Study RFXID 9701

Title A randomized, double blind, study of rifaximin 800 mg a day (400 mg BID) to a standard ciprofloxacin regimen (500 mg BID) in the treatment of bacterial infectious diarrhea in travelers
NOTE This study was sponsored by Alfa Wasserman, the original owner of rifaximin and not by Salix the current applicant

Study dates June 24, 1997 – September 19, 1998

Principal Investigators and Study Sites

Herbert Dupont Clinical Infectious Disease Texas Medical Center (Principal Investigator)

Study Summary

A phase III, randomized, double blind, parallel group, and multicenter study that was conducted in adult travelers affected by acute infectious diarrhea in Mexico and Jamaica Patients began treatment within 72 hours of onset of diarrhea The duration of the study was 4 – 5 days that included 3 days of treatment followed by a post treatment evaluation 24 to 48 hours after the last dose

The study consisted of a pretreatment / baseline visit (Day 0), up to three days of self-administered treatment with rifaximin or oral ciprofloxacin (Days 1 – 3), and a final clinical evaluation (Days 4 or 5) Stool specimens for identification of enteric pathogens were collected prior to the first dose and 48 to 72 hours after the last dose of study drug was administered Each day during the study, patients maintained diary cards for recording the time and date of study drug administration, the time and form (formed, soft, watery) of any stool passed including the patient's assessment of whether blood or mucus was present, enteric signs and symptoms (nausea, vomiting, abdominal pain/cramps, excess gas, fecal urgency, tenesmus and fever), and adverse events Safety was evaluated by monitoring the occurrence of adverse events, vital signs, and by conducting routine clinical laboratory tests (hematology, chemistry and urinalysis) and physical examinations

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

- Rifaximin 800 mg daily delivered as 2 x 200-mg tablets plus 1 x ciprofloxacin placebo tablet PO BID

- Rifaximin placebo daily delivered as 2 x 0-mg tablets plus 1 x ciprofloxacin 500-mg tablet PO BID

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

The primary objectives of the study were to compare the clinical efficacy of rifaximin 800 mg/day to ciprofloxacin (1000 mg/day) in the treatment of infectious diarrhea in travelers, to compare the microbiological outcome of the 3 day rifaximin and ciprofloxacin regimens, and to compare to safety of the 2 agents by measuring the occurrence of any drug-related AE, regardless of intensity and nature

The inclusion/exclusion criteria, study design, and analyses were the same as those performed for study 9801 with the exception that this study was a non-inferiority study Efficacy analyses were performed using the intent-to-treat (ITT) population defined as all patients who were randomized to treatment Protocol violators and patient dropouts were considered part of the ITT population and were included in the efficacy analyses Microbiological analyses were performed on the subset of the ITT population from whose stool specimens at pre-treatment were positive for pathogens and who had a culture performed on post-treatment stool specimens

Amendments

This study was not amended

Patient Disposition and Evaluability/Demographics

187 patients were enrolled in this study at centers located in Mexico and Jamaica Ninety-three (50%) patients were randomized to rifaximin and 94 (50%) were randomized to ciprofloxacin Eighty-one (87%) rifaximin and 82 (87%) ciprofloxacin patients were treated at one of the Mexican sites One patient in the rifaximin group terminated the study early due to an adverse event All 187 patients randomized to the study were included in the ITT analyses

Table 24
Disposition of Patients – RFID9701

	Rifaximin 400 mg BID		Ciprofloxacin 500 mg BID		Total
Population	**n**	**%**	**n**	**%**	
Randomized	93	--	94	--	187
Completed treatment	92	99	90	96	182
Withdrawn from study	1	1	4	4	5
Adverse event[1]	0	0	1	1	1
Death	0	0	0	0	0
Lost to follow-up	1	1	0	0	1
Non-compliance[2]	0	0	2	2	2
Other*	0	0	1	1	1

[1] Patient was removed from the study due to the use of inhalants for undiagnosed asthma

[2] One patient never began treatment and failed to return to the clinic for any visits and to return the daily diaries another patient lost the study medication after receiving one dose of study drug and failed to return the daily diaries

*Subject 202, a 25-year old white female, was enrolled at the Mexican center on July 20, 1998 and began treatment with ciprofloxacin later that day The subject took the first two doses of the study medication, she was removed from the study on Day 2 because she was found to have Cryptosporidium parvum in the initial stool sample She took no subsequent study medication and did not return the daily diaries after the first day of treatment There were no AEs reported for this subject This subject was not included in the efficacy evaluable population "

The patient was a [redacted], and withdrew consent when she became aware that Cryptosporidium parvum was isolated from her initial stool sample Although at the time she did not know her treatment, she believed that rifaximin may not be effective, and wanted to be removed from the study She was not removed from the study by the investigator because Cryptosporidium parvum was isolated. Note that Section 3 3 of the protocol, Exclusion Criteria, does not exclude any patient based on the baseline pathogen identified

Table 25
Study Sites and Patient Disposition -RFID9701

Site	Country	Rifaximin 400 mg BID N = 93 (100%)	Ciprofloxacin 500 mg BID N = 94 (100%)
	Mexico	32 (34%)	37 (39%)
	Mexico	15 (16%)	15 (16%)
	Mexico	2 (2%)	1 (1%)
	Mexico	14 (15%)	12 (13%)
	Jamaica	12 (13%)	12 (13%)
	Mexico	18 (19%)	17 (18%)

Protocol Violations

Twenty-eight percent (53/187) of the patients had protocol violations (25/93 rifaximin (27%) and 28/94 ciprofloxacin (30%) The type of protocol violations were comparable between the treatment groups Eleven patients (5 (5%) rifaximin, 6 (6%) ciprofloxacin) had inclusion/exclusion criteria violations

Table 26
Number (%) of Patients with Protocol Violations – RFID9701

	Rifaximin 400 mg BID (n=93)		Ciprofloxacin 500 mg BID (n=94)	
	n	%	n	%
Concomitant medication	16	17	20	21
Did not return the daily diary for ≥ 1 day	5	5	9	10
Missed 2 or more doses	6	7	5	5
Failed to return to clinic	0	0	1	1

Demographics

Demographic characteristics for sex, race, age, and weight were comparable between the treatment groups More patients were female (58% rifaximin and 54% ciprofloxacin), white (82% rifaximin and 79% ciprofloxacin), and between the ages of 18 and 59 As per the applicant, "There were no significant treatment-by-center interactions for the demographic characteristics (p = 0 221)"

Table 27
Demographic Characteristics – ITT Population – RFID9701

	Rifaximin 400 mg BID (n=93)		Ciprofloxacin 500 mg BID (n=94)	
Demographic Characteristic	**n**	**%**	**n**	**%**
Sex				
Male	39	42	43	46
Female	54	58	51	54
Race				
White	76	82	74	79
Black	0	0	5	5
Other	17	18	15	16
Age (years)				
Mean (SD)	26 3	10	25 6	9
Median (Min, Max)	22 0	18, 57	21 0	18, 59

Baseline Disease Characteristics

As per the applicant, "Baseline disease characteristics for type of illness, duration of illness, and total number of unformed stools were comparable between the treatment groups (p = 0 466)

Overall, the incidence of baseline clinical symptoms was comparable between the treatment groups (p ≥ 0 157) Tenesmus was present at baseline in 47 of 93 (51%) rifaximin patients and in 36 of 94 (38%) ciprofloxacin patients, this difference approached statistical significance (p = 0 094)

Table 28
Baseline Disease Characteristics – RFID9701

	Rifaximin 400 mg BID (n=93)		Ciprofloxacin 500 mg BID (n=94)	
Baseline Disease Characteristics	**n**	**%**	**n**	**%**
Type of Illness				
Leukocyte positive, agent specific	21	23	27	29
Leukocyte positive, agent negative	15	16	14	15
Leukocyte negative, agent specific	22	24	20	21
Leukocyte negative, agent negative	32	34	32	34
Not stated	3	3	1	1
Total Number of Unformed Stools				
Mean (SD)	6	3	6 1	4
Median (Min, Max)	5	3, 15	5 0	3, 23
Duration (hours) of Illness				
Mean (SD)	30 4	21	27 2	18
Median (Min, Max)	27	2 5, 71 5	23 3	3, 68 5
Clinical Symptoms				
Nausea	53	57	56 3	67
Vomiting	18	19	16	17
Abdominal pain/Cramps	85	91	84	89
Excess gas/Flatulence	63	69	68	72
Urgency	71	76	70	75
Tenesmus	47	51	36	38
Fever	8	9	8	9
Dysentery	4	4	9	10

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

Medical Officer's Comment *Notable was the small number of subjects who participated in this trial with dysentery retrospectively defined by the applicant as subjects who presented with any of the signs or symptoms of dysentery based on the following definitions (1) temperature >100 0°F (2) blood in stool, (3) mucus in stool or (4) leukocytes in the stool*

Concomitant Medications

Twenty-six percent (24/93) of subjects randomized to rifaximin reported taking no medications during the 24 hours preceding enrollment, 34% (32/93) reported taking a medication which was judged as having no effect on the efficacy endpoints, 39% (36/93)

reported taking a symptomatic antidiarrheal compound and 1% (1/93) reported taking an antimicrobial against enteric pathogens

Twenty-seven percent (25/94) of ciprofloxacin subjects received no medications None received antimicrobials

Compliance

The treatment groups were comparable with respect to the mean number of tablets taken and for each of the two daily doses for the three days of treatment

Primary Efficacy Endpoint Time-to-Last Unformed Stool

TLUS was analyzed for the ITT population As per the applicant, results of the primary efficacy analysis demonstrated that rifaximin is equivalent to ciprofloxacin in the time to last unformed stool (p=0 006, Kaplan-Meier) Median TLUS was 25 7 hours (95% CI, 20 9–38 0) for the rifaximin group, and 25 0 hours (95% CI, 18 5–35 2) for the ciprofloxacin group A TLUS of 0 hours, indicating the patients had met the criteria for wellness immediately after initiation of treatment was reported for 7 of 93 (7 5%) rifaximin patients and 20 of 95 (21 3%) ciprofloxacin patients Twelve of the 93 (12 9%) rifaximin patients and 11 of 94 (11 7%) ciprofloxacin patients had a censored TLUS The estimated hazard ratio for comparing the TLUS of rifaximin to ciprofloxacin was 0 82 (95% LCL, 0 60–1 11), above the 95% one-sided lower CI limit of 0 63 for demonstrating that rifaximin was equivalent to ciprofloxacin in the TLUS

Medical Officer's Comment As in study 9801, the MO also elected to perform the primary efficacy analysis on an MITT population consisting of those subjects with a positive culture at baseline (N = 43 rifaximin, N = 48 ciprofloxacin) Of note that the TLUS was the same for the ciprofloxacin subjects independent of the presence or absence of a bacterial pathogen and slightly prolonged for the rifaximin subjects with a pathogen As discussed previously the MO has concerns regarding the antimicrobial activity of this compound and suggests that an additional study to further assess these issues is necessary

Table 29
TLUS FDA MITT

Study 9701	Rifaximin N=43	Cipro N=48
Median TLUS	27 3	25 0

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

Secondary efficacy variables were based on the stool record and the record of symptoms maintained in the patient diary Results of the secondary efficacy assessment demonstrated that rifaximin was equivalent to ciprofloxacin in all but two variables tested. The incidence of nausea was significantly lower in the rifaximin group than in the ciprofloxacin group over the 24–48 and 48–72 hour interval and the incidence of tenesmus was significantly higher in the rifaximin group than in the ciprofloxacin group over 0–24 hours

Improvement in Diarrheal Syndrome

Improvement in the diarrheal syndrome occurred when there was a reduction of 50% or more in the number of unformed stools passed during a 24-hour period compared with the number of stools passed during the 24 hours immediately preceding enrollment in the study Improvement in diarrheal syndrome was comparable between the rifaximin and ciprofloxacin treatment groups, occurring in approximately 60% of patients from both treatment groups over the 0–24 hour time period and in over 80% of patients over the 24–48 time period More ciprofloxacin patients, however, had achieved wellness immediately after initiation of treatment compared to rifaximin patients (21 3% versus 7 5%, respectively)

Table 30
Improvement in Diarrheal Syndrome – RFID9701

Number (%) of Patients	Rifaximin (n=93)	Ciprofloxacin (n=94)
Improvement in Diarrheal Syndrome[1]		
0 – 24 hours	54 (58 1%)	60 (63 8%)
24 – 48 hours	77 (82 8%)	80 (85 1%)

[1] Data to calculate improvement in diarrheal syndrome were not available for one ciprofloxacin patient during the 0 – 24 hour interval and for 2 ciprofloxacin and one rifaximin patient during the 24 – 48 hour interval

Number of Unformed Stools per Time Interval

The mean number of unformed stools decreased during each time interval for each treatment group with the mean slightly lower for the ciprofloxacin group than for the rifaximin group There was a significant trend over time ($p<0$ 001) but no significant difference between the treatment groups in terms of number of unformed stools ($p=0$ 267)

Table 31
Number of Unformed Stools Passed Per Time Interval – RFID9701

Dose Group	Time Interval (hours)				
	0-24	24-48	48-72	72-96	96-120
[1]Rifaximin	3 4 ± 3 4 0 – 23	1 7 ± 2 2 0 – 13	1 0 ± 1 9 0 – 11	0 8 ± 1 7 0 – 7	0 6 ± 1 3 0 – 7
	n=93	n=92	n=92	n=91	n=89
[1]Ciprofloxacin	3 0 ± 3 3 0 – 15	1 5 ± 2 0 0 – 8	0 8 ± 1 6 0 – 9	0 4 ± 0 9 0 – 5	0 3 ± 0 9 0 – 5
	n=93	n=92	n=92	n=87	n=85

[1] Mean ± SD and range of Unformed Stools Passed Per Time Interval

Number of Patients Cured

The percent of patients who were cured was comparable between the treatment groups Eighty-seven percent (81/93) of rifaximin patients and 88% (83/94) of the ciprofloxacin patients became well during the study According to the investigator assessment, wellness was achieved by Day 3 for 74/93 (80%) and 77/94 (82%) patients in the rifaximin and ciprofloxacin groups, respectively According to the patient assessment, wellness was achieved for 73/93 (79%) and 58/94 (62%) patients in the rifaximin and ciprofloxacin groups, respectively

Number of Treatment Failures

Ten percent (9/93) of the rifaximin patients and 6% (3/94) ciprofloxacin patients failed treatment All failures occurred after 72 hours of treatment and were due to wellness not being declared by the end of the observation period

Relapses There were 3 rifaximin (009, 011, 146) and 2 ciprofloxacin (056, 075) patients who relapsed after the end of treatment Further information on these subjects was not provided **If such subjects were deemed failures, the failure rate would be 12/93 (13%) rifaximin vs 5/94 (5%) ciprofloxacin**

Changes in Clinical Symptoms

All 187 patients enrolled in the study had at least one clinical symptom at baseline Four days after the start of treatment, there was no statistically significant difference between the rifaximin and ciprofloxacin dose groups in the percent of patients with clinical symptoms (abdominal pain, nausea, vomiting, flatulence, urgency, fever, tenesmus) (p=0 66, Fisher's Exact Test)

Microbiologic Efficacy

Fifty-four percent of subjects (50/93) in the rifaximin group and 49% (46/94) in the ciprofloxacin group had no pathogen at pretreatment

When an assessment was made of only those subjects with a pathogen or pathogens at pretreatment, the rate of clinical cure was different between treatment groups Specifically, the cure rate of 32% in the rifaximin group was less than the 42% rate in the ciprofloxacin group

Table 32
Clinical Response by Patient with a Baseline Pathogen

ITT	Rifaximin (n=93)	Ciprofloxacin (n=94)
No pathogen at baseline	50 (54%)	46 (49%)
Pathogen at baseline	43 (46%)	48 (51%)
Clinical response in subjects with baseline pathogen		
Cure	30 (32%)	39 (42%)
Failure	7 (8%)	5 (5%)
No re-culture	6 (7%)	4 (4%)

By pathogen eradication rates were as follows

Table 33
Microbiological Cure Rate by Pathogen (Study RFID9701)

Pathogen	Rifaximin 400 mg bid		Ciprofloxacin 500 mg bid	
	No	No Eradicated (%)	No	No Eradicated (%)
Escherichia coli	35	24/35 (69%)	36	30/36 (83%)
Shigella sonnei	4	3/4 (75%)	1	1/1 (100%)
Shigella flexneri	1	1/1 (100%)	5	4/5 (80%)
Salmonella species	0	0	1	1/1 (100%)
Salmonella Group C1	2	1/2 (50%)	3	2/3 (67%)
Salmonella Group C2	1	1/1 (100%)	2	2/2 (100%)
Campylobacter jejuni	2	2/2 (100%)	0	0
Entamoeba histolytica	1	0/1 (0%)	0	0
Giardia Lamblia	0	0	1	0/1 (0%)
Cryptosporidium parvum	1	1/1 (100 %)	2	1/2 (50%)
TOTAL	47	33/47 (70%)	51	41/51 (80%)

Eleven rifaximin as compared to 1 ciprofloxacin subject developed superinfections Newly isolated pathogens included ETEC in 1 ciprofloxacin and 8 rifaximin subjects and *Shigella flexneri* in 2 rifaximin subjects and *Shigella sonnei* in 1 rifaximin subject MICs ranged from 0 25 – 64 mcg/mL for the ETEC and were 8 and 16 mcg/ml for the *Shigella flexneri* and 256 for the *Shigella sonnei*

ADDENDUM to MOR for 9701 On May 23, 2002, the MO received an email response from the applicant clarifying the microbiologic data from study 9701 The applicant reclassified patients for unknown reasons This reclassification resulted in a decrease in overall microbiologic efficacy as well as a decrease in specific rates versus Escherichia coli and Shigella sonnei.

The revised microbiology tables follow

Table 32A
Clinical Response by Patient with a Baseline Pathogen

ITT	Rifaximin (n=93)	Ciprofloxacin (n=94)
No pathogen at baseline	47 (51%)	46 (49%)
Pathogen at baseline	46 (49%)	48 (51%)
Clinical response in subjects with baseline pathogen		
Cure	32 (34%)	41 (44%)
Failure	12 (13%)	5 (5%)
No re-culture	2 (2%)	2 (2%)

By pathogen efficacy rates were as follows

Table 33A
Microbiological Cure Rate by Pathogen (Study RFID9701)

Pathogen	Rifaximin 400 mg bid		Ciprofloxacin 500 mg bid	
	No	No Eradicated (%)	No	No Eradicated (%)
Escherichia coli	37	24/37 (65%)	36	30/36 (83%)
Shigella sonnei	5	3/5 (60%)	1	1/1 (100%)
Shigella flexneri	1	1/1 (100%)	5	4/5 (80%)
Salmonella species	0	0	1	1/1 (100%)
Salmonella Group C1	2	1/2 (50%)	3	2/3 (67%)
Salmonella Group C2	1	1/1 (100%)	2	2/2 (100%)
Campylobacter jejuni	2	2/2 (100%)	0	0
Entamoeba histolytica	1	0/1 (0%)	0	0
Giardia Lamblia	0	0	1	0/1 (0%)
Cryptosporidium parvum	1	1/1 (100 %)	2	1/2 (50%)
TOTAL	50	33/50 (66%)	51	41/51 (80%)

Conclusion from study 9701

The applicant was successfully able to demonstrate that rifaximin at a dose of 400 mg PO BID (800 mg/day) was non-inferior to an approved product, ciprofloxacin in decreasing the TLUS (primary efficacy parameter) in both the prespecified ITT population and in the FDA MITT population thus showing that rifaximin had clinical activity independent of the presence or absence of a positive culture

Rates of microbiologic efficacy were similar between treatments and numerically superior, in favor of ciprofloxacin

Study RFID9601

Title A randomized, double blind, study of 3 dosing regimens of rifaximin to a standard TMP/SMX regimen in the treatment of travelers diarrhea

NOTE This Phase II dose response study was sponsored by Alfa Wasserman, the original owner of rifaximin and not by Salix the current applicant

Study dates June 26, 1996 – October 15, 1996

Principal Investigators

Herbert Dupont, Clinical Infectious Disease Texas Medical Center (Principal Investigator)

Study Summary

Phase II, randomized, double-blind, parallel dose-response, multicenter study conducted in adult travelers affected by acute infectious diarrhea The study consisted of a pretreatment / baseline visit (Day 0), up to five days of self-administered treatment with rifaximin at 200 mg TID, 400 mg TID, or 600 mg TID or TMP/SMX (160/800) BID (Days 1 – 5), post-treatment clinical evaluations within 48 to 72 hours after discontinuing therapy, which included a global response to therapy assessed by the patient and the investigator (Days 7 – 8) Stool specimens for identification of enteric pathogens were collected prior to the first dose and 24 hours after the last dose of study drug was administered (Day 6) Each day during the study, patients maintained diary cards for recording the time and form (formed, soft, watery) of any stool passed including the presence of blood or mucus, enteric signs and symptoms (nausea, abdominal pain, cramps, vomiting, tenesmus and fever), and adverse events Patients graded the severity of each symptom as absent, mild (tolerable), moderate (distressing), or severe (incapacitating and prohibiting normal activities) Safety was evaluated by monitoring the occurrence of adverse events, vital signs, and by conducting routine clinical laboratory tests (hematology, chemistry and urinalysis) and physical examinations

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

- Rifaximin 600 mg daily delivered as 1 x 200-mg tablet PO q8h, plus 2 x rifaximin placebo tablets PO qh8, plus 1 x matching placebo TMP/SMX tablet PO q12h
- Rifaximin 1200 mg daily delivered as 2 x 200-mg tablets PO q8h plus 1 x rifaximin placebo tablet PO qh8, plus 1 x matching placebo TMP/SMX tablet PO q12h

- Rifaximin 1800 mg daily delivered as 3 x 200-mg tablets PO q8h plus 1 x matching placebo TMP/SMX tablet PO q12h
- Rifaximin placebo delivered as 3 x 0-mg rifaximin placebo tablets PO qh8 plus 1 x 160/800 mg TMP/SMX q12h

Included were male and female travelers at least 18 years of age with acute diarrhea if they had at least 3 unformed stools within the 24 hours preceding study enrollment and at least one or more signs of enteric infection within 72 hours preceding study enrollment (nausea, vomiting, abdominal pain/cramps, excessive gas/flatulence, fecal urgency, tenesmus, or dysentery)

Patients were excluded from participation in the study for any of the following reasons duration of diarrhea more than 72 hours prior to study enrollment, active heart, lung, kidney, or intestinal disease, seizure disorder, use of more than two doses of a symptomatic anti-diarrheal compound within 8 hours preceding study enrollment, use of any dose of a symptomatic antidiarrheal compound within 2 hours preceding study enrollment, or use of any antimicrobial agent with an expected activity against enteric bacterial pathogens within the week preceding study enrollment, pregnant or breast feeding (females only)

Medical Officer's Comments *Differences between this study and studies 9701 and 9801 included the following*

- *Prolonged duration of treatment*

- *The population analyzed in study 9601 was an MITT consisting of those subjects who were randomized took at least 2 days of treatment and who completed 2 or more daily diaries*

- *The definition of wellness differed in that fever was excluded In studies 9701 and 9801 it was as follows*

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

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

- *The statistical analysis differed in that the primary objective was to assess the effectiveness of the 3 rifaximin regimens as well as their safety and tolerability Each regimen was also compared to TMP/SMX but there was no predefined level of significance*

Patient Disposition and Evaluability

Seventy-six patients were enrolled in this study at one of 5 study sites Sixty-two percent (47) were enrolled at the Mexico The remaining patients were enrolled as follows 9 (12%) at Mexico, 8 (11%) at Mexico, 8 (11%) at and 4 (5%) at , Mexico As can be appreciated in the following table, approximately 50% of the subjects came from 1 Mexican center

Table 34
Study Sites study RFID9601

Site	Country	Rifaximin 200 mg TID N = 19	Rifaximin 400 mg TID N = 19	Rifaximin 600 mg TID N = 19	TMP/SMX BID N = 19
	Mexico	10	11	13	13
	Mexico	4	2	1	1
	Mexico	1	1	1	1
	Mexico	2	3	2	2
	Mexico	2	2	2	2

Four patients {one 200 mg TID rifaximin (1/19) (5%), one 400 TID mg rifaximin (1/19 (5%), and 2 TMP/SMX (2/19 (10%)} withdrew early due either to noncompliance with the protocol (n=2), or failure to return to the clinic (n=2) All patients who withdrew early had been enrolled at the , Mexico No patients withdrew because of an AE Patients who took at least two days of study medication and completed two or more daily diaries were included in the efficacy analysis Of the 76 randomized patients, 72 were included in the efficacy analysis (57 rifaximin and 17 TMP/SMX)

Table 35
Disposition of Patients – Study RFID9601

	Rifaximin 200 mg TID	Rifaximin 400 mg TID	Rifaximin 600 mg TID	TMP/SMX BID
Randomized	**19**	**19**	**19**	**19**
Completed treatment	18	18	19	17
Withdrawn from study	1	1	0	2
Adverse event	0	0	0	0
Death	0	0	0	0
Failure to return	0	0	0	2
Noncompliance	1	1	0	0

Protocol Violations
Two violations to the inclusion/exclusion criteria were reported One subject took 5 doses of medication and did not complete treatment and the other took 2 days and gave the rest of his medication to a friend and refused to fill out the diary

Demographics

Demographic characteristics for patient age, sex, and race at enrollment were comparable between the 200 mg TID, 400 mg TID, and TMP/SMX groups There were twice as many males (12 male, 7 female) treated with the highest rifaximin dose (600 mg TID) Mean patient age was similar for all rifaximin (25 years) and TMP/SMX (24 years) patients Most patients from each treatment group were white (45/55 rifaximin and 15/17 TMP/SMX)

Table 36
Demographic Characteristics – Study RFID9601

Demographic Characteristic	Rifaximin 200 mg TID N = 18	Rifaximin 400 mg TID N = 18	Rifaximin 600 mg TID N = 19	TMP/SMX BID N=17
Sex				
Male	6	8	12	8
Female	12	10	7	9
Race				
White	12	17	16	15
Asian	1	0	0	0
Black	0	0	2	0
Hispanic	5	1	1	1
Other	0	0	0	1
Age (years)				
Mean	24 ± 8 3	26 ± 8 8	24 ± 7 8	24 ± 5 6
Median	21 0	21 0	21 0	23 0

Baseline Disease Characteristics

The number of unformed stools during the 24 hours preceding treatment was comparable between treatment groups (median = 5 5 for 200 mg TID rifaximin and 5 0 for all other groups) The duration of pretreatment illness was comparable between all rifaximin groups (median = 26 hours) and was slightly lower than the TMP/SMX group (median = 36 hours) Baseline disease characteristics were similar between all rifaximin patients and TMP/SMX patients

Table 37
Baseline Characteristics of the Recruited Patients – Study RFID9601

Baseline Characteristics	Rifaximin 200 mg TID N = 18	Rifaximin 400 mg TID N = 18	Rifaximin 600 mg TID N = 19	TMP/SMX BID N=17
Duration of pretreatment illness (hours)				
Mean ± SD	23 ± 20 6	30 ± 13 3	31 ± 17 6	34 ± 14 6
Median	17 3	28 6	27 5	35 9
Number of unformed stools in the 24 hours before treatment				
Mean ± SD	6 ± 2 4	6 ± 2 9	6 ± 5 0	7 ± 4 2
Median	5 5	5 0	5 0	6 0

Treatment Compliance

Treatment compliance was measured by monitoring the number of tablets returned and the time of return against the planned administration Almost all patients completed the study treatment as planned (see protocol violations)

Primary Efficacy Analysis

Time-to-Last Unformed Stool (TLUS)

TLUS was analyzed for the 72 patients who took at least two days of study medication and completed two or more daily diaries Result of the primary efficacy analysis demonstrated that there were no significant differences in the time to last unformed stool between the treatment groups The shortest median time to last unformed stool was seen in the 200 mg TID rifaximin group

Table 38
Mean and Median TLUS – Study RFID9601

	Rifaximin 200 mg TID N = 18	Rifaximin 400 mg TID N = 18	Rifaximin 600 mg TID N = 19	TMP/SMX BID N=17
TLUS				
Mean ± SD	36 9 ± 37 06	38 6 ± 24 43	53 0 ± 43 5	55 7 ± 50 20
Median	26 25	40 50	35 00	47 00

Medical Officer's Comment *The MO is unable to explain the differences in TLUS between the rifaximin treatment groups It is unclear why these subjects at higher doses had a more prolonged course as compared to the lower dose group in view of the fact that the doing interval was the same for all 3 groups When only those subjects with a baseline pathogen were assessed (FDA MITT) the median TLUS was prolonged for all rifaximin subjects independent of dose and less for the TMP/SMX subjects As in study 9701 this finding raises concerns about the antimicrobial activity of rifaximin*

Table 39
Median TLUS FDA MITT– Study RFID9601

Study 9601	Rifaximin 200 mg TID N=10	Rifaximin 400 mg TID N=5	Rifaximin 600 mg TID N=3	TMP/SMX BID N=7
Median TLUS	33 25	52	60	13 5

* one less subject in the high group than stated in Table 3 of the 9601 study report Table 8 states that subject 57 had ETEC ST/LT at baseline but this subject is not listed in the dataset or Appendix 16 4 as to having a pathogen pre-treatment.

Secondary Efficacy Analyses

Improvement in Diarrheal Syndrome

Fifty-six percent (56%) of the rifaximin 200 mg TID patients, 44% of the rifaximin 400 mg TID, and 53% of the rifaximin 600 mg TID subjects improved clinically within the first 24 hours of treatment as compared to 65% of the TMP/SMX subjects These had increased to 83%, 78%, 89%, and 76% per treatment group respectively at 48 hours

Table 40
Improvement in Diarrheal Syndrome – Study RFID9601

	Rifaximin 200 mg TID N = 18	Rifaximin 400 mg TID N = 18	Rifaximin 600 mg TID N = 19	TMP/SMX BID N=17
24 hours				
Number (%) of patients	10 (56)	8 (44)	10 (53)	11 (65)
48 hours				
Number (%) of patients	15 (83)	14 (78)	17 (89)	13 (76)

Number of Unformed Stools per Time Interval

The mean number of unformed stools decreased during each interval for each treatment group

Table 41
Number of Unformed Stools Passed at Different Intervals – Study RFID9601

	Rifaximin 200 mg TID N = 18	Rifaximin 400 mg TID N = 18	Rifaximin 600 mg TID N = 19	TMP/SMX BID N=17
	Mean (± SD) Number of Unformed Stools Per Interval (Number Reporting)			
0-12 Hours	2 5 ± 2 85	1 9 ± 1 43	2 4 ± 2 29	1 6 ± 1 22
12-24 Hours	0 8 ± 1 25	1 2 ± 1 06	0 8 ± 0 92	0 8 ± 0 95
24-48 Hours	1 1 ± 1 59	1 7 ± 1 68	1 3 ± 1 38	1 2 ± 1 52
72-96 Hours	0 3 ± 0 77	0 1 ± 0 32	0 6 ± 1 30	0 9 ± 1 27
96-120 Hours	0 2 ± 0 65	0 2 ± 0 51	0 4 ± 0 83	0 6 ± 1 06

Clinical Response

Eighty-nine percent (89%) (16/18) of the subjects treated with 200 mg TID of rifaximin were cured as compared to 100% (18/18) of the 400 mg TID rifaximin subjects, 90% (17/19) of the 600 mg TID rifaximin subjects and 82% (14/17) of the TMP/SMX subjects,

Table 42
Clinical Response to Treatment – Study RFID9601

	Rifaximin 200 mg TID N = 18	Rifaximin 400 mg TID N = 18	Rifaximin 600 mg TID N = 19	TMP/SMX BID N=17
Number (%) of patients				
Cure	16 (89%)	18 (100%)	17 (90%)	14 (82%)
Failure	2 (11%)	-	2 (10%)	3 (18%)

Microbiologic Efficacy

Of note was the difference in microbiologic eradication rates between the rifaximin treatment arms with 100% efficacy for the 200 mg TID arm decreasing to 60% for the 400 mg TID and 50% for the 600 mg TID arms All failures were associated with baseline pathogens that were susceptible to rifaximin

Table 43
Microbiological Cure Rate by Pathogen (Study RFID9601)

Pathogen	Rifaximin 200 mg TID		Rifaximin 400 mg TID		Rifaximin 600 mg TID		TMP/SMX BID	
	No	No Eradicated (%)	No	No Eradicated (%)	No	No Eradicated (%)	No	No Eradicated (%)
Escherichia coli	7	7/7 (100 0%)	3	1/3 (33 3%)	2	2/2 (100 0%)	6	6/6 (100 0%)
Shigella sonnei	1	1/1 (100 0%)	0	---	1	0/1 (00 0%)	0	---
Salmonella Group C1	1	1/1 (100 0%)	0	-	1	0/1 (00 0%)	1	1/1 (100 0%)
Salmonella Group C2	0	---	1	1/1 (100 0%)	0	---	0	---
Campylobacter jejuni	2	2/2 (100 0%)	0	--	0	---	0	---
Crytosporidium parvum	0	---	1	1/1 (100 0%)	0	--	0	--
TOTAL	11	11/11 (100%)	5	3/5 (60%)	4	2/4 (50%)	7	7/7 (100%)

Conclusions from study 9601

The applicant was able to show that across five efficacy measurements TLUS, improvement of diarrheal symptoms, number of total unformed stools, microbiologic cure, and investigator and patient global assessment, rifaximin 200 mg TID was as effective as the 400 mg TID or 600 mg TID dose regimens for the treatment of infectious diarrhea After 2 to 3 days of treatment, patients and investigators assessed that rifaximin at all doses had cured the infectious diarrhea

Dysentery

Medical Officer's Comment As rifaximin is poorly absorbed from the GI tract, concerns exist regarding it's efficacy in subjects with dysentery or diarrheal syndromes associated with enteroinvasive pathogens

The applicant performed a retrospective analysis of the TLUS in subjects who presented with any of the signs or symptoms of dysentery based on the following definitions (1) temperature >100 0°F, (2) blood in stool, (3) mucus in stool, or (4) leukocytes in the stool As per the applicant, "72/401 (43%) of rifaximin subjects had symptoms of dysentery as compared to 67/94 (71%) of ciprofloxacin subjects and 46/129 (36%) of placebo subjects were in this category Median TLUS was 32 5, 25, and 70 5 hours respectively

If a stricter definition of dysentery was used (blood in stool plus either mucous or leukocytes), 38/401 (9%) rifaximin-treated patients, 16/129 (12%) placebo-treated patients, and 20/94 (21%) ciprofloxacin-treated patients presented with dysentery The median TLUS was 36 37 hours for the rifaximin-treated patients and 30 54 hours for the ciprofloxacin treated patients, while for placebo-treated patients, the median TLUS could not be calculated due to insufficient data The median TLUS for this subset of rifaximin-treated patients with dysentery did not differ from the overall rifaximin-treated patients

Medical Officer's Comment

As per the Principles and Practices of Infectious Diseases (Mandell 2001), dysentery is characterized by the presence of leucocytes in the stool As can be seen in the tables of baseline characteristics, a small proportion of subjects had dysentery The MO requested that the applicant provide clinical outcomes and TLUS for patients with and without leukocytes in the stool

From pivotal study 9801, there were 20 subjects on the 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

For those subjects receiving the 400 mg TID dose, 17 (15%) had leukocytes in the stool Fifteen (88%) were classified as cures with a median TLUS of 36 6 as compared to 32 9 for all 400 mg TID subjects Twenty-three placebo patients had leukocytes in the stool and 11 were classified as cures The applicant could not provide a median TLUS for this group

In study 9701 39% (36/93%) of the subjects that received the 400 mg BID dose had leukocytes in the stool and 31 (86%) were cured with a median TLUS of 23 3 as compared to a median TLUS of 35 7 hours for all 400 mg BID rifaximin-treated subjects

Similarly 41 ciprofloxacin-treated subjects had leukocytes (44%) in the stool Thirty-five of these 41 (85%) were classified as cures with a median TLUS of 24 8

Five of nineteen (26%) of subjects treated with the proposed 200 mg TID dose in study 9601 had leukocytes in the stool and all (100%) were classified as cures with a median TLUS of 40 hours

D Efficacy Conclusions

The applicant provided the results of 2 phase III studies and 1 phase II study in support of their application for the approval of rifaximin 200 mg PO TID x 3 days in the treatment of traveler's diarrhea

Of note is the similar design of the phase III studies as compared to the phase II study where the duration of treatment was 5 days as opposed to 3 days

Also of note is that the dose of 200 mg TID proposed by the applicant was utilized in only one trial (study 9801) and not in study 9701 There were a few additional patients in the phase II trial that received the proposed dose, albeit for 2 more days as compared to the phase III subjects

The applicant was informed by the FDA that efficacy results (both clinical and microbiological) obtained at doses higher that the proposed dose cannot be used in support of an application The applicant's position is that extremely high intraluminal concentrations of rifaximin are attained independent of dose and thus pooling of both the clinical and microbiological results should be allowed The MO points out the high variability of the results between rifaximin treatment groups and additionally, disagrees with the pooling of the data for microbiologic efficacy and further disagrees with the extrapolation of outcome from higher to lower doses The MO is also unclear as to the true antimicrobial activity of this agent As stated in CID, "Traveler's diarrhea includes both pathogen-specific illness and diarrheal illness without a known pathogen, a study performed in a population of travelers may therefore provide evidence of efficacy against either a specific pathogen or this syndrome in general" The MO determined that the applicant provided data from one pivotal study using a dose of 200 mg PO TID for three days that showed a reduction in time to last unformed stool in patients with traveler's diarrhea However the microbiologic efficacy has not been convincingly established

In Studies RFID9701 and RFID9801, time to last unformed stool (TLUS) was predefined as the primary efficacy endpoint Rifaximin was found to be significantly better than

placebo in study RFID 9801 (p = 0 0001 for the rifaximin 200 mg TID versus placebo group and p = 0 0001 for the rifaximin 400 mg TID versus placebo group) In study RFID9701 using a rifaximin dose of 400 mg BID, rifaximin was found to be non-inferior to ciprofloxacin, an approved comparator (p=0 006, Kaplan-Meier)

Of note the doses differed between the studies In RFID9801, the rifaximin doses were 200 mg TID and 400 mg TID and in RFID9701 the rifaximin dose was 400 mg BID

A comparison of 4 different dose levels of rifaximin evaluated in Studies RFID9601, RFID9701, and RFID9801, 600 mg/day (200 mg TID), 800 mg/day (400 mg BID), 1200 mg/day (400 mg TID) or 1800 mg/day (600 mg TID) showed similar degrees of efficacy Based upon comparisons across studies, each of these values compare favorably with that observed for placebo treated patients (TLUS 60 0 hours) and with ciprofloxacin

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

Study	Total Daily Dose	Schedule	Median TLUS (hours)	Median TLUS FDA MITT
RFID9801	600 mg/day	TID	32 5	30
RFID9801	1200 mg/day	TID	32 9	32 8
RFID9801	Placebo	TID	60 0	59 3
RFID9701	800 mg/day	BID	25 7	27 3
RFID9701	Ciprofloxacin	BID	25 0	25 0
RFID9601	600 mg/day	TID	26 2	33 25
RFID9601	1200 mg/day	TID	40 5	52
RFID9601	1800 mg/day	TID	35 0	60
RFID9601	TMP/SMX	BID	47 0	13 5

The applicant provided an integrated summary of microbiologic efficacy with total pathogen eradication rates independent of dose The applicant's rationale for this was that the submission contained primarily subjects with ETEC and as there was no difference in eradication rates versus this pathogen independent of dose, it was appropriate to provide pooled microbiology results Additionally, this group of subjects was deemed a homogenous population suitable to evaluate the relationship between eradication and TLUS Patients with fecal cultures that were positive for ETEC at baseline had similar improvements in TLUS whether they were eradicated or not eradicated, 30 75 hours versus 32 50 hours (p=0 530), respectively As per the applicant, these data confirm that for both ETEC patients who were eradicated or not eradicated the 200 mg TID rifaximin is as efficacious as the higher dosing levels It should be noted however that similar argument could be made for the placebo arm where independent of the TLUS the eradication rates were the same as those attained on rifaximin Thus concerns exist regarding the antimicrobial nature of this compound especially in cases of more invasive disease

For patients presenting with a dysentery-like picture, rifaximin produced a similar TLUS to that observed with ciprofloxacin and TMP/SMX, 36 1 hours versus 25 0 hours and 33 8 hours, respectively It should be noted however that only 7 rifaximin treated patients (total database) and only 3 subjects from the 200 mg TID arm of study 9801 actually had dysentery (i e blood or mucous in stool associated with fever)

Overall, the rifaximin, ciprofloxacin, and TMP/SMX TLUS results were similar and represented an improvement over the TLUS of the placebo treatment group, 70 5 hours thus indicating that this product had similar activity with regards to the primary efficacy parameter as the antimicrobial comparators

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

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

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

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

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

Regarding the 200 mg TID dose, it appeared that this dose produced similar symptomatic improvement as higher rifaximin doses Eradication rates for ETEC were similar with 200 mg TID, 400 mg TID, or 600 mg TID rifaximin Eradication of ETEC did not correlate with clinical improvement Thus, in placebo patients, where eradication rates of ETEC were high, the eradication rates, but not improvement in clinical symptoms, were similar to patients treated with rifaximin, ciprofloxacin, and TMP/SMX This argument supports the use of the 200 mg TID dose as the minimum effective dose as well as justifies the pooling of organisms across doses

Although the MO can accept this argument for the 200 mg PO TID dose, this argument cannot support the extrapolation of microbiologic efficacy across doses from higher to lower Further the similar microbiologic efficacy between placebo and rifaximin, but not between placebo and ciprofloxacin or TMP/SMX, generates doubts regarding the antimicrobial activity of this compound

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

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

The MO concluded that

In the single pivotal study that utilized the proposed rifaximin dose of 200 mg PO TID for three days, rifaximin shortened the time to last unformed stool as compared to placebo

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

Rifaximin should also not be used in subjects with clinical evidence of dehydration If no symptomatic improvement is apparent within 48 hours, consideration should be given to modification of the treatment regimen

VI Integrated Review of Safety

A Brief Statement of Conclusions

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 included in the ISS database were qualitatively and quantitatively similar to the adverse events in the ISS database

The data available in the NDA support that rifaximin can be safely administered at a dose of 200 mg TID per day for the treatment of traveler's diarrhea

B Description of Patient Exposure

At the End-of-Phase II meeting on September 21, 1998 it was agreed that the safety database would consist of at least 500 patients The submitted database consists of 798 patients (504 rifaximin, 294 control) who received at least one dose of study medication in five studies three studies in travelers diarrhea (ID) and two studies in hepatic

encephalopathy (HE) As per the applicant, "the data from the HE studies augment the safety database for rifaximin and provide a broader clinical experience for assessing the safety profile of rifaximin"

The safety information was supplemented by safety data from 1,647 patients treated with rifaximin in 57 other studies sponsored by Alfa Wassermann SpA that did not meet one or more of the four criteria for inclusion in the ISS database

Safety data from eight phase I pharmacokinetic studies with rifaximin in healthy volunteers and patients were also provided

In order for a study to be included in the safety database, the following criteria (pre-NDA meeting 1/12/01) had to be met

- Total rifaximin dose of at least 600 mg/day
- Protocol, CRF, and study report or publication available
- Essential regulatory documents available
- Study monitored by the sponsor and/or at least one site visit with a compliance review performed in order to verify source documents and adherence to Good Clinical Practice (GCP)

The three ID studies in the safety database are

- Study RFID9801 A Randomized, Double-Blind, Parallel, Comparative, Placebo-Controlled Study of Rifaximin at 600 mg/day (200 mg, TID) and 1200 mg/day (400 mg, TID) in the Treatment of Bacterial Infectious Diarrhea in Travelers
- Study RFID9701 Double-Blind Randomized Trial Comparing Rifaximin to a Standard Regimen of Ciprofloxacin in the Treatment of Travelers' Diarrhea
- Study RFID9601 Double-blind Randomized Trial Comparing 3 Dosage Regimens of Rifaximin with a Standard Regimen of TMP/SMX for Treatment of Traveler's Diarrhea

The two HE studies in the safety database are

- Study RFHE9701 Efficacy and Safety Evaluation of Rifaximin in Comparison to Lactitol in the Treatment of Hepatic Encephalopathy Multi-Center, Double-Blind, Double-dummy, Parallel Group, Randomized Study
- Study RFHE9702 A Multi-Center, Double-Blind, Dose Finding Study to Evaluate in Patients with Hepatic Encephalopathy

The three ID studies were conducted in Guatemala, Jamaica, Kenya, and Mexico The two HE studies were conducted in Spain and the UK

Table 44
Summary of Study Characteristics

	Studies in the ISS Safety Database				
	RFID9801	**RFID9701**	**RFID9601**	**RFHE9701**	**RFHE9702**
Phase of Development	III	III	II	III	II
Study Design	Parallel groups, double-blind, placebo control	Parallel groups, double-dummy, active control	Parallel groups, double-blind, active control, dose-ranging	Parallel groups, double-dummy, active control	Parallel groups, double-blind, dose ranging
Sponsor	Salix	AW	AW	AW	AW
Population	Infectious diarrhea in travelers	Infectious diarrhea in travelers	Infectious diarrhea in travelers	Hepatic encephalopathy	Hepatic encephalopathy
Doses of rifaximin	200 mg TID 400 mg TID	400 mg BID	200 mg TID 400 mg TID 600 mg TID	1200 mg QD	200 mg TID 400 mg TID 800 mg TID
Days of Dosing	3 days	3 days	5 days	10 days	7 days
Patients Enrolled	380	187	76	104	54
Patients Dosed	379	186	76	103	54
Patients Dosed w/ rifaximin (Number dosed)	200 mg TID (n=124) 400 mg TID (n=126)	400 mg BID (n=93)	200 mg TID (n=19) 400 mg TID (n=19) 600 mg TID (n=19)	1200 mg QD (n=50)	200 mg TID (n=18) 400 mg TID (n=19) 800 mg TID (n=17)
Control (Number treated)	Placebo (n=129)	Ciprofloxacin (n=93)	TMP/SMX (n=19)	Lactitol (n=53)	NA

AW = Alfa Wassermann

The total number of rifaximin ID subjects was 400 and the ID control subjects was 241 143 subjects received rifaximin 200 mg TID, 93 received 400 mg BID, 145 received 400 mg TID, and 19 received 600 mg TID

The total number of rifaximin HE subjects was 104 and the HE control subjects was 53 18 subjects received rifaximin 200 mg TID, 69 received 1200 mg/day, and 17 received 800 mg TID

The total number of rifaximin patients receiving the 200 mg TID dose was 161

Methods and Specific Findings of Safety Review

Of the 798 patients included in the safety database, there were 504 rifaximin and 294 control subjects who received at least one dose of study medication in 3 infectious diarrhea studies (RFID9801, RFID9701, RFID9601) or 2 HE studies (RFHE9701, RFHE9702) All of the rifaximin patients received a dose of at least 600 mg per day

Patient Disposition Of the 505 rifaximin patients enrolled and randomized, one subject (study 9801, rifaximin 200 mg TID #2003) never received study medication Additionally, one ciprofloxacin patient from study 9701 (#65) and 1 lactitol subject (#52) from study HE9701 never received study medication

Nineteen rifaximin subjects and 22 control subjects, discontinued treatment from the infectious diarrhea studies Of note, a larger number discontinued from study 9801 on both study arms as compared to 9701 or 9601 The primary reason for discontinuation in 9801 was lack of efficacy (7 at the 400 mg TID dose and 4 at the 200 mg TID dose) No subject discontinued due to lack of efficacy on the rifaximin arms of the other trials

Table 45
Summary of Infectious Diarrhea Study Discontinuations

Study Number	Discontinuations	
	Rifaximin	Control
RFID9601	2	2
RFID9701	1	1
RFID9801	16	19
Total	19	22

For a detailed listing of patients who discontinued, see Appendix 1

Table 46
Reason for Discontinuation

Reason	Rifaximin ID N = 400	Control ID N = 241	Rifaximin HE N = 104	Control HE N = 53	ALL Rifaximin N = 504	ALL Control N = 294
AE	1 (0 3%)	0	4 (3 8%)	3 (5 7%)	5 (1%)	3 (1%)
Lost to F/u	1 (0 3%)	3 (1 2%)	0	0	1 (0 2%)	3 (1%)
Other	6 (1 5%)	0	3 (2 9%)	0	9 (1 8%)	0
Unknown	0	1 (0 4%)	0	0	0	1 (0 3%)
Lack of Efficacy	11 (2 8%)	18 (7 5%)	3 (2 9%)	4 (7 5%)	14 (2 8%)	22 (7 5%)
Total	19 (4 8%)	22 (9 1%)	10 (9 6%)	7 (13 2%)	29 (5 8%)	29 (9 9%)

Few patients were lost to follow-up, reflective of the short follow-up in these studies (EOT = last visit) Additionally only one infectious diarrhea subject withdrew due to an AE

Demographics

As per the applicant "There were no statistically significant treatment group differences in patient demographics for all patients, ID patients and HE patients"

There was a higher proportion of men than women in both all patients treatment groups (52% vs 48% for rifaximin and 53% vs 47% for the control) The mean age of all patients was 34 years in the rifaximin group and 33 5 years in the control group The patients were primarily <65 years old (≥ 90%) and white (≥ 85%)

The infectious diarrhea subpopulation included more women than men in both treatment groups (51% vs 49% rifaximin and 52% vs 49% control) Mean age of the rifaximin and control ID patients were 27 7 years and 27 years, respectively 97% in the rifaximin group and 99% in the control group were < 65 years old and most of the ID patients in both groups were white (83%), followed by Hispanic (14% and 11%), black (2% and 3%), Asian (1% and 3%), and other (1% and 0)

The hepatic encephalopathy subpopulation differed from the ID in that the subjects were older (mean age of the rifaximin HE group was 58 vs 63 control HE) More subjects were > 65 years and more subjects were male (rifaximin HE 63%, control 74%) as compared to the ID subpopulation

Medical Officer's Comment *This difference is to be expected based on the epidemiology of the diseases under treatment Hepatic encephalopathy occurs in the setting of cirrhosis is usually ETOH related and is usually seen in an older population than that of travelers to exotic sites who tend to be younger*

Table 48
Underlying Disease Status

	Rifaximin ID (N=400)	Control ID (N=241)	Rifaximin HE (N=104)	Control HE (N=53)
Duration of Pre-treatment Illness (days)				
Mean (SD)	1 4 (0 9)	1 3 (0 8)	798 1 (1319 3)	1592 1 (1842 3)
Median (Range)	1 2 (0-5 1)	1 2 (0 1-3 6)	99 5 (0-5475)	730 0 (0-7300)
Baseline Hepatic Impairment				
Yes	22 (6%)	11 (5%)	83 (80%)	43 (81%)
No	303 (76%)	166 (69%)	21 (20%)	8 (15%)
Missing	75 (19%)	64 (27%)	0	2 (4%)
Baseline Renal Impairment				
Yes	-	-	3 (3%)	5 (9%)
No	326 (82%)	179 (74%)	100 (96%)	47 (89%)
Missing	74 (18%)	62 (26%)	1 (1%)	1 (2%)

Hepatic impairment at baseline = total bilirubin AST, or ALT ≥1 5 x upper limit of normal
Renal impairment at baseline = serum creatinine ≥1 5 x upper limit of normal

Duration of Treatment

504 subjects in the all rifaximin group received at least one dose of study medication and all received at least 600 mg Four hundred eighty three (96%) in the all rifaximin group and 279 (94%) in the all control group received at least 3 days of study medication Treatment duration ranged from <1 to 11 days Duration of treatment was similar between the rifaximin and control groups for all patients within the ID and HE sub groupings Four hundred rifaximin ID subjects received at least 1 dose and 383 of these, 96% received 600 mg/day for 3 days duration Treatment duration ranged from <1 to 5 days

One hundred four in the rifaximin HE subject group received at least one dose of study medication and 100 (96 2%) completed at least 3 days of treatment at a dose of at least 600 mg/day Treatment duration for HE was more prolonged and ranged from <1 to 11 days

Medical Officer's Comment *Of note a larger number of rifaximin ID patients received 4 and 5 days of treatment as compared to the rifaximin ID control arm Similarly, a larger number of rifaximin HE patients had more prolonged course of treatment as compared to the control arm subjects*

Table 49
Duration of Treatment

	ALL Rifaximin (N=504)	ALL Control (N=294)	Rifaximin ID (N=400)	Control ID (N=241)	Rifaximin HE (N=104)	Control HE (N=53)
= 1 day	8 (1 6%)	6 (2%)	7 (1 8%)	6 (2 5%)	1 (1%)	-
1 - = 2 days	13 (2 6%)	9 (3 1%)	10 (2 5%)	8 (3 3%)	3 (2 9%)	1 (1 9%)
2 - = 3 days	192 (38 1%)	142 (48 3%)	190 (47 5%)	141 (58 5%)	2 (1 9%)	1 (1 9%)
3 - = 4 days	143 (28 4%)	72 (24 5%)	140 (35%)	69 (28 6%)	3 (2 9%)	3 (5 7%)
4 - = 5 days	81 (16 1%)	47 (16%)	53 (13 3%)	17 (7 1%)	28 (26 9%)	30 (56 6%)
5 - = 6 days	3 (0 6%)	4 (1 4%)	0	0	3 (2 9%)	4 (7 5%)
6 - = 7 days	59 (11 7%)	9 (3 1%)	0	0	59 (56 7%)	9 (17%)
7 - = 8 days	1 (0 2%)	0	0	0	1 (1%)	0
8 - = 9 days	2 (0 4%)	1 (0 3%)	0	0	2 (1 9%)	1 (1 9%)
9 - = 10 days	2 (0 4%)	2 (0 7%)	0	0	2 (1 9%)	2 (3 8%)
10- = 11 days	0	2 (0 7%)	0	0	0	2 (3 8%)

Dose Rifaximin ID 200 mg TID 143, 400 mg BID 93, 400 mg TID 145, 600 mg TID 19
Dose Rifaximin HE 60200 mg TID 18, 1200 mg QD 69, 800 mg TID 17

AEs

As per the applicant, "In summary, there were no differences in the reported adverse events rates between rifaximin and control groups for either patient population (ID or HE) In addition, there were no clinically meaningful patterns of individual adverse event differences between treatment groups "

Medical Officer's Comment *Adverse events reported at ≥ 2% are presented by study for the two Phase III studies (RFID9801 and RFID9701) that comprised 86% (343/400) of the ID rifaximin patients and 92% (222/241) of the ID control patients in the safety database The safety profile of rifaximin in each study was comparable to the control arm However, the adverse event rates in RFID9801 are higher than in RFID9701 As per the applicant this difference was because worsening of enteric disease symptoms were recorded as adverse events in 9801 study but not in 9701*

Table 50
Adverse Events Occurring at ≥2% in 9801

Adverse Event	Rifaximin 600 mg/day (N=124)	Rifaximin 1200 mg/day (N=126)	Placebo (N=129)
Flatulence	32 (26%)	36 (29%)	42 (33%)
Abdominal pain	21 (17%)	28 (22%)	23 (18%)
Tenesmus	19 (15%)	14 (11%)	19 (15%)
Fecal incontinence	16 (13%)	21 (17%)	20 (16%)
Nausea	16 (13%)	20 (16%)	18 (14%)
Headache	15 (12%)	22 (18%)	12 (9%)
Pyrexia	8 (7%)	7 (6%)	9 (7%)
Vomiting	5 (4%)	3 (2%)	3 (2%)
AST increased	4 (3%)	0	4 (3%)
Constipation	4 (3%)	3 (2%)	3 (2%)
Chest pain	2 (2%)	1 (1%)	1 (1%)
Diarrhea	2 (2%)	2 (2%)	8 (6%)
Hematuria	2 (2%)	0	1 (1%)
Myalgia	2 (2%)	0	-
Nasopharyngitis	0	2 (2%)	1 (1%)
Sunburn	2 (2%)	-	0
Weakness	2 (2%)	1 (1%)	3 (2%)
Blood in stool	1 (1%)	0	2 (2%)
Dizziness	1 (1%)	5 (4%)	5 (3 9)
Migraine	1 (1%)	0	2 (2%)
Pain	1 (1%)	1 (1%)	2 (2%)
Fatigue	0	4 (3%)	0
ALT increased	0	0	2 (2%)
Back pain	0	1 (1%)	2 (2%)
Loose stool	0	0	2 (2%)
Muscle cramps	0	1 (1%)	2 (2%)
Taste disturbance	0	0	2 (2%)

Table 51
Incidence of Adverse Events that are ≥2% in RFID9701

Adverse Event	Rifaximin 800 mg/day (N=93)	Ciprofloxacin 1000 mg/day (N=93)
Headache NOS	10 (11%)	12 (13%)
Constipation	6 (7%)	2 (2%)
Asthenia	3 (3%)	1 (1%)
Pharyngitis NOS	3 (3%)	0

Dizziness (exc vertigo)	2 (2%)	4 (4%)
Somnolence	2 (2%)	0
Viral infection NOS	2 (2%)	0
Vomiting NOS	1 (1%)	2 (2%)
Nausea	0	3 (3%)
Pyrexia	0	3 (3%)
Dry skin	0	1 (1%)
Dyspepsia	0	2 (2%)
Eructation	0	2 (2%)
Nervousness	0	2 (2%)
Syncope	0	2 (2%)
Taste disturbance	0	2 (2%)

Rifaximin ID (N = 400)

Sixty0one percent (243/400) of all rifaximin ID patients had and AE (N = 475) as compared to 59%) (141/241) of the ID control subjects (N = 291) Both the control and the rifaximin ID patients had more AEs as compared to the HE subjects

A table of all AEs can be found below

Table 52
All AEs

AEs	ALL Rifaximin (N=504)	ALL Control (N=294)	Rifaximin ID (N=400)	Control ID (N=241)	Rifaximin HE (N=104)	Control HE (N=53)
# Patients with Any AE	275 (55%)	156 (53%)	243 (61%)	141 (59%)	32 (31%)	15 (28%)
# of AEs	536	311	475	291	61	20
Blood and Lymphatic System						
All	**3 (0 6%)**	**0**	**0**	**0**	**0**	**0**
Anemia	2 (0 4%)	0	0	0	0	0
Coagulation Disorder	1 (0 2%)	0	0	0	1 (1%)	0
Cardiac						
All	**2 (0 4%)**	**1 (0 3%)**	**1 (0 3%)**	**1 (0 4%)**	**1 (1%)**	**0**
Edema	1 (0 2%)	0	0	0	1 (1%)	0
Palpitations	1 (0 2%)	1 (0 3%)	1 (0 3%)	1 (0 4%)	0	0
Ear and Labyrinth						
All	**3 (0 6%)**	**1 (0 3%)**	**3 (0 8%)**	**1 (0 4%)**	**0**	**0**
Earache	1 (0 2%)	1 (0 3%)	1 (0 3%)	1 (0 4%)	0	0
Motion sickness	1 (0 2%)	0	1 (0 3%)	0	0	0
Vertigo	1 (0 2%)	0	1 (0 3%)	0	0	0

Eye						
All	**0**	2 (0 7%)	**0**	**2 (0 8%)**	**0**	**0**
Conjunctivitis	0	1 (0 3%)	0	1 (0 4%)	0	0
Dry eye	0	1 (0 3%)	0	1 (0 4%)	0	0
GI disorders						
All	**194 (38 5%)**	**108 (36 7%)**	**178 (44 5%)**	**103 (42 7%)**	**16 (15 4%)**	**5 (9 4%)**
Abdominal distension	3 (0 6%)	1 (0 3%)	3 (0 8%)	1 (0 4%)	0	0
Abdominal Pain	52 (10 3%)	24 (8 2%)	51 (12 8%)	24 (10%)	1 (1%)	0
Upper Abd Pain	3 (0 6%)	1 (0 3%)	2 (0 5%)	0	1 (1%)	1 (1 9%)
Ascites	2 (0 4%)	0	0	0	0	0
Constipation	19 (3 8%)	9 (3 1%)	10 (4 8%)	9 (3 7%)	0	0
Urgency	1 (0 2%)	1 (0 3%)	1 (0 3%)	1 (0 4%)	0	0
Diarrhea	9 (1 8%)	9 (3 1%)	4 (1%)	8 (3 3%)	5 (4 8%)	1 (1 9%)
Dry Mouth	0	1 (0 3%)	0	1 (0 4%)	0	0
Dry Throat	1 (0 2%)	0	1 (0 3%)	0	0	0
Dyspepsia	2 (0 4%)	3 (1%)	2 (0 5%)	2 (0 8%)	0	1 (1 9%)
Eructation	0	2 (0 7%)	0	2 (0 8%)	0	0
Fecal abn	2 (0 4%)	1 (0 3%)	2 (0 5%)	1 (0 4%)	0	0
Fecal Inc	37 (7 3%)	20 (6 8%)	37 (9 3%)	20 (8 3%)	0	0
Flatulence	70 (13 9%)	42 (14 3%)	70 (17 5%)	42 (17 4%)	0	0
GI Hemorraghe	4 (0 8%)	1 (0 3%)	0	0	4 (3 8%)	1 (1 9%)
Gingival Disorder	1 (0 2%)	0	1 (0 3%)	0	0	0
Dry Lip	1 (0 2%)	2 (0 7%)	1 (0 3%)	0	0	0
Loose Stools	0	0	0	2 (0 8%)	0	0
Melena	1 (0 2%)	0	0	0	1 (1%)	0
Nausea	49 (9 7%)	22 (7 5%)	43 (10 8%)	22 (9 1%)	6 (5 8%)	0
Peritonitis	0	1 (0 3%)	0	0	0	0
Proctalgia	1 (0 2%)	0	1 (0 3%)	0	0	0
Sore Throat	4 (0 8%)	0	4 (1%)	0	0	0
Tenesmus	34 (6 7%)	20 (6 8%)	34 (8 5%)	20 (8 3%)	0	0
Vomiting	15 (3%)	8 (2 7%)	12 (3%)	6 (2 5%)	3 (2 9%)	2 (3 8%)
General						
All	**45 (8 9%)**	**25 (8 5%)**	**43 (10 8%)**	**23 (9 5%)**	**2 (1 9%)**	**1 (1 9%)**
Hangover	1 (0 2%)	1 (0 3%)	1 (0 3%)	1 (0 4%)	0	0
Asthenia	3 (0 6%)	1 (0 3%)	3 (0 8%)	1 (0 4%)	0	0
Chest Pain	3 (0 6%)	1 (0 3%)	3 (0 8%)	1 (0 4%)	0	0
Fatigue	13 (3%)	1 (0 3%)	13 (3 3%)	1 (0 4%)	0	0
Flu	2 (0 4%)	1 (0 3%)	2 (0 5%)	1 (0 4%)	0	0
Malaise	1 (0 2%)	1 (0 3%)	1 (0 3%)	1 (0 4%)	0	0
Multiorgan Failure	0	1 (0 3%)	0	0	0	1 (1 9%)

Pain	2 (0 4%)	2 (0 7%)	2 (0 5%)	2 (0 8%)	0	0
Pyrexia	18 (3 6%)	13 (4 4%)	16 (4%)	12 (5%)	2 (1 9%)	1 (1 9%)
Rigors	2 (0 4%)	1 (0 3%)	2 (0 5%)	1 (0 4%)	0	0
Weakness	7 (1 4%)	4 (1 4%)	7 (1 8%)	4 (1 7%)	0	0
Hepatobiliary						
All	**2 (0 4%)**	**0**	**0**	**0**	**2 (1 9%)**	**0**
Hepatic Failure	1 (0 2%)	0	0	0	1 (1%)	0
Portal Hypertension	1 (0 2%)	0	0	0	1 (1%)	0
Immune system						
All	**22 (4 4%)**	**7 (2 4%)**	**16 (4%)**	**3 (1 2%)**	**6 (5 8%)**	**4 (7 5%)**
Bronchopneumonia	1 (0 2%)	0	0	0	1 (1%)	0
Fungal Infection	0	1 (0 3%)	0	1 (0 4%)	0	0
Genital Candidiasis	1 (0 2%)	0	0	0	1 (1%)	0
HSV	1 (0 2%)	0	1 (0 3%)	0	0	0
VZV	0	1 (0 3%)	0	0	0	0
Infection	1 (0 2%)	0	0	0	1 (1%)	1 (1 9%)
Nasopharyngitis	8 (1 6%)	1 (0 3%)	8 (2%)	1 (0 4%)	0	0
Peritonitis	0	1 (0 3%)	0	0	0	1 (1 9%)
Pharyngitis	3 (0 6%)	0	3 (0 8%)	0	0	0
Pneumonia	0	1 (0 3%)	0	0	0	1 (1 9%)
Sepsis	1 (0 2%)	0	0	0	1 (1%)	0
Septic Shock	1 (0 2%)	0	0	0	1 (1%)	0
Sinusitis	1 (0 2%)	0	1 (0 3%)	0	0	0
URI	2 (0 4%)	0	2 (0 5%)	0	0	0
UTI	2 (0 4%)	2 (0 7%)	0	1 (0 4%)	2 (1 9%)	1 (1 9%)
Viral Infection	2 (0 4%)	0	2 (0 5%)	0	0	0
Trauma						
All	**3 (0 6%)**	**1 (0 3%)**	**3 (0 8%)**	**1 (0 4%)**	**0**	**0**
Bite	1 (0 2%)	0	1 (0 3%)	0	0	0
Injury	0	1 (0 3%)	0	1 (0 4%)	0	0
Sunburn	2 (0 4%)	0	2 (0 5%)	0	0	0
Laboratory						
All	**12 (2 4%)**	**7 (2 4%)**	**9 (2 3%)**	**7 (2 9%)**	**3 (2 9%)**	**0**
Increased ALT	0	2 (0 7%)	0	2 (0 8%)	0	0
Increased AST	4 (0 8%)	4 (1 4%)	4 (1%)	4 (1 7%)	0	0
Heme + Stool	1 (0 2%)	2 (0 7%)	1 (0 3%)	2 (0 8%)	0	0
Hypertension	1 (0 2%)	0	1 (0 3%)	0	0	0
Endoscopy	1 (0 2%)	0	0	0	1 (1%)	0
Glycosuria	1 (0 2%)	0	1 (0 3%)	0	0	0
Hematuria	2 (0 4%)	1 (0 3%)	2 (0 5%)	1 (0 4%)	0	0
Paracentesis	1 (0 2%)	0	0	0	1 (1%)	0
Weight Gain	1 (0 2%)	0	0	0	1 (1%)	0

Metabolism and Nutritional						
All	**6 (1%)**	**2 (0 7%)**	**5 (1 3%)**	**1 (0 4%)**	**1 (1%)**	**1 (1 9%)**
Anorexia	2 (0 4%)	0	2 (0 5%)	0	0	0
Decreased Appetite	1 (0 2%)	1 (0 3%)	1 (0 3%)	1 (0 4%)	0	0
Dehydration	2 (0 4%)	0	2 (0 5%)	0	0	0
Hyperkalemia	0	1 (0 3%)	0	0	0	0
Hypokalemia	1 (0 2%)	0	0	0	1 (1%)	1 (1 9%)
Musculoskeletal and Connective Tissue Disorders						
All	**10 (2%)**	**8 (2 7%)**	**9 (2 3%)**	**8 (3 3%)**	**1 (1%)**	**0**
Back Pain	2 (0 4%)	3 (1%)	2 (0 5%)	3 (1 2%)	0	0
Muscle Cramps	2 (0 4%)	2 (0 7%)	1 (0 3%)	2 (0 8%)	1 (1%)	0
Muscle twitches	1 (0 2%)	0	1 (0 3%)	0	0	0
Muscle weakness	1 (0 2%)	0	1 (0 3%)	0	0	0
Myalgia	3 (0 6%)	1 (0 3%)	3 (0 8%)	1 (0 4%)	0	0
Neck Pain	1 (0 2%)	1 (0 3%)	1 (0 3%)	1 (0 4%)	0	0
Neck stiffness	1 (0 2%)	0	1 (0 3%)	0	0	0
Limb Pain	0	1 (0 3%)	0	1 (0 4%)	0	0
CNS disorders						
All	**71 (14 1%)**	**43 (14 6%)**	**64 (16%)**	**40 (16 6%)**	**7 (6 7%)**	**3 (5 7%)**
Dizziness	8 (1 6%)	9 (3 1%)	8 (2%)	9 (3 7%)	0	0
Grand Mail Seizure	1 (0 2%)				1 (1%)	0
Headache	50 (9 9%)	25 (8 5%)	50 (12 5%)	25 (10 4%)	6 (5 8%)	3 (5 7%)
Hepatic Encephalopathy	6 (1 2%)	0	0	0	0	0
Insomnia	1 (0 2%)	3 (1%)	1 (0 3%)	3 (1 2%)	0	0
Migraine	0	3 (1%)	3 (0 8%)	2 (0 8%)	0	0
Myasthenia	1 (0 2%)	1 (0 3%)	1 (0 3%)	1 (0 4%)	0	0
Paresthesia	1 (0 2%)	1 (0 3%)	1 (0 3%)	1 (0 4%)	0	0
Somnolence	2 (0 4%)	1 (0 3%)	2 (0 5%)	1 (0 4%)	0	0
Syncope	0	2 (0 7%)	0	2 (0 8%)	0	0
Taste Disturbance	0	4 (1 4%)	0	4 (1 7%)	0	0
Taste Loss	1 (0 2%)	0	1 (0 3%)	0	0	0
Psychiatric Disorders						
All	**1 (0 2%)**	**4 (1 4%)**	**0**	**4 (1 7%)**	**1 (1%)**	**0**
Aggression	1 (0 2%)	0	0	0	1 (1%)	0
Confusion	0	1 (0 3%)	0	1 (0 4%)	0	0
Nervousness	0	3 (1%)	0	3 (1 2%)	0	0
Nightmares	0	1 (0 3%)	0	1 (0 4%)	0	0
Renal and UT Disorders						
All	**4 (1%)**	**1 (0 3%)**	**2 (0 5%)**	**0**	**2 (1 9%)**	**1 (1 9%)**
Polyuria	1 (0 2%)	0	1 (0 3%)	0	0	0
ARF	2 (0 4%)	1 (0 3%)	0	0	2 (1 9%)	1 (1 9%)

Frequency	1 (0 2%)	0	1 (0 3%)	0	0	0
Reproductive						
All	**3 (0 6%)**	**1 (0 3%)**	**2 (0 5%)**	**1 (0 4%)**	**1 (1%)**	**0**
Dysmenorrhea	1 (0 2%)	1 (0 3%)	1 (0 3%)	1 (0 4%)	0	0
Irregularity	1 (0 2%)	0	1 (0 3%)	0	0	0
Penile Disorder	1 (0 2%)	0	0	0	1 (1%)	0
Respiratory Tract Disorders						
All	**6 (1 2%)**	**4 (1 4%)**	**4 (1%)**	**4 (1 7%)**	**2(1 9%)**	**0**
Asthma	0	1 (0 3%)	0	1 (0 4%)	0	0
Cough	1 (0 2%)	0	1 (0 3%)	0	0	0
Dyspnea	1 (0 2%)	2 (0 7%)	1 (0 3%)	2 (0 8%)	0	0
Nasal Congestion	2 (0 4%)	1 (0 3%)	2 (0 5%)	1 (0 4%)	0	0
Pleural Effusion	1 (0 2%)	0	0	0	1 (1%)	00
Respiratory disorder	1 (0 2%)	0	0	0	1 (1%)	0
RT Hemorraghe	1 (0 2%)	0	0	0	1 (1%)	0
Allergic Rhinitis	0	1 (0 3%)	0	1 (0 4%)	0	0
Rhinorrhea	1 (0 2%)	0	1 (0 3%)	0	0	0
Skin and ST Disorders						
All	**7 (1 4%)**	**6 (2%)**	**5 (1 3%)**	**6 (2 5%)**	**2(1 9%)**	**0**
Clamminess	1 (0 2%)	0	1 (0 3%)	0	0	0
Allergic Dermatitis	0	1 (0 3%)	0	1 (0 4%)	0	0
Dermatitis	2 (0 4%)	2 (0 7%)	1 (0 3%)	2 (0 8%)	1 (1%)	0
Dry Skin	0	1 (0 3%)	0	1 (0 4%)	0	0
Pruritus	1 (0 2%)	0	0	0	1 (1%)	0
Macular Rash	1 (0 2%)	0	1 (0 3%)	0	0	0
Maculopapular Rash	1 (0 2%)	0	1 (0 3%)	0	0	0
Skin Disorder	0	1 (0 3%)	0	1 (0 4%)	0	0
Increased Sweating	1 (0 2%)	1 (0 3%)	1 (0 3%)	1 (0 4%)	0	0
Vascular Disorders						
All	**2 (0 4%)**	**2 (0 7%)**	**2 (0 5%)**	**1 (0 4%)**	**0**	**1 (1 9%)**
Hot flushes	2 (0 4%)	0	2 (0 5%)	0	0	0
Hypertension	0	2 (0 7%)	0	1 (0 4%)	0	1 (1 9%)

Medical Officer's Comment *GI AEs were more frequent on the rifaximin arm as compared to the control arm with the exception of diarrhea that was more frequent on the control arm (p = 0 05) Interestingly, fatigue headache and nasopharyngitis were more frequent on the rifaximin ID arm and the difference in the incidence of fatigue was statistically significant (p = 0 02) No explanation was provided for this and the fatigue was not associated with anemia or other events that would explain it*

Table 53
Summary of Adverse Events Reported by ≥1% of ID Patients

Adverse Event	Rifaximin (N=400)	Control (N=241)	P-Value[a]
No of Patients with AEs	243 (61%)	141 (59%)	0 6178
Flatulence	70 (18%)	42 (17%)	1 0000
Abdominal pain NOS	51 (13%)	24 (10%)	0 3122
Headache NOS	50 (13%)	25 (10%)	0 4488
Nausea	43 (11%)	22 (9%)	0 5895
Fecal incontinence	37 (9%)	20 (8%)	0 7750
Tenesmus	34 (9%)	20 (8%)	1 0000
Constipation	19 (5%)	9 (4%)	0 6906
Pyrexia	16 (4%)	12 (5%)	0 5557
Fatigue	**13 (3%)**	**1 (0 4%)**	**0 0221**
Vomiting nos	12 (3%)	6 (3%)	0 8085
Dizziness (exc vertigo)	8 (2%)	9 (4%)	0 2091
Nasopharyngitis	8 (2%)	1 (0 4%)	0 1641
Weakness	7 (2%)	4 (2%)	1 0000
AST increased	4 (1%)	4 (2%)	0 4824
Diarrhea nos	4 (1%)	8 (3%)	0 0658
Sore throat NOS	4 (1%)	0	0 3027

[a] Fisher Exact Test
Notes Control = placebo treated patients (RFID9801), ciprofloxacin treated patients (RFID9701), and TMP/SMX treated patients (RFID9601)

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

Adverse events reported for ≥ 1% and < 2% of the ID rifaximin or ID control patients, respectively, were weakness (2%, 2%), AST increase (1%, 2%), sore throat (1%, 0%), and diarrhea (1%, 3%) As per the applicant, "none of these differences reached statistical significance "

Rifaximin HE
For a table of AES in the HE patients , see Appendix 1

The expected pattern of adverse events for HE patients differed from that for ID patients As noted in the demographics, the HE patients were ill and had many associated medical conditions The duration of treatment was longer in that subgroup and thus the period of adverse event collection was longer

BID) Studies RFID9701 and RFID9601 were ex-US sponsored studies (by Alfa Wassermann) while study RFID9801 was conducted by Salix

Adverse events seen more frequently with the 200 mg TID or 400 mg TID dose were flatulence, abdominal pain, nausea, fecal incontinence, tenesmus, and nasopharyngitis

The incidence of severe adverse events in rifaximin ID patients also did not appear to be dose-related Severe adverse events were reported in 15% of patients treated at 200 mg TID, 4% of patients treated at 400 mg BID, 19% of patients at 400 mg TID,, and 5% of patients at 600 mg TID

Therefore, there does not appear to be a dose effect of rifaximin on the adverse event profile In study RFID9801 containing 2 dose groups (200 mg TID and 400 mg TID), there were no significant trends in adverse event rates, drug-related adverse events or laboratory measured safety parameters
For further details on AEs by dose in the HE dataset, please see Appendix I

Drug Related AEs

Thirty-seven percent (184/504) of all rifaximin subjects had a drug-related AE as compared to 36% (106/294) of the all control patients A breakdown into ID and HE subjects, revealed that 176/400 ID rifaximin patients (44%) had a drug-related AE as compared to 104/241 (43%) ID controls There was a large numerical difference between the incidence of drug-related events on the ID arms as compared to the HE arms where 8/104 (7%) of HE rifaximin subjects had a drug-related AE as compared to 2/53 (4%) of the HE control subjects

The incidence of drug-related adverse events did not differ significantly between rifaximin and control treated ID patients, and, the incidence of drug-related adverse events did not differ significantly between rifaximin and control treated HE patients but there appeared to be a notable difference between the treatment groups

Additionally, there was a notable difference in the reporting of such events between the trials with 60 – 70% of subjects with drug-related AEs in trial 9801 as compared to 5% on the rifaximin arm in trial 9701

The individual drug-related adverse events reported for 1% or more of the ID rifaximin patients (reported for ID rifaximin and ID control, respectively) were flatulence (17%, 17%), abdominal pain (12%, 9%), headache (8%, 5%), nausea (9%, 8%), fecal incontinence (6%, 6%), tenesmus (5%, 6%), constipation (3%, 3%), pyrexia (2%, 3%), vomiting (2%, 3%), fatigue (1%, 0%), diarrhea (1%, 3%), dizziness (exc vertigo) (1%, 3%), and AST increased (1%, 2%)

The individual drug-related adverse events reported for 1% or more of the HE rifaximin patients were nausea (3%, 0%), diarrhea (3%, 2%), and ascites (2%, 0%) Edema, weight

increased, and genital candidiasis were reported in 1 (1%) of the rifaximin HE subjects and none of the controls

Headache and fatigue appeared to be the most frequent non-GI drug-related AEs for the rifaximin-treated subjects Dizziness and fever were the most frequent non-GI drug-related AEs for the control subjects

Of note, all cases of increased AST (drug-related), occurred in the 200 mg TID ID rifaximin group Four of 5 cases of fatigue occurred in the 400 mg TID day ID rifaximin group and 1 in the ID 600 mg group There were 10 cases of headache in the 200 mg TID ID group, 1 case in 400 mg BID ID group, 19 cases in the 400 mg TID ID group, none in the 600 mg TID group and none in the HE subjects

Of note, none of the treatment-related AEs were considered definitely related to treatment Eleven events from 7/504 ID rifaximin subjects (1 4%) were probably related and the remaining 321 events seen in 178/504 subjects were possibly related

Table 54
Drug-Related Adverse Events in ≥1% of Patients

Adverse Event	Rifaximin ID (N=400)	Control ID (N=241)	Rifaximin HE (N=104)	Control HE (N=53)	ALL Rifaximin N = 504	All Control N = 294
Patients with Drug-Related AEs	176 (44%)	104 (43%)	8 (8%)	2 (4%)	184 (37%)	106 (36%)
Flatulence	66 (17%)	42 (17%)	0	0	66 (13%)	42 (14%)
Abdominal pain	46 (12%)	21 (9%)	0	0	46 (9%)	21 (7%)
Nausea	35 (9%)	19 (8%)	3 (3%)	0	38 (8%)	19 (7%)
Headache	30 (8%)	12 (5%)	0	0	30 (6%)	12 (4%)
Fecal Incontinence	25 (6%)	15 (6%)	0	0	25 (5%)	15 (5%)
Tenesmus	21 (5%)	14 (6%)	0	0	21 (4%)	14 (5%)
Constipation	11 (3%)	7 (3%)	0	0	11 (2%)	7 (2 %)
Pyrexia	9 (2%)	6 (3%)	0	0	9 (2%)	6 (2%)
Vomiting	8 (2%)	4 (2%)	1 (1%)	0	9 (2%)	4 (1%)
Dizziness	5 (1%)	6 (3%)	0	0	5 (1%)	6 (2%)
Fatigue	5 (1%)	0	0	0	5 (1%)	
Diarrhea	4 (1%)	7 (3%)	3 (3%)	1 (2%)	7 (1%)	8 (3%)
Edema	0	0	1 (1%)	0	1 (0 2%)	0
Upper Abdominal Pain	2 (0 5%)	0	0	1 (2%)	2 (0 4%)	1 (0 3%)
Ascites	0	0	2 (2%)	0	2 (0 4%)	0
Genital Candidiasis	0	0	1 (1%)	0	1 (0 2%)	0
Increased AST	4 (1%)	4 (2%)	0	0	4 (1%)	4 (1%)
Increased Weight	0	0	1 (1%)	0	1 (0 2%)	0

Drug related means possible, probable, or certain
Notes Control = placebo treated patients (RFID9801), ciprofloxacin treated patients (RFID9701), and TMP/SMX treated patients (RFID9601)

Table 55
Drug-Related Adverse Events in by Study/Dose (ID subjects)

	RFID9801			RFID9701	
Adverse Event	**Rifaximin 600 mg (N=124)**	**Rifaximin 1200 mg (N=126)**	**Placebo (N=104)**	**Rifaximin 800 mg (N=93)**	**Cipro (N=93)**
Patients with Drug-Related AEs	74 (60%)	88 (70%)	90 (87%)	5 (5%)	9 (10%)
Flatulence	30 (24%)	36 (29%)	42 (33%)	0	0
Abdominal pain	19 (15%)	26 (20%)	21 (16%)	0	0
Nausea	14 (11%)	19 (15%)	18 (14%)	0	1 (1%)
Headache	10 (8%)	19 (15%)	10 (8%)	1 (1%)	1 (1%)
Fecal Incontinence	12 (10%)	13 (10%)	15 (12%)	0	0
Tenesmus	13 (11%)	8 (6%)	14 (11%)	0	0
Constipation	4 (3%)	3 (2%)	3 (2%)	0	0
Pyrexia	3 (2%)	6 (5%)	6 (5%)	0	0
Vomiting	4 (3%)	3 (2%)	3 (2%)	0	1 (1%)
Dizziness	0	4 (3%)	5 (4%)	1 (1%)	1 (1%)
Fatigue	0	4 (3%)	0	0	0
Malaise	1 (1%)	0	0	0	0
Diarrhea	2 (2%)	2 (2%)	7 (5%)	0	0
Upper Abdominal Pain	0	0	0	0	0
Increased AST	4 (3%)	0	4 (3%)	0	0
Fecal Abnormality	1 (1%)	1 (1%)	0	0	0
Dry Lip	1 (1%)	0	0	0	0
Abdominal Distension	1 (1%)	2 (2%)	1 (1%)	0	0
Pain	1 (1%)	0	1 (1%)	0	0
Dry Throat	1 (1%)	0	0	0	0
Dyspepsia	0	2 (2%)	0	0	1 (1%)
Loose Stools	0	0	2 (2%)	0	0
Chest Pain	2 (2%)	1 (1%)	1 (1%)	0	0
Upper Abdominal Pain	0	1 (1%)	0	0	0
Dry Mouth	0	0	1 (1%)	0	0
Palpitations	0	0	1 (1%)	1 (1%)	0
Dry Eye	0	0	1 (1%)	0	0
Conjunctivitis	0	0	1 (1%)	0	0
Earache	0	0	0	0	1 (1%)
Flu	0	1 (1%)	0	1 (1%)	0
Rigors	0	1 (1%)	0	0	0
Weakness	1 (1%)	0	2 (2%)	0	0

Sunburn	1 (1%)	0	0	0	0
Blood in stool	1 (1%)	0	0	0	0
Increases BP	0	1 (1%)	0	0	0
Glycosuria	0	1 (1%)	0	0	0
Hematuria	2 (2%)	0	0	0	0
Decreased Appetite	0	1 (1%)	0	0	0
Back Pain	0	1 (1%)	2 (2%)	0	0
Muscle Cramps	0	1 (1%)	2 (2%)	0	0
Muscle Twitches	0	1 (1%)	0	0	0
Muscle Weakness	0	1 (1%)	0	0	0
Myalgia	1 (1%)	0	1 (1%)	0	0
Limb Pain	0	0	1 (1%)	0	0
Insomnia	0	0	0	1 (1%)	1 (1%)
Migraine	1 (1%)	0	2 (2%)	0	0
Paresthesia	0	1 (1%)	0	0	0
Taste Disturbance	0	0	1 (1%)	0	1 (1%)
Taste Loss	1 (1%)	0	0	0	0
Somnolence	0	0	1 (1%)	0	0
Nightmare	0	0	1 (1%)	0	0
Polyuria	1 (1%)	0	0	0	0
Urinary Frequency	1 (1%)	0	0	0	0
Menstrual Irregularity	0	1 (1%)	0	0	0
Asthma	0	0	1 (1%)	0	0
Dyspnea	1 (1%)	0	0	0	1 (1%)
Nasal Congestion	0	1 (1%)	1 (1%)	0	0
Clamminess	1 (1%)	0	0	0	1 (1%)
Dermatitis	0	1 (1%)	0	0	1 (1%)
Macular Rash	0	1 (1%)	0	0	0
Hot Flushes	1 (1%)	1 (1%)	0	0	0
Hypertension	0	0	1 (1%)	0	0

In 9601 there were 19 subjects on the 200 mg TID dose, 5 (26%) of whom had drug-related AEs as compared to 19 subjects on the 400 mg TID mg arm with 2 (10%) of subjects with TMP/SMX was received by the control recipients of whom 5 had drug-related AEs (26%) The AEs were varied and included 1 complaint of fatigue at the 200 mg TID dose as well as 3 complaints of constipation at the 200 mg TID dose and 4 on the TMP/SMX arm

Severe AEs

The incidence of severe adverse events did not differ significantly between the rifaximin and control groups Thirteen percent (67/504) rifaximin patients had a severe AE (N = 89) as compared to 12% (35/294) of the control patients (N = 62 events) Fourteen

percent (54/400) of the ID rifaximin subjects had a severe AE (N = 71) as compared to 13% (13/104) of the HE rifaximin subjects (N = 18)

Severe AEs reported in the ID patients were primarily from the GI tract and those in the HE patients were primarily associated with complications of hepatic encephalopathy

Table 56
Severe Adverse Events

Adverse Event	Rifaximin ID (N=400)	Control ID (N=241)	Rifaximin HE (N=104)	Control HE (N=53)	ALL Rifaximin N = 504	All Control N = 294
Patients with Severe AEs	54 (14%)	27 (11%)	13 (13%)	5 (9%)	67 (13%)	35 (12%)
Abdominal pain	14 (4%)	8 (3%)	0	0	14 (3%)	8 (3%)
Nausea	12 (3%)	5 (2%)	0	0	12 (2%)	5 (2%)
Fecal incontinence	9 (2%)	8 (3%)	0	0	9 (2%)	8 (3%)
Urgency	1 (0 3%)	0	0	0	1 (0 2%)	0
Flatulence	9 (2%)	9 (4%)	0	0	9 (2%)	9 (3%)
Vomiting	7 (2%)	0	0	0	7 (1%)	0
Tenesmus	5 (1%)	5 (2%)	0	0	5 (1%)	5 (2%)
Diarrhea	2 (0 5%)	2 (0 8%)	0	0	3 (0 6%)	2 (0 7%)
Constipation		1 (0 4%)	0	0	0	1(0 3%)
Headache	4 (1%)	3 (1%)	0	0	4 (1%)	3 (1%)
Dizziness	0	3 (1%)	0	0	0	3 (1%)
Gastrointestinal hemorrhage	0	0	3 (3%)	1 (2%)	0	1(0 3%)
Hepatic encephalopathy	0	0	3 (3%)	2 (4%)	3 (0 6%)	2 (0 7%)
Acute renal failure	0	0	2 (2%)	0	2 (0 4%)	0
Anemia	0	0	1 (1%)	0	1 (0 2%)	0
Coagulation disorder	0	0	1 (1%)	0	1 (0 2%)	0
Diarrhea	0	0	1 (1%)	0	1 (0 2%)	0
Hepatic Failure	0	0	1 (1%)	0	1 (0 2%)	0
Portal Hypertension	0	0	1 (1%)	0	1 (0 2%)	0
Dry eye	0	0	0	1 (2%)	0	1(0 3%)
Asthenia	1(0 3%)	0	0	0	1 (0 2%)	0
Chest Pain	0	1 (0 4%)	0	0	0	1(0 3%)
Fatigue	2 (0 5%)	0	0	0	2 (0 4%)	0
Malaise	0	1 (0 4%)	0	0	0	1(0 3%)
Multiorgan Failure	0	0	0	1 (2%)	0	1(0 3%)
Pyrexia	0	1(0 4%)	0	0	0	1(0 3%)
Pain	0	1(0 4%)	0	0	0	1(0 3%)
Rigors	0	1(0 4%)	0	0	0	1(0 3%)
Bronchopneumonia	0	0	1 (1%)	0	1 (0 2%)	0

Peritonitis	0	0	0	1 (2%)	0	1(0 3%)
Pneumonia	0	0	0	1 (2%)	0	1(0 3%)
Sepsis	0	0	1 (1%)	0	1 (0 2%)	0
Septic shock	0	0	1 (1%)	0	1 (0 2%)	0
Glycosuria	1(0 3%)	0	0	0	1 (0 2%)	0
Muscle Cramps	1(0 3%)	0	0	0	1 (0 2%)	0
Back Pain	0	1 (0 4%)	0	0	0	1(0 3%)
Neck Pain	0	1 (0 4%)	0	0	0	1(0 3%)
Insomnia	0	1 (0 4%)	0	0	0	1(0 3%)
Migraine	1(0 3%)	0	0	0	1 (0 2%)	0
Myasthenia	0	1 (0 4%)	0	0	0	1(0 3%)
Somnolence	0	0	0	0	1 (0 2%)	0
Taste Loss	1(0 3%)	0	0	0	1 (0 2%)	0
Nervousness	0	1 (0 4%)	0	0	0	1(0 3%)
Pleural effusion	0	0	1 (1%)	0	1 (0 2%)	0

Notes Control = placebo treated patients (RFID9801) ciprofloxacin treated patients (RFID9701) and TMP/SMX treated patients (RFID9601)

Deaths

No deaths occurred in the infectious diarrhea studies

Deaths in Hepatic encephalopathy (HE) Studies

In the HE studies 5% (8/157) of patients (5% rifaximin [5/104], 6% lactitol [3/53]) died within 30 days of their last dose of study medication, The cause of death was considered unrelated to study drug for all 8 patients

Four of the patients (2 rifaximin, 2 lactitol) had completed the study, two (1 rifaximin, 1 lactitol) had discontinued due to lack of efficacy, and two rifaximin patients had discontinued because of an adverse event

For detailed death summaries, see Appendix 1

Discontinuations and Withdrawals

Fifty-eight subjects withdrew early for any reason adverse event (n=8), lost to follow-up (n=4), other reasons (n=9), unknown reasons (n=1), or lack of efficacy (n=36)

One of four hundred (0 2%) ID rifaximin and 7 (5%) of the 153 HE patients (4/104, 4% rifaximin, 3/53, 6% lactitol) withdrew due to AEs The rifaximin ID patient (2103) in the 200 mg TID group experienced mild nausea, moderate indisposition/lack of appetite and severe loss of taste after the first day of treatment and withdrew from study because of these AEs All of the events were resolved by the next day The indisposition/lack of appetite was considered possibly related to treatment and the nausea and loss of taste as probably related to treatment