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

Table 16
Median TLUS by Analysis Center ITT Population

Median TLUS in Hours	**Treatment Group**		
(Kaplan-Meier Estimates)	**Rifaximin**	**Placebo**	**Cipro**
All Centers	**(N=197)** **32 0**	**(N=101)** **65 5**	**(N=101)** **28 8**
Calcutta, India (#100)	(N=43) 24 5	(N=23) NC	(N=23) 24 1
Goa India (#101)	(N=58) 72 0	(N=29) 69 7	(N=30) 70 5
Antigua, Guatemala (#107) & Lima, Peru (#269)	(N=53) 23 5	(N=26) 42 4	(N=27) 20 8
Guadalajara, Mexico (#200), Cuernavaca Mexico (#242) & Puerto Vallarta, Mexico (#249)	(N=43) 33 0	(N=23) 26 7	(N=21) 15 5

When TLUS was assessed for only those sites where the study was performed in an acceptable manner rifaximin was found to be effective at shortening the duration of diarrhea relative to placebo The relative risk (rifaximin/placebo) for TLUS for Calcutta and Guatemala/Peru was 2 17 (95% CI=1 44-3 27 P=0 0002)

Table 17
Median TLUS by Analysis Center excluding Goa and Mexico ITT Population

Median TLUS in Hours	**Treatment Group**		
(Kaplan-Meier Estimates)	**Rifaximin**	**Placebo**	**Cipro**
Calcutta/Guatemala/Peru	(N= 96) 23 85	(N=49) 65 5	(N= 50) 23 60

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

Table 18
Median TLUS in Hours/MITT

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

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

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

Table 19
Median TLUS by Analysis Center excluding Goa and Mexico MITT Population

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

Analyses of TLUS were performed for MITT subjects with Escherichia coli only a population for which the applicant supplied adequate data to support an approval

Table 20
Median TLUS for MITT by specific pathogens

Median TLUS in Hours/MITT	**Treatment Group**		
Study RFID9801	**Rifaximin** N = 125	**Placebo** N = 129	**Ciprofloxacin** **NA**
Escherichia coli only	N = 53 28 4	N = 54 57 8	
Study RFID3001	**Rifaximin** (N=128)	**Placebo** (N=62)	**Ciprofloxacin** (N=58)
Escherichia coli only	N = 64 23 9	N = 33 26 7	(N= 36) 23 4

As can be seen above 51 6% of the rifaximin-treated MITT subjects had Escherichia coli only as compared to 53 2% of the placebo-treated patients and 62 1% of the ciprofloxacin treated subjects Of note however are the very similar TLUS results for the rifaximin placebo and ciprofloxacin –treated subjects (Escherichia coli only) These results indicate that independent of treatment improvement would occur for this subgroup whereas for subjects with all other pathogens TLUS was prolonged independent of treatment A question developing from this data is whether the isolated E coli was indeed pathogenic

A by-center breakdown of the above table shows that the similarity in the pooled results is no longer present

Table 21
Median TLUS for MITT by specific pathogens by Center
***Escherichia coli* only**

Median TLUS in Hours/MITT	**Treatment Group**		
	Rifaximin (N=64)	**Placebo** (N=33)	**Ciprofloxacin** (N=36)
All Centers/	**23 9**	**26 7**	**23 4**
Calcutta, India (#100)	(N = 15) 45 3	(N = 7) 65 5	(N = 11) 17 7
Goa, India (#101)	(N = 12) 44 25	(N = 7) 69 7	(N = 11) 70 3
Antigua, Guatemala (#107) & Lima, Peru (#269)	(N = 24) 8 75	(N = 11) 24 1	(N = 5) 5 8
Guadalajara, Mexico (#200), Cuernavaca, Mexico (#242) & Puerto Vallarta, Mexico (#249)	(N = 13) 35 3	(N = 8) 4 8	(N =5) 9 1

NC = not calculable, distribution did not attain 75th percentile

As in previous analyses results between treatment arms are conflicting especially at the Mexican sites where TLUS was prolonged The general conclusion drawn from this data is that rifaximin may have had a beneficial effect on TLUS in subjects with Escherichia

coli only at the Calcutta and Guatemalan sites but the value of this result is questionable given small patient numbers

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

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

An attempt was made to calculate median TLUS for those subjects with Shigella spp and Campylobacter spp isolated in baseline stool culture however the numbers of isolates were small and in subjects with these isolates as sole pathogens the numbers became even smaller Specifically of 18 total patients with Shigella spp (not speciated) 10 had this isolate as a sole pathogen 7 of these subjects were treated with rifaximin and had a median TLUS of 42 6 hours, 2 were treated with placebo and one had a median TLUS of 31 8 hours while the other failed (TLUS > 120 hours) and one was treated with ciprofloxacin That patient had a TLUS of — hours Of the 7 rifaximin-treated subjects with Shigella spp as their sole pathogen 5 had Shigella sonnei The median TLUS in this very small subgroup was 30 6 hours and the mean was 34 hours No placebo-treated subjects had Shigella sonnei isolated in the stool and only one ciprofloxacin-treated subject had this pathogen That subject had a TLUS of — hours —

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

The MO concluded that while in study RFID9801, the applicant was able to show a statistically significant difference in the primary efficacy parameter of TLUS between rifaximin and placebo, a similar result was not consistently shown in study RFID3001 However the MO did agree that there was a trend towards decreased TLUS when the results were assessed by center There were inconsistent results between the centers that the MO believes due to a larger number of invasive pathogens at the Goa site and the relatively few patients at the Mexican site The beneficial effect of rifaximin on the primary efficacy parameter of TLUS was primarily seen in subjects who had no identifiable causative pathogen

Subgroup analyses

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

- fecal leukocyte-positive illness,

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

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

As per the applicant, in study RFID3001, median TLUS was shorter in the rifaximin group compared to the placebo group for all subgroups except that of subjects with inflammatory/invasive pathogens where more than half of the rifaximin-treated subjects (N = 46) failed and in the very small subgroup of subjects with other agents where 3/6 placebo patients and 3/5 ciprofloxacin-treated patients failed and the TLUS could not be calculated The results were statistically significant in favor of rifaximin in subjects with fecal leukocyte-positive illness (p=0 0011), subjects with diarrheagenic *E coli* but without evidence of inflammatory/invasive pathogens (p=0 0476), and subjects with agent-negative illness (p=0 0024) Of note however was the small and not significant difference between TLUS for rifaximin-treated subjects versus placebo in subjects with agent-specific disease (rifaximin 40 3 hours versus placebo 48 8)

Table 22
Subgroup Analysis for Time to Last Unformed Stool ITT Population

Time to Last Unformed Stool (hours)	Treatment Group			P-value[a]
	Rifaximin (N=197)	Placebo (N=101)	Ciprofloxacin (N=101)	Rifaximin vs Placebo
Subjects with Fecal Leukocyte-Positive Illness	(N=91)	(N=45)	(N=38)	0 0011*
Median TLUS[b]	29 0	72 0	23 4	
95% Confidence Interval of Median TLUS	24 0 – 46 0	36 6 – NC	15 5 – 31 3	
N (%) Censored	15 (16 5%)	21 (46 7%)	2 (5 3%)	
Subjects with Fecal Leukocyte Negative Illness	(N=106)	(N=56)	(N=63)	0 2809
Median TLUS[b]	35 8	48 3	44 1	
95% Confidence Interval of Median TLUS	23 8 – 48 0	25 6 – 71 6	24 1 – 70 3	
N (%) Censored	31 (29 2%)	18 (32 1%)	20 (31 7%)	
Subjects with Inflammatory/Invasive Pathogens	(N=46)	(N=19)	(N=13)	0 9741
Median TLUS[b]	NC	67 5	65 0	
95% Confidence Interval of Median TLUS	47 3 – NC	36 6 – NC	24 4 - NC	
N (%) Censored	24 (52 2%)	10 (52 6%)	5 (38 5%)	
Subjects with Diarrheagenic *E coli* (no evidence of inflammatory/invasive pathogens)	(N=74)	(N=38)	(N=46)	0 0476*
Median TLUS[b]	24 0	38 0	23 4	
95% Confidence Interval of Median TLUS	10 2 – 35 3	22 8 – 65 5	7 5 – 45 8	
N (%) Censored	8 (10 8%)	10 (26 3%)	7 (15 2%)	
Subjects with Other Agents (no evidence of inflam / invasive pathogens or diarrheagenic *E coli*)	(N=10)	(N=6)	(N=5)	0 3644
Median TLUS[b]	65 3	NC	NC	
95% Confidence Interval of Median TLUS	24 4 – NC	68 8 – NC	30 8 – NC	
N (%) Censored	3 (30 0%)	3 (50 0%)	3 (60 0%)	
Subjects with Agent-Specific Illness	(N=130)	(N=63)	(N=64)	0 1436
Median TLUS[b]	40 3	48 8	28 3	
95% Confidence Interval of Median TLUS	24 5 – 48 0	32 2 – 72 0	17 7 – 55 1	
N (%) Censored	35 (26 9%)	23 (36 5%)	15 (23 4%)	
Subjects with Agent-Negative Illness	(N=67)	(N=38)	(N=37)	0 0024*
Median TLUS[b]	23 5	71 6	29 7	
95% Confidence Interval of Median TLUS	17 3 – 44 1	34 1 – NC	20 8 – 44 1	
N (%) Censored	11 (16 4%)	16 (42 1%)	7 (18 9%)	

[a] P-value is 2 sided and calculated using a log-rank test
[b] Estimated using the Kaplan-Meier method
* Statistically significant difference between rifaximin and placebo
NC = not calculable, median TLUS could not be calculated if more than one-half of subjects in the group failed to achieve wellness
inflam = inflammatory

A similar analysis was performed in RFID9801 for patients with and without leukocytes in the stool There were 20 subjects on the rifaximin 200 mg TID arm with leukocytes in the stool (20/129, 15%) Of these, 14 (70%) were classified as cures and 6 (30%) as failures The TLUS for this group was 45 1 as compared to the median TLUS for all 200 mg TID subjects of 32 hours TLUS was not calculable for placebo patients with fecal leucocyte positive stool in that study because more than half failed treatment

Table 23
Time to Last Unformed Stool for Subgroups Defined by Presence or Absence of Fecal Leukocyte Illness (RFID9801) ITT Population

	Treatment Group		P-value[a]
Time to Last Unformed Stool (hours)	Rifaximin 600 mg/day	Placebo	Rifaximin vs Placebo
Subjects with Fecal Leukocyte-Positive Illness	(N=20)	(n=23)	0 067[a]
Median TLUS	45 1	NC	
95% Confidence Interval of Median TLUS	NC	NC	0 039*[b]
Subjects with Fecal Leukocyte Negative Illness	(N=102)	(N=105)	0 0004*[a]
Median TLUS[b]	32 5	57 0	
95% Confidence Interval of Median TLUS	25 8 – 42 5	42 5 – 77 6	0 002*[b]

Reference RFID9801 In text Tables 35 and 36 (from Tables 14 2 8a and 16 1 9 4h)
[a] Log Rank Test (survival model)
[b] Generalized Wilcoxon Test (survival model)
* Statistically significant difference between rifaximin and placebo
NC = not calculable median TLUS could not be calculated if more than one-half the subjects in a group failed to achieve wellness

The Agency requested that the applicant provide analyses of TLUS wellness and microbiologic eradication for subjects with fever and/or blood in the stool for subjects in study RFID3001 In both the ITT and MITT populations, it was clear that the presence or absence of fever at baseline played a major role in efficacy with fewer rifaximin and placebo-treated subjects with fever becoming well when this parameter was present TLUS was either not calculable in this group because of the large number of patients with censored data (1 e failures) or it was prolonged Only those subjects treated with ciprofloxacin had lower TLUS and increased percentages of subjects cured Similar results were not seen for the presence or absence of blood in the stool at baseline in the ITT population but the presence or absence of blood at baseline had a clear effect on efficacy in the MITT population again with similar TLUS and clinical cure rates in the rifaximin and placebo-treated populations Similar analyses were not performed for study RFID9801 where fewer subjects had fever and/or blood in the stool at baseline

Table 24
TLUS, Wellness and Microbiologic Eradication Rates in Subjects with Fever and Blood in the Stool at Baseline Study RFID3001

Group	Rifaximin	Placebo	Ciprofloxacin
Fever at Baseline			
TLUS	NC	51 1	23 4
Wellness	12/25 (48%)	8/12 (66 7%)	12/14 (85 7%)
Eradication	14/25 (56%)	6/12 (50%)	12/14 (85 7%)
Blood at Baseline			
TLUS	63 5	69 7	55 5
Wellness	24/42 (57 1%)	14/25 (56%)	13/18 (72 2%)
Eradication	26/42 (61 9%)	12/25 (48%)	13/18 (72 2%)
Fever and Blood at Baseline			
TLUS	NC	NC	36 5
Wellness	6/14 (42 9%)	3/7 (42 9%)	7/8 (87 5%)
Eradication	8/14 (57 1%)	3/7 (42 9%)	7/8 (87 5%)

NC = not calculable, distribution did not attain 75th percentile

Secondary endpoints NOTE The Applicant performed a number of secondary endpoint analyses Only those analyses considered important in the decision to approve such as the analyses of wellness are include in this review

Wellness and Failure

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

5 *No unformed stools within a 48-hour period with no fever (with or without other clinical symptoms), or*

6 *No watery stools and no more than 2 soft stools within a 24 hour period with no fever and no other clinical symptoms except for mild excess gas/flatulence*

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

In study RFID9801 99/125 (79 2%) of rifaximin-treated ITT subjects achieved wellness as compared to 78/129 (60 5%) of placebo-treated subjects Similar results were obtained for the MITT population In study RFID3001 76 6% rifaximin-treated subjects

were classified as clinical cures as compared to 61 4% of placebo recipients Of note, in study RFID3001, the treatment failure rate with rifaximin was slightly more than double that observed with ciprofloxacin (14 7% vs 6 9%, respectively) A by center breakdown of the results revealed continuing issues with the Goa site whereas the results of the Mexican centers were more consistent with those of the other sites lending weight to the argument that the median TLUS value is not the only, and perhaps not always the ideal, statistic to use to assess efficacy While the median TLUS at Mexican centers for the ITT population was larger for rifaximin (median=33 0h) than for placebo (median=26 7h), a greater percentage of rifaximin subjects achieved wellness (N=36/43 83 7%) than did placebo subjects (N=15/23 65 2%) suggesting that early during therapy placebo subjects achieved wellness faster than rifaximin subjects but did not continue to improve throughout the treatment and follow-up period On the other hand rifaximin subjects were somewhat delayed in initial response but continued to achieve wellness after the initial placebo response had begun to cease

Table 25

Wellness-ITT RFID9801 and RFID3001 TOC Visit (24 – 48 hours post-treatment)

	Rifaximin	Placebo	Cipro
Overall RFID9801	99/125 (79 2%)	78/129 (60 5%)	N/A
Overall RFID3001	151/197 (76 6%)	62/101 (61 4%)	79/101 (78 2%)
By Center RFID3001			
Calcutta, India	38/43 (88 4%)	11/23 (47 8%)	21/23 (91 3%)
Goa, India	30/58 (51 7%)	15/29 (51 7%)	16/30 (53 3%)
Guatemala and Peru	47/53 (88 7%)	21/26 (80 8%)	26/27 (96 3%)
Mexico sites	36/43 (83 7%)	15/23 (65 2%)	16/21 (76 2%)

Table 26
Wellness-MITT TOC Visit (24 – 48 hours post-treatment)

	Rifaximin	Placebo	Cipro
Overall RFID9801	56/65 (86 2%)	34/55 (61 8%)	NA[a]
Overall RFID3001	94/128 (73 4)	40/62 (64 5)	43/58 (74 1)
By Center RFID3001			
Calcutta, India	25/29 (86 2)	7/16 (43 8)	16/17 (94 1)
Goa, India	18/41 (43 9)	10/18 (55 6)	10/20 (50 0)
Guatemala and Peru	30/33 (90 9)	14/16 (87 5)	8/9 (88 9)
Mexico sites	21/25 (84 0)	9/12 (75 0)	9/12 (75 0)

In RFID3001 the applicant performed a post hoc analysis of wellness excluding ITT subjects with fever and/or blood in the stool at baseline The proportions of subjects achieving wellness were similar to the overall ITT population for the placebo and ciprofloxacin groups and >10% higher than the overall ITT population for the rifaximin group indicating that those subjects with dysentery-like symptoms fared better on ciprofloxacin than on rifaximin Similar analyses were not performed for study RFID9801

Microbiology

Medical Officer's Comment *Although minor differences existed between the 2 studies regarding overall pathogen eradication rates the results of both studies confirmed that rifaximin did not have superior microbiologic activity to that of placebo*

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

In study RFID 3001 overall eradication rates were again similar between the rifaximin and placebo arms at visit 2 and although in the MITT population at Visit 3, a slightly greater proportion of subjects in the rifaximin group than in the placebo group had an overall microbiological response of eradication (61 6% vs 51 7%) these results were not significant and again raised concerns about the true microbiologic activity of rifaximin Results obtained on the ciprofloxacin arm were numerically superior to those obtained on the placebo or rifaximin treatment arms A by center and by pathogen breakdown of the results also did not reveal a significant difference between rifaximin and placebo at any level

Table 27
Overall Microbiological Response TOC Visit (24 – 48 hours post-treatment) RFID3001 and RFID9801 (MITT Population)

	RFID3001			RFID9801	
	Rifaximin 600 mg/day (N=197)	Placebo (N=101)	Ciprofloxacin (N=101)	Rifaximin 600 mg/day (N=125)	Placebo (N=129)
	Number (%) of Subjects				
MITT population	128	62	58	65	55
Overall microbiological response					
Eradication	77 (61 6)	31 (51 7)	46 (80 7)	47 (73 4)	41 (75 9)
Persistence	48 (38 4)	29 (48 3)	11 (19 3)	17 (26 6)	13 (24 1)
Not tested/Missing	3	2	1	1	1

Table 28
Microbiologic Eradication rate by Pathogen TOC Visit (24 – 48 hours post-treatment) Study RFID3001

Genus (Species)	Number (%) of MITT/MEE Subjects		
	Rifaximin (N=125)	Placebo (N=62)	Ciprofloxacin (N=58)
Aeromonas (hydrophila)	2/3 (66 7%)	1/1 (100%)	1/1 (100%)
Campylobacter (jejuni)	9/25 (36 0%)	4/10 (40 0%)	6/9 (66 7%)
Plesiomonas sp	3/3 (100%)	-	-
Plesiomonas shigelloides	1/1(100%)	1/2 (50 0%)	-
Salmonella Group B	1/3 (33 3%)	-	-
Salmonella Group C1	1/1 (100%)	1/1 (100%)	1/1 (100%)
Salmonella Group C2	-	-	1/1 (100%)
Shigella boydii	1/1 (100%)	-	-
Shigella flexneri	2/2 (100%)	2/4 (50 0%)	1/1 (100%)
Shigella sonnei	7/8 (87 5%)	1/1 (100%)	1/1 (100%)
Vibrio cholerae	2/2 (100%)	-	-
Providencia	1/1 (100%)	-	1/1 (100%)
Diarrheagenic *E coli*	62/83 (74 7%)	30/43 (69 8%)	43/45 (95 6%)
Cryptosporidium parvum	2/6 (33 3%)	1/4 (25 0%)	2/6 (33 3%)
Entamoeba histolytica	1/3 (33 0%)	-	-
Giardia lamblia	6/15 (40 0%)	2/8 (25 0%)	3/5 (60 0%)

Table 29
Microbiologic Eradication rate by Pathogen TOC Visit (24 – 48 hours post-treatment) Study RFID9801

Pathogen	RFID 9801 Rifaximin 200 mg TID		RFID9801 Placebo	
	No	No Eradicated (%)	No	No Eradicated (%)
Escherichia coli	60	45/60 (75%)	54	40/54 (74%)
Shigella sonnei	3	3/3 (100%)	2	2/2 (100%)
Shigella flexneri	2	½ (50%)	0	0
Salmonella Group C1	3	2/3 (67%)	1	1/1 (100%)
Salmonella Group C2	0	0	1	1/1 (100%)
Campylobacter jejuni	4	3/4 (75%)	1	0/1
Crytosporidium parvum	18	12/18 (67%)	1	1/1 (100%)

Clinical and Microbiological Outcome by Baseline Pathogen Category

The applicant provided an analysis of clinical and microbiological outcome by baseline pathogen category in the MITT population Study RFID3001 contained a higher proportion of subjects having invasive/inflammatory pathogens (45/128, 35%) than did RFID9801 (9/65, 13 8%)

In study RFID3001, pathogen eradication rates were identical (55 6%) between rifaximin and placebo-treated subjects with inflammatory/invasive pathogens Pathogen eradication rate was much higher (10/13, 77%) for the ciprofloxacin-treated patient in this category although there were only 13 subjects with invasive pathogens as compared to 45 on the rifaximin arm In study RFID9801 6/9 rifaximin-treated subjects with inflammatory/invasive pathogens had pathogen eradication (67%) as compared to 8/9, 89% of placebo subjects in this category

Amongst the pathogens categorized as inflammatory/invasive were *Campylobacter jejuni, Salmonella* spp and *Shigella* Rifaximin demonstrated inadequate clinical and microbiologic efficacy against *Campylobacter jejuni* and *Salmonella* spp in RFID3001 Clinical and microbiological efficacy was noted in rifaximin-treated subjects against *Shigella sonnei,* , but the median TLUS *for Shigella* spp was 45 7 hours as compared to 24 hours in rifaximin-treated subjects with diarrheagenic E coli There were too few isolates of *Shigella sonnei* on the other treatment arms as well as in study RFID9801 to allow for valid comparisons

In study RFID3001, among subjects with diarrheagenic *E coli* the median TLUS was 24 hours as compared to 23 4 hours for similar ciprofloxacin-treated patients and 38 hours in placebo-treated subjects Similarly 89% of rifaximin-treated subjects as compared to 82 5% of ciprofloxacin-treated subjects and 73 7% of placebo-treated subjects achieved wellness In those subjects where no pathogen was identified median TLUS was 23 5 hours for rifaximin-treated subjects, 29 7 for ciprofloxacin-treated subjects and 71 6 hours for placebo-treated subjects Wellness was achieved in 82 6, 83 7 and 56 4% of those patients per treatment arm respectively

In study RFID9801, median TLUS for rifaximin was similar among subjects with any pathogen (rifaximin 31 5 hours, placebo 60 hours) and subjects with diarrheagenic *E coli* (rifaximin 29 8 hours, placebo 56 7 hours) and wellness was achieved among similar proportions of subjects in these subgroups (86 2% for any pathogen, 84 1% for diarrheagenic *E coli*) Wellness was achieved by a higher proportion of subjects with diarrheagenic *E coli* (84 1%) than subjects with no pathogen identified at pretreatment (70 0%)

Medical Officer's Comment *Of concern in the determination to approve or not was the dichotomy between the clinical results and the microbiologic eradication results It was the MO s conclusion that rifaximin does not perform as a conventional antimicrobial with regards to pathogen eradication and thus to use this parameter as a determination of efficacy in inappropriate*

Table 30
Clinical and Microbiological Outcome by Baseline Pathogen Category TOC Visit (24 – 48 hours post-treatment)
RFID3001 and RFID9801 (MITT Population)

	RFID3001			RFID9801	
Pathogen Category[a] Pathogen	**Rifaximin (N=128)**	**Placebo (N=62)**	**Ciprofloxacin (N=58)**	**Rifaximin (N=65)**	**Placebo (N=55)**
Median TLUS (hours)[b]					
Any Pathogen [No of Subjects]	40 3 [128]	48 3 [62]	28 3 [58]	31 5 [65]	60 0 [55]
Inflam /Invasive Pathogens	NC [45]	67 5 [18]	65 0 [13]	34 0 [9]	NC [9]
Campylobacter	NC [25]	NC [10]	71 4 [9]	NC [2]	NC [2]
Salmonella spp	NC [4]	58 3 [1]	13 1 [2]	37 9 [2]	NC [2]
Shigella spp	44 8 [11]	31 8 [5]	16 6 [2]	16 9 [4]	NC [2]
Shigella sonnei	45 7 [8]	120 0 [1]	15 6 [1]	6 8 [2]	NC [2]
Diarrheagenic *E coli*	24 0 [73]	38 0 [38]	23 4 [40]	29 8 [44]	56 7 [44]
EAEC	24 1 [24]	23 9 [16]	23 7 [15]		--
ETEC LT	26 4 [29]	38 0 [10]	23 4 [11]	22 7 [9]	49 4 [14]
ETEC-ST	6 0 [11]	68 4 [7]	0 0 [4]	28 8 [19]	58 8 [18]
ETEC-ST/LT	24 1 [21]	NC [10]	24 8 [13]	40 7 [16]	56 8 [12]
Other Agents	65 3 [10]	NC [6]	NC [5]	39 9 [12]	NC [2]
No Pathogens (ITT Population)	23 5 [69]	71 6 [39]	29 7 [43]	44 0 [60]	54 5 [74]
Clinical Wellness (%)					
Any Pathogen	94/128 (73 4)	40/62 (64 5)	43/58 (74 1)	56/65 (86 2)	34/55 (61 8)
Inflammatory/Invasive Pathogens	22/45 (48 9)	9/18 (50 0)	8/13 (61 5)	8/9 (88 9)	3/9 (33 3)
Campylobacter	6/25 (24 0)	3/10 (30 0)	4/9 (44 4)	1/2 (50 0)	0/2 (0 0)
Salmonella spp	0/4 (0 0)	1/1 (100)	2/2 (100)	2/2 (100)	1/2 (50 0)
Shigella spp	11/11 (100)	3/5 (60 0)	2/2 (100)	4/4 (100)	1/2 (50 0)
Shigella sonnei	8/8 (100)	0/1 (0 0)	1/1 (100)	2/2 (100)	1/2 (50 0)
Diarrheagenic *E coli*	65/73 (89 0)	28/38 (73 7)	33/40 (82 5)	37/44 (84 1)	30/44 (68 2)
EAEC	22/24 (91 7)	12/16 (75 0)	12/15 (80 0)	--	-
ETEC-LT	25/29 (86 2)	8/10 (80 0)	9/11 (81 8)	9/9 (100)	9/14 (64 3)
ETEC-ST	11/11 (100)	4/7 (57 1)	4/4 (100)	18/19 (94 7)	12/18 (66 7)
ETEC-ST/LT	17/21 (81 0)	5/10 (50 0)	11/13 (84 6)	10/16 (62 5)	9/12 (75 0)
Other Agents	7/10 (70 0)	3/6 (50 0)	2/5 (40 0)	11/12 (91 7)	1/2 (50 0)
No Pathogens (ITT Population)	57/69 (82 6)	22/39 (56 4)	36/43 (83 7)	42/60 (70 0)	46/74 (62 2)
Microbiological Eradication (%)					
Any Pathogen	77/128 (60 2)	31/62 (50 0)	46/58 (79 3)	47/65 (72 3)	41/55 (74 5)
Inflammatory/Invasive Pathogens	25/45 (55 6)	10/18 (55 6)	10/13 (76 9)	6/9 (66 7)	8/9 (88 9)
Campylobacter	9/25 (36 0)	4/10 (40 0)	6/9 (66 7)	1/2 (50 0)	1/2 (50 0)
Salmonella spp	2/4 (50 0)	1/1 (100)	2/2 (100)	1/2 (50 0)	2/2 (100)
Shigella spp	10/11 (90 9)	3/5 (60 0)	2/2 (100)	3/4 (75 0)	2/2 (100)
Shigella sonnei	7/8 (87 5)	1/1 (100)	1/1 (100)	2/2 (100)	2/2 (100)
Diarrheagenic *E coli*	56/73 (76 7)	24/38 (63 2)	37/40 (92 5)	33/44 (75 0)	36/44 (81 8)
EAEC	21/24 (87 5)	12/16 (75 0)	14/15 (93 3)	-	

ETEC-LT	20/29 (69 0)	8/10 (80 0)	9/11 (81 8)	6/9 (66 7)	12/14 (85 7)
ETEC-ST	8/11 (72 7)	4/7 (57 1)	4/4 (100)	13/19 (68 4)	14/18 (77 8)
ETEC-ST/LT	18/21 (85 7)	5/10 (50 0)	13/13 (100)	14/16 (87 5)	10/12 (83 3)
Other Agents	4/10 (40 0)	0/6 (0 0)	2/5 (40 0)	11/12 (91 7)	1/2 (50 0)

[a] Subgroups are mutually exclusive Diarrheagenic *E coli* subgroup excludes subjects with inflammatory/invasive pathogens 'Other agents" subgroup excludes subjects with diarrheagenic *E coli* and inflammatory/invasive pathogens

[b] For median TLUS, the number of subjects included in the calculations is displayed in brackets

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

Note Inconsistency between the E coli denominators in Table 20 and 29 are explained by the method of classifying the subjects In the agency analysis (Table 20) the 128 MITT patients were classified as follows those who had E coli as the sole pathogen those who had E coli with another pathogen and those who didn't have E coli i e but had another pathogen The sponsor classified the 128 MITT patients as those who had an inflammatory or invasive pathogen (these patients could have also had E coli) those who had E coli but no evidence of any inflammatory or invasive pathogen (these patients could have some other pathogen though) and all other agents without evidence of inflammatory or invasive pathogens or E coli See executive summary for MO analyses by specific pathogen

C Efficacy Conclusions

Salix Pharmaceuticals resubmitted a new drug application (NDA) 21-361 for the use of rifaximin tablets at a dose of 200 mg PO TID for 3 days in the treatment of traveler's diarrhea The proposed dosing schedule is a 200 mg tablet TID for 3 days (600 mg QD) NDA 21-361 was originally submitted on December 21, 2001 Inlcuded in the application were the results of a second adequate and well-controlled Phase III trial (RFID3001) as requested in an approvable letter issues on October 25, 2002 This trial was requested in order to confirm the results of trial RFID9801 and was required to show a clinically meaningful benefit and a statistically significant reduction in the duration of diarrhea between rifaximin and placebo regimens

The current application also consisted of an Integrated Summary of Efficacy (ISE), an Integrated Summary of Safety (ISS) as well as pharmacokinetic studies

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

Eligible subjects showed evidence of acute diarrhea, defined as 3 or more unformed stools during the 24 hours preceding enrollment, accompanied by one or more of the following signs and symptoms abdominal pain or cramps, excessive gas/flatulence, nausea, vomiting, fever (≥100°F or ≥37 8°C), fecal urgency, tenesmus, or dysentery (passage of bloody stool), total duration of diarrhea was to be no more than 72 hours A

pretreatment stool was collected from all subjects, verified as "unformed" and tested for the presence of enteropathogens Subjects ≥18 years of age were enrolled at sites in Mexico, Guatemala, Peru, Jamaica, India, and Kenya

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

With regards to the primary efficacy parameter TLUS in the ITT population, similar results were obtained between the studies indicating consistency in the ability of rifaximin to decrease morbidity in subjects suffering from traveler's diarrhea Specifically, in study RFID9801 median TLUS was 32 5 hours in the rifaximin 200 mg TID group, and 58 6 hours in the placebo group

In study RID 3001, the median TLUS in the rifaximin ITT population, (32 0 hours) was less than that in the placebo group (65 5 hours) and the median TLUS in the ciprofloxacin group was 28 8 hours However, the acceptability of the pooled results was called into question because of significant treatment-by center interactions necessitating that results be reported by center These interactions were caused by the failure of the positive control at the Goa center and the failure of the negative control at the Mexican site When TLUS was assessed for only those sites where the study was performed in an acceptable manner rifaximin was found to be effective at shortening the duration of diarrhea relative to placebo The relative risk (rifaximin/placebo) for TLUS for Calcutta and Guatemala/Peru was 2 17 (95% CI=1 44-3 27, P=0 0002)

Table 31
Median TLUS by Analysis Center excluding Goa and Mexico
ITT Population RFID3001

Median TLUS in Hours	**Treatment Group**		
(Kaplan-Meier Estimates)	**Rifaximin**	**Placebo**	**Cipro**
Calcutta/Guatemala/Peru	(N= 96)	(N=49)	(N= 50)
	23 85	65 5	23 60

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

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

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

Table 32
Median TLUS by Analysis Center excluding Goa and Mexico
RFID3001 MITT Population

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

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

Table 33
Median TLUS for MITT by specific pathogens

Median TLUS in Hours/MITT	**Treatment Group**		
Study RFID9801	**Rifaximin** N = 125	**Placebo** N = 129	**Ciprofloxacin** **NA**
Escherichia coli only	N = 53 28 4	N = 54 57 8	
Study RFID3001	**Rifaximin** (N=128)	**Placebo** (N=62)	**Ciprofloxacin** (N=58)
Escherichia coli only	N = 64 23 9	N = 33 26 7	(N= 36) 23 4

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

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

An attempt was made to calculate median TLUS for those subjects with *Shigella* spp and *Campylobacter* spp isolated in baseline stool culture however, the numbers of isolates were small and in subjects with these isolates as sole pathogens, the numbers became even smaller Specifically, of 18 total patients with *Shigella* spp (not speciated), 10 had

this isolate as a sole pathogen 7 of these subjects were treated with rifaximin and had a median TLUS of 42 6 hours, 2 were treated with placebo and one had a median TLUS of 31 8 hours while the other failed (TLUS > 120 hours), and one was treated with ciprofloxacin That patient had a TLUS of — hours Of the 7 rifaximin-treated subjects with Shigella spp as their sole pathogen, 5 had Shigella sonnei The median TLUS in this very small subgroup was 30 6 hours and the mean was 34 hours No placebo-treated subjects had *Shigella sonnei* isolated in the stool and only one ciprofloxacin-treated subject had this pathogen That subject had a TLUS of — hours —

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

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

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

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

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

7 No unformed stools within a 48-hour period with no fever (with or without other clinical symptoms), or

8 No watery stools and no more than 2 soft stools within a 24 hour period with no fever and no other clinical symptoms except for mild excess gas/flatulence

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

In study RFID9801 99/125 (79 2%) of rifaximin-treated ITT subjects achieved wellness as compared to 78/129 (60 5%) of placebo-treated subjects Similar results were obtained for the MITT population In study RFID3001, 76 6% rifaximin-treated subjects were classified as clinical cures as compared to 61 4% of placebo recipients Of note, in study RFID3001, the treatment failure rate with rifaximin was slightly more than double that observed with ciprofloxacin (14 7% vs 6 9%, respectively) A by center breakdown of the results revealed continuing issues with the Goa site whereas the results of the Mexican centers were more consistent with those of the other sites lending weight to the argument that the median TLUS value is not the only, and perhaps not always the ideal, statistic to use to assess efficacy While the median TLUS at Mexican centers for the ITT population was larger for rifaximin (median=33 0h) than for placebo (median=26 7h), a greater percentage of rifaximin subjects achieved wellness (N=36/43, 83 7%) than did placebo subjects (N=15/23, 65 2%) suggesting that early during therapy, placebo subjects achieved wellness faster than rifaximin subjects, but did not continue to improve throughout the treatment and follow-up period On the other hand, rifaximin subjects were somewhat delayed in initial response, but continued to achieve wellness after the initial placebo response had begun to cease

Table 33

Wellness- TOC Visit (24 – 48 hours post-treatment) ITT RFID9801 and RFID3001

	Rifaximin	Placebo	Cipro
Overall RFID9801	99/125 (79 2%)	78/129 (60 5%)	N/A
Overall RFID3001	151/197 (76 6%)	62/101 (61 4%)	79/101 (78 2%)
By Center RFID3001			
Calcutta, India	38/43 (88 4%)	11/23 (47 8%)	21/23 (91 3%)
Goa, India	30/58 (51 7%)	15/29 (51 7%)	16/30 (53 3%)
Guatemala and Peru	47/53 (88 7%)	21/26 (80 8%)	26/27 (96 3%)
Mexico sites	36/43 (83 7%)	15/23 (65 2%)	16/21 (76 2%)

The Agency requested that the applicant provide analyses of TLUS, wellness and microbiologic eradication for subjects with fever and/or blood in the stool for subjects in study RFID3001 In both the ITT and MITT populations, it was clear that the presence or absence of fever at baseline played a major role in efficacy with fewer rifaximin and placebo-treated subjects with fever becoming well when this parameter was present TLUS was either not calculable in this group because of the large number of patients with censored data (1 e failures) or it was prolonged Only those subjects treated with ciprofloxacin had lower TLUS and increased percentages of subjects cured Similar results were not seen for the presence or absence of blood in the stool at baseline in the ITT population but the presence or absence of blood at baseline had a clear effect on efficacy in the MITT population again with similar TLUS and clinical cure rates in the

rifaximin and placebo-treated populations Similar analyses were not performed for study RFID9801 where fewer subjects had fever and/or blood in the stool at baseline

Table 34
TLUS, Wellness and Microbiologic Eradication Rates in Subjects with Fever and Blood in the Stool at Baseline Study RFID3001

Group	Rifaximin	Placebo	Ciprofloxacin
Fever at Baseline			
TLUS	NC	51 1	23 4
Wellness	12/25 (48%)	8/12 (66 7%)	12/14 (85 7%)
Eradication	14/25 (56%)	6/12 (50%)	12/14 (85 7%)
Blood at Baseline			
TLUS	63 5	69 7	55 5
Wellness	24/42 (57 1%)	14/25 (56%)	13/18 (72 2%)
Eradication	26/42 (61 9%)	12/25 (48%)	13/18 (72 2%)
Fever and Blood at Baseline			
TLUS	NC	NC	36 5
Wellness	6/14 (42 9%)	3/7 (42 9%)	7/8 (87 5%)
Eradication	8/14 (57 1%)	3/7 (42 9%)	7/8 (87 5%)

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

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

In study RFID 3001 overall eradication rates were again similar between the rifaximin and placebo arms at visit 2 (24 hours after the first dose) and although in the MITT population at Visit 3 (24 – 48 hours after the last dose), a slightly greater proportion of subjects in the rifaximin group than in the placebo group had an overall microbiological response of eradication (61 6% vs 51 7%) these results were not significant and again raised concerns about the true microbiologic activity of rifaximin and the appropriateness of using this parameter as a determinant of efficacy for this drug Results obtained on the ciprofloxacin arm were numerically superior to those obtained on the placebo or rifaximin treatment arms A by center and by pathogen breakdown of the results also did not reveal a significant difference between rifaximin and placebo at any level

Table 35
Microbiologic Eradication rate by Pathogen TOC Visit (24 – 48 hours post-treatment) Study RFID3001

Genus (Species)	Number (%) of MITT/MEE Subjects		
	Rifaximin (N=125)	Placebo (N=62)	Ciprofloxacin (N=58)
Aeromonas (hydrophila)	2/3 (66 7%)	1/1 (100%)	1/1 (100%)
Campylobacter (jejuni)	9/25 (36 0%)	4/10 (40 0%)	6/9 (66 7%)
Plesiomonas sp	3/3 (100%)	-	-
Plesiomonas shigelloides	1/1(100%)	1/2 (50 0%)	-
Salmonella Group B	1/3 (33 3%)	-	-
Salmonella Group C1	1/1 (100%)	1/1 (100%)	1/1 (100%)
Salmonella Group C2	-	-	1/1 (100%)
Shigella boydii	1/1 (100%)	-	-
Shigella flexneri	2/2 (100%)	2/4 (50 0%)	1/1 (100%)
Shigella sonnei	7/8 (87 5%)	1/1 (100%)	1/1 (100%)
Vibrio cholerae	2/2 (100%)	-	-
Providencia	1/1 (100%)	-	1/1 (100%)
Diarrheagenic *E coli*	62/83 (74 7%)	30/43 (69 8%)	43/45 (95 6%)
Cryptosporidium parvum	2/6 (33 3%)	1/4 (25 0%)	2/6 (33 3%)
Entamoeba histolytica	1/3 (33 0%)	-	
Giardia lamblia	6/15 (40 0%)	2/8 (25 0%)	3/5 (60 0%)

Table 36
Microbiologic Eradication rate by Pathogen TOC Visit (24 – 48 hours post-treatment) Study RFID9801

Pathogen	RFID 9801 Rifaximin 200 mg TID		RFID9801 Placebo	
	No	No Eradicated (%)	No	No Eradicated (%)
Escherichia coli	60	45/60 (75%)	54	40/54 (74%)
Shigella sonnei	3	3/3 (100%)	2	2/2 (100%)
Shigella flexneri	2	½ (50%)	0	0
Salmonella Group C1	3	2/3 (67%)	1	1/1 (100%)
Salmonella Group C2	0	0	1	1/1 (100%)
Campylobacter jejuni	4	3/4 (75%)	1	0/1
Crytosporidium parvum	18	12/18 (67%)	1	1/1 (100%)

Overall, it appeared as if rifaximin was effective in reducing the TLUS in subjects in subjects with agent-negative disease or in those with *Escherichia coli* isolated from pretreatment stool culture These results were confirmed in two Phase III clinical trials Rifaximin did not appear to be effective in subjects with inflammatory/invasive pathogens including *Campylobacter jejuni, Salmonella* spp and *Shigella* spp Regarding *Shigella sonnei,* the median TLUS *for Shigella* spp (7 subjects)

was 42 6 hours as compared to 24 hours in rifaximin-treated subjects with diarrheagenic *E coli* Additionally microbiologic efficacy was shown in only 7 subjects with this organism as a sole causative pathogen Regarding *Escherichia coli*, a requested pathogen for which there was adequate data, the data were encouraging In study RFID9801, TLUS in the subset of subjects with this pathogen was less in rifaximin-treated subjects as compared to placebo A similar trend was seen in study RFID3001 when subjects with *Escherichia coli* only were assessed Finally, as in the first review cycle, eradication rates were similar between the rifaximin and placebo treatment arms indicating that rifaximin does not appear to cause clinical improvement directly via microbiologic eradication

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

VI Integrated Review of Safety

A Brief Statement of Conclusions from original safety review

The most frequently (≥5%) reported AEs from the 400 infectious diarrhea (ID) rifaximin patients in the ISS database were gastrointestinal and were also symptoms of the disease under study e g , abdominal pain, fecal incontinence, flatulence, nausea, and tenesmus

No deaths occurred in the ID studies One serious adverse event, worsening of diarrhea, was reported by a placebo patient in an ID study

One (0 25%) of the 400 ID rifaximin patients in the ISS database withdrew because of an adverse event (mild nausea, moderate indisposition/lack of appetite and severe loss of taste) All of the events were considered treatment-related and were resolved within 2 days

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

No reports of overdose have occurred with rifaximin High doses of rifaximin may disrupt the gut microflora as a result of the pharmacological action of rifaximin Based on rifaximin's low systemic absorption and its good tolerability in multiple dose toxicity studies in rats and dogs, at 1000 mg/kg/day and 300 mg/kg/day respectively, supportive treatment should be adequate if an overdose occurs.

Safety data from 103 hepatic encephalopathy (HE) patients treated with rifaximin and included in the ISS database showed that nausea and hepatic encephalopathy were the only adverse events reported at an incidence of ≥ 5% Safety data from an additional 1,647 patients treated with rifaximin in other published and unpublished studies not

Table 37 Completed Phase 2/3 Studies of Rifaximin for the Treatment of Infectious Diarrhea in Travelers

Protocol #/ (Sponsor) # of Investigators/ Countries	Study Design	Treatment Groups	# of Subjects	Mean Age (Range)	Gender	Race
RFID3001 (Salix) 7 investigators/ 4 countries (Guatemala India Mexico Peru)	Parallel groups double blind placebo and active controlled	Rifaximin 200 mg TID x 3 days Placebo TID x 3 days Ciprofloxacin 500 mg BID x 3 days	197 101 101	32 5 (18 79) 33 4 (18 80) 34 2 (18 72)	50% M 50% F 55% M 45% F 51% M 49% F	84% W <1% B 10% H 4% A 2% O 82% W 1% B 8% H 7% A 2% O 79% W 3% B 12% H 4% A 2% O
RFID9801 (Salix) 3 investigators/ 3 countries (Mexico Kenya, Guatemala)	Parallel groups double blind placebo controlled	Rifaximin 200 mg TID x 3 days Rifaximin 400 mg TID x 3 days Placebo TID x 3 days	125 126 129	29 0 (18 72)[b] 29 0 (18 66) 28 3 (16 69)	54% M 46% F 48% M 52% F 51% M 49% F	83% W 1% B 16% O 84% W 3% B 13% O 87% W 2% B 11% O
RFID9701 (Wasserman) 3 investigators/ 2 countries (Mexico Jamaica)	Parallel groups double blind double dummy active controlled	Rifaximin 400 mg BID x 3 days Ciprofloxacin 500 mg BID x 3 days	93 94	26 3 (18 57) 25 6 (18 59)	42% M 58% F 46% M 54% F	82% W 18% O 79% W 5% B 16% O
RFID9601 (Wasserman) 3 investigators/ 1 country (Mexico)	Parallel groups double blind double dummy active controlled	Rifaximin 200 mg TID x 5 days Rifaximin 400 mg TID x 5 days Rifaximin 600 mg TID x 5 days TMP/SMX 160/800 mg BID x 5 days	18 18 19 17	23 90 (19 52) 25 80 (19 46) 24 00 (19-45) 24 41 (19 38)	33% M 67% F 44% M 56% F 63% M 37% F 47% M 53% F	67% W 28% H 5% A 94% W 6% H 84% W 5% H 11% B 88% W 6% H 6% O

Table 38 Studies of Rifaximin in Other Indications Not Included in the Original NDA

Protocol # (Sponsor) # of Investigators/ Countries	Study Design	Treatment Groups	# of Subjects	Mean Age (Range)	Gender	Race
Indication Hepatic Encephalopathy						
RIF/HE/INT/99 (Salix and Wasserman) 11 investigators/ 4 countries (US Poland Hungary UK)	Randomized parallel group double blind, placebo controlled	Rifaximin 400 mg TID with meals x 14 days Placebo TID with meals x 14 days	48 45	53 6 (37 73) 53 3 (27 76)	65% M 35% F 51% M 49% F	85% W 15% O 82% W 7% B 11% O
Indication Crohn s Disease						
RFCD2001 (Salix) 1 investigator/ 1 country (US)	Open label	Rifaximin 200 mg TID x 16 weeks	29	44 6 (20 74)	38% M 62% F	97% W 3% B

Protocol # (Sponsor) # of Investigators/ Countries	Study Design	Treatment Groups	# of Subjects	Mean Age (Range)	Gender	Race
Indication Pouchitis						
RFPO2001 (Salix) 12 investigators/ 1 country (US)	Randomized double blind, placebo controlled	Rifaximin 200 mg TID x 28 days Placebo TID x 28 days	Study is ongoing 12 as of 31 October 2003	Unknown	Unknown	Unknown

Salix = Salix Pharmaceuticals Inc Wasserman = Alfa Wasserman S p A US = United States UK = United Kingdom TID = three times a day M = male F = female W = White O = Other
B = Black

Table 39 Completed Phase 1 Studies of Rifaximin Not Included in the Original NDA

Protocol # (Sponsor)/ # of Investigators/ Countries	Study Design	Treatment Groups	# of Subjects	Mean Age (Range)	Gender	Race
Bioavailability of Commercial Rifaximin						
RFPK1001 (Salix) 1 investigator/ 1 country (US)	Open label single dose randomized crossover	Rifaximin 400 mg test (commercial scale up lot) x 1 dose Rifaximin 400 mg reference (clinical lot) x 1 dose	14	28 9 (20 44)	50% M 50% F	50% W 29% B 14% H 7% O
Pharmacokinetics of Rifaximin in Subjects with Shigellosis						
RFPK1004 (Salix) 1 investigator/ 1 country (US)	Open label pharmacokinetic	Rifaximin 200 mg Q8h x 3 days in subjects challenged with *Shigella flexneri* as soon as they met the case definition of diarrhea	15 Enrolled 13 Dosed	32 5 (18-45)	69% M 31% F	15% W 77% B 8% H
Effect of Rifaximin on the Pharmacokinetics of Ethinyl Estradiol and Norgestimate						
RFDI1001 (Salix) 1 investigator/ 1 country (US)	Open label crossover pharmacokinetic drug interaction	Ethinyl estradiol 0 07 mg and norgestimate 0 50 mg on Day 0 followed by a 7-day washout Rifaximin 200 mg Q8h x 3 days beginning with 2 doses on Day 11 and ending with a single dose of rifaximin 200 mg concomitant with ethinyl estradiol 0 07 mg and norgestimate 0 50 mg on Day 14	28	28 5 (19 44)	100% F	43% W 18% B 36% H 4% O
Effect of Rifaximin on the Pharmacokinetics of IV and PO Midazolam						
RFDI1002 (Salix) 1 investigator/	Open label randomized crossover	Treatment Group A midazolam 2 mg IV on Days 0 6 and 10 and	27	27 6 (18 51)	48% M 52% F	63% W 15% B 22% H

Protocol # (Sponsor)/ # of Investigators/ Countries	Study Design	Treatment Groups	# of Subjects	Mean Age (Range)	Gender	Race
1 country (US)	pharmacokinetic drug interaction	midazolam 6 mg PO on Days 26 32 and 36 with rifaximin 200 mg Q8h on Days 3 – 10 and Days 29 – 36 Treatment Group B midazolam 6 mg PO on Days 0 6 and 10 and midazolam 2 mg IV on Days 26 32 and 36 with rifaximin 200 mg Q8h on Days 3 – 10 and Days 29 – 36				

Salix = Salix Pharmaceuticals Inc US = United States Q8h = every 8 hours IV = intravenous PO = oral M = male F = female W = White O = Other B = Black H = Hispanic

APPEARS THIS WAY
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B Description of Patient Exposure

Across the 2 pivotal studies, > 85% of the subjects treated with rifaximin 600 mg/day, placebo, or ciprofloxacin received at least 3 days of treatment

Table 40
Study Drug Exposure

	Number (%) of Subjects		
Exposure	Rifaximin 600 mg/day (N=320)	Placebo (N=228)	Ciprofloxacin (N=100)
Number of Days of Treatment[a]			
1	4 (1 3%)	2 (0 9%)	1 (1 0%)
2	13 (4 1%)	15 (6 6%)	2 (2 0%)
3	86 (26 9%)	75 (32 9%)	26 (26 0%)
4	216 (67 5%)	135 (59 2%)	70 (70 0%)
5	1 (0 3%)	1 (0 4%)	1 (1 0%)
6	0 (0 0%)	0 (0 0%)	
7	0 (0 0%)	0 (0 0%)	
At Least 3 Days of Treatment	303 (94 7%)	211 (92 5%)	97 (97%)

Reference Safety Update Table 4 2

[a] Days on study drug were based on date (calendar days) rather than 24-hour time intervals shown on the diary cards Therefore, subjects may have received study drug over 4 calendar days but only over a 72-hour time period

Patient Disposition

As safety by dose was assessed in the review of the original NDA submission, the MO elected to present the safety data from the pivotal studies where the requested dose of rifaximin 600 mg day versus placebo and/or ciprofloxacin was utilized

The safety population of the pivotal studies was comprised of 320 rifaximin 600 mg/day recipients and 228 placebo recipients As per the applicant, "A statistically significantly (p=0 0177) greater proportion of placebo subjects (14 9%) prematurely discontinued study participation compared with rifaximin 600 mg/day subjects (8 1%)" The most common reason for premature discontinuation from the study in both treatment groups was treatment failure, which was reported in a greater number of placebo subjects (13 2%) than rifaximin 600 mg/day subjects (6 9%) The incidence of premature discontinuation due to adverse events was similar between the treatment groups (0 9% rifaximin 600 mg/day and 0 4% placebo)

Medical Officer's Comment *The MO amended the applicant's table with the addition of a ciprofloxacin column Of note safety data were unavailable on one subject and thus 100 subjects were included in the final safety dataset A smaller proportion of*

ciprofloxacin-treated subjects discontinued treatment compared with the rifaximin and placebo arms with significantly less subjects discontinuing due failure (ciprofloxacin 2% vs rifaximin 6 9%% vs placebo 13 2%) A greater proportion of ciprofloxacin-treated subjects discontinued due to AEs although the numbers were very small

Table 41
Disposition of Subjects

Disposition	Number (%) of Subjects		
	Rifaximin 600 mg/day	Placebo	Ciprofloxacin 1000 mg/day
Subjects Enrolled	324	230	101
Subjects in Safety Population[b]	320 (100%)	228 (100%)	100 (100%)
Safety Population Subjects Who Prematurely Discontinued Study Participation	26 (8 1%)	34 (14 9%)	7 (7%)
Lack of Efficacy	22 (6 9%)	30 (13 2%)	2 (2%)
Not Lack of Efficacy Total	4 (1 3%)	4 (1 8%)	5 (5%)
Adverse Event	3 (0 9%)	1 (0 4%)	3 (3%)
Other Reasons	1 (0 3%)	3 (1 3%)	1 (1%)

Demographics

No major differences were observed between the treatment groups for any of the demographic characteristics Subject age ranged from 16-80 years, mean age was 31 3 years in the rifaximin group, 34 2 years for the ciprofloxacin group, and 30 4 years in the placebo group Less than 3% of the subjects in either treatment group were ≥65 years of age The majority of the subjects in both treatment groups were white with a comparable distribution of males and females between the treatment groups There was a higher proportion of black subjects enrolled in the ciprofloxacin group

Table 42
Subject Demographics

Demographic Characteristics	Number (%) of Subjects		
	Rifaximin 600 mg/day (N=320)	Placebo (N=228)	Ciprofloxacin 1000 mg/day (N = 101)
Age (years)			
N	316	228	101
Mean (SE)	31 3 (0 73)	30 4 (0 82)	34 2 (14 36)
Median	26 0	25 0	28 0
Range	18-79	16-80	18 – 72
Age			
<65 years	307 (97 2%)	224 (98 2%)	
≥65 years	9 (2 8%)	4 (1 8%)	
Gender			
Male	167 (52 2%)	121 (53 1%)	52 (51 5%)
Female	153 (47 8%)	107 (46 9%)	49 (48 5%)
Race			
White	269 (84 1%)	193 (84 6%)	80 (79 2%)
Hispanic	35 (10 9%)	21 (9 2%)	3 (3 0%)
Black	2 (0 6%)	3 (1 3%)	12 (11 9%)
Asian	9 (2 8%)	9 (3 9%)	4 (4 0%)
Other	5 (1 6%)	2 (0 9%)	2 (2 0%)

Reference Safety Update Table 2 2
SE = standard error

No major differences were observed between the treatment groups for the baseline disease characteristics Mean number of unformed stools in the 24 hours before treatment ranged from 3-30 hours, with a mean of 6 9 stools in the rifaximin and ciprofloxacin groups and 6 4 stools in the placebo group Dysentery was reported in 4 1% of the rifaximin subjects and 4 4% of the placebo subjects The majority of the subjects in both treatment groups did not have invasive pathogens identified at baseline (85 0% rifaximin and 90 4% placebo)

Table 43
Subject Disease Characteristics

Disease Characteristics	Number (%) of Subjects: Rifaximin 600 mg/day (N=320)	Placebo (N=228)	Ciprofloxacin 1000 mg/day N = 101
Number of Unformed Stools in 24 Hours Before Treatment			
N	315	221	101
Mean (SE)	6 9 (0 24)	6 4 (0 28)	6 9
Median	5 0	5 0	6 0
Range	3-30	3-30	3 - 29
Dysentery			
Yes	13 (4 1%)	10 (4 4%)	
No	307 (95 9%)	218 (95 6%)	
Subjects with Invasive Pathogens at Baseline			
Yes	48 (15 0%)	22 (9 6%)	64 (63 4%)
No	272 (85 0%)	206 (90 4%)	

Reference Safety Update Table 3 2
SE = standard error
[a]Two-sample t-test
[b]Fisher s exact test

AEs

Across the 2 pivotal studies, no differences were observed between the rifaximin 600 mg/day and placebo groups for the overall incidence of adverse events or for the incidence of adverse events associated with any specific system organ class The incidence of GI AEs was greater in the rifaximin recipients than the ciprofloxacin and the incidence of these events was greatest in the placebo recipients Although most AEs in rifaximin-treated subjects appear to be GI in nature the difference in the reported incidences in the safety data seen below was probably due to the different methods of reporting AEs in studies RFID9801 and RFID3001 In RFID9801, GI events were reported as AEs while this was not the case in RFID3001 Finally the incidence of GI AEs may e due to the underlying disease process

As per the applicant, "A statistically significant difference (0 0105) was observed for the incidence of diarrhea NOS (sic), possibly indicating a lack of efficacy among placebo subjects (4 8%) compared with rifaximin subjects (0 6%)"

Table 44
Adverse Events Occurring in ≥1% of Subjects

System Organ Class MedDRA Preferred Term	Number (%) of Subjects Rifaximin 600 mg/day (N=320)	Placebo (N=228)	Ciprofloxacin 1000 mg/day (N=100)
Any Adverse Event	142 (44 4%)	122 (53 5%)	24 (24 0%)
Gastrointestinal Disorders	**94 (29 4%)**	**97 (42 5%)**	**14 (14 0%)**
Flatulence	36 (11 3%)	45 (19 7%)	2 (2 0%)
Abdominal Pain NOS	23 (7 2%)	23 (10 1%)	0 (0%)
Rectal Tenesmus	23 (7 2%)	20 (8 8%)	1 (1 0%)
Defecation Urgency	19 (5 9%)	21 (9 2%)	2 (2 0%)
Nausea	17 (5 3%)	19 (8 3%)	2 (2 0%)
Constipation	12 (3 8%)	8 (3 5%)	8 (8 0%)
Vomiting NOS	7 (2 2%)	4 (1 8%)	2 (2 0%)
Diarrhea NOS	2 (0 6%)	11 (4 8%)	0 (0%)
Fecal abnormality NOS	4 (1 3%)	1(0 4%)	0 (0%)
General Disorders and Administration Site Conditions	17 (5 3%)	17 (7 5%)	2 (2 0%)
Pyrexia	10 (3 1%)	10 (4 4%)	1 (1 0%)
Weakness	2 (0 6%)	3 (1 3%)	0 (0%)
Nervous System Disorders	38 (11 9%)	30 (13 2%)	5 (5 0%)
Headache	31 (9 7%)	21 (9 2%)	5 (5 0%)
Dizziness	3 (0 9%)	7 (3 1%)	2 (2 0%)
Ear and Labyrinth disorders	4 (1 3%)	0 (0%)	0 (0%)
Laboratory	7 (2 2%)	6 (2 6%)	1 (1 0%)
AST Increased	4 (1 3%)	4 (1 8%)	0 (0%)
Decreased RBC	0 (0%)	0 (0%)	1 (1 0%)
Musculoskeletal	6 (1 9%)	6 (2 6%)	1 (1 0%)
Renal and Urinary	7 (2 2%)	1 (0 4%)	0 (0%)
Respiratory	8 (2 5%)	7 (3 1%)	1 (1 0%)

NOS = not otherwise specified

RFID3001 also studied the active control agent, ciprofloxacin The adverse event profile of rifaximin 600 mg/day was similar to that observed with ciprofloxacin 1000 mg/day The incidence of headache was similar among rifaximin and placebo-treated subjects (9 7% and 9 2%) as compared to 5% on the ciprofloxacin arm while the incidence of constipation was higher among ciprofloxacin-treated subjects (8 0% versus 3 8%)

Drug Related AEs

No differences were observed between the rifaximin 600 mg/day and placebo groups for the overall incidence of drug-related adverse events or for the incidence of drug-related adverse events associated with any specific system organ class

Table 45
Drug-Related Adverse Events

System Organ Class MedDRA Preferred Term	Number (%) of Subjects Rifaximin 600 mg/day (N=320)	Placebo (N=228)	Ciprofloxacin (N=100)
Any Adverse Event	95 (29 7%)	100 (43 9%)	14 (14 0%)
Blood and Lymphatic	2 (0 6%)	0 (0%)	1 (1%)
Lymphocytosis	2 (0 6%)	0 (0%)	1 (1%)
Monocytosis	1 (0 3%)	0 (0%)	0 (0%)
Neutropenia	2 (0 6%)	0 (0%)	0 (0%)
Cardiac	0 (0%)	1 (0 4%)	0 (0%)
Palpitations	0 (0%)	1 (0 4%)	0 (0%)
Eye Disorders	0 (0%)	2 (0 9%)	0 (0%)
Conjunctivitis	0 (0%)	1 (0 4%)	0 (0%)
Dry eye	0 (0%)	1 (0 4%)	0 (0%)
Gastrointestinal Disorders	72 (22 5%)	87 (38 2%)	8 (8%)
Flatulence	31 (9 7%)	44 (19 3%)	0 (0%)
Abdominal Pain NOS	19 (5 9%)	21 (9 2%)	0 (0%)
Nausea	15 (4 7%)	19 (8 3%)	1 (1%)
Rectal Tenesmus	13 (4 1%)	14 (6 1%)	0 (0%)
Defecation Urgency	12 (3 8%)	15 (6 6%)	0 (0%)
Constipation	11 (3 4%)	6 (2 6%)	7 (7%)
Diarrhea NOS	**2 (0 6%)**	**9 (3 9%)**	0 (0%)
Abdominal distention	1 (0 3%)	1 (0 4%)	1 (1%)
Dry Mouth	0 (0%)	2 (0 9%)	0 (0%)
Dry throat	1 (0 3%)	0 (0%)	0 (0%)
Fecal abnormality	2 (0 6%)	0 (0%)	0 (0%)
Hyperacidity	0 (0%)	1 (0 4%)	0 (0%)
Dry Lip	1 (0 3%)	0 (0%)	0 (0%)
Vomiting	0 (0%)	0 (0%)	1 (1%)
General Disorders and Administration Site Conditions	7 (2 2%)	9 (3 9%)	2 (2%)
Pyrexia	3 (0 9%)	6 (2 6%)	1 (1%)
Chest Pain	2 (0 6%)	1 (0 4%)	0 (0%)
Malaise	1 (0 3%)	0 (0%)	0 (0%)
Pain NOS	1 (0 3%)	1 (0 4%)	0 (0%)
Weakness	1 (0 3%)	2 (0 9%)	0 (0%)
Asthenia	0 (0%)	0 (0%)	1 (1%)
Injury	1 (0 3%)	0 (0%)	0 (0%)

Sunburn	1 (0 3%)	0 (0%)	0 (0%)
Nervous System Disorders	21 (6 6%)	20 (8 8%)	3 (3%)
Headache	**17 (5 3%)**	**13 (5 7%)**	2 (2%)
Dizziness	1 (0 3%)	5 (2 2%)	1 (1%)
Abnormal Dreams	1 (0 3%)	0 (0%)	0 (0%)
Dysgeusia	0 (0%)	1 (0 4%)	0 (0%)
Migraine Nos	3 (0 9%)	2 (0 9%)	0 (0%)
Somnolence	0 (0%)	1 (0 4%)	0 (0%)
Taste Disturbance	0 (0%)	1 (0 4%)	0 (0%)
Taste Loss	1 (0 3%)	0 (0%)	0 (0%)
Psychiatric	0 (0%)	1 (0 4%)	0 (0%)
Nightmares	0 (0%)	1 (0 4%)	0 (0%)
Renal and Urinary	4 (1 3%)	0 (0%)	0 (0%)
Hematuria	2 (0 9%)	0 (0%)	0 (0%)
Polyuria	1 (0 3%)	0 (0%)	0 (0%)
Increased frequency	1 (0 3%)	0 (0%)	0 (0%)
Respiratory and Thoracic	1 (0 3%)	3 (1 3%)	0 (0%)
Asthma	0 (0%)	1 (0 4%)	0 (0%)
Dyspnea	1 (0 3%)	0 (0%)	0 (0%)
Nasal congestion	0 (0%)	1 (0 4%)	0 (0%)
Throat Irritation	0 (0%)	1 (0 4%)	0 (0%)
Skin	1 (0 3%)	0 (0%)	0 (0%)
Clamminess	1 (0 3%)	0 (0%)	0 (0%)
Vascular	1 (0 3%)	1 (0 4%)	0 (0%)
Hot flushes	1 (0 3%)	0 (0%)	0 (0%)
Hypertension	0 (0%)	1 (0 4%)	0 (0%)
Musculoskeletal	1 (0 3%)	5 (2 2%)	0 (0%)
Back pain	0 (0%)	2 (0 9%)	0 (0%)
Muscle cramps	0 (0%)	2 (0 9%)	0 (0%)
Myalgia	1 (0 3%)	0 (0%)	0 (0%)
Limb Pain	0 (0%)	1 (0 4%)	0 (0%)
Metabolic and Nutritional	1 (0 3%)	0 (0%)	0 (0%)
Anorexia	1 (0 3%)	0 (0%)	0 (0%)
Investigations	6 (1 9%)	4 (1 8%)	1 (1%)
ALT Increased	0 (0%)	2 (0 9%)	0 (0%)
AST Increased	4 (1 3%)	4 (1 8%)	0 (0%)

Blood in stool	1 (0 3%)	0 (0%)	0 (0%)
Blood in urine	1 (0 3%)	0 (0%)	0 (0%)
Decreased RBC	0 (0%)	0 (0%)	1 (1%)

NOS = not otherwise specified

A statistically significant difference was observed for the incidence of drug-related diarrhea, possibly indicating a lack of efficacy among placebo subjects (3 9%) compared with rifaximin subjects (0 6%)

As above, treatment-related AEs appeared to be primarily from the GI tract and the CNS Headache and dizziness were equally attributed to treatment on both the placebo and rifaximin arms

Within each study, the incidences of drug-related adverse events between the rifaximin 600 mg/day and placebo groups were similar

Severe AEs

Across the 2 pivotal studies, the majority of the adverse events were mild or moderate in intensity More placebo subjects experienced severe adverse events (12 7%) compared with the rifaximin 600 mg/day group (7 5%) The fewest severe AEs were reported from the ciprofloxacin-treated subjects in study 3001 The most common types of severe adverse events experienced in rifaximin- and placebo-treated subjects were gastrointestinal disorders (5 0% rifaximin and 8 8% placebo) The specific types of severe gastrointestinal disorders experienced in both groups included abdominal pain NOS, nausea, defecation urgency, and flatulence

Table 46
Incidence of Severe Adverse Events Safety Population

MedDRA System Organ Class Preferred Term of Severe AEs	Rifaximin (N=320)	Placebo (N=228)	Ciprofloxacin (N=100)
No (%) Subjects Reporting Severe AEs	24 (7 5%)	29 (12 7%)	3 (3 0%)
Gastrointestinal Disorders	16 (5%)	20 (8 8%)	1 (1%)
Constipation	0 (0%)	1 (0 4%)	1 (1 0%)
Abdominal Pain	5 (1 6%)	7 (3 1%)	0 (0%)
Defecation Urgency	2 (0 6%)	8 (3 5%)	0 (0%)
Diarrhea	2 (0 6%)	2 (0 9%)	0 (0%)
Flatulence	4 (1 3%)	9 (3 9%)	0 (0%)
Nausea	4 (1 3%)	3 (1 3%)	0 (0%)
Rectal Tenesmus	3 (0 9%)	4 (1 8%)	0 (0%)
Vomiting	2 (0 6%)	0 (0%)	0 (0%)
General Disorders and Administration Site Conditions	0 (0%)	5 (2 2%)	0 (0%)
Fatigue	0 (0%)	1 (0 4%)	0 (0%)
Pyrexia	0 (0%)	2 (0 9%)	0 (0%)
Chest Pain	0 (0%)	1 (0 4%)	0 (0%)
Pain NOS	0 (0%)	1 (0 4%)	0 (0%)
Infections and Infestations	1 (0 3%)	1 (0 4%)	0 (0%)
Dysentery NOS	1 (0 3%)	0 (0%)	0 (0%)
Malaria NOS	0 (0%)	0 (0%)	1 (1 0%)
Respiratory tract infection NOS	0 (0%)	1 (0 4%)	0 (0%)
Musculoskeletal and Connective Tissue Disorders	0 (0%)	2 (0 9%)	0 (0%)
Tendonitis	0 (0%)	1 (0 4%)	0 (0%)
Back Pain	0 (0%)	1 (0 4%)	0 (0%)
Nervous System Disorders	5 (1 6%)	4 (1 8%)	1 (1%)
Headache	2 (0 6%)	2 (0 9%)	1 (1 0%)
Migraine NOS	2 (0 6%)	0 (0%)	0 (0%)
Taste Loss	1 (0 3%)	0 (0%)	0 (0%)
Dizziness	0 (0%)	2 (0 9%	0 (0%)
Renal and Urinary Disorders	1 (0 3%)	0 (0%)	0 (0%)
Dysuria	1 (0 3%)	0 (0%)	0 (0%)
Respiratory, Thoracic and Mediastinal Disorders	1 (0 3%)	0 (0%)	0 (0%)
Rhinorrhea	1 (0 3%)	0 (0%)	0 (0%)

Deaths

No deaths occurred in the infectious diarrhea studies

Discontinuations and Withdrawals

Seven subjects (3 rifaximin, 1 placebo, and 3 ciprofloxacin) prematurely discontinued treatment from the infectious diarrhea studies due to 1 or more adverse events Three of the 7 subjects experienced adverse events considered possibly or probably related to study drug, including constipation and vomiting NOS in 1 ciprofloxacin subject each, and nausea, taste loss, and anorexia in 1 rifaximin subject

Table 47
Subjects Who Prematurely Discontinued Due to Adverse Events

Study	Subject Number	Preferred Term	Severity	Relationship
Rifaximin Treatment Group (600 mg/day)				
RFID3001	107-0062	Nasal Passage Irritation	Mild	Not related
		Weight Decreased	Moderate	Not related
RFID3001	249-0281	Dysentery NOS	Severe	Not related
RFID9801	02103	Nausea	Mild	Probably related
		Taste Loss	Severe	Probably related
		Anorexia	Moderate	Possibly related
Placebo Treatment Group				
RFID3001	101-0450	Cough	NA	Not related
		Respiratory Tract Infection NOS	Severe	Not related
		Dehydration	Mild	Not related
Cipro Treatment Group (1000 mg/day)				
RFID3001	100-0391	Constipation	Severe	Possibly related
RFID3001	100-0398	Malaria NOS	Severe	Not related
RFID3001	200 0291	Vomiting NOS	Moderate	Possibly related

Reference Safety Update Table 17
NA= not available NOS = not otherwise specified

Serious AEs

Three subjects (1 rifaximin and 2 placebo) experienced 4 serious adverse events in the 4 infectious diarrhea studies conducted in travelers All 3 subjects required hospitalization Although 3 of the 4 serious adverse events were considered severe, only 1 (diarrhea NOS in a placebo subject) was considered possibly related to study drug

Table 48
Subjects Who Experienced Serious Adverse Events in Studies

Study	Subject Number	Preferred Term	Severity	Relationship	Action Taken
Rifaximin Treatment Group (600 mg/day)					
RFID3001	249-0281	Dysentery NOS	Severe	Not related	Drug stopped
Placebo Treatment Group					
RFID3001	101-0450	Respiratory Tract Infection NOS	Severe	Not related	Drug stopped
		Dehydration	Mild	Not related	Drug stopped
RFID9801	02094	Diarrhea NOS	Severe	Possibly related	Drug stopped

Reference Safety Update Table 18
NOS = not otherwise specified

Labs

Blood chemistry testing was not obtained in study 3001 The only new data pertain to hematology assessment In the original submission, blood chemistry (serum creatinine,

AST, ALT, and total bilirubin) and hematology (white blood cell count, hemoglobin, and platelets) parameters were evaluated in 5 ISS studies including three ID studies and 2 HE studies

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

A detailed listing of ID patients who developed abnormal LFTs revealed that 4 placebo and 4 rifaximin 200 TID patients developed increased aspartate aminotransferase during study 9801 (up to 2 – 3 x ULN) Two of the placebo subjects also had increased ALT For a detailed listing of these subjects see original MOR Appendix I

Across the 2 pivotal studies (9801 and 3001), no statistically significant differences were observed between the rifaximin 600 mg/day and placebo groups for the proportions of subjects who experienced shifts from baseline to post-treatment in WBC, hemoglobin or platelet counts The majority of the subjects in both treatment groups had normal hematology values at baseline that remained normal after treatment

Across the 2 pivotal studies, no statistically significant differences were observed between the rifaximin 600 mg/day and placebo groups for the proportions of subjects with normal baseline values who met the criteria for a substantially abnormal hematology value

Table 49
Substantially Abnormal Hematology Values Adjusting for Abnormal Baseline Values (Rifaximin 600 mg/day versus Placebo)

	Rifaximin 600 mg/day (N=320)	Placebo (N=228)	
Laboratory Variable	Post Baseline n/N (%)	Post Baseline n/N (%)	p-value[a]
WBC (10^9/L)			
<75% of LLN	1/296 (0 3%)	0/209 (0 0%)	1 0000
<90% of LLN	6/296 (2 0%)	4/209 (1 9%)	1 0000
Hemoglobin (g/dL)			
<75% of LLN	0/299 (0 0%)	0/211 (0 0%)	NC
<90% of LLN	0/299 (0 0%)	0/211 (0 0%)	NC
Platelets (10^9/L)			
<75% of LLN	1/290 (0 3%)	2/206 (1 0%)	0 5730
<90% of LLN	5/290 (1 7%)	4/206 (1 9%)	1 0000

Reference Safety Update Table 15 2
LLN = lower limit of normal, NC = not calculated
[a] Fisher s exact test

Conclusions

Overall, 593 subjects were exposed to rifaximin doses of 600 mg/day, 800 mg/day, 1200 mg/day, or 1800 mg/day in the traveler's diarrhea studies Three hundred twenty of these subjects received the requested dose and duration of treatment of 200 mg TID

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

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

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

No subjects died during the Phase 2/3 studies One (0 2%) rifaximin-treated subject experienced a serious adverse event (dysentery NOS) and 3 (0 5%) rifaximin-treated subjects prematurely discontinued treatment due to adverse events (nasal passage irritation and weight decreased, dysentery NOS, nausea, taste loss, and anorexia) No clinically important changes in WBC counts, hemoglobin, or platelet counts were observed following treatment with rifaximin

Adverse Events by Presence of Dysentery

Thirteen subjects in the rifaximin group (4 1%) and 10 placebo (4 4%) subjects had dysentery at baseline, defined by the presence of gross blood in the stool Six rifaximin and 4 placebo subjects with dysentery has AEs Most events were from the GI tract In general, due to the small number of subjects who had the dysentery at baseline, no meaningful comparisons can be made between subjects with and without dysentery

Phase I Studies

Four additional Phase 1 studies have been completed by the applicant since the original filing One of the studies assessed the bioavailability of commercial scale-up manufacturing on a single oral dose of rifaximin (RFPK1001), another study assessed the pharmacokinetics of rifaximin in subjects with shigellosis (RFPK1004) and two of the studies were drug interactions trials that assessed the effect of rifaximin on an oral contraceptive (RFDI1001) and midazolam (RFDI1002) pharmacokinetics

Brief summaries of the safety data from those studies are presented below

RFPK1001 The Effect of Commercial Scale-up Manufacturing on the Bioavailability of a Single (2 x 200 mg) Oral Dose of Rifaximin, 200 mg Tablets, in Healthy Volunteers

Protocol RFPK1001 was an open-label, randomized, crossover study of 2 tablet lots of rifaximin Subjects were randomly assigned to 1 of 2 study groups to receive 2 doses of oral rifaximin (400 mg/dose) Each dose of rifaximin was administered during a study period that lasted 6 days and doses were separated by 5 days

Fourteen subjects were randomized and completed treatment Equal numbers of males and females were enrolled in the study Median subject age was 25 years (range 20-44 years)

Twelve subjects (85 7%) of the 14 subjects enrolled in the study experienced AEs all of which were mild or moderate in severity Most AEs were from the GI and CNS and included epigastric discomfort in 3 and headache in 4 Other AEs experienced in more than 2 subjects included pruritus, erythema, and dysmenorrhea Three adverse events in 2 subjects were considered to be related to treatment with rifaximin (mild pruritus in 1 subject, and mild epigastric discomfort and moderate headache in 1 subject)

There were no deaths, serious adverse events, or premature terminations due to adverse events reported during the study

No significant changes were observed for any subject in hematology values, serum chemistry values, or urinalysis results

RFPK1004 The Evaluation of the Pharmacokinetics of Rifaximin in Subjects with Shigellosis

Phase 1, single-site, open-label, pharmacokinetic study of oral rifaximin, given every 8 hours for 3 days, for a total of 9 doses The study was divided into 3 phases a screening phase, an inpatient phase, and a post-treatment phase Volunteers were admitted to the

on Day 0 On Day 1, after eating a light breakfast, subjects fasted for at least 90 minutes and then were challenged with *Shigella flexneri* 2a Rifaximin treatment (200 mg every 8 hours for 3 days) was initiated in challenged subjects as soon as they met the case definition of diarrhea

All volunteers remained in the inpatient facility at least through Day 7 for assessments, blood draws and stool samples/cultures, and were discharged between Days 7-10 when they had a negative stool culture for *S flexneri*

Rescue therapy, ciprofloxacin (500 mg orally twice daily [BID]) for 3 days, was initiated in challenged subjects if the following conditions were met

- if the subject developed shigellosis and did not respond to rifaximin (i e , 3 doses) within 24-48 hours after initiation of treatment (shigellosis was defined as temperature >101 °F, diarrhea or dysentery present along with more than 1 constitutional symptom and >1 gastrointestinal symptom rated as severe), or
- if a subject developed severe diarrhea and did not respond to rifaximin therapy within 24 hours and progressed to meet the case definition of "severe" diarrhea (passage of ≥10 grade 3-5 stools in a 24-hour period, or >1000 g of grade 3-5 stools in 24 hours), or
- If the Investigator considered it to be clinically indicated

Regardless of when rescue therapy was initiated, the subject completed the course of rifaximin and the blood draws associated with the pharmacokinetic study Subjects were discharged once they completed the assessments, blood draws, and had a negative stool culture for the *S flexneri* All volunteers were asked to return to the outpatient clinic 7 to 10 days after their last day of rifaximin for an assessment of vital signs, adverse events, concomitant medications, a stool sample for culture, and urine pregnancy tests (female subjects only)

Physical examinations and routine laboratory analyses were performed at Screening, Day 0 and upon discharge Vital signs (temperature, heart rate, blood pressure, respiratory rate) were obtained during screening, at Day 0, approximately every 8 hours on Days 1 through 7, and upon discharge If a subject developed severe diarrhea, vital signs were taken every 30 minutes until they returned to baseline ranges All adverse events were assessed during the course of the study

Fifteen adult subjects were challenged with *S flexneri* 2a, of whom 13 developed diarrhea or dysentery and were treated with rifaximin Of these 13 subjects, 6 were

determined to have severe dysentery requiring rescue therapy with ciprofloxacin (100%) while the remaining 7 developed mild to moderate disease Two of the seven subjects with mild to moderate disease met the criteria for rescue therapy and were treated On the day of discharge, 1 subject with mild disease, who initially had several stool cultures negative for *S flexneri*, had a stool sample taken that was positive As a result of this subject's relapse, the Investigator decided that this subject and subjects who had not initially received ciprofloxacin should be placed on therapy prohylactically Thus, all 13 subjects within the safety population, the 6 subjects with severe disease, the 7 subjects with mild to moderate disease and the 2 subjects who did not receive rifaximin, received treatment with ciprofloxacin

Of the 13 subjects who were treated with rifaximin, 9 subjects (69 2%) were male and 4 (30 8%) were female The mean age was 32 5 years (range 18 0 to 45 0 years)

Six of thirteen subjects (46 2%) experienced adverse events during the study Body systems in which adverse events occurred in ≥2 subjects included musculoskeletal and connective tissue disorders (3 subjects, 23 1%), gastrointestinal disorders (2 subjects, 15 4%), and respiratory, thoracic and mediastinal disorders (2 subjects, 15 4%) Cough was the only specific adverse event that occurred in ≥2 subjects (2, 15 4%) All adverse events experienced were either mild or moderate in severity and were considered by the Investigator to be unrelated to study drug

No subjects withdrew from the study due to an adverse event No deaths or serious adverse events occurred during the study

No subject was found to have any clinically meaningful change in hematology, chemistry or urinalysis laboratory findings

RFDI1001 An Open-Label, Controlled Clinical Study to Assess the Effect of Rifaximin on the Pharmacokinetics of a Single Dose of Ethinyl Estradiol and Norgestimate in Healthy Female Volunteers

Open-label, crossover, pharmacokinetic drug interaction study of the effect of rifaximin 200 mg PO every 8 hours for 3 days (9 consecutive oral doses) on the pharmacokinetics of a single dose of an oral contraceptive (Ortho-Cyclen) Routine laboratory analyses, physical examinations and vital signs (temperature, heart rate, blood pressure, respiratory rate) were obtained during screening, at the end of the study, and as clinically indicated throughout the study All adverse events were assessed during the course of the study All study subjects who received at least 1 dose of study medication were included in the safety analysis

Twenty-eight female subjects were enrolled in the study and received at least 1 dose of study medication The mean age of the subjects was 28 5 years (range 19 0 to 44 0 years) Two subjects discontinued study participation due to protocol violations prior to dose administration in the second treatment period

Almost twice as many subjects (85 7%) experienced at least 1 adverse event when taking Ortho-Cyclen® alone as compared to taking Ortho-Cyclen® and rifaximin (46 2%) in combination The majority of adverse events were mild in intensity Reported adverse events were consistent with those documented for oral contraceptives and rifaximin, and were not unexpected

In Treatment Interval I (Ortho-Cyclen® alone), 18 subjects (64 3%) experienced adverse events that were considered by the Investigator to be related to study drug During Treatment Interval II (rifaximin alone), 13 subjects (50 0%) experienced adverse events that were considered to be related to study drug, while in Treatment Interval III (Ortho-Cyclen® + rifaximin), 9 subjects (34 6%) experienced adverse events considered to be related to study drug Both Ortho-Cyclen® and rifaximin were given during Treatment Interval III and it was not possible to ascribe relationship to either drug
No subject withdrew from the study due to adverse events There were no deaths, other serious adverse events, or adverse events leading to discontinuation of study drug during the study No subjects became pregnant during the course of the study In addition, no subject was found to have a clinically meaningful change in chemistry laboratory findings or upon urinalysis There were no clinically significant changes in physical examination findings in study subjects between screening and the end of study
The most frequently observed clinically significant laboratory finding was a decrease in hemoglobin and hematocrit between screening and exit labs, observed in 9 subjects This decrease was believed to be secondary to the total blood volume withdrawn during this study, as well as blood loss during menses in these female subjects All subjects' hemoglobin and hematocrit subsequently returned to normal levels

RFDI1002 The Effect of Rifaximin on the Pharmacokinetics of Single Doses of Intravenously and Orally Administered Midazolam in Healthy Male and Female Volunteers

Open-label, 2-period, 2-treatment, randomized, crossover, pharmacokinetic drug-interaction study to determine the effect of oral rifaximin 200 mg administered every 8 hours for 3 days (9 consecutive doses) and every 8 hours for 7 days (21 consecutive doses) on the pharmacokinetics of a single dose of either midazolam 2 mg intravenous (IV) (given over 30 minutes) or midazolam 6 mg PO syrup Study subjects were randomly assigned to Treatment Group A (midazolam IV in Period 1 and midazolam PO in Period 2) or Treatment Group B (midazolam PO in Period 1 and midazolam IV in Period 2)

Period 1 Study subjects received a single dose of midazolam on Day 0 after which serial blood samples were collected at specified intervals to determine the plasma concentration-time profiles of midazolam and 1'-hydroxymidazolam Beginning on Day 3 at 4 PM, subjects received oral rifaximin 200 mg every 8 hours for 7 days On the mornings of Day 6 and Day 10, respectively, subjects received their 9th or 21st dose of rifaximin along with a single dose of midazolam after which serial blood samples were collected at specified intervals to determine the plasma concentration-time profiles of midazolam and 1'-hydroxymidazolam In addition, for the first 8 hours after dosing on Days 6 and 10, serial blood samples were collected for determination of plasma rifaximin concentrations

Period 2 Following a 2-week washout, study subjects received a single dose of midazolam on Day 26 after which serial blood samples were collected at specified intervals to determine the plasma concentration-time profiles of midazolam and 1'-hydroxymidazolam Beginning on Day 29 at 4 PM, subjects received oral rifaximin 200 mg every 8 hours for 7 days On the mornings of Day 32 and Day 36, respectively, subjects received their 9th or 21st dose of rifaximin along with a single dose of midazolam, after which serial blood samples were collected at specified intervals to determine the plasma concentration-time profile of midazolam and 1'-hydroxymidazolam In addition, for the first 8 hours after dosing on Days 32 and 36, blood samples were collected for determination of plasma rifaximin concentrations Pharmacokinetic analyses of midazolam, 1'-hydroxymidazolam and rifaximin plasma concentration-time profiles were conducted Routine laboratory analyses, physical examinations, and vital signs (temperature, heart rate, blood pressure, respiratory rate) were obtained during screening, at the end of the study, and as clinically indicated throughout the study Pulse oximetry was measured 15 minutes prior to and 4 hours after each midazolam dose

The study enrolled 27 healthy subjects, 13 male (48 1%) and 14 female (51 9%) subjects The mean age was 27 6 years (range 18 0 to 51 0 years)

Of the 27 subjects enrolled, 22 subjects (81 5%) experienced at least 1 adverse event in both Interval 1a (IV midazolam alone) and in Interval 1b (IV midazolam + rifaximin)

Twenty subjects (74 1%) experienced at least 1 adverse event during Interval 2a (PO midazolam alone), and 22 subjects (81 5%) experienced at least 1 adverse event during Interval 2b (PO midazolam + rifaximin) Three subjects (11 1%) experienced an adverse event during the washout period All adverse events were considered mild, with the exception of 1 subject who experienced moderate events during Interval 1b (IV midazolam and rifaximin)

The addition of rifaximin to midazolam (PO or IV) did not notably increase or decrease the number of subjects reporting adverse events or the severity of those adverse events reported While it must be noted that an increased number of subjects did report gastrointestinal complaints during those intervals in which rifaximin was given, these types of adverse events have been described previously with administration of rifaximin and were not unexpected

In Interval 1a, 21 subjects (77 8%) experienced adverse events that were considered by the investigator to be related to study drug During Interval 1b, 22 subjects (81 5%) experienced adverse events that were considered to be study drug-related During Intervals 2a and 2b, 17 (63 0%) and 22 (81 5%) subjects, respectively, experienced adverse events that were determined to be related

One subject (3 7%) experienced adverse events during the washout period that were determined to be related to study drug In comparison, nearly equal numbers of subjects experienced related adverse events when treated with midazolam alone as compared to when midazolam and rifaximin were administered concurrently

No deaths or other serious adverse events occurred during the course of this study No female subjects became pregnant during the course of this study

One subject withdrew from the study due to an adverse event This subject presented with symptoms consistent with viral infection on Day 29 The subject was given 400 mg of ibuprofen on Day 30 for 1 day and 2 teaspoons of Robitussin-DM on Day 36, with minimal relief of her symptoms The subject discontinued dosing on Day 30, however, she continued to be monitored within the clinical study facility Her symptoms improved and she was discharged without further action required The subject reported that her symptoms resolved as of Day 39 with no sequelae

Four subjects had clinically significant changes in laboratory findings Two subjects were noted to have increased WBC counts on Day 36, which were within normal range upon repeat testing on Days 42 and 48 Also, 1 subject had persistently low values for hemoglobin and hematocrit on Days 29, 36, 48, and 55 The Investigator determined that the decrease was most likely secondary to the total blood volume required for this study, 470 mL, as well as blood loss occurring during menses This subject was later determined to have iron deficiency anemia, which she reported had been previously diagnosed by her primary care physician Additionally, 1 subject was reported to have an increased glucose on Day 29 This subject had an initial glucose of 92 mg/dL

comparing changes from baseline in physical exams, vital signs, laboratory parameters, and adverse events

Ninety three subjects were randomized in the study, 48 received rifaximin and 45 received placebo Similar proportions of subjects completed the study (83 3% rifaximin, 86 7% placebo) Demographic characteristics were similar between the treatment groups The mean age was 53 6 years in the rifaximin group and 53 3 years in the placebo group

No statistically significant differences were observed between the groups for the proportions of subjects who experienced any adverse event (41 7% rifaximin, 31 1% placebo), any drug-related adverse event (25 0% rifaximin, 22 2% placebo), any serious adverse event (12 5% rifaximin, 8 9% placebo), or any serious drug-related adverse event (2 1% rifaximin, 4 4% placebo) Additionally, no significant difference was observed between the groups for the proportion of subjects who withdrew due to adverse events (10 4% rifaximin, 6 7% placebo)

No statistically significant differences were observed between the groups for the incidence of any specific adverse event Among rifaximin-treated subjects, the most commonly reported adverse events included nausea (8 3%), abdominal distension (4 2%), dyspepsia (4 2%), flatulence (4 2%), headache NOS (4 2%), insomnia (4 2%), and pruritus NOS (4 2%) Among placebo-treated subjects, the most commonly reported adverse events included diarrhea NOS (6 7%), fatigue (6 7%), headache NOS (6 7%), flatulence (4 4%), abdominal pain NOS (4 4%), pyrexia (4 4%), and hyperkalemia (4 4%)

Drug-related adverse events were reported by 12 (25 0%) subjects in the rifaximin group and 10 (22 2%) subjects in the placebo group Nausea (6 3%) was the most frequently reported drug-related adverse event in the rifaximin group, and headache NOS (6 7%) was the most frequently reported drug-related adverse event in the placebo group

One (2 2%) rifaximin subject died during the study Subject 06-024 was a 52-year-old female who developed severe acute renal failure and severe abnormal hepatic function NOS on Day 10 of rifaximin treatment The events were associated with a viral infection that started with a high fever, which subsequently led to oliguria and elevated serum creatinine On Day 12, rifaximin therapy was discontinued Additional treatment was administered, however, the subject did not improve, oliguria persisted, and pulmonary edema developed The subject subsequently died of symptoms of cardiorespiratory insufficiency on Day 18 The death was not related to study drug, but related to a viral infection and hepatorenal insufficiency

Six (12 5%) rifaximin subjects and 4 (8 9%) placebo subjects experienced serious adverse events Serious adverse events reported among rifaximin-treated subjects included ascites, esophageal varices hemorrhage, peritoneal hemorrhage, hepatic failure, hepatic function abnormal NOS, suicidal ideation, calculus renal NOS, and renal failure acute Serious adverse events reported among placebo-treated subjects included anemia NOS, gastrointestinal hemorrhage NOS, colitis pseudomembraneous, hyperkalemia,

hepatic encephalopathy, and azotemia All of the events were serious as they led to hospitalization None of the serious adverse events experienced by rifaximin subjects were considered related to study drug Among placebo subjects who experienced serious adverse events, 2 (colitis pseudomembranous and hepatic encephalopathy) were considered possibly or probably related to study drug

Five (10 4%) rifaximin subjects and 3 (6 7%) placebo subjects experienced adverse events that led to premature discontinuation of study drug Adverse events that led to premature discontinuation of study drug among rifaximin-treated subjects included peritoneal hemorrhage, bradycardia NOS, gastrointestinal infection NOS, esophageal varices hemorrhage, renal failure acute, hepatic function abnormal NOS, and calculus renal NOS Adverse events that led to premature discontinuation of study drug among placebo-treated subjects included diarrhea NOS, gastrointestinal hemorrhage NOS, hyperkalemia, anemia NOS, and azotemia None of the adverse events that led to premature discontinuation in either treatment group were considered by the investigator to be related to study drug

Laboratory test results, vital signs, and physical examinations revealed no trends of clinical concern

Crohn's Disease Study (RFCD2001)

Phase 2, single-center, open-label clinical trial with primary objective to evaluate the safety and efficacy of rifaximin in the treatment of active Crohn's disease over a 16-week period Subjects were treated with open-label rifaximin 200 mg TID for 16 weeks After providing informed consent, subjects were to return to the clinic 1, 2, 3, and 4 months following the first dose of rifaximin and 2 weeks after the Month 4 or early termination visit CDAI scores were used to assess the overall disease activity of each subject at the Screening Visit and at each monthly visit The CDAI included 8 indices Daily diaries were used to document 5 indices general well-being, abdominal pain, number of liquid stools per day, fever, and use of Lomotil®, Imodium®, codeine, or tincture of opium Assessments of presence or absence of abdominal mass, hematocrit and weight completed the CDAI indices

Thirty (30) subjects were enrolled in the study Of these, 1 subject (#039-0031) did not receive any rifaximin and had no post-baseline assessments Therefore, 29 subjects received rifaximin during the study and had at least 1 post-baseline assessment Twenty-three (76 7%) subjects completed treatment and 7 (23 3%) subjects withdrew from the study early Reasons leading to early study withdrawal were lost to follow-up (3 subjects), adverse event (2 subjects), subject request (1 subject), and lack of efficacy (1 subject)

The mean age of the subjects was 44 6 years and age ranged from 20 to 74 years The majority of subjects were white (96 6%) and most were female (62 1%) Eight (27 6%) subjects were receiving steroids at baseline The mean duration of steroid use for 5 of

these subjects was 49 2 days Duration of steroid use was not calculated for the remaining 3 subjects who had only estimated dates for when steroid use began

Among the 25 subjects who had both the start and stop dates of study drug administration recorded, the mean number of days on rifaximin was 108 1 The majority of these subjects (88 0%) received treatment for at least 90 days

Adverse events experienced during the Treatment Phase were reported in 21 (72 4%) subjects The most commonly experienced adverse events during the Treatment Phase were abdominal pain NOS, fatigue, and headache NOS, each reported by 4 (13 8%) subjects

The majority of the adverse events experienced were mild or moderate in intensity Only 1 (3 4%) subject experienced adverse events during treatment that were considered by the Investigator to be related to rifaximin administration (palpitations, abdominal distension, fatigue, diarrhea NOS, and peripheral swelling)
No deaths were reported during the study One (1, 3 4%) subject experienced a serious adverse event during treatment (oropharyngeal swelling), however, the event was not considered by the Investigator to be related to rifaximin

Three (10 3%) subjects prematurely withdrew from rifaximin therapy due to 1 or more adverse events Gastrointestinal disorders were the most common types of events that led to premature withdrawal, however, no specific adverse event that led to withdrawal was reported by more than 1 subject One (1) subject prematurely withdrew due to severe abdominal pain and anal fistula, indicating a lack of efficacy

No clinically meaningful changes from baseline to the final visit were noted in laboratory parameters

Pouchitis Study (RFPO2001)

Phase 2, multicenter, randomized, double-blind clinical trial with primary objective to evaluate the safety and efficacy of rifaximin 1200 mg/day compared to placebo in the treatment of pouchitis in subjects with a prior abdominal colectomy and ileal pouch-anal anastomosis for ulcerative colitis over a 28-day period Following the 28-day blinded treatment phase, subjects are treated for 28 days with open-label rifaximin

The study was initiated in May 2003 and is currently ongoing As of 31 October 2003, a total of 12 subjects have been randomized in the study and 2 subjects have been enrolled as control subjects No deaths, serious adverse events, or discontinuations due to adverse events have been reported