TABLE 6
Rate of Emergence of Spontaneous Mutants
Anaerobic Strains (Wilkins-Chalgren Agar)

Microorganism		Rifaximin	Vancomycin
Clostridium difficile Pis	2 x MIC	1×10^{-8}	0
	4 x MIC	0	0
	8 x MIC	0	0
Clostridium difficile Man	2 x MIC	0	0
	4 x MIC	0	0
	8 x MIC	0	0
Clostridium perfringens 1	2 x MIC	$>10^{-6}$	0
	4 x MIC	9.3×10^{7}	0
	8 x MIC	9.6×10^{7}	0
Clostridium perfringens 2	2 x MIC	$>10^{-6}$	0
	4 x MIC	7.2×10^{-6}	0
	8 x MIC	1.3×10^{7}	0
Fusobacterium nucleatum 1	2 x MIC	$>10^{-6}$	nt
	4 x MIC	9.3×10^{7}	
	8 x MIC	9.6×10^{7}	
Fusobacterium nucleatum 2	2 x MIC	$>10^{-6}$	nt
	4 x MIC	7.2×10^{6}	
	8 x MIC	1.3×10^{7}	
Bacteroides distasonis 1	2 x MIC	0	nt
	4 x MIC	0	
	8 x MIC	0	
Bacteroides distasonis 2	2 x MIC	0	nt
	4 x MIC	0	
	8 x MIC	0	
Bacteroides fragilis 1	2 x MIC	1.7×10^{7}	nt
	4 x MIC	1×10^{-8}	
	8 x MIC	1×10^{-8}	
Bacteroides fragilis 2	2 x MIC	5×10^{-8}	nt
	4 x MIC	4×10^{-8}	
	8 x MIC	4×10^{-8}	
Peptostreptococcus magnus 1	2 x MIC	0	0
	4 x MIC	0	0
	8 x MIC	0	0
Peptostreptococcus magnus 2	2 x MIC	0	0
	4 x MIC	0	0
	8 x MIC	0	0
Peptostreptococcus micros 1	2 x MIC	0	0
	4 x MIC	0	0
	8 x MIC	0	0
Peptostreptococcus micros 2	2 x MIC	0	0
	4 x MIC	0	0
	8 x MIC	0	0

nt = Not tested

The data in the above table indicate that vancomycin-resistant strains were not selected

Rifaximin-resistant *Clostridium difficile* clones were not found except for one isolate which expressed mutants at 2 x MIC with a frequency of 1 x 10^{-8} Drug resistant mutants of *Clostridium perfringens* were easily selected at 2 x MIC (incidence >10^{-6}), and with a rate ranging from 7 2 x 10^{-6} (4 x MIC) to 1 3 x 10^{7} (8 x MIC) under more stringent experimental conditions Similar results were obtained with *Fusobacterium nucleatum* Spontaneous rifaximin-resistant mutants of *Bacteroides fragilis* were found with an incidence ranging from 1 7 x 10^{7} to 1 x 10^{-8} Rifaximin resistant mutants were not detected with the remaining species examined (*B distasonis, P magnus,* and *P micros*)

The same experiment was repeated using six *Clostridium difficile* isolates and employing blood-supplemented Wilkins-Chalgren agar This reduced the generation time for the organism Under these conditions rifaximin-resistant mutants were found at the lowest drug concentration studied (2 x MIC) with an incidence of 1 x 10^{-8} in two of the six isolates employed These results are not much different from those seen without blood-supplementation of the agar

A similar experiment was performed using aerobic bacteria High bacterial inocula (10^{8}-10^{10} cfu/mL) were added to Mueller-Hinton agar containing each antibiotic at various concentrations above the MIC (2, 4, and 8 times) After incubation at 37 C for 24 hours in aerobic and 36-48 hours under anaerobic conditions, surviving colonies were counted The frequency of resistant mutants to the drug was calculated as the ratio of the number of resistant cells compared to the number of cells in the original inoculum The results for Gram-positive cocci are shown in TABLE 7 No vancomycin-resistant mutants were found in this experiment TABLE 8 gives the results for Gram-negative bacteria

TABLE 7
Rate of Emergence of Spontaneous Mutants
Aerobic Gram-Positive Cocci

Microorganism		Rifaximin Aerobic	Rifaximin Anaerobic	Neomycin Aerobic	Neomycin Anaerobic
Staphylococcus aureus (MR)	2 x MIC	1.7×10^{-6}	6×10^{-8}	9×10^{-8}	nt
	4 x MIC	1.1×10^{7}	4×10^{-8}	nt	
	8 x MIC	1×10^{-8}	1×10^{-8}	nt	
Staphylococcus aureus (MR)	2 x MIC	1.2×10^{7}	1.1×10^{7}	6×10^{-6}	nt
	4 x MIC	2.3×10^{7}	1.1×10^{7}	4.1×10^{-6}	
	8 x MIC	1.6×10^{-8}	8×10^{-8}	3.2×10^{-6}	
Staphylococcus aureus (MS)	2 x MIC	1×10^{-6}	5×10^{-8}	6.5×10^{7}	6.2×10^{7}
	4 x MIC	8.7×10^{7}	1×10^{-8}	6.3×10^{7}	1.9×10^{7}
	8 x MIC	8.7×10^{-8}	0	5×10^{-8}	1.8×10^{7}
Staphylococcus aureus (MS)	2 x MIC	1.8×10^{-6}	1.1×10^{7}	2.6×10^{-6}	1×10^{-8}
	4 x MIC	2.6×10^{7}	5×10^{-8}	1.1×10^{-6}	0
	8 x MIC	8×10^{-8}	0	4×10^{7}	0
Enterococcus faecalis 1	2 x MIC	5×10^{-6}	1×10^{-6}	nt	nt
	4 x MIC	2.3×10^{-6}	1.9×10^{7}		
	8 x MIC	1.2×10^{8}	9×10^{8}		
Enterococcus faecalis 2	2 x MIC	1.3×10^{-8}	1.2×10^{7}	nt	nt
	4 x MIC	0	9×10^{8}		
	8 x MIC	0	0		
Enterococcus faecium 1	2 x MIC	$>10^{5}$	1.5×10^{7}	nt	nt
	4 x MIC	2.3×10^{7}	9×10^{-8}		
	8 x MIC	1.1×10^{-8}	0		
Enterococcus faecium 2	2 x MIC	$>10^{5}$	1×10^{-8}	1.6×10^{-6}	nt
	4 x MIC	3.2×10^{7}	1×10^{-8}	nt	
	8 x MIC	1.1×10^{-8}	0		

nt = not tested (MIC ≥ 64 µg/mL) MR = methicillin-resistant MS = methicillin-susceptible

The data in the above table demonstrate that under aerobic conditions the incidence of drug-resistant mutants ranged from 1.7×10^{-6} (2 x MIC) to 1×10^{-8} (8 x MIC) Under anaerobic conditions the figures varied from 1.1×10^{7} to 1×10^{-8} Under both aerobic and anaerobic conditions, spontaneous rifaximin-resistant enterococci arose in an unpredictable way depending on the strain tested and on the antibiotic level used

Spontaneous mutations can easily be detected when a low concentration of drug is present At higher concentrations rates are lower Rates also appear somewhat lower under anaerobic conditions This is probably due to the slower growth rate under anaerobic conditions Even at 8 x MIC the spontaneous mutation rate is higher than seen with many other drugs Rifaximin is probably similar to rifampin in that mutations may occur rapidly with use This may not be a problem, however, since this drug will not be used systemically and a very high concentration of the drug will be present at the site of infection

TABLE 8
Rate of Emergence of Spontaneous Mutants (Aerobic Gram-Negative Bacteria)

Microorganism		Rifaximin Aerobic	Rifaximin Anaerobic	Neomycin Aerobic	Neomycin Anaerobic
Citrobacter freundii 1438	2 x MIC	4×10^{-8}	nt	0	0
	4 x MIC	0		0	0
	8 x MIC	0		0	0
Citrobacter freundii 1539	2 x MIC	5×10^{7}	nt	1×10^{-8}	0
	4 x MIC	0		0	0
	8 x MIC	0		0	0
Providencia rettgeri 141	2 x MIC	2×10^{-8}	3.1×10^{7}	0	nt
	4 x MIC	0	0	0	
	8 x MIC	0	0	0	
Providencia rettgeri 187	2 x MIC	4×10^{-8}	1×10^{-8}	3×10^{7}	nt
	4 x MIC	3×10^{-8}	0	2×10^{-8}	
	8 x MIC	1×10^{-8}	0	0	
Morganella morganii 1	2 x MIC	1×10^{-8}	2×10^{-8}	5×10^{-8}	0
	4 x MIC	0	0	0	0
	8 x MIC	0	0	0	0
Morganella morganii 2	2 x MIC	1.3×10^{7}	$>10^{5}$	6×10^{-8}	0
	4 x MIC	3×10^{-8}	4.2×10^{7}	0	0
	8 x MIC	2×10^{8}	3×10^{7}	0	0
Proteus mirabilis 1	2 x MIC	3.5×10^{7}	0	nt	nt
	4 x MIC	1.5×10^{7}	0		
	8 x MIC	9×10^{-8}	0		
Proteus mirabilis 2	2 x MIC	7×10^{-8}	1.4×10^{7}	nt	nt
	4 x MIC	7×10^{-8}	1.3×10^{7}		
	8 x MIC	5×10^{-8}	1.3×10^{7}		
Proteus vulgaris 1	2 x MIC	8.3×10^{7}	>10-5	nt	nt
	4 x MIC	7×10^{7}	4.2×10^{7}		
	8 x MIC	9×10^{-8}	4×10^{7}		
Proteus vulgaris 2	2 x MIC	9.7×10^{7}	$>10^{-5}$	nt	nt
	4 x MIC	5×10^{7}	1.1×10^{7}		
	8 x MIC	2×10^{-8}	1.1×10^{7}		
Salmonella enteritidis 1	2 x MIC	2.6×10^{-6}	0	8×10^{-8}	nt
	4 x MIC	1.6×10^{7}	0	2×10^{-8}	
	8 x MIC	6×10^{-8}	0	0	
Salmonella enteritidis 2	2 x MIC	3×10^{-6}	0	1×10^{7}	nt
	4 x MIC	1.2×10^{7}	0	8×10^{-8}	
	8 X MIC	$2 X 10^{-8}$	0	0	
Escherichia coli 085 ETEC	2 x MIC	1×10^{-8}	0	1.8×10^{-6}	nt
	4 x MIC	0	0	2.6×10^{7}	
	8 x MIC	0	0	8×10^{8}	
Escherichia coli 0159 ETEC	2 x MIC	$>10^{-5}$	$>10^{5}$	1.4×10^{-6}	1.8×10^{7}
	4 x MIC	3×10^{-8}	0	0	0
	8 x MIC	3×10^{-8}	0	0	0
Escherichia coli 0125 EPEC	2 x MIC	1×10^{-8}	0	1.2×10^{5}	0
	4 x MIC	0	0	7×10^{-8}	0
	8 x MIC	0	0	0	0
Escherichia coli 086 EPEC	2 x MIC	1.2×10^{-8}	1×10^{-8}	$>10^{5}$	$>10^{5}$
	4 x MIC	0	1×10^{-8}	1.6×10^{6}	1×10^{-8}
	8 x MIC	0	1×10^{-8}	1×10^{-8}	0

nt = not tested (MIC ≥ 64 µg/mL) ETEC = Enterotoxigenic *E coli* EPEC = Enteropathogenic *E coli*

The data in the above table demonstrate that at low concentrations (2 x MIC) some of the Gram-negative organisms had high spontaneous mutation rates of around 10^{-6} The rate was much lower at 8 x MIC Once again the rates were usually lower under anaerobic conditions The rates for most Gram-negative bacteria generally appear to be lower than those seen with Gram-positive bacteria

MULTISTEP SELECTION OF RESISTANCE

The sponsor performed a study (13) using a multistep assay method to determine the selection of rifaximin mutants For testing anaerobic organisms the inocula was prepared by picking five different colonies from growth on Columbia blood agar plates The colonies were suspended in 10 mL of Wilkins-Chalgren broth The samples were incubated for 48 hours at 37 C under anaerobic conditions The inoculum was then adjusted to 0 5 McFarland turbidity The inoculum was adjusted to 10^6 cfu/mL and a series of tubes with two-fold dilutions of the drug were inoculated After incubation, a 0 1-mL aliquot was transferred from tubes containing growth to another series of tubes containing serial dilutions of the drugs being tested The MIC was compared for each series of tubes The experiments were concluded when the test bacteria were able to grow in media containing at least 100 µg/mL of the drug under study A similar experiment was performed with aerobic strains These strains were tested in Mueller-Hinton agar under aerobic conditions They were also tested under anaerobic conditions

Under these test conditions, *Clostridium difficile* and *Peptostreptococcus* species failed to grow in broth containing rifaximin at a concentration higher than 0 5 x MIC *Clostridium perfringens* showed a rapid increase in MIC values from 0 125 µg/mL to ≥128 µg/mL after 4 transfers *Fusobacterium nucleatum* MICs increased from 4-8 µg/mL to ≥128 µg/mL after only 2-3 transfers *Bacteroides* species MICs increased from 0 25 µg/mL to ≥128 µg/mL in 4-5 transfers

Staphylococcus aureus MICs increased from 0 008-0 6 µg/mL to ≥128 µg/mL in 5 transfers *Enterococcus faecalis* isolates increased from 8-32 µg/mL to ≥128 µg/mL in only 2-3 transfers The increases were similar or slightly faster under anaerobic conditions

Most Gram-negative bacteria showed increases in MIC to ≥128 µg/mL in only 2-3 transfers Most MICs started out at 16-32 µg/mL

The rate of selection of spontaneous rifaximin-resistant mutants was correlated to the drug concentration employed and to the bacterial species tested At the highest dose used (8 x MIC), the frequency of emergence of spontaneous mutants ranged from $<1 \times 10^9$ to $1\ 6 \times 10^8$ for Gram-positive aerobic and anaerobic cocci For Gram-negative bacteria the range was $<1 \times 10^9$ to $1\ 7 \times 10^7$ In comparison to Gram-positive cocci, drug-resistant mutants of Gram-negative bacteria usually emerged with a slightly lower incidence Rates were lower under anaerobic conditions These values are higher than those seen with most fluoroquinolones When grown in sub-inhibitory concentrations of rifaximin all organisms showed a rapid increase in MIC values Rifaximin, which is similar to rifampin in structure and mode of action, probably has rifampin's tendency to select resistant strains with treatment This drug is going to be used for diarrhea, however The proposed oral dosing leads to extremely high intraluminal concentrations of the drug which should prevent the development of resistance

A study (14) was performed to investigate the possible selection, by rifaximin, of strains of *Mycobacterium tuberculosis* resistant to rifampin Serial concentrations of rifaximin (6, 20, 90, and 270 ng/mL) were used These concentrations are in excess of the amount of drug expected in systemic fluids from intestinal absorption after oral dosing The concentrations used were all well below the MIC values for pathogens that cause diarrhea Five *Mycobacterium tuberculosis* strains that were isolated from tuberculosis patients were tested Each of the five strains was incubated with each of the four drug concentrations The MICs of rifaximin and rifampin were determined for the five strains before and after incubation with the four rifaximin concentrations TABLE 9 shows the results of this study The MIC values were the same before and after exposure to the drug Incubation with sub-inhibitory concentrations of rifaximin does not seem to increase rifampin MIC values for *Mycobacterium tuberculosis*

TABLE 9
Susceptibility of Five *M tuberculosis* Strains

Strain	Rifampin MIC (µg/mL)		Rifaximin MIC (µg/mL	
	Before Incubation	After Incubation	Before Incubation	After Incubation
1	0 5	0 5	0 5	0 5
2	0 5	0 5	0 5	0 5
3	0 25	0 25	1	1
4	0 25	0 25	0 5	0 5
5	0 25	0 25	0 5	0 5

EVALUATION OF EMERGENCE OF RESISTANCE *IN VIVO*

The appearance in the feces of resistant bacteria after oral treatment with rifaximin was investigated (15) Ten healthy volunteers received 400 mg of rifaximin twice daily for five days Bacteriological monitoring of the feces demonstrated only about a 1 log reduction in the number of *Enterobacteriaceae* per gram of feces The number of both aerobic and anaerobic cocci dropped by 2 logs A slight decrease in the number of anaerobic rods was seen Values 2 days after treatments ended were about the same as those seen on the last treatment day Evaluations made 1-2 weeks after treatment showed a return to initial values Resistance developed in 30% to 90% of the strains isolated After treatment ended there was a rapid disappearance of the resistant bacteria, according to the authors Aerobic species showed a more rapid return to the sensitive strains Resistant anaerobic bacteria, especially anaerobic rods, persisted for a longer time Three months after treatment resistant strains could no longer be detected

What is actually happening is that the drug is killing the susceptible strains so that only the resistant strains are left After treatment ends the susceptible strains grow once more and it becomes harder to detect the resistant strains They are still there but are masked by all the susceptible strains Since the drug has more activity against anaerobic rods it keeps killing them longer as the drug concentration decreases over time after treatment

An experiment (16) was performed in immunocompetent guinea pigs to see if oral treatment with rifaximin would cause cross-resistance in *Mycobacterium tuberculosis* towards rifampin Groups of twenty guinea pigs, which were infected subcutaneously with *M tuberculosis*, were treated with either 60 mg/kg of rifaximin, 30 mg/kg of rifampin or used as control animals Animals were sacrificed after 90 days and samples were taken from liver, spleen, and lung Susceptibility testing was performed on sample isolates The MIC value for both drugs remained 0 5 µg/mL after treatment Treatment with rifaximin does not increase rifaximin or rifampin MIC value for *Mycobacterium tuberculosis* in this model

The effects of rifaximin treatment on enterococcal resistance to rifaximin and cross-resistance to rifampin were evaluated on clinical isolates obtained from clinical study RFID9801 (17) The MIC values were determined for *Enterococcus* isolated from Day 0 and Day 3 fecal samples of 27 patients Nine patients received 600 mg (200 mg t i d) rifaximin/day, 10 patients received 1200 mg (400 mg t i d) rifaximin/day, and 8 patients received placebo The results are shown in TABLE 10 These data demonstrate that in almost all cases the MICs were identical before and after treatment There were a few isolates in which the MIC increased by one dilution (within the assay error) There were slightly more 2-fold increases for rifampin than for rifaximin One isolate had a 4-fold rifampin increase in MIC The 2-fold increases for each drug were not seen in the same isolates It appears that treatment with rifaximin does not increase enterococcal MIC values for rifaximin or rifampin

TABLE 10
MIC Results for Enterococci (STUDY RFID9801)

Subject ID	Treatment Group	Rifaximin MIC (µg/mL)		Rifampin MIC (µg/mL)	
		DAY 0	DAY 3	DAY 0	DAY 3
1123	Placebo	4	4	2	4
1132	Placebo	64	64	0 25	0 25
1152	Placebo	64	64	8	8
1153	Placebo	64	64	4	8
1159	Placebo	8	8	4	4
1173	Placebo	16	32	4	4
1177	Placebo	64	64	4	4
1178	Placebo	8	8	1	2
1121	600 mg/day	32	32	2	2
1124	600 mg/day	32	64	8	8
1128	600 mg/day	8	8	16	16
1154	600 mg/day	64	64	16	16
1158	600 mg/day	32	32	2	2
1169	600 mg/day	8	8	2	2
1179	600 mg/day	16	16	1	1
1180	600 mg/day	8	8	4	4
3118	600 mg/day	16	16	1	2
1125	1200 mg/day	64	64	2	2
1130	1200 mg/day	64	64	8	8
1155	1200 mg/day	64	64	2	2
1156	1200 mg/day	64	64	2	2
1167	1200 mg/day	16	16	0 5	2
1172	1200 mg/day	32	32	1	2
1174	1200 mg/day	8	8	0 25	0 5
1176	1200 mg/day	8	8	2	2
3115	1200 mg/day	16	32	2	4
3119	1200 mg/day	64	64	0 5	0 5

PRECLINICAL EFFICACY (*IN VIVO*)

PHARMACOKINETICS/BIOAVAILABILITY

Rifaximin is a semi-synthetic antimicrobial derived from rifamycin SV The rifamycins are a group of structurally similar, complex macrocyclic compounds Rifaximin is a structural analogue of rifampin The primary difference between rifaximin and rifampin is the presence of the pyridoimidazo system in rifaximin

Rifaximin is poorly absorbed after oral administration Following oral administration negligible systemic absorption occurs Fecal concentrations of rifaximin, following an oral dose of 400 mg twice daily (800 mg/day) for three days was determined to be about 8,000 µg/gram of feces Three days after treatment the mean rifaximin fecal concentration was about 4,400 µg/gram of feces and five days post-treatment the concentration was about 3,300 µg/gram of feces

After administration of single oral doses ranging from 50 mg to 400 mg rifaximin to healthy subjects only trace amounts of rifaximin were detected in the plasma and urine A study using ^{14}C-rifaximin given to healthy subjects showed negligible plasma and urinary recovery rates Nearly all (>96%) of the radioactivity was recovered in feces

ANIMAL PROPHYLATIC AND THERAPEUTIC STUDIES

An analysis of the bacterial flora of rat feces after treatment with rifaximin was performed (18) Immunocompetent rats were treated with 50 mg/kg of rifaximin for 3 days Another group of rats was used as controls When compared to control animals treated animals showed a significant drop in the number of aerobic bacteria and in the number of *Salmonella* and *Shigella* present There was no significant drop in the number of coliforms or aerobic lactobacilli

The antimycobacterial activity of oral rifaximin was studied in immunocompetent the guinea pigs (19) Groups of 15 animals were infected subcutaneously and treated with rifaximin or rifampin orally immediately after infection Group 1 was used as controls, Group 2 received 30 mg/kg/day of rifaximin, Group 3 received 60 mg/kg/day of rifaximin, Group 4 received 30 mg/kg/day of rifampin After four months of treatment samples of liver, spleen, and lung tissue were taken In the control group the infection was extensive, the animals that received rifaximin showed the same degree of infection as the control group, the animals that received rifampin showed only a very low degree of infection After 4 months of therapy with rifaximin the MIC of the *M tuberculosis* used in the study was 0 1 µg/mL, the same as before treatment This experiment shows that oral rifaximin does not control *Mycobacterium tuberculosis* infection in guinea pigs

In mice intraperitoneally infected with a lethal dose of *Stapylococcus aureus* rifaximin was ineffective orally but was active subcutaneously (N2182) The oral 50% effective dose (ED_{50}) for rifaximin was greater than 10 mg/kg while the subcutaneous ED_{50} was 0 46 µg/mL Gentamicin was also ineffective orally with an ED_{50} value greater than 10 mg/kg while oral rifampin was highly effective with an oral ED_{50} value of 0 15 mg/kg

These experiments suggest that rifaximin does not work against systemic pathogens when administered orally due to its lack of oral absorption

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

ISOLATES/RELEVANCE TO APPROVED INDICATIONS

The sponsor has presented two Phase III studies and one Phase II study to support the proposed indication

In the Phase II study –RFID9601—Rifaximin was dosed at 200 mg, 400 mg or 600 mg twice a day for 5 days Post-treatment stool samples were obtained 24 hours after the last dose

In Phase III study –RFID9701—Rifaximin was dosed at 400 mg twice daily for 3 days Post-treatment stool samples were obtained 48-72 hours after the last dose

In Phase III study –RFID9801—Rifaximin was dosed at 200 mg or 400 mg three times a day for 3 days Post-treatment stool samples were obtained 24-48 hours after the last dose

The proposed clinical dose is 200 mg three times a days for 3 days Only study RFID9801 used this dose

Samples of all available isolates were transported to the — — for determination of MICs Each available isolate was speciated Minimum inhibitory concentrations were determined for rifaximin by agar dilution testing according to the National Committee for Clinical Laboratory Standards (NCCLS) guidelines

There were 12 of 427 isolates where the — identified a different species than that identified at the clinical site In all 12 cases, however, the genus did not change There were also three instances where the clinical site did not establish a genus or species, but an isolate was provided and speciated by the — In these cases, the data from the — — was included in the microbiology analysis The clinical sites used biochemical tests to identify the isolate The — used serology for *Salmonella* and *Shigella* species, hippurate hydrolysis for *Campylobacter* species, and biochemical tests for *Aeromonas* and *Vibrio* species TABLE 11 summarizes the differences between clinical sites and the —

TABLE 11
Summary of Speciation Differences between Clinical Site
And

Study No	Patient No	Speciation Results	
		Clinical Site	
RFID9601	17	*Shigella flexneri*	*Shigella sonnei*
RFID9701	13	*Shigella sonnei*	*Shigella flexneri*
	30	*Shigella sonnei*	*Shigella flexneri*
	54	*Shigella sonnei*	*Shigella flexneri*
	57	*Shigella sonnei*	*Shigella flexneri*
	65	*Shigella sonnei*	*Shigella flexneri*
	70	*Shigella sonnei*	*Shigella flexneri*
	73	*Shigella sonnei*	*Shigella flexneri*
	85	*Shigella sonnei*	*Shigella flexneri*
	141	*Shigella sonnei*	*Shigella flexneri*
	146	*Shigella sonnei*	*Shigella flexneri*
RFID9801	2083	*Campylobacter coli*	*Campylobacter jejuni*

Two randomized, comparative, controlled, Phase III studies RFID9701 and RFID9801, provide the primary support for the clinical efficacy of rifaximin for the treatment of infectious diarrhea in travelers RFID9701 compared the clinical efficacy and safety of rifaximin to a standard regimen of ciprofloxacin RFID9801 is a placebo-controlled study that investigated the superiority of rifaximin In each study medication was taken for three days with one to two days of additional observation after the end of treatment Supportive information is provided by one dose-comparison Phase II study, RFID9601 This study compared three dose regimens to a standard regimen of trimethoprim/sulfamethoxazole in the treatment of travelers diarrhea Study medication was taken for 5 days TABLE 12 summarizes the Phase III controlled studies and the Phase II dose-ranging study

TABLE 12
Summary of Primary Clinical Trials for Rifaximin in the Treatment of Infectious Diarrhea in Travelers

Study	Study Design	Rifaximin Dose Regimen	Comparator Drug	Patient Population	Patients Enrolled	ITT Population[1]	Microbiological Population[2]
RFID9801	Randomized, double-blind, placebo controlled parallel group	200 mg tid x 3 days 400 mg tid x 3 days	Placebo	Infectious diarrhea in travelers	Total 380 Rifaximin 200 mg tid (n=125) 400 mg tid (n=126) Placebo (n=129)	Total 380 Rifaximinin 200 mg tid (n=125) 400 mg tid (n=126) Placebo (n=129)	218/380 (57%)
RFID9701	Randomized, double-blind, active-controlled, parallel group	400 mg bid x 3 days	Ciprofloxacin	Infectious diarrhea in travelers	Total 187 Rifaximin (n = 93) Ciprofloxacin (n=94)	Total 187 Rifaximin (n=93) Ciprofloxacin (n=94)	87/187 (47%)
RFID9601	Randomized, double-blind, dose-comparison	200 mg tid x 5 days 400 mg tid x 5 days 600 mg tid x 5 days	TMP/SMX	Infectious diarrhea in travelers	Total 76 Rifaximin 200 mg tid (n=19) 400 mg tid (n=19) 600 mg tid (n=19) TMP/SMX (n-19)	Total 72 Rifaximin 200 mg tid (n=18) 400 mg tid (n=18) 600 mg tid (n=19) TMP/SMX (n=17)	27/72 (38%)

[1] For studies RFID9801 and RFID9701, the ITT (intent-to-treat) population was defined as all patients who were randomized to treatment, and for study RFID9601, the ITT population was all patients who were randomized took at least 2 days of medication and completed two or more daily diaries

[2] Patients with both a pre-treatment and post-treatment stool sample

TMP/SMX =trimethoprim/sulfamethoxazole

The sponsor conducted an analysis on the dose-related effects of the eradication of ETEC (enterotoxigenic *Escherichia coli*), the most common organism identified at baseline As shown in TABLE 13, no dose-related effects were observed in the eradication of ETEC, therefore, the sponsor deemed it appropriate to pool the microbiological data from all three studies Although it appears that there is little if any dose effect on the eradication of ETEC, this may not be true for the other pathogens There were very few other pathogens in these studies, therefore, an analysis of dose-related effects on them may not give a true representation A summary of each of the three studies will, therefore, be given after a review of the pooled data

TABLE 13
Eradication Rate of ETEC Isolates by Rifaximin Dose

	Microbiological Eradication			
	RFID9801		RFID9701	
Specific Pathogen	200 mg tid n/N (%)	400 mg tid n/N (%)	400 mg bid n/N (%)	TOTAL n/N (%)
Total ETEC	38/49 (77 6)	31/42 (73 8)	26/37 (70 3)	95/128 (74 2)
ETEC heat labile	8/11 (72 7)	10/12 (83 3)	5/5 (100)	23/28 (82 1)
ETEC heat labile/ heat stabile	17/19 (89 5)	8/10 (80 0)	7/10 (70 0)	32/39 (82 1)
ETEC heat stable	13/19 (68 4)	13/20 (65 0)	14/22 (63 6)	40/61 (65 5)

For each efficacy study (RFID9601, RFID9701, and RFID9801), patients gave a stool sample at baseline before any treatment and 24-72 hours after completing treatment These stool samples were cultured for enteropathogens Patients were considered to be evaluable for pathogen eradication if they had a pathogen identified in the baseline stool sample and a post-treatment stool sample was available

Of the 401 rifaximin-treated patients in each of the three studies, 196 patients (49%) with 218 pathogens were evaluable for microbiological response Of the remaining 205 patients, the majority were not evaluable because no pathogen was identified at baseline In the combined control groups, 116 of 242 (48%) patients with 128 pathogens were evaluable for pathogen eradication TABLE 14 summarizes the pooled eradication rates by pathogen and compares the microbiological and clinical cure rates for the rifaximin treated patients TABLE 15 compares the microbiological cure rates for the rifaximin treated patients with the microbiological cure rates for the comparator treated patients by pathogen

Data in TABLE 14 show that there were only a few isolates of any species except *Escherichia coli* and *Cryptosporidium parvum* that were treated with rifaximin There were ten isolates of *Shigella sonnei* and ten (nine microbiologically evaluable) isolates of *Salmonella* Group C1, but not all of these were treated with the proposed rifaximin dose

TABLE 14
Clinical and Bacteriological Response (Studies RFID9801, RFID9701, and RFID9601)

Specific Pathogen	No with Culture Pre-Treat	No with Culture Pre & Post	Clinical Outcome Cure n/N (%)	Clinical Cure with Micro Cure	Micro Outcome Cure n/N (%)	Micro Cure with Clinical Cure	Median TLUS
*Giardia lamblia**	10	8	7/8 (87 5)	57 1%	5/8 (62 5)	80 0%	32 50
*Entamoeba histolytica**	5	3	1/3 (33 3)	100 0%	3/3 (100)	33 3%	NA
*Cryptosporidium parvum**	34	29	26/29 (89 7)	65 4%	18/29 (62 1)	94 4%	41 25
Shigella species	1	1	1/1 (100)	100 0%	1/1 (100)	100 0%	36 08
Shigella flexneri	4	4	3/4 (75 0)	66 7%	2/4 (50 0)	100 0%	18 90
Shigella sonnei	10	10	9/10 (90 0)	77 8%	7/10 (70 0)	100 0%	30 00
Salmonella Group C1	10	9	7/9 (77 8)	57 1%	6/9 (66 7)	66 7%	35 00
Salmonella Group C2	5	4	3/4 (75 0)	66 7%	3/4 (75 0)	66 7%	21 33
Campylobacter jejuni	6	6	5/6 (83 3)	100 0%	5/6 (83 3)	100 0%	53 50
Aeromonas hydrophila	1	1	1/1 (100 0)	100 0%	1/1 (100 0)	100 0%	NA
Plesiomonas shigelloides	1	1	1/1 (100 0)	100 0%	1/1 (100 0)	100 0%	0 00
Vibrio fluvialis	2	1	1/1 (100 0)	100 0%	1/1 (100 0)	100 0%	30 25
Vibrio parahemolyticus	1	1	0/1 (0 0)	NA	1/1 (100 0)	NA	NA
ETEC heat labile	36	32	27/32 (84 4)	81 5%	27/32 (84 4)	81 5%	25 25
ETEC heat stable	64	64	54/64 (84 4)	64 8%	43/64 (67 2)	81 4%	30 25
ETEC heat labile/stable	48	44	33/44 (75 0)	75 0%	35/44 (79 6)	71 4%	32 50
TOTAL			179/218 (82 1)		159/218 (72 9)		

Percentages are based on total number of Rifaximin patients with sample analyzed at both baseline and post-treatment visits
Clinical CURE with Micro CURE represents % of patients with a clinical cure who also experienced a microbiological cure
Micro CURE with Clinical CURE represents % of patients with a microbiological cure who also experienced a clinical cure
* These organisms were not cultured but were detected using assays that use monoclonal antibodies for the qualitative detection of specific antigens

TABLE 15
Pathogen Eradication Rates in Microbiologically Evaluable Patients
(Studies RFID9801, RFID9701, and RRID9601

	Rifaximin (All Doses)		Control[1]	
Pathogen	Baseline Data n/N (%)[2]	Microbiological Cure n/N (%)[2]	Baseline Data n/N (%)[2]	Microbiological Cure n/N (%)[2]
Escherichia coli	140/218 (64 2)	105/140 (75 0)	91/128 (71 1)	78/91 (85 7)
ETEC heat labile	32/218 (14 7)	27/32 (84 4)	27/128 (21 1)	25/27 (92 6)
ETEC heat labile/ stable	44/218 (20 2)	35/44 (79 5)	25/128 (19 5)	21/25 (84 0)
ETEC heat stable	64/218 (29 4)	43/64 (67 2)	39/128 (30 5)	32/39 (82 1)
Salmonella Group	13/218 (6 0)	9/13 (69 2)	8/128 (6 3)	8/8 (100)
Shigella Group	15/218 (6 9)	10/15 (66 7)	7/128 (5 5)	7/7 (100)
Cryptosporidia	29/218 (13 5)	18/29 (62 1)	12/128 (9 4)	8/12 (66 7)
C jejuni	6/218 (2 8)	5/6 (83 3)	2/128 (1 6)	1/2 (50 0)
Others	15/218 (6 9)	12/15 (80 0)	8/128 (6 3)	7/8 (87 5)
TOTAL	----	159/218 (72 9)	----	109/128 (85 2)

[1] Includes placebo, ciprofloxacin, and Trimethoprim/sulfamethoxazole
[2] Patients with more than one baseline pathogen are counted more than once

The overall eradication rate for rifaximin is lower than for the comparators It must also be remembered that one of the comparators is placebo Since the data is pooled it is impossible to tell if rifaximin is better than placebo or how it compares to ciprofloxacin

A total of 427 clinical isolates from the three studies were obtained and tested to determine their MICs TABLE 16 provides the MIC values obtained for these clinical isolates For the 427 isolates the rifaximin MIC_{50} and MIC_{90} values for the individual genera ranged from 4-32 µg/mL and 8-64 µg/mL, respectively The highest MIC seen was 512 µg/mL which was about 15-fold below the estimated maximum fecal concentration of rifaximin (8,000 µg/mL) observed after dosing of 200 mg t i d The vast majority of isolates were *Escherichia coli* TABLE 15 also does not state what dose of rifaximin was used Many of the isolates might have come from patients treated with a rifaximin regime other than that which is proposed

TABLE 16
MICs of Rifaximin against Clinical Isolates (Studies RFID9601, RFID9701, RFID9801)

Organism	Number of Isolates	µg/mL		
		MIC_{50}	MIC_{90}	MIC Range
Aeromonas	3	16	16	8-16
Aeromonas hydrophila	2			16
Aeromonas sobria	1			8
Campylobacter	11	32	64	8-64
Campylobacter coli	1			64
Campylobacter jejuni	10			8-64
ETEC	347	32	64	0 098-512
ETEC LT	93			2-512
ETEC ST	151			0 25-256
ETEC ST/LT	103			0 098-12
Plesiomonas shigelloides	2	4	8	4-8
Salmonella	32	32	50	6 25-64
Salmonella Group C1	20			6 25-64
Salmonella Group C2	12			8-64
Shigella	27	32	64	0 98-256
Shigella flexneri	13			8-64
Shigella sonnei	14			0 098-256
Vibrio	5	16	32	8-32
Vibrio fluvialis	3			8-32
Vibrio parahemolyticus	2			16-32
Total	427	32	64	0 98-512

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

TABLE 17 compares the MICs of the pre-treatment organisms to those organisms isolated from the post-treatment stool Overall the MIC_{50} and MIC_{90} did not change

TABLE 17
Comparison of Pre-Treatment and Post-Treatment MICs of Rifaximin against Clinical Isolates from Studies RFID9801, RFID9701, and RFID9601

Organism	No of Isolates	Pre-Treatment (µg/mL)			No of Isolates	Post-Treatment (µg/mL)		
		MIC_{50}	MIC_{90}	Range		MIC_{50}	MIC_{90}	Range
Aeromonas species	2	8	16	8-16	1	---	---	16
Campylobacter spp	7	25	32	8-64	4	32	64	32-64
ETEC LT	64	16	64	2-256	29	32	64	4-512
ETEC ST	103	25	64	0 5-256	48	16	64	0 25-256
ETEC ST/LT	72	32	64	0 098-512	31	32	64	4-128
Plesiomonas species	2	4	8	4-8	0	---	---	---
Salmonella species	23	32	50	6 25-64	9	16	32	6 25-64
Shigella species	21	32	64	0 098-64	6	16	32	0 098-256
Vibrio species	4	16	32	8-32	1	---	---	32
TOTAL	298	32	64	0 098-512	129	32	64	0 098-512

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

There were fifty patients that had the same pathogen identified pre-treatment and post-treatment TABLE 18 shows the shift in the MICs for these organisms In no instance was there a greater than four-fold increase in the MIC and in 82% (41/50) of the isolates the MIC either decreased or remained the same

TABLE 18
Shift in MICs for Eradication Failures of Clinical Isolates
Studies RFID9801, RFID9701, and RFID96

MIC Change	2-fold	4-fold	>4-fold	Total
Increase	7	2	0	9
Decrease	4	2	1	7
No Change				34
Total				50

TABLE 19 shows the relationship between eradication and the primary clinical endpoint, Time to Last Unformed Stool (TLUS) TLUS was defined as the interval beginning with the first dose of study drug and ending with the last unformed stool passed Clinical cure was defined as no unformed stools within a 48-hour period with no fever or no watery stools and no more than two soft stools within a 24-hour period with no fever and no other clinical symptoms

From TABLE 19 it can be seen that the median time to last unformed stool was similar for patients with ETEC eradication and those who failed to eradicate baseline ETEC strains (30 75 versus 32 50 hours, respectively) There appears to be little if any correlation between pathogen eradication and the time to last unformed stool

TABLE 19
Correlation between Eradication of Baseline ETEC Strains and Median TLUS
Studies RFID9801, RFID9701, and RFID9601

Microbiological Evaluable Patients	Median TLUS (hours)				
	200 mg tid	400 mg bid	400 mg tid	600 mg tid	Total
All Patients (n=140)	28 42	37 33	30 25	68 75	30 75
Patients with Microbiological ETEC Eradication (n=105)	26 50	37 67	29 63	68 75	30 75
Patients who Failed to Eradicate Baseline ETEC Organism (n = 35)	32 50	36 33	30 25	NA	32 50

NA = No data available

STUDY RFID9601

This was a Phase II dose-comparison study Three dose regimens of rifaximin (200 mg, 400 mg, and 600 mg three times daily) were compared to a standard regimen of trimethoprim/sulfamethoxazole (TMP/SMX) in the treatment of travelers' diarrhea Study medication was taken for 5 days The sponsor is proposing a dose regimen of 200 mg three times daily for 3 days The dosing in this study is, therefore, not equivalent to the proposed dose for this product (200 mg tid for 3 days)

A total of 76 patients were enrolled in this study at one of five sites in Mexico Four patients (one 200 mg rifaximin, one 400 mg rifaximin, and 2 TMP/SMX) withdrew early due either to noncompliance with the protocol (n=2), or failure to return to the clinic (n=2) The other 72 patients were included in the efficacy analysis (55 rifaximin and 17 TMP/SMX) TABLE 20 gives a summary of the microbiological results of this study

TABLE 20
Summary of Microbiological Results Study RFID9601

Subject No	Treatment	Pathogen	Microbiological Outcome	TMP Susceptibility	Rifaximin MIC (µg/mL)	
					Pretreatment	Posttreatment
5	Rifaximin-M	*Cryptosporidium 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

In this study there were only four pathogens that were not eradicated All four were treated with rifaximin There were no new pathogens isolated post-treatment The rifaximin MIC values for the four failures were the same before and after treatment

TABLE 21 shows the microbiological cure rate for each pathogen The rifaximin MIC values ranged from <0 098 µg/mL to 50 0 µg/mL Most of the pathogens were *Escherichia coli*

TABLE 21
Microbiological Cure Rate by Pathogen (Study RFID9601)

Pathogen	200 mg tid Rifaximin		400 mg tid Rifaximin		600 mg tid Rifaximin		TMP/SMX	
	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	—
Cryptosporidium 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%)

The data in the above Table indicate that there were too few of any species to draw any reliable conclusions about the eradication rate

STUDY RFID9701

This was a Phase III comparative study It was a randomized, double-blind active controlled, parallel group study comparing 400 mg of rifaximin taken twice a day with 500 mg ciprofloxacin taken twice a day for treatment of infectious diarrhea in travelers

A total of 187 patients were enrolled in this study at study centers located in both Mexico and Jamaica Ninety-three patients were randomized to treatment with rifaximin and ninety-four patients were randomized to ciprofloxacin Most patients were treated at the center in Mexico Eighty-one (87 1%) of the rifaximin patients and 83 (87 2%) of the ciprofloxacin were treated in Mexico One patient in the rifaximin group terminated the study early due to an adverse event All 187 patients randomized to the study were included in the intent-to-treat efficacy population

Fifty-three of 187 (28 3%) patients had protocol violations that were considered to be major These included 25 of 93 rifaximin (26 9%) and 28 of 94 ciprofloxacin (29 8%) patients Most violations were due to the administration of concomitant medications that could affect the study outcome

TABLE 22 summarizes the bacteriological response for the intent-to-treat (ITT) population A subject was noted as having a bacteriological cure if there was a negative post-treatment culture for all pathogens identified in the pre-treatment culture

TABLE 22
Bacteriological Response for ITT Population (Study RFID9701)

Pre-Treatment Culture Post-Treatment Outcome	Rifaximin (N=93)	Ciprofloxacin (N=94)
No pathogen pre-treatment	50 (53 8%)	46 (48 9%)
≥1 Pathogen pre-treatment		
Cure	30 (32 3%)	39 (41 5%)
Failure	7 (7 5%)	5 (5 3%)
No post-treatment culture	6 (6 5%)	4 (4 3%)

A bacteriological cure was seen in 30/43 subjects (69 8%) in the rifaximin group and in 39/48 subjects (81 3%) in the ciprofloxacin group with at least one pathogen isolated in the pre-treatment culture It appears that ciprofloxacin had a better eradication rate than rifaximin

TABLE 24 shows the bacteriological response for the intent-to-treat (ITT) population by pathogen for the ciprofloxacin treated group TABLE 25 shows the same information for the rifaximin treated group

Pathogens isolated in the post-treatment culture that were not present in the pre-treatment culture (newly isolated pathogens) were noted for eleven subjects in the rifaximin treated group, but in only one subject in the ciprofloxacin treated group TABLE 23 summarizes data on newly isolated pathogens It appears that rifaximin treatment may lead to more new infections than ciprofloxacin treatment

TABLE 23
Subjects with Newly Isolated Pathogens (Study RFID9701)

Subject No	Treatment	New Pathogen	Rifaximin MIC (µg/mL)
19	Rifaximin	ETEC ST	32
20	Rifaximin	ETEC ST/LT	32
57	Rifaximin	*Shigella flexneri*	8
68	Rifaximin	ETEC LT	64
80	Rifaximin	ETEC ST	8
85	Rifaximin	*Shigella flexneri*	16
93	Rifaximin	*Shigella sonnei*	256
131	Rifaximin	ETEC ST	0 5
134	Rifaximin	ETEC ST	64
139	Rifaximin	ETEC ST/LT	4
187	Rifaximin	ETEC ST	0 25
13	Ciprofloxacin	ETEC LT	8

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

TABLE 24--Bacteriological Response for Ciprofloxacin 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	Cure	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	Cure	16	---
190	Ciprofloxacin	ETEC ST/LT	Cure	16	---
191	Ciprofloxacin	*Cryptosporidium parvum*	Failure	Not done	---
		ETEC ST	Cure	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	*Cryptosporidium 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 Not done = No susceptibility testing was performed

TABLE 25--Bacteriological Response for Rifaximin 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	*Cryptosporidium parvum*	Cure	Not done	---
		ETEC ST/LT	Cure	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	No Post	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	Cure	8	---
209	Rifaximin	ETEC ST/LT	Failure	16	8
210	Rifaximin	*Campylobacter jejuni*	Cure	32	---
		ETEC ST	Cure	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
Not done = No susceptibility testing was performed

TABLE 26 shows the microbiological cure rate for each pathogen The rifaximin MIC values ranged from <0 098 µg/mL to 50 0 µg/mL Most of the pathogens were *Escherichia coli*

TABLE 26
Microbiological Cure Rate by Pathogen (Study RFID9701)

Pathogen	Rifaximin 400 mg bid		Ciprofloxacin 500 mg bid	
	No	No Eradicated (%)	No	No Eradicated (%)
Escherichia coli	35	24/35 (68 6%)	36	30/36 (83 3%)
Shigella sonnei	4	3/4 (75 0%)	1	1/1 (100 0%)
Shigella flexneri	1	1/1 (100 0%)	5	4/5 (80 0%)
Salmonella species	0		1	1/1 (100 0%)
Salmonella Group C1	2	1/2 (50 0%)	3	2/3 (66 6%)
Salmonella Group C2	1	1/1 (100 0%)	2	2/2 (100 0%)
Campylobacter jejuni	2	2/2 (100 0%)	0	---
Entamoeba histolytica	1	0/1 (0 0%)	0	---
Giardia Lamblia	0	---	1	0/1 (0 0%)
Cryptosporid um parvum	1	1/1 (100 0%)	2	1/2 (50 0%)
TOTAL	47	33/47 (70 2%)	51	41/51 (80 3%)

From the above TABLE it can be seen that there were very few of any organisms other than *Escherichia coli* The dosage regimen in this study was not the one proposed for the product in this application (200 mg tid for 3 days) It appears that the eradication rate for rifaximin is not as good as for ciprofloxacin

STUDY RFID9801

This was a Phase III placebo controlled study It investigated the superiority of rifaximin dosed at 200 mg tid and 400 mg tid versus placebo Subjects were dosed for 3 days followed by a post-treatment evaluation between 24 and 48 hours after the last dose

A total of 380 patients were enrolled in the study centers located in Mexico, Guatemala, and Kenya There were 125 subjects in the rifaximin 600 mg group (200 mg tid), 126 subjects in the rifaximin 1200 mg group (400 mg tid), and 129 in the placebo group Most patients (n=195) were enrolled at the Mexico site, 66 placebo, 64 rifaximin 600 mg, and 65 rifaximin 1200 mg Kenya enrolled 85 patients (30, 28, and 27 in the placebo, rifaximin 600 mg, and rifaximin 1200 mg groups, respectively) Guatemala enrolled 100 patients (33, 33, and 34 in the placebo, rifaximin 600 mg, and rifaximin 1200 mg groups respectively) All 380 patients were included in the intent-to-treat (ITT) analysis

A total of 344 patients completed the study Comparable numbers of patients from each treatment group completed the study, 115 (92 0%), 119 (94 4%), and 110 (85 3%) in the rifaximin 600 mg, rifaximin 1200 mg, and placebo groups, respectively Of the 36 patients who terminated the study early, 27 terminated prior to completing study medication, and 9 patients after dosing was complete The primary reason for early termination was treatment failure More placebo patients terminated the study after dosing was complete (n=8) than patients form the rifaximin 600 mg (n=0) and

rifaximin 1200 mg (n=1) groups One patient in the 600 mg rifaximin group terminated the study on day 1 due to nausea and a loss of taste

The percentage of patients with protocol violations was similar across the treatment groups There were 19 (14 7%), 21 (16 8%), and 20 (15 9%) patients with protocol violations in the placebo, 600 mg rifaximin, and 1200 mg rifaximin groups, respectively Thirty patients took a concomitant medication that was likely to affect efficacy, 11 (8 5%), 11 (8 8%), and 8 (6 3%) patients in the placebo, 600 mg rifaximin, and 1200 mg rifaximin groups, respectively

TABLE 27 summarizes the bacteriological response for the intent-to-treat (ITT) population A subject was noted as having a bacteriological cure if there was a negative post-treatment culture for all pathogens identified in the pre-treatment culture

TABLE 27
Bacteriological Response for ITT Population (Study RFID9801)

Pre-Treatment Culture Post-Treatment Outcome	Placebo N=129	Rifaximin 600 mg N = 125	Rifaximin 1200 mg N = 126
No pathogen pre-treatment	68 (52 7%)	54 (43 2%)	66 (52 4%)
≥1 Pathogen pre-treatment	61 (47 3%)	71 (56 8%)	60 (47 6%)
Cure	41 (31 8%)	48 (38 4%)	34 (27,0%)
Failure	13 (10 1%)	17 (13 6%)	21 (16 7%)
No post-treatment culture	6 (4 7%)	5 (4 0%)	5 (4 0%)
Missing	1 (0 8%)	1 (0 8%)	0 (0 0%)

A bacteriological cure was seen in 41/61 subjects (67 2%) in the placebo group, in 48/71 subjects (67 6%) in the rifaximin 600 mg group, and in 34/60 subjects (56 7%) in the rifaximin 1200 mg group with at least one pathogen isolated in the pre-treatment culture It appears that placebo treatment is as good as rifaximin in eradicating pathogens The lower dose also seems to be slightly better than the higher dose

TABLE 29 shows the bacteriological response for the intent-to-treat (ITT) population by pathogen for the placebo treated group TABLE 30 shows the same information for the rifaximin 600 mg (200 mg tid) treated group and TABLE 31 shows this information for the rifaximin 1200 mg (400 mg tid) treated group

Pathogens isolated in the post-treatment culture that were not present in the pre-treatment culture (newly isolated pathogens) were noted for twenty-four subjects in the placebo treated group and the rifaximin 600 mg treated group Twenty subjects had newly isolated pathogens in the rifaximin 1200 mg treated group TABLE 28 summarizes data on newly isolated pathogens

TABLE 28
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	*Cryptosporidium parvum*	Not done
2006	Placebo	*Cryptosporidium 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	*Cryptosporidium 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 28 (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	*Cryptosporidium 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	*Cryptosporidium parvum*	Not done
2035	Rifaximin 600 mg	*Cryptosporidium parvum*	Not done
2039	Rifaximin 600 mg	ETEC LT	16
2075	Rifaximin 600 mg	*Salmonella* Group C2	64
2087	Rifaximin 600 mg	*Cryptosporidium 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	*Cryptosporidium 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

TABLE 29
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	---
		Cryptospondium parvum	Cure	Note done	---
		ETEC ST/LT	Cure	32	---
2008	Placebo	*Cryptospondium parvum*	Failure	Not done	Not done
		ETEC ST	Cure	16	---
2021	Placebo	ETEC LT	Cure	32	---
		Aeromonas sobria	Cure	8	---
2024	Placebo	*Cryptospondium parvum*	Cure	Not done	---
		ETEC ST	Failure	64	64
2025	Placebo	*Giardia lambila*	No Post	Not done	---
2030	Placebo	*Cryptospondium 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
Not done = No susceptibility testing was performed

TABLE 29 (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
		Cryptosporidium parvum	Cure	Not done	---
2086	Placebo	ETEC LT	No Post	64	---
2089	Placebo	ETEC LT	Cure	32	---
		Cryptosporidium parvum	Cure	Not done	---
2094	Placebo	ETEC LT	Failure	32	32
2096	Placebo	*Cryptosporidium parvum*	No Post	Not done	---
2098	Placebo	ETEC LT	Cure	64	---
2100	Placebo	*Cryptosporidium parvum*	Cure	Not done	---
		ETEC ST	No Post	64	---
2104	Placebo	*Cryptosporidium parvum*	Cure	Not done	---
		ETEC ST	Cure	4	---
2107	Placebo	*Cryptosporidium parvum*	Failure	Not done	Not done
		Campylobacter coli	Cure	64	---
2110	Placebo	*Cryptosporidium 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
Not done = No susceptibility testing was performed

TABLE 30
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	*Cryptosporidium 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	*Cryptosporidium 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	*Cryptosporidium 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	*Cryptosporidium parvum*	Cure	Not done	—
		ETEC ST/LT	Cure	32	—
2010	Rifaximin 600 mg	ETEC ST	Failure	16	32
2012	Rifaximin 600 mg	*Cryptosporidium parvum*	Cure	Not done	—
2015	Rifaximin 600 mg	*Cryptosporidium parvum*	Cure	Not done	—
		ETEC ST/LT	Cure	512	—
		Vibrio fluvialis	Cure	16	—
2023	Rifaximin 600 mg	*Cryptosporidium parvum*	Failure	Not done	Not done
		ETEC ST	Cure	4	—
2026	Rifaximin 600 mg	*Cryptosporidium 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
Not done = No susceptibility testing was performed

TABLE 30 (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	*Cryptosporidium 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	*Cryptosporidium parvum*	Cure	Not done	---
2071	Rifaximin 600 mg	ETEC ST/LT	Cure	16	---
2075	Rifaximin 600 mg	*Cryptosporidium 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	*Cryptosporidium parvum*	Cure	Not done	---
2093	Rifaximin 600 mg	*Cryptosporidium 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	*Cryptosporidium parvum*	No Post	Not done	---
		Campylobacter jejuni	Cure	8	---
2102	Rifaximin 600 mg	*Cryptosporidium parvum*	Cure	Not done	---
2105	Rifaximin 600 mg	*Cryptosporidium parvum*	Cure	Not done	---
2109	Rifaximin 600 mg	*Cryptosporidium parvum*	Failure	Not done	Not done
		Shigella flexneri	Failure	16	16
2113	Rifaximin 600 mg	*Cryptosporidium 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
Not done = No susceptibility testing was performed

TABLE 31
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	*Cryptosporidium parvum*	Failure ?	Not done	—
1167	Rifaximin 1200 mg	ETEC ST/LT	Cure	32	—
1172	Rifaximin 1200 mg	*Cryptosporidium 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	*Cryptosporidium parvum*	Cure	Not done	—
		ETEC ST/LT	Failure	16	16
2027	Rifaximin 1200 mg	ETEC ST	Cure	32	—
2029	Rifaximin 1200 mg	*Cryptosporidium parvum*	Failure	Not done	Not done
		Entamoeba histolytica	Cure	Not done	—
		ETEC ST	Cure	64	—
2036	Rifaximin 1200 mg	*Cryptosporidium 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
Not done = No susceptibility testing was performed

TABLE 31 (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	---
		Cryptosporidium parvum	No Post	Not done	---
2080	Rifaximin 1200 mg	*Cryptosporidium parvum*	Failure	Not done	Not done
		ETEC ST	Cure	4	---
2081	Rifaximin 1200 mg	ETEC ST	Failure	16	32
2085	Rifaximin 1200 mg	*Cryptosporidium parvum*	No Post	Not done	---
		ETEC LT	Cure	8	---
2091	Rifaximin 1200 mg	*Cryptosporidium parvum*	Cure	Not done	---
2092	Rifaximin 1200 mg	*Cryptosporidium parvum*	No Post	Not done	---
		Entamoeba histolytica	No Post	Not done	---
2101	Rifaximin 1200 mg	*Cryptosporidium parvum*	Failure	Not done	Not done
2106	Rifaximin 1200 mg	*Cryptosporidium parvum*	Failure	Not done	Not done
		Vibrio parahaemolyticus	Cure	16	---
2108	Rifaximin 1200 mg	*Cryptosporidium parvum*	Failure	Not done	Not done
		ETEC ST	Failure	16	16
2111	Rifaximin 1200 mg	ETEC LT	No Post	16	---
2114	Rifaximin 1200 mg	*Cryptosporidium 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
Not done = No susceptibility testing was performed

TABLE 32 shows the microbiological cure rate for each pathogen The rifaximin MIC values ranged from 1 µg/mL to 512 µg/mL Most of the pathogens were *Escherichia coli*

TABLE 32
Microbiological Cure Rate by Pathogen (Study RFID9801)

Pathogen	Placebo		Rifaximin 200 mg tid		Rifaximin 400 mg tid	
	No	No Eradicated (%)	No	No Eradicated (%)	No	No Eradicated (%)
Escherichia coli	54	40/54 (74 1%)	54	38/54 (70 4%)	41	27/41 (65 9%)
Shigella species	0	----	0	----	1	1/1 (100 0%)
Shigella sonnei	2	2/2 (100 0%)	2	2/2 (100 0%)	1	1/1 (100 0%)
Shigella flexneri	0	----	2	1/2 (50 0%)	1	0/1 (0 0%)
Salmonella Group C1	1	1/1 (100 0%)	2	1/2 (50 0%)	4	3/4 (75 0%)
Salmonella Group C2	1	1/1 (100 0%)	0	----	3	1/3 (33 3%)
Campylobacter jejuni	1	0/1 (0 0%)	2	1/2 (50 0%)	0	----
Campylobacter coli	1	1/1 (100 0%)	0	----	0	----
Aeromonas sobria	1	1/1 (100 0%)	0	----	0	---
Aeromonas hydrophila	0	----	0	----	1	1/1 (100 0%)
Entamoeba histolytica	1	1/1 (100 0%)	1	1/1 (100 0%)	3	2/3 (66 6%)
Giardia lambila	4	3/4 (75 0%)	6	4/6 (66 6%)	3	1/3 (33 3%)
Cryptosporidium parvum	11	7/11 (63 6%)	18	12/18 (66 6%)	14	4/14 (28 6%)
Plesiomonas shigelloides	1	1/1 (100 0%)	0	----	1	1/1 (100 0%)
Vibrio fluvialis	0	----	1	1/1 (100 0%)	1	0/1 (0 0%)
Vibrio parahaemolyticus	1	1/1 (100 0%)	0	----	1	1/1 (100 0%)
TOTAL	79	59/79 (74 7%)	88	61/88 (69 3%)	75	43/75 (57 3%)

From the above TABLE it can be seen that there were very few of any organisms other than *Escherichia coli* Only one arm in this study used the proposed dosage regimen (200 mg tid for 3 days) Both rifaximin dosage regimens had about the same eradication rate with the lower dose giving slightly better eradication The eradication rate for placebo was as good as or better than that for the drug Only about half the patients had an organism detected pre-treatment There were only four *Shigella* species and two *Salmonella* species treated with the proposed dose

The data from all these studies combined indicate that rifaximin is no better than placebo at eradicating pathogens Only about half the patients in these studies had a pre-treatment pathogen detected Rifaximin appears to be slightly less effective in eradicating pathogens than is ciprofloxacin but the difference may not be significant

Almost all the *Cryptosporidium parvum* patients were from Kenya Many of them had another pathogen along with the *Cryptosporidium parvum* These other organisms may be the cause of the diarrhea About 20% of the patients in each group had new pathogens detected after treatment

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