

It should be pointed out that the applicant's proposed dose of 200 mg TID for 3 days was utilized in only 1 trial (study 9801). There were a few additional patients in the phase II trial that received this dose albeit for 2 more days as compared to the phase III subjects. The applicant was informed by the FDA prior to NDA submission that efficacy results (both clinical and microbiological) obtained at doses higher than the proposed dose will provide only limited supporting data for the application. The applicant's position was that extremely high intraluminal concentrations of rifaximin are attained independent of dose and thus pooling of both the clinical and microbiological results should be allowed.

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.

Only study RFID9801 was considered pivotal by the FDA review team. Study RFID9701 was considered supportive because the doses utilized in that trial were higher than the proposed 200 TID dose and the dosing interval was BID as opposed to TID.

Prior to the submission of the NDA and after a review of summary data, the division found that

insufficient data to support an approval and it was suggested that Salix should perform an additional study prior to the submission of their NDA application (3 arm study including the proposed dosing regimen, a placebo arm, and an active control arm). This study would serve as a second pivotal trial and would confirm the clinical effectiveness of rifaximin. Additionally, it is hoped that the microbiologic efficacy of the compound will also be clarified.

For the NDA under review, the MO reviewed a random 20% sample of the submitted CRFs. Subjects were assessed for key elements including (i) presence of diarrhea, (ii) absence of severe dehydration, (iii) lack of previous effective treatment, (iv) infection details with cultures pre and post treatment, and (v) TLUS. The MO determined that the applicant adequately followed the approved protocols and that the transcription of the data to the datasets was accurate. The MO accepted the applicant's populations.

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 infectious diarrhea 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 FDA performed this analysis on a modified intent-to-treat (MITT) population from all 3 studies consisting of subjects who had a pathogen isolated at baseline.

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 PO TID versus placebo group and $p = 0.0001$ for the rifaximin 400 mg PO TID for 3 days versus placebo group). Median TLUS was significantly shorter in both rifaximin groups compared to placebo, 32.5 hours in the rifaximin 200 mg PO TID group, 32.9 hours in the 400 mg PO TID group, and 60.0 hours in the placebo group.

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.

In RFID9601, the median TLUS for the rifaximin groups was 35.00 hours (26.25 hours [200 mg three times daily], 40.50 hours [400 mg three times daily], 35.00 hours [600 mg three times daily]) and 47.00 hours for the TMP/SMX group.

A comparison of the 4 different dose levels of rifaximin evaluated in Studies RFID9601, RFID9701, and RFID9801, 600 mg/day (200 mg TID), 800 mg/day (400 mg BID), 1200 mg/day (400 mg TID) or 1800 mg/day (600 mg TID) showed similar degrees of efficacy. Each of these values compare favorably with that observed for placebo treated patients from study RFID9801 (TLUS 60.0 hours) and with ciprofloxacin (study RFID9701).

The TLUS values obtained for the FDA MITT population were consistent with those obtained for the ITT populations in studies 9801 and 9701.

Dose Regimen and Median TLUS of 4 Rifaximin Dose Groups (ITT)

Study	Total Daily Dose	Schedule	Median TLUS (hours)	Median TLUS FDA MITT
RFID9801	600 mg/day	TID	32.5	30
RFID9801	1200 mg/day	TID	32.9	32.8
RFID9801	Placebo	TID	60.0	59.3
RFID9701	800 mg/day	BID	25.7	27.3
RFID9701	Ciprofloxacin	BID	25.0	25.0
RFID9601	600 mg/day	TID	26.2	33.25
RFID9601	1200 mg/day	TID	40.5	52
RFID9601	1800 mg/day	TID	35.0	60
RFID9601	TMP/SMX	BID	47.0	13.5

The MO performed an analysis on patients with leukocytes in the stool after determining that this patient subgroup is representative of subjects with dysentery

In study 9801 there were 20 subjects with leukocytes in the stool (20/129, 15%). Of these, 14 (70%) were determined to be cures and 6 (30%) to be failures. The TLUS for this group was 45.07 as compared to the median TLUS for all 200 mg TID subjects of 32 hours. For those subjects receiving the 400 mg TID dose, 17 (15%) had leukocytes in the stool and 15 (88%) were determined to be cures with a median TLUS of 36.6 as compared to 32.9 for all 400 mg TID subjects. Twenty-three placebo patients had leukocytes in the stool and 11 were cures. The applicant could not provide a median TLUS for this group. The MO determined that the applicant did not provide an adequate sample size in order to accurately assess rifaximin's effectiveness in subjects with dysentery.

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

The applicant provided an integrated summary of microbiologic efficacy with total pathogen eradication rates independent of dose. The applicant's rationale for this was that the submission contained primarily subjects with enterotoxigenic *Escherichia coli* (ETEC) and as there was no difference in eradication rates versus this pathogen independent of dose, it was appropriate to provide pooled microbiology results. Additionally, this group of subjects was deemed a homogenous population suitable to evaluate the relationship between eradication and TLUS. Patients with fecal cultures that

were positive for ETEC at baseline had similar improvements in TLUS whether they were eradicated or not eradicated, 30 75 hours versus 32 50 hours ($p=0.530$), respectively. As per the applicant these data confirm that for both ETEC patients who were eradicated or not eradicated the 200 mg TID rifaximin dose is as efficacious as the higher dosing levels. It should be noted however that similar argument could be made for the placebo arm, where independent of the TLUS, the eradication rates were the same as those attained on rifaximin.

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 (%)
<i>Escherichia coli</i>	60	45/60 (75%)	37	24/37 (65%)	49	32/49 (65%)	2	2/2 (100%)
<i>Shigella sonnei</i>	3	3/3 (100%)	5	3/5 (60%)	1	1/1 (100%)	1	0/1
<i>Shigella flexneri</i>	2	½ (50%)	1	1/1 (100%)	1	0/1	0	0
<i>Salmonella Group C1</i>	3	2/3 (67%)	2	½ (50%)	4	3/4 (75%)	1	0/1
<i>Salmonella Group C2</i>	0	0	1	1/1 (100%)	4	2/4 (50%)	0	0
<i>Campylobacter jejuni</i>	4	3/4 (75%)	2	2/2 (100%)	0	0	0	0
<i>Cryptosporidium parvum</i>	18	12/18 (67%)	1	1/1 (100%)	15	5/15 (33%)	0	0
<i>Giardia lamblia</i>	5	4/5 (80%)	0	0	0	0	0	0
<i>Entamoeba histolytica</i>	1	1/1 (100%)	0	0	0	0	0	0
<i>Vibrio fluvialis</i>	1	1/1 (100%)	0	0	0	0	0	0
<i>Aeromonas hydrophila</i>	0	0	0	0	1	1/1 (100%)	0	0
<i>Plesiomonas shigelloides</i>	0	0	0	0	1	1/1 (100%)	0	0
<i>Vibrio parahaemolyticus</i>	0	0	0	0	1	1/1 (100%)	0	0

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

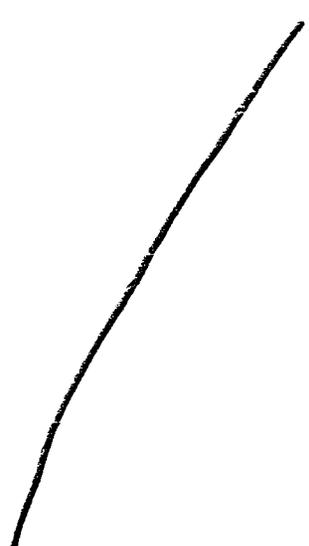
For rifaximin patients with ETEC, eradication rates of 75%, 70%, 65%, and 100% were seen with total daily doses of 600 mg, 800 mg, 1200 mg, and 1800mg respectively.

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.

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 total doses of 600 mg/day, 800 mg/day, or 1200 mg/day 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. As per the applicant, "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 effect of this compound.



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

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

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

When adverse event data were pooled for the three infectious diarrhea studies (RFID9801, RFID9701 and RFID9601), there was no difference in the adverse event rate for infectious diarrhea rifaximin patients compared to infectious diarrhea control patients (NOTE: the control group was comprised of subjects receiving placebo, ciprofloxacin, and trimethoprim/sulfamethaxazole). The incidence of fatigue was higher for the ID rifaximin group than for the infectious diarrhea composite control group (infectious diarrhea rifaximin rate = 3%, infectious diarrhea composite control rate = 0.4%). There were no associated symptoms such as lethargy, anemia or other CNS events indicating that this may be a chance finding rather than a clinically significant pattern.

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

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

Severe adverse events reported in 1% or more of rifaximin infectious diarrhea patients were abdominal pain (14 or 4%), nausea (12 or 3%), fecal incontinence (9 or 2%),

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

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

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

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

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

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

Special Populations

Efficacy

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

Recommendations

The MO concluded that

In 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

The MO is recommending that rifaximin be considered approvable in the treatment of traveler's diarrhea associated with ETEC. The issuance of an approval is dependent upon the completion and review of an additional controlled study that confirms the results from study RFID 9801 at the proposed dose. This study should also adequately address all concerns regarding microbiologic efficacy and provide evidence that distinguishes the microbiologic efficacy of rifaximin from that of placebo

Based on the currently available microbiologic data, Rifaximin should not be considered approvable for the treatment of subjects with dysentery (bloody stools), as clinical and microbiologic efficacy have not been established in this group. Rifaximin should also not be used in subjects with clinical evidence of dehydration. If no symptomatic improvement is apparent within 48 hours, consideration should be given to modification of the treatment regimen

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

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

Escherichia coli

I Introduction and Background

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

Applicant Salix Pharmaceuticals

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

Date of Submission December 21, 2001

CDER Stamp date December 26, 2001

Date Submission received by reviewer January 9, 2002

Date Review Begun January 9, 2002

Date Review Completed October 10, 2002

Drug Name Rifaximin

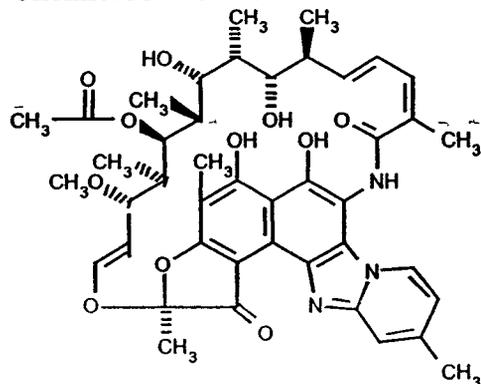
Proprietary Name LUMENAX™

Pharmacologic Category Rifamycin

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

Molecular formula C₄₃H₅₁N₃O₁₁

Molecular weight 785.89

Chemical structure**Dosage Form** Tablets**Route of Administration** Oral

Strengths 200 mg tablets

Proposed Indications and Usage

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

Escherichia coli

Related INDs IND

IND 52,980 (Salix,

IND ‘

IND ‘

Materials Reviewed

NDA volumes

JMP datasets submitted 12/21/2001

CDROM with WORD documents submitted 12/21/2001
CDROM with complete submission submitted 1/22/02
ACCESS Dataset submitted 1/22/02
Revised JMP datasets submitted 1/22/02
Email 1/29 identifying 19 patients who discontinued treatment
Email 1/19 containing a patient listing by study site
JMP datasets submitted 2/21/2002 (lab)
Email 4/3 identifying patients with stool leucocytes

Abbreviations

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

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

B State of Armamentarium for Indication(s)

(Literature Review)

Diarrhea is one of the most frequent health problems that affects travelers. The frequency varies depending on the economic level of the region visited but ranges between 20 – 50%. The economic impact is estimated at \$116 per patient or \$28 per traveler¹

The clinical picture consists of frequent watery, loose stool accompanied by nausea, vomiting, abdominal pain, cramping, or bloating, fever, and blood in the stool. A more formal definition is the passage of 3 or more unformed stools per 24 hours with at least 1 accompanying symptom. Recovery usually occurs spontaneously within 5 days although cases of persistent diarrhea more often due to protozoa have been described. Enterotoxigenic *Escherichia coli* is the most frequently implicated pathogen associated

with traveler's diarrhea, followed by enteroaggregative *Escherichia coli*, *Shigella* spp, *Salmonella* spp, *Campylobacter* spp, and intestinal protozoans

Isolation rates of the etiologic agents vary by travel location and season. ETEC is found in approximately 20 – 40% of travelers. A new cause of traveler's diarrhea, - - - - - enteroaggregative *Escherichia coli* has recently been identified and appears to account for approximately 25% of cases of traveler's diarrhea and accounted for 28% of cases previously characterized as of unknown etiology. Ciprofloxacin is effective for EAEC.

Shigella spp, *Campylobacter jejuni*, and *Salmonella* spp are isolated less frequently. *Shigella* spp accounts for 15 – 20% of cases and is often associated with bloody stools. Fluoroquinolone treatment is preferred because of increasing resistance to TMP/SMX. *Campylobacter jejuni* is found in approximately 5% of cases in the Caribbean but in 33% of travelers to Thailand. *Salmonella* can also be a pathogen but less frequently than ETEC.

Prevention is imperative but often not instituted or maintained by travelers.

Current treatment options include bismuth subsalicylate (Pepto-Bismol), a safe and efficacious treatment for mild traveler's diarrhea. More severe or prolonged cases respond to therapy with a quinolone antibiotic or TMP/SMX."

All patients with traveler's diarrhea should take fluids and electrolytes. Many patients will require no other therapy or can be treated symptomatically to decrease the number of unformed stools and shorten the duration of diarrhea. Bismuth subsalicylate reduces the number of unformed stools by approximately 50 percent, probably as a result of the antisecretory action of its salicylate moiety, although it also has antibacterial and anti-inflammatory properties. The drug decreases symptoms associated with viral gastroenteritis. Loperamide reduces diarrhea (both the frequency of passage of stools and the duration of illness) by up to 80 percent as compared with no treatment because of its ability to decrease intestinal motility, enhance the intestinal absorption of fluids and electrolytes, and decrease intestinal secretion. Loperamide should not be used in patients with fever or dysentery because of the infrequent potential for exacerbation of diarrhea in patients with an invasive bacterial infection, e.g., *Shigella* or *Salmonella*. Some patients with traveler's diarrhea who receive symptomatic therapy do not respond, and others may have a relapse when the drug is stopped.

Antibacterial drugs are more effective in curing the intestinal infection, but their onset of action is slower than that of bismuth subsalicylate or loperamide. Antimicrobial therapy is recommended after the passage of the third unformed stool in a 24-hour period, for diarrhea associated with moderate-to-severe abdominal pain or cramps, fever, or dysentery, and for symptoms that recur when drugs that relieve them are discontinued. For travelers to the noncoastal areas of Mexico in the summer, TMP/SMX is standard therapy. This combination may also be suitable in other areas, but a fluoroquinolone antibiotic is the drug of choice for most adults traveling to high-risk parts of the world.

The fluoroquinolone drugs differ from one another in their efficacy; norfloxacin, ciprofloxacin, and ofloxacin are all suitable and available in the US. After the initiation of antimicrobial therapy, diarrhea lasts 16 to 30 hours, whereas it lasts 59 to 93 hours if untreated, the average duration of illness before treatment in the studies cited was approximately 24 hoursⁱⁱⁱ

C Important Milestones in Product Development

Salix obtained the North American rights to rifaximin from Alfa-Wassermann Italy in March 1997 and filed an IND (52,980) shortly thereafter. In 1998, Salix received orphan drug designation from the Office of Orphan Products Development for rifaximin in the treatment of hepatic encephalopathy. In February 1998, the applicant requested a meeting with the DSPIDPs to discuss the development of rifaximin for _____ diarrhea in the US. The sponsor intended to submit completed study 9701 as well as an additional study (9801) in support of an NDA. At that time, the protocol for study 9801 was under development. In November 1998, the applicant submitted a statistical analysis plan (#010) for study 9701 (completed prior to the meeting) and then a revised plan on 1/29/99. The FDA requested clarification and then responded to a second revised analysis plan (#015) on 4/9/99. The FDA statistician suggested that a 2-sided 95% CI was preferable with an alpha equal to 0.25 for a 1-sided test.

In a FAX dated 9/9/99, the FDA commented on changes made by the applicant to protocol 9801 (A randomized DB, PC study of Rifaximin at 200 mg TID and 400 mg TID versus placebo). The applicant had proposed increasing the sample size to 120 patients per arm or 360 total in order to increase the safety database. The FDA was in agreement with this change. The applicant also proposed changing the definition of treatment failure to "continuing illness after 120 hours of treatment" from 72 hours. The FDA commented that formal acceptance could not be made as there were internal inconsistencies as the remainder of the protocol required only 72 hours of treatment. The MO found no response to this comment.

On 10/9/00 the applicant requested a pre-NDA meeting (IND 52,980 (#036)) and submitted a premeeting package (#039). The FDA requested that the applicant be prepared to comment on the feasibility of obtaining an _____ diarrhea claim in view of the fact that the microbiological information obtained from the clinical studies primarily pertained to enterotoxigenic *Escherichia coli* (ETEC). Additionally an explanation of how an approval would be granted for the 200 mg TID dose in the face of clinical trials using predominantly higher doses was requested. The meeting took place on 01/12/01.

Additionally, the FDA stated that Salix would receive a deferral for all age groups up to 12. The adult data could be used to support a claim for the 12 – 16 YO group (2/12/00, pre NDA meeting 21 CFR 314.55/pediatric study requirement)

The FDA again requested that a rationale be provided for the proposed 200 mg TID dose in view of the completion of the clinical studies at higher doses

As much information as possible was requested concerning the biolink between the generic ciprofloxacin used in study 9801 and the approved Bayer formulation

On 11/2/01 Salix submitted clinical microbiology information from study 9801 (#055 and #056) as requested at the 1/12/01 meeting. A teleconference followed on 12/7/01 and a FAX was sent on 12/14/01

The following comments are of significance

- 1) 
- 2) The Division questioned how the data submitted would support the proposed dose of 200 mg TID as the studies were performed using different doses and dosing regimens
- 3) It was suggested that Salix perform an additional study prior to the submission of their NDA application. This study should be a 3 arm study including the proposed dosing regimen, a placebo arm, and an active control arm
- 4) The applicant was requested to provide data supporting the comparability of the rifaximin formulations used in the clinical studies with that proposed for approval
- 5) The sponsor was requested to provide information establishing a biolink between the Spanish generic ciprofloxacin formulation used in study 9701 and the Spanish Bayer formulation as well as the US Bayer ciprofloxacin formulation

Medical Officer's Comment During the drug development phase of rifaximin it appears as if 3 issues were repeatedly dealt with. Those include _____ the lack of an adequate efficacy database at the 200 mg TID dose, and the continuing issue of the establishment of a biolink between the ciprofloxacin formulation used in study 9701

and the Spanish Bayer formulation to which a biolink could be established for the US formulation. These issues were not adequately addressed prior to the submission of the NDA. On February 1, 2002, the sponsor submitted a proposed protocol for study RFID3001 (IND 52,980, #058). The proposed study is a three-arm study comparing rifaximin at the proposed 200 mg PO TID for 3 days dose to ciprofloxacin to placebo. In a FAX on 3/27/02, the following comments were made:

“Please note that the review of NDA 21-361 is on-going. Based upon our review to date, the clinical microbiologic efficacy data from study RFID9801, in general, do not appear to distinguish the antimicrobial activity of rifaximin from that of placebo. Therefore, we recommend that the protocol for proposed Study RFID3001 be modified in order to provide the data needed to adequately assess both clinical and microbiological efficacy. For example, you might consider performing daily stool cultures on each patient in order to examine antimicrobial effects over time as a means of demonstrating microbiological efficacy.”

It will also be important to examine the correlation between clinical outcome by baseline pathogen and clinical microbiologic efficacy by baseline pathogen on a per patient basis. This analysis will be of particular interest because of the possibility that the clinical microbiologic efficacy assessment may be made during a time when the patient is receiving antimicrobial therapy.”

Other issues that were ongoing during the NDA review included:

- inadequate stability data
- drug substance and inadequately delineated manufacturing process
- Inadequate documentation of biolink between US Cipro and European generic formulation utilized in study 9701 (issue resolved during NDA review)

Antimicrobial Agents Approved for Infectious Diarrhea

(Excerpts from approved labels)

Cipro® (ciprofloxacin) Oral Suspension, Cipro® Tablets

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

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

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

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

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

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

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

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

ACTION

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

Bactrim Pediatric suspension, Tablets, DS Tablets

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

Septra® Suspension, Tablets, DS Tablets

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

Prior FDA Reviews and Guidances**Ciprofloxacin for Infectious Diarrhea – Precedent of Prior Approval
NDA 19-537 AP 1987**

The original approved label (1987) stated that ciprofloxacin was indicated for the treatment of “infectious diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexneri** *Shigella sonnei** when an antibacterial is indicated

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

The approval was based on 4 studies, one of which was performed in Mexico and was considered a study of traveler’s diarrhea The others were performed within the U S

D83-028-01 Dupont (Texas) – mostly American students going to Mexico
 D84-008-01 Sande (San Francisco) – stratified into homosexual and heterosexual men
 D84-051-01 Trenholme (Chicago) – acute infectious diarrhea in outpatients
 D84-051-02 Tanner (Utah) – same as Chicago study but enrolled few patients

All the studies compared ciprofloxacin 500 mg BID with TMP-SMX and placebo. The reviewing medical officer determined that evaluable patients were only those who had a pre and post treatment culture. Thus of 120 patients, only 44 were considered evaluable for efficacy.

ETEC was the most common isolate in the traveler's diarrhea study. *Campylobacter jejuni* was the most common isolate in the American studies.

Table 1
Numbers of isolates of various organisms in NDA 19-537

	ETEC	<i>Campylobacter jejuni</i>	<i>Shigella sonnei</i>	<i>Shigella flexneri</i>	<i>Shigella enteritidis</i>	<i>Shigella boydii</i>
TOTAL	19/19	11/12	7/7	4/4	3/3	0/0-

An efficacy supplement (SNDA 19-537, S-016) was submitted in 1993 to add the organisms *Shigella boydii* and *Shigella dysenteriae* to the label and to remove the asterisks from the organisms *Shigella flexneri* and *Shigella sonnei* for the infectious diarrhea indication. Data was submitted from three studies included in the original NDA as well as data from a study conducted in Bangladesh that compared ciprofloxacin 500 mg BID to ampicillin 500 mg QID.

Table 2
Numbers of isolates of various organisms in SNDA 19-537 (S-016)

	<i>Shigella sonnei</i>	<i>Shigella flexneri</i>	<i>Shigella dysenteriae</i>	<i>Shigella boydii</i>
TOTAL	2/2	34/35	11/11	4/4

The reviewing MO concluded that ciprofloxacin was safe and effective in the treatment of infectious diarrhea caused by *Shigella boydii*, *Shigella dysenteriae*, *Shigella flexneri* or *Shigella sonnei*.

The MO noted that although there were only 4 isolates of *Shigella boydii*, an approval with an asterisk was granted given the exquisite sensitivity of *Shigella* spp overall to ciprofloxacin.

The label was amended to its current format.

Ciprofloxacin is indicated for “Infectious diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella boydii**, *Shigella dysenteriae*, *Shigella flexneri*, and *Shigella sonnei** when antibacterial therapy is indicated
 * = Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients”

Medical Officer’s Comment *The total number of isolates for each organism in the ciprofloxacin NDA and supplement with eradication rates was*

**Table 3
 Pathogen Eradication Rates
 SNDA 19-537 (S-016)**

	ETEC	<i>Campylobacter jejuni</i>	<i>Shigella sonnei</i>	<i>Shigella flexneri</i>	<i>Shigella enteritidis</i>	<i>Shigella boydii</i>	<i>Shigella dysenteriae</i>
TOTAL	19/19	11/12	9/9	38/39	3/3	4/4	11/11

Comment *Thus it appears that the Division has granted an approval for organisms for a given indication when there are less than 10 isolates. Examples include the original approval of ciprofloxacin for infectious diarrhea where an approval was granted for *Shigella flexneri* and *Shigella sonnei* based on 7 and 4 isolates respectively with 100% efficacy as well as the SNDA approval where there was data for more than 10 isolates for other organisms within the same genus and where the antimicrobial activity of the drug could be expected to be similar e.g. approving *Shigella boydii* with only 4 isolates based on data with *Shigella flexneri* and other *Shigella* organisms*

Guidance The FDA did not address either travelers or infectious diarrhea in the 1997 ODE IV Evaluability Criteria and 1992 Points-to-Consider documents

Guidelines for the development of anti-infective drugs for acute infectious diarrhea including traveler’s diarrhea, were published in Clinical Infectious Diseases 1992,15(Suppl 1) S228 – 35

Medical Officer’s Comment *Of note the primary author was Dr Herbert Dupont, the primary investigator of the trials submitted in support of this NDA*

Acute infectious diarrhea is defined as 3 or more unformed stools per day plus one or more of the following signs and symptoms of enteric infection abdominal pain or cramps, nausea, vomiting, fever, dysentery, fecal urgency, and tenesmus of ≤ 72 hours duration and a pretreatment stool sample in which the pathogen of interest is isolated. Traveler’s diarrhea was defined as acute diarrhea occurring in a resident of an industrialized country during a temporary stay in a developing region of Latin America, Africa, or Southern Asia. Stool samples from such cases should be assessed for ETEC, *Salmonella*, *Shigella*, *Campylobacter jejuni*, *Aeromonas* spp, *Plesiomonas* spp, *Giardia lamblia*, *Cryptosporidium* spp, and *Entamoeba histolytica*. According to the guidelines,

“Traveler’s diarrhea includes both pathogen-specific illness and diarrheal illness without a known pathogen, a study performed in a population of travelers may therefore provide evidence of efficacy against either a specific pathogen or this syndrome in general”

Definitions of outcome include

Continuing illness The passage of more than 2 watery stools in a 24 hour period or the presence of enteric symptoms and any number of watery stools in a 24 hour period

Cure The patient has experienced a 24 hour period during which there are no symptoms and no watery stools or fewer than 2 watery stools or a 48 hour period with or without symptoms and without watery stools

Failure the clinical deterioration or worsening of symptoms after at least 24 hours of treatment or illness continuing after 5 full days of treatment

Excluded should be subjects who received an antimicrobial in any dosage after disease onset except for metronidazole. Additionally, 1 or 2 doses of bismuth subsalicylate, loperamide or other compounds that relieve symptoms are not grounds for exclusion. More doses are

Other guidelines include the suggestion that patients be examined prior to treatment and that a stool sample be obtained for culture. A daily diary should be kept for symptom assessment. Patients should be seen daily or at least prior to treatment and at follow-up that should occur 24 – 72 hours after completing a course of treatment. At that time, a follow-up stool specimen should be obtained.

The 2 most important parameters of clinical efficacy for the indication are

- 1) The decrease in the intensity and severity of symptoms (including the number of unformed stools per day), and
- 2) The decrease in the duration of illness or the TLUS

Other parameters include the decrease in unformed stool and the eradication of the infecting organism

Evaluable should be those patients who are observed for 48 hours post treatment or for 5 days. Recurrence should be considered a new illness.

Medical Officer’s Comment *Of note, the guidelines suggest that all or most patients should be considered clinically evaluable independent of the presence of a pathogen. However, a subject or a pathogen cannot be considered evaluable in the absence of a clinical outcome.*

D. Other Relevant Information

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

Table 4
Rifaximin Approval Status by Country

Country	Date of First Approval	Tradename(s)
Italy	April 1985	Normix
Vietnam	June 1995	Normix
Venezuela	October 1995	Normix, Flonorm
Bulgaria	September 1996	Normix
Mexico	June 1998	Redactiv, Flonorm
Spain	July 1998	Redactiv, Zaxin
Pakistan	November 1998	Normix
Romania	December 1998	Normix
Hungary	December 1998	Normix
Columbia	March 1999	Flonorm
Czech Republic	May 1999	Normix
Argentina	December 1999	Normix
Lebanon	January 2001	Normix

In Italy the approved indications are

- Acute and chronic intestinal infections caused by Gram-positive and Gram-negative bacteria
- Diarrhea caused by an altered balance of intestinal microflora (e.g., summer diarrhea, traveler's diarrhea, enterocolitis)
- Pre- and post-operative prophylaxis of infective complications in gastrointestinal surgery
- Adjunctive therapy in hyperammonemia (hepatic encephalopathy)

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

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

A Pharmacology and Toxicology

The proposed regimen of one 200 mg tablet given three times daily for 3 days is equal to a dose of 600 mg/day which is equivalent to 8.6 mg/kg for a 70 kg subject and 353 mg/m² for a patient with 1.7 m² body surface area (BSA)

Results from nonclinical studies demonstrated that there were no adverse systemic effects that would preclude the intended oral clinical use of rifaximin

Rifaximin did not show significant pharmacologic effects in mice on neurobehavior, locomotion, motor coordination, gastrointestinal motility, proconvulsant activity, hexobarbital-induced sleep time, and interaction with diazepam. No significant effects were seen on gastric acid secretion, gastric mucosa, or urinary volume and electrolytes in rats. Rifaximin was also devoid of meaningful effects on hemodynamics and respiration in dogs, or autonomic function in cats.

Single oral doses of 2000 mg/kg rifaximin were nontoxic to mice and rats. Multiple dose oral toxicity studies at doses as high as 1000 mg/kg/day (or 6000 mg/m²) for 4 weeks and at doses of 300 mg/kg/day (or 1800 mg/m²) for 6 months were conducted in rats with dosing duration ranging from 4 weeks to 6 months. Rifaximin appeared to be nontoxic to the rat with the exception of a decrease in weight gain and a decrease in peripheral lymphocyte count.

Multiple dose oral toxicity studies were conducted in dogs with dosing duration ranging from 1 week to 9 months. In non-GLP studies, rifaximin at daily oral doses ranging from 3 g/kg/day (or 60,000 mg/m²) for 7 days to 100 mg/kg/day (or 2,000 mg/m²) for 26 weeks was nontoxic to the dog. In a GLP study, repeat oral administration of rifaximin at 1000 mg/kg/day (or 20,000 mg/m²) for 39 weeks was nontoxic to the dog. Except for orange-colored feces/fur and non-specific stress-induced thymic atrophy/involution, no consistent clinical pathologic or histopathologic changes attributable to rifaximin were observed in the dog.

Rifaximin at oral doses as high as 300 mg/kg/day (or 1,800 mg/m²) had no adverse effects on general fertility of treated male and female rats. Similarly, oral doses as high as 300 mg/kg/day to pregnant rats had no adverse effects on postnatal development and reproductive performance of the offspring.

Rifaximin was not teratogenic following oral administration during organogenesis at doses as high as 300 mg/kg/day in rats (or 1,800 mg/m²) and 1000 mg/kg/day in rabbits (or 8,500 mg/m²). There was evidence of slight maternal toxicity (i.e., decreased weight gain and food consumption) and slight embryotoxicity (i.e., increased incidence of incomplete ossification of cranial bones and pelvic bones).

in rat fetuses and increased incidence of fetuses with an additional 13th rib or an additional vertebra in the thoracolumbar region in rabbit fetuses)

B. Microbiology

The mechanism of action of rifaximin is similar to that of rifampin, its structural analogue and that it inhibits DNA-dependent RNA polymerase activity in susceptible cells. Rifaximin selectively inhibited RNA synthesis in *Escherichia coli* indicating that the mechanism of action for rifaximin is similar to that of rifampin.

Rifaximin exhibits antibacterial activity against both Gram-positive and Gram-negative bacteria. In clinical studies, it was shown to be effective against localized gastrointestinal pathogens that cause infectious diarrhea. Because of the negligible systemic absorption of rifaximin, clinical effectiveness against systemic infections has not been studied.

Usually, MIC breakpoints are established on systemic exposure levels, i.e., drug levels in the plasma. However, because rifaximin is essentially unabsorbed and the therapeutic site of action is the GI tract, the applicant determined that the clinically relevant concentration is that in the feces. Fecal concentrations of rifaximin measured one day post-treatment following a three day 400 mg rifaximin BID dosing regimen, had a mean rifaximin concentration of about 8,000 µg of rifaximin/g of feces (range — µg/g, N=4). Assuming equivalent densities (1 g/mL) this is equivalent to 8,000 µg rifaximin/mL. No susceptibility breakpoints are being proposed based on the intended indication and the extremely high fecal levels of rifaximin in combination with range of MICs observed.

For the 1,607 clinical isolates tested, the highest MIC established was 1024 µg/mL. As noted above, the fecal concentration of rifaximin was determined to be about 8,000 µg/mL or almost 8-fold higher than the highest MIC established for these clinical pathogens. Clostridium species was found to be the most sensitive organism to rifaximin, MIC₉₀ = 0.005 - 2 µg/mL. These studies established that the MIC₅₀ and MIC₉₀ ranges for *Escherichia coli* were 8 - 64 µg/mL and 16 - 128 µg/mL, respectively. The overall MIC₅₀ and MIC₉₀ ranges for the 1,607 isolates were 0.001–128 µg/mL and 0.005–256 µg/mL, respectively.

NOTE The above were established utilizing the 400 mg BID dose and not the proposed 200 mg TID proposed dose.

C. Pharmacokinetics and Pharmacodynamics

Pharmacokinetic studies have demonstrated negligible systemic exposure to rifaximin, i.e., less than 1%. Fecal concentrations of rifaximin, following an oral dose of 400 mg rifaximin twice daily (800 mg/day) for three days was determined to be about 8,000 µg rifaximin/g feces (777 – 15,503 µg/g, N=4). By post-

treatment day 3, the mean rifaximin fecal concentration was about 4,400 µg/g (31-19,620 µg/g, N=14) and by post-treatment day 5 it was about 3,300 µg/g (55 – 9655 µg/g, N=3) These data indicate that rifaximin, regardless of dose, essentially remains unabsorbed in the gastrointestinal tract

For further detailed information, Please refer to the appropriate review

III Description of Clinical Data and Sources

A Overall Data

2 clinical trials (RFID9801 and RFID9701) were considered pivotal by the applicant for establishing the clinical efficacy of rifaximin in the treatment of traveler's diarrhea. A third study (RFID9601) was included as a supportive of efficacy study. RFID9801 was conducted by the applicant Salix under FDA guidance and was a Phase III, randomized, placebo-controlled study designed to support a claim of efficacy for rifaximin in the treatment of traveler's diarrhea (EOP meeting for IND 52,980, September 21, 1998). RFID9701, a Phase III study comparing rifaximin to ciprofloxacin, was developed and conducted by Alfa Wassermann and then transferred to Salix for analysis. The statistical analysis plan for RFID9701 was prepared by Salix under FDA guidance (EOP meeting, September 21, 1998). RFID9601, a Phase 2 dose-ranging study, was conducted by Alfa Wassermann.

A total of 15 other published studies of rifaximin in infectious diarrhea or traveler's diarrhea and an additional four unpublished studies that included over 400 patients treated with rifaximin were referenced.

B Table Listing the Clinical Trials**Table 5**

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

Patients were all travelers with infectious diarrhea

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

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

Postmarketing Experience

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

IV Clinical Review Methods

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

The applicant submitted 2 clinical trials (RFID9801 and RFID9701) considered pivotal for establishing the clinical efficacy of rifaximin in the treatment of traveler's diarrhea as well as a third study (RFID9601) considered supportive of efficacy. Additionally, a total of 15 other published studies of rifaximin in infectious diarrhea or traveler's diarrhea and an additional four unpublished studies that included over 400 patients treated with rifaximin were referenced.

In order to assess the overall data quality and integrity of the datasets, the MO reviewed a random sample of the CRFs from each of the pivotal and supportive studies. Twenty percent of the CRFs were reviewed and cross-checked with the CRTs (JMP datasets) to ensure accurate transcription of the data. During the initial phase of this review the MO discovered inconsistencies in the identification of the investigators and sites in the datasets. This was discussed with the applicant and a satisfactory explanation as well as revised datasets were provided. The resubmitted datasets were assessed for accuracy and no problems were discovered.

Subsequent to the review of the CRFs, the MO reviewed each study separately as well as all published literature reports considered supportive by the sponsor.

During the course of the review, the MO found that the applicant had not provided a separate review of microbiologic efficacy for each study but that an integrated summary of microbiologic efficacy was done instead. The applicant's rationale for this was that an analysis of the dose-related effects of rifaximin on the eradication of ETEC, the most common organism identified at baseline in the two primary efficacy studies (RFID9801 and RFID9701) revealed that there were none. Therefore, it was deemed appropriate to pool the microbiological data from all three studies (RFID9801, RFID9701 and RFID9601) for microbiological analyses.

The MO deemed it necessary to do a by study analysis because it was determined that it was not appropriate to extrapolate results from higher to lower doses. Additionally, eradication rates were not consistent within the same dose group as well as across study groups.

B Were Trials Conducted in Accordance with Accepted Ethical Standards

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

C Evaluation of Financial Disclosure

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

V Integrated Review of Efficacy

A Brief Statement of Conclusions

Two adequate and well-controlled studies of rifaximin for the treatment of traveler's diarrhea were submitted for review. In studies RFID9701 (rifaximin 400 mg BID vs ciprofloxacin 500 mg BID) and RFID9801 (rifaximin 200 mg TID, 400 mg TID, and placebo), time to last unformed stool (TLUS) was predefined as the primary efficacy endpoint. Rifaximin was found to be significantly better than placebo in study RFID 9801 ($p = 0.0001$ for the rifaximin 200 mg TID versus placebo group and $p = 0.0001$ for the rifaximin 400 mg TID versus placebo group) and non-inferior to ciprofloxacin, an approved comparator, in study RFID9701 ($p=0.006$, Kaplan-Meier).

There were several secondary endpoints such as improvement in diarrheal syndrome and improvement in clinical symptoms and rifaximin was effective as measured by several of these.

The effectiveness of the 200 mg TID and 400 mg TID rifaximin doses appeared to be the same as measured by TLUS, thus the applicant chose the lowest effective dose as that for which they are seeking approval.

Of note were the very similar pathogen 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 similar rates raised serious concerns regarding the true antimicrobial activity of rifaximin.

The safety profile of rifaximin in the three controlled infectious diarrhea 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 GI in nature and were consistent with symptoms of the disease under treatment e.g., abdominal pain, fecal incontinence, flatulence, nausea, and tenesmus, which occurred in $\geq 5\%$ of patients. No serious adverse events with rifaximin use and no deaths were reported in the ID trials.

B Detailed Review of Trials by Indication

As per the MO only one (RFID 9801) of the randomized, double-blind, multicenter phase III studies submitted by the applicant as pivotal trials provided the primary support for

the clinical efficacy of rifaximin in the treatment of infectious diarrhea in travelers at the proposed 200 mg PO TID for 3 days dose. The other (RFID9701) was considered supportive because the dosing regimen (400 mg PO BID) was not the same as that requested for approval (200 mg PO TID) and the clinical efficacy rates were lower in study 9701 at the higher daily dose as compared to 9801. This difference appeared to be due to the dosing interval and served to indicate the need for TID as opposed to BID dosing.

Supportive information was also provided by the dose-comparison phase II study RFID9601, that compared three dose regimens and the bacteriological response of rifaximin to a standard regimen of TMP/SMX in the treatment of traveler's diarrhea.

Due to the above, the MO elected to first review study 9801, the pivotal study of this submission.

Study RFXID 9801

Title A randomized, double-blind, parallel-group, placebo controlled study of rifaximin 600 mg a day (200 mg TID) and 1200 mg/day (400 mg TID) in the treatment of bacterial infectious diarrhea in travelers

Study dates May 14, 1999 – July 30, 2000

Principal Investigators, Sites and Patient Numbers

Herbert Dupont MD	Clinical Infectious Disease Department of Int Med Texas Medical Center	Guadalajara, Mexico Morelia, Mexico	Rifaximin (600 mg/day) 64 Rifaximin (1200 mg/day) 65 Placebo 66
David Sack MD	Johns Hopkins University Vaccine Testing Unit	Antigua, Guatemala	Rifaximin (600 mg/day) 33 Rifaximin (1200 mg/day) 34 Placebo 33
Robert Steffen MD	Institute for Social and Preventative Medicine University of Zurich	Mombasa, Kenya	Rifaximin (600 mg/day) 28 Rifaximin (1200 mg/day) 27 Placebo 30

Study Summary

A phase III, randomized (1:1:1), double-blind, parallel-group, multicenter study that was conducted in adult travelers suffering from acute infectious diarrhea in Mexico, Kenya, and Guatemala. Patients began treatment within 72 hours of onset of diarrhea. The duration of the study was 4 – 5 days including 3 days of treatment followed by a post treatment evaluation 24 to 48 hours after the last dose.

The study consisted of a pretreatment / baseline visit (informed consent, history, physical, laboratory, randomization, and receipt of drug and diary), self-administered treatment

with rifaximin or placebo on days 1 – 3, a final clinical evaluation on day 4, and collection of patient diary cards on day 5 or daily during the study. Stool specimens for quantification and identification of enteric pathogens and classification of ETEC were collected prior to the first dose and 48 to 72 hours after the last dose of study drug was administered. Patients maintained daily diary cards for recording the time and form (formed, soft, watery) of all stools passed, the time and date of study drug administration, the presence or absence of enteric signs and symptoms (abdominal pain/cramps, excessive gas/flatulence, nausea, vomiting, fever, fecal urgency, blood and/or mucus, tenesmus), adverse events, and use of concomitant medications. At follow-up, stool samples were analyzed for evidence of dysentery, i.e., presence of gross blood. Safety was evaluated by monitoring the occurrence of adverse events, both reported and observed, vital signs, and by conducting routine clinical laboratory tests (hematology, chemistry, and urinalysis) and physical examinations. Stool was cultured at a local lab for *Shigella*, *Salmonella*, *Campylobacter jejuni*, *Aeromonas*, *Vibrio*, *Plesiomonas*, and *Yersinia enterocolitica*. Protozoa were identified by an ELISA at a central laboratory. — Additionally if *Escherichia coli* was present, 5 colonies were isolated and sent to the central lab for further processing.

Patients were treated with one of the following treatment regimens for up to three consecutive days:

- Rifaximin 600 mg/day delivered as 1 x 200-mg tablet plus 1 x placebo tablet PO TID
- Rifaximin 1200 mg/day delivered as 2 x 200-mg tablets PO TID
- 2 placebo tablets PO TID

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

The primary objective of the study was to compare the safety and efficacy of rifaximin 200 mg TID (600 mg/day) and 400 mg TID (1200 mg/day) to placebo in the treatment of infectious diarrhea in travelers. A TID regimen was chosen due to the poor systemic absorption of rifaximin and the belief that more frequent exposure would lead to more efficacy given the rapid bowel transit that occurs during diarrhea.

Eligible for inclusion were male and female adult travelers at least 16 years of age with acute diarrhea who had at least 3 unformed stools within the 24 hours preceding randomization and at least one of the signs and symptoms of enteric infection, e.g., abdominal pain or cramps, nausea, vomiting, fever (≥ 100 °F or 37.8 °C), dysentery (passage of bloody stool), fecal urgency, excessive gas/flatulence, or tenesmus.

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

- 1 or more symptoms of moderate to severe dehydration,
- Acute diarrhea for more than 72 hours prior to randomization,
- Moderate to severe dehydration,

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

Concomitant medication for the treatment of pre-existing conditions other than diarrhea was allowed during the study as long as there was no interference with the expected activity of rifaximin. Acetaminophen was also allowed and subjects were encouraged to increase their fluid intake. Antimotility agents as well as other antidiarrheal agents were not allowed.

Efficacy analyses were performed using the intent-to-treat (ITT) population defined as all patients who were randomized to treatment. Protocol violators and patient dropouts were considered part of the ITT population and were included in the efficacy analyses.

Microbiological analyses were performed on the subset of the ITT population from whose stool specimens at pre-treatment were positive for pathogens and who had a culture performed on post-treatment stool specimens.

The primary efficacy endpoint was the time to last unformed stool (TLUS) defined as the interval beginning with the first dose of study drug and ending with the last unformed stool passed, after which wellness (clinical cure) was declared. TLUS was determined from the data collected from the following time intervals: 0–24 hours, 24–48 hours, 48–72 hours, 72–96 hours, 96–120 hours. Patients who met the criteria for clinical cure (defined below in secondary efficacy variables) immediately after the start of the study and prior to passing any unformed stools were defined as having a TLUS of 0 hours. Patients who terminated the study early due to treatment failure were noted as having a censored TLUS as of 120 hours. Patients who terminated the study early due to other reasons (AE, patient request, intercurrent illness) or because they completed the study without achieving a clinical cure were noted as having a censored TLUS as of the time of the last available information on unformed stools.

Secondary efficacy variables included

- Improvement of Diarrheal Syndrome: reduction of 50% or more in the number of unformed stools (watery or soft) passed during a 24-hour interval compared to the

number of stools passed during the 24 hours immediately preceding enrollment in the study

- Number of Unformed Stools Passed per Time Interval of Interest – the number of unformed stools (soft or watery) passed during the intervals 0–24 hours, 24–48 hours, 48–72 hours, 72–96 hours, and 96–120 hours after the first dose of study medication

Clinical cure was defined as follows

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

Treatment failure was defined as

- Clinical deterioration or worsening of clinical symptoms after at least 24 hours of therapy, or
- Subject too ill to continue in a placebo-controlled study, or
- Illness continuing after 120 hours

Also assessed were

Persistence and Severity of Clinical Symptoms – number (%) of patients experiencing the following clinical symptoms during the intervals 0–24 hours, 24–48 hours, 48–72 hours, 72–96 hours, 96–120 hours after the first dose of study medication: nausea, vomiting, fever, abdominal pain/cramps, excess gas/flatulence, tenesmus, urgency

Microbiologic Cure: post-treatment culture that was negative for the pre-treatment etiologic pathogen

Statistics

RFID9801 was a superiority study. Unless otherwise stated, all of the applicant's statistical tests were performed at the 0.05 significance level, using a two-tailed test. Analyses with a p-value between 0.05 and 0.10 were noted in the results section as approaching significance.

Amendments

The protocol was amended twice, first on 1/20/99 prior to subject enrollment after consultation with the FDA and second on 7/20/99.

The initial amendment clarified the definitions of TLUS and clinical cure to those specified above, modified the randomization method to specify a randomization code for each site, made numerous minor modifications to the inclusion criteria as well as the patient diaries, specified rigorous assessment of treatment by center interactions, eliminated the overall comparison of the treatment groups and only specified that each of the rifaximin groups will be compared to the placebo group with respect to TLUS using the log-rank and generalized Wilcoxon (Gehan-Breslow) tests at a significance level of 0.025. Additionally, as per FDA request, 2-sided 97.5% confidence intervals for the difference in median TLUS (rifaximin groups - placebo group) would be calculated.

Amendment 2 increased the sample size of the study to 360 subjects, modified the definition of continuing illness to begin at 120 hours instead of 72 hours (to minimize the amount of censoring when determining TLUS), modified the methods for recording dysentery so that only personnel qualified to make a determination would assess dysentery, and updated information on sponsor resource personnel.

Patient Disposition and Evaluability/Demographics

380 patients were enrolled in the study at centers located in Mexico, Guatemala, and Kenya, 125 (33%) in the rifaximin 200 mg TID group, 126 (33%) in the rifaximin 400 mg TID group, and 129 (34%) in the placebo group. 195/380 (51%) were enrolled at the Mexico site (Site 01), (66, 64, and 65 in the placebo, rifaximin 200 mg TID, and rifaximin 400 mg TID groups, respectively), 85 (22%) were enrolled at site 2 in Kenya (30, 28, and 27 in the placebo, rifaximin 200 mg TID, and rifaximin 400 mg TID groups, respectively), and 100 were enrolled in Guatemala (33, 33, and 34 in the placebo, rifaximin 200 mg TID, and rifaximin 400 mg TID groups, respectively). One additional patient, for a total of 381 patients, was randomized but never received study drug, the CRF was not recovered, and the patient had no information entered in the database. 380 patients were included in the ITT efficacy analysis.

Medical Officer's Comment Although the applicant specified in the study report as well as in form 1572 that there were other investigators and sites other than the 3 primary investigators and sites, a breakdown of enrollment or efficacy by site was not provided in the initial submission. This information was requested and submitted on 2/19/02. As per the applicant, all subjects were assessed by qualified medical personnel and the primary investigator for each country evaluated all the CRFs for all sites within the country. As can be seen from the following table, the largest single site that enrolled 1/3 of all subjects was that in Guatemala. Otherwise there seemed to be a more balanced enrollment from the 6 Mexican sites and the 2 Kenyan

Table 6
Patients by site

Site	Country	Placebo	Rifaximin 200 mg TID	Rifaximin 400 mg TID
		129 (100%)	125 (100%)	126 (100%)
	Guatemala	33 (26%)	33 (26%)	34 (27%)
	Mexico	17 (13%)	19 (15%)	18 (14%)
	Mexico	8 (6%)	7 (6%)	7 (6%)
	Mexico	15 (12%)	12 (10%)	13 (10%)
	Mexico	6 (5%)	5 (4%)	5 (4%)
	Mexico	15 (12%)	12 (10%)	13 (10%)
	Kenya	24 (19%)	22 (18%)	21 (17%)
	Kenya	6 (5%)	6 (5%)	6 (5%)
	Mexico	5 (4%)	9 (7%)	9 (7%)

Ninety-one percent (344/380) of the patients completed the study (115 (92%), 119 (94%), and 110 (85%) in the rifaximin 200-mg TID, rifaximin 400 mg TID, and placebo groups, respectively) 36 patients (9%) terminated early, 27 (7.1%) prior to completing study medication, and 9 (2%) patients after dosing was complete. The primary reason for early termination was treatment failure. Eight (6%) of the placebo patients terminated the study after dosing was complete as compared to none of the 200 mg TID rifaximin patients and 1 (1%) rifaximin 400-mg TID patient. One patient in the 200 mg TID rifaximin group terminated the study on day 1 due to an adverse event.

Table 7
Disposition of Patients – RFID9801

Disposition	Number (%) of Subjects		
	Placebo	Rifaximin 200 mg TID	Rifaximin 400 mg TID
Enrolled (Randomized)	129	125	126
Completed Study	110 (85%)	115 (92%)	119 (94%)
Terminated Study	19 (15%)	10 (8%)	7 (6%)
Termination After Dosing Complete	8 (6%)	0	1 (1%)
Early Termination (< 9 doses or 3 days)	11 (9%)	10 (8%)	6 (5%)
Reason for Early Termination			
Treatment Failure	10 (8%)	4 (3%)	6 (5%)
Noncompliance	0	3 (2%)	0
Adverse Event*	0	1 (1%)	0
Lost to Follow-up	1 (1%)	0	0
Other / Administrative	0	2 (2%)	0

*Nausea, loss of taste, lack of appetite / indisposition on study day 1

Protocol Violations

The number of patients with protocol violations was similar across the treatment groups (19 (15%), 21 (17%), and 20 (16%) patients from the placebo, 200-mg TID rifaximin, and 400-mg TID rifaximin groups, respectively) Thirty patients took a concomitant medication that was likely to affect efficacy, (11 (9%), 11 (9%), and 8 (6%) patients from the placebo, 200-mg TID rifaximin, and 400-mg TID rifaximin groups, respectively) The most common prohibited medications were aspirin-like or ibuprofen taken for pain or headache Other concomitant medications included antimotility agents, absorbent agents, antisecretory agents, and antimicrobial drugs with expected activity against enteric pathogens

Table 8
Protocol Violations – RFID9801

Violation*	Number (%) of Subjects		
	Placebo N = 129	Rifaximin 600 mg N = 125	Rifaximin 1200 mg N = 126
Inclusion/Exclusion Criteria Not Met	4 (3%)	3 (2%)	6 (5%)
Acute diarrhea for more than 72 hours*	2 (2%)	3 (2.4)	6 (5%)
Antimicrobial taken within 7 days of entry*	1 (1%)	0	0
Other active, significant disease(s)*	1 (1%)	0	0
Other Protocol Violations	15 (12%)	18 (14%)	14 (11%)
Medication likely affecting efficacy*	11 (9%)	11 (9%)	8 (6%)
Failed to take ≥5 doses in first 2 days*	6 (5%)	7 (6%)	6 (5%)
Failed to complete diary on day 1 or 2*	4 (3%)	2 (2%)	2 (2%)
Subject unblinded inappropriately*	1 (1%)	1 (1%)	2 (2%)
Failed to return to clinic after randomization*	0	2 (2%)	0

*Patients may be counted in more than one category

Populations

Thirty-one patients were excluded from the efficacy evaluable population (10 placebo, 9 rifaximin 200 mg TID and 12 rifaximin 400 mg TID) 1 rifaximin 200 mg TID subject was excluded from the safety population (ITT = all subjects randomized)

Table 9
Populations

	Number (%) of Subjects		
	Placebo	Rifaximin 600 mg	Rifaximin 1200 mg
All subjects	129	125	126
ITT	129	125	126
Efficacy Evaluable	119	116	114
Inclusion/Exclusion Criteria Not Met*	4 (3%)	3 (2%)	6 (5%)
Failed to complete diary on day 1 or 2*	4 (3%)	2 (2%)	2 (2%)
Failed to take ≥5 doses in first 2 days*	6 (5%)	7 (6%)	6 (5%)
Safety	129	124	126
Randomized, not treated	0	1 (1%)	0

* Patients may be counted in more than one category

Medical Officer's Comment The MO elected to perform all analyses on the applicant's ITT population and not the efficacy evaluable as the differences between the 2 populations were very small. However, the MO also determined that an MITT population

consisting of those patients who had a baseline pathogen would be a more important population on which to perform the analyses

Demographics

Demographic characteristics for age, gender, and race were comparable between the treatment groups. Patient age ranged from 16 to 72 years, with a mean age of 28.3 years in the placebo group and 29 years in the rifaximin groups. Most patients were white. Significant treatment-by-site interactions were noted for age and gender. Mean age was higher at the Kenya site (36.5 years in the placebo group and 43.1 years in the 400-mg TID rifaximin group) compared to the Mexico and Guatemala sites (range 23.7 to 28.2 years for all treatment groups).

For gender, the percentage of males to females by treatment group at the Kenya site was reversed compared to the other two sites.

Table 10
Demographics

Demographic Characteristic	Placebo N = 129	Rifaximin 200 mg TID N = 125	Rifaximin 400 mg TID N = 126
Age (Years)			
n	129	121*	124*
Mean ± SEM	28.3 ± 0.9	29.0 ± 1.1	29.0 ± 1.0
Range	16 – 69	18 – 72	18 – 66
Sex			
Male	66 (51%)	68 (54%)	61 (48%)
Female	63 (49%)	57 (46%)	65 (52%)
Race			
White	112 (87%)	104 (83%)	106 (84%)
Black	2 (2%)	1 (1%)	4 (3%)
Other	15 (12%)	20 (16%)	16 (13%)

*Four 600 mg subjects and Two 1200 mg subjects had no recorded birthdate

Disease Characteristics

In each treatment group, 47% to 51% of patients had at least one enteric pathogen in the pretreatment stool sample. In addition, 37% to 42% of patients had diarrhea classified as leukocyte negative and had no enteric pathogen isolated in the pretreatment stool sample.

Duration of pretreatment illness was similar amongst the treatment arms and the median ranged from 30 – 32 hours.

Number of unformed stools was also similar between treatment arms with a median of 5 in the 24 hours preceding enrollment. Abdominal pain/cramps and urgency were the most common symptoms noted at baseline, reported in 86% to 92% of patients in each.

treatment group Excessive gas, flatulence (from 77% to 80%) and nausea (53% to 59%) were also commonly reported Based on the presence of gross blood in the pretreatment stool samples, there were very few reports of patients with dysentery (3 placebo, 2 rifaximin 200 TID mg, 1 rifaximin 400 mg TID)

Table 11
Disease Characteristics at Baseline (ITT Population) – RFID9801

Disease Characteristic	Placebo N = 129	Rifaximin 200 mg TID N = 125	Rifaximin 400 mg TID N = 126
Type of Illness			
Leukocyte Negative, Agent Negative**	48 (37%)	43 (34%)	53 (42%)
Leukocyte Negative, Agent Specific**	52 (40%)	55 (44%)	52 (41%)
Leukocyte Positive, Agent Negative**	14 (11%)	5 (4%)	10 (8%)
Leukocyte Positive, Agent Specific**	9 (7%)	14 (11%)	7 (6%)
Leukocyte/Agent Missing or Not Tested**	6 (5%)	8 (6%)	4 (3%)
Duration of Pretreatment Illness (Hours)*			
N	126	121	125
Mean ± SEM	34.1 ± 1.7	35.2 ± 1.8	36.0 ± 2.0
Median	31.8	30.0	31.8
Range	2.5 – 76.5	1.5 – 122.9	1.3 – 96.0
Number of Unformed Stools in Previous 24 Hours			
N	121	119	122
Mean ± SEM	6.1 ± 0.3	6.1 ± 0.3	5.7 ± 0.3
Median	5.0	5.0	5.0
Range	3 – 25	3 – 20	3 – 25
Symptom Present			
Abdominal Pain/Cramps	118 (92%)	108 (86%)	111 (88%)
Urgency	111 (86%)	108 (86%)	110 (87%)
Excess Gas/Flatulence	103 (80%)	96 (77%)	100 (79%)
Nausea	72 (56%)	74 (59%)	67 (53%)
Tenesmus	46 (36%)	43 (34%)	39 (31%)
Fever	32 (25%)	26 (21%)	26 (21%)
Vomiting	12 (9%)	20 (16%)	14 (11%)
Gross Blood			
No Evidence	125 (97%)	120 (96%)	124 (98%)
Yes (Evidence)	3 (2%)	2 (2%)	1 (1%)
Missing or Not Tested	1 (1%)	3 (2%)	1 (1%)

** Agent negative = baseline culture for pre-treatment pathogens negative, agent specific = baseline pre-treatment culture positive, agent missing = no culture results available

*Three subjects in the placebo group, four in the 600 mg group, and one in the 1200 mg group had no time of onset (but day of onset was given) or else no time of first dose (02-003 and 02-033)

***Medical Officer's Comment** Of note the higher incidence of vomiting at baseline in subjects that received the 200 mg PO TID regimen as compared to those on placebo or the 400 mg TID regimen Also notable was the very small number of subjects who participated in this trial with dysentery*

**APPEARS THIS WAY
ON ORIGINAL**

Pre-treatment and Concomitant Medications

69% of placebo recipients as compared to 64 % of rifaximin 600 mg and 66% of rifaximin 1200 mg recipients received a concomitant medication

Thirty patients took medications that were likely to affect efficacy and included antimotility agents, absorbent agents, antisecretory agents, aspirin, ibuprofen, and antimicrobial drugs with expected activity against enteric bacterial pathogens

Fluoroquinolones taken before completion of the study were administered as rescue medication in 12 placebo, 1 rifaximin 200 mg TID, and 4 rifaximin 400 mg TID patients

Table 12
Concomitant Medications – RFID9801

	Placebo N = 129	Rifaximin 200 mg TID N = 125	Rifaximin 400 mg TID N = 126
Any Concomitant Medication	89 (69%)	80 (64%)	83 (66%)
Medication			
Aminoquinolones	27 (21%)	24 (19%)	20 (16%)
Anilides	21 (16%)	15 (12%)	23 (18%)
Progestogens, Estrogens, Combinations	14 (11%)	12 (10%)	18 (14%)
Propionic Acid Derivatives	5 (4%)	9 (7%)	16 (13%)
Fluoroquinolones	12 (9%)	1 (1%)	4 (3%)
Multivitamins, Other Combinations	4 (3%)	5 (4%)	7 (5%)
Antipropulsives	6 (5%)	5 (4%)	2 (2%)
Other Antihistamines for Systemic Use	4 (3%)	4 (3%)	4 (3%)
Biguanides	3 (2%)	2 (2%)	6 (5%)
Hormonal Contraceptives	2 (2%)	3 (2%)	4 (3%)
Selective Serotonin Reuptake Inhibitors	5 (3%)	1 (1%)	3 (2%)
Ascorbic Acid (Vitamin C)	3 (2%)	3 (2%)	1 (1%)
Glucocorticoids	1 (1%)	5 (4%)	1 (1%)
Beta-2-Adrenoceptor Agonists	1 (1%)	4 (3%)	2 (2%)
Multivitamins with Minerals	1 (1%)	1 (1%)	4 (3%)

Treatment Compliance

Treatment compliance was measured by recording the number of doses of study medication taken during the study. There were 102 (79%) placebo, 99 (79%) rifaximin

200 mg TID 107 (85%) rifaximin 400 mg TID patients who took all 9 doses of study medication as per the protocol

Table 13
Compliance – RFID9801

Total Number of Doses	Placebo N = 129	Rifaximin 200 mg TID N = 125	Rifaximin 400 mg TID N = 126
Number (%) of Subjects With			
All 9 Doses	102 (79%)	99 (79%)	107 (85%)
8 Doses	16 (12%)	14 (11%)	11 (9%)
7 Doses	2 (2%)	5 (4%)	2 (2%)
< 7 Doses	9 (7%)	7 (6%)	6 (5%)

Primary Efficacy Endpoint Time to Last Unformed Stool (TLUS)

ITT population

As per the applicant, “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 600-mg versus placebo group and $p = 0.0001$ for the rifaximin 1200-mg versus placebo group) “

Median TLUS was 32.5 hours in the rifaximin 200 mg TID group, 32.9 hours in the 400 mg TID group, and 60 hours in the placebo group. Confidence Intervals (CIs) based on the Cox hazard ratio for TLUS, demonstrated a significantly shorter time to wellness in the rifaximin groups than in the placebo groups. The hazard ratios were above the two-sided 97.5% lower confidence limit of 1.0 for comparing time to wellness in the rifaximin 200 mg TID group versus placebo (1.81, 97.5% CI 1.34 – 2.45) and in the rifaximin 400 mg TID group versus placebo (1.34, 97.5% CI range 1.15 – 1.55).

Table 14
Distribution of Time to Last Unformed Stool ITT – RFID9801

	Placebo N = 129	Rifaximin 200 mg TID N = 125	Rifaximin 400 mg TID N = 126
TLUS in Hours (Kaplan-Meier Estimates)			
Median TLUS (50% With TLUS Less Than)	60.0	32.5	32.9
95% Confidence Interval of Median TLUS	48.4 – 92.0	28.4 – 43.6	24.8 – 44.0
P-Value Comparing Active Drug to Placebo (Pairwise Treatment Group Comparisons)			
Wald Statistic		0.0001	0.0001
97.5% Confidence Interval		(1.34, 2.45)	(1.15, 1.55)

Medical Officer's Comment. The TLUS was similar between the rifaximin arms. A breakdown by site revealed that the median TLUS was the shortest at the Guatemalan site where 33% of the subjects were enrolled as compared to the Kenyan site.

The MO requested that the FDA statistician assess these differences and comment on the pooling of the data. As per the applicant "The differences in distribution did not interfere with the overall evaluation of treatment-group differences and it was considered valid to pool TLUS results from the three treatment groups"

The FDA analysis agreed with that of the sponsor.

Additionally of interest is the more prolonged TLUS at the higher rifaximin dose as compared to the lower at the Mexican site.

Table 15
Time to Last Unformed Stool ITT by Site– RFID9801

Mean TLUS in hours	Placebo	Rifaximin 200 mg TID	Rifaximin 400 mg TID
Mexico	59.1	32.5	46.1
Kenya	74.3	42.7	30.3
Guatemala	49	28.9	23.3

A TLUS of 0 hours, indicating wellness was achieved immediately after the start of treatment, was achieved by 29 patients. The proportion of patients achieving a TLUS of 0 hours was similar across all treatment groups: 8 (6.2%), 11 (8.8%), and 10 (7.9%) patients in the placebo, rifaximin 200 mg TID, and rifaximin 400 mg TID groups, respectively. Censored TLUS values were higher in the placebo group compared to rifaximin: 51 (39.5%) placebo patients versus 26 (20.8%) and 24 (19.0%) rifaximin 200 mg TID and 400 mg TID patients, respectively, had a censored TLUS. Five of these patients (1 placebo, 3 rifaximin 200 mg

TID, 1 rifaximin 400 mg TID) had a censored TLUS value greater than 120 hours, indicating that these patients did not respond to treatment and had continuing records of unformed stools beyond 120 hours. Four patients (1 placebo, 3 rifaximin 200 mg TID) had no TLUS defined according to the definition in the protocol and the statistical analysis plan. In all four patients, TLUS was undefined due to insufficient treatment as well as a lack of sufficient follow-up information. These patients are included in the ITT analysis by setting TLUS = 120 hours (censored).

The MO and FDA statistician assessed the TLUS on the FDA MITT population and found that the TLUS for the placebo MITT was 59.3, 30 hours for the 200 mg TID and 32.8 hours for the 400 mg TID population. These results are consistent with those of the ITT population.

Additional analyses were performed on those subjects from Kenya with and without cryptosporidium. Those 200 mg TID subjects without cryptosporidium had a TLUS of 28.3 hours and the 400 mg TID subjects had a TLUS of 30.2 hours. Those subjects with cryptosporidium had TLUS of 44.2 and 33.6 respectively. These results seem to indicate that the presence of cryptosporidium at the Kenyan site led to increased TLUS, however, the results from the 400 mg TID group do not support his hypothesis and the numbers are too small overall to allow for valid conclusions to be drawn.

Secondary Efficacy Endpoints

NOTE The Applicant performed a number of secondary endpoint analyses and p-values for these multiple comparisons are presented. The reader is cautioned that the numerous p-values presented are not adjusted for the multiple comparisons that have been performed.

Improvement in Diarrheal Syndrome

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. 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 these differences were not statistically significant ($p = 0.062$).

Table 16
Improvement in Diarrheal Syndrome – RFID9801

	Placebo N = 129	Rifaximin 200 mg TID N = 125	Rifaximin 400 mg TID N = 126	P-Value
Interval [Number Improved (%)]^a				
0 – 24 Hours	60/121 (49.6)	68/117 (58.2)	72/122 (59.0)	0.266 ^b
24 – 48 Hours	86/118 (72.9)	101/116 (87.1)	94/120 (78.3)	0.026 ^b
48 – 72 Hours	89/113 (78.8)	105/115 (91.3)	102/116 (87.9)	0.018 ^b
72 – 96 Hours	96/110 (87.3)	103/112 (92.0)	103/116 (88.8)	ND
96 – 120 Hours	86/98 (87.8)	93/94 (98.9)	96/102 (94.1)	ND

^aDenominator for percent improved is number in treatment group minus number of subjects missing an assessment of diarrheal improvement

^bp-value from chi-square test for 2x3 table (missing results excluded from analysis)

^cp-value from chi-square test for 2x2 table of pairwise comparison (missing results excluded from analysis), pairwise comparisons done only if overall chi-square significant at 0.05 level

Number of Unformed Stools per Time

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. As per the applicant, “A repeated measures analysis comparing the treatment groups was statistically significant ($p = 0.0001$) and pairwise comparisons of each rifaximin group versus placebo were significant at the same level ($p = 0.0001$)”

Table 17
Number of Unformed Stools Per Time Interval – RFID9801

	Placebo N = 129	Rifaximin 200 mg TID N = 125	Rifaximin 400 mg TID N = 126	P-Value
Mean Number of Unformed Stools Per Interval (Number Reporting)				0.0001 ^a
0 – 24 Hours	3.8 (128)	3.1 (122)	3.1 (126)	
24 – 48 Hours	2.6 (125)	1.6 (121)	1.6 (124)	
48 – 72 Hours	1.8 (120)	0.9 (120)	1.0 (120)	
72 – 96 Hours	1.5 (116)	0.7 (116)	0.6 (120)	
96 – 120 Hours	0.9 (102)	0.5 (97)	0.5 (102)	
P-Values (Rifaximin Versus Placebo)		0.0001 ^b	0.0001 ^b	

^ap-value from repeated measures ANOVA with terms for treatment, time (interval), and treatment by time interaction

^bp-value from Dunnett’s test of pairwise comparison in repeated measures model (reported if significant overall treatment group differences found)

Number of Patients Cured

Patients satisfied the definition of wellness or cure by having either a 48-hour period with no unformed stools and no fever, or a 24-hour period with no watery stools, no more than two soft stools, and no clinical symptoms. The cure rates were similar for both rifaximin groups (79% for 200 mg TID, and 81% for 400 mg TID) and higher compared to placebo (61%). As per the applicant, “pairwise comparisons of the proportion of cures in each rifaximin group compared to placebo were statistically significant ($p = 0.001$)”

Table 18
Number of Patients Achieving Cure or Wellness – RFID9801

	Placebo N = 129	Rifaximin 200 mg TID N = 125	Rifaximin 400 mg TID N = 126	P-Value
Wellness [Number (%) of Subjects]				
Yes (Clinical Cure)	78 (61%)	99 (79%)	102 (81%)	0.001 ^a
No (Failure)	45 (35%)	20 (16%)	21 (17%)	
Neither Clinical Cure nor Failure	4 (3%)	3 (2%)	3 (2%)	
Missing	2 (2%)	3 (2%)	-	
P-Values for Overall Pairwise Comparisons (Rifaximin vs Placebo)		0.001 ^b	0.001 ^b	

^ap-value from chi-square test for 2x3 table (missing or “neither” included as non-cure)

^bp-value from chi-square test for 2x2 table of pairwise comparison

Changes in Clinical Symptoms

All patients from each dose group had at least one clinical symptom at baseline. As per the applicant “At the 96-hour timepoint, changes in clinical symptoms (abdominal pain, nausea, vomiting, flatulence, urgency, fever, tenesmus) were statistically different between the rifaximin groups and placebo ($p=0.034$, Fisher’s Exact Test)”

Table 19
**Changes in All Clinical Symptoms from Baseline to End of Treatment
Study RFID9801**

End of Treatment ¹	Rifaximin (n=251) ²	Placebo (n=129) ²
No symptoms	102/251 (40.6%)	38/129 (29.5%)
At least one symptom ³	149/251 (59.4%)	91/129 (70.5%)
p value	0.034 (Fisher's Exact Test)	

¹ End of treatment was defined as 96 hours after the start of treatment

² Includes patients who had at least one clinical symptom at baseline

³ Patients who had symptoms after 96 hours and who dropped out of the study were considered symptomatic

At follow-up, only two patients had laboratory evidence of gross blood in stool in the end-of-treatment stool sample

Microbiologic Efficacy:

Treatment groups were compared with respect to the number (percent) of subjects with microbiological cure, defined as a post-treatment culture that was negative for the pretreatment etiologic pathogen

Fifty-three percent (68/129) in the placebo group, 44% (55/125) in the 200 mg TID group, and 52% (66/126) in the 400 mg TID group had no pathogen isolated at pretreatment. Of note, a higher percentage of rifaximin 200 mg TID subjects had a baseline pathogen compared to the other groups

Of note were inter-center differences both in the presence or absence of pathogens and in the pathogens isolated. Nine of 11 *Salmonella* spp cases were from Mexico and none were from Guatemala. At the Mexican and Guatemalan sites, almost 60% of the patients had no baseline pathogen, whereas 70% of the Kenyan site had at least one baseline pathogen. Also, no one from the Guatemalan site had more than 1 baseline pathogen. No explanation can be provided for these phenomena.

When an assessment was made of only those subjects with a pathogen or pathogens at pretreatment, the rate of microbiological cure did not provide much differentiation among treatment groups. Specifically, the cure rate of 75% in the placebo group was numerically superior to the 70 % rate in the 200 mg TID group and to the 66 % rate in the 400 mg TID group.

Table 20
Clinical Efficacy in Patients with/without baseline pathogen

ITT	Placebo N = 129	Rifaximin 200 mg TID N = 125	Rifaximin 400 mg TID N = 126
No pathogen at baseline	68 (53%)	55 (44%)	66 (52%)
Pathogen at baseline	61 (47%)	70 (56%)	60 (48%)
Clinical response in subjects with baseline pathogen			
Cure	41 (67%)	48 (69%)	34 (57%)
Failure	13 (21%)	17 (24%)	21 (35%)
No re-culture	6 (10%)	3 (4%)	5 (8%)
Missing	1 (2%)	2 (3%)	0

No treatment group differences were noted in eradication rates for individual pathogens although pathogen eradication rates were numerically superior on the placebo arm as compared to the treatment arms

Table 21
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 (%)
<i>Escherichia coli</i>	54	40/54 (74%)	54	38/54 (70%)	41	27/41 (66%)
<i>Shigella</i> species	0	0	0	0	1	1/1 (100%)
<i>Shigella sonnei</i>	2	2/2 (100%)	2	2/2 (100%)	1	1/1 (100%)
<i>Shigella flexneri</i>	0	0	2	1/2 (50%)	1	0/1 (0%)
<i>Salmonella</i> Group C1	1	1/1 (100%)	2	1/2 (50%)	4	3/4 (75%)
<i>Salmonella</i> Group C2	1	1/1 (100%)	0	0	3	1/3 (33%)
<i>Campylobacter jejuni</i>	1	0/1 (0%)	2	1/2 (50%)	0	0
<i>Campylobacter coli</i>	1	1/1 (100%)	0	0	0	0
<i>Aeromonas sobria</i>	1	1/1 (100%)	0	0	0	0
<i>Aeromonas hydrophila</i>	0	0	0	0	1	1/1 (100%)
<i>Entamoeba histolytica</i>	1	1/1 (100%)	1	1/1 (100%)	3	2/3 (67%)
<i>Giardia lamblia</i>	4	3/4 (75%)	6	4/6 (67%)	3	1/3 (33%)
<i>Cryptosporidium parvum</i>	11	7/11 (64%)	18	12/18 (67%)	14	4/14 (29%)
<i>Plesiomonas shigelloides</i>	1	1/1 (100%)	0	0	1	1/1 (100%)
<i>Vibrio fluvialis</i>	0	0	1	1/1 (100%)	1	0/1 (0%)
<i>Vibrio parahaemolyticus</i>	1	1/1 (100%)	0	0	1	1/1 (100%)
TOTAL	79	59/79 (75%)	88	61/88 (69%)	75	43/75 (57%)

Three of the 18 isolates of *Cryptosporidium parvum* on the 200 mg TID arm were from patients in Mexico (1 cure 1 fail, 1 missing), none were from subjects in Guatemala, and the remaining 15 on the 200 mg TID arm were from subjects in Kenya (as well as 11 of the placebo arm isolates and 12 of the 400 mg TID arm isolates (80%) of total)

The FDA statistician assessed the effect of the presence or absence of cryptosporidium on the TLUS and found that there was an effect towards more prolonged duration of illness. It should be noted however, that the number of subjects in each treatment group was < 20.

Further assessment of the *Cryptosporidia* isolates revealed that only 6 of the 18 isolates on the 200 mg TID arm were sole pathogens. All 6 were eradicated but 2 of the 6 were found to have breakthrough or new infections with ETEC LT.

There were 4 *Cryptosporidia* with ETEC ST/LT (all eradicated with 2 breakthrough infections, 1 ETEC LT and 1 *Salmonella*), 2 *Cryptosporidia* with ETEC LT (both eradicated), 1 each *Cryptosporidia* with ETEC ST/LT and *Vibrio fluvialis*, ETEC ST, and *Shigella flexneri* and ETEC ST/LT (all eradicated), 1 cryptosporidium with *Campylobacter jejuni* (eradicated with breakthrough ETEC LT), and 1 cryptosporidium with *Shigella flexneri* (eradicated with breakthrough ETEC ST/LT).

Of note, TLUS was more prolonged in those subjects with parasites as compared to those without. In the group with parasites the comparison of either rifaximin group to placebo was not significant at the 0.025 level.

Table 22
Patients without parasites

	Placebo N = 112	Rifaximin 200 mg TID N = 96	Rifaximin 400 mg TID N = 105
TLUS in Hours (Kaplan-Meier Estimates)			
Median TLUS (50% With TLUS Less Than)	60	32.2	28.5
p value		0.0005	0.0002

Table 23
Patients with parasites

	Placebo N = 15	Rifaximin 200 mg TID N = 24	Rifaximin 400 mg TID N = 18
TLUS in Hours (Kaplan-Meier Estimates)			
Median TLUS (50% With TLUS Less Than)	60.8	37.3	43.8
p value		0.033	0.123

Breakthrough or new infections

Nineteen percent (24/129) placebo ITT subjects as compared to 19% (24/125) rifaximin 200 mg TID and 16% (20/126) rifaximin 400 mg TID subjects were found to have new pathogens at the EOT. These included 1 *Campylobacter jejuni* in 1 subject from each rifaximin treatment group, 17 *Escherichia coli* from the placebo subjects, 17 from the rifaximin 200 mg TID subjects, and 18 from the rifaximin 400 mg TID subjects. *Salmonella* was newly isolated in 3 placebo subjects and 1 rifaximin 200 mg TID subject and *Shigella* in no subjects.

Four 200 mg TID subjects, one 400 mg TID subject and 3 placebo subjects were found to have *Cryptosporidium parvum* post treatment.

Medical Officer's Comment *The sponsor did not collect information regarding recurrence of clinical disease in this study. It should be noted that the IDSA guidelines suggest that such recurrences be considered failures.*

Conclusions from study 9801

The applicant was successfully able to demonstrate that rifaximin at 200 mg PO TID (600 mg/day) or 400 mg PO TID (1200 mg/day) was superior to placebo in decreasing the TLUS (primary efficacy parameter) in both the prespecified ITT population and in the FDA MITT population, thus showing that rifaximin had activity independent of the presence or absence of a positive culture.

The FDA assessed the TLUS on the FDA MITT population and found that the TLUS for the placebo MITT was 59.3, 30 hours for the 200 mg TID and 32.8 hours for the 400 mg TID population. These results are consistent with those of the ITT population.

Rates of microbiologic efficacy were similar across treatment arms and versus placebo. The reason for this is unclear and raises concerns regarding the true antimicrobial nature of this compound, although it is also possible that the study design and timing of microbiologic assessments were not appropriate to be able to demonstrate microbiologic efficacy.