097	Rifaximin 600 mg	*Crytosporidium parvum*	No Post	Not done	-
		Campylobacter jejuni	Cure	8	---
2102	Rifaximin 600 mg	*Crytosporidium parvum*	Cure	Not done	----
2105	Rifaximin 600 mg	*Crytosporidium parvum*	Cure	Not done	----
2109	Rifaximin 600 mg	*Crytosporidium parvum*	Failure	Not done	Not done
		Shigella flexneri	Failure	16	16
2113	Rifaximin 600 mg	*Crytosporidium parvum*	Cure	Not done	- -
2116	Rifaximin 600 mg	ETEC LT	Failure	16	32
3005	Rifaximin 600 mg	ETEC ST	Failure	16	16
3007	Rifaximin 600 mg	ETEC ST	Failure	8	16
3015	Rifaximin 600 mg	*Giardia lambila*	Cure	Not done	----
3018	Rifaximin 600 mg	ETEC ST/LT	Failure	32	32
3020	Rifaximin 600 mg	ETEC ST	Failure	32	32
3045	Rifaximin 600 mg	ETEC LT	Cure	16	- -
3050	Rifaximin 600 mg	ETEC LT	Failure	32	32
3057	Rifaximin 600 mg	ETEC LT	Failure	32	32
3058	Rifaximin 600 mg	ETEC ST/LT	Cure	32	----
3067	Rifaximin 600 mg	*Giardia lambila*	Cure	Not done	----
3072	Rifaximin 600 mg	ETEC ST/LT	Cure	8	----
3076	Rifaximin 600 mg	*Giardia lambila*	Cure	Not done	----
3079	Rifaximin 600 mg	*Giardia lambila*	Cure	Not done	--
3090	Rifaximin 600 mg	ETEC ST	Failure	64	64
3092	Rifaximin 600 mg	ETEC ST/LT	Cure	32	-- -
3094	Rifaximin 600 mg	ETEC ST/LT	Cure	64	----
3105	Rifaximin 600 mg	ETEC ST	Cure	32	-
3113	Rifaximin 600 mg	ETEC ST	Cure	32	-
3118	Rifaximin 600 mg	ETEC ST	Cure	16	-
3120	Rifaximin 600 mg	ETEC ST/LT	Cure	32	

ETEC = enterotoxigenic *Escherichia coli* LT = heat-labile ST = heat-stable

No Post = No post treatment culture test available

TABLE 29

Bacteriological Response for Rifaximin-1200 mg ITT Population (Study RFID9801)

Subject No	Treatment	Pathogen	Microbiological Outcome	Rifaximin MIC (μg/mL)	
				Pretreatment	Posttreatment
1024	Rifaximin 1200 mg	*Shigella sonnei*	Cure	4	---
		ETEC ST	Cure	128	---
1034	Rifaximin 1200 mg	*Shigella flexneri*	Failure	32	32
		ETEC LT	Cure	32	---
1046	Rifaximin 1200 mg	*Salmonella* Group C1	Cure	32	---
		ETEC ST	Cure	8	---
1047	Rifaximin 1200 mg	ETEC ST/LT	Cure	16	---
1064	Rifaximin 1200 mg	ETEC ST	Failure	8	16
1071	Rifaximin 1200 mg	*Giardia lambila*	Cure	Not done	---
1073	Rifaximin 1200 mg	ETEC ST	Cure	128	- --
1076	Rifaximin 1200 mg	*Salmonella* Group C1	Failure	32	16
1082	Rifaximin 1200 mg	*Salmonella* Group C2	Failure	8	32
1084	Rifaximin 1200 mg	ETEC LT	Cure	16	---
1086	Rifaximin 1200 mg	*Plesiomonas shigelloides*	Cure	4	---
1102	Rifaximin 1200 mg	ETEC ST	Cure	4	---
1105	Rifaximin 1200 mg	ETEC LT	Cure	4	
1127	Rifaximin 1200 mg	*Salmonella* Group C1	Cure	32	
1130	Rifaximin 1200 mg	*Salmonella* Group C2	Cure	32	---
1145	Rifaximin 1200 mg	ETEC ST	Cure	32	--
1156	Rifaximin 1200 mg	*Crytosporidium parvum*	Failure ?	Not done	--
1167	Rifaximin 1200 mg	ETEC ST/LT	Cure	32	---
1172	Rifaximin 1200 mg	*Crytosporidium parvum*	Cure	Not done	---
2005	Rifaximin 1200 mg	*Entamoeba histolytica*	Cure	Not done	--
		ETEC ST/LT	Cure	1	- -
2009	Rifaximin 1200 mg	ETEC ST	Failure	16	16
2011	Rifaximin 1200 mg	*Salmonella* Group C2	No Post	64	---
		ETEC ST/LT	No Post	128	---
		Vibrio fluvialis	Not Post	8	---
2014	Rifaximin 1200 mg	ETEC LT	Cure	64	----
2022	Rifaximin 1200 mg	*Crytosporidium parvum*	Cure	Not done	-- -
		ETEC ST/LT	Failure	16	16
2027	Rifaximin 1200 mg	ETEC ST	Cure	32	----
2029	Rifaximin 1200 mg	*Crytosporidium parvum*	Failure	Not done	Not done
		Entamoeba histolytica	Cure	Not done	---
		ETEC ST	Cure	64	---
2036	Rifaximin 1200 mg	*Crytosporidium parvum*	Cure	Not done	---
		ETEC LT	Failure	32	32
2038	Rifaximin 1200 mg	ETEC LT	Cure	64	----
2073	Rifaximin 1200 mg	ETEC ST	Failure	32	64
		Aeromonas hydrophila	Cure	16	---

ETEC = enterotoxigenic *Escherichia coli*; LT = heat-labile, ST = heat-stable

No Post = No post treatment culture test available

TABLE 29 (Continued)
Bacteriological Response for Rifaximin-1200 mg ITT Population (Study RFID9801)

Subject No	Treatment	Pathogen	Microbiological Outcome	Rifaximin MIC (μg/mL)	
				Pretreatment	Posttreatment
2077	Rifaximin 1200 mg	ETEC LT	No Post	64	---
		Giardia lambila	No Post	Not done	---
		Crytosporidium parvum	No Post	Not done	---
2080	Rifaximin 1200 mg	*Crytosporidium parvum*	Failure	Not done	Not done
		ETEC ST	Cure	4	---
2081	Rifaximin 1200 mg	ETEC ST	Failure	16	32
2085	Rifaximin 1200 mg	*Crytosporidium parvum*	No Post	Not done	---
		ETEC LT	Cure	8	---
2091	Rifaximin 1200 mg	*Crytosporidium parvum*	Cure	Not done	--
2092	Rifaximin 1200 mg	*Crytosporidium parvum*	No Post	Not done	---
		Entamoeba histolytica	No Post	Not done	---
2101	Rifaximin 1200 mg	*Crytosporidium parvum*	Failure	Not done	Not done
2106	Rifaximin 1200 mg	*Crytosporidium parvum*	Failure	Not done	Not done
		Vibrio parahaemolyticus	Cure	16	---
2108	Rifaximin 1200 mg	*Crytosporidium parvum*	Failure	Not done	Not done
		ETEC ST	Failure	16	16
2111	Rifaximin 1200 mg	ETEC LT	No Post	16	- -
2114	Rifaximin 1200 mg	*Crytosporidium parvum*	Failure	Not done	Not done
2118	Rifaximin 1200 mg	ETEC LT	Failure	32	32
		Salmonella Group C1	Cure	32	---
3002	Rifaximin 1200 mg	ETEC ST	Failure	16	32
3017	Rifaximin 1200 mg	ETEC ST/LT	Cure	8	---
3019	Rifaximin 1200 mg	ETEC ST	Cure	64	---
3026	Rifaximin 1200 mg	ETEC ST/LT	Cure	64	---
3047	Rifaximin 1200 mg	ETEC ST	Cure	32	---
3048	Rifaximin 1200 mg	ETEC ST/LT	Cure	32	---
3054	Rifaximin 1200 mg	ETEC ST/LT	Failure	16	16
3055	Rifaximin 1200 mg	*Shigella* species	Cure	Not done	---
3072	Rifaximin 1200 mg	ETEC ST	Failure	16	16
3083	Rifaximin 1200 mg	ETEC ST/LT	Cure	32	---
3088	Rifaximin 1200 mg	ETEC ST	Cure	32	32
3103	Rifaximin 1200 mg	*Giardia lambila*	Failure	Not done	Not done
		ETEC LT	Cure	8	---
3111	Rifaximin 1200 mg	ETEC LT	Cure	32	---
3115	Rifaximin 1200 mg	ETEC LT	Cure	32	---

ETEC = enterotoxigenic *Escherichia coli*, LT = heat-labile, ST = heat-stable
No Post = No post treatment culture test available

Subjects with Newly Isolated Pathogens (Study RFID9801)

Subject No	Treatment	New Pathogen	Rifaximin MIC (μg/mL)
1023	Placebo	ETEC ST	8
1044	Placebo	ETEC LT	16
1069	Placebo	ETEC LT	4
1103	Placebo	ETEC LT	4
1135	Placebo	ETEC ST	64
1141	Placebo	ETEC LT	16
2004	Placebo	*Crytosporidium parvum*	Not done
2006	Placebo	*Crytosporidium parvum*	Not done
2008	Placebo	ETEC LT	16
2013	Placebo	ETEC ST	32
2018	Placebo	ETEC ST	64
2021	Placebo	ETEC ST/LT	32

2037	Placebo	ETEC ST/LT	32
2076	Placebo	*Salmonella* Group C2	16
2079	Placebo	*Crytosporidium parvum*	Not done
		Entamoeba histolytica	Not done
2083	Placebo	*Campylobacter coli*	32
2107	Placebo	*Salmonella* Group C1	8
2112	Placebo	ETEC LT	16
2115	Placebo	*Salmonella* Group C1	16
		Vibrio fluvialis	32
2117	Placebo	ETEC LT	64
3011	Placebo	ETEC ST	32
3021	Placebo	ETEC ST	256
3028	Placebo	ETEC ST/LT	16
3097	Placebo	ETEC ST/LT	32

ETEC = enterotoxigenic *Escherichia coli* LT = heat-labile ST = heat-stable

TABLE 26 (Continued)
Subjects with Newly Isolated Pathogens (Study RFID9801)

Subject No	Treatment	New Pathogen	Rifaximin MIC (µg/mL)
1028	Rifaximin 600 mg	ETEC LT	8
1065	Rifaximin 600 mg	*Giardia lambila*	Not done
		ETEC LT	Not done
1067	Rifaximin 600 mg	ETEC ST	4
1110	Rifaximin 600 mg	*Campylobacter jejuni*	64
		Giardia lambila	Not done
1128	Rifaximin 600 mg	*Crytosporidium parvum*	Not done
		Aeromonas hydrophila	16
1149	Rifaximin 600 mg	ETEC LT	32
2001	Rifaximin 600 mg	ETEC LT	32
2010	Rifaximin 600 mg	*Giardia lambila*	Not done
2015	Rifaximin 600 mg	ETEC LT	512
2034	Rifaximin 600 mg	*Crytosporidium parvum*	Not done
2035	Rifaximin 600 mg	*Crytosporidium parvum*	Not done
2039	Rifaximin 600 mg	ETEC LT	16
2075	Rifaximin 600 mg	*Salmonella* Group C2	64
2087	Rifaximin 600 mg	*Crytosporidium parvum*	Not done
2090	Rifaximin 600 mg	ETEC LT	32
2093	Rifaximin 600 mg	ETEC LT	16
2097	Rifaximin 600 mg	ETEC LT	32
2109	Rifaximin 600 mg	ETEC ST/LT	64
3015	Rifaximin 600 mg	ETEC ST	32
3031	Rifaximin 600 mg	ETEC ST	64
3051	Rifaximin 600 mg	ETEC ST/LT	16
3058	Rifaximin 600 mg	ETEC LT	32
3072	Rifaximin 600 mg	ETEC LT	8
3092	Rifaximin 600 mg	ETEC LT	32
1108	Rifaximin 1200 mg	ETEC ST/LT	64
1117	Rifaximin 1200 mg	ETEC ST	16
1145	Rifaximin 1200 mg	ETEC ST/LT	32
1146	Rifaximin 1200 mg	ETEC ST	Not done
1156	Rifaximin 1200 mg	ETEC ST	32
1157	Rifaximin 1200 mg	ETEC ST	64
1160	Rifaximin 1200 mg	ETEC ST	32
1167	Rifaximin 1200 mg	ETEC ST	64
3114	Rifaximin 1200 mg	ETEC ST/LT	32
2002	Rifaximin 1200 mg	*Crytosporidium parvum*	Not done
2014	Rifaximin 1200 mg	ETEC ST/LT	64
2017	Rifaximin 1200 mg	ETEC ST	64
2027	Rifaximin 1200 mg	*Campylobacter jejuni*	32
3017	Rifaximin 1200 mg	ETEC ST	8
3060	Rifaximin 1200 mg	ETEC ST/LT	8
3088	Rifaximin 1200 mg	ETEC ST/LT	32
3089	Rifaximin 1200 mg	ETEC ST/LT	32
3093	Rifaximin 1200 mg	ETEC ST	16
3099	Rifaximin 1200 mg	ETEC ST/LT	32
3100	Rifaximin 1200 mg	ETEC ST/LT	64

ETEC = enterotoxigenic *Escherichia coli*, LT = heat-labile, ST = heat-stable

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Medical Officer's Review of NDA 21-361(N 000 SU)

4 Month Safety Update
LUMENAX™ (rifaximin)

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

Escherichia coli (

Applicant Salix Pharmaceuticals

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

Date of Submission April 19, 2002
CDER Stamp Date April 23, 2002
Date Submission received by reviewer May 10, 2002
Date Review Begun May 13, 2002
Date Review Completed May 14, 2002

Drug Name Rifaximin

Proprietary Name LUMENAX™

Pharmacologic Category Rifamycin

Safety Update

The reporting period of this 4-month safety update is November 11, 2000 through February 18, 2002 No studies in infectious diarrhea, including traveler's diarrhea, were ongoing, initiated or completed Data from one ongoing double blind, randomized, comparative study in hepatic encephalopathy was included in the update

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

When adverse event data were pooled for the three ID studies (RFID9801, RFID9701 and RFID9601), there was no difference in the adverse event rate for ID rifaximin patients compared to ID control patients The incidence of fatigue was higher for the ID rifaximin group than for the ID control group (ID rifaximin rate = 3%, ID control rate = 0 4%,)

There were no associated symptoms such as lethargy, anemia or other CNS events indicating that this may be a chance finding rather than a clinically significant pattern

AEs reported for 2% or more of the ID rifaximin and ID control patients, respectively, were flatulence (18%, 17%), abdominal pain (13%, 10%), headache (13%, 10%), nausea (11%, 9 1%), fecal incontinence (9%, 8%), tenesmus (9%, 8%), constipation (5%, 4%), pyrexia (4%, 5%), fatigue (3%, 0 4%), vomiting (3%, 3%), nasopharyngitis (2%, 0 4%), and dizziness (exc vertigo) (2%, 4%)

Adverse events reported for ≥ 1% and < 2% of the ID rifaximin or ID control patients, respectively, were weakness (2%, 2%), AST increase (1%, 2%), sore throat (1%, 0%), and diarrhea (1%, 3%),

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

The applicant provided data from an ongoing phase III, double blind, multicenter, multinational study in adult patients with hepatic encephalopathy (HE) intolerant to lactulose (RIF/HE/INT/99) The study was designed to investigate the clinical effectiveness and tolerability of a 14-day treatment with rifaximin (400 mg PO TID, 1200 mg/day total dose) or placebo in patients suffering from HE intolerant to lactulose or lactitol

As of February 18, 2002, 71 of the 72 patients randomized to receive treatment with rifaximin or placebo have been treated The subjects were primarily Caucasian (94 4%), male (59 2%), and all were between the ages of 28 and 76 years (median 52 years)

18/71 patients (25 4%) reported at least one AE Most were from the GI (9, 12 7%) or the GU tracts (4, 5 6%) AEs reported in more than one patient included diarrhea (3), hepatic function abnormal (2), and pruritus (2)

10 subjects (14%) reported treatment related AEs These included diarrhea (3), abdominal distension, flatulence, dyspepsia, nausea, constipation, lower extremity edema, pyrexia, increased Cr, increased potassium, increased BUN, increased uric acid, fluid retention, dizziness, headache, insomnia, and increased frequency (1 each) There were also 2 reports of pruritus

One death (06-024) occurred after serious adverse events judged unrelated to treatment (Acute hepatic insufficiency, acute renal insufficiency, and viral infection)

Four additional patients (02-005, 04-089, 21-107, and 21-112) reported serious AEs none of which was judged as treatment related These SAEs included bradycardia, peritoneal hemorrhage, and hepatic insufficiency (02-005), gastrointestinal bleeding rupture of esophageal varices (04-089), renal stone (21-107), and refractory ascites (21-112)

5 patients, including the patient who died (04-106, 04-074, 06-24, 20-066, and 21-107), discontinued treatment because of an AE These included diarrhea (04-016), gastrointestinal infection (04-074), acute hepatic insufficiency, acute renal insufficiency, viral infection (06-024), abdominal distention (20-066), and renal stone (21-107)

Medical Officer's Comment *The reported AEs were similar to those reported in the previously reviewed HE studies and were not unexpected There does not appear to be a relationship between rifaximin and the AEs*

Spontaneous, Postmarketing Surveillance Summary

No spontaneous postmarketing reports were received during the reporting period

There have been no additional marketing approvals received for rifaximin nor has rifaximin been withdrawn from any country for which a marketing authorization was previously obtained

Publications

There were no new clinical publications on rifaximin during the reporting period

Nonclinical Data

No nonclinical toxicology studies were initiated or completed during the reporting period

Conclusions

Blinded adverse event data from the ongoing study (RIF/HE/INT/99) in 71 patients suffering from HE were consistent with the AE data previously reported in the ISS for HE patients treated with rifaximin in studies RFHE9701 and RFHE9702 The reported events were consistent with the underlying disease processes

There are no ongoing studies in infectious diarrhea and no changes to the conclusion previously drawn regarding the safety of rifaximin in an adult population suffering from traveler's diarrhea

Regina Alivisatos, MD
DSPIDP, HFD-590

Concurrence only
HFD-590/DIVDir/AlbrechtR

Cc
Orig NDA 21-361
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HFD-590/MTL/CoxE
HFD-590/CSO/WillardD
HFD-590/Micro/Dionne
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