

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Meeting of the
Gastrointestinal Drugs Advisory Committee (GIDAC)
to evaluate
Rifaximin 550mg Tablets
for the proposed indication of
Maintenance of Remission of
Hepatic Encephalopathy (HE)
in patients 18 years old and older**

February 23, 2010

FDA Briefing Document

Division of Gastroenterology Products

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Drug: Xifaxan (rifaximin) Tablets, 550 mg
Drug Type: Antibiotic
Applicant: Salix Pharmaceuticals

Proposed Indication: The maintenance of remission of hepatic encephalopathy for patients 18 years of age or older

Orphan Designation: Yes

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XIFAXAN 550 mg TABLETS
February 23, 2010

Meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC) to evaluate Xifaxan (rifaximin) Tablets for the proposed indication of maintenance of remission of hepatic encephalopathy in patients 18 years of age or older.

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FDA SUMMARY MEMORANDUM
with Draft Questions for the Committee

Advisory Committee Meeting for Xifaxan® – February 23, 2010

DATE: January 25, 2010

FROM: Donna Griebel, M.D.
Director, Division of Gastroenterology Products, FDA

TO: Members, Gastrointestinal Drugs Advisory Committee (GIDAC)

SUBJECT: GIDAC Meeting on February 23, 2010, to evaluate Xifaxan® (NDA 022554) for the proposed indication of maintenance of remission of hepatic encephalopathy (HE) in patients ≥ 18 years of age.

Introduction

Thank you for your participation in the upcoming GIDAC meeting to be held on February 23, 2010. Enclosed is the background package for the meeting in which Xifaxan (rifaximin) will be discussed. This memorandum summarizes the contents of the background package and, most importantly, the key issues and draft questions for discussion at the meeting.

Xifaxan was initially approved for marketing in the U.S. in 2004. The currently approved indication is treatment of patients (≥ 12 years of age) with travelers' diarrhea caused by noninvasive strains of *E. coli*. Salix Pharmaceuticals, Inc. is requesting marketing approval of an efficacy supplement for Xifaxan to add a new indication for maintenance of remission from hepatic encephalopathy (HE) in patients ≥ 18 years of age.

Summary of Briefing Package Contents

The FDA background package for this meeting contains reviews generated by Center for Drug Evaluation and Research (CDER) staff, together with some documents provided for reference. The briefing materials consist of the following:

Clinical Review

This review focuses on the placebo-controlled, randomized trial conducted by the applicant in subjects with chronic liver disease who had a history in the 6 months prior to study entry of ≥ 2 episodes of overt HE that were a Conn score ≥ 2 . Subjects in the randomized trial had a baseline Conn score of 0 or 1. Also presented are safety

data from a treatment extension, open label, single arm trial that enrolled patients who had participated in the randomized trial and new patients. The clinical review section (Tab 2) represents collaboration between the clinical and pharmacology/toxicology reviewer(s); there is no separate Pharmacology/Toxicology review.

Neurology Consult Review

Because of the specialized nature of some of the endpoints used in the randomized, placebo-controlled trial, the Division sought expert opinions on those endpoints from CDER's Division of Neurology Products. The Neurology Review addresses the validity of the assessment tool for the primary endpoint and raises questions about how and whether it was consistently used to perform assessments in the trial. The reviewer expresses concern regarding the interpretability of the observed clinical outcomes in light of these issues.

Clinical Pharmacology Review

The efficacy supplement proposes a dose of Xifaxan that is higher than the currently approved dose and a chronic duration of administration in patients with hepatic impairment. This review evaluates new pharmacokinetic data that reveal exposure to Xifaxan is higher than dose proportional in this population with hepatic impairment compared to healthy subjects. These data indicate that patients with hepatic impairment have a greater propensity for absorption of Xifaxan than healthy volunteers.

Biostatistics Review Summary

The statistical review focuses on the randomized, placebo-controlled trial. This review presents the statistical analyses for the primary and key secondary endpoints, in addition to various exploratory and subgroup analyses, which further address the interpretation of the study results.

Office of Surveillance and Epidemiology Consult Review

Xifaxan has been approved for marketing in the U.S. for over six years. A review of available postmarketing adverse event reporting data was performed by the Office of Surveillance and Epidemiology.

Microbiology Consult Review Summary

The Applicant submitted information for review in support of the proposed content of the microbiology section of the labeling. The Division of Special Pathogens and Transplant Products performed a microbiology review, and their review summary is included in this background package. The publications that describe in-vitro studies were considered insufficient to support the proposed labeling due to lack of information regarding specific methodology. Reports from two clinical trials for short-term use in the treatment of Traveler's Diarrhea did not correlate changes in pathogen eradication with significant alteration of gut flora or describe a unique mechanism of action.

Guidance for Industry – Providing Evidence of Effectiveness for Human Drugs and Biological Products

One of the key issues identified during the review of this application was the strength of evidence for the effectiveness of Xifaxan for the proposed indication of maintenance of remission from HE in patients ≥ 18 years of age. To help frame the Committee's deliberations on whether the evidence standard has been met, this FDA guidance document is provided as background on the regulatory requirements for evidence of effectiveness.

Current Xifaxan Labeling

This is the current FDA approved labeling (package insert) for Xifaxan. Xifaxan was approved for marketing in the U.S. in 2004. The most recent update of the labeling was approved in January 2007.

Proposed Xifaxan Labeling

This is a copy of the applicant's proposed labeling for Xifaxan submitted in this application.

The reviews included in the current background package represent the findings and opinions of the CDER staff, based on their evaluation of the respective sections of the submission from Salix Pharmaceuticals, Inc. These documents contain statements of their findings and conclusions and other statements that stem from their reviews and interpretations of the data presented. It must be emphasized that these documents do not represent final decisions or Division conclusions, and that no regulatory decision on the status of this application has been made. Indeed, the advice that GIDAC provides on these issues will receive full consideration in our final deliberative process.

The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

FDA Issues and Questions

The applicant conducted a single randomized, placebo-controlled trial to evaluate the impact of Xifaxan on time to first breakthrough event of HE in subjects with chronic liver disease who had a history of ≥ 2 episodes of overt HE with a severity of Conn score ≥ 2 . The primary endpoint, time to first breakthrough overt HE episode (defined as increase of Conn score to Grade ≥ 2 or an increase in Conn and asterixis score of 1 grade each), reached statistical significance. The hazard ratio for the risk of experiencing breakthrough overt HE in the Xifaxan group relative to the risk in the placebo group was 0.421, 95% CI (0.276 to 0.641) during the 6-month treatment period ($p < 0.0001$).

The observed outcome on its face is persuasive, even for a single trial. However, the study's primary endpoint was assessed utilizing the Conn score, which requires a subjective assessment and depends on clinician judgment. There is concern that the Conn grading system is imprecise and insufficiently sensitive at differentiating milder levels of severity of HE. Of added concern to the reviewers was the score that defined an event did not have to be assigned based on a direct assessment conducted during a clinic visit, but could also be assigned based on a telephone visit, caregiver assessment, or upon the basis of a non-investigator clinical report from a hospitalization. These assessments could be made in a retrospective fashion (including discussion with a clinician that may have evaluated the patient during an episode). Similar concerns were raised about how reliably the Conn scores that established a patient's eligibility for the study were assigned.

Multiple analyses of efficacy are presented in the briefing document. The majority of the analyses were not included in the Applicant's pre-specified Multiplicity Adjustment Strategy for testing key secondary endpoints. It is important to note that the p-values and confidence intervals reported corresponding to these additional analyses are presented with no adjustment for multiplicity. These nominal p-values and confidence intervals are presented as part of the overall exploratory assessment of the efficacy of Xifaxan and are not viewed as providing evidence of efficacy.

It is difficult to conduct clinical trials in this population and it is important that the data collected in this development program be analyzed thoroughly and thoughtfully. The principal efficacy issue confronting the Division in the evaluation of this application is whether the totality of the submitted data constitutes sufficient evidence that permits a conclusion that a clinically meaningful effect of Xifaxan in reduction of recurrence of HE events in a population of patients with a history of HE related to underlying liver disease has been established.

An important issue is the risk/benefit assessment. Xifaxan is an antibiotic for which the proposed use is chronic. Although its absorption is low in healthy volunteers, pharmacokinetic studies in patients with hepatic impairment demonstrate that systemic absorption is higher in this population. The placebo-controlled safety data are limited to the 6 months of the randomized, controlled trial. The reviewers identified a possible increase in hepatic events in the patients treated with Xifaxan, but this finding was

difficult to interpret in light of the small number of events and the relatively small size of the clinical trial. The hepatic events in the open label safety study cannot be interpreted because the natural history of the disease involves progression of hepatic dysfunction

In the randomized controlled trial the overall numbers of serious and common adverse events were similar in both the treatment and placebo groups. The SAE of infection was higher in the Xifaxan group, due mainly to increase incidence of pneumonia and *C. difficile* colitis (Table 37 in Clinical Review), as were SAEs in the categories Gastrointestinal disorders and General Disorders (edema and pyrexia).

Analysis of mortality by Child's class, showed some increase in mortality in the Child's C patients (a small subset of the total study population) in the Xifaxan group, but the small number of observations does not permit conclusions. There were deaths in the Xifaxan arm that the reviewer considered possibly related to Xifaxan, and these are discussed in detail in the safety section of the clinical review.

To help the Division address these issues, the Committee will be asked to provide their responses to the following questions. (Please be advised that these are draft questions, which may be subject to some revision prior to the time of the Committee Meeting.)

DRAFT QUESTIONS FOR THE COMMITTEE

EFFICACY:

1. How should remission be defined in overt episodic hepatic encephalopathy (HE)?
2. In clinical trials conducted to support approval of products for **decreasing the risk** of developing of episodes of overt HE, what clinically meaningful endpoints should be evaluated (as primary and key secondary endpoints) and how should they be measured?
3. In clinical trials conducted to support approval of products developed for the **treatment** of HE, what clinically meaningful endpoints should be evaluated (as primary and key secondary endpoints) and how should they be measured?
4. Study RFHE3001 enrolled a patient population in which 2/3 of patients had a baseline Conn Score of 0 and 1/3 had a baseline Conn Score of 1. The study evaluated time to breakthrough HE event as defined by the increase in Conn Score ≥ 2 or increase in Conn Score of 1 and increased asterixis grade by 1.
 - a. Does an increase in time to breakthrough HE event, so defined, constitute reduction in the risk of developing episodes of overt HE?
 - b. Do increases in time to breakthrough HE events (as defined above) represent clinical benefit? Please identify the specific benefit.
5. Do the clinical data in the Xifaxan application provided substantial evidence of efficacy for decreasing the risk of developing episodes of overt HE?
 - a. If yes, which clinical data provided substantial evidence of efficacy? Specifically, which endpoints?
 - b. If no, what are the deficiencies in the clinical data that make you consider the evidence to be less than substantial?
 - c. Are there additional analyses or trials you feel should be conducted?

SAFETY:

6. Has the safety of Xifaxan at the proposed dose and duration been adequately assessed in cirrhotic patients with a history of HE? If not, what additional analyses or trials are needed? In answering this question consider the adequacy of the submitted safety data addressing the following:
 - a. Child's Class C patients
 - b. Risk for development of resistant bacteria
 - c. Cardiac safety i.e., potential for QT prolongation
 - d. Risk for *C. difficile* colitis

7. Is the safety of Xifaxan at the proposed dose and duration acceptable in cirrhotic patients with a history of HE?

RISK/BENEFIT ASSESSMENT:

8. In light of the safety and efficacy data presented in this application, do you feel the risk benefit profile supports approval of Xifaxan for decreasing the risk of developing episodes of overt HE?

CLINICAL REVIEW

Application Type	Type 6 (parent NDA 021-361) 505(b)(1)
Application Number(s)	NDA 22-554
Priority or Standard	Priority
Submit Date(s)	June 24, 2009
Received Date(s)	June 24, 2009
PDUFA Goal Date	March 24, 2010 (after major amendment clock extension)
Division / Office	Division of Gastroenterology Products
Reviewer Name(s)	Lara Dimick, M.D., F.A.C.S.
Review Completion Date	
Established Name	Xifaxan®
(Proposed) Trade Name	Rifaximin
Therapeutic Class	Miscellaneous class semi- synthetic antibiotic derived from rifamycin
Applicant	Salix Pharmaceuticals, Inc.
Formulation(s)	Immediate release tablet
Dosing Regimen	550mg orally twice per day
Indication(s)	Maintenance of remission of Hepatic Encephalopathy (HE) in patients 18 years of age and

Intended Population(s)	older Patients with cirrhosis or portal hypertension and history of Hepatic Encephalopathy
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1 Executive Summary

1.1 Statement of Purpose

This background package is prepared to present the FDA's evaluation of the New Drug Application for Rifaximin for the proposed indication of maintenance of remission of hepatic encephalopathy (HE) to the members of the Gastrointestinal Drugs Advisory Committee (GIDAC). In the meeting we will ask the committee to assess the strength of the evidence submitted to support marketing approval of rifaximin for this indication. We will also ask for input on the need for additional studies or clinical trials before or after marketing.

1.2 Clinical Summary

The rifaximin tablet 550 mg strength is a new strength of the currently approved XIFAXAN® (rifaximin) Tablets, 200 mg XIFAXAN tablets, which are approved for the treatment of patients (≥ 12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli*. The 550 mg tablets were developed by Salix Pharmaceuticals, Inc. (Salix), for the proposed indication of maintenance of remission from hepatic encephalopathy (HE) in patients' ≥ 18 years of age. The proposed dose for this indication is one 550 mg tablet administered orally two times a day. The drug is intended to be used long term.

Rifaximin is a poorly absorbed, oral antibiotic derived from rifamycin, which has a broad spectrum of activity against Gram-positive and Gram-negative, aerobic, and anaerobic enteric bacteria.

The clinical efficacy of rifaximin for the maintenance of remission of HE is based on results from the single double-blind, placebo-controlled study RFHE3001. Additional safety data for this indication is provided from the open-label study RFHE3002. The Applicant also submitted study reports from trials in patients hospitalized with overt HE in an effort to provide support for the maintenance of remission indication, and publications describing rifaximin use in overt HE over durations of more than 6 months.

1.2.1 Efficacy Summary

The primary efficacy parameter for the double-blind, placebo controlled study RFHE3001 was the occurrence of an episode of breakthrough overt HE during treatment. Reduction of breakthrough HE episode in the rifaximin group was observed in the analysis of the primary efficacy endpoint, time to first breakthrough with an overt HE episode. Breakthrough overt HE episodes were experienced by 31 of 140 subjects in the rifaximin group and by 73 of 159 subjects in the placebo group during the 6-month

treatment period. The hazard ratio for the risk of experiencing breakthrough overt HE in the rifaximin group relative to the risk in the placebo group was 0.421 with a 95% CI (0.276, 0.641), $p < 0.0001$, during the 6-month treatment period, indicating a 57.9% reduction in risk of breakthrough.

In RFHE3001, analysis of the prespecified important secondary endpoint time to first HE-related hospitalization (19 rifaximin; 36 placebo) (i.e., hospitalization directly resulting from HE [15 rifaximin; 29 placebo] or hospitalization complicated by HE [4 rifaximin; 7 placebo]) demonstrated a reduction in risk of HE related hospitalization in the rifaximin group, when compared with placebo, during the 6-month treatment period; hazard ratio of 0.500, 95% CI (0.287, 0.873), $p = 0.0129$. Hepatic encephalopathy-related hospitalizations were reported for 19 of 140 subjects and 36 of 159 subjects in the rifaximin and placebo groups, respectively.

Although the analysis of the primary endpoint appeared statistically significant in this single study, the FDA reviewers raised concerns about the interpretability of the observed outcome of this study. The primary endpoint is subjective and hinges on observer evaluation of subtle differences in neurologic function. There were review concerns regarding the ability to consistently apply the West Haven-Conn score in this study. Patients had to have a Conn score of 0 to 1 at study entry and needed only to shift to Conn score 2 to be defined as having an HE event. It is unclear whether clinicians can consistently and uniformly delineate between a Conn score of 1 and 2. In addition, the study allowed for Conn scores to be assigned not by direct observation but based on information provided by caregivers and patients during telephone contacts or from information obtained from hospitalizations.

In the rifaximin group, 8 patients were determined to have breakthrough episodes of hepatic encephalopathy based on direct observation by study site personnel, while 22 patients were diagnosed to have such episodes by indirect means; thus, only 27.7% of patients in the treatment group diagnosed with breakthrough episodes of hepatic encephalopathy had that determination made by direct observation. In the placebo group, 30 patients were determined to have breakthrough episodes of hepatic encephalopathy based on direct observation, while 40 patients were diagnosed to have such episodes by indirect means; thus, in the placebo group a higher proportion of the events, 42.9%, were diagnosed by direct observation. This is summarized in the table below.

Table 1: Method of Diagnosing Breakthrough Hepatic Encephalopathy

	Placebo N = 70	Rifaximin N = 30	Total N = 100
Direct (at site)	30 (42.9%)	8 (27.7%)	38 (38.0%)
Indirect Hospitalized	19 (27.1%)	12 (40.0%)	34 (34.0%)
Indirect - Other	21 (30.0%)	10 (33.3%)	28 (28.0%)

Of patients with data available from the breakthrough HE page of the CRF (3 placebo and one rifaximin patients with missing data)

Analysis of whether indirect diagnosis was made at the hospitalization (Breakthrough HE Hospitalization), which would imply diagnosis was made by observation of a clinician, although not the investigator, approximately 30% of patients in each group (33.3% in Rifaximin and 30.0% in Placebo) were diagnosed neither with clinician observation in a hospital visit nor an evaluation by an investigator during a site visit.

The Division of Neurology Products consult review concluded that the report of Study RFHE3001 did not provide enough evidence to establish that rifaximin is efficacious, based on the primary endpoint and the limitations of its assessment in this study. Please refer to the neurology review under Tab 3 of this briefing document.

Significance tests were conducted for all secondary efficacy endpoints using a pre-specified hierarchical analysis. Results of this significance testing were reported in the pre-specified hierarchical order, from endpoint number 1 through number 5, until a non-significant p-value was encountered ($p > 0.05$), which consequently classified all subsequent significance tests as exploratory in nature. The nominal p-values and confidence intervals for multiple additional analyses are presented as part of the overall exploratory assessment of the efficacy of rifaximin and are not viewed as providing evidence of efficacy. From the statistical standpoint, the analysis of the numerous additional endpoints and their varied *post-hoc* analyses can not provide evidence of a positive treatment effect.

An observation to note in the review was that exploration of the efficacy results reveals that Months Two through Four are the major contributors to the overall six month results.

1.2.2 Safety Summary

The important safety data for rifaximin in the maintenance of remission of HE comes from the **Primary Analysis Population**, which is defined by the Applicant as the patients in studies RFHE3001 and RFHE3002. In addition, there are some safety data for rifaximin in the **Secondary Analysis Population**, which is defined by the Applicant as the patients with active HE treated with rifaximin in acute short-term interventional

trials (up to 15 days). Safety data for rifaximin were also provided from the **Supportive Analysis Population**, which is defined by the Applicant as patients treated with rifaximin in trials for other indications (e.g., treatment/prevention of travelers' diarrhea, irritable bowel syndrome). The Applicant also submitted post-marketing surveillance data, and safety information from published literature for rifaximin used in the interventional treatment of subjects with active HE. The Secondary and Supportive data are from short term use, and do not add significantly to the over all conclusions.

The Primary Analysis Population is divided into the **Randomized Controlled Trial (RCT) Population** (exposure during the 6 month RCT) and the **Long Term Rifaximin Experience Population**. The latter is further subdivided into Continuing Rifaximin (from RFHE3001), New Rifaximin, and All Rifaximin Populations for the purpose of analysis. The Continuing Rifaximin population consists of patients from RFHE3001 who received treatment with rifaximin, on the RCT, and elected to continue on rifaximin in the treatment extension study (RFHE3002). The New Rifaximin population consists of placebo patients from RFHE3001 and new patients who enrolled in RFHE3002.

The Primary Analysis Population included 336 subjects with a mean exposure of 273.8 days (SD 160.92). Subjects exposed to rifaximin at the proposed dose for 6 months or longer totaled 257. Exposure to rifaximin at the indicated dose for 12 months or longer totaled 114 subjects. There were a low percentage of subjects with MELD scores above 18 (8-9%) in the data set, which makes meaningful evaluation of subjects with severe hepatic impairment difficult. No subjects with MELD Scores above 25 enrolled in these trials.

The rates of adverse events were high in this population of chronically ill patients. The most frequent adverse events were gastrointestinal. In the randomized controlled trial (RCT) Study population, the proportion of subjects with Treatment Emergent Adverse Events (TEAEs) was similar between subjects receiving rifaximin (80.0%) and placebo (79.9%). The rate of SAEs, however, was higher in the rifaximin group. The SAE of infection was higher in the Xifaxan group, due mainly to increase incidence of pneumonia and *C. difficile* colitis (Table 37). In the Primary Analysis Population there were 546 serious adverse events (SAE) occurring in 63 (39.6%) of placebo subjects and in 165 (49.1%) of All Rifaximin Subjects, including breakthrough HE episodes. The most frequent serious adverse events were hepatic cirrhosis, ascites, esophageal varices hemorrhage, acute renal failure, and pneumonia (excluding HE episodes that were SAEs due to hospitalization).

In the **Primary Safety Population** the mortality rate was 7% in both the treatment and placebo groups. In the **Long Term Rifaximin Experience Population**, a total of 36 subject deaths (10.7%) were recorded for All Rifaximin, inclusive of 10 rifaximin treated subjects who died during the RCT Study. The majority of deaths in both the placebo group and the rifaximin group appear to have been related to worsening hepatic function and underlying disease progression. Esophageal variceal hemorrhage was the

second most common SAE resulting in death. Analysis of mortality by Child's class showed some increase in mortality in the Child's C patients in the rifaximin group, but numbers were too small to permit conclusions. There were deaths in the rifaximin treatment arm that the reviewer considered possibly related to rifaximin, which are discussed in detail In Section 7.3.1.

Post marketing surveillance events of anaphylactic reactions and cases of rifaximin-induced *C. difficile* colitis have been reported (including one death). Two (2) events of clostridium colitis (*C. difficile*) occurred in rifaximin-treated subjects in the RCT Study and 3 additional TEAEs of clostridium colitis were recorded in the open-label RFHE3002 study.

The safety concerns noted in the FDA review include:

- The Applicant did not gather follow-up data on patients who developed adverse events. The subjects were dropped from the study at the time of an adverse event that prompted withdrawal of the drug or if the subjects developed HE. Data on the length of hospitalization for HE events were not captured.
- There is a history of hepatotoxicity in cirrhotic patients taking drugs from this class (Rifampin). While rifaximin is poorly absorbed, pharmacokinetic studies indicate higher systemic exposures in this patient population with hepatic impairment. Evaluation of the data for hepatotoxicity in this dataset is confounded by the underlying liver disease in these patients. However, there were two deaths in the rifaximin group from progressive liver disease in patients with relatively low MELD scores at study entry. See Section 7.3.1.
- There are not adequate efficacy and safety data on use of rifaximin in Child's-Pugh Class C patients and/ patients with MELD scores above 25. This group of patients was excluded from these studies. Because they would be at high risk for development of HE, one would anticipate that the product will be used in this population if approved for the proposed indication.
- Thorough QT study was not performed and ECGs were not performed in the phase 3 trials.
- Pharmacokinetic trials have been not performed in renally impaired patients. Renal insufficiency is common in this population. The combination of renal and hepatic impairment could have an additive impact on increasing drug exposure in this population.

2 Introduction and Regulatory Background

Rifaximin was approved under the trade name Xifaxan®, NDA 21-361, by the Division of Special Pathogens for the treatment of traveler's diarrhea in patient's ≥ 12 years of age. The current application is submitted as an efficacy supplement, 505(b)(1) to the Division of Gastroenterology Products for the proposed orphan indication of the maintenance of remission of Hepatic Encephalopathy (HE) in patients 18 years of age and older. Rifaximin has been granted a Priority Review as there are no other approved drugs for this indication.

2.1 Product Information

Rifaximin Tablets are an immediate release solid dosage for oral administration. Each tablet contains 550 mg of rifaximin, a semi-synthetic, poorly absorbed antibiotic. Rifaximin Tablets, 550 mg are a new strength of rifaximin using the same formulation as the currently approved Xifaxan® (rifaximin) Tablets, 200 mg, which is indicated for traveler's diarrhea. The proposed dosage and administration is one 550 mg tablet administered orally two times a day (total daily dose 1100mg/day). The 200mg tablet formulation of rifaximin that was approved under NDA 21-361 on May 25, 2004, uses the identical drug substance as that in the new rifaximin 550 mg tablet dosage form.

The proposed indication for rifaximin 550mg twice daily is for maintenance of remission of hepatic encephalopathy (HE) in patient's ≥ 18 years of age.

2.2 Tables of Currently Available Treatments for Proposed Indications

The treatment of hepatic encephalopathy requires first evaluating and eliminating precipitating factors for HE and other causes of neurologic dysfunction (see Table 1). There are no drugs currently approved for the "maintenance of remission of HE".

Lactulose, a poorly absorbed disaccharide, is approved "for the prevention and treatment of Portosystemic encephalopathy including the stages of hepatic coma and pre-coma. Controlled studies have shown that lactulose solution therapy reduced the blood ammonia levels by 25 to 50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in 75% of patients, which is as least as satisfactory a that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose therapy. In the treatment of chronic portal-systemic encephalopathy, lactulose has been given for over 2 years in controlled trials". Lactulose dosing is limited by the adverse effect of diarrhea.

Neomycin is approved for “adjuvant therapy in the treatment of hepatic coma by reduction of the ammonia forming bacteria in the intestinal tract. The subsequent reduction in ammonia has resulted in neurologic improvement”. However neomycin can only be used short-term due to nephrotoxicity and ototoxicity.

Metronidazole is another antibiotic frequently used to treat or prevent hepatic encephalopathy, (but not specifically approved for this indication). It is not well tolerated long-term secondary to GI side effects (see Table 2). Other aminoglycoside antibiotics have been used in the past, but are currently not recommended because of increased toxicity seen in liver failure patients. There are also other therapies currently under investigation for the treatment of this disorder (see Table 3).

Table 1: Common Precipitating Factors and Concurrent Causes of Encephalopathy

Intracranial hematomas, cerebral vascular accident
Encephalitis
Thyroid dysfunction
Hypoglycemia
Hypoxia, Hypercapnia
Drug intoxication (sedatives, narcotics, psychotropic drugs, alcohol)
Dehydration (fluid restriction, diuretics, diarrhea, vomiting, paracentesis)
Acidosis, Alkalosis
Sepsis, fever (spontaneous bacterial peritonitis)
Uremia, Azotemia
Hypotension/hypovolemia (GI bleed, shock, peripheral vasodilatation)
Excessive protein intake (protein restriction no longer recommended)
Constipation
Acidosis, alkalosis
Electrolyte imbalance (Hyponatremia, Hypokalemia, Mn and Zn deficiency)
Anemia (GI bleed, chronic)
Surgery (multifactorial)

Table 2: Drugs used to Treat or Prevent Hepatic Encephalopathy

Drug name	Drug class	Indication	Side Effects	Mechanism
Lactulose	Poorly absorbed disaccharide	-Prevention and Treatment of portal-systemic encephalopathy -Decrease blood ammonia concentration	Diarrhea limits dose Dosage titrated to number of bowels movements Sweet taste	Lowers plasma levels of ammonia by changing nitrogen metabolism in colonic flora and increasing fecal excretion of nitrogen.
Metronidazole	Antibiotic	No indication for HE	GI upset bad taste	acts indirectly by inhibiting the metabolism of urea by deaminating bacteria, thus reducing the production of ammonia and other potential toxins
Neomycin	Aminoglycoside antibiotic	Adjuvant therapy in hepatic coma	Cannot be used long-term due to Neuro- and Nephrotoxicity	Same as above
Vancomycin & Paromomycin	Aminoglycoside antibiotic	No indication for HE	Cannot be used long-term due to Neuro- and Nephrotoxicity	Same as above

Table 3: Therapies under Investigation for the treatment of HE

Investigational Therapy	Rational
Probiotics, Symbiotics	Altering the colonic flora-particularly, reducing urease-producing bacteria and promoting the growth of non-urease-producing species
Acarbose	Lowers postprandial glucose and increases polysaccharide in gut and alters gut flora
Acetyl- <i>L</i> -carnitine	May lower blood ammonia levels by enhancing metabolic energy production and promoting ureagenesis
Sodium benzoate, sodium phenylacetate	“Ammonia trapping” principle and reduces serum ammonia levels by combining with it to form hippuric acid, which is then excreted in the urine
Liver-support devices	Employ extracorporeal circulation through an artificial liver support principle, consisting of viable cells or extraction/filtration equipment, primarily in patients with acute HE and cerebral edema associated with fulminant hepatic failure
Ornithine aspartate	Reduces ammonia levels by increasing hepatic ammonia disposal and its peripheral metabolism
Bromocriptine	Modifies central neurotransmitter balance
Flumazenil	Acts as agonist at the benzodiazepine receptors of central type

2.4 Important Safety Issues with Consideration to Related Drugs

Refer to Section 7.2.6

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 4: Regulatory Activity

Date	Activity	Purpose	Agenda
Feb. 10, 1998	Granted orphan status	-	-
Oct 14, 1999	IND submitted	Maintain remission HE	-
Dec. 13, 2004	Type C meeting	Clinical Development plan	Primary end-point discussion
Nov. 14, 2007	Type C meeting	Design of PK studies	FDA recommends PK studies in all three Childs' classes
Dec. 16, 2008	Type B meeting	Pre-NDA	End-point and protocol issues discussed

In accordance with the Pediatric Research Equity Act (PREA), the Applicant is not required to submit a pediatric assessment when the drug is an orphan-designated indication.

2.6 Other Relevant Background Information

Hepatic encephalopathy, also known as hepatic coma or portal-systemic encephalopathy (PSE) is a serious, rare, complex, episodic, neuropsychiatric syndrome associated with advanced liver disease. HE may occur at any age, but the peaks parallel those of fulminant liver disease (peak = 40's), and cirrhosis (peak = late 50's). Both genders are affected in roughly equal proportions, reflecting the underlying liver disease. Hepatic encephalopathy may be associated with acute liver failure, portal-systemic bypass with no intrinsic hepatocellular disease, or cirrhosis and portal hypertension with portal-systemic shunting of blood. Hepatic encephalopathy associated with the latter is most common.

Hepatic encephalopathy is manifested as a continuum of mental status deterioration, psychomotor dysfunction, impaired memory, increased reaction time, sensory abnormalities, poor concentration, disorientation, and coma. Changes may be observed in personality, consciousness, behavior, and neuromuscular function. Neuromotor signs may include hyperreflexia, rigidity, myoclonus, and asterixis (a coarse, myoclonic "flapping" muscle tremor). The clinical diagnosis of overt HE in subjects with advanced liver disease and portal-systemic shunting is based on two concurrent types of symptoms: impaired mental status (as generally defined by Conn Score) and symptoms of impaired neuromotor functioning (asterixis). See Table 5 and Table 6.

Table 5: Conn Score – West Haven Criteria

Conn score 0	No personality or behavioral abnormality detected
Conn score 1	Trivial lack of awareness, euphoria or anxiety; shortened attention span; impairment of addition or subtraction.
Conn score 2	Lethargy; disorientation for time; obvious personality change; inappropriate behavior.
Conn score 3	Somnolence to semi-stupor, responsive to stimuli; confused; gross disorientation; bizarre behavior.
Conn score 4	Coma; unable to test mental state

Table 6: Asterixis Grade

Grade 0	No tremors
Grade 1	Rare flapping motions
Grade 2	Occasional, irregular flaps
Grade 3	Frequent flaps
Grade 4	Almost continuous flapping motions

Recurrent, overt, episodic HE (see definition and nomenclature, below) is common among patients with liver cirrhosis. There is an association between mortality and a history of overt HE episodes. In patients with liver cirrhosis and a history of recurrent, overt HE episodes, survival probability was 42% at 1 year, and 23% at 3 years after experiencing an HE episode.¹ In another analysis, the occurrence of an HE episode of Conn score 2 in patients with cirrhosis was reported to be associated with a 4-fold increase in the risk of death².

The etiology and pathogenesis of HE are not known. The main tenet for the postulated pathogenesis of HE is that nitrogenous substances derived from the gut adversely affect brain function. These compounds gain access to the systemic circulation as a result of decreased hepatic function or portal-systemic shunts. Once in brain tissue, the compounds produce alterations of neurotransmission that affect consciousness and behavior. The most important of these compounds is thought to be ammonia, a byproduct of protein digestion that is normally detoxified by the liver. However, correlation of serum ammonia levels with mental state in cirrhosis is inconsistent, in part, because the blood-brain barrier permeability to ammonia is increased to a variable extent in this population. Brain ammonia levels in patients with HE have been reported to adversely affect both excitatory and inhibitory central nervous system (CNS) neurotransmission, and metabolism³.

The neurological symptoms of HE are attributed to global CNS depression from nitrogenous compounds that result in excitation of gamma-aminobutyric acid (GABA) and decreased neurotransmission of glutamate. Other gut-derived toxins have also been implicated. Some of these neurotoxins also accumulate and alter CNS function, including mercaptans, phenols, manganese, short chain fatty acids, bilirubin and a variety of neuroactive medications⁴.

Overt HE episodes can be precipitated by comorbid conditions or may be precipitated by unknown reasons (i.e., spontaneous). Known factors that precipitate or contribute to the occurrence of an overt HE episode (i.e., concomitant comorbid conditions) include azotemia; sedatives, tranquilizers, or analgesics; gastrointestinal (GI) bleeding; dietary protein; metabolic alkalosis; infection; constipation; dehydration; and porto-caval bypass surgery, or TIPS (Transjugular Intrahepatic Portosystemic Shunt) procedure, which also increases portal-systemic shunting of blood⁵.

Hepatic encephalopathy has been classified into 3 types (A, B, or C). Hepatic encephalopathy associated with cirrhosis is categorized as type C and further subcategorized based on the duration (episodic versus resistant/persistent) and intensity (overt versus minimal) of neurological symptoms (see Table 8 below).

Table 8: Categorization of Hepatic Encephalopathy

Type	Description	Subcategory	Subdivision
A	Encephalopathy associated w/ acute liver failure		
B	Encephalopathy associated w/ portosystemic bypass, no intrinsic hepatocellular disease		
C	Encephalopathy associated w/ cirrhosis or portal hypertension/portosystemic shunts	Overt, episodic HE	Precipitated Spontaneous Recurrent(relapsing)
		Persistent HE	Mild Severe Tx dependent
		Minimal HE	

In persistent HE, subjects do not experience complete remission of neurological symptoms. In recurrent, overt, episodic HE, which is the most common subcategory, patients experience episodes of neurological dysfunction, which can last for several hours up to several days, followed by remission to baseline neurological function. The severity of overt, episodic HE is characterized by clinical symptoms of mental status deterioration as defined by Conn (see Table 6) and the presence of neuromotor disturbances such as asterixis (see Table 7). Eligible subjects in Study RFHE3001 were reported to have recurrent, overt, episodic, Type C hepatic encephalopathy. The primary efficacy parameter for trial RFHE3001 was based on Conn score assessments and asterixis assessments.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This NDA was submitted as paper in CTD format. The Applicants Case Report Forms (CRF) did not contain the complete neuropsychiatric evaluations necessary to adequately confirm the Conn score assignments made. Physical exam data in the CRF's are scant and poorly documented (i.e. the degree of ascites). The Applicant did not follow up on many of the pertinent details needed for a complete safety evaluation. When patients became ill and hospitalized they were dropped from the trial. Medical records or laboratory reports were not obtained.

3.2 Compliance with Good Clinical Practices

Alfa Wassermann, the product innovator, conducted the majority of nonclinical studies of rifaximin in the 1980s, and several studies were conducted prior to the implementation of GLP standards in 1986. Salix has conducted long-term carcinogenicity studies to examine rifaximin use for proposed indications with long-term use. Thus, the non-clinical studies include earlier studies and later GLP-compliant studies.

The clinical trials appeared to be conducted in accordance with acceptable ethical standards and appropriate informed consent. There were no issues identified with protocol violations or site inspections. Site selection for investigation and verification by DSI was complicated by the large number of sites (70), all with low numbers of patients. Fifty-one sites were in the United States, 5 in Canada and 14 in Russia. The Russian sites accounted for 27% of the randomized subjects, but reported low incidence of adverse events and longer times to breakthrough hepatic encephalopathy. The reviewers requested evaluation of 5 sites, the two largest in the United States and three sites in Russia (the Highlighted rows in Table 7 below). Inspection of sites 876, 754 or 478 was not requested because the AE rates are in line with the overall percentage of patients and the observed Times to Breakthrough Hepatic Encephalopathy (TBTHE) were relatively short. The 3 sites in Russia and two in California examined by DSI were found acceptable to support the NDA. Although minor issues were noted at Dr. Poordad's and Dr. Gorbakov's sites, the findings are unlikely to impact data integrity.

Table 7: Site Evaluation – Trial RFHE3001

Site ID	Investigator Location	% Pts. (N)	Deaths	% AE	Time to breakthrough HE (days) (TBTHE)				
					Mean	STD	Median	Min.	Max.
351	Fred Poordad Los Angeles, CA USA	5% (15)	2	7.1	190	137.0	169.0	57	555
799	Muhammad Sheikh Fresno, CA USA	4.6% (14)	0	3.2%	165.2	74.0	169.0	29	366
876	Ravikumar Vemuru Odessa, TX USA	4.0% (12)	0	4.7	133.7	64.6	167.5	11	177
938	Olga Alexeeva Nizhny Novgorod, Russia	4% (12)	0	1.0	115	61.8	142.0	13	170
754	Benedict Maliakkal Rochester, NY USA	3.3% (10)	1	3.4	130.8	96.8	130.0	13	349
905	Valadimir Gorbakov Moscow, Russia	3.3% (10)	1	0.44	162.5	34.8	169.0	66	190
478	Kimberly Beavers Ashville, NC USA	3.0% (9)	1	2.0	99.0	64.8	104.0	7	172
894	Vladimir Rafalsky Smolensk Russia	3% (9)	0	0.44	169.4	2.5	169.0	168	176
Data Summary By Country									
	USA	68.5 205	6	77.2	130.4	85.4	168.0	3	555
	Russia	26.7 (80)	3	12.5	147.5	45.7	169.0	13	206
	Canada	4.6 (14)	0	10.2	94.1	65.5	79.5	9	177
Overall Data Summary									
	Rifaximin	140			146.6	72.3	169	5	555
	Placebo	159			121.6	78.6	167	3	457
	Total	299	9		133.3	76.6	168	3	555

3.3 Financial Disclosures

There were no significant financial conflicts of interest identified.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no review issues identified regarding the manufacturing of the product.

4.2 Clinical Microbiology

The Applicant submitted information for review in support of the proposed content of the microbiology section of the labeling. The Division of Special Pathogens and Transplant Products performed a microbiology review. They found the publications included for review do not support the applicant's proposed changes to the microbiology section of the rifaximin labeling (refer to the Microbiology Review). The three articles describing in-vitro studies were insufficient due to lack of information regarding specific methodology. Two clinical trials for short-term use in the treatment of Traveler's Diarrhea did not compare the rate of pathogen eradication between rifaximin and an aminoglycoside, nor did either study correlate such changes with significant alteration of gut flora or describe a unique mechanism of action.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology-Toxicology Reviewer reported the following:

The Applicant has conducted a full battery of nonclinical studies, which included repeat-dose toxicology studies of up to 26-weeks in rats and 39-weeks in dogs. The pharmacokinetic data from a 26-week oral toxicity study in rats and a 39-week oral toxicity study in dogs show that rifaximin has variable, but low systemic absorption.

Over the course of drug development, chronic oral toxicity studies in rats and dogs were performed in duplicate. There were discrepancies in toxicity, specifically in the histopathology results (primarily in the small intestine and liver), between duplicate studies in each of the species. There is no obvious explanation for these conflicting results, because toxicity was not correlated with dose levels between studies in the same species. Although absorption of rifaximin is minimal, one possible explanation for the discrepancies in the toxicity studies may be a variation in plasma exposure between the different studies.

The AUC values that occurred in the toxicity studies (42 to 127 ng·hr/ml) were generally lower than the mean AUC observed in cirrhotic patients (130 ng·hr/ml with a range from 28 to 359 ng·hr/ml). Therefore, the toxicity studies in animals do not provide assurance of safety for the use of rifaximin in cirrhotic patients.

The Applicant conducted an *in vitro* study to test the effects of rifaximin on the hERG potassium channels expressed in human embryonic kidney cells. Rifaximin concentrations of $\geq 30 \mu\text{M}$ had a statistically significant increase in inhibition of the hERG channel. The IC_{50} for the inhibitory effect of rifaximin on hERG potassium current was estimated to be $30 \mu\text{M}$.

The Applicant conducted carcinogenicity studies in rats and mice. The incidence of malignant schwannomas in the heart showed a statistically significant positive dose response relationship in male rats. Although none of the pair wise comparisons were statistically significant, the incidence of these tumors in high dose rats (5 %) was outside the range of the historical control data provided (up to 1.7 %). In the Tg.rasH2 mouse carcinogenicity study, there was no dose response by trend analysis for any tumor type, and tumor incidences were comparable to historical control data.

It should be noted that the pre-clinical studies submitted by the Applicant, are limited in their ability to provide meaningful information about the potential systemic toxicity of rifaximin, as all the studies were done in healthy animals where the absorption of orally administered rifaximin was minimal.

4.4 Clinical Pharmacology

See Clinical Pharmacology Review Summary - Tab 4.

4.4.1 Mechanism of Action

Rifaximin binds to the beta-subunit of the bacterial DNA dependent RNA polymerase, resulting in inhibition of bacteria protein synthesis. Rifaximin is practically insoluble in water and poorly absorbed after oral administration, thus it is intended to be used locally to treat disease conditions where the desired site of action is the gastrointestinal tract.

4.4.2 Pharmacodynamics

See Clinical Pharmacology Review Summary - Tab 4.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant submitted results from one placebo-controlled, randomized, phase 3 clinical trial, RFHE3001. The results of this trial will be reviewed in depth in Section 6 - Efficacy Review. They also submitted one open-label, single arm, treatment extension trial, RFHE3002. These data will be reviewed in Section 5.3 and in Section 7: Safety Review.

The Applicant also submitted a report of one phase 2 trial and two phase 3 trials performed to evaluate rifaximin for the **treatment** of Hepatic Encephalopathy. (See Sections 5.3 and 7) All three trials were small and varied in design. It should be noted that the phase 2 dose ranging trial failed to elucidate a dose relationship for the main objective parameters. Both of the Phase 3 **treatment** trials failed on the primary endpoint.

The remainder of the trials submitted in support and listed in Table 8 was conducted for other indications. They are relevant only as part of the integrated safety data in Section 7.

Table 8: Studies/Clinical Trails

Study ID	Trial Type	Trial Design	Number Centers	Number subjects	Dosage	Duration
Primary integrated analysis - Rifaximin for the maintenance of remission of HE						
RFHE3001	Efficacy Pivotal Phase 3	Randomized, placebo controlled, double blind pts w/ HE	70	299 RFX: 140 Placebo:159	RFX 550mg bid or placebo	6 months
RFHE3002	Safety Phase 3	Open label, Tx extension Pts w/ HE	70	267 From3001:152 New:115	RFX 550mg bid	On-going, 2 years
Secondary Supportive Trials – Rifaximin for the Acute Treatment of overt HE						
RFHE9701	Efficacy and Safety Phase 3	Randomized, active control Blinded Pts w/ HE		103 RFX: 50 Lactitol:53	RFX 400mg t.i.d or lactitol	5-10 days
RFHE9702	Efficacy and Safety Phase 2	Randomized, dose finding Pts w/ HE		54 RFX 200mg tid:18 RFX 400mg tid:19 RFX 800mg tid:17	RFX 200mg t.i.d, 400mg t.i.d or 800mg t.i.d	7 days
RFHE9901	Efficacy and Safety Phase 3	Randomized, placebo controlled, pts w/ HE & intol. to lactulose		93 RFX: 48 Placebo: 45	RFX 400 t.i.d or placebo	14 days
Supportive Trials–Rifaximin for the Treatment of Traveler’s diarrhea						
RFID9601	Efficacy and safety Phase 3	Randomized, active control, parallel group, blinded, dose ranging	Multi – center Mexico	72 RFX 200mg: 18 RFX 400mg: 18 RFX 600mg: 19 TMP/SMX: 17	RFX 200mg, 400mg, or 600mg t.i.d TMP/SMX 160/800mg b.i.d	5 days
RFID9701	Efficacy and safety Phase 3	Randomized, active control, parallel group, blinded	Multi-center Mexico and Jamaica	187 RFX: 93 Cipro: 94	RFX 400mg bid Cipro 500mg bid	3 days
RFID9801	Efficacy and safety Phase 3	Randomized, comparative, parallel group, blinded	Multi-center Mexico, Kenya, Guatemala	379 RFX 200mg: 124 RFX 400mg: 126 Placebo: 129	RFX 200mg or 400mg t.i.d or placebo	3 days
RFID3001	Efficacy and safety Phase 3	Randomized, placebo and active control, parallel group, blinded	Guatemala India Mexico Peru	399 RFX: 199 CIPRO: 100 Placebo: 100	RFX 200mg t.i.d Cipro 500mg bid Placebo	3 days

Study ID	Trial Type	Trial Design	Number Centers	Number subjects	Dosage	Duration
Supportive Trials in Rifaximin for the Prevention of Traveler's diarrhea						
RFID2001	Efficacy and safety Phase 2	Randomized, placebo control, blinded, prophylactic use in subjects challenged with <i>shigella flexneri</i>	Single center US	25 RFX: 15 Placebo: 10	RFX 200mg t.i.d	3 days
RFID3003	Efficacy and safety Phase 3	Randomized, placebo control, blinded, prophylactic use in healthy subjects traveling to Mexico		210 RFX: 106 Placebo: 104	RFX 600mg daily or placebo	14 days
RFID3004	Efficacy and safety Phase 3	Randomized, placebo control, blinded, prophylactic use in healthy subjects traveling outside the US	Multi-center	133 RFX: 107 Placebo: 26	RFX 600mg daily or placebo	14 days
RFID3005	Efficacy and safety Phase 3	Randomized, placebo control, blinded, prophylactic use in healthy subjects traveling from Thailand to Switzerland		231 RFX: 117 Placebo: 114	RFX 600mg daily or placebo	8 – 15 days
RFID3006	Safety Phase 3	Randomized, double blind in healthy volunteers		593 RFX 600mg qd: 234 RFX 600mg bid: 241 Placebo: 118	RFX 600mg daily RFX 600mg bid placebo	14 days
Additional Supportive Rifaximin Trials:						
Indication: IBS						
RFIB2001	Efficacy and safety Phase 2	Randomized, placebo control, blinded,	Multi-center US	674 RFX 275mg bid 14 days: 95 RFX 550mg bid 14 days: 190 RFX 550mg bid 28 days: 96 RFX 1100mg bid 14 days: 99 Placebo; 195	RFX 275mg bid RFX 550mg bid RFX 550mg bid RFX 1100mg bid placebo	14 – 28 days

Study ID	Trial Type	Trial Design	Number Centers	Number subjects	Dosage	Duration
Indication: Crohn's Disease						
RFCD2001	Efficacy Phase 2	Open label, subject's w/ active Crohn's disease	Single center	29 RFX: 29	RFX 200mg t.i.d	16 wks
Indication: Pouchitis						
RFPO2001	Efficacy Phase 2	2-phase (double-blind and open label) placebo control in subject's w/ pouchitis	Multi-center	20 RFX: 8 Placebo: 10 Control: 2	RFX 400mg t.i.d or placebo or control	28 – 56 days
Phase 1 Rifaximin Studies						
RFPK1007	Phase 1 PK, bio-availability	Open-label, randomized 2-part	Single center	28	Multiple differ doses	9 or 14 days
RFDI1008	Phase 1 PK drug interaction	Open-label, randomized	Single center	24	Interaction with midazolam	16 days

5.2 Review Strategy

The Applicant submitted results from only one randomized, placebo-controlled clinical trial and one open-label, single arm, treatment extension study. There are additional data submitted from trials for PK and other indications (see Table 8). Literature references and post-marketing experience from other countries were referenced and reviewed, from a safety standpoint. The major focus of this review, however, is the single randomized, placebo-controlled clinical trial and the open-label treatment extension study.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Pivotal Clinical Trial RFHE3001

RFHE3001 is the only randomized, controlled phase 3 trial conducted by the Applicant for the proposed indication, and its design is briefly summarized here.

RFHE3001 is a randomized, placebo controlled, double blinded, multi-center, multi-country trial designed to evaluate the efficacy, safety and tolerability of rifaximin 550mg

bid, administered for 6 months in maintaining remission from hepatic encephalopathy. A total of 69 investigators at 70 sites in Russia, Canada and the United States participated. The primary objective of the study was to evaluate the maintenance of remission of previously demonstrated recurrent, episodic hepatic encephalopathy, as measured by increases in the Conn score and asterixis grade. The secondary objective was to compare the safety, tolerability and quality of life (QoL) measurements between rifaximin and placebo groups.

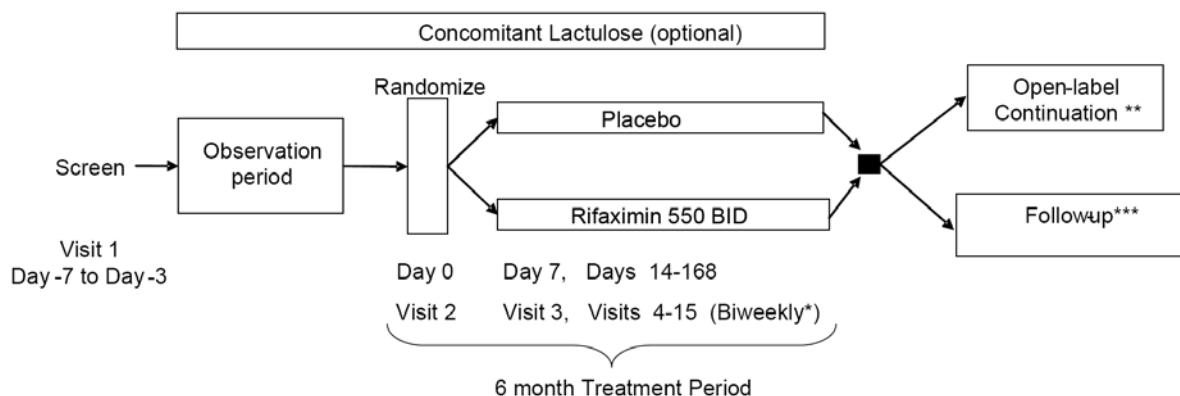
Eligible subjects had a history of ≥ 2 episodes of overt HE associated with chronic liver disease (e.g. cirrhosis or portal hypertension), with a documented severity equivalent to Conn score ≥ 2 , within 6 months prior to screening. At least 1 of the prior episodes must have been verifiable from medical records; the second episode could be unverified, (for example by report of the patient or caregiver).

The primary efficacy endpoint was the time to first breakthrough overt HE episode. A breakthrough overt HE episode was defined as an increase of Conn score to Grade ≥ 2 (i.e., from 0 or 1) or an increase in Conn and asterixis score of 1 grade each for those subjects who entered the study with a Conn score of 0. Time to first breakthrough overt HE episode was the duration from time of first dose of study drug to the first breakthrough overt HE episode. Subjects were discontinued from the study at the time of breakthrough overt HE episode. The duration of HE episodes was not captured in this study.

Subjects who completed the study and did not experience a breakthrough overt HE episode (i.e., treatment success) were censored at the time of their 6-month visit. Subjects who terminated early for reasons other than a breakthrough overt HE episode were contacted at 6 months from randomization to determine if they had experienced a breakthrough overt HE episode or other outcome (i.e. mortality status); and, if the subject reportedly had no breakthrough overt HE event prior to contact, he/she was censored at the time of contact. In this way, the Applicant reported that complete capture had been achieved for breakthrough overt HE episodes up to 6 months post-randomization. Twenty placebo and 22 rifaximin patients terminated early for reasons other than breakthrough HE (i.e., adverse event).

After participation in the current, double-blind study, all subjects who were withdrawn for a breakthrough overt HE episode and subjects who completed 6 months of double-blind treatment had the option to roll-over to an open-label continuation study (RFHE3002). The end-of-study visit was considered the screening visit for the continuation study (RFHE3002). Subjects who did not enroll in the open-label continuation study within 16 days of the end-of study/early termination visit completed a follow-up visit (Day 182 ± 2). See Figure 1: RFHE3001 Trial Design Scheme.

Figure 1: RFHE3001 Trial Design Scheme



5.3.2 RFHE3002 Treatment Extension Study

This study was a safety study. The primary objective for this open label, single arm study was to gather long-term safety information for rifaximin 550 mg BID in approximately 500 subjects with a history of HE. A total of 55 investigators at 56 sites in the United States, Canada, and Russia participated in the study. Treatment in the ongoing RFHE3002 study was planned to continue for at least 24 months on an outpatient basis or until regulatory approval of rifaximin for the maintenance of remission in patients with a history of HE, or until the Applicant closes the study, whichever comes first.

All eligible subjects had a history of HE, a Conn score of 0 to 2 at enrollment, and either successfully participated in a previous HE study with rifaximin (i.e., RFHE3001), or were new subjects enrolled with ≥ 1 verifiable episode of HE within 12 months of screening. Subjects who had participated in RFHE3001 and experienced an HE episode or associated symptoms were eligible for this extension study only if the investigator and subject did not perceive study medication as a possible cause of the HE episode or symptoms. Unlike study RFHE3001, subjects were not required to withdraw from the study after experiencing a breakthrough overt HE episode.

The baseline characteristics of the population in RFHE3002 show that of the 266 patients enrolled; 68.4% had Conn scores of 0, 27.4% had Conn scores of 1 and only 3.8% had Conn scores of 2. A total of 267 subjects enrolled in this study, 152 from the double-blind study RFHE3001 and 115 as new subjects. Seventy patients rolled over from RFHE3001 who were on rifaximin in that study and 196 patients were new to rifaximin. Therefore, 82 placebo patients were rolled over from RFHE3001.

Subjects who experienced an episode of recurrent HE (i.e., defined as an increase of Conn score to Grade ≥ 2 (i.e., 0 or 1 to ≥ 2), an increase in Conn and asterixis score of

1 grade each for those subjects who entered the study with a Conn score of 0, and an increase in Conn score to ≥ 3 for subjects who entered the extension study with a Conn score of 2 at study entry) during the study were not automatically withdrawn, but could continue on open-label medication unless withdrawal was requested by the subject or the investigator.

In trial, RFHE3002, the planned enrollment was 500 subjects. The total enrolled by the interim data cutoff was 267 subjects. The total rolled-over from RFHE3001 was 152 subjects (57% of the study population at the interim cutoff). The new subjects who were not rolled over from RFHE3001 totaled 115. Subjects at select study sites within North America also had the opportunity to participate in a pharmacokinetic (PK) substudy during their participation in RFHE3002. The pharmacokinetic substudy analysis population totaled 25 subjects with Child-Pugh A and B.

Safety endpoints of the trial included:

- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), grouped by body system, relationship to study medication, and severity.
- Change from baseline in clinical laboratory parameters at Months 1 and 3, and every 3 months thereafter through end of trial.
- Changes from baseline in vital sign measurements at Months 1 and 3, and every 3 months thereafter through EOT.

All analyses were performed using the Safety population (N=266), which included all subjects who received at least 1 dose of study medication and provided at least 1 post baseline safety assessment. For the summary tables, data were presented in 2 groups ("continuing rifaximin" and "new rifaximin") and overall (i.e., all subjects). Data are available for all subjects up to 12 February 2009 (clinical cutoff date). Additional data have been retrieved for some subjects beyond 12 February 2009 and are included in the database.

Disposition, Demographics, and Baseline Characteristics

A total of 267 subjects were enrolled in this study:

152 (57%) of these subjects rolled over from the double-blind study (RFHE3001)
115 (43%) were new subjects

A total of 208 subjects (78%) were still ongoing in the study at the clinical data cutoff for this interim report

Of the 267 subjects enrolled; 266 (99.6%) were included in the Safety population for this interim analysis; the subject excluded from the Safety population did not have a post-baseline safety assessment.

A total of 59 subjects (22%) discontinued treatment early,
16 subjects (6%) due to liver transplant,
18 subjects (7%) due to death,
8 subjects (3%) due to an AE
9 subjects (3%) who requested to withdraw from the study,
7 subjects (3%) due to “other” reasons, and
1 subject (0.4%) due to recurrent HE episode

Note that subjects may have discontinued early for more than 1 reason (e.g., AE/SAE and recurrent HE episode); only the primary reason is given above.

In the Safety population, median age was 57.0 years (minimum, maximum: 21, 82 years), most subjects were white (90.2%), and the majority were male (59.4%). Demographic characteristics were comparable between new and continuing subjects and were similar to those in the double-blind study RFHE3001 (median age of 56.0 years, 86.0% white, and 60.9% male). The mean time since first diagnosis of HE was 20.85 months (range, 0.5 to 162.7 months). The mean (SD) MELD score was 12.2 (3.82) and most subjects had MELD scores of either ≤ 10 (35.7%) or 11 through 18 (55.6%) at baseline. These characteristics were comparable between the new and continuing rifaximin groups and were similar to those in the double-blind study RFHE3001. Most subjects had baseline Conn scores of either 0 (68.4%) or 1 (27.1%) and asterixis grades of 0 (74.8%) or 1 (20.3%).

The safety results of this trial are discussed in Section 7 and additional results from the 120-day safety update can be found in Section 7.7.1

5.3.3 Additional Phase 2 and Phase 3 trials conducted to evaluate rifaximin for Treatment of HE, which were submitted to support efficacy

5.3.3.1 RFHE9702 Phase 2: Dose Ranging; Acute Treatment of HE

This phase 2, seven day, randomized, multicentre, dose-finding, double-blind, parallel-group study compared three dose levels of rifaximin: rifaximin 600 mg/day, 1200 mg/day and 2400 mg/day taken orally over seven days, in adults with portosystemic encephalopathy Grade I, II or III. The study was conducted in the United Kingdom. The primary efficacy endpoint was the Porto-Systemic Encephalopathy (PSE) index at the end of study. The PSE index, a composite assessment of HE symptoms, includes mental state (Conn score), asterixis, venous ammonia levels, NCT, and EEG.

Patients were assessed at screening (baseline), and days 3, 5 and 7. Blood samples were collected at baseline and on days 3, 5 and 7 for determination of blood ammonia. Mental function tests and EEGs were carried out at baseline and day 7. Fecal pH measurements were carried out at baseline and days 3, 5 and 7. Physical examination and medical history were recorded at baseline. Blood samples for routine biochemistry and hematology tests were collected at screen and on day 7.

Of the 54 subjects enrolled, one withdrew consent and 3 were lost to follow-up. A total of 18, 19, and 17 subjects were randomized to the 600 mg, 1200 mg, and 2400 mg rifaximin daily dose groups, respectively. Most subjects had mental state/Conn scores of 1 at baseline: 1, 1, and 0 subjects had Conn scores of 0; 14, 12, and 13 subjects had Conn scores of 1; and 3, 6, and 4 subjects had Conn scores of ≥ 2 in the 600 mg, 1200 mg, and 2400 mg rifaximin groups, respectively.

The 3 groups were comparable in PSE index at baseline, although not all subjects had a baseline determination. Improvements (i.e., decreases) in PSE index were observed in all treatment groups from baseline to end of treatment. Mean improvements in PSE index (by analysis of covariance) at end of treatment was 25.8%, 30.8%, and 32.4% in the 600 mg, 1200 mg, and 2400 mg rifaximin daily dose groups, respectively.

The small number of adverse events observed in this trial that were considered to be treatment-related displayed no consistent pattern or dose-relationship.

The applicant concluded that although rifaximin elicited an improvement in the clinical status of patients in this study compared to baseline, and was well tolerated overall, the investigation failed to elucidate the dose relationship in relation to the main objective parameters.

5.3.4 RFHE 9701 Phase 3: Active Control; Acute Treatment of HE

Trial RFHE9701 was a multi-centre, double-blind, double-dummy, parallel group, randomized trial that evaluated the efficacy and safety of rifaximin in comparison to lactitol for treatment of hepatic encephalopathy in cirrhotic patients with grade I to III acute or recurrent Hepatic Encephalopathy (H.E.).

A total of 103 patients were treated (50 patients with Rifaximin and 53 patients with Lactitol) and were evaluable in the intention-to-treat analysis. A total of 16/103 (15.53%) subjects discontinued the study treatment; 8 withdrawals were due to adverse events (5 patients in the Rifaximin group and 3 patients in the Lactitol group); 7 withdrawals were due to lack of efficacy (3 patients in the Rifaximin group and 4 patients in the Lactitol group) and 1 was due to concomitant disallowed medication (1 patient in the Rifaximin

group). The number of patients who completed the study was 87 (41 patients in the Rifaximin group and 46 patients in the Lactitol group).

Patients of both sexes, 18 years or older of age, affected by liver cirrhosis diagnosed on the basis of clinical and laboratory data, who had developed an acute or recurrent episode of grade I to III H.E. according to the criteria of Parsons-Smith et al (18) modified by Conn et al (8)., that had started less than 48 h before randomization with presence of a H.E. Index > 0 were eligible,.

Criteria for evaluation for efficacy were:

Primary end-points:

1. Improvement of H.E. syndrome (Mental State assessed using the criteria of Parsons-Smith et al., modified by Conn et al) (i.e. the Conn Score)
2. Therapeutic effect by calculating the H.E. Efficacy index;
3. Decrease in blood ammonia levels;
4. Decrease in H.E. Index.

Secondary variables:

1. Decrease in asterixis
2. Decrease in number connection test score
3. Decrease in EEG values
4. Decrease in H.E. Punctuation score sum
5. Number of bowel evacuations
6. Overall efficacy assessment (4-point scale).

Safety was evaluated with adverse events, blood counts and plasma biochemistry.

Improvement in mental state (Conn score), i.e., a decrease in Conn score during the study, was reported for 80% of rifaximin-treated subjects and for 81.6% of lactitol-treated subjects. **There was no difference found between treatment groups.** Venous ammonia levels were reported to decrease at a faster rate in the rifaximin group than in the lactitol group. At the end-of-treatment time point (12-24 hours after last dose), mean values had decreased from 131.5 µg/dL at baseline to 85.7 µg/dL in the rifaximin group and from 150.7 to 126.0 µg/dL in the lactitol group. Venous ammonia levels were lower at end of treatment in the rifaximin group when compared with the lactitol group. Although the Applicant concluded that rifaximin showed a statistical significant improvement in treatment effect, lowering of ammoniemia and normalization of electroencephalogram abnormalities, **there was no improvement in Conn Score on the rifaximin arm relative to the comparator.**

5.3.3.3 RFHE9901 Phase 3 Placebo Controlled; Acute treatment of HE

This double-blinded, placebo-controlled study enrolled patients with a documented history of mild to moderate (mental status of grade 1 or 2) **chronic HE who were intolerant to lactulose or lactitol**. Performed January 2001 to October 2002, the primary objective of this study was to investigate the efficacy and safety of a 14-day course of rifaximin in this patient population. Eligible patients were men or women older than 18 years but younger than 75 years with documented history of chronic, mild to moderate (mental status of grade 1 or 2) HE, known liver cirrhosis, negative urine benzodiazepine, intolerance to lactulose or lactitol, and no alcohol abuse for at least 6 months prior to enrollment in the study. The patients in this study had a higher Child's class at entry than RFHE3001 (pivotal trial); with approximately 60% having Child's class B and 30% having Child's class C at entry.

The primary efficacy endpoint was the overall response rate, defined as the percentage of patients who showed improvement, of mental state of 1 grade or more in comparison to baseline grade (Day 1, pretreatment). Secondary endpoints were PSE index, asterixis grade, NCT grade, blood ammonia concentration grade, blood ammonia concentration, mini mental state exam (MMSE) score, and EEG (when available). The PSE Index is a composite score based on measurements of the mental status, asterixis, NCT, ammonia grade, and EEG when available. The Mental state scale is exactly the same as Conn score.

Of the 93 patients enrolled and randomized, 45 received placebo and 48 received rifaximin. Most subjects had Conn scores of 0 or 1 at baseline. The distribution of subjects by mental state/Conn scores at baseline, in rifaximin and placebo respectively, was: 10.4% (rifaximin) versus 6.7% (placebo) had a Conn score of 0; 75% versus 88.9% had a Conn score 1; and 14.6% versus 4.4% had a Conn score of 2. Lactulose was discontinued 24 - 48 hours prior to beginning the trial. Patients were classified as responders if they showed improvement of mental state of 1 grade or more in comparison to baseline.

The primary efficacy variable, overall response rate in mental state/Conn score, was not statistically different between the rifaximin group and placebo group.

Response rate was defined as the change in baseline mental grade (Conn score) to the mental grade (Conn) score at the Day 14 visit or the last available mental grade prior to the Day 14 visit but following at least 10 days of study treatment. Patients were classified as responders if they showed improvement of mental state of 1 grade or more in comparison to baseline. Overall response rates for the ITT population, defined as change in mental grade (Conn) score of 1, were 49% in the placebo group and 42% in the rifaximin group. An interaction was noted in response rates relative to treatment group and region. Response rates in Europe were 32% and 50% in the rifaximin and placebo groups respectively, while in North America response rates were 59% and 47%, respectively. When the response rate was analyzed by factor, significant

interactions were noted for race by treatment group. Response rates were higher for rifaximin-treated patients compared to placebo-treated patients in the North American region and for nonwhites. All nonwhite patients were located in North America. Exploratory analyses also examined the association of response with factors including mental state grade, sex, and diet (high/low calories, high/low protein). Results did not reveal any other factors associated with response.

Results did not differ between treatment groups for the secondary efficacy parameters of Portosystemic encephalopathy (PSE) index, number connection test (NCT), blood ammonia concentration or mini mental state exam (MMSE). The secondary efficacy parameter of asterixis grade did show categorical improvement (decrease from baseline) at a higher rate for patients in the rifaximin group versus patients in the placebo group at each visit from Day 7 forward. Mean change from baseline for asterixis grade also improved more at each visit and at endpoint for patients in the rifaximin group relative to those in the placebo group.

Subjects in the rifaximin group showed greater improvement in asterixis grade relative to subjects in the placebo group. Decreases from baseline in asterixis grade were more pronounced at Day 3, Day 7, Day 10, and Day 14/final assessment in the rifaximin group when compared to placebo. In the rifaximin group, 60.9% of subjects were reported to have experienced no change in asterixis grade and 39.1% experienced improvements from baseline to final assessment. In the placebo group, 90.7% of subjects were reported to have experienced no change in asterixis grade and 9.3% experienced improvements from baseline to final assessment. Note that from the statistical standpoint, the analysis of the numerous secondary endpoints and their varied *post-hoc* analyses can not establish evidence of a positive treatment effect.

Overall, evaluations of other secondary efficacy variables (PSE index, NCT grade, venous ammonia concentration, MMSE) did not show any significant differences between the rifaximin group and placebo group.

One patient in the rifaximin group died from adverse events considered unrelated to study drug. Six nonfatal serious adverse events were reported for 5 patients in the rifaximin group. Of these, 5 events were considered unrelated to study drug and 1 event (suicidal ideation) was considered to be unlikely related to study drug. Six nonfatal serious adverse events were reported for 4 patients in the placebo group. Of these, 4 events were considered unrelated to study drug and 2 events were considered to be possibly or probably related to study drug. Five patients in the rifaximin group and 3 patients in the placebo group discontinued the study due to adverse events. All adverse events resulting in discontinuation for patients in the rifaximin group were considered unrelated to study drug. No differences were found between the rifaximin and placebo groups for laboratory tests, vital signs, and physical examinations results.

There is no evidence of significant improvement in efficacy for rifaximin-treated patients relative to placebo-treated patients in Conn Score in this population who entered the study with HE, but Conn score of 0-1. An analysis of the impact on asterixis, which was a secondary endpoint, suggested a favorable impact asterixis.

6 Review of Efficacy

Efficacy Summary

It is important to note that for the secondary endpoints, p-values and confidence intervals reported in this briefing document are presented with no adjustment for multiplicity. These nominal p-values and confidence intervals are presented as part of the overall exploratory assessment of the efficacy of rifaximin and are not viewed as providing evidence of efficacy. From the statistical standpoint, the analysis of the numerous secondary endpoints and their varied *post-hoc* analyses do not establish evidence of a positive treatment effect for Rifaximin in maintenance of remission of hepatic encephalopathy.

The primary efficacy parameter for the double-blind, placebo controlled study RFHE3001 was the occurrence of an episode of breakthrough overt HE during treatment. Reduction of breakthrough in the rifaximin group ($p < 0.0001$ for between-group difference in relative risk) was observed in the analysis of the primary efficacy endpoint, time to first breakthrough with an overt HE episode. Breakthrough overt HE episodes were experienced by 31 of 140 subjects in the rifaximin group and by 73 of 159 subjects in the placebo group during the 6-month treatment period. The hazard ratio for the risk of experiencing breakthrough overt HE in the rifaximin group relative to the risk in the placebo group was 0.421, 95%CI (0.276, 0.641) during the 6-month treatment period, a 57.9% reduction in risk of breakthrough.

Although the analysis of the primary endpoint appeared statistically significant in this single study, the FDA reviewers raised concerns about the interpretability of the observed outcome of this study. The primary endpoint assessment is subjective and hinges on observer evaluation of subtle differences in neurologic function. There were review concerns regarding the ability to consistently apply the West Haven-Conn score in this study. Patients had to have a Conn score of 0 to 1 at study entry and needed only to shift to Conn score ≥ 2 to be defined as having a breakthrough HE episode (i.e., 0 or 1 to ≥ 2), or an increase in Conn and asterixis score of 1 grade each for those subjects who entered the study with a Conn score of 0. It is unclear whether clinicians can consistently and uniformly delineate between a Conn score of 1 and 2. Also, breakthrough definition required only a change in Conn score of 1 grade for those who entered the study with a Conn score of 1 (i.e. from 1 to 2). In addition, the study allowed for Conn scores to be assigned based on verbally reported information provided by caregivers and patients in telephone interviews.

In the rifaximin group, 8 patients were determined to have breakthrough episodes of hepatic encephalopathy based on direct observation by study site personnel, while 22 patients were diagnosed to have such episodes by indirect means; thus, only 27.7% of patients in the treatment group diagnosed with breakthrough episodes of hepatic encephalopathy had that determination made by direct observation. In the placebo group, 30 patients were determined to have breakthrough episodes of hepatic encephalopathy based on direct observation, while 40 patients were diagnosed to have such episodes by indirect means; thus, in the placebo group a higher proportion of the events, 42.9%, were diagnosed by direct observation. This is summarized in the table below.

Table 9: Method of Diagnosing Breakthrough Hepatic Encephalopathy

	Placebo N = 70	Rifaximin N = 30	Total N = 100
Direct (at site)	30 (42.9%)	8 (27.7%)	38 (38.0%)
Indirect Hospitalized	19 (27.1%)	12 (40.0%)	34 (34.0%)
Indirect - Other	21 (30.0%)	10 (33.3%)	28 (28.0%)

Of patients with data available from CRF

When the patients who were indirectly diagnosed were analyzed by admission to the hospital with a diagnosis of HE (Breakthrough HE Hospitalization), which would imply that diagnosis was made by observation of a clinician, although not the investigator, it is apparent that approximately 30% of patients with breakthrough HE in each group (33.3% in Rifaximin and 30.0% in Placebo) were diagnosed neither by clinician observation in a hospital visit nor an evaluation by an investigator during a site visit. The proportion of this event was slightly higher in the rifaximin arm.

Consult review from the Division of Neurology Products concluded that the report of Study RFHE3001 did not provide robust evidence to establish that rifaximin is efficacious, based on the primary endpoint. The reviewer raised concerns regarding the validity of the assessment tool for the primary endpoint and the interpretability of the observed clinical findings based on this tool. Please refer to the neurology review under Tab 3 of this briefing document.

In RFHE3001, analysis of the prespecified important secondary endpoint time to first HE-related hospitalization (i.e., hospitalization directly resulting from HE or hospitalization complicated by HE) demonstrated a 50% reduction in risk of hospitalization due to HE in the rifaximin group, when compared with placebo, during the 6-month treatment period ($p = 0.0129$ for between-group difference in relative risk). Hepatic encephalopathy-related hospitalizations were reported for 19 of 140 subjects and 36 of 159 subjects in the rifaximin and placebo groups, respectively.

Significance tests were conducted for all secondary efficacy endpoints using a pre-specified hierarchical analysis. Results of this significance testing were reported in the pre-specified hierarchical order, from endpoint number 1 through number 5, until a non-significant p-value was encountered ($p > 0.05$), which consequently classified all subsequent significance tests as exploratory in nature. The nominal p-values and confidence intervals for multiple additional analyses are presented as part of the overall exploratory assessment of the efficacy of rifaximin and are not viewed as providing evidence of efficacy. From the statistical standpoint, the analysis of the numerous additional endpoints and their varied *post-hoc* analyses can not provide evidence of a positive treatment effect.

An observation to note in the review was that exploration of the efficacy results reveals that Months Two through Four are the major contributors to the overall six month results.

6.1 Indication

RFHE3001 is a randomized, placebo controlled, double blinded, multi-center, multi-country, trial to evaluate the efficacy, safety and tolerability of rifaximin 550mg bid for 6 months in maintaining remission from hepatic encephalopathy. A total of 69 investigators at 70 sites in Russia, Canada and the United States participated. The study period was from December 19, 2005 through August 15, 2008. The primary objective of the study was to evaluate the maintenance of remission from previously demonstrated recurrent, episodic hepatic encephalopathy, as measured by the Conn score and asterixis grade. The secondary objective was to compare the safety, tolerability and quality of life (QoL) measurements between rifaximin and placebo.

6.1.1 Methods

Eligible subjects had a history of ≥ 2 episodes of overt HE associated with chronic liver disease (e.g. cirrhosis or portal hypertension) with a documented severity equivalent to Conn score ≥ 2 within 6 months prior to screening. At least 1 of the prior episodes must have been verifiable from medical records. Hepatic encephalopathy episodes primarily attributed to gastrointestinal (GI) hemorrhage requiring ≥ 2 units of blood by transfusion, medications (e.g. narcotics, tranquilizers, sedatives), renal failure requiring dialysis, or central nervous system (CNS) insult such as a subdural hematoma were not counted as a qualifying, prior episode of HE. Eligible subjects were required to be in remission at the baseline assessment (defined as Conn score of 0 or 1).

The study included a screening visit (during the interval from Days -7 to -3), an Observation Period (screening visit to Day -1), and a Treatment Period (Days 0 to 168) that included an end-of-study visit (Day 168 ± 2). Subjects underwent evaluations of mental status (Conn score) and neuromotor functioning (asterixis grade) for determination of the occurrence of a breakthrough overt HE episode at each in-person

study visit, during telephone interviews, and from sources including caregiver reports, hospital discharge summaries, and from subject diaries. A breakthrough overt HE episode was defined as an increase of Conn score to Grade ≥ 2 (i.e., change from 0 or 1 to ≥ 2) or an increase in Conn and asterixis score of 1 grade each for those subjects who entered the study with a Conn score of 0. The study's plan for detecting an HE breakthrough event relied partially upon assigning a Conn score of 2 or even 1, and an asterixis score based on telephone interview, caregiver report, subject diaries, and hospital discharge summaries. The ability to reliably determine these Conn scores and changes in Conn scores based on telephone interviews, caregiver reports and hospital records can be questioned when the criteria for each grade are considered. The scoring systems are reproduced in the tables below.

The Applicant educated the investigators in an additional neurologic evaluation method, the Hepatic Encephalopathy Scoring Algorithm (HESA). The HESA was to be used at baseline and at study visits.

Table 9: Conn Score – West Haven Criteria

Conn score 0	No personality or behavioral abnormality detected
Conn score 1	Trivial lack of awareness, euphoria or anxiety; shortened attention span; impairment of addition or subtraction.
Conn score 2	Lethargy; disorientation for time; obvious personality change; inappropriate behavior.
Conn score 3	Somnolence to semi-stupor, responsive to stimuli; confused; gross disorientation; bizarre behavior.
Conn score 4	Coma; unable to test mental state

Table 10: Asterixis Grade

Grade 0	No tremors
Grade 1	Rare flapping motions
Grade 2	Occasional, irregular flaps
Grade 3	Frequent flaps
Grade 4	Almost continuous flapping motions

Subjects discontinued from the study at the time of breakthrough overt HE. Subjects who terminated early for reasons other than a breakthrough overt HE episode were contacted at 6 months or later from randomization to determine if they had experienced a breakthrough overt HE episode or other outcome (i.e., mortality status). Complete capture was attempted for breakthrough overt HE episodes for ≥ 6 months post-randomization.

Statistical Methods

The study populations used in the analyses were as follows:

- Intent-to-treat population (ITT) included all randomized subjects who received at least 1 dose of study drug.
- Safety population included all randomized subjects who received at least 1 dose of study drug and provided at least 1 post-baseline safety assessment.

The study population, ITT population and the safety population were all the same in this study and included all 299 subjects in each category.

Medical Officer's Comments:

A major concern in this clinical trial design is that the entry criteria and primary endpoint for this study are subjective and rely upon an observer's subjective assessment. It is not clear that observers can consistently delineate between the small changes that could define an event in this study, and the observer's assessments did not need to be made by direct observation, e.g., phone interviews and caregiver report could be used to assign a Conn's score. However, the trial was randomized and blinded.

The trial was intended to address overt, episodic HE, however the design included patients with minimal HE (Conn score 1) at baseline which is not technically a patient in remission, but one with minimal HE. In addition, 91% of patients in the trial were taking lactulose at study entry, which suggests those patients might have had persistent HE. The trial was also not designed to capture the length of HE episodes. This information was requested from the Applicant; however they were unable to provide the data.

In the rifaximin group, 8 patients were determined to have breakthrough episodes of hepatic encephalopathy based on direct observation by study site personnel, while 22 patients were diagnosed to have such episodes by indirect means; thus, only 27.7% of patients in the treatment group diagnosed with breakthrough episodes of hepatic encephalopathy had that determination made by direct observation. In the placebo group, 30 patients were determined to have breakthrough episodes of hepatic encephalopathy based on direct observation, while 40 patients were diagnosed to have such episodes by indirect means; thus, in the placebo group a higher proportion of the events, 42.9%, were diagnosed by direct observation. This is summarized in the table below.

Table 1: Method of Diagnosing Breakthrough Hepatic Encephalopathy

	Placebo N = 70	Rifaximin N = 30	Total N = 100
Direct (at site)	30 (42.9%)	8 (27.7%)	38 (38.0%)
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Indirect - Other	21 (30.0%)	10 (33.3%)	28 (28.0%)

Of patients with data available from CRF

When the patients who were indirectly diagnosed were analyzed by admission to the hospital with a diagnosis of HE (Breakthrough HE Hospitalization), which would imply that diagnosis was made by observation of a clinician, although not the investigator, it is apparent that approximately 30% of patients, with breakthrough HE, in each group

(33.3% in Rifaximin and 30.0% in Placebo) where diagnosed neither with clinician observation in a hospital visit nor an evaluation by an investigator during a site visit.

Medical Reviewer's Comments:

While Conn score and asterixis grade are widely used clinically, they have not been validated as end points for clinical trials to support product approvals. A validated end point for the evaluation of Hepatic Encephalopathy has not yet been established. The Evaluation of Minimal Hepatic Encephalopathy or lower levels of HE (Conn score 0 vs. 1; or 1 vs. 2) is especially difficult and requires additional psychometric and neuropsychological testing. According to the 11th World Congress of Gastroenterology working party consensus, diagnosis of minimal HE requires a normal mental status examination and impairment in the performance of at least two psychometric tests; the values being corrected for age and education level relative to a healthy control group of individuals.⁶

The Applicant educated the investigators in an additional neurologic evaluation method, the Hepatic Encephalopathy Scoring Algorithm (HESA). The HESA is a scoring system that requires both clinical evaluation and neuropsychiatric testing. The neuropsych testing includes the number connection test, the dot connection test and memory tests. The Applicant instructed investigators that Conn score 0 should be assigned only to subjects with normal HESA clinical and neuropsychiatric testing. Subjects with abnormal neuropsychiatric testing evaluations were to be assigned a Conn score of 1 or higher. Conn score of 2 should correlate with difficulty completing neuropsychiatric testing and more obvious clinical symptoms, (lethargy, disorientation, inappropriate behavior). The Applicant did not capture these HESA evaluations in the Case Report Forms (CRF). The CRF captured physical exams, Conn Score, asterixis grade and critical flicker frequency (CFF) (See discussion of CFF below). The Applicant directed investigators to override any evaluations of HESA with clinical evaluation of the Conn score. However, they also stated a Conn score of 1 should be assigned to subjects with a clinical Conn score of 0 and abnormal neuro-psychiatric testing. Thus without the actual HESA work sheets it is difficult to evaluate exactly how Conn scores were assigned.

In evaluating efficacy in neuropsychological disorders the Division of Neurology Products requires a positive co-primary outcome for a global impression of change in the patient's cognitive status, to increase confidence that change in the neuropsychological evaluation is clinically meaningful. Because of the specialized nature of some of the endpoints used in the randomized, placebo-controlled trial, the Division sought expert opinions on those endpoints from CDER's Division of Neurology Products. The Neurology Review addresses the validity of the assessment tool for the primary endpoint and the interpretability of the observed clinical findings based on this tool.

Critical Flicker Frequency (CFF) scoring was performed on subjects and recorded in the CRFs. The CFF is a strobe light test that records the frequency that a subject is able to

distinguish constant from flickering light. CFF appears to detect a broad spectrum of neuropsychological abnormalities ranging from visual signal processing (retinal gliopathy) to cognitive functions, and it has been applied to the study of several neurological disorders such as multiple sclerosis and Alzheimer's disease. There is some literature in the last few years showing correlation between low CFF (below 39 Hz) and minimal HE. However, the CFF scoring system, has not been validated.

6.1.2 Demographics

Number of Subjects: Planned: 250; randomized: 299; intent-to-treat (ITT): 299; safety: 299.

Demographic and baseline characteristics were generally comparable between the two groups in the ITT population. The mean time since first diagnosis of advanced liver disease for the ITT population was 56.2 months (range, 1.7 to 323.4 months). Most subjects had MELD scores of either ≤ 10 (27.4%) or 11 to 18 (63.5%) at baseline. Conn score at baseline was 0 (66.9%) or 1 (33.1%) and most subjects had asterixis grade 0 (68.2%) or grade 1 (28.8%). There were more males than females, males constituted 67.3% of the rifaximin group and 53.6% of the placebo group.

Unknown (i.e., spontaneous occurrences of HE) was the recorded contributing factor for most HE episodes that occurred during the 6-month period prior to enrollment. The types of contributing factors for HE episodes were reported at similar frequencies in the rifaximin and placebo groups.

Although there were no notable differences in baseline characteristics between placebo and rifaximin groups in Russia or in North America, subjects in Russia had fewer stools per day (mean = 1.2 stools/day) than in the United States and Canada (mean = 3.0 stools/day). According to the Applicant the lower stool count in Russia was likely due to lower lactulose use in Russia compared with the United States and Canada. Subjects in Russia received an average of 2.44 cups/day of lactulose, and subjects in the United States and Canada received an average of 5.57 cups/day during the course of the study (1 cup = 15 mL [10 g lactulose/15 mL]).

Table 11: Demographic Characteristics by Treatment Group

Characteristic Category or statistic	Placebo N = 159	Rifaximin N = 140	Total N = 299
Age (years)			
n	159	140	299
Mean (SD)	56.8 (9.18)	55.5 (9.57)	56.2 (9.38)
Median (Min, max)	57.0 (21, 78)	55.0 (26, 82)	56.0 (21, 82)
Age group – n (%)			
< 65	128 (80.5)	113 (80.7)	241 (80.6)
≥ 65	31 (19.5)	27 (19.3)	58 (19.4)
Sex – n (%)			
Male	107 (67.3)	75 (53.6)	182 (60.9)
Female	52 (32.7)	65 (46.4)	117 (39.1)
Ethnicity – n (%)			
Hispanic or Latino	28 (17.6)	21 (15.0)	49 (16.4)
Not Hispanic or Latino	131 (82.4)	119 (85.0)	250 (83.6)
Race			
American Indian/Alaskan native	3 (1.9)	5 (3.6)	8 (2.7)
Asian	8 (5.0)	4 (2.9)	12 (4.0)
Black/African American	5 (3.1)	7 (5.0)	12 (4.0)
Native Hawaiian/Pacific islander	1 (0.6)	2 (1.4)	3 (1.0)
White	139 (87.4)	118 (84.3)	257 (86.0)
Other	3 (1.9)	3 (2.1)	6 (2.0)
Missing	0	1 (0.7)	1 (0.3)
Country – n (%)			
United States	112 (70.4)	93 (66.4)	205 (68.6)
Canada	6 (3.8)	8 (5.7)	14 (4.7)
Russia	41 (25.8)	39 (27.9)	80 (26.8)

Medical Officers Comments:

The criteria for randomization of patients into the trial eliminated patients with severe hepatic insufficiency (only 9% of subjects had MELD score 19 – 25; no subjects had MELD score over 25). Therefore, there are little data for rifaximin use in patients with severe hepatic impairment.

6.1.3 Subject Disposition

A total of 299 subjects were randomized to receive rifaximin (140 subjects) or placebo (159 subjects) in this study. As specified in the protocol, subjects were to be withdrawn from the study after experiencing a breakthrough overt HE episode. Breakthrough overt HE episode was the primary reason for early study withdrawal for 28 of 140 subjects (20%) in the rifaximin group and 69 of 159 subjects (43.4%) in the placebo group. Primary reasons for early study discontinuation other than breakthrough overt HE episode were AEs (15 subjects), subject request (15 subjects), death (9 subjects), development of exclusion criteria (4 subjects), liver transplant (1 subject), and other reason (4 subjects).

Table 12: Disposition RFHE3001

	Placebo (N = 159) n (%)	550mg Rifaximin BID (N = 140) n (%)	Total (N = 299) n (%)
Subjects Treated	159 (100.0%)	140 (100.0%)	299 (100.0%)
Subjects Completed the Study	66 (41.5%)	88 (62.9%)	154 (51.5%)
Subjects Discontinued Early from the Study	93 (58.5%)	52 (37.1%)	145 (48.5%)
Primary Reason for Discontinuation			
Occurrence of an Adverse Event	7 (4.4%)	8 (5.7%)	15 (5.0%)
Development of any Exclusion Criteria	3 (1.9%)	1 (0.7%)	4 (1.3%)
Pregnancy	0	0	0
Subject Request to Withdraw	9 (5.7%)	6 (4.3%)	15 (5.0%)
Breakthrough HE episode	69 (43.4%)	28 (20.0%)	97 (32.4%)
Liver Transplant	1 (0.6%)	0	1 (0.3%)
	3 (1.9%)	6 (4.3%)	9 (3.0%)
	1 (0.6%)	3 (2.1%)	4 (1.3%)
Subjects Discontinued and Retrospectively Determined at Follow-Up to have experienced a Breakthrough HE episode	4 (2.5%)	2 (1.4%)	6 (2.0%)
Death			
Other			

Please note that the prior disposition table presented is derived from the termination CRF page.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the time to first breakthrough overt HE episode. A breakthrough overt HE episode was defined as an increase of Conn score to Grade ≥ 2 (i.e., change from 0 or 1 to ≥ 2) or an increase in Conn and asterixis score of 1 grade each for those subjects who entered the study with a Conn score of 0. Time to first breakthrough overt HE episode was the duration from time of first dose of study drug to the first breakthrough overt HE episode.

Because subjects discontinued at the time of breakthrough overt HE episode, the duration or severity of HE episodes was not captured in this study. Subjects who completed the study and did not experience a breakthrough overt HE episode were censored at the time of their 6-month visit. Subjects who terminated early for reasons other than a breakthrough overt HE episode were contacted at 6 months from randomization to determine if subjects had experienced a breakthrough overt HE episode or other outcome (i.e., mortality status). If it was determined that the subject had experienced no breakthrough overt HE episode prior to being contacted, then he/she was censored at that time of contact. In this manner the Applicant attempted to completely capture all breakthrough overt HE episodes up to 6 months post-randomization.

Primary efficacy endpoint: time to first breakthrough overt HE

A breakthrough overt HE episode, as defined for this study (see definition above), could involve a shift in Conn score to 2 or a shift in Conn score from zero to 1 coupled with an increase in asterixis score of 1 grade. The latter category of changes would be anticipated to be relatively subtle. Breakthrough overt HE episodes were experienced by 31 of 140 (22.1%) subjects in the rifaximin group and by 73 of 159 (45.9%) subjects in the placebo group during the 6-month treatment period (up to Day 170). Comparison of Kaplan-Meier estimates of time to breakthrough overt HE between groups showed a protective effect of rifaximin ($p < 0.0001$). The hazard ratio for the risk of experiencing breakthrough overt HE in the rifaximin group relative to the risk in the placebo group was 0.421, 95% CI (0.276, 0.641) during the 6-month treatment period, a 57.9% reduction in risk compared with placebo. See Figure 2 and Table 13.

Figure 2: Comparison of Time to First Breakthrough Overt HE Episode in Study RFHE3001 (rifaximin versus placebo groups)

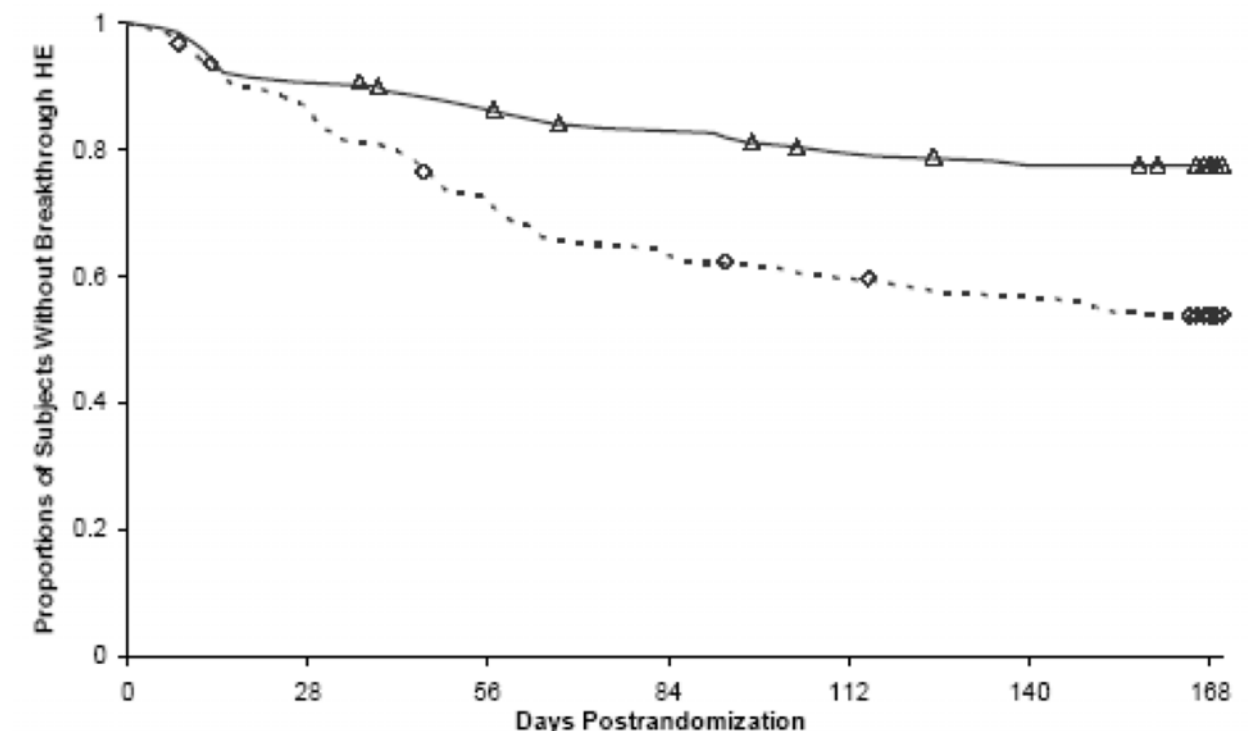


Table 13: Study RFHE3001: Kaplan-Meier Estimates and Statistical Analyses of Time to First Breakthrough Overt HE (up to 6 Months of Treatment, Day 170) (ITT Population)

Placebo (N = 159)						Rifaximin (N = 140)				
Treat- ment interval (days)	At risk ^a	Number of events ^b	Cumula- tive number of events	Event prob- ability (SE) ^c	Probability of no breakthrough overt HE ^d	At risk ^a	Number of events ^b	Cumula- tive number of events	Event prob- ability (SE) ^c	Probability of no breakthrough overt HE ^d
0 to <28	158	20	20	0.13 (0.03)	1.0000	140	13	13	0.09 (0.02)	1.0000
28 to <56	137	23	43	0.17 (0.03)	0.8734	126	4	17	0.03 (0.02)	0.9071
56 to <84	113	14	57	0.12 (0.03)	0.7262	120	6	23	0.05 (0.02)	0.8783
84 to <140	98	10	67	0.10 (0.03)	0.6363	112	7	30	0.06 (0.02)	0.8344
140 to <168	84	6	73	0.07 (0.03)	0.5713	98	1	31	0.01 (0.01)	0.7820
≥168	38	0	73	0	0.5305	46	0	31	0	0.7740
Hazard ratio:		0.421 ^e								
95% CI:		(0.276, 0.641)								
p-value		< 0.0001								
Table footnotes are on the next page.										

Source: Summary Table 14.2.1a, RFHE3001 study report (Module 5.3.5.1.1).

Abbreviations: CI = confidence interval; SE = standard error.

a Number of subjects at risk during the treatment interval, estimated using the life table method. Assuming that censored cases were at risk for half of the interval, they only counted for half in figuring the number at risk.

b Number of events occurring during the treatment interval.

c Estimate of the probability of experiencing breakthrough overt HE during the treatment interval. Standard error (SE) estimated by using Greenwood's formula.

d Estimate of the probability of no breakthrough overt HE until at least the beginning of the next treatment interval.

e Hazard ratio estimate (hazard of breakthrough overt HE in the rifaximin group compared with the placebo group) determined from the Cox proportional hazards model. P-value based on the Score statistic.

Treatment effect adjusted for prognostic factors by covariate analyses

The following prognostic factors were found to be independent predictors of breakthrough overt HE episodes: baseline age, MELD score, duration of current verified remission, and number of prior HE episodes.

See Table 14.

Table 14: Analysis of Primary Efficacy Endpoint Adjusted for Covariates: Time to Onset of Breakthrough HE Episode up to Six Month (Day 170) Population: ITT

Individual Covariate Effects on Time to Onset of Breakthrough HE Episode	P-value from Log-Rank Test
Sex (Male, Female)	0.9508
Age (<=50, >50)	0.0160
Race (White, Non-white)	0.9820
Baseline MELD (<=10, 11-18, 19-24)	0.0003
Baseline Conn Score (0,1)	0.2287
Diabetes at Screening (Yes, No)	0.2240
Duration of Verified Remission (<=90, >90)	0.1089
Number of HE Episodes Within the Past 6 Months (2, >2)	0.0022
Covariates with p-value<=0.11 were included in the Cox proportional hazards model	

From Applicant table 14.2.1c

To control for the effects of these factors on outcome due to chance imbalances between treatment groups, they were included in a multivariate analysis performed by the Applicant using the Cox proportional hazards model. Results from this multivariate analysis still showed that rifaximin treatment, after adjusting for significant prognostic factors, resulted in a 59.7% reduction, when compared with placebo, in the risk of experiencing a breakthrough overt HE episode during the course of this study ($p < 0.0001$).

Sensitivity analyses

Overt episodic HE is marked by single or recurrent episodes of neuropsychiatric impairment usually precipitated by specific conditions or risk factors (i.e., comorbid conditions). Because subjects who had ongoing comorbid conditions (i.e., known precipitating factors for HE episodes) at the time of randomization may have been unstable, the Applicant conducted a sensitivity analysis of the primary efficacy endpoint, where these subjects were excluded from the analysis. **Ongoing comorbid conditions selected by the Applicant for this analysis included analgesic use, constipation, infection, and portal shunt surgery.** The analysis showed that rifaximin treatment resulted in reductions in the risk of breakthrough overt HE in subjects with or without these selected co-morbidities. Risk reduction was 0.248, 95% CI (0.108, 0.571) ($p = 0.0004$) in subjects who had comorbid conditions and 0.512 (95% CI: 0.313 to 0.839) ($p = 0.0068$) in subjects without comorbid conditions. The impact appeared to be greater in this exploratory analysis in patients defined by the sponsor as having comorbid conditions.

Concomitant medications indicated for the treatment or prevention of HE could have influenced the effect of rifaximin on the outcome of the primary endpoint, so the Applicant conducted a second sensitivity analysis whereby subjects satisfying this condition were excluded from the ITT population. Rifaximin treatment still resulted in a

reduction in the risk of breakthrough overt HE in subjects who were not taking concomitant medications for treatment or prevention of HE; hazard ratio of rifaximin to placebo was 0.419, 95% CI (0.275, 0.640) ($p < 0.0001$).

Responder Analyses

The Division submitted a Request for Information to the Applicant requesting additional responder analyses in which a responder is defined as a patient who had not experienced breakthrough HE by each month sequentially for six months.

The Applicant replied on October 12, 2009 with two tables in which the proportion of responders is presented by cumulative time on study, with each sequential month in the six month period. The two tables defined the non-responders differently. In Table 15 the non-responders are all patients who discontinued for any reason. Table 16 defines non-responders as only subjects who discontinued for breakthrough HE episodes. In both tables, the p value was calculated using Cochran-Mantel-Haenszel Test, adjusted by analysis region. The findings by either analysis demonstrate that a difference between arms becomes evident as early as the end of the second month on study.

Table 15: Number and Percentage of Subjects Who Did Not Experience a Breakthrough HE during Specified Periods - Population: ITT

	Placebo (N = 159) n/N (%)	550mg Rifaximin BID (N = 140) n/N (%)	p-Value ¹
Responder Throughout Entire 6 Months	80/159 (50%)	100/140 (71%)	0.0002
Responder Throughout First 5 Months	87/159 (55%)	102/140 (73%)	0.0013
Responder Throughout First 4 Months	92/159 (58%)	106/140 (76%)	0.0012
Responder Throughout First 3 Months	99/159 (62%)	113/140 (81%)	0.0005
Responder Throughout First 2 Months	112/159 (70%)	119/140 (85%)	0.0030
Responder Throughout First 1 Month	135/159 (85%)	127/140 (91%)	0.1414

Note: A responder was a subject who did not experience a breakthrough HE episode throughout the entire specified period (6 months, 5 months, etc.) in the study.

[1] P-Value was calculated using Cochran-Mantel-Haenszel Test, adjusted by analysis region.

Table 16: Number and Percentage of Subjects Who Did Not Experience a Breakthrough HE During Specified Periods (Subjects Who Discontinued from Study Due to Any Reason Other Than Breakthrough HE and Did not Have Breakthrough HE Information Prior to the End of the Specified Period Were Excluded from the Analysis) Population: ITT

	Placebo (N = 159) n/N (%)	550mg Rifaximin BID (N = 140) n/N (%)	p-Value ¹
Responder Throughout Entire 6 Months	80/153 (52%)	100/131 (76%)	<.0001
Responder Throughout First 5 Months	87/154 (57%)	102/133 (77%)	0.0003
Responder Throughout First 4 Months	92/155 (59%)	106/134 (79%)	0.0003
Responder Throughout First 3 Months	99/156 (64%)	113/136 (83%)	0.0002
Responder Throughout First 2 Months	112/156 (72%)	119/138 (86%)	0.0028
Responder Throughout First 1 Month	135/157 (86%)	127/140 (91%)	0.2230

Note: A responder was a subject who did not experience a breakthrough HE episode throughout the entire specified period (6 months, 5 months, etc.) in the study. Subjects who discontinued from study due to any reason other than breakthrough HE and did not have breakthrough HE information prior to the end of the specified period were excluded from the analysis for that specified period.

[1] P-Value was calculated using Cochran-Mantel-Haenszel Test, adjusted by analysis region.

Breakthrough-HE episode as a consequence of any precipitating complications

Additional analysis was requested of the Applicant to determine whether the observed breakthrough-HE episodes occurred as a consequence of precipitating complications (sepsis, any GI bleeding, ascites, SBP, etc.).

Spontaneous (unknown) was most frequently recorded (53 subjects) as the precipitating factor for breakthrough episodes. Other conditions that were considered to be precipitating factors included infection (14 subjects), constipation (14 subjects), dehydration (9 subjects), dietary protein (2 subjects), and GI hemorrhage (2 subjects). See Table 17. This was captured on the CRF page 118 Breakthrough episodes.

Table 17: Summary of Breakthrough HE Episode Factors by Treatment Group
Population: ITT

Factor	Placebo (N = 159) n (%)	550mg Rifaximin BID (N = 140) n (%)	Total (N = 299) n (%)
Infection	8 (5.0%)	6 (4.3%)	14 (4.7%)
GI Hemorrhage requiring <2 units of blood by transfusion	2 (1.3%)	0	2 (0.7%)
Azotemia	0	0	0
Constipation	11 (6.9%)	3 (2.1%)	14 (4.7%)
Dietary Protein	2 (1.3%)	0	2 (0.7%)
Metabolic (e.g. Hypokalemic Alkalosis)	0	1 (0.7%)	1 (0.3%)
Dehydration	6 (3.8%)	2 (1.4%)	8 (2.7%)
Spontaneous (Unknown)	39 (24.5%)	14 (10.0%)	53 (17.7%)
Medication (Sedatives, Tranquilizers, Analgesics)	1 (0.6%)	2 (1.4%)	3 (1.0%)
GI Hemorrhage Requiring ≥2 units of blood by transfusion	0	0	0
Renal Failure requiring Dialysis	0	0	0
TIPS or Surgical Shunt Placement	0	0	0
CNS Insult	0	0	0
Other	7 (4.4%)	5 (3.6%)	12 (4.0%)
Not Available	3 (1.9%)	4 (2.9%)	7 (2.3%)

Note: Early termination subjects were contacted on or after 6 months from randomization to determine if they had experienced a breakthrough HE episode or other outcome. The breakthrough HE episode factors were not collected. These subjects were summarized as Not Available

Medical Officer's Comments:

The majority of the contributing factors were not well documented, and often little data were available supporting the assignment of these diagnoses.

Analysis of Concomitant Antibiotic Use

The Division requested data on concomitant antibiotic use and length of antibiotic use, as chronic prophylactic use has been reported to increase survival and decrease episodes of spontaneous bacterial peritonitis in patients⁷. The Applicant provided the following information. Approximately 27% of patients participating in RFHE3001 took an antibiotic during the course of the study (28% placebo; 25% rifaximin).

Table 18: Antibiotic Use by Treatment

Number of Days	Placebo (N = 159) n (%)	Rifaximin 550 mg BID (N = 140) n (%)
10 days or less	23 (14.5%)	20 (14.3%)
>10 - 30 days	12 (7.5%)	10 (7.1%)
>30 - 60 days	4 (2.5%)	3 (2.1%)
>60 - 90 days	2 (1.3%)	0
> 90 days	4 (2.5%)	2 (1.4%)

Source: Applicant response to information request Dec 23, 2009

There were 24 patients who took antibiotics for more than 30 days OR for the indication of prophylaxis of SBP (16 placebo; 8 rifaximin). An exploratory analysis on this small subset of 24 patients shows a reduction in risk of breakthrough overt HE in the rifaximin group (2 breakthrough HE/8 patients) compared with placebo (8 breakthrough HE/16 patients) hazard ratio=0.5, 95% CI (0.106, 2.358) (p=0.3717). This apparent reduction in risk is consistent with predefined primary and subgroup analyses.

The Applicant has performed an additional analysis of the potential influence of concomitant antibiotic use (> 30 days or for SBP prophylaxis) on the primary endpoint, time to breakthrough HE. The results indicate concomitant antibiotic use had no significant influence on outcome with respect to time to breakthrough HE (p=0.3715). The treatment effect remained consistent (57.5% reduction in risk) when concomitant antibiotic use was included in the Cox proportional hazards model (hazard ratio=0.425, 95% CI (0.279, 0.648) (p<0.0001).

Analysis by Child's-Pugh Class

Rifaximin treatment resulted in reductions in the risk of breakthrough overt HE, when compared to placebo, across Child-Pugh A, B, and C classes. The risks of breakthrough overt HE episodes were reduced in the rifaximin group compared to placebo by 66% in Child-Pugh A subjects, by 56% in Child-Pugh B subjects, and by 66% in Child-Pugh C subjects.

Table 19: Breakthrough Overt HE Episodes by Child-Pugh Class and by Treatment Group – RFHE3001

	Rifaximin 550 mg BID	Placebo	Hazard ratios (95% CI) ^a	p-value ^a
Child-Pugh A (5-6), n	46	56		
Breakthrough overt HE, n (%)	8 (17.4)	26 (46.4)	0.339 (0.153, 0.749)	0.0050
No breakthrough overt HE, n (%)	38 (82.6)	30 (53.6)		
Child-Pugh B (7-9), n	65	72		
Breakthrough overt HE, n (%)	15 (23.1)	32 (44.4)	0.442 (0.239, 0.816)	0.0073
No breakthrough overt HE, n (%)	50 (76.9)	40 (55.6)		
Child-Pugh C (10-15), n	17	14		
Breakthrough overt HE, n (%)	5 (29.4)	9 (64.3)	0.345 (0.115, 1.037)	0.0474
No breakthrough overt HE, n (%)	12 (70.6)	5 (35.7)		

Source: Table 2 (Section 10); Abbreviations: BID = twice daily; CI=confidence interval.




Note: Twelve subjects in the rifaximin group and 17 in the placebo group had missing Child-Pugh classification at baseline.

Child-Pugh subscores, total score (5-15), and classifications (A,B, or C) were obtained post study.

a Hazard ratio, 95% CI, and p-value determined from time to breakthrough HE analysis using Cox proportional hazards model with effect for treatment.

Rifaximin was also found to reduce the risk of breakthrough HE across MELD categories, though for the MELD category of 19 -24 the numbers are too small to permit meaningful analysis. See Table 20.

Table 20: Time to First Breakthrough Overt HE Episode by Subgroup (up to 6 Months of Treatment, Day 170) (ITT Population)

MELD ≤ 10		N=34	N=48	p=0.0123
MELD 11 - 18		N=94	N=96	p=0.0002
MELD 19 - 24		N=12	N=14	p=0.2090

Discussion of Study Efficacy Results

Medical Officer's Comments:

The primary endpoint validity and reproducibility is open to question. Approximately 30% of patients in the trial were assigned a Conn score and diagnosis of breakthrough HE without direct observation by a site investigator or a physician at a hospital. The complete HESA work sheets were not included in the CRF's and thus the Conn scores assigned could not be validated. The Division of Neurology Products consult review concluded that the report of Study RFHE3001 did not provide enough evidence to establish that rifaximin is efficacious, based on the primary endpoint and the limitations of its assessment in this study. Please refer to the neurology review under Tab 3 of this briefing document. No validated endpoints have been established for clinical trials in Hepatic Encephalopathy

6.1.5 Analysis of Secondary Endpoints(s)

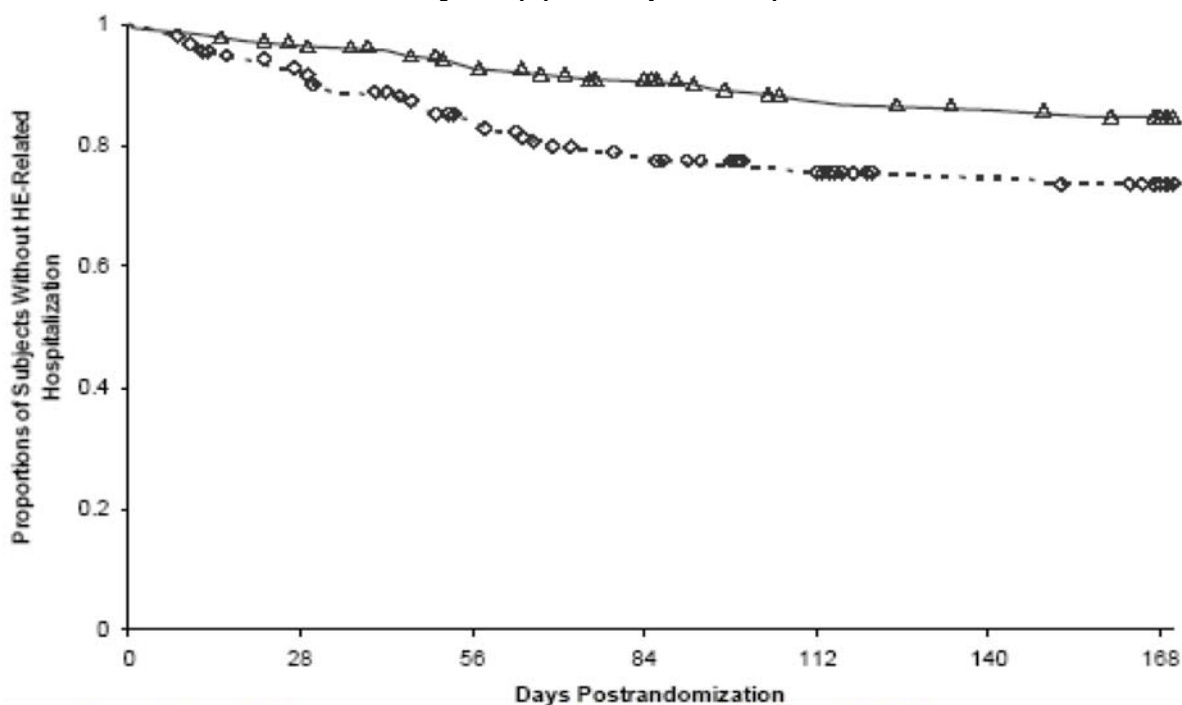
Key secondary endpoints were prospectively placed in hierarchical order as shown below and statistical testing was performed according to this order.

1. Time to first HE-related hospitalization.
2. Time to any increase from baseline in Conn score (mental state grade)
3. Time to any increase from baseline in asterixis grade.
4. Mean change from baseline in fatigue domain score on the Chronic Liver Disease Questionnaire (CLDQ) at end of treatment.
5. Mean change from baseline in venous ammonia concentration at end of treatment.

1. Time to first HE-related hospitalization

Hospitalizations due to HE were reported for 19 of 140 (13.6%) rifaximin treated subjects and 36 of 159 (22.6%) subjects in the placebo groups. Rifaximin appeared to reduce the risk of HE-related hospitalization during the 6-month treatment period; in the rifaximin group relative to placebo was 0.500, 95% CI (0.287, 0.873) ($p = 0.0129$).

Figure 3: Time to First HE-Related Hospitalization (up to 6 Months of Treatment, Day 170) (ITT Population)



Source: [Summary Figure 14.2.2](#), Section 14.2, corresponding [Data Listings 16.2.6.4.1](#) and [16.2.6.4.2](#), Appendix 16.2.6.

Note: Dashed line represents rifaximin group and solid line represents placebo group. Open circles and open triangles represent censored subjects. Subjects who discontinued prior to hospitalization due to HE and prior to completion of the 6-month treatment period were censored at the time of discontinuation. Hepatic encephalopathy-related hospitalization was recorded on the HE-related hospitalization CRF. For some subjects who had no entry on the HE-related hospitalization CRF, the occurrence of HE-related hospitalization was determined from the SAE CRF page.

Table 21: Analyses of Time to First HE-Related Hospitalization (up to 6 Months of Treatment, Day 170) (ITT Population)

Placebo (N = 159)						Rifaximin (N = 140)				
Treatment interval (days)	At risk ^a	Number of events ^b	Cumulative number of events	Event probability (SE) ^c	Probability of no HE-related hospitalization ^d	At risk ^a	Number of events ^b	Cumulative number of events	Event probability (SE) ^c	Probability of no HE-related hospitalization ^d
0 to <28	155	11	11	0.07 (0.02)	1.0000	139	4	4	0.03 (0.01)	1.0000
28 to <56	132	12	23	0.09 (0.03)	0.9288	130	4	8	0.03 (0.02)	0.9711
56 to <84	108	7	30	0.06 (0.02)	0.8440	119	4	12	0.03 (0.02)	0.9411
84 to <140	88	4	34	0.05 (0.02)	0.7893	106	5	17	0.05 (0.02)	0.9094
140 to <168	72	2	36	0.03 (0.02)	0.7535	92	2	19	0.02 (0.02)	0.8665
≥168	34	0	36	0	0.7525	43	0	19	0	0.8475
Hazard ratio:										
95% CI:										
p-value										

Source: [Summary Table 14.2.2.1](#), Section 14.2, corresponding [Data Listings 16.2.6.4.1](#) and [16.2.6.4.2](#), Appendix 16.2.6.

Abbreviations: CI = confidence interval; SE = standard error.

a Number of subjects at risk during the treatment interval, estimated using the life table method. Assuming that censored cases were at risk for half of the interval, they only counted for half in figuring the number at risk.

b Number of events occurring during the treatment interval.

c Estimate of the probability of experiencing HE-related hospitalization during the treatment interval. Standard error estimated by using Greenwood's formula.

d Estimate of the probability of no HE-related hospitalization until at least the beginning of the next treatment interval.

e Hazard ratio estimate (hazard of HE-related hospitalization in the rifaximin group compared with the placebo group) determined from the Cox proportional hazards model. P-value based on the Score statistic.

The Division requested further information from the Applicant with analysis of whether the breakthrough-HE episode resulted in any hospitalization or not. We also requested information on length of stay for hospital admission for breakthrough HE episodes. The Applicant replied that data were not collected and not available for duration of hospitalization for breakthrough HE episodes.

The Applicant did provide the analyses below of Breakthrough HE Hospitalizations.

- Breakthrough HE hospitalization: Forty-four (15 Rifaximin, 29 Placebo) of the 104 subjects diagnosed with a protocol-defined breakthrough HE episode were hospitalized specifically due to the breakthrough HE episode.
- HE-caused hospitalization: In addition to the 44 patients in bullet 1, there were four patients in the placebo group who were hospitalized with a diagnosis of HE, however, the site investigator felt that they did not meet breakthrough criteria. When those patients were included in the analysis, forty-eight (15 Rifaximin; 33 Placebo) of the 299 subjects had HE-caused hospitalization (i.e., hospitalization directly resulting from breakthrough HE or HE symptoms not meeting breakthrough criteria).

- HE-related hospitalization: In addition to the 44 patients in bullet 1, there were four Rifaximin patients and 7 placebo patients who were hospitalized for other reasons but subsequently developed HE while in the hospital. Hence fifty-five (19 Rifaximin; 36 Placebo) of the 299 subjects had HE-related hospitalization (i.e., hospitalization directly resulting from HE or hospitalization complicated by HE).
- All-cause hospitalization: One hundred six subjects (46 Rifaximin; 60 Placebo) of the 299 subjects were hospitalized for any reason.

Table 22: Proportion of Breakthrough HE events that caused Hospitalization and did not cause Hospitalization

	Placebo (N = 73) n (%)	550mg Rifaximin BID (N = 31) n (%)
Breakthrough-HE Episode Resulting Any Hospitalization		
Yes (HE event caused hospitalization)	29 (39.7%)	15 (48.4%)
No (HE event w/o hospitalization)	44 (60.3%)	16 (51.6%)
Time to Breakthrough HE Episode Resulting Any Hospitalization Analysis		
Hazard Ratio [1]:	0.491	
95% CI:	(0.263, 0.916)	
p-value:	0.0225	

[1] Hazard ratio estimate (hazard of breakthrough HE for rifaximin compared to placebo) obtained from Cox proportional hazards model with effect for treatment, stratified by analysis region. P-value based on the Score statistic.

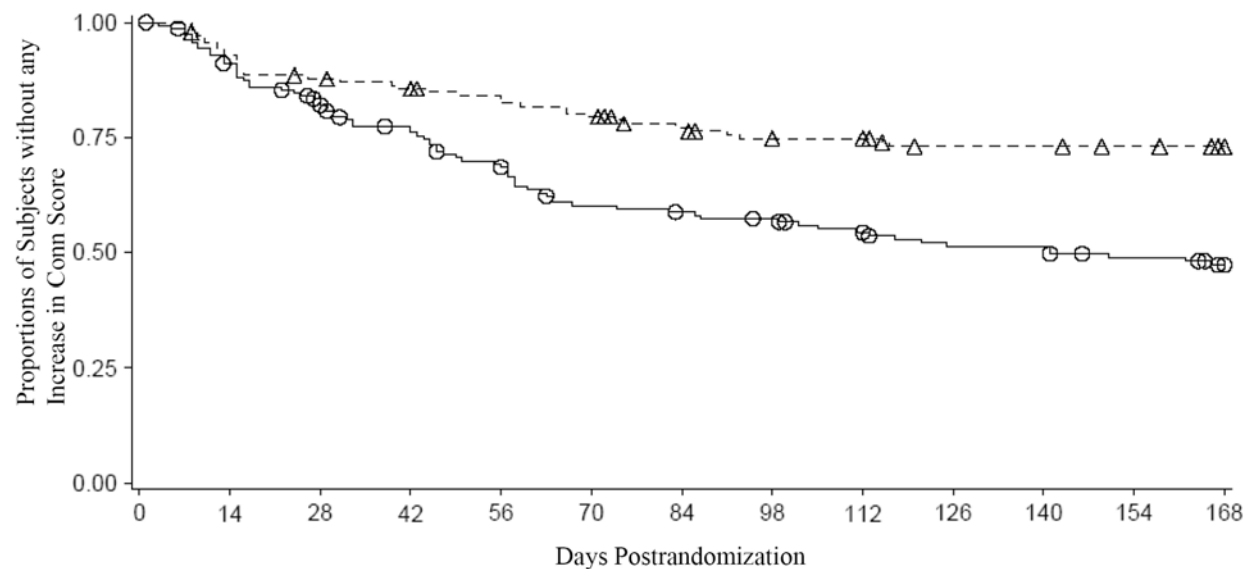
Medical Officer's Comment:

A higher proportion of the HE events in the placebo arm did not result in hospitalization.

2. Time to any increase from baseline in Conn score

Breakthrough overt HE episodes were experienced by 31 of 140 (22.1%) subjects in the rifaximin group and by 73 of 159 (45.9%) subjects in the placebo group during the 6-month treatment period (up to Day 170) in the primary efficacy analysis. A prespecified secondary endpoint was a comparison of time to increase from baseline in Conn score. Increases in Conn score were reported for 37 of 140 (26.4%) subjects treated with rifaximin and 77 of 159 (48.4%) subjects in the placebo group. The time to first increase in Conn score was longer on the rifaximin arm than on placebo; hazard ratio in the rifaximin group relative to placebo was 0.463, 95% CI (0.312, 0.685) ($p < 0.0001$) during the 6-month treatment period

Figure 4: Time to First Increase in Conn Score (up to 6 Months of Treatment, Day 170) (TT Population)



Source: Summary Figure 14.2.3, Section 14.2, corresponding Data Listing 16.2.6.5, Appendix 16.2.6.
Note: Dashed line represents rifaximin group and solid line represents placebo group. Open circles and open triangles represent censored subjects. Subjects who discontinued prior to the first increase in Conn score and prior to completion of the 6-month treatment period were censored at the time of discontinuation

Table 23: Kaplan-Meier Estimates and Statistical Analyses of Time to First Increase in Conn Score (up to 6 Months of Treatment, Day 170) (ITT Population)

Placebo (N = 159)						Rifaximin (N = 140)				
Treatment interval (days)	At risk ^a	Number of events ^b	Cumulative number of events	Event probability (SE) ^c	Probability of no increase in Conn score ^d	At risk ^a	Number of events ^b	Cumulative number of events	Event probability (SE) ^c	Probability of no increase in Conn score ^d
0 to <28	156	26	26	0.17 (0.03)	1.0000	139	17	17	0.012 (0.03)	1.0000
28 to <56	125	21	47	0.17 (0.03)	0.8333	119	5	22	0.04 (0.02)	0.8777
56 to <84	100	15	62	0.15 (0.04)	0.6928	109	9	31	0.08 (0.03)	0.8407
84 to <140	80	10	72	0.13 (0.04)	0.5883	94	5	36	0.05 (0.02)	0.7713
140 to <168	62	5	77	0.08 (0.03)	0.5143	79	0	36	0	0.7302
≥168	27	0	77	0	0.4729	37	1	37	0.03 (0.03)	0.7302
Hazard ratio:										
95% CI:										
p-value										

Source: [Summary Table 14.2.2.2](#), Section 14.2, corresponding [Data Listing 16.2.6.5](#), Appendix 16.2.6.

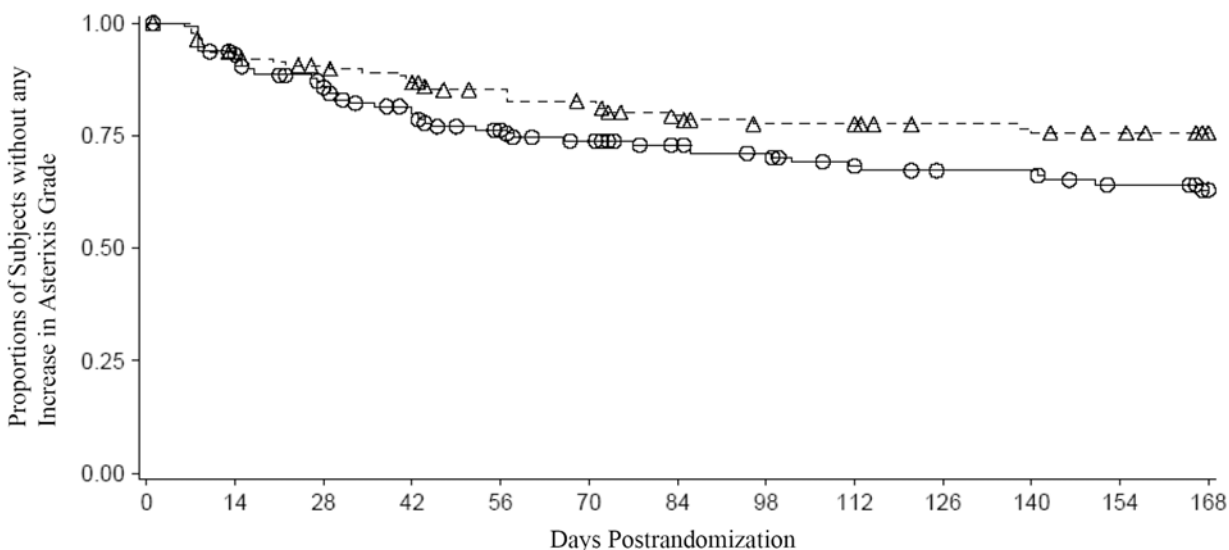
Abbreviations: CI = confidence interval; SE = standard error.

- a Number of subjects at risk during the treatment interval, estimated using the life table method. Assuming that censored cases were at risk for half of the interval, they only counted for half in figuring the number at risk.
- b Number of events occurring during the treatment interval.
- c Kaplan-Meier estimate of the probability of experiencing an increase in Conn score during the treatment interval. Standard error estimated by using Greenwood's formula.
- d Estimate of the probability of no increase in Conn score until at least the beginning of the next treatment interval.
- e Hazard ratio estimate (hazard of experiencing an increase in Conn score in the rifaximin group compared with the placebo group) determined from the Cox proportional hazards model. P-value based on the Score statistic.

3. Time to any increase from baseline in asterixis grade

Breakthrough overt HE episodes were experienced by 31 of 140 (22.1%) subjects in the rifaximin group and by 73 of 159 (45.9%) subjects in the placebo group during the 6-month treatment period (up to Day 170) in the primary efficacy analysis. Analysis of time to any increase from baseline in asterixis grade was a prospectively defined secondary endpoint of interest. Increases in asterixis grade were reported for 32 of 140 (22.8%) subjects and 50 of 159 (31.4%) subjects in the rifaximin and placebo groups, respectively. The comparison of subjects with events in the primary analysis to that of the secondary asterixis grade analysis indicates that many of the events in the primary analysis in the placebo arm were defined by Conn Score assessment. The time to increase in asterixis grade (i.e., worsening in neuromotor functioning) was not significantly different between placebo and rifaximin; hazard ratio in the rifaximin group relative to placebo was 0.646, 95% CI (0.414 to 1.008) ($p = 0.0523$). Therefore, due to the prespecified gate-keeping approach to handle multiplicity, any analyses that follow are exploratory in nature.

Figure 5: Time to First Increase in Asterixis Grade (up to 6 Months of Treatment, Day 170) (ITT Population)



Source: Summary Figure 14.2.4, Section 14.2, corresponding Data Listing 16.2.6.5, Appendix 16.2.6.
Note: Dashed line represents rifaximin group and solid line represents placebo group. Open circles and open triangles represent censored subjects. Subjects who discontinued prior to the first increase in asterixis grade and prior to completion of the 6-month treatment period were censored at the time of discontinuation.

Table 24: Kaplan-Meier Estimates and Statistical Analyses of Time to First Increase in Asterixis Grade (up to 6 Months of Treatment, Day 170) (ITT Population)

Placebo (N = 159)						Rifaximin (N = 140)				
Treatment interval (days)	At risk ^a	Number of events ^b	Cumulative number of events	Event probability (SE) ^c	Probability of no increase in asterixis grade ^d	At risk ^a	Number of events ^b	Cumulative number of events	Event probability (SE) ^c	Probability of no increase in asterixis grade ^d
0 to <28	154	20	20	0.13 (0.03)	1.0000	137	13	13	0.10 (0.03)	1.0000
28 to <56	120	15	35	0.13 (0.03)	0.8697	116	7	20	0.06 (0.02)	0.9048
56 to <84	91	4	39	0.04 (0.02)	0.7610	101	7	27	0.07 (0.03)	0.8499
84 to <140	76	6	45	0.08 (0.03)	0.7275	87	3	30	0.03 (0.02)	0.7910
140 to <168	61	4	49	0.07 (0.03)	0.6701	74	1	31	0.01 (0.01)	0.7637
≥168	27	1	50	0.04 (0.04)	0.6262	34	1	32	0.03 (0.03)	0.7534
Hazard ratio: 0.646 ^e										
95% CI: (0.414, 1.008)										
p-value 0.0523										

Source: [Summary Table 14.2.2.3](#), Section 14.2, corresponding [Data Listing 16.2.6.5](#), Appendix 16.2.6.

Abbreviations: CI = confidence interval; SE = standard error.

- a Number of subjects at risk during the treatment interval, estimated using the life table method. Assuming that censored cases were at risk for half of the interval, they only counted for half in figuring the number at risk.
- b Number of events occurring during the treatment interval.
- c Kaplan-Meier estimate of the probability of experiencing an increase in asterixis grade during the treatment interval. Standard error estimated by using Greenwood's formula.
- d Estimate of the probability of no increase in asterixis grade until at least the beginning of the next treatment interval.
- e Hazard ratio estimate (hazard of experiencing an increase in asterixis grade in the rifaximin group compared with the placebo group) determined from the Cox proportional hazards model. P-value based on the Score statistic.

4. Changes from baseline in Chronic Liver Disease Questionnaire (CLDQ)-fatigue domain score at end of treatment

Subjects ranked their level of fatigue by using a 7-point scale from the worst response (1, high degree of fatigue) the best response (7, minimal fatigue). Minimal differences between rifaximin and placebo groups were observed in the changes from baseline in CLDQ fatigue score.

5. Changes from baseline in venous ammonia levels at end of treatment

In the current study, venous ammonia levels were highly variable over the course of the study. Subjects in the rifaximin group were observed to have greater reductions in venous ammonia levels compared to placebo-treated subjects.

Table 25: Mean (SD) Changes from Baseline in Venous Ammonia Level by Treatment Group (ITT Population)

	Placebo N = 159 (µg/dL)	Rifaximin N = 140 (µg/dL)	P-Value ^a
Baseline	n = 149	n = 132	
Mean (SD) venous ammonia level	92.1 (55.24)	87.9 (47.76)	
End of treatment	n = 143	n = 132	
Mean (SD) venous ammonia level	88.6 (45.61)	83.9 (45.02)	
Change from baseline to end of treatment	n = 133	n = 125	
Mean (SD) change in venous ammonia level	-1.2 (60.98)	-5.7 (46.77)	p = 0.0391

Source: [Summary Table 14.2.2.5](#), Section 14.2; corresponding [Data Listing 16.2.6.6](#), Appendix 16.2.6.

Note: Baseline value was the last available value prior to first dose of study drug, and end of treatment value was the last available postbaseline value during the treatment period.

a P-value was calculated using analysis of covariance with effects for treatment and geographic analysis region, and baseline as a covariate.

From Applicant RFHE3001 Clinical Study Report Table 23

Medical Officer's Comments:

There is no direct correlation with serum ammonia, clinical chemistry levels or liver function tests and diagnosis of HE. Serum ammonia levels are commonly drawn in clinical practice; however, outside of very specific handling, serum ammonia does not correlate well with the clinical evaluation of the patient. In this study, there was not a defined protocol for handling of serum venous ammonia levels. Therefore, we question whether the results are reliable and clinically meaningful.

Please note that this secondary endpoint analysis was conducted after time to increase to asterixis grade (which was shown to be not significantly significant between the treatment arms) hence the analysis is exploratory in nature, due to the prespecified gate-keeping strategy adopted to analyze secondary endpoints. Therefore, the p-value (p = 0.0391) results cannot be interpreted as statistically significant.

Other secondary efficacy endpoints

Tracking of Conn scores and asterixis grades: changes from baseline in Conn scores and asterixis grades

Additional analyses were conducted to explore whether there may be a treatment effect with respect to the proportions of subjects who had changes of -1 (improvement) or 0 (no change); or 1, 2, or 3 (worsening) in Conn score from baseline to end of treatment (last post-baseline assessment or assessment at time of breakthrough HE). In the rifaximin group, higher proportions of subjects were reported to have Conn score changes of -1 or no change (77.1% versus 53.9% of placebo subjects) and lower proportions of subjects had Conn score changes of 1, 2, 3, or 4. A similar proportion of

patients in each arm had a 2 point increase in Conn score. The greatest difference between the two treatment arms was in the proportion of patients who were reported to have a 1 point increase in Conn score. However, there were also a higher proportion of patients in the placebo arm who were reported to have a 3 point increase in Conn score, 7% vs. 2%.

Similarly, an exploration of changes from baseline to end of treatment in asterixis grade, revealed that a higher proportion of subjects in the rifaximin group versus the placebo group were reported to have changes from baseline in asterixis grades of -2, -1, and 0 (88.5% versus 77.0%), and a lower proportion had changes of 1, 2, 3, or 4 (11.6% versus 23.2%). Most of the patients in the study who were reported to have an increase in asterixis grade had a 1 point increase in the grade.

Table 26: Changes in Conn Score and Asterixis Grade from Baseline to End of Treatment or to Assessment at Breakthrough Overt HE Episode (ITT Population)

Change from baseline to end of treatment or to assessment at breakthrough overt HE episode ^a	Placebo N = 159 n (%)	Rifaximin N = 140 n (%)	Odds Ratio ^b of rifaximin to placebo (95% CI)	P-value ^b
Conn score				
n	152	135	2.46 (1.56, 3.87)	< 0.0001
-1	14 (9.2)	24 (17.8)		
0	68 (44.7)	80 (59.3)		
1	38 (25.0)	13 (9.6)		
2	19 (12.5)	15 (11.1)		
3	11 (7.2)	2 (1.5)		
4	2 (1.3)	1 (0.7)		
Asterixis grade				
n	117	121	1.92 (1.08, 3.42)	0.0262
-2	1 (0.9)	1 (0.8)		
-1	9 (7.7)	15 (12.4)		
0	80 (68.4)	91 (75.2)		
1	18 (15.4)	9 (7.4)		
2	7 (6.0)	3 (2.5)		
3	1 (0.9)	2 (1.7)		
4	1 (0.9)	0		

Source: [Summary Tables 14.2.3.2](#) and [14.2.3.3](#), Section 14.2, corresponding [Data Listings 16.2.6.1](#) and [16.2.6.5](#), Appendix 16.2.6.

Abbreviations: CI = confidence interval.

- a Baseline value was the last available value prior to first dose of study drug, and end of treatment value was the assessment at breakthrough overt HE episode for subjects who had breakthrough HE and the last available postbaseline value for subjects without breakthrough HE during the treatment period.
- b P-value was calculated using proportional odds model with effects for treatment and geographic analysis region.

Other secondary efficacy endpoints

1. Time to diagnosis of spontaneous bacterial peritonitis (SBP).

Time to diagnosis of SBP was not analyzed because only 7 subjects experienced SBP. These SBP data were presented in a data listing.

2. Mean change from baseline in critical flicker frequency (CFF) values at each post-baseline assessment and at end of treatment.

Increases in CFF results might represent improvement in neurological function in patients with HE, but this has not been validated. This methodology was explored in this study and the analysis of this secondary endpoint is exploratory. It was not included in the list of key secondary endpoints for hierarchical analysis. The nominal p-values and confidence intervals for this additional analysis cannot be viewed as providing evidence of efficacy. From the statistical standpoint, the analysis of the numerous additional endpoints in this application, and their varied *post-hoc* analyses can not provide evidence of a positive treatment effect. Subjects in the rifaximin group were observed to have greater increases in CFF relative to baseline at end of treatment when compared with placebo. Mean changes (\pm SD) in CFF results were 0.945 (\pm 4.75) in the rifaximin group versus 0.355 (\pm 4.70) in the placebo group.

Table 27: Mean (SD) Changes from Baseline in CFF Test Results by Treatment Group (ITT Population)

	Placebo N = 159 (Hz)	Rifaximin N = 140 (Hz)	P-Value ^a
Baseline	n = 159	n = 140	
Mean (SD) CFF result	37.41 (6.03)	36.90 (5.47)	
End of treatment	n = 155	n = 139	
Mean (SD) CFF result	37.60 (5.98)	37.81 (4.88)	
Change from baseline to end of treatment	n = 155	n = 139	
Mean (SD) change in CFF result	0.355 (4.70)	0.945 (4.75)	p = 0.0320

Source: [Summary Table 14.2.3.1](#), Section 14.2; corresponding [Data Listing 16.2.6.8](#), Appendix 16.2.6.

Note: Baseline value was the last available value prior to first dose of study drug, and end of treatment value was the last available postbaseline value during the treatment period.

a P-value was calculated using analysis of covariance with effects for treatment and geographic analysis region, and baseline as a covariate.

6.1.6 Other Endpoints

Tertiary efficacy endpoints included:

1. Mean change from baseline in CLDQ scores at each post-baseline assessment and at end of treatment.
2. Mean change from baseline in Epworth Sleepiness Scale (ESS) total score at each post-baseline assessment and at end of treatment.
3. Proportion of subjects who had an ESS total score ≥ 10 at each post-baseline assessment and at end of treatment.

4. Mean change from baseline in SF-36 QoL scores at each post-baseline assessment and at end of treatment.

Reviewer Comment: Analysis by the Applicant revealed no consistent differences between placebo and rifaximin groups in the changes from baseline in all the above measurements during the course of the study.

5. Average daily lactulose usage (cup/day, and 1 cup = 15 mL).
See also Section 6.1.10 Additional Efficacy Issues/Analyses

Approximately 91% of subjects in each treatment group received concomitant lactulose during the course of the study (See 6.1.10 Additional Efficacy Issues/Analyses and Table 28). Daily lactulose use over the total 6-month treatment period and lactulose use by study day were similar between rifaximin and placebo groups. Mean (\pm SD) daily lactulose use was 3.14 (\pm 2.096) cups/day in the rifaximin group and 3.51 (\pm 2.592) cups/day in the placebo group (In-Text Table 26). One cup of lactulose is equal to 15 mL (10 g lactulose/15 mL).

Lactulose use over time was consistent in both treatment groups during the course of the study; mean (\pm SD) rates of change were 0.0030 (\pm 0.03767) and 0.0076 (\pm 0.10595) cups per day in the rifaximin and placebo groups, respectively (In-Text Table 26).

Medical Officer's Comment:
As lactulose was used in 91% of patients in both placebo and rifaximin groups, the efficacy of rifaximin as a stand alone treatment has not been evaluated in RFHE 3001. It is not clear that rifaximin should be used alone instead of as adjunctive therapy with lactulose.

6. Duration (in days) of HE-related serious adverse events (SAEs) leading to hospitalization. For the duration of HE-related SAEs leading to hospitalization.

The Applicant reported that available data were not sufficient for analysis.

6.1.7 Subpopulations

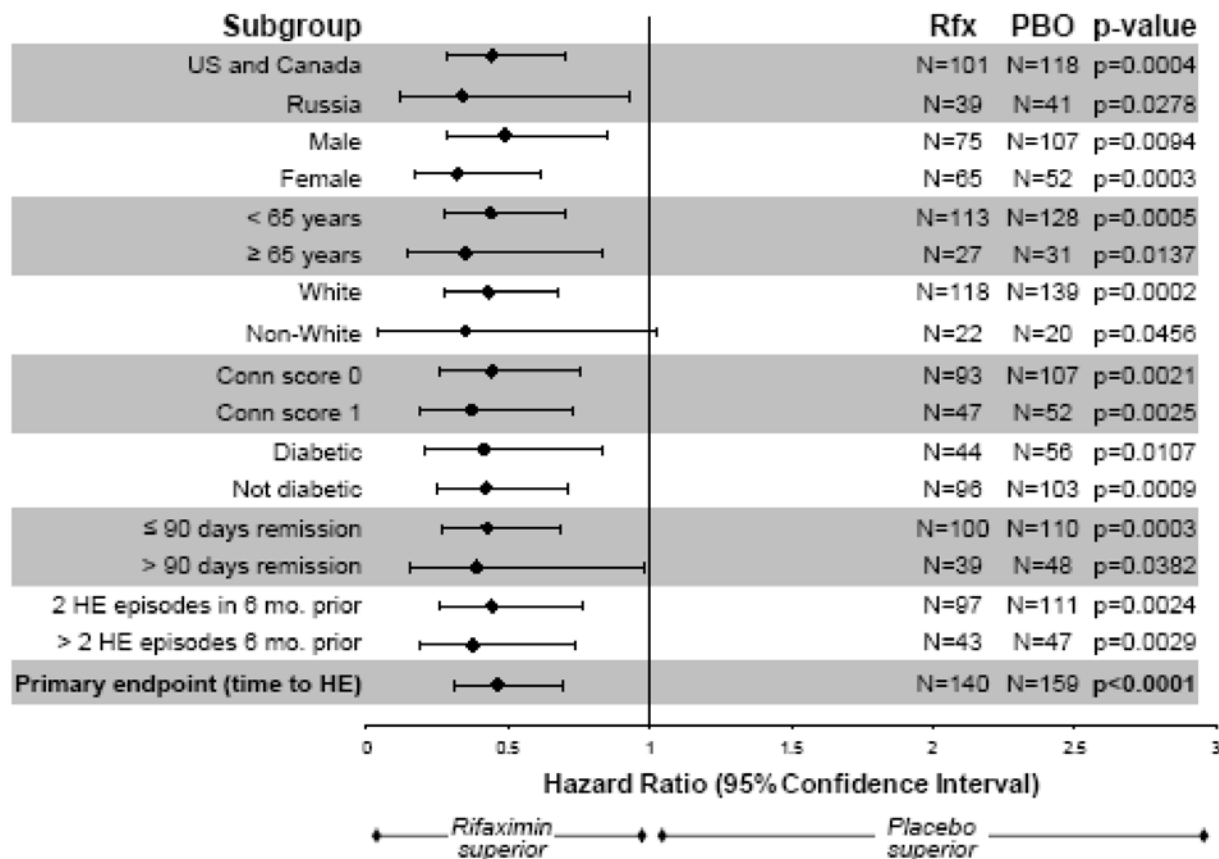
Subgroup analyses

Subgroup analyses were conducted to determine the robustness of the observed rifaximin treatment effect for the primary efficacy endpoint. Outcomes for the primary efficacy endpoint were evaluated in the following subgroups: geographic analysis region (North America versus Russia), sex, age (< 65 versus ≥ 65 years), and race (white versus nonwhite), baseline MELD level (≤ 10 , 11 - 18, 19 - 24), baseline Conn score (0 versus 1), prior lactulose use (yes versus no), diabetes at Baseline (yes versus no), duration of current verified remission (≤ 90 days versus > 90 days), and the number of

HE episodes within the 6 months prior to randomization (2 versus > 2). The effect of rifaximin treatment in reducing the risk of experiencing breakthrough overt HE episodes during the 6-month treatment period was consistent across all subgroups.

Hazard ratios for the risk of experiencing breakthrough overt HE in the rifaximin group relative to the placebo group, 95% CIs, and p-values from the Cox proportional hazards model are presented in Figure 6 below. Hazard ratios of less than 1 indicate that the outcome favors rifaximin and those greater than 1 indicate an outcome that favors placebo.

Figure 6: Time to First Breakthrough Overt HE Episode by Subgroup (up to 6 Months of Treatment, Day 170) (ITT Population)



Analyses by baseline MELD score and by prior lactulose use resulted in subgroups with small numbers of subjects, MELD score of 19 to 24 (n = 26) and no prior lactulose use (n = 26). In the no prior lactulose use and baseline MELD score 19 to 24 subpopulations, trends favoring rifaximin were observed. For the other prior lactulose use and MELD score subgroups, rifaximin treatment appeared to reduce the risk of experiencing breakthrough overt HE episodes over the 6-month treatment period.

Medical Officer's Comment:

As lactulose was used in 91% of patients in both placebo and rifaximin groups, the efficacy of rifaximin as a stand alone treatment has not been evaluated in RFHE 3001. It is not clear that rifaximin should be used alone instead of as adjunctive therapy with lactulose.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Refer to the Clinical Pharmacology Review Summary under Tab 4

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

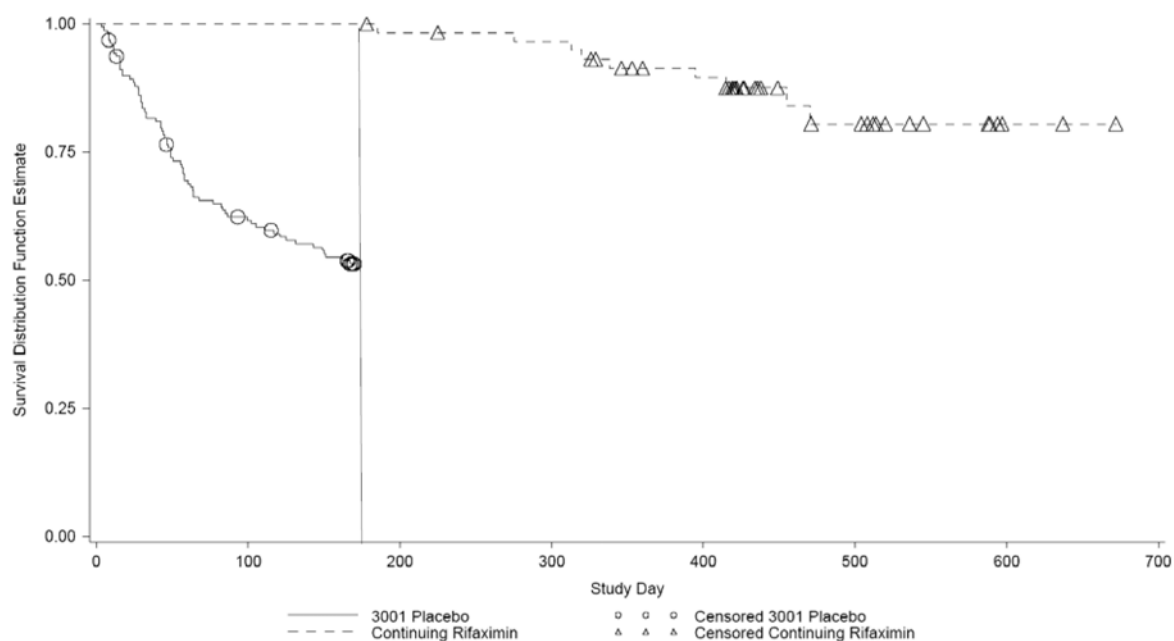
The Applicant contends that similarity of the slopes of the time to first breakthrough overt HE episode profiles between the rifaximin group in study RFHE3001 and new-to-rifaximin subjects who entered the RFHE3002 open label study is evidence of consistency of effect between the two studies. Similar proportions of subjects had breakthrough overt HE in the rifaximin group of RFHE3001 (22%, 31 of 140 [rifaximin group]) and in the new-to-rifaximin subjects in the open label trial RFHE3002 (27.6%, 54 of 196).

The Applicant reports that data from RFHE3002 provide information on the long-term durability of rifaximin for the protection against breakthrough overt HE episodes. Rifaximin treated subjects from RFHE3001 who were in remission at the end of RFHE3001 (6 months treatment) were followed during open-label study RFHE3002 (n=60). Time to first breakthrough HE episode is shown in Figure 7 for the rifaximin rollover subjects (RFHE3001 plus RFHE3002) compared to the time to event data obtained in study RFHE3001 for the placebo subjects. The incidence of breakthrough overt HE in rollover rifaximin subjects was historical compared to placebo subjects in RFHE3001 in an exploratory cross study comparison. The incidence of breakthrough HE episode for rifaximin subjects during the extension phase was lower than the cross study comparison to the RFHE3001 placebo group. The Applicant contends that these results demonstrate that rifaximin has a durable protective effect that continued in RFHE3002 (median exposures to rifaximin were 168 days in RFHE3001 and 253 days in RFHE3002).

Medical Officer's Comments:

The Applicant's analysis that compares the rifaximin treated subjects in RFHE3002 to the placebo group in RFHE3001 is exploratory and based on cross trial comparisons. No definite conclusions can be drawn from this analysis.

Figure 7: Kaplan Meier Estimates of Distribution of Time to First Breakthrough HE for Continuing Rifaximin Subjects Who Did Not Have an HE Episode in RFHE3001 vs. Placebo



6.1.10 Additional Efficacy Issues/Analyses

Lactulose Use

A total of 273 of 299 subjects (91.3%) received lactulose as a prior medication and as a concomitant medication during the study (See Table 28). The percentages of subjects who took lactulose were similar between the placebo (91.2%) and rifaximin (91.4%) groups during the course of the study. Three subjects (2 [placebo] and 1 [rifaximin]) were not treated with lactulose before entering the study but started lactulose use during the treatment period. Subjects in Russia received an average of 2.44 cups/day of lactulose and subjects in the United States and Canada received an average of 5.57 cups/day during the course of the study (1 cup = 15 mL [10 g lactulose/15 mL]).

Daily lactulose use over the total 6-month treatment period (see Table 28) and lactulose use by study day (see Figure 8) were similar between rifaximin and placebo groups. Mean (\pm SD) daily lactulose use was 3.14 (\pm 2.096) cups/day in the rifaximin group and 3.51 (\pm 2.592) cups/day in the placebo group. One cup of lactulose is equal to 15 mL (10 g lactulose/15 mL).

Lactulose use over time was consistent in both treatment groups during the course of the study; mean (\pm SD) rates of change were 0.0030 (\pm 0.03767) and 0.0076 (\pm 0.10595) cups per day in the rifaximin and placebo groups, respectively.

Medical Officer's Comment:

As lactulose was used in 91% of patients in both placebo and rifaximin groups, the efficacy of rifaximin as a stand alone treatment has not been evaluated in RFHE 3001. It is not clear that rifaximin should be used alone instead of as adjunctive therapy with lactulose.

Table 28: Daily Lactulose Use during the Treatment Period by Treatment Group (ITT Population)

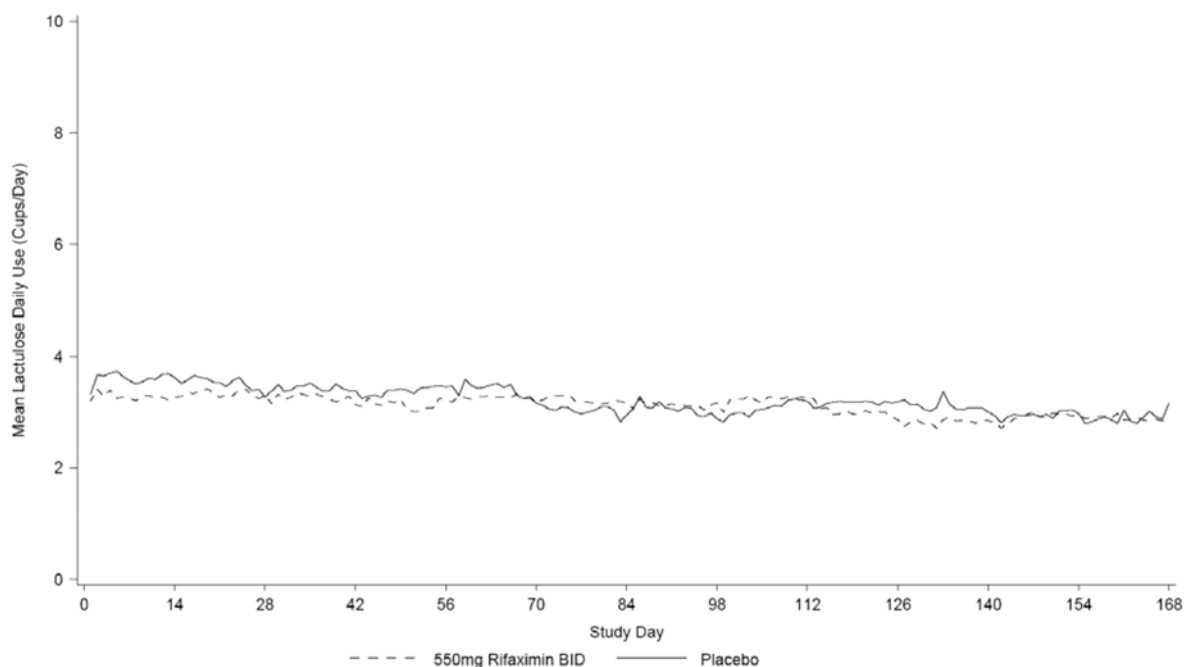
	Placebo N = 159	Rifaximin N = 140
Average daily lactulose use during the treatment period – (cups/day)^a		
n	142	132
Mean (SD)	3.51 (2.592)	3.14 (2.096)
Median (min, max)	2.82 (0, 11.8)	2.82 (0, 9.0)
Lactulose use change rate – (cups/day)^a		
n	142	132
Mean (SD)	0.0076 (0.10595)	0.0030 (0.03767)
Median (min, max)	0.0 (-0.136, 1.0)	0.0 (-0.158, 0.321)
Lactulose use during the treatment period – n (%)		
Yes	145 (91.2)	128 (91.4)
No	14 (8.8)	12 (8.6)
Prior lactulose use – n (%)		
Yes	145 (91.2)	128 (91.4)
No	14 (8.8)	12 (8.6)

Source: [Summary Tables Table 14.1.6a](#), and [14.2.4.5](#), Section 14.2; corresponding [Data Listing 16.2.6.14](#), Appendix 16.2.6.

a One cup = 15 mL lactulose at 10 g/15 mL.

Note: The daily diary asked for the total number of units of lactulose received on each study day. Therefore, subjects recorded lactulose units by entering the number of cups/tablespoons or by entering the number of mL (after multiplying number of cups/tablespoons times 15 [1 cup = 15 mL]). Twenty-seven subjects had diary entries of ≥ 15 units. These entries were reviewed against the CRF, the concomitant medication log, study comment log, drug dispensation log, and other source documents. For these 27 subjects, lactulose units that were determined to be entered in mL were divided by 15 to convert mL of lactulose to cups of lactulose.

Figure 8: Daily Lactulose Use by Treatment Group (ITT Population)



Note: Subjects with missing lactulose use information were excluded

Medical Officer's Comments:

Lactulose use was similar in the treatment and placebo arms. It was used by the majority of patients and does not appear to have been a confounding factor, if its use was recorded accurately. The Applicant has not performed a food effects study with lactulose.

7 Review of Safety

Safety Summary

The important safety data for rifaximin in the maintenance of remission of HE comes from the **Primary Analysis Population**, which is defined by the Applicant as the patients in studies RFHE3001 and RFHE3002. In addition, there are some safety data for rifaximin in the **Secondary Analysis Population**, which is defined by the Applicant as the patients with active HE treated with rifaximin in acute short-term interventional trials (up to 15 days). Safety data for rifaximin were also provided from the **Supportive Analysis Population**, which is defined by the Applicant as patients treated with rifaximin in trials for other indications (e.g., treatment/prevention of travelers' diarrhea, irritable bowel syndrome). The Applicant also submitted post-marketing surveillance data, and safety information from published literature for rifaximin used in the

interventional treatment of subjects with active HE. The Secondary and Supportive data are from short term use, and do not add significantly to the over all conclusions.

The Primary Analysis Population is divided into the **Randomized Controlled Trial (RCT) Population** (exposure during the 6 month RCT) and the **Long Term Rifaximin Experience Population**. The latter is further subdivided into Continuing Rifaximin (from RFHE3001), New Rifaximin, and All Rifaximin Populations for the purpose of analysis. The Continuing Rifaximin population consists of patients from RFHE3001 who received treatment with rifaximin, on the RCT, and elected to continue on rifaximin in the treatment extension study (RFHE3002). The New Rifaximin population consists of placebo patients from RFHE3001 and new patients who enrolled in RFHE3002.

The Primary Analysis Population included 336 subjects with a mean exposure of 273.8 days (SD 160.92). Subjects exposed to rifaximin at the proposed dose for 6 months or longer totaled 257. Exposure to rifaximin at the indicated dose for 12 months or longer totaled 114 subjects. There were a low percentage of subjects with MELD scores above 18 (8-9%) in the data set, which makes meaningful evaluation of subjects with severe hepatic impairment difficult. No subjects with MELD Scores above 25 enrolled in these trials.

The rates of adverse events were high in this population of chronically ill patients. The most frequent adverse events were gastrointestinal. In the randomized controlled trial (RCT) Study population, the proportion of subjects with Treatment Emergent Adverse Events (TEAEs) was similar between subjects receiving rifaximin (80.0%) and placebo (79.9%). The rate of SAEs, however, was higher in the rifaximin group. The SAE of infection was higher in the Xifaxan group, due mainly to increase incidence of pneumonia and *C. difficile* colitis (Table 37). In the Primary Analysis Population there were 546 serious adverse events (SAE) occurring in 63 (39.6%) of placebo subjects and in 165 (49.1%) of All Rifaximin Subjects, including breakthrough HE episodes. The most frequent serious adverse events were hepatic cirrhosis, ascites, esophageal varices hemorrhage, acute renal failure, and pneumonia (excluding HE episodes that were SAEs due to hospitalization).

In the **Primary Safety Population** the mortality rate was 7% in both the treatment and placebo groups. In the **Long Term Rifaximin Experience Population**, a total of 36 subject deaths (10.7%) were recorded for All Rifaximin, inclusive of 10 rifaximin treated subjects who died during the RCT Study. The majority of deaths in both the placebo group and the rifaximin group appear to have been related to worsening hepatic function and underlying disease progression. Esophageal variceal hemorrhage was the second most common SAE resulting in death. Analysis of mortality by Child's class showed some increase in mortality in the Child's C patients in the rifaximin group, but numbers were too small to permit conclusions. There were deaths in the rifaximin treatment arm that the reviewer considered possibly related to rifaximin, which are discussed in detail In Section 7.3.1.

Post marketing surveillance events of anaphylactic reactions and cases of rifaximin-induced *C. difficile* colitis have been reported (including one death). Two (2) events of clostridium colitis (*C. difficile*) occurred in rifaximin-treated subjects in the RCT Study and 3 additional TEAEs of clostridium colitis were recorded in the open-label RFHE3002 study.

The safety concerns noted in the FDA review include:

- The Applicant did not gather follow-up data on patients who developed adverse events. The subjects were dropped from the study at the time of an adverse event that prompted withdrawal of the drug or if the subjects developed HE. Data on the length of hospitalization for HE events were not captured.
- There is a history of hepatotoxicity in cirrhotic patients taking drugs from this class (Rifampin). While rifaximin is poorly absorbed, pharmacokinetic studies indicate higher systemic exposures in this patient population with hepatic impairment. Evaluation of the data for hepatotoxicity in this dataset is confounded by the underlying liver disease in these patients. However, there were two deaths in the rifaximin group from progressive liver disease in patients with relatively low MELD scores at study entry. See Section 7.3.1.
- There are not adequate efficacy and safety data on use of rifaximin in Child's-Pugh Class C patients and/ patients with MELD scores above 25. This group of patients was excluded from these studies. Because they would be at high risk for development of HE, one would anticipate that the product will be used in this population if approved for the proposed indication.
- Thorough QT study was not performed and ECGs were not performed in the phase 3 trials.
- Pharmacokinetic trials have been not performed in renally impaired patients. Renal insufficiency is common in this population. The combination of renal and hepatic impairment could have an additive impact on increasing drug exposure in this population.

7.1 Methods

The safety evaluation will include analyses pooling studies into three separate categories:

1. **Primary Data** – RFHE 3001 and 3002 at proposed indicated dose – duration of study exposure 6 months to 2 years
 - a. RCT (Randomized Controlled trial) RFHE3001

- b. Long Term experience - RFHE3001 (excluding placebo) and RFHE3002
 - **New Rifaximin** - Placebo patient from RFHE3001 and newly enrolled patients in RFHE3002
 - **Continuing Rifaximin** - Rifaximin patients from RFHE3001 that rolled over to RFHE3001
 - **All Rifaximin** - Both above groups
2. **Secondary Data** – RFHE 9701, 9702, & 9901 – data from acute treatment trials for HE – duration of exposure ≤ 14 days
3. **Supportive Data** – all other trials for other indications (Traveler's diarrhea, IBS, Crohn's, etc) and Phase 1 trials

The Safety population is defined as all subjects who were enrolled in one of the clinical studies for rifaximin who received at least one dose of the study medication, and provided at least one post-baseline safety assessment.

Medical Officer's Comments:

The Primary Data Set is the only data from long term use of rifaximin in patients with cirrhosis, and is the most relevant data. The Secondary Data are from acute treatment of HE, 14 days or less in smaller number of patients (See Section 5.3). The Supportive Data are almost all for treatment of Traveler's Diarrhea and for very short durations in a relatively healthy population. This review will examine the Primary Data most closely.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Data for the **randomized controlled trial RFHE3001** trial (RCT) population are presented according to the double-blind study treatment assignment that the subjects actually received. The treatment groups are presented in the tables as 'Placebo' and 'Rifaximin 550 mg BID,' respectively; in that order unless otherwise specified.

Subjects in the **Primary safety population** who received at least 1 dose of rifaximin in either the randomized trial, RFHE3001, or the open-label extension study RFHE3002 were pooled for the long term rifaximin experience analysis. At the time of the data cutoff for the original NDA submission, RFHE3002 was ongoing. Data from the ongoing RFHE3002 trial was available for all subjects up to 12 February 2009 (clinical cutoff date) for this NDA submission. The experience of subjects while on placebo during the RFHE3001 trial was not included in the long term safety analyses. Safety data were summarized by group ('Continuing Rifaximin' and 'New Rifaximin') and overall ('All Rifaximin' subjects). The 'Continuing Rifaximin' group included safety data for subjects who received rifaximin in the double-blind trial RFHE3001 and rolled over into trial RFHE3002, continuing on rifaximin. The 'New Rifaximin' group included those subjects who received placebo in RFHE3001 and rolled over into RFHE3002 plus the new

subjects who did not participate in RFHE3001, but who enrolled in RFHE3002 on the basis of a demonstrated history of overt HE. For the Long Term Rifaximin Experience tables, the treatment groups will be presented in the tables as:

- **New Rifaximin**
- **Continuing Rifaximin**
- **All Rifaximin Subjects**

For the **Secondary integrated safety** analysis of rifaximin in the acute treatment of overt HE, safety data from RFHE9701, RFHE9702, and RFHE9901 (RIF/HE/INT/99) are pooled and summarized. Safety data are summarized by treatment (rifaximin, lactitol, and placebo) and rifaximin doses ('600 mg', '1200 mg', '2400 mg', and 'Total Rifaximin'). This group received only 14 days or less of rifaximin.

The **Supportive safety population** is further divided into Treatment of Travelers' Diarrhea (TD), and other trials on IBS, Crohn's Disease, and pouchitis are analyzed separately, as well as Phase 1 trials.

7.1.2 Categorization of Adverse Events

For the primary integrated analysis, treatment-emergent AEs (TEAEs) were defined as any event with a start date occurring on or after treatment Day 1 or, if it was pre-existing, worsening after treatment Day 1. Given that new events and worsening conditions were captured as unique entries on the AE case report form (CRF) pages, treatment-emergent AEs were identified as those events with start dates after the date of the first dose. Date of first dose, however, was defined differently for the RCT and Long Term safety populations. For the RCT Study population, the date of first dose refers to the first dose of randomized treatment (i.e., rifaximin or placebo). For the Long Term Rifaximin Experience population, the date of first dose referred to the first dose of rifaximin across all studies in which the subject participated.

A subject reporting the same preferred term more than once was counted only once for the summary of that event, using the event with the most severe intensity or closest relationship to the study drug. Adverse event summary tables were based on pooled data from the same population. Treatment-emergent AEs were summarized by body system and preferred term as follows

- All TEAEs
- Common TEAE (occurring in >3% of any treatment arm)
- Serious TEAEs (SAEs)
- TEAEs resulting in discontinuation from study
- Serious TEAEs resulting in discontinuation from study
- TEAEs of special interest (respiratory and GI infections)
- TEAEs by intensity
- TEAEs by investigator-assessed relationship to study drug
- All deaths.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

Total exposure to rifaximin at the indicated dose in these two phase 3 trials is 336 subjects. At the time of the data cutoff for this ISS, most subjects had received rifaximin for > 3 months (297/336 subjects). Subjects exposed to rifaximin at the indicated dose for 6 months or longer total 257. Exposure to rifaximin at the indicated dose, for 12 months or longer, totals 114 subjects. Combined data represent approximately 252 person years of exposure to rifaximin 550 mg tablets BID in the primary analysis studies. In the Primary population (RFHE3001 & 3002), for All Rifaximin Subjects, 90% of the patients were 80% compliant with there dosing regimen.

Table 29: Rifaximin Exposure ^a

	RFHE3001		Long Term Exposure – RFHE 3001 & RFHE3002		
Exposure duration	Placebo	Rifaximin 550 bid	New Rifaximin	Continuing Rifaximin	All Rifaximin
n	159	140	196	140	336
Mean	105.7	130.3	265.1	286.1	273.8
SD	62.71	56.47	120.04	204.78	160.92
Median	110.0	168.0	253.0	171.5	253.0
Min	6	10	7	10	7
Max	176	178	680	840	840
Exposure duration					
Day 1 to < month 1	22(13%)	13 (9.3%)	3(1.5%)	9(6.4%)	12(3.6%)
Month 1 to < month 3	44(27.7%)	23(16.4%)	8(4.1%)	19(13.6%)	27(8.0%)
Month 3 to < month 6	37(23.3%)	31(22.1%)	23(11.7%)	17(12.1%)	40(11.9%)
Month 6 to < month 9	56(35.2%)	73(52.1%)	46(23.5%)	29(20.7%)	75(22.3%)
Month 9 to < month 12			62(31.6%)	6(4.3%)	68(20.2%)
Month 12 to < month 15			27(13.8%)	11(7.9%)	38(11.3%)
Month 15 to < month 18			19(9.7%)	23(16.4%)	42(12.5%)
Month 18 to < month 21			4(2.0%)	11(7.9%)	15(4.5%)
Month 21 to < month 24			3(1.5%)	9(6.4%)	12(3.6%)
≥ month 24			1(0.5%)	6(4.3%)	7(2.1%)

^a From Applicants tables

In RFHE3001, there were no notable differences between the rifaximin and placebo arms in mean numbers of days of treatment across baseline Child-Pugh A, B, and C . In the placebo crossover group (RFHE3002) and the rifaximin rollover group (RFHE3001/3002), mean numbers of days of rifaximin therapy was generally similar across baseline Child-Pugh classes; with the exception of Child-Pugh C subjects in the placebo crossover group, who had lower mean duration of rifaximin exposure. Mean duration of rifaximin exposure was approximately 3-fold longer in placebo crossover subjects and 4.6- fold longer in rifaximin rollover subjects in RFHE3002 compared to

rifaximin subjects in RFHE3001. Total duration of rifaximin exposure, determined by comparison of person years of exposure (PEYs), was approximately 2-fold longer in placebo crossover subjects (94 PEYs) and 2.4-fold longer in rifaximin rollover subjects (112 PEYs) in RFHE3002, compared to rifaximin subjects (46 PEYs) in RFHE3001.

In addition, the safety data base included over 2000 subjects who received rifaximin for acute HE and other indications (generally for less than 14 days) in doses ranging from 550mg to 2400mg/day. In the Secondary Safety Population (acute Tx. of HE), 152 subjects were exposed to rifaximin for 14 days or less and most received doses of 1200 mg/day (n=117). In the Supportive Safety Population, data for treatment of traveler's diarrhea, 593 subjects were exposed for 5 days or less, and in the prevention of Traveler's diarrhea trials 820 subjects were exposed, most (80%) for 14-15 days, all with varying doses (from 600mg to 1800mg per day).

Demographics

See Table 30: Demographics – Primary Analysis Population

In the RCT Study population (RFHE3001), most subjects were white, male and less than 65 years of age. A higher percentage of placebo-treated subjects were male (67.3% vs. 53.6%) compared with the rifaximin group and conversely a larger percentage of rifaximin treated subjects were female (46.4% vs. 32.7%). Other demographic characteristics, including age, race, ethnicity, and weight, were similar between treatment groups. The median (min, max) age was 55.0 (26, 82) years in the rifaximin group and 57.0 (21, 78) years in the placebo group. Subjects ≥ 65 years of age were well represented in both the rifaximin (27 subjects [19.3%]) and placebo (31 subjects [19.5%]) treatment groups.

A total of 205, 14, and 80 subjects were randomized in the RCT Study population from the United States, Canada, and Russia, respectively. The relative distributions of subjects by demographic characteristic were comparable between treatment groups (see study RFHE3001 Clinical Study Report).

In the Long Term Rifaximin Experience population, demographics were generally comparable between subjects in the New Rifaximin group (entered the extension study without prior exposure to rifaximin) and subjects in the Continuing Rifaximin group. Slightly more subjects in the New Rifaximin group were male compared with subjects in the Continuing Rifaximin group. Additionally, a larger proportion of subjects in the New Rifaximin group were enrolled in the US (84.2% vs. 66.4%) and fewer subjects in the New Rifaximin group were enrolled in Russia (12.8% vs. 27.9%) than in the Continuing Rifaximin group.

Medical Officer's Comments:

No review issues were identified regarding difference in demographics.

Table 30: Demographics - Primary Analysis Population

Category	RTC Population		Long Term Population		
	Double-Blind Study Tx Placebo N (%) (N = 159)	Rifaximin 550mg bid N (%) (N = 140)	New Rifaximin 550mg bid N (%) N = 196	Continuing Rifaximin 550mg bid N (%) N = 140	All Rifaximin Subjects N (%) N = 336
SEX (n,%)					
Male	107 (67.3)	75 (53.6)	120 (61.2)	75 (53.6)	195 (58.0)
Female	52 (32.7)	65 (46.4)	76 (38.8)	65 (46.4)	141 (42.0)
Age					
< 65 y	128 (80.5)	113 (80.7)	157 (80.1)	113 (80.7)	270 (80.4)
≥ 65 y	31 (19.5)	27 (19.3)	39 (19.9)	27 (19.3)	66 (19.6)
Mean (SD)	56.8 (19.8)	55.5 (9.57)	57.2 (9.01)	55.5 (9.57)	56.5 (9.27)
Median (min,max)	57.0 (21,78)	55.0 (26,82)	57.0 (21,81)	55.0 (26,82)	56.0 (21,82)
Race (n,%)					
American Indian/Alaskan	3 (1.9)	5 (3.6)	1 (0.5)	5 (3.6)	6 (1.8)
Asian	8 (5.0)	4 (2.9)	5 (2.6)	4 (2.9)	9 (2.7)
Black	5 (3.1)	7 (5.0)	8 (4.1)	7 (5.0)	15 (4.5)
Pacific Islander	1 (.06)	2 (1.4)	0	2 (1.4)	2 (0.6)
White	139 (87.4)	118 (84.3)	181 (92.3)	118 (84.3)	299 (89.0)
Other	3 (1.9)	3 (2.1)	1 (0.5)	3 (2.1)	4 (1.2)
	RTC Population		Long Term Population		

	Placebo	Rifaximin	New Rifaximin	Continuing Rifaximin	All Rifaximin Subjects
Missing	0	1 (.07)	0	1 (0.7)	1 (0.3)
Ethnicity (n,%)					
Hispanic or Latino	28 (17.6)	21 (15.0)	24 (12.2)	21 (15.0)	45 (13.4)
Non- Hispanic	131 (82.4)	119 (85.0)	172 (87.8)	119 (85.0)	291 (86.6)
Weight (kg) (N, %)					
Mean (SD)	88.04 (19.1)	87.02 (22.86)	86.62 (19.06)	87.02 (22.86)	86.78 (20.694)
Median (min, max)	86.60 (46.1, 137.7)	83.05 (49.0, 165.6)	83.75 (49.0, 142.9)	83.05 (40.4, 165.6)	83.55 (40.4, 165.6)

From Applicants table

Baseline Characteristics

Hepatic encephalopathy disease characteristics measured at baseline were generally comparable between the treatment groups in the RCT Study population. Hepatic and renal disease characteristics were also comparable between rifaximin- and placebo-treated subjects in the RCT Study population. Mean (\pm SD) MELD score at baseline was 13.1 (3.64) in the rifaximin group and 12.7 (3.94) in the placebo group; most subjects in each group had MELD scores ranging from 11 to 18 (rifaximin: 67.1%; placebo: 60.4%). The mean time since first diagnosis of advanced liver disease for the RCT Study population was > 50 months in both groups, but longer in the placebo group (60.5 months vs. 51.2 months). The majority of subjects in each group had serum creatinine levels at baseline < 1.5 times the upper limit of normal. See Table 31

Medical Officers Comments:

Of note is the low percentage of subjects with MELD scores above 18 (8-9%), which makes meaningful evaluation of the safety of rifaximin in subjects with severe hepatic impairment very difficult. There were no subjects with MELD Scores above 25 enrolled in these trials.

Table 31: History of Hepatic Encephalopathy and Other Baseline Characteristics (RCT Study and Long Term Rifaximin Experience Populations)

Category	RCT Study Population		Long Term Rifaximin Experience Population		
	Double-Blind Study Treatment		New Rifaximin 550 mg BID (N = 196)	Continuing Rifaximin 550 mg BID (N = 140)	All Rifaximin Subjects (N = 336)
	Placebo (N = 159)	Rifaximin 550 mg BID (N = 140)			
Duration of Current Remission of HE (days)					
N	158	139	192	139	331
Mean (SD)	73.1 (51.33)	68.8 (47.68)	121.9 (113.51)	68.8 (47.68)	99.6 (95.38)
Median (Min, Max)	61.0 (12, 205)	55.0 (8, 222)	76.5 (1, 378)	55.0 (8, 222)	63.0 (1, 378)
≤ 90 days in remission	110 (69.2)	100 (71.4)	103 (52.6)	100 (71.4)	203 (60.4)
> 90 days in remission	48 (30.2)	39 (27.9)	89 (45.4)	39 (27.9)	128 (38.1)
Missing	1 (0.6)	1 (0.7)	4 (2.0)	1 (0.7)	5 (1.5)
Time Since First Diagnosis of HE (months)					
N	159	139	196	139	335
Mean (SD)	21.85 (26.41)	20.84 (23.13)	20.92 (26.20)	20.84 (23.13)	20.88 (24.93)
Median (Min, Max)	11.00 (0.6, 179.4)	11.75 (0.5, 125.1)	10.61 (0.5, 162.7)	11.75 (0.5, 125.1)	10.93 (0.5, 162.7)
Number of HE Episodes in the Past 6 or 12 Months – n (%) ^a					
1	0	0	57 (29.7)	0	57 (17.2)
2	111 (70.3)	97 (69.3)	74 (38.5)	97 (69.3)	171 (51.5)
3	35 (22.2)	29 (20.7)	27 (14.1)	29 (20.7)	56 (16.9)
4	8 (5.1)	5 (3.6)	16 (8.3)	5 (3.6)	21 (6.3)
5	1 (0.6)	7 (5.0)	7 (3.6)	7 (5.0)	14 (4.2)
6	2 (1.3)	1 (0.7)	5 (2.6)	1 (0.7)	6 (1.8)
7	0	1 (0.7)	2 (1.0)	1 (0.7)	3 (0.9)
8	0	0	1 (0.5)	0	1 (0.3)
9	1 (0.6)	0	2 (1.0)	0	2 (0.6)
10	0	0	1 (0.5)	0	1 (0.3)
Continued					

Category	RCT Study Population		Long Term Rifaximin Experience Population		
	Double-Blind Study Treatment		New Rifaximin 550 mg BID (N = 196)	Continuing Rifaximin 550 mg BID) (N = 140)	All Rifaximin Subjects (N = 336)
	Placebo (N = 159)	Rifaximin 550 mg BID (N = 140)			
Conn Score – n (%)					
Grade 0	107 (67.3)	93 (66.4)	126 (64.3)	93 (66.4)	219 (65.2)
Grade 1	52 (32.7)	47 (33.6)	59 (30.1)	47 (33.6)	106 (31.5)
Grade 2	0	0	10 (5.1)	0	10 (3.0)
Grade 3	0	0	1 (0.5)	0	1 (0.3)
Grade 4	0	0	0	0	0
Asterixis Grade – n(%)					
Grade 0	108 (67.9)	96 (68.6)	141 (71.9)	96 (68.6)	237 (70.5)
Grade 1	45 (28.3)	41 (29.3)	42 (21.4)	41 (29.3)	83 (24.7)
Grade 2	5 (3.1)	2 (1.4)	7 (3.6)	2 (1.4)	9 (2.7)
Grade 3	1 (0.6)	1 (0.7)	6 (3.1)	1 (0.7)	7 (2.1)
Grade 4	0	0	0	0	0
Time Since First Diagnosis of Advanced Liver Disease (months)					
Mean (SD)	60.51 (64.89)	51.22 (49.17)	75.63 (81.20)	51.22 (49.17)	65.46 (70.61)
Median (Min, Max)	39.04 (2.0, 323.4)	38.02 (1.7, 260.5)	49.16 (2.7, 515.8)	38.02 (1.7, 260.5)	44.93 (1.7, 515.8)
MELD Score					
N	158	140	191	140	331
Mean (SD)	12.7 (3.94)	13.1 (3.64)	12.3 (3.94)	13.1 (3.64)	12.6 (3.83)
Median (Min, Max)	12.4 (6, 23)	13.1 (6, 24)	12.1 (6, 24)	13.1 (6, 24)	12.5 (6, 24)
MELD Score Category – n (%)					
≤ 10	48 (30.2)	34 (24.3)	74 (37.8)	34 (24.3)	108 (32.1)
11 – 18	96 (60.4)	94 (67.1)	102 (52.0)	94 (67.1)	196 (58.3)
≥ 19	14 (8.8)	12 (8.6)	15 (7.7)	12 (8.6)	27 (8.0)
Missing	1 (0.6)	0	5 (2.6)	0	5 (1.5)
Continued					

Category	RCT Study Population		Long Term Rifaximin Experience Population		
	Double-Blind Study Treatment		New Rifaximin 550 mg BID (N = 196)	Continuing Rifaximin 550 mg BID (N = 140)	All Rifaximin Subjects (N = 336)
	Placebo (N = 159)	Rifaximin 550 mg BID (N = 140)			
Renal Impairment (serum creatinine^b) – n(%)					
≥ 1.5 ULN	3 (1.9)	4 (2.9)	3	4 (2.9)	7 (2.1)
< 1.5 ULN	156 (98.1)	136 (97.1)	189 (96.4)	136 (97.1)	325 (96.7)
Missing	0	0	4 (2.0)	0	4 (1.2)

Source: ISS Tables 2.2.1 and 2.2.2, Appendix C

Abbreviations: SD = standard deviation; min = minimum; max = maximum; ULN = upper limit of normal; BID = twice daily; HE = hepatic encephalopathy; MELD = model end stage liver disease; and RCT = randomized controlled trial.

a For the RCT Study population, the number of HE episodes in the past 6 months are presented; for the Long Term Rifaximin Experience population the number of HE episodes in the last 12 months are presented.

b Normal range for serum creatinine was 53 to 124 umol/L.

7.2.2 Explorations for Dose Response

Only one dose level was studied in the target population for the proposed indication, therefore there is insufficient information to draw a conclusion about the exposure-response relationship in terms of safety and efficacy.

7.2.3 Metabolic, Clearance, and Interaction Workup

Refer the Clinical Pharmacology Summary Review under Tab 4

7.2.4 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Rifaximin is a non-aminoglycoside semi-synthetic antibiotic (miscellaneous class), derived from rifamycin SV. The rifamycins are a group of structurally similar complex macrocyclic antibiotics originally isolated from *S. mediterranei*. The prefix "rifa-" is the official USAN and INN stem designating antibiotics that are rifamycin derivatives. This family includes the following:

- rifabutin
- rifalazil
- rifametane
- rifamexil
- rifamide
- rifampin (rifampicin in Europe and Japan)
- rifapentine
- rifaxidin
- rifaximin
- rifomycin

Rifampin

Rifampin, used for the treatment of tuberculosis, has been used extensively world wide. Adverse events associated with rifampin are hypersensitivity and anaphylactic reactions. acute renal failure and hepatitis are also reported. The Warning Section of the label states:⁸

Rifampin has been shown to produce liver dysfunction. Fatalities associated with jaundice have occurred in patients with liver disease and in patients taking rifampin with other hepatotoxic agents. Patients with impaired liver function should be given rifampin only in cases of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of liver function, especially SGPT/ALT and SGOT/AST should be carried out prior to therapy and then every 2 to 4 weeks during therapy. If signs of hepatocellular damage occur, rifampin should be withdrawn.

In some cases, hyperbilirubinemia resulting from competition between rifampin and bilirubin for excretory pathways of the liver at the cell level can occur in the early days of treatment. An

isolated report showing a moderate rise in bilirubin and/or transaminase level is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating the tests, noting trends in the levels, and considering them in conjunction with the patient's clinical condition.

Under Precautions; General, the label states:

Rifampin is not recommended for intermittent therapy; the patient should be cautioned against intentional or accidental interruption of the daily dosage regimen since rare renal hypersensitivity reactions have been reported when therapy was resumed in such cases.

Review of the literature for rifampin, reveals an associated dose related “flu like” syndrome that is IgG mediated, the incidence increases markedly with intermittent dosing or interrupted doses. There are also reports of rare severe anaphylactic reactions; thrombocytopenia and hemolysis; acute renal failure, usually associated with hemolysis; and rash and fever that are IgE mediated. The time interval between the onset of treatment and events of anaphylactic reaction is highly variable. Most patients present with prodromes, mainly rash, before the development of frank anaphylaxis, and, in most cases, the reaction occurs after re-exposure to rifampin. Clinical findings include a variety of symptoms, such as fever, exanthema, dyspnea, abdominal pain, and vomiting. Patients who are HIV seropositive are at higher risk for these adverse reactions.⁹

Drug Induced Liver Injury (DILI) have been reported with rifampin, however most reported cases are in patients being treated for Tuberculosis and on combination therapy with other hepatotoxic agents. At least two of these cases have positive rechallenges with rifampin. One observational study in France that examined liver toxicity in anti-tuberculosis treatment noted the median time to development of liver toxicity was 14 days, and independent risk factors were abnormal baseline ALT and bilirubin levels.¹⁰ Rifampin has also been used to treat pruritus in Primary Biliary Cirrhosis (PBC) and adverse events of hepatitis, some with decreased hepatic synthetic function, have been reported. The reported incidence of rifampin hepatitis is 7.3 – 12.5% in patients with PBC, even with doses as low as 150mg day. Hepatitis can reverse with withdrawal of rifampin.¹¹

The Applicant contends that rifaximin is poorly absorbed and therefore will not produce systemic toxicity. Pre-clinical studies were all done on animals with normal GI tracts and normal liver and renal function. These animals would be expected to be poor absorbers and rapid metabolizers of rifaximin. Patients with hepatic dysfunction have been shown to have increased absorption than healthy volunteers and may be at higher risk for toxicity. See Pharmacology Review Summary in Tab 4.

There are other examples of poorly absorbed drugs that cause significant systemic toxicity. Neomycin sulfate (which was originally approved for the treatment of Hepatic

Coma) is 97% eliminated unchanged in the feces. The absorbed fraction is rapidly distributed in the tissues and is excreted by the kidney, in keeping with the degree of renal function.¹² Yet neomycin is known to be associated with adverse reactions, nephro- and neuro- toxicities which do occur with oral administration. The incidence of aminoglycoside-induced nephrotoxicity is substantially greater in patients with advanced liver disease than in patients without liver disease^{13,14,15}.

7.3 Major Safety Results

During blinded treatment in the RCT Study population, the proportion of subjects with TEAEs was similar between subjects receiving rifaximin tablets 550 mg BID (80.0%) and placebo (79.9%). No differences were observed in the incidence of moderate (37.1%, 34.0%) or mild TEAEs (16.4%, 15.1%) in rifaximin and placebo subjects, respectively. Severe TEAEs were recorded in a higher percentage of placebo-treated subjects (rifaximin: 26.4%; placebo: 30.8%), as were drug-related TEAEs (rifaximin: 19.3%; placebo: 21.4%) and SAEs (rifaximin: 36.4%; placebo: 39.6%).

The percentage of subjects with any TEAEs (87.2%), severe TEAEs (41.4%), and SAEs (49.1 %) was higher for All Rifaximin subjects in the Long Term Rifaximin Experience population compared with the RCT Study groups, which was attributed by the Application to the increased time on the open-label study. Overall event rates (per 100 person years) for subjects experiencing death, TEAEs, SAEs, or TEAEs leading to study discontinuation, were lower in All Rifaximin subjects or comparable between All Rifaximin subjects and the RCT Study groups. Additionally, a lower percentage of All Rifaximin subjects in the Long Term Rifaximin Experience population experienced a drug related TEAE (13.7%) compared with the rifaximin (19.3%) and placebo (21.4%) groups in the RCT Study population.

Note exposures in the New Rifaximin group were longer with a mean of 265 days (SD 120 days).

Table 32: Summary of adverse events – excluding non-serious HE events

Category	RFHE3001			Long Term Population		
	Placebo N = 159 N (%)	Rifaximin N = 140 N (%)	Total N = 299 N (%)	New Rifaximin N = 196	Continuing rifaximin N = 140	Total N = 336 N (%)
TEAEs	127 (79.9%)	112 (80.0%)	239 (79.9%)	172 (87.8%)	121 (86.4%)	293 (87.2%)
Serious TEAEs	63(39.6%)	51 (36.4%)	114(38.1%)	94 (48.0%)	71 (50.7%)	165 (49.1%)
TEAE drug related	34(21.4%)	27 (19.3%)	61 (20.4%)	15 (7.7%)	31 (22.1%)	46 (13.7%)
TEAE by severity						
Severe	49 (30.8%)	37 (26.4%)	86 (28.8%)	80 (40.8%)	59 (42.1%)	139 (41.4%)
Moderate	54 (34.0%)	52 (37.1%)	106(35.5%)	59 (30.1%)	44 (31.4%)	44 (31.4%)
Mild	106(35.5%)	23 (16.4%)	47 (15.7%)	33 (16.8%)	18 (12.9%)	51 (15.2%)
TEAE w/ D/C drug	45 (28.3%)	30 (21.4%)	75 (25.1%)	30 (15.3%)	42 (30.0%)	72 (21.4%)
Deaths	11 (6.9%)	10 (7.1%)	21 (7.0%)	19 (9.7%)	17 (12.1%)	36 (10.7%)

From Applicant tables 5.1.1b and 5.1.2

If a subject experienced more than 1 adverse event, the subject is counted only once for the worst severity.

For subjects who experienced an AE leading to discontinuation, the investigator selected the reason for termination as either due to AE, due to breakthrough HE, or due to liver transplant.

The summary of 'Deaths While on Study Drug' includes subject deaths recorded during treatment, including through 5 days after the last dose. The summary of 'All Deaths' includes subject deaths during treatment or within 30 days after the last dose.

7.3.1 Deaths

See Table 33: Deaths Listings - Rifaximin for a summary of the deaths

In the primary safety pool mortality rate was 7% in both the treatment and placebo groups in RFHE3001.

Twenty-one subjects died during the **double-blind RFHE3001** study or within 30 days following the last dose, 11 subjects (6.9%) in the placebo group and 10 subjects (7.1%) in the rifaximin group. Of the recorded deaths in the RFHE3001 study, a total of 12 subjects died (rifaximin: 6; placebo: 6) while receiving study drug, including through 5 days after last dose. None of the SAEs resulting in an outcome of death that occurred

during the RCT Study or within 30 days after the last dose were considered by the investigators to be related to study drug. Table 33 also summarizes 4 additional subjects who died after completion of the protocol-defined interval for collection of SAEs (up to 30 days after last dose of study drug). The deaths for these 4 subjects (rifaximin: 2; placebo: 2) were not collected on the SAE CRF page and are not summarized in the ISS for the RCT Study population. Instead, information regarding the deaths of these 4 subjects were recorded on the non-breakthrough HE early termination CRF page for subjects who withdrew early for reasons other than breakthrough HE.

In the **Long Term Rifaximin Experience population**, a total of 36 subject deaths (10.7%) were recorded for All Rifaximin subjects during the maintenance of remission of overt HE studies. The total number of deaths was inclusive of the 10 rifaximin treated subjects who died during the RCT Study. In addition to the deaths in RFHE3001, 23 subjects died during the RFHE3002 study or within 30 days after the last dose date. Three (3) additional subjects died in RFHE3002 after completion of the planned interval for collection of SAEs (up to 30 days after last dose of the study drug).

The majority of deaths in both the placebo group and the rifaximin group appear to have been related to worsening hepatic function and underlying disease progression. Esophageal varices with hemorrhage is the second most common SAE resulting in death and resulted in the deaths of 3 rifaximin treated subjects and 2 placebo subjects. Three rifaximin treated subjects, and 2 placebo treated subjects died with hepatocellular carcinoma. Five rifaximin treated subjects died with a primary SAE of infection (sepsis and pneumonia). One rifaximin treated subject, who received 74 days of treatment, then a liver transplant, had sputum positive for AFB prior to death. This is concerning secondary to the possibility of cross resistance developing with rifampin. Two patients treated with rifaximin developed *C. difficile* colitis prior to death. No placebo patients developed *C. difficile* colitis.

Table 33: Deaths Listings - Rifaximin

Trial-Center-Patient	Age (yrs)	Race/ Sex	Dose (mg)	Time SAE/death/ exposure (days)	Cirrhosis at baseline MELD	Description of events prior to death
3001-0351-0001	70	CF	1100	48/+9 /48	PBC, Hep C, Varices ascites 15	CHF w/ no prior Hx of cardiomegaly
3001-0351-0012	45	BF	1100	67/67 /67	EtOH cirrhosis, hep. B, varices, edema 11	Acute N&V, worsening cirrhosis, pulm. HTN, pul. cultures +
3001-0679-0005	52	CM	1100	+10/+10 /29	Hep. C, varices ascites, ESLD 7	Died at home – no autopsy
3001-0706-0002	69	CF	1100	+2/+2 /?40	Ascites, palliative care for ESLD 12	Died at home-no autopsy ? Hepatic failure
3001-0760-0001	51	CM	1100	159/+1 /159	Varices, portal HTN, ascites, jaundice 16	DIC, died during transplant, C dif colitis , ?PE/MI thrombosed cardiac stent
3001-0762-0001	45	CF	1100	+8/+10 /166	Autoimmune hepatitis, varices, ascites, portal HTN, adrenal insuf. 16	ESLD, died with transplant rejection and portal vein thrombosis, MSOF
3001-0902-0002	57	CF	1100	45/+2 /66	PBC, ascites pancreatitis 16	Breakthrough HE, subacute liver necrosis (no autopsy), hepatorenal syndrome
3001-0904-0002	30	CF	1100	104/104 /104	Hep C, EtOH abuse, Portal HTN 8	Elevated LFT's noted- ?EtOH, then variceal bleed with death

Trial-Center-Patient	Age (yrs)	Race/ Sex	Dose (mg)	Time SAE/death/ exposure (days)	Cirrhosis at baseline MELD	Description of events prior to death
3001-0905-0009	59	CM	1100	+27/+43 /142	Portal HTN, varices 15	Resistant ascites, death 2 nd to variceal bleed
3001-0935-0005	52	CF	1100	125/125 /125	Portal HTN, hepatorenal syndrome, varices 13	Died at home 2 nd to GI bleed, no autopsy
3001-0754-0008b	52	BM	1100	?/+110 /21	Hep C, ^ tot bili, history shunt 11	Ongoing EtOH abuse, discontinued 2 nd to HE, then death 2 nd ESLD
3001-0893-0005b	55	CF	1100	?/+114 /21	Hep B, Hx MI Pancreatitis, varices 17	Discontinued 2 nd hydrothorax, then death 3 months later 2 nd cirrhosis?
3001-0488-0003	63	AM	1100	240/249 /P/249	Cryptogenic cirrhosis, varices, jaundice, DM 17	Worsening cirrhosis of unknown etiology, SBP, hepatorenal failure, no autopsy
3001-0547-0001	60	BM	1100	166/+14 /173	EtOH cirrhosis, Hep C, obesity, HTN 11	Hepatocellular carcinoma, inoperable
3001-0586-0004	73	CF	1100	47/+4	PBC, IDDM, CRF, Hx UTI's, HTN, a fib 12	Worsening cirrhosis and HE, ATN, death
3001-0760-0003	54	BF	1100	372/372 P/372	EtOH, Hep C, drug abuse, varices, ascites rheumatoid arthritis, CHF, SCD 13	Pancreatitis, HE, cardiac arrest at home DOA, no autopsy
3001-0876-0005	69	CM	1100	198/+1 P/207	Cirrhosis, varices, hepatic neoplasm 21	Hepatocellular carcinoma, spinal compression Fx, hospice, death

Trial-Center-Patient	Age (yrs)	Race/ Sex	Dose (mg)	Time SAE/death/ exposure (days)	Cirrhosis at baseline MELD	Description of events prior to death
9999-0478-0053	60	CF	1100	281/+10 /281	NASH, morbid obesity, IDDM, varices, COPD 9	Acute renal and resp. failure s/p femur Fx repair
9999-0662-0060	56	CM	1100	+16/+34 67	EtOH, Hep C, IV drug use, Varices, ascites, TIPS 18	Worsening cirrhosis, cellulitis, ATN, MELD 39, liver transplant w/ post-op death
9999-0757-0051	56	CM	1100	258/258	Hep C, varices, obesity, HTN, edema, jaundice, a fib, shunt 9	Liver cancer, dehydration, HE, DNR death, no autopsy
9999-0760-0051	53	CF	1100	+1/+38 47	EtOH, Hep C, varices, ascites, pancytopenia 13-16	HE and hyperkalemia recurrent, worsening cirrhosis and ATN, sepsis, c-diff colitis , DNR, death no autopsy
9999-1025-0051	49	CM	1100	+33/+35 72	EtOH cirrhosis, GI bleed, ascites, CRF 14	Transplant successful, subsequent fungal peritonitis, sputum + AFB , sepsis, DIC, MSOF, death
9999-1025-0054	51	CF	1100	+2/+2 169	Biliary cirrhosis, bile duct stricture w/ drain, renal failure, sleep apnea, varices, edema, pancytopenia 21	<i>E. coli</i> sepsis, staph cholangitis, GI bleed, Worsening cirrhosis, sepsis , ATN, UTI, hospice, death, no autopsy
9999-1025-0055	64	CM	1100	+1/+1 404	Hemochromatosis, cirrhosis, DM, CAD, CHF, valve Dz 10-13	Viral diarrhea w/ HE, resolved then Found dead at home

Trial-Center-Patient	Age (yrs)	Race/ Sex	Dose (mg)	Time SAE/death/ exposure (days)	Cirrhosis at baseline MELD	Description of events prior to death
9999-1025-0060	48	BF	1100	+1/+1 174	Hep C, IV drug abuse, varices, asthma 19	Cryptococcal meningitis, recurrent HE, worsening cirrhosis, ATN, sepsis, death, no autopsy
9999-1025-0064	71	CF	1100	112/119 119	Hep C, anemia, CAD, ascites, varices 23	HE, renal insuff, ?SBP, dialysis, worsening cirrhosis, ascites, HE, hepatic failure, death
3001-0894-0009	60	CF	1100	+1/+6 P/185	Hep C, varices, obesity, chronic pyelonephritis 7	GI bleed with death
3001-0897-0002	49	CM	1100	211/217	EtOH, Hep B, ascites, pancreatitis, jaundice 15-17	Worsening cirrhosis, DT's, HE, pneumonia, pulm. insuff, death
3001-0901-0002	44	CM	1100	50/+18 P/50	Cirrhosis, ascites edema 20	GI hemorrhage and hepatorenal failure, death, autopsy done
3001-0902-0005	57	CM	1100	+1/+1 P/89	Cirrhosis, anemia, pancreatitis, ascites 11	Cardiovascular failure? Death, no autopsy
3001-0908-0002	69	CM	1100	143/+27 P/143	Cirrhosis, varices, ascites, HTN, angina, COPD, pancreatitis 10	GI hemorrhage, HE, renal failure, death

Trial-Center-Patient	Age (yrs)	Race/ Sex	Dose (mg)	Time SAE/death/ exposure (days)	Cirrhosis at baseline MELD	Description of events prior to death
3001-0397-0002	56	CM	1100	+4/+14/ 20/271	EtOH abuse, Hep C, varices, COPD 11	Died post-op from colon resection from hemorrhage, septic shock, MSOF
3001-0397-0004	60	CF	1100	+1/+27/ 36/238	EtOH cirrhosis, varices, jaundice 13	Multiple episodes of HE, Death 2 nd lobar pneumonia
3001-0547-0002	67	CF	1100	534/+1 /139/368	NASH w/ cirrhosis, DM, CAD, CHF, Hx CVA 19	Recurrent GI bleeding, anasarca, compression fx, pancytopenia, coagulopathy, renal failure, resp failure, death
3001-0566-0002	53	CF	1100	+1/+3 /169/233	Cirrhosis, HTN, portal HTN, GI bleeds, pancreatitis 15	Recurrent esophageal variceal bleeding with death
3001-0591-0005	65	CF	1100	+1/+29 169/151	Cirrhosis, varices, ascites, DM, HTN, thrombocytopenia Dementia, CRF 17	ESRD, dialysis, HE, worsening cirrhosis and death, no autopsy
3001-0760-0002	59	CF	1100	+3/+28 170/157	Hep C, ascites, HTN, asthma, IDDM, varices, CRI, COPD 13	Hepatocellular carcinoma, suicide attempts, hospice care, death
3001-0876-0006	59	HM	1100	455/+7 166/295	EtOH cirrhosis, IDDM, TIPS, 16	Facial cellulitis, strep sepsis, HE, ATN, death
9701-01-010	59	CF	1200	3	Hep C, GI bleed, portal HTN	Progressive deterioration with unknown facts w/in 30 days of Tx

Trial-Center-Patient	Age (yrs)	Race/ Sex	Dose (mg)	Time SAE/death/ exposure (days)	Cirrhosis at baseline MELD	Description of events prior to death
9701-01-017	75	CF	1200	7	Cryptogenic cirrhosis, ascites, recurrent HE, dehydration, DM	Admitted with acute HE and constipation, auto immune hypoglobulinemia, increasing LFT's, bronchopneumonia day 7 w/ death
9701-01-061	62	CF	1200	7	Hep C cirrhosis, 3y of HE, ascites, SBP splenomegaly jaundice	Admitted HE 2 nd dehydration, s. <i>pneumoniae</i> pneumonia day 4, CVA, MSOF, death day +17
9701-02-027	61	CM	1200	5	EtOH cirrhosis, 8y of HE	Admitted with HE and rapid deterioration with study drug D/C day 5 and death from ESLD day +5
9701-02-028	63	CM	1200	1	EtOH cirrhosis, 9y HE, CHF, COPD, Hx gastric ca.	Admitted with HE w/ rapid deterioration and only one day study drug, death next day
9701-03-031	50	CM	1200	9	EtOH cirrhosis, 1y HE, ESLD	Out pt., acute GI bleed with death +2d from hepatorenal failure
9701-07-068	70	CM	1200	4	EtOH cirrhosis, grade 1 HE, s/p shunt, ascites, jaundice	Admitted w/ HE and increase ascites, then sepsis and death due to plum edema day +1
9701-09-093	61	CM	1200	2	EtOH cirrhosis, 10y grade 3 HE, GI bleed	Admitted GI bleed and HE, then sepsis and death day 2
9702-02-016	55	CF	2400	7	PBC 2 nd hepatocellular ca, 2m grade 1 HE,	Death day +2 2 nd to GI bleed, ATN & DIC post tumor injection
9702-02-017	58	CF	1200	7	EtOH cirrhosis, 4d grade 1 HE,	Death day +3 2 nd to ATN and SBP

Trial-Center-Patient	Age (yrs)	Race/ Sex	Dose (mg)	Time SAE/death/ exposure (days)	Cirrhosis at baseline MELD	Description of events prior to death
9901-06-024	52	F	1200		Hep C cirrhosis, Hx MVA w/ splenectomy and hepatitis	Admitted with HE and improved on study drug, then day 10 fever and hepatorenal failure and died with volume overload and pulm. failure day +8

The FDA requested that the Applicant conduct an analysis of mortality by baseline hepatic function using Childs-Pugh Classification. Of the recorded deaths in the RFHE3001 study (rifaximin: 10, placebo: 11), 12 subjects died (rifaximin: 6; placebo: 6) while receiving study drug, including through 5 days after last dose, and 9 subjects died within 30 days of study withdrawal. The proportions of subjects who died increased across Child-Pugh categories A, B, and C in RFHE3001 (Table 34). There were no notable differences reported between rifaximin and placebo groups in the proportion of subjects who died among Child-Pugh A, B, and C subjects, although there was a numerically higher proportion of patients with Child-Pugh C who died in the rifaximin arm. The number of patients in the study with Child-Pugh C disease was relatively small, however, making this apparent difference difficult to interpret. According to the investigator, the SAEs resulting in death among subjects who were Child-Pugh C were congestive cardiac failure (subject 351-0001, rifaximin); esophageal varices hemorrhage (subject 456-0004, placebo); multi-organ failure, portal vein thrombosis, and liver transplant rejection (subject 762-0001, rifaximin); and primary biliary cirrhosis (subject 902-0002, rifaximin). No event resulting in death was considered related to study drug by the investigator.

Table 34: Deaths by Child-Pugh Classification (baseline) - RFHE3001

	Rifaximin 550 mg BID N =140	Placebo N =159
Child-Pugh A (5-6)	n=46	n=56
Person exposure years ^a	17	18
Deaths, n (%)	2 (4.3)	2 (3.6)
Deaths/PEY	0.12	0.11
Child-Pugh B (7-9)	n=65	n=72
Person exposure years ^a	24	21
Deaths, n (%)	3 (4.6)	8 (11.1)
Deaths/PEY	0.125	0.38
Child-Pugh C (10-12)	n=17	n=14
Person exposure years ^a	5	4
Deaths, n (%)	3 (17.6)	1 (7.1)
Deaths/PEY	0.6	0.25
Missing n (%)	n=12 2 (16.7)	n=17 0

Source: Table 7.1 (Section 10); Abbreviation: BID = twice daily.

Note: Child-Pugh subscores, total score (5-15), and classifications (A, B, or C) were obtained post study.

a Person exposure years is (mean exposure in days/365.25) × number of subjects.

During long-term treatment in RFHE3002, the overall incidence of deaths increased when compared to RFHE3001. In study RFHE3002 (consistent with results in RFHE3001), the proportions of subjects who died increased across Child-Pugh categories A, B, and C (Table 34). When adjusting for longer exposure in study RFHE3002, the death rates (i.e., deaths/PEYs) were higher in rifaximin subjects in

RFHE3001 than in placebo crossover subjects and rifaximin rollover subjects across Child-Pugh classes (Table 34 and Table 35).

Table 35: Deaths by Child-Pugh Classification (baseline) - RFHE3002

Child-Pugh classification	Placebo crossover ^b N =82	Rifaximin rollover ^c N =70
Child-Pugh A (5-6)	n=36	n=32
Person exposure years ^a	45	52
Deaths, n (%)	3 (8.3)	4 (12.5)
Deaths/PEY	0.07	0.08
Child-Pugh B (7-9)	n=37	n=31
Person exposure years ^a	44	52
Deaths, n (%)	8 (21.6)	6 (19.4)
Deaths/PEY	0.18	0.12
Child-Pugh C (10-12)	n=7	n=5
Person exposure years ^a	5	8
Deaths, n (%)	3 (42.9)	1 (20.0)
Deaths/PEY	0.2	0.375
Missing	n=2	n=2
Deaths, n (%)	2 (100)	2 (100)

Source: Table 7.2 (Section 10); Abbreviation: BID = twice daily.

Note: Data are shown for subjects who participated in RFHE3001 and RFHE3002. Child-Pugh subscores, total score (5-15), and classifications (A,B, or C) were obtained post study, and were recorded for subjects at the start of RFHE3001, but not in study RFHE3002.

b Placebo crossover subjects received placebo in RFHE3001 and rifaximin in the RFHE3002.

c Rifaximin rollover (also referred to as continuing rifaximin) subjects received rifaximin in RFHE3001 and RFHE3002.

Medical Officer's Comments:

While the Applicant reports no difference in death rates, it is interesting to note in Trial RFHE3001; the Childs C patients had a higher 17.6% (#3) death rate in the rifaximin group vs. the 7.1% (#1) in the placebo group. Additionally in RFHE3002 there are 3 deaths (42.9%) in the placebo cross-over group who were treated with rifaximin. These deaths could be attributed to other confounding factors related to the underlying disease, but the contribution of potentially higher rifaximin systemic exposure in this population cannot be excluded. While the numbers are too small to permit any definite conclusions; this reviewer does not believe that the Applicant has established that rifaximin does not have a negative impact on mortality in this subgroup of patients with significant hepatic impairment.

The FDA requested additional analysis of time to death up to last contact. The analysis includes 25 deaths (13 placebo and 12 rifaximin) because during post-study acquisition of information for complete capture, i.e., complete follow-up per protocol specified primary outcome, 4 additional subjects who died were identified. There was no significant difference between treatment groups in the risk of death in study RFHE3001 detected in this additional analysis. Note that the original submission reported 21 deaths (11 placebo and 10 rifaximin).

The reviewer questions the investigator attribution for the following subject deaths:

706-0002 death is labeled as hepatic failure. Patient had a MELD Score of 12 at screening with a Conn Score of 0 and asterixis grade of 0. She died at home after developing rapid worsening of her condition, after 35 days (estimated) of exposure to the drug, and electing not to seek further treatment. She was on rifaximin until just prior to death

351-0012 death was attributed to worsening cirrhosis, baseline MELD was 11. Patient developed sudden onset gastroenteritis after < 2 months exposure to study drug (lactulose also stopped by patient?) and death occurred after 67 days of exposure. The patient had positive cultures from a lung biopsy. Autopsy reported cirrhosis, pulmonary hypertension and dilated cardiomegaly.

*679-0005 was diagnosed having a cardiac death by the investigator but this reviewer believes that the cause of death is **unknown**, based on the information available. The subject had a baseline MELD of just 7 and no listed complications of cirrhosis, yet died suddenly at home after just 29 days of exposure to study drug.*

762-0001 death was attributed to transplant complication, but the records submitted do not state why the patient was placed on the transplant list. This subject was on study drug for over 5 months.

893-0005 was stable with baseline MELD score of 17 at study entry, but after 21 days of drug exposure developed worsening cirrhosis with edema and hydrothorax. No information is given for the subsequent 114 days, however the patient expired and the death was attributed to cirrhosis.

Medical Officer's Comments:

The reviewer is concerned by the fact that two of the above patients had low baseline MELD scores and subsequently showed sudden deterioration while on study drug; however, the reviewer recognizes that the clinical course in cirrhosis can be variable and is not completely predictable based on MELD and Child's Pugh class.

7.3.2 Nonfatal Serious Adverse Events

The rates of adverse events were high in this population of very ill patients. In the primary analysis population there were 546 severe adverse event (SAE) incidents occurring in 63 (39.6%) of placebo subjects and in 165 (49.1%) of All Rifaximin Subjects. Secondary to the high number of SAE events they will be listed and analyzed by System Organ Class (SOC) and Preferred Term (PT).

Table 36: Severe Adverse Events – Long Term Population

MedDRA System Organ Class	RCT Study Population		Long Term Rifaximin Experience Population		
	Placebo (PEY = 46.0) ^a (N = 159) n (%)	Rifaximin (PEY = 50.0) ^a (N = 140) n (%)	New Rifaximin (PEY = 142.3) ^a (N = 196) n (%)	Continuing Rifaximin (PEY = 109.7) ^a (N = 140) n (%)	All Rifaximin Subjects (PEY = 251.9) ^a (N = 336) n (%)
Any SAE	63 (39.6)	51 (36.4)	94 (48.0)	71 (50.7)	165 (49.1)
Blood and Lymphatic System Disorders	0	5 (3.6)	8 (4.1)	9 (6.4)	17 (5.1)
Cardiac Disorders	5 (3.1)	5 (3.6)	5 (2.6)	5 (3.6)	10 (3.0)
Gastrointestinal Disorders	11 (6.9)	16 (11.4)	35 (17.9)	27 (19.3)	62 (18.5)
General Disorders and Administration Site Conditions	4 (2.5)	6 (4.3)	12 (6.1)	7 (5.0)	19 (5.7)
Hepatobiliary Disorders	10 (6.3)	7 (5.0)	27 (13.8)	17 (12.1)	44 (13.1)
Immune System Disorders	0	1 (0.7)	2 (1.0)	2 (1.4)	4 (1.2)
Infections and Infestations	9 (5.7)	11 (7.9)	28 (14.3)	22 (15.7)	50 (14.9)
Metabolism and Connective Tissue Disorders	4 (2.5)	7 (5.0)	17 (8.7)	10 (7.1)	27 (8.0)
Neoplasms Benign, Malignant and Unspecified	3 (1.9)	3 (2.1)	4 (2.0)	6 (4.3)	10 (3.0)
Nervous System Disorders	36 (22.6)	18 (12.9)	51 (26.0)	26 (18.6)	77 (22.9)
Renal and Urinary Disorders	6 (3.8)	2 (1.4)	14 (7.1)	4 (2.9)	18 (5.4)
Respiratory, Thoracic, and Mediastinal Disorders	4 (2.5)	4 (2.9)	11 (5.6)	5 (3.6)	16 (4.8)
Vascular Disorders	2 (1.3)	1 (0.7)	3 (1.5)	1 (0.7)	4 (1.2)

Table 37 Summary of SAEs in $\geq 1\%$ of Rifaximin-Treated Subjects in Any Group or Placebo-Treated Subjects in the RCT Study (RCT Study and Long Term Rifaximin Experience Populations)

MedDRA System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population		
	Double-Blind Study Treatment		New Rifaximin 550 mg BID (PEY = 142.3) ^a (N = 196) n (%)	Continuing Rifaximin 550 mg BID (PEY = 109.7) ^a (N = 140) n (%)	All Rifaximin Subjects (PEY = 251.9) ^a (N = 336) n (%)
	Placebo (PEY = 46.0) ^a (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) ^a (N = 140) n (%)			
Any SAE	63 (39.6)	51 (36.4)	94 (48.0)	71 (50.7)	165 (49.1)
Blood and Lymphatic System Disorders	0	5 (3.6)	8 (4.1)	9 (6.4)	17 (5.1)
Anemia	0	4 (2.9)	7 (3.6)	7 (5.0)	14 (4.2)
Cardiac Disorders	5 (3.1)	5 (3.6)	5 (2.6)	5 (3.6)	10 (3.0)
Cardiac failure congestive	2 (1.3)	2 (1.4)	2 (1.0)	2 (1.4)	4 (1.2)
Atrial fibrillation	2 (1.3)	1 (0.7)	0	1 (0.7)	1 (0.3)
Gastrointestinal Disorders	11 (6.9)	16 (11.4)	35 (17.9)	27 (19.3)	62 (18.5)
Ascites	4 (2.5)	4 (2.9)	7 (3.6)	6 (4.3)	13 (3.9)
Abdominal pain	1 (0.6)	2 (1.4)	7 (3.6)	3 (2.1)	10 (3.0)
Gastrointestinal hemorrhage	3 (1.9)	1 (0.7)	6 (3.1)	4 (2.9)	10 (3.0)
Esophageal varices hemorrhage	2 (1.3)	4 (2.9)	1 (0.5)	6 (4.3)	7 (2.1)
Vomiting	0	3 (2.1)	1 (0.5)	5 (3.6)	6 (1.8)
Upper gastrointestinal hemorrhage	2 (1.3)	0	3 (1.5)	1 (0.7)	4 (1.2)
Ileus	0	0	2 (1.0)	1 (0.7)	3 (0.9)
Lower gastrointestinal hemorrhage	0	1 (0.7)	2 (1.0)	1 (0.7)	3 (0.9)
Nausea	0	1 (0.7)	1 (0.5)	2 (1.4)	3 (0.9)
Abdominal pain upper	0	0	2 (1.0)	0	2 (0.6)
Varices esophageal	0	0	2 (1.0)	0	2 (0.6)
General Disorders and Administration Site Conditions	4 (2.5)	6 (4.3)	12 (6.1)	7 (5.0)	19 (5.7)
Generalized edema	2 (1.3)	3 (2.1)	2 (1.0)	3 (2.1)	5 (1.5)
Chest pain	0	1 (0.7)	3 (1.5)	1 (0.7)	4 (1.2)
Asthenia	1 (0.6)	0	3 (1.5)	0	3 (0.9)

MedDRA System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population		
	Double-Blind Study Treatment		New Rifaximin 550 mg BID (PEY = 142.3) ^a (N = 196) n (%)	Continuing Rifaximin 550 mg BID (PEY = 109.7) ^a (N = 140) n (%)	All Rifaximin Subjects (PEY = 251.9) ^a (N = 336) n (%)
	Placebo (PEY = 46.0) ^a (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) ^a (N = 140) n (%)			
Hepatobiliary Disorders	10 (6.3)	7 (5.0)	27 (13.8)	17 (12.1)	44 (13.1)
Hepatic failure	1 (0.6)	1 (0.7)	13 (6.6)	4 (2.9)	17 (5.1)
Hepatic cirrhosis	6 (3.8)	3 (2.1)	6 (3.1)	7 (5.0)	13 (3.9)
Cirrhosis alcoholic	0	1 (0.7)	3 (1.5)	1 (0.7)	4 (1.2)
Biliary cirrhosis primary	0	1 (0.7)	2 (1.0)	1 (0.7)	3 (0.9)
Liver disorder	0	0	2 (1.0)	1 (0.7)	3 (0.9)
Immune System Disorders	0	1 (0.7)	2 (1.0)	2 (1.4)	4 (1.2)
Liver transplant rejection	0	1 (0.7)	0	2 (1.4)	2 (0.6)
Infections and Infestations	9 (5.7)	11 (7.9)	28 (14.3)	22 (15.7)	50 (14.9)
Cellulitis	2 (1.3)	3 (2.1)	7 (3.6)	6 (4.3)	13 (3.9)
Pneumonia	1 (0.6)	4 (2.9)	4 (2.0)	4 (2.9)	8 (2.4)
Urinary tract infection	1 (0.6)	2 (1.4)	3 (1.5)	5 (3.6)	8 (2.4)
Peritonitis bacterial	3 (1.9)	1 (0.7)	6 (3.1)	1 (0.7)	7 (2.1)
Clostridium colitis	0	2 (1.4)	3 (1.5)	2 (1.4)	5 (1.5)
Lobar pneumonia	0	0	1 (0.5)	3 (2.1)	4 (1.2)
Bacteremia	1 (0.6)	1 (0.7)	2 (1.0)	1 (0.7)	3 (0.9)
Gastroenteritis	0	1 (0.7)	2 (1.0)	1 (0.7)	3 (0.9)
Septic shock	0	0	2 (1.0)	1 (0.7)	3 (0.9)
Sepsis	2 (1.3)	0	0	0	0
Metabolism and Connective Tissue Disorders	4 (2.5)	7 (5.0)	17 (8.7)	10 (7.1)	27 (8.0)
Hyperkalemia	0	2 (1.4)	6 (3.1)	2 (1.4)	8 (2.4)
Hyponatremia	1 (0.6)	1 (0.7)	7 (3.6)	1 (0.7)	8 (2.4)
Hyperglycemia	1 (0.6)	1 (0.7)	4 (2.0)	1 (0.7)	5 (1.5)
Dehydration	1 (0.6)	1 (0.7)	2 (1.0)	1 (0.7)	3 (0.9)

MedDRA System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population		
	Double-Blind Study Treatment		New Rifaximin 550 mg BID (PEY = 142.3) ^a (N = 196) n (%)	Continuing Rifaximin 550 mg BID (PEY = 109.7) ^a (N = 140) n (%)	All Rifaximin Subjects (PEY = 251.9) ^a (N = 336) n (%)
	Placebo (PEY = 46.0) ^a (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) ^a (N = 140) n (%)			
Hypoglycemia	1 (0.6)	0	2 (1.0)	0	2 (0.6)
Neoplasms Benign, Malignant and Unspecified	3 (1.9)	3 (2.1)	4 (2.0)	6 (4.3)	10 (3.0)
Hepatic neoplasm malignant	2 (1.3)	2 (1.4)	4 (2.0)	3 (2.1)	7 (2.1)
Nervous System Disorders	36 (22.6)	18 (12.9)	51 (26.0)	26 (18.6)	77 (22.9)
Hepatic encephalopathy	34 (21.4)	16 (11.4)	46 (23.5)	24 (17.1)	70 (20.8)
Mental impairment	0	0	2 (1.0)	1 (0.7)	3 (0.9)
Dizziness	1 (0.6)	0	2 (1.0)	0	2 (0.6)
Metabolic encephalopathy	0	0	2 (1.0)	0	2 (0.6)
Syncope	1 (0.6)	2 (1.4)	0	2 (1.4)	2 (0.6)
Renal and Urinary Disorders	6 (3.8)	2 (1.4)	14 (7.1)	4 (2.9)	18 (5.4)
Renal failure acute	4 (2.5)	2 (1.4)	10 (5.1)	3 (2.1)	13 (3.9)
Renal failure	2 (1.3)	0	5 (2.6)	0	5 (1.5)
Respiratory, Thoracic, and Mediastinal Disorders	4 (2.5)	4 (2.9)	11 (5.6)	5 (3.6)	16 (4.8)
Pleural effusion	0	2 (1.4)	2 (1.0)	2 (1.4)	4 (1.2)
Dyspnea	0	0	3 (1.5)	0	3 (0.9)
Hydrothorax	0	1 (0.7)	2 (1.0)	1 (0.7)	3 (0.9)
Respiratory failure	1 (0.6)	0	2 (1.0)	1 (0.7)	3 (0.9)
Vascular Disorders	2 (1.3)	1 (0.7)	3 (1.5)	1 (0.7)	4 (1.2)
Hypotension	2 (1.3)	1 (0.7)	0	1 (0.7)	1 (0.3)

Source: ISS Tables 5.4.1.1 and 5.4.2.1, Appendix C

Abbreviations: SAE = serious adverse event; BID = twice daily; PEY = person-years of exposure; and RCT = randomized controlled trial.

a Person-years of exposure was computed as the sum of exposure days for all subjects included in the analysis divided by 365.25.

Note: Serious adverse events are summarized alphabetically by SOC and by descending order of frequency within each SOC using 'All Rifaximin Subjects.'

Note: A total of 19 subjects had SAEs that were not included in the ISS tables because these SAEs were not entered into the clinical database before database freeze for the ongoing study RFHE3002. This total count of 19 subjects includes the 5 subject deaths (subject numbers 3001-0397-0001, 3001-0397-0002 [gastrointestinal tract adenoma], 3001-0456-0001, 9999-0757-0051, and 9999-1025-0063) that were reported after database freeze. Narrative descriptions of the SAEs/deaths are included in Section 5.

Table 37 presents treatment-emergent SAEs in ≥ 2 rifaximin- or placebo-treated subjects in each Child-Pugh class in RFHE3001. The profile of SAEs by baseline Child-Pugh class is consistent with the profile of treatment-emergent AEs presented below. The incidence of SAEs was highest among subjects who were Child-Pugh C (rifaximin: 47.1%; placebo: 50%), and lower among Child-Pugh B subjects (rifaximin: 38.5%; placebo: 36.1%) and Child-Pugh A subjects (rifaximin: 28.3%; placebo: 41.1%). There were no remarkable between-group differences (rifaximin versus placebo) in the types and frequencies of SAEs in each Child-Pugh class. Similar results were observed in the analysis of SAEs by MELD score in that there was a trend toward increasing incidences of SAEs at higher MELD scores, and there were no notable between-group differences in SAEs across MELD score categories.

The most frequent SAEs (i.e., experienced by ≥ 5 subjects total) were hepatic cirrhosis (in 3 rifaximin, 6 placebo subjects), ascites (in 4 rifaximin, 3 placebo subjects), esophageal varices hemorrhage (in 4 rifaximin, 2 placebo subjects), acute renal failure (in 2 rifaximin, 4 placebo subjects), and pneumonia (in 4 rifaximin, 1 placebo subjects), excluding HE episodes that were SAEs due to hospitalization. Of the 43 subjects who experienced the most frequent SAEs, only 6 were Child-Pugh A and 37 were Child-Pugh B or C. The frequent SAEs occurred at comparable rates between rifaximin and placebo groups, although rifaximin subjects had higher rates of esophageal varices (see total column in Table 4.1 [Section 10]: 3.1% rifaximin, versus 1.4% placebo) and pneumonia (3.1% rifaximin, versus 0.7% placebo) in RFHE3001. There were two patients in RFHE3001 who developed *C. difficile* colitis and three in RFHE3002. No placebo patients developed *C. difficile* colitis.

Pneumonia is common in cirrhotic patients in both the hospital and community settings. The incidence of community acquired pneumonia has been shown to range between 7% and 23% in cirrhotic patients. In study RFHE3001, pneumonia SAEs were experienced by 4 rifaximin treated subjects (3.1%) and 1 placebo-treated subject (1.4%). In review of SAE reports of pneumonia, the subjects had several predisposing risk factors for pneumonia, including the following: chronic liver disease, alcoholism, hepatitis C, hepatic hydrothorax, chronic obstructive pulmonary disease, portal hypertension, diabetes mellitus, and smoking.

During RFHE3001 plus RFHE3002 experience, 5 subjects in the placebo crossover group and 1 subject in the rifaximin rollover group experienced pneumonia SAEs (see Section 7.2). Pneumonia SAE event rates were similar between the RFHE3001 rifaximin group (0.13 events/PEY) and the placebo crossover/rifaximin rollover groups (0.13 events/PEY).

Medical Officer's Comments:

The incidence of treatment-emergent adverse events (TEAE) increased as the liver function worsened. Nonetheless, the incidence of TEAE increased with decline in liver function in placebo groups as well, and the TEAE rate was similar between rifaximin

treatment group and placebo group among patients with the same Child-Pugh Class liver function, except deaths which was numerically higher in the rifaximin arm. Based on the current information, there is no obvious correlation with the degree of liver impairment and incidence of adverse event. It should be noted that relatively limited safety data are available for patients with severe liver impairment in this NDA.

Table 37: Treatment-emergent SAEs Experienced by ≥ 2 Subjects in Either Treatment Group by Child-Pugh Class – RFHE3001

System Organ Class Preferred Term	Child-Pugh A (5-6)		Child-Pugh B (7-9)		Child-Pugh C (10-12)	
	Rifaximin 550 mg BID N = 46	Placebo N = 56	Rifaximin 550 mg BID N = 65	Placebo N = 72	Rifaximin 550 mg BID N = 17	Placebo N = 14
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any SAEs	13 (28.3)	23 (41.1)	25 (38.5)	26 (36.1)	8 (47.1)	7 (50.0)
Blood and Lymphatic System Disorders	1 (2.2)	0	3 (4.6)	0	0	0
Anemia	1 (2.2)	0	2 (3.1)	0	0	0
Gastrointestinal Disorders	7 (15.2)	3 (5.4)	8 (12.3)	5 (6.9)	1 (5.9)	2 (14.3)
Ascites	0	1 (1.8)	3 (4.6)	2 (2.8)	1 (5.9)	0
Gastrointestinal haemorrhage	0	1 (1.8)	1 (1.5)	2 (2.8)	0	0
Oesophageal varices haemorrhage	2 (4.3)	0	2 (3.1)	1 (1.4)	0	1 (7.1)
Vomiting	2 (4.3)	0	1 (1.5)	0	0	0
General Disorders and Administration Site Conditions	0	1 (1.8)	2 (3.1)	3 (4.2)	3 (17.6)	0
Generalized oedema	0	1 (1.8)	2 (3.1)	1 (1.4)	0	0
Hepatobiliary Disorders	1 (2.2)	4 (7.1)	2 (3.1)	6 (8.3)	3 (17.6)	0
Hepatic cirrhosis	0	1 (1.8)	2 (3.1)	5 (6.9)	1 (5.9)	0
Infections and Infestations	2 (4.3)	1 (1.8)	7 (10.8)	4 (5.6)	1 (5.9)	2 (14.3)
Cellulitis	0	0	2 (3.1)	1 (1.4)	0	1 (7.1)
Pneumonia	1 (2.2)	0	3 (4.6)	1 (1.4)	0	0
Nervous System Disorders	5 (10.9)	14 (25.0)	9 (13.8)	14 (19.4)	3 (17.6)	6 (42.9)
Hepatic encephalopathy	5 (10.9)	14 (25.0)	7 (10.8)	13 (18.1)	3 (17.6)	5 (35.7)
Syncope	0	0	2 (3.1)	1 (1.4)	0	0
Renal and Urinary Disorders	0	4 (7.1)	2 (3.1)	2 (2.8)	0	0
Renal failure acute	0	3 (5.4)	2 (3.1)	1 (1.4)	0	0
Respiratory, Thoracic and Mediastinal Disorders	1 (2.2)	1 (1.8)	2 (3.1)	1 (1.4)	1 (5.9)	1 (7.1)
Pleural effusion	0	0	2 (3.1)	0	0	0

Source: Table 4.1 (Section 10); Abbreviations: TEAE = treatment-emergent adverse event; RCT = randomized controlled trials; and BID = twice daily.

Note: Twelve subjects in the rifaximin group and 17 in the placebo group had missing Child-Pugh classification. Child-Pugh subscores, total score (5-15), and classifications (A,B, or C) were obtained post study.

7.3.3 Dropouts and/or Discontinuations

Table 38: TEAEs Resulting in Study Discontinuation in $\geq 1\%$ of Long Term Rifaximin Experience (From Applicant submission, table 43, page 134 ISS)

MedDRA System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population		
	Double-Blind Study Treatment		New Rifaximin	Continuing Rifaximin	All Rifaximin Subjects
	Placebo (PEY = 46.0) ^a (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) ^a (N = 140) n (%)	550 mg BID (PEY = 142.3) ^a (N = 196) n (%)	550 mg BID (PEY = 109.7) ^a (N = 140) n (%)	(PEY = 251.9) ^a (N = 336) n (%)
Any TEAEs Resulting in Study Discontinuation	45 (28.3)	30 (21.4)	30 (15.3)	42 (30.0)	72 (21.4)
Gastrointestinal Disorders	3 (1.9)	3 (2.1)	5 (2.6)	4 (2.9)	9 (2.7)
Esophageal varices hemorrhage	0	2 (1.4)	0	3 (2.1)	3 (0.9)
Abdominal pain	0	0	2 (1.0)	0	2 (0.6)
Gastrointestinal hemorrhage	1 (0.6)	0	2 (1.0)	0	2 (0.6)
Ascites	2 (1.3)	0	0	0	0
Hepatobiliary Disorders	3 (1.9)	3 (2.1)	18 (9.2)	9 (6.4)	27 (8.0)
Hepatic failure	0	1 (0.7)	11 (5.6)	4 (2.9)	15 (4.5)
Hepatic cirrhosis	2 (1.3)	0	3 (1.5)	2 (1.4)	5 (1.5)
Cirrhosis alcoholic	0	1 (0.7)	2 (1.0)	1 (0.7)	3 (0.9)
Infections And Infestations	4 (2.5)	2 (1.4)	2 (1.0)	4 (2.9)	6 (1.8)
Peritonitis bacterial	2 (1.3)	1 (0.7)	0	1 (0.7)	1 (0.3)
Neoplasms Benign, Malignant, and Unspecified	0	0	3 (1.5)	2 (1.4)	5 (1.5)
Hepatic neoplasm malignant	0	0	3 (1.5)	1 (0.7)	4 (1.2)
Nervous System Disorders	30 (18.9)	14 (10.0)	1 (0.5)	14 (10.0)	15 (4.5)
Hepatic encephalopathy	30 (18.9)	14 (10.0)	1 (0.5)	14 (10.0)	15 (4.5)

Source: ISS Tables 5.5.1.1b and 5.5.2.1, Appendix C

Abbreviations: PEY = person-years of exposure; RCT = randomized controlled trials; BID = twice daily; and TEAE = treatment emergent adverse event.

^a Person-years of exposure was computed as the sum of exposure days for all subjects included in the analysis divided by 365.25.

Note: TEAEs are summarized alphabetically by SOC and by descending order of frequency within each SOC using 'All Rifaximin Subjects.'

Disposition by Child-Pugh Class and by MELD Score in RFHE3001

Table 39 and Table 40 show subject disposition by Child-Pugh class and by MELD score, respectively. Child-Pugh class at baseline was determined post study (at the request of the Division) in RFHE3001 only, and MELD score was calculated using clinical laboratory test results obtained throughout studies RFHE3001 and RFHE3002. In RFHE3001, 12 subjects in the rifaximin group and 17 in the placebo group had missing baseline Child-Pugh classification. Among 270 subjects with recorded Child-Pugh class, most subjects were Child-Pugh B (65/128 rifaximin, and 72/142 placebo). A total of 31 subjects were Child-Pugh C.

Table 39: Disposition by Child-Pugh Classification (baseline) – RFHE3001

	Child-Pugh A (5-6)		Child-Pugh B (7-9)		Child-Pugh C (10-15)	
	Rifaximin 550 mg BID N = 46	Placebo N = 56	Rifaximin 550 mg BID N = 65	Placebo N = 72	Rifaximin 550 mg BID N = 17	Placebo N = 14
Primary reason for early discontinuation:						
Adverse event	0	2 (3.6)	4 (6.2)	4 (5.6)	2 (11.8)	0
Request to withdraw	2 (4.3)	5 (8.9)	2 (3.1)	3 (4.2)	1 (5.9)	0
Liver transplant	0	0	0	1 (1.4)	0	0
Death	2 (4.3)	0	3 (4.6)	3 (4.2)	1 (5.9)	0
Other	0	0	2 (3.1)	1 (1.4)	0	0

Source: Table 3.1; Abbreviations: BID = twice daily.

Notes: Twelve subjects in the rifaximin group and 17 in the placebo group had missing Child-Pugh classification. Child-Pugh subscores, total score (5-15), and classifications (A,B, or C) were obtained post study. Discontinuations due to breakthrough overt HE episode are not included in this table since subjects withdrew from the study at the time of first breakthrough overt HE episode (primary efficacy outcome), in accordance with the study protocol.

Table 40: Disposition by MELD Score (baseline) – RFHE3001

	MELD Category: ≤ 10		MELD Category: 11-18		MELD Category: ≥ 19	
	Rifaximin 550 mg BID N = 34	Placebo N = 48	Rifaximin 550 mg BID N = 94	Placebo N = 96	Rifaximin 550 mg BID N = 12	Placebo N = 14
Primary reason for early discontinuation:						
Adverse event	0	4 (8.3)	7 (7.4)	2 (2.1)	1 (8.3)	1 (7.1)
Request to withdraw	3 (8.8)	2 (4.2)	3 (3.2)	7 (7.3)	0	0
Liver transplant	0	0	0	1 (1.0)	0	0
Death	1 (2.9)	0	5 (5.3)	2 (2.1)	0	1 (7.1)
Developed exclusion criteria	1 (2.9)	1 (2.1)	0	2 (2.1)		
Other	1 (2.9)	0	2 (2.1)	1 (1.0)	0	0

Source: Table 3.2; Abbreviations: MELD = Model End Stage Liver Disease; BID = twice daily.

Note: Discontinuations due to breakthrough overt HE episode are not included in this table since subjects withdrew from the study at the time of first breakthrough overt HE episode (primary efficacy outcome), in accordance with the study protocol.

The profile of AEs resulting in early study discontinuation across Child-Pugh class during long term rifaximin therapy was analyzed in subjects who entered RFHE3002

after participation in RFHE3001 in Table 41. As expected during long-term treatment in RFHE3002, the overall incidences of AEs resulting in study withdrawal increased when compared to RFHE3001.

Ascites, congestive cardiac failure, esophageal varices hemorrhage, and hepatic cirrhosis were the most frequently occurring AEs resulting in early study discontinuation in RFHE3001. These SAEs are compared by Child-Pugh class in rifaximin-treated subjects in RFHE3001 and RFHE3002 in Table 41. Hepatic failure resulting in study discontinuation was experienced by higher percentages of subjects during long-term rifaximin therapy (4 subjects each in the placebo crossover and rollover rifaximin groups) compared with rifaximin therapy in RFHE3001 (0 subjects in the RFHE3001 rifaximin group). The increased frequency of hepatic failure during long-term treatment would be expected in light of the natural history of progression of liver disease and the increasing time of follow-up on study in RFHE3002.

When adjusting for longer exposure in study RFHE3002, the event rates (i.e., events/PEYs) for AEs resulting in early study discontinuation were higher in rifaximin subjects in RFHE3001 than in placebo crossover subjects and rifaximin rollover subjects across Child-Pugh classes (Table 41); with the exception of hepatic failure, which occurred at a lower event rate in RFHE3001 than in the RFHE3002 rifaximin groups.

Table 41: Comparison of the Most Frequent AEs Leading to Early Study Withdrawal – Rifaximin Experience in RFHE3001 and in RFHE3001 plus RFHE3002

RFHE3001 experience (rifaximin and placebo) ^a						
	Child-Pugh A (5-6)		Child-Pugh B (7-9)		Child-Pugh C (10-15)	
	Rifaximin 550 mg BID N = 46	Placebo N = 56	Rifaximin 550 mg BID N = 65	Placebo N = 72	Rifaximin 550 mg BID N = 17	Placebo N = 14
Person exposure years ^b	17	18	24	21	5	4
Ascites, n (%)	0	0	0	2 (2.8)	0	0
Event rate/PEY	0	0	0	0.10	0	0
Congestive cardiac failure, n (%)	0	0	0	1 (1.4)	1 (5.9)	0
Event rate/PEY	0	0	0	0.05	0.20	0
Oesophageal varices haemorrhage, n (%)	1 (2.2)	0	1 (1.5)	0	0	0
Event rate/PEY	0.06	0	0.04	0	0	0
Hepatic cirrhosis, n (%)	0	0	0	2 (2.8)	0	0
Event rate/PEY	0	0	0	0.10	0	0
Hepatic failure, n (%)	0	0	0	0	0	0
Event rate/PEY	0	0	0	0	0	0
RFHE3001 and RFHE3002 experience (rifaximin only) ^a						
	Child-Pugh A (5-6)		Child-Pugh B (7-9)		Child-Pugh C (10-15)	
	Placebo crossover ^c N = 36	Rifaximin rollover ^d N = 32	Placebo crossover ^c N = 37	Rifaximin rollover ^d N = 31	Placebo crossover ^c N = 7	Rifaximin rollover ^d N = 5
Person exposure years ^b	45	52	44	52	5	8
Ascites, n (%)	0	1 (3.1)	0	0	0	0
Event rate/PEY	0	0.02	0	0	0	0
Congestive cardiac failure, n (%)	0	0	0	0	0	0
Event rate/PEY	0	0	0	0	0	0
Oesophageal varices haemorrhage, n (%)	0	1 (3.1)	1 (2.7)	0	0	0
Event rate/PEY	0	0.02	0.02	0	0	0
Hepatic cirrhosis, n (%)	0	0	1 (2.7)	1 (3.2)	0	0
Event rate/PEY	0	0	0.02	0.02	0	0
Hepatic failure, n (%)	1 (2.8)	0	2 (5.4)	3 (9.7)	1 (14.3)	1 (20.0)
Event rate/PEY	0.02	0	0.05	0.06	0.20	0.125

Source: Tables 4.5 and 4.8 (Section 10); Abbreviations: BID = twice daily.

Notes: Twelve subjects in the rifaximin group and 17 in the placebo group had missing Child-Pugh classification in RFHE3001. Child-Pugh subscores, total score (5-15), and classifications (A,B, or C) were obtained post study, and were recorded for subjects at the start of RFHE3001, but not in study RFHE3002. Therefore, to include RFHE3002 experience, data are shown for subjects who participated in RFHE3001 and RFHE3002. Two subjects in the placebo crossover group and 2 in the rifaximin rollover (continuing rifaximin) group had missing Child-Pugh classification.

a HE episodes that were SAEs due to hospitalization and were also reported as AEs resulting in early study withdrawal were excluded from this table.

b Person exposure years is (mean exposure in days/365.25) × number of subjects.

c Placebo crossover subjects received placebo in RFHE3001 and rifaximin in the RFHE3002.

d Rifaximin rollover (also referred to as continuing rifaximin) subjects received rifaximin in RFHE3001 and RFHE3002.

7.3.4 Significant Adverse Events

An analysis of TEAEs of special interest was performed for this ISS on the basis of known side effects and potential side effects of antibiotics as a drug class, with specific focus on adverse events that might be suggestive of bacterial resistance. These special interest AEs included respiratory infections, GI-related infections, and symptoms of GI or respiratory infections.

Diarrhea was the most common special interest TEAE in both the rifaximin (15 subjects [10.7%]) and placebo (21 subjects [13.2%]) treatment groups. Diarrhea can be a symptom of bacterial infection, but its prevalence in study RFHE3001 may have been due to the high percentage of subjects in each treatment group (rifaximin: 77.9%; placebo: 78.6%) who used lactulose during the study.

Table 42: Special Interest TEAEs in ≥ 1% of Either Treatment Group in the RCT Study Population or in ≥ 1% of All Rifaximin Subjects in the Long Term Rifaximin Experience Population

MedDRA System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population		
	Double-Blind Study Treatment		New Rifaximin 550 mg BID	Continuing Rifaximin 550 mg BID	All Rifaximin Subjects
	Placebo (PEY = 46.0) ^a (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) ^a (N = 140) n (%)	(PEY = 142.3) ^a (N = 196) n (%)	(PEY = 109.7) ^a (N = 140) n (%)	(PEY = 251.9) ^a (N = 336) n (%)
Any Special Interest TEAE	35 (22.0)	34 (24.3)	60 (30.6)	43 (30.7)	103 (30.7)
Gastrointestinal Disorders	26 (16.4)	21 (15.0)	35 (17.9)	26 (18.6)	61 (18.2)
Diarrhea	21 (13.2)	15 (10.7)	18 (9.2)	18 (12.9)	36 (10.7)
Gastrointestinal hemorrhage	3 (1.9)	1 (0.7)	8 (4.1)	4 (2.9)	12 (3.6)
Gastritis	0	2 (1.4)	2 (1.0)	2 (1.4)	4 (1.2)
Hematochezia	1 (0.6)	2 (1.4)	1 (0.5)	2 (1.4)	3 (0.9)
Infections And Infestations	10 (6.3)	14 (10.0)	29 (14.8)	21 (15.0)	50 (14.9)
Pneumonia	1 (0.6)	4 (2.9)	7 (3.6)	5 (3.6)	12 (3.6)
Peritonitis bacterial	4 (2.5)	2 (1.4)	7 (3.6)	4 (2.9)	11 (3.3)
Clostridium colitis	0	2 (1.4)	3 (1.5)	2 (1.4)	5 (1.5)
Bacteremia	2 (1.3)	1 (0.7)	2 (1.0)	2 (1.4)	4 (1.2)
Lobar pneumonia	0	0	1 (0.5)	3 (2.1)	4 (1.2)
Sepsis	2 (1.3)	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.6)	2 (1.4)	9 (4.6)	3 (2.1)	12 (3.6)
Pleural effusion	1 (0.6)	2 (1.4)	5 (2.6)	2 (1.4)	7 (2.1)
Pulmonary edema	0	0	3 (1.5)	1 (0.7)	4 (1.2)

Source: ISS Tables 5.9.1 and 5.9.2, Appendix C

Abbreviations: PEY = person-years of exposure; TEAE = treatment-emergent adverse event; RCT = randomized controlled trial; and BID = twice daily.

a Person-years of exposure was computed as the sum of exposure days for all subjects included in the analysis divided by 365.25.

Note: TEAEs are summarized alphabetically by SOC and by descending order of frequency within each SOC using 'All Rifaximin Subjects.'

Infection

Bacterial infections are typically more prevalent in subjects with impaired hepatic function, mainly due to altered host defenses, including decreased function of macrophages, neutrophils, monocytes, and disturbed phagocytosis with less destruction of bacteria.¹⁶ The presence of HE in the course of cirrhosis and severe hepatic dysfunction can correlate directly with an even higher prevalence of bacterial infections.^{17,18} In addition, other factors in this subject population may contribute to a

higher incidence of infections, including but not limited to the following: frequent or prolonged hospitalizations; age-related susceptibility; immunologic susceptibility (clearance of enteric organisms from the portal circulation is impaired by portosystemic shunt and impaired Kupffer cell function); non surgical and surgical GI interventions; and concomitant medications (e.g., proton pump inhibitors, systemic antibiotics). Other extrinsic factors such as alcoholism, malnutrition, GI hemorrhage, and altered permeability of intestinal mucosa can also predispose individual subjects to bacterial infections.¹⁹

Infections often associated with cirrhotic patients occurred infrequently in rifaximin treated subjects in the Primary Analysis studies, including meningitis (1 subject [meningitis cryptococcal]) and endocarditis (0 subjects).

Sepsis was cited as the cause of death for 3 rifaximin-treated subjects in RFHE3002. Among All Rifaximin subjects in the Long Term population, 4 experienced a TEAE of bacteremia. TEAEs of enterococcal bacteremia, escherichia bacteremia, klebsiella bacteremia, pseudomonal bacteremia, and staphylococcal bacteremia were experienced by 1 subject each. More placebo-treated subjects experienced TEAEs of bacteremia (2 vs. 1) and sepsis (2 vs. 0) during the double blind comparison (RFHE3001), and 1 subject in each group experienced urosepsis. Overall, the Applicant felt these events in the primary studies appeared with the expected incidence for this population.

Medical Officer's Comments:

It is difficult to evaluate this data in light of the increased risk in this population. The risk for increased resistant infections with the long term use of an antibiotic remains a clinical concern.

Spontaneous Bacterial Peritonitis

In the RFHE3001 study, the incidence of SBP was higher in the placebo group (2.5%) compared with the rifaximin group (1.4%). Bacterial peritonitis is an expected adverse event in cirrhotic patients, with an incidence that has been shown to vary between 10 and 30% during a single hospitalization, and approximately half of these episodes are present at the time of hospitalization.²⁰ The 1-year probability for the development of the first episode of SBP in cirrhotic patients with ascites is approximately 10%.²¹ The frequency of SBP increased in rifaximin subjects after 6 months of treatment, but in total only 11 rifaximin-treated subjects (3.3%) experienced SBP in the primary analysis studies. The event rate per 100 person years of exposure for SBP was 4.4 in All Rifaximin subjects in the Long Term population, compared with 4.0 and 8.7 in rifaximin and placebo-treated subjects in the RCT Study population, respectively.

Urinary Tract Infection

The incidence of UTI's, which are also frequently observed in cirrhotic patients, was higher in placebo- treated subjects (8.8% vs. 5.7%) in the RCT Study (RFHE3001). The event rate for 100 exposure years was nearly 2-fold higher in RCT placebo subjects (30.4) compared with All Rifaximin subjects (16.3) in the Long Term population. The large majority of all subjects who experienced UTI's in the primary studies were female. Table 37

Clostridium difficile colitis

Two (2) events of clostridium colitis (*C. difficile*) occurred in rifaximin-treated subjects in the RCT Study (RFHE3001) and 3 additional TEAEs of clostridium colitis were recorded in the open-label RFHE3002 study. The 2 events in the RCT Study were considered by the assessing investigator to be drug-related. To better understand the 2 cases of clostridium colitis (*C. difficile*) infection that were considered by the investigator to be related to study drug in RFHE3001 (Subject numbers 3001-0469-0003 and 3001-0760-0001 [rifaximin group]) and the 3 additional cases of *C. difficile* in RFHE3002 (Subjects 3001-0743-0006, 9999-0760-0051, and 9999-0799-0051), the clinical background for each subject was reviewed against known risk factors for *C. difficile* infection, as reported in published literature. The Applicant concluded that with multiple confounding factors present in each subject who experienced *c. difficile* in the primary studies, a causal association could not be established. The co-founding factors included other antibiotic use and inpatient hospital admission.

C. difficile infection has been previously associated with several systemic antibiotics, however the incidence of *C. difficile* infection associated with rifaximin is unknown. Two cases have been reported to Salix from an unpublished abstract of a retrospective chart review of 92 adult patients who received Xifaxan (rifaximin) to prevent hepatic encephalopathy between December 2005 and April 2007 (see Section 3.2). In both cases, the patients received between 10-30 days of rifaximin therapy for the treatment of HE and were subsequently hospitalized due to peritonitis. In each case the patient was treated with antibiotics for the event of peritonitis (ceftriaxone and ciprofloxacin or etapenem) and developed a *c. difficile* infection 8-10 days later in the hospital.

Medical Officer's Comments:

While the Applicant does not find a causal relationship with rifaximin and colitis in the NDA data set, there were no cases of C. difficile colitis in the placebo group. Because antibiotic administration increases development of C. difficile infections, it seems likely that an increased incidence of C. difficile colitis could result from chronic administration of rifaximin.

Campylobacter colitis

One additional rifaximin-treated subject of note (in Subject 3001-0655-0007) in the RFHE3002 study experienced a special interest TEAE that was considered related to study drug and satisfied the definition of an SAE. A 58-year-old white man with decompensated liver disease due to hepatitis C-induced hepatic cirrhosis was hospitalized on 12 Jun 2008, for infectious colitis – *Campylobacter*, and hypokalemia. Stool culture was obtained and returned negative for *C. difficile*, but positive for *Campylobacter*. The subject showed rapid improvement after treatment with IV hydration, levofloxacin, IV metronidazole, oral vancomycin, and potassium replacements. After a temporary interruption in study medication, the subject continued participation in the study and was an ongoing subject at the time of the clinical data cutoff for this ISS.

Medical Officer's Comments:

There are no other cases of colitis but this merits monitoring in post marketing should this product be approved for long term use.

Pneumonia

The incidence of community acquired pneumonia has been shown to range between 7% and 23% in cirrhotic patients.

In the RCT Study population; pneumonia was experienced by 4 subjects in the rifaximin group (2.9%) versus 1 subject in the placebo group (0.6%).

In the Long Term Rifaximin Experience population, pneumonia was experienced by 12 subjects (3.6%), and lobar pneumonia by 4 subjects (1.2%) for a total of 16 subjects (4.8%) with pneumonia. An additional 7 subjects developed pleural effusion.

Medical Officer's Comments:

While the increased incidence of pneumonia in the rifaximin group compared to the placebo group is concerning, it is difficult to draw firm conclusions about the risk in this population already at high risk for these complications.

Anemia

Subjects in the rifaximin group in the RCT study also had a higher incidence of TEAEs of anemia (7.9% vs. 3.8%) compared with the placebo group. Anemia is an event frequently associated with liver disease. A higher proportion of rifaximin-treated subjects had a medical history of anemia (30.7%) in the RCT Study compared with placebo-treated subjects (17%). Of the 11 subjects who experienced anemia in the rifaximin group, 7 had a prior medical history of anemia. By contrast, only 1 of the 6 subjects in the placebo group who experienced anemia had a prior medical history of the event. Six

subjects in the study experienced anemia considered to be severe in intensity, including 4 subjects (2.9%) in the rifaximin group and 2 subjects (1.3%) in the placebo group. None of the events of anemia that occurred during the study in either treatment group were considered to be drug-related by the assessing investigator. Four subjects in the rifaximin group experienced events of anemia considered to be serious (2.9%); the percentage of All Rifaximin subjects with anemia was 9.5% (32 subjects). Thirteen of these subjects had a medical history of anemia. None of these events were considered to be drug related.

On an exposure-normalized basis, the event rate for anemia per 100 person years was 22.0 in the rifaximin group in the RCT study. Lower event rates for anemia were observed in the All Rifaximin subjects in the Long Term population, 12.7 per 100 person years, and in the RCT placebo group, 13.0 per 100 person years

Medical Officer's Comments:

The increased incidence of anemia in the treatment group appears to be a result of differences in the populations at baseline and not drug related.

Thrombocytopenia

Thrombocytopenia, which is of interest in cirrhotic patients and presents serious complications for subjects at risk for GI or esophageal bleeding, occurred in only a few subjects in the RCT Study (rifaximin: 2 subjects; placebo: 1 subject). Among All Rifaximin subjects in the Long Term population a total of 12 subjects experienced thrombocytopenia (3.6%). The overall event rate per 100 years of exposure for thrombocytopenia was similar between All Rifaximin subjects (4.8) and rifaximin-treated subjects in the RCT Study (4.0), suggesting no increase in incidence with longer exposure. Nearly all subjects who experienced a TEAE of thrombocytopenia had platelet counts below the lower limit of normal at baseline. Based on TEAE reports of thrombocytopenia, extended rifaximin exposure does not appear to have a detrimental effect on platelet function.

7.3.5 Submission Specific Primary Safety Concerns

Analysis of the Potential for Drug-Induced Liver Injury

In accordance with draft FDA guidance on premarketing evaluation of drug-induced liver injury, a supplemental analysis was conducted for the primary analysis populations to identify any potential signals of hepatotoxicity. This review includes data from the 120-day update and a supplemental information request response dated December 1st 2009.

The analysis of the potential for hepatotoxicity in this population is confounded by the fact that all subjects in the primary analysis studies had preexisting liver cirrhosis at study entry, so results should be interpreted with caution. In fact, more subjects in each group in the RCT Study met the criteria of ALT or AST ≥ 3 times the ULN and bilirubin > 2 times the ULN at baseline than at any post-baseline study time point. More than a quarter of subjects in each group had a bilirubin lab value > 2 times the ULN at baseline.

In the RCT Study population, 10 rifaximin-treated subjects (7.1%) and 15 placebo-treated subjects (9.4%) had a peak aminotransferase (i.e., ALT or AST) lab value ≥ 3 times the ULN and also a peak total bilirubin lab value ≥ 2 times the ULN at baseline. Twenty-two (22) rifaximin treated subjects (15.9%) and 17 placebo-treated subjects (11.0%) met these criteria at post-baseline time points. Most of the subjects who met the criteria in each treatment group had elevated AST in association with elevated bilirubin. In total, 39 rifaximin-treated subjects had a post-baseline AST lab value ≥ 5 times the ULN in the primary studies (Long Term Rifaximin Experience population) up to the time of this safety update and 3 of these subjects had an AST lab value ≥ 10 times the ULN. Several of these subjects had elevated AST at screening or baseline and at multiple visits during the double-blind and open label studies. Nine (9) rifaximin-treated subjects had a post-baseline ALT lab value ≥ 5 times the ULN and 1 of these subjects (3001-0566-0007) had a post-baseline ALT laboratory value ≥ 10 times the ULN. Only one of the subjects with a post-baseline ALT laboratory value ≥ 5 times the ULN (9999-0807-0007) had a post-baseline elevation in bilirubin ≥ 2 times the ULN; the peak elevation in bilirubin was exactly 2 times the ULN and occurred at a different study visit. This subject had high bilirubin throughout participation, including predose.

In the RCT Study population, 2 subjects in each treatment group had a post-baseline peak ALT lab value ≥ 3 times the ULN and a post-baseline bilirubin lab value > 2 times the ULN who did not meet this criteria at baseline. One of the rifaximin-treated subjects (3001-754-0008) only met the criteria after being off study drug for approximately 45 days. Similar trends in liver function as measured by elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin, are noted in subjects who died in both rifaximin and placebo treatment groups.

Similar trends were observed for All Rifaximin subjects in the Long Term Rifaximin Experience population, where 10 subjects experienced a post-baseline peak ALT lab value ≥ 3 times the ULN and a post-baseline bilirubin lab value > 2 times the ULN (inclusive of the 2 rifaximin-treated subjects counted in the RCT Study population and excluding subjects who met the criteria at baseline). None of these subjects discontinued as a result of elevated aminotransferase or bilirubin values, and in the majority of instances elevated liver function tests returned to lower values or normalized at subsequent visits. The majority of these rifaximin-treated subjects had elevated bilirubin (>2 times the ULN) at 3 or more time points during the primary analysis studies, including predose.

Overall, findings with respect to elevations in liver enzymes were consistent with the population under study. Elevations of liver function tests were relatively frequent in subjects in the primary studies and were observed both during treatment and off treatment (e.g., screening, baseline, postdose).

The Division requested the Applicants' evaluation of possible liver toxicity in light of the known liver toxicity in this drug class, and the unknown effects of systemic exposure (i.e., little pre-clinical data), and the apparent increased absorption and increased risk of this population. The Applicant concluded; "poor oral absorption and resulting low systemic, hepatic, and biliary concentrations of rifaximin result in substantially lower risks of induction- or transporter mediated hepatotoxicity as compared with rifampin. While the risk of idiosyncratic hepatotoxicity is unknown, the lower exposures of rifaximin to the liver as compared with rifampin may reduce this risk as well."

Change in underlying Hepatic Disease

When the data from RFHE3001 was analyzed by change in MELD score during the study duration there was little change in the MELD score. The Applicant contends that this shows there was no deterioration in hepatic function during the 6 month study.

Table 43: Change in MELD Score RFHE3001

	Rifaximin	Placebo
Change from baseline to last assessment (end of treatment) in MELD Score		
n	131	145
Mean (SD)	0.06 (2.823)	0.20 (2.785)
Median (Min, Max)	-0.16 (-11.7, 11.2)	0.00 (-7.1, 19.6)

Medical Officer's Comments:

The Applicant reports that the lack of change in MELD score during the 6 month treatment period in RFHE3001 shows that rifaximin does not cause deterioration in hepatic function. However, they then contend that all the cases of hepatic failure and/or death are attributable to the deterioration expected to be seen in these patients. These positions seem inconsistent.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

See Table 44 and Table 45

Treatment-emergent AEs were most frequently reported in the GI disorders System Organ Class (SOC) (rifaximin: 51.4%; placebo: 42.1%) in the RCT Study population (RFHE3001). Other SOCs where TEAEs were reported in $\geq 25\%$ of all RCT subjects were as follows (rifaximin vs. placebo):

- Nervous system disorders (37.9% vs. 40.3%)
- General disorders and administration site conditions (40% vs. 32.7%)
- Infections and infestations (32.9% vs. 30.8%)
- Respiratory, thoracic and Mediastinal disorders (25.7% vs. 24.5%).

Overall, the incidence of TEAEs was similar between treatment groups and the most frequently observed events were disorders and events frequently associated with subjects with advanced liver disease (e.g., peripheral edema, ascites) or with a history of overt HE (e.g., HE episode, dizziness, fatigue).

Subjects in the rifaximin group in the RCT study also had a higher incidence of TEAEs of anemia (7.9% vs. 3.8%) compared with the placebo group. Anemia is an event frequently associated with liver disease. The reviewer agrees with the Applicant that the anemia does not appear to be drug related.

Treatment-emergent AEs in the RCT Study population that occurred in 3% of rifaximin-treated subjects and at least twice as often (by proportion) in the rifaximin group as in placebo group were;

- Anemia (7.9% vs. 3.8% placebo)
- Arthralgia (6.4% vs. 2.5%)
- Pyrexia (6.4% vs. 3.1%)
- Dehydration (3.6% vs. 1.3%)
- Hyperkalemia (3.6% vs. 1.3%).

For All Rifaximin subjects in the primary analysis studies, the most frequent TEAEs (i.e., $\geq 10\%$ of subjects) were peripheral edema (18.2%), nausea (15.8%), ascites (13.1%), urinary tract infections (12.2%), abdominal pain (11.9%), fatigue (11.3%), diarrhea (10.7%), muscle spasms (10.4%), and dizziness (10.1%).

The overall percentage of all rifaximin subjects in the primary analysis studies who experienced TEAEs (87.2%) was slightly higher than the placebo (79.9%) and rifaximin

(80.0%) groups in the RCT Study population. However, event rates for subjects experiencing TEAEs were comparable between the populations, indicating that the higher percentage in the Long Term population were attributable to the increased time on the open-label study and increased duration under observation.

The most notable difference between the analysis populations was in the incidence of hepatic failure, which occurred in 17 subjects (5.1%) in the Long Term Rifaximin Experience Population and in only 1 subject in each treatment group in the RCT Study population. There was a difference between the Long term and RCT populations in that there were an increased number of liver transplants in the RFHE3002 study compared with RFHE3001. Investigators frequently attributed the preferred terms hepatic failure, hepatic cirrhosis, and alcohol cirrhosis as the final diagnosis in deaths associated with the progression of underlying liver disease. In addition to the 7 subjects who experienced an SAE of hepatic failure with an outcome of death in the primary studies, 3 additional subjects treated with rifaximin experienced events of hepatic cirrhosis or alcoholic cirrhosis with an outcome of death. None of the events of hepatic failure, hepatic cirrhosis, or alcoholic cirrhosis in rifaximin-treated subjects with an outcome of death were considered by the investigator to be related to study medication.

Table 44: TEAEs occurring in ≥ 5% of subjects in the primary Analysis Population

System Organ Class ^b Preferred Term	RCT Study Population ^a		Long Term Rifaximin Experience Population		
	Double-Blind Study Treatment		New Rifaximin 550 mg BID	Continuing Rifaximin 550 mg BID	All Rifaximin Subjects
	Placebo (PEY = 46.0) ^c (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) ^c (N = 140) n (%)	(PEY = 142.3) ^c (N = 196) n (%)	(PEY = 109.7) ^c (N = 140) n (%)	(PEY = 251.9) ^c (N = 336) n (%)
Any TEAEs	127 (79.9)	112 (80.0)	172 (87.8)	121 (86.4)	293 (87.2)
Blood and Lymphatic System Disorders	8 (5.0)	15 (10.7)	28 (14.3)	21 (15.0)	49 (14.6)
Anemia	6 (3.8)	11 (7.9)	17 (8.7)	15 (10.7)	32 (9.5)
Gastrointestinal Disorders	67 (42.1)	72 (51.4)	111 (56.6)	86 (61.4)	197 (58.6)
Nausea	21 (13.2)	20 (14.3)	27 (13.8)	26 (18.6)	53 (15.8)
Ascites	15 (9.4)	16 (11.4)	23 (11.7)	21 (15.0)	44 (13.1)
Abdominal pain	13 (8.2)	12 (8.6)	24 (12.2)	16 (11.4)	40 (11.9)
Diarrhea	21 (13.2)	15 (10.7)	18 (9.2)	18 (12.9)	36 (10.7)
Vomiting	14 (8.8)	10 (7.1)	16 (8.2)	17 (12.1)	33 (9.8)
Constipation	10 (6.3)	9 (6.4)	18 (9.2)	12 (8.6)	30 (8.9)
Abdominal pain upper	8 (5.0)	9 (6.4)	7 (3.6)	13 (9.3)	20 (6.0)
Abdominal distension	12 (7.5)	11 (7.9)	6 (3.1)	12 (8.6)	18 (5.4)
General Disorders and Administration Site Conditions	52 (32.7)	56 (40.0)	73 (37.2)	64 (45.7)	137 (40.8)
Edema peripheral	13 (8.2)	21 (15.0)	35 (17.9)	26 (18.6)	61 (18.2)
Fatigue	18 (11.3)	17 (12.1)	16 (8.2)	22 (15.7)	38 (11.3)
Pyrexia	5 (3.1)	9 (6.4)	7 (3.6)	11 (7.9)	18 (5.4)
Asthenia	12 (7.5)	4 (2.9)	8 (4.1)	5 (3.6)	13 (3.9)
Hepatobiliary Disorders	14 (8.8)	11 (7.9)	36 (18.4)	22 (15.7)	58 (17.3)
Hepatic failure	1 (0.6)	1 (0.7)	13 (6.6)	4 (2.9)	17 (5.1)

Continued

System Organ Class ^b Preferred Term	RCT Study Population ^a		Long Term Rifaximin Experience Population		
	Double-Blind Study Treatment		New Rifaximin 550 mg BID (PEY = 142.3) ^c (N = 196) n (%)	Continuing Rifaximin 550 mg BID (PEY = 109.7) ^c (N = 140) n (%)	All Rifaximin Subjects (PEY = 251.9) ^c (N = 336) n (%)
	Placebo (PEY = 46.0) ^c (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) ^c (N = 140) n (%)			
Infections and Infestations	49 (30.8)	46 (32.9)	80 (40.8)	58 (41.4)	138 (41.1)
Urinary tract infection	14 (8.8)	8 (5.7)	24 (12.2)	17 (12.1)	41 (12.2)
Cellulitis	3 (1.9)	3 (2.1)	11 (5.6)	6 (4.3)	17 (5.1)
Nasopharyngitis	10 (6.3)	10 (7.1)	4 (2.0)	10 (7.1)	14 (4.2)
Metabolism and Nutrition Disorders	21 (13.2)	28 (20.0)	53 (27.0)	39 (27.9)	92 (27.4)
Dehydration	2 (1.3)	5 (3.6)	9 (4.6)	11 (7.9)	20 (6.0)
Hypokalemia	3 (1.9)	2 (1.4)	14 (7.1)	5 (3.6)	19 (5.7)
Musculoskeletal and Connective Tissue Disorders	32 (20.1)	31 (22.1)	49 (25.0)	43 (30.7)	92 (27.4)
Muscle spasms	11 (6.9)	13 (9.3)	19 (9.7)	16 (11.4)	35 (10.4)
Arthralgia	4 (2.5)	9 (6.4)	7 (3.6)	13 (9.3)	20 (6.0)
Back pain	10 (6.3)	9 (6.4)	7 (3.6)	12 (8.6)	19 (5.7)
Nervous System Disorders	64 (40.3)	53 (37.9)	78 (39.8)	61 (43.6)	139 (41.4)
Hepatic encephalopathy ^a	34 (21.4)	17 (12.1)	46 (23.5)	25 (17.9)	71 (21.1)
Dizziness	13 (8.2)	18 (12.9)	15 (7.7)	19 (3.6)	34 (10.1)
Headache	17 (10.7)	14 (10.0)	12 (6.1)	16 (11.4)	28 (8.3)
Psychiatric Disorders	29 (18.2)	27 (19.3)	28 (14.3)	34 (24.3)	62 (18.5)
Depression	8 (5.0)	10 (7.1)	11 (5.6)	14 (10.0)	25 (7.4)
Insomnia	11 (6.9)	10 (7.1)	8 (4.1)	12 (8.6)	20 (6.0)
Renal and Urinary Disorders	12 (7.5)	10 (7.1)	27 (13.8)	18 (12.9)	45 (13.4)
Renal failure acute	5 (3.1)	2 (1.4)	14 (7.1)	3 (2.1)	17 (5.1)
Respiratory, Thoracic and Mediastinal Disorders	39 (24.5)	36 (25.7)	43 (21.9)	42 (30.0)	85 (25.3)
Dyspnea	7 (4.4)	9 (6.4)	16 (8.2)	12 (8.6)	28 (8.3)
Cough	11 (6.9)	10 (7.1)	5 (2.6)	11 (7.9)	16 (4.8)

Continued

System Organ Class ^b Preferred Term	RCT Study Population ^a		Long Term Rifaximin Experience Population		
	Double-Blind Study Treatment		New Rifaximin 550 mg BID (PEY = 142.3) ^c	Continuing Rifaximin 550 mg BID (PEY = 109.7) ^c	All Rifaximin Subjects (PEY = 251.9) ^c
	Placebo (PEY = 46.0) ^c (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) ^c (N = 140) n (%)	(N = 196) n (%)	(N = 140) n (%)	(N = 336) n (%)
Skin and Subcutaneous Tissue Disorders	24 (15.1)	29 (20.7)	34 (17.3)	37 (26.4)	71 (21.1)
Pruritis	10 (6.3)	13 (9.3)	14 (7.1)	14 (10.0)	28 (8.3)
Rash	6 (3.8)	7 (5.0)	12 (6.1)	10 (7.1)	22 (6.5)

Source: ISS Tables 5.2.1.1b and 5.2.2.1, Appendix C

Abbreviations: TEAE = treatment-emergent adverse event; HE = hepatic encephalopathy; RCT = randomized controlled trial; BID = twice daily; and PEY = person years of exposure.

- a Given that HE was the expected outcome of the RCT study, non-serious HE events related to breakthrough HE were not considered as AEs and were excluded from this table. ISS Table 5.2.1.1a includes the non serious HE event related to breakthrough HE which were reported as adverse events.
- b The numbers and percentages for each system organ class in the table above include all TEAEs in the system organ class; the system organ class numbers shown were not limited to TEAEs that occurred in ≥ 5% subjects in the treatment groups.
- c Person-years of exposure was computed as the sum of exposure days for all subjects included in the analysis divided by 365.25.

Note: TEAEs are presented alphabetically by system organ class, and by descending order of frequency among All Rifaximin Subjects (Long Term Rifaximin Experience population) within each system organ class.

Table 45: TEAEs Occurring in ≥ 5% of Rifaximin-Treated Subjects and at a Higher Frequency than in the Placebo Group - RCT Study Population

System Organ Class ^a Preferred Term	Placebo N = 159 n (%)	Rifaximin N = 140 n (%)
Subjects with Any TEAEs	127 (79.9)	112 (80.0)
Blood and lymphatic system disorders	8 (5.0)	15 (10.7)
Anemia	6 (3.8)	11 (7.9)
Gastrointestinal disorders	67 (42.1)	72 (51.4)
Nausea	21 (13.2)	20 (14.3)
Ascites	15 (9.4)	16 (11.4)
Abdominal pain	13 (8.2)	12 (8.6)
Abdominal distension	12 (7.5)	11 (7.9)
Constipation	10 (6.3)	9 (6.4)
Abdominal pain upper	8 (5.0)	9 (6.4)
General disorders and administration site conditions	52 (32.7)	56 (40.0)
Fatigue	18 (11.3)	17 (12.1)
Edema peripheral	13 (8.2)	21 (15.0)
Pyrexia	5 (3.1)	9 (6.4)
Infections and infestations	49 (30.8)	46 (32.9)
Nasopharyngitis	10 (6.3)	10 (7.1)
Musculoskeletal and connective tissue disorders	32 (20.1)	31 (22.1)
Muscle spasms	11 (6.9)	13 (9.3)
Back pain	10 (6.3)	9 (6.4)
Arthralgia	4 (2.5)	9 (6.4)
Nervous System Disorders	64 (40.3)	53 (37.9)
Dizziness	13 (8.2)	18 (12.9)
Psychiatric disorders	29 (18.2)	27 (19.3)
Insomnia	11 (6.9)	10 (7.1)
Depression	8 (5.0)	10 (7.1)
Respiratory, Thoracic and Mediastinal Disorders	39 (24.5)	36 (25.7)
Cough	11 (6.9)	10 (7.1)
Dyspnea	7 (4.4)	9 (6.4)
Skin and subcutaneous tissue disorders	24 (15.1)	29 (20.7)
Pruritus	10 (6.3)	13 (9.3)
Rash	6 (3.8)	7 (5.0)

Source: ISS Table 5.2.1.1b, Appendix C

Abbreviations: TEAE = treatment-emergent adverse event; and RCT = randomized controlled trial.

a The numbers and percentages for each system organ class in the table above include all TEAEs in the system organ class; the system organ class numbers shown were not limited to TEAEs that occurred in ≥ 5% subjects in either treatment group.

Note: Treatment-emergent AEs are summarized alphabetically by SOC and by descending order of frequency within each SOC based on the number of events among all subjects in the RCT Study population.

7.4.2 Laboratory Findings

Treatment-emergent AEs commonly associated with abnormal clinical laboratory test results that were reported for at least 5% of subjects overall were anemia (11.8%), hypokalemia (7.5%), and hyperkalemia (6.3%).

Hematology

In the RCT Study population, shifts from baseline were observed for subjects receiving rifaximin that were not also observed in the placebo group. Among the hematology parameters, higher incidences of shifts from normal to low at end of treatment (EOT) were observed in the rifaximin group compared with the placebo group for red blood cell counts (10.2% vs. 6.9%), neutrophils (3.2% vs. 1.4%), monocytes (7.1% vs. 2.8%), absolute neutrophils (7.1% vs. 4.1%), and lymphocytes (12.7% vs. 6.9%). Higher incidences of shifts from normal to low at EOT were observed in the placebo group compared with the rifaximin group, respectively, for hemoglobin (11.0% vs. 8.7%) and lymphocytes (14.5% vs. 10.3%). A higher incidence of shift from normal to high at EOT were observed for basophils in the rifaximin group (8.7%) compared with the placebo group (2.8%). Other shifts from normal were comparable between treatment groups. See Table 46

The event rate for anemia per 100 PEY was 11.8 in All Rifaximin subjects compared with 22.0 in the RCT Study rifaximin group and 13.0 in the RCT Study placebo group. A notably higher proportion of rifaximin treated subjects had a medical history of anemia compared with placebo-treated subjects in the RCT Study population (31% vs. 17%).

The profiles of shifts for the Long Term Rifaximin Experience population at 6 months, 12 months, 18 months, and last value were qualitatively similar to shifts observed in the RCT Study population for both the placebo and rifaximin groups.

Prothrombin time (PT) and international normalized ratio (INR) shifted from normal to high at last value in 9.3% and 9.6% of rifaximin-treated subjects, respectively. These shifts were comparable to the placebo group in the RCT Study population, and consistent with a population of subjects with advanced liver disease.

Table 46: Shifts in Hematology Test Results from Normal at Baseline to High or Low at the End of Treatment (RCT Study Populations) or Last Value (Long Term Rifaximin Experience Population)

Parameter	RCT Study Population				Long Term Rifaximin Experience Population	
	Placebo		Rifaximin 550 mg BID		Cumulative 120-Day Results	
	n (%)		n (%)		n (%)	
	N→H	N→L	N→H	N→L	N→H	N→L
	EOT	EOT	EOT	EOT	Last Value	Last Value
Hemoglobin (g/dL)	0	16 (11.0)	1 (0.8)	11 (8.7)	4 (1.2)	58 (17.0)
Hematocrit (Ratio)	3 (2.1)	11 (7.6)	0	10 (7.9)	4 (1.2)	51 (14.9)
Platelets (x10 ⁹ /L)	0	8 (5.6)	0	8 (6.3)	0	20 (6.0)
PT (Seconds)	15 (11.3)	0	13 (10.5)	0	31 (9.3)	1 (0.3)
INR (Ratio)	16 (12.0)	0	10 (8.1)	1 (0.8)	32 (9.6)	2 (0.6)
RBC (x10 ¹² /L)	0	10 (6.9)	0	13 (10.2)	0	36 (10.5)
WBC (x10 ⁹ /L)	4 (2.8)	8 (5.5)	1 (0.8)	9 (7.1)	7 (2.0)	29 (8.5)
Neutrophils (%)	10 (6.9)	2 (1.4)	13 (10.3)	4 (3.2)	47 (13.8)	4 (1.2)
Lymphocytes (%)	2 (1.4)	21 (14.5)	3 (2.4)	13 (10.3)	7 (2.1)	55 (16.1)
Monocytes (%)	16 (11.0)	4 (2.8)	11 (8.7)	9 (7.1)	47 (13.8)	14 (4.1)
Eosinophils (%)	5 (3.4)	0	5 (4.0)	0	8 (2.3)	0
Basophils (%)	4 (2.8)	0	11 (8.7)	0	30 (8.8)	0
Abs Neutrophils (x10 ⁹ /L) ^b	4 (2.8)	6 (4.1)	2 (1.6)	9 (7.1)	17 (5.0)	21 (6.2)
Abs Lymphocytes (x10 ⁹ /L) ^b	0	10 (6.9)	0	16 (12.7)	1 (0.3)	50 (14.7)
Abs Monocytes (x10 ⁹ /L) ^b	3 (2.1)	0	0	0	7 (2.1)	0
Abs Eosinophils (x10 ⁹ /L) ^b	1 (0.7)	0	2 (1.6)	0	4 (1.2)	0
Abs Basophils (x10 ⁹ /L) ^b	0	0	0	0	1 (0.3)	0

Source: ISS Tables 6.4.1 and 6.4.2, Appendix C

Abbreviations: N→H =Normal to High; N→L =Normal to Low; Abs = absolute; EOT = end of treatment; BID = twice daily; PT = prothrombin time; INR = international normal ratio; RBC = red blood cells; and WBC = white blood cells.

Note: Percentages in parentheses are based on the number of subjects with clinical hematology data at baseline and the analysis time point.

Serum Chemistry

Mean AST (U/L) increased from 64.0 at Day 0 to 76.0 at EOT in the rifaximin group and decreased from 68.2 to 64.3 in the placebo group, in the RFHE3001 trial. Mean gamma GT (U/L) increased by 21.2 in the rifaximin group from baseline to EOT and decreased by -5.9 in the placebo group. Direct and total bilirubin (umol/L) increased by 6.7 and 10.2, respectively, from baseline to EOT in the placebo group and by only 0.3 and 2.4 in the rifaximin group.

A higher incidence of shifts from normal to high at EOT were observed in the rifaximin group for creatinine (8.5% vs. 3.4%), lactate dehydrogenase (LDH) levels (17.2% vs. 6.9%), blood alkaline phosphatase (11.5% versus 5.5%), and gamma GT (7.7% vs. 2.1%). Among subjects in the placebo group, a higher incidence of shifts was observed from normal to high at EOT for urea (BUN) (8.9% vs. 4.6%) and from normal to low for calculated creatinine clearance (9.7% vs. 4.6%).

Electrolyte imbalances are common in this population with its use of both diuretic and potassium-sparing diuretic use. The changes in electrolytes appear to be equal between treatment and placebo groups.

Table 47: Shifts in Chemistry Laboratory Test Results from Normal at Baseline to High or Low at the End of Treatment or Last Value (RCT Study and Long Term Rifaximin Experience Populations)

Parameter	RCT Study Population				Long Term Rifaximin Experience Population	
	Placebo n (%)		Rifaximin 550 mg BID n (%)		All Rifaximin Subjects 550 mg BID n (%)	
	N→H	N→L	N→H	N→L	N→H	N→L
	EOT	EOT	EOT	EOT	Last Value	Last Value
Creatinine (umol/L)	5 (3.4)	1 (0.7)	11 (8.5)	3 (2.3)	32 (9.3)	4 (1.2)
Calc. Creatinine Clearance (mL/min)	8 (5.5)	14 (9.7)	6 (4.6)	6 (4.6)	15 (4.4)	30 (8.8)
Urea (BUN) (mmol/L)	13 (8.9)	8 (5.5)	6 (4.6)	6 (4.6)	26 (7.5)	15 (4.3)
Uric Acid (umol/L)	13 (8.9)	2 (1.4)	8 (6.1)	0	38 (11.0)	6 (1.7)
Glucose, Random, Serum (mmol/L)	15 (10.3)	3 (2.1)	14 (10.8)	4 (3.1)	43 (12.4)	2 (0.6)
Albumin (g/L)	1 (0.7)	8 (5.5)	0	7 (5.4)	2 (0.6)	24 (6.9)
Calcium (mmol/L)	3 (2.1)	11 (7.5)	0	11 (8.5)	7 (2.0)	15 (4.3)
Sodium (mmol/L)	2 (1.4)	12 (8.2)	0	8 (6.2)	1 (0.3)	40 (11.6)
Potassium (mmol/L)	3 (2.1)	7 (4.8)	3 (2.3)	6 (4.6)	7 (2.0)	18 (5.2)
Chloride (mmol/L)	0	3 (2.1)	0	1 (0.8)	2 (0.6)	13 (3.8)
LDH (U/L)	10 (6.9)	1 (0.7)	22 (17.2)	1 (0.8)	54 (15.8)	1 (0.3)
Alkaline Phosphatase (U/L)	8 (5.5)	0	15 (11.5)	0	39 (11.3)	0
AST (U/L)	7 (4.8)	0	7 (5.4)	0	23 (6.6)	0
ALT (U/L)	16 (11.0)	0	15 (11.5)	0	36 (10.4)	0
Gamma GT (U/L)	3 (2.1)	0	10 (7.7)	0	40 (11.6)	0
Direct Bilirubin (umol/L)	5 (3.5)	0	4 (3.1)	0	7 (2.1)	0
Total Bilirubin (umol/L)	12 (8.2)	0	13 (9.9)	0	29 (8.4)	0

Source: ISS Tables 6.5.1 and 6.5.2, Appendix C

Abbreviations: N→H =Normal to High; N→L =Normal to Low; ABS = absolute; EOT = end of treatment; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; GT = glutamyltransferase; RCT = randomized controlled trial; and BID = twice daily.

Note: Percentages in parentheses are based on the number of subjects with clinical hematology data at baseline and the analysis time point.

Table 48: Treatment-Emergent AEs Associated with Abnormal Laboratory Results in at Least 1% of All Rifaximin Subjects in the Long Term Rifaximin Experience Population

Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		Cumulative 120-Day Results (PEY = 346.7) ^b (N=348)
	Placebo (PEY = 46.0) ^b (N = 159)	Rifaximin 550 mg BID (PEY = 50.0) ^b (N = 140)	
	n (%)	n (%)	n (%)
Anemia ^a	6 (3.8)	11 (7.9)	41 (11.8)
Hypokalemia ^a	3 (1.9)	2 (1.4)	26 (7.5)
Hyperkalemia ^a	2 (1.3)	5 (3.6)	22 (6.3)
Hyperglycemia ^a	2 (1.3)	3 (2.1)	17 (4.9)
Hyponatremia ^a	2 (1.3)	3 (2.1)	17 (4.9)
Hypomagnesemia ^a	0	1 (0.7)	16 (4.6)
Thrombocytopenia ^a	1 (0.6)	2 (1.4)	14 (4.0)
Jaundice	7 (4.4)	5 (3.6)	12 (3.4)
Hypoglycemia ^a	2 (1.3)	3 (2.1)	11 (3.2)
Blood creatinine increased	1 (0.6)	1 (0.7)	9 (2.6)
Coagulopathy ^a	0	0	9 (2.6)
Hematuria	1 (0.6)	2 (1.4)	6 (1.7)
Hypoalbuminemia	2 (1.3)	1 (0.7)	6 (1.7)
Hypocalcemia	0	1 (0.7)	6 (1.7)
Splenomegaly	1 (0.6)	1 (0.7)	6 (1.7)
Ammonia increased ^a	3 (1.9)	1 (0.7)	5 (1.4)
International normalized ratio increased	2 (1.3)	1 (0.7)	5 (1.4)
Aspartate aminotransferase increased	0	0	4 (1.1)
Blood bilirubin increased	0	0	4 (1.1)
Gamma-glutamyltransferase increased	1 (0.6)	0	4 (1.1)
Metabolic acidosis ^a	0	0	4 (1.1)
Proteinuria	0	2 (1.4)	4 (1.1)

Source: ISS Tables 5.2.1.1a/b, 5.2.2.1, and 5.4.2.1, Appendix C

Abbreviations: PEY = person-years of exposure; TEAE = treatment-emergent adverse event; RCT = randomized controlled trial; and BID = twice daily.

a At least 1 of these TEAEs met the criteria for a serious adverse event in a rifaximin-treated subject.

b Person-years of exposure was computed as the sum of exposure days for all subjects included in the analysis divided by 365.25.

Urinalysis

Changes from baseline to EOT in the RCT Study population in urinalysis parameters were minimal and there were no notable differences between rifaximin-treated subjects and placebo-treated subjects. Likewise, there were no clinically meaningful changes in

urinalysis parameters from baseline to last value among All Rifaximin subjects in the Long Term Rifaximin Experience population.

7.4.3 Vital Signs

No clinically significant mean changes in systolic or diastolic blood pressure, pulse rate, body temperature, or body weight were observed during treatment in the RCT Study or in the Long Term Rifaximin Experience population. There were no clinically meaningful differences observed in mean changes from baseline between treatment groups in the RCT Study population for vital sign parameters.

7.4.4 Electrocardiograms (ECGs)

A thorough QT study was not conducted for rifaximin. Although the systemic absorption after oral administration is limited, rifaximin is systemically available to an appreciable degree in this population. The systemic exposure to rifaximin in this patient population after 550 mg twice daily dosing is about 16-20 times higher than that in healthy subjects after 200 mg three times a day dosing, which is a dosing regimen for the approved treatment of patients with traveler's diarrhea.

The Applicant has conducted an *in vitro* study to test the effects of rifaximin on the hERG potassium channels expressed in human embryonic kidney cells. Rifaximin concentrations of $\geq 30 \mu\text{M}$ resulted in a statistically significant increase in inhibition of the hERG channel. The IC_{50} for the inhibitory effect of rifaximin on hERG potassium current was estimated to be $30 \mu\text{M}$.

The Applicant did not perform ECG's on subjects in either of the major studies that are the foundation for this NDA.

7.4.5 Special Safety Studies/Clinical Trials

None reported

7.4.6 Immunogenicity

The Applicant does not address the issue of anaphylactic reactions to rifaximin. Arthralgia (6.4% vs. 2.5%) and pyrexia (6.4% vs. 3.1%) both occur with increased frequency in the rifaximin group compared to the placebo group. There was a 15.1% incidence of pruritis or rash in the placebo group vs. 20.7% in the rifaximin group. No anaphylactic reactions are reported in the Hepatic Encephalopathy Phase 3 trials, or in the integrated summary of safety data. Rash, pyrexia and arthralgia are listed in the current labeling. Anaphylactic reactions have been reported in the post marketing

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not examined by the Applicant

7.5.2 Time Dependency for Adverse Events

AEs with an onset date > 5 days following discontinuation of rifaximin in the primary studies (i.e., RFHE3001 and RFHE3002) were evaluated. Greater than 5 days following last dose was selected to allow for a sufficient washout period of rifaximin tablet treatment. Given that the RFHE3002 trial was ongoing, only subjects who had received rifaximin and subsequently concluded rifaximin treatment in the primary studies were included in the supplemental table. Overall, the types of AEs reported after the last dose of study drug were qualitatively similar to the AEs reported during the studies and were consistent with the population under study.

7.5.3 Drug-Demographic Interactions

Common AE's by Sex

There were few notable differences in the safety profile of rifaximin between male and female subjects in the primary analysis studies. In the RCT Study population, the pattern and frequencies of TEAEs were similar between the rifaximin and placebo groups for both male and female subjects. The most notable differences in the incidence of specific preferred terms occurred between rifaximin-treated females (N=65) and placebo-treated females (N=52). Treatment-emergent TEAEs of anemia (12.3% vs. 3.8%), fatigue (15.4% vs. 7.7%), peripheral edema (16.9% vs. 9.6%), dizziness (13.8% vs. 7.7%), dyspnea (10.8% vs. 1.9%), insomnia (10.8% vs. 3.8%) and pruritis (15.4% vs. 1.9%) were all more common among rifaximin-treated females. Treatment-emergent TEAEs of abdominal distension (15.4% vs. 9.2%), urinary tract infection (19.2% vs. 7.7%), headache (19.2% vs. 9.2%), and HE (25.0% vs. 10.8%) were more common among placebo-treated females.

Similar trends were observed in the Long Term Rifaximin population with a comparable AE profile between male and female subjects treated with rifaximin. Treatment-emergent AEs occurring in $\geq 5\%$ of all male subjects (N=195) in the Long Term population and proportionally at least twice as often compared with female subjects (N=141) were depression (9.7% vs. 4.3%), cellulitis (7.2% vs. 2.1%), and hyperglycemia (6.2% vs. 2.1%). Treatment-emergent AEs occurring in $\geq 5\%$ of all female subjects and at least twice as often compared with male subjects urinary tract infection (19.9% vs. 6.7%), upper respiratory tract infection (5.7% vs. 2.6%), jaundice (5.0% vs. 1.0%), and

pain (5.0% vs. 1.5%). The frequency of other TEAEs was generally comparable between gender subgroups.

Common AE's by Age Group

Overall, there were few notable differences observed in the safety profile of rifaximin when comparing subjects' ≥ 65 years and < 65 years of age. Comparisons between age groups were limited due to the smaller number of subjects ≥ 65 years old (N = 66) treated with rifaximin in the primary analysis studies. In the RCT Study population, the pattern and frequencies of TEAEs were similar between the rifaximin and placebo groups in subjects < 65 years of age. Rifaximin-treated subjects ≥ 65 years of age in the RCT Study experienced a lower percentage of TEAEs (66.7%) compared with rifaximin-treated subjects < 65 years (83.2%). In the Long Term Rifaximin population, the percentage of subjects experiencing TEAEs was comparable between age groups.

Common AE's by Race

Few non-white subjects enrolled in the primary analysis studies (N=51), and there were no remarkable differences observed in the safety profile of rifaximin relative to placebo when comparing white and non-white subjects. In the Long Term Rifaximin Experience population, the incidence of TEAEs was comparable for non-white subjects (91.9%) and white subjects (86.6%), and a similar pattern of TEAEs was observed in both groups.

AE's by Geographic Location

Overall, subjects who participated at study sites in North America had a markedly higher incidence of TEAEs than subjects who participated in Russia in both the RCT Study (90.9% vs. 50.0%) and Long Term Rifaximin Experience (94.5% vs. 56.3%) populations. While the overall incidence of TEAEs was higher in North America, the pattern and frequency of TEAEs was similar between rifaximin- and placebo-treated subjects regardless of analysis region in the RCT Study population. In the North America region the incidence of subjects experiencing at least 1 TEAE was 92.1% in the rifaximin group versus 89.8% in the placebo group. In Russia, the incidence of TEAEs was 48.7% in the rifaximin group versus 51.2% in the placebo group.

Medical Officer's Comments:

It appears that there was lower reporting of Adverse Events overall in Russia. However, site inspection found no irregularities in documentation.

7.5.4 Drug-Disease Interactions

Common AE's by Hepatic Function

Hepatic function was analyzed using each subject's baseline MELD score, with a higher score corresponding with worsened hepatic function. For the analysis, subjects were divided into 3 MELD baseline score categories: ≤ 10 , 11-18, and ≥ 19 .

For both the rifaximin and placebo treatment groups the incidence of TEAE's was highest among subjects with a baseline MELD score ≥ 19 (rifaximin: 91.7%; placebo: 100.0%), and lower among subjects with a baseline MELD score between 11 and 18 (rifaximin: 85.1%; placebo: 87.5%) and with a baseline MELD score ≤ 10 (rifaximin: 61.8%; placebo: 58.3%). While the overall incidence of TEAE's during the study was incrementally higher among subjects with more severely impaired hepatic function at baseline, there were no remarkable between-group differences (rifaximin vs. placebo) in the types and frequencies of TEAEs in each MELD score category.

The pattern of TEAE's observed in the RCT Study population for MELD score subgroups was also observed in the Long Term Rifaximin Experience population. As in the RCT Study groups, a correlation was observed between increasing MELD scores and a higher incidence of TEAE's.

Common AE's by Baseline Renal Function

Only a small number of subjects (N=7) had a serum creatinine level $\geq 1.5X$ ULN at baseline and comparisons between treatment groups were limited. No dose modifications are recommended for patients based on renal function.

Medical Officer's Comments:

Renal Impairment is common in this patient population and more safety data should be obtained in patients with both renal dysfunction and cirrhosis.

7.5.5 Drug-Drug Interactions

Reference Pharmacology Review Summary in Tab 4.

7.6 Additional Submissions / Safety Issues

7.6.1 Secondary and Supportive Safety Population Results

Acute Treatment of Hepatic Encephalopathy Studies

Adverse Events: Similar percentages of subjects experienced at least 1 TEAE in the rifaximin (35.5%), lactitol (28.3%), and placebo (31.1%) treatment groups. In each group the incidence of TEAEs was highest in the GI disorders SOC. Among rifaximin-treated subjects the most frequently occurring GI disorders were nausea (5.9% vs. 2.2% placebo), diarrhea (3.9% vs. 6.7% placebo), and GI hemorrhage (2.6% vs. 2.2% placebo). Hepatic encephalopathy, the indication under study, was recorded as a TEAE for 7 rifaximin treated subjects (4.6%), 3 lactitol-treated subjects (5.7%), and 1 placebo-treated subject (2.2%). The overall pattern of common TEAEs in this population was qualitatively similar to the profile of frequent events in the primary analysis populations.

Overall, 20 out of 152 subjects (13.2%) in the rifaximin group experienced at least 1 severe TEAE, compared with 5 of 53 lactitol-treated subjects (9.4%) and 4 of 45 placebo-treated subjects (8.9%). Severe TEAEs occurred in multiple rifaximin subjects and included GI hemorrhage (3 subjects), renal failure acute (3 subjects), HE (3 subjects), and hepatic failure (2 subjects).

In these studies, drug-related TEAEs were recorded for 15 rifaximin treated subjects (9.9%), 2 lactitol-treated subjects (3.8%), and 7 placebo-treated subjects (15.6%). The higher incidence of drug-related TEAEs in the rifaximin group and the placebo group compared with the lactitol group was largely due to a higher proportion of drug-related TEAEs in the RFHE9901 study compared with studies RFHE9701 and RFHE9702. For the rifaximin group, all drug-related TEAEs which occurred in multiple subjects were in the GI disorders SOC. Diarrhea (4 subjects) and nausea (3 subjects) were the most frequently reported drug related TEAEs among rifaximin-treated subjects. The overall pattern of SAE in these studies was also qualitatively similar to the patterns observed in the primary analysis studies.

Deaths: Among the 98 subjects treated with control agents (53 lactitol and 45 placebo), 4 subjects (4.1%) died during the study or within 30 days after last dose of study medication. An additional 2 subject deaths were reported for lactitol-treated subjects in a safety update (November 06, 2003) to NDA 21-361, however, these deaths were not recorded in the clinical database for the study and could not be verified. When these deaths are added, a total of 6 subject deaths (6.1%) occurred in the control group. None of the deaths in control subjects from the clinical dataset were considered to be related to study drug by the assessing investigator and an assessment of relationship was not

performed for the additional death identified from the safety database or the additional deaths recorded in NDA 21-361.

Most subject deaths from the acute treatment of HE studies appear to have been associated with progression of liver disease (e.g., hepatic failure, abnormal hepatic failure) or conditions frequently associated with subjects with advanced liver disease (e.g., HE, GI hemorrhage [variceal hemorrhage], peritonitis bacterial [SBP], acute renal failure). The pattern of deaths in these studies was qualitatively similar to the patterns observed in the primary analysis studies. As in the primary analysis studies, nearly all subjects who died during or following the acute treatment of HE studies had additional evidence of hepatic decompensation in their medical history besides HE.

Three subjects (1 rifaximin and 2 placebo) experienced 4 serious adverse events in the rifaximin studies for the treatment of TD. All 3 subjects experienced SAEs that required hospitalization. Each subject experienced an SAE considered to be severe in intensity; however, only 1 event (diarrhea NOS in placebo subject 02094 [study RFID9801]) was judged to be possibly related to study drug. Gastrointestinal hemorrhage (3 subjects) and HE (3 subjects) were the only TEAEs leading to discontinuation in multiple rifaximin treated subjects.

Treatment of TD Safety Studies

In the treatment of TD studies, TEAEs were most frequently experienced in the gastrointestinal disorders SOC for both the rifaximin (33.1%) and control (29.7%) treatment groups. The most frequently experienced TEAEs in both the rifaximin and control treatment groups, respectively, were flatulence (12.5% and 10.7%) and headache (11.3% and 8.9%).

Other adverse events experienced by $\geq 5\%$ of rifaximin-treated subjects and in a higher percentage of subjects in the rifaximin group compared with the control group were abdominal pain NOS (8.9% vs. 5.5% placebo), nausea (7.4% vs. 5.7%), defecation urgency (6.9% vs. 5.3%), and rectal tenesmus (6.4% vs. 5.0%). Each of these TEAEs are among the signs and symptoms frequently associated with TD.

Eye disorders were experienced by a statistically significant ($p = 0.0323$) greater proportion of control-treated subjects (0.9%) compared with rifaximin-treated subjects (0%); however, the overall incidence of these types of events was $< 1\%$. No other statistically significant differences were observed between the treatment groups for the overall incidence of adverse events associated with any specific system organ class.

Gastrointestinal disorders were the most common SOC for drug-related events in both treatment groups (rifaximin: 26.0%; control: 23.7%). Flatulence was the most frequently occurring drug-related TEAE in each group (rifaximin: 11.5%; control: 10.0%). Other drug-related TEAEs occurring in at least 5% of subjects in the rifaximin group were (rifaximin vs. control) headache (6.2% vs. 4.1%), abdominal pain NOS (7.8% vs. 4.8%),

and nausea (6.1% vs. 4.8%). Three subjects (1 rifaximin and 2 placebo) experienced 4 serious adverse events in the rifaximin studies for the treatment of TD. All 3 subjects experienced SAEs that required hospitalization.

Seven subjects (3 rifaximin, 1 placebo, and 3 ciprofloxacin) prematurely discontinued from the TD studies due to a TEAE. Among rifaximin-treated subjects, 2 subjects experienced severe TEAEs resulting in discontinuation (dysentery NOS and taste loss).

Rifaximin in the Treatment of Crohn's Disease - RFCD2001

Study RFCD2001 was a phase 2, single-center, open-label study in subjects with active Crohn's disease, determined by clinically accepted diagnostic criteria, including endoscopic and histologic methods, as well as a Crohn's Disease Activity Index (CDAI) score histologic methods, as well as a Crohn's Disease Activity Index (CDAI) score. Twenty-nine (29) subjects participated in the study and were treated with open-label rifaximin 200 mg TID for 16 weeks. Adverse events experienced during the treatment phase were reported in 21 (72.4%) subject. The most commonly experienced adverse events during the treatment phase were abdominal pain not otherwise specified (NOS), fatigue, and headache NOS, each reported by 4 (13.8%) subjects. No deaths were reported during the study. Three (3, 10.3%) subjects had adverse events that led to premature withdrawal of rifaximin therapy.

7.6.2 120-day Safety Update

The Applicant submitted a 120-day safety update that included:

- Data from the ongoing treatment extension safety trial (with data from 12 more patients)
- Supportive data from a newly completed clinical trial with rifaximin for Irritable Bowel Syndrome
- Preliminary safety data from Phase 1 pharmacokinetic studies
- Updated post marketing data.

No new data from the only placebo controlled trial RFHE3001 was submitted.

For the Long Term Rifaximin Experience population, rifaximin safety data are presented from the closed RFHE3001 study and from the RFHE3002 open-label study. At the time of the 120-day Safety Update, the RFHE3002 study was ongoing. Data presented from the ongoing RFHE3002 study are available for all subjects in the Long Term Rifaximin Experience up to 22 June 2009 (clinical data retrieval cutoff date). Additional data retrieved for some subjects beyond 22 June 2009 were included in the 120-day Safety Update if available in the database at the time of the data freeze (14 September 2009).

Disposition

Table 49: Disposition of Subjects in RFHE3002 – 120-day update

Disposition Parameter	New Rifaximin 550 mg BID n (%)	Continuing Rifaximin 550 mg BID n (%)	All Rifaximin Subjects n (%)
Total Enrollment for RFHE3002	210 (100.0)	70 (100.0)	280 (100.0)
Safety Population ^a	208 (99.0)	70 (100.0)	278 (99.3)
Enrollment Status			
Ongoing	142 (67.6)	45 (64.3)	187 (66.8)
Subjects who discontinued early from the study	68 (32.4)	25 (35.7)	93 (33.2)
Death	20 (9.5)	9 (12.9)	29 (10.4)
Liver transplant ^b	13 (6.2)	6 (8.6)	19 (6.8)
Subject request to withdraw	13 (6.2)	5 (7.1)	18 (6.4)
Other ^c	13 (6.2)	2 (2.9)	15 (5.4)
Adverse event	7 (3.3)	2 (2.9)	9 (3.2)
Development of exclusion criteria	2 (1.0)	0	2 (0.7)
Breakthrough HE episode	0	1 (1.4)	1 (0.4)

Source: ISS Table 1, Appendix C; Abbreviations: HE = hepatic encephalopathy; AE = adverse event; and BID = twice daily.

- a Two subjects (9999-1025-0057 and 9999-0478-0069) in RFHE3002 did not have post-baseline safety assessments and were excluded from the Safety population.
- b In total, Salix is aware of 23 subjects who had a liver transplant in the RFHE3002 study. However, 3 of these subjects underwent liver transplants that were reported following the database freeze for this 120-day Safety Update. One additional subject (9999-0807-0051) had a different primary reason for discontinuation from study on CRF termination page (occurrence of an adverse event).
- c 'Other' included Subject 3001-0591-0002 who had a non-compliant caregiver; Subjects 3001-0367-0001, 9999-0750-0052, and 9999-0764-0051 due to noncompliance; Subjects 3001-0351-0003, 3001-0556-0003, 9999-0659-0051, 3001-0743-0002, 9999-0752-0051, and 9999-0882-0054 who were lost to follow up; Subject 9999-1025-0054 who discontinued per physician's discretion; Subjects 3001-0591-0005 and 3001-0807-0006 due to inability to comply with study visits; Subject 9999-0757-0053 due to the subject moving to another state; and Subject 9999-0754-0052 who was transferred to a long-term nursing home.

Table 50: Extent of Exposure to Rifaximin in the Primary Analysis Populations – 120day update

Category	RCT Study Population		ALL RIFAXIMIN SUBJECTS (Long Term Rifaximin Experience Population)		
	Double-Blind Study Treatment		Original ISS Results (PEY = 251.9) ^a (N = 336) n (%)	New Safety Results (N = 211) ^c n (%)	Cumulative 120-Day Results (PEY = 346.7) ^a (N = 348) n (%)
	Placebo (PEY = 46.0) ^a (N = 159)	Rifaximin 550 mg BID (PEY = 50.0) ^a (N = 140)			
Exposure duration (days)^b					
Mean (SD)	105.7 (62.71)	130.3 (56.47)	273.8 (160.92)	164.2 (59.39)	363.9 (226.19)
Median (Min, Max)	110.0 (6, 176)	168.0 (10, 178)	253.0 (7, 840)	168.0 (4, 359)	403.0 (7, 1008)
Number of subjects on study drug n (%)					
Day 1 to < Month 1 (Day 28)	22 (13.8)	13 (9.3)	12 (3.6)	6 (2.8)	14 (4.0)
Month 1 to < Month 3 (Day 84)	44 (27.7)	23 (16.4)	27 (8.0)	17 (8.1)	31 (8.9)
Month 3 to < Month 6 (Day 168)	37 (23.3)	31 (22.1)	40 (11.9)	70 (33.2)	38 (10.9)
Month 6 to < Month 9 (Day 252)	56 (35.2)	73 (52.1)	75 (22.3)	99 (46.9)	42 (12.1)
Month 9 to < Month 12 (Day 336)			68 (20.2)	18 (8.5)	21 (6.0)
Month 12 to < Month 15 (Day 420)			38 (11.3)	1 (0.5)	36 (20.3)
Month 15 to < Month 18 (Day 504)			42 (12.5)	0	62 (17.8)
Month 18 to < Month 21 (Day 588)			15 (4.5)	0	43 (12.4)
Month 21 to < Month 24 (Day 672)			12 (3.6)	0	27 (7.8)
≥ Month 24			7 (2.1)	0	34 (9.8)

Source: ISS Tables 3.1, 3.2, and 8, Appendix C

Abbreviations: PEY = person-years of exposure; SD = standard deviation; min = minimum; max = maximum; RCT = randomized controlled trial; and BID = twice daily.

a Person-years of exposure was computed as the sum of exposure days for all subjects included in the analysis divided by 365.25.

b Exposure duration = date of last dose – date of first dose + 1.

c The 'New Safety Results' column includes new exposure data collected since the time of the original ISS. This may include exposure to study drug that occurred but was not collected prior to the database freeze for the original ISS. Therefore, some subjects may have new exposure to drug included in this 120-day update that may be longer than the time difference between database freezes for the original ISS and 120-day update.

Demographics and baseline characteristics did not change appreciably with the additional data.

Extent of Exposure

Mean (\pm SD) exposure for All Rifaximin subjects (550 mg BID) in the HE program at the time of the database freeze for this 120-day update was 363.9 (226.19) days (approximately 1 year); median (minimum, maximum) exposure was 403.0 (7, 1008) days. The mean duration of exposure in All Rifaximin subjects was nearly 3-fold longer than the treatment durations observed in the RCT Study groups. See Table 50.

Combined cumulative data for the 120-day Safety Update represent approximately 347 person years of exposure to rifaximin 550 mg tablets BID in the primary analysis studies. For comparison, in the RCT Study population, rifaximin-treated subjects had 50 person years of exposure and placebo-treated subjects had 46 person years of exposure. At the time of the data cutoff for this safety update, most subjects had received rifaximin for ≥ 3 months (303/348 subjects). A total of 265 subjects had received rifaximin for ≥ 6 months and 202 subjects for ≥ 1 year. Eighteen (18) additional subjects had at least 4 months of rifaximin exposure in the Long Term Rifaximin Experience population at the time of the data cutoff for this safety update, including 10 additional subjects with at least 5 months of rifaximin exposure.

The mean exposure in the rifaximin for IBS trials was 14.8 days and in the safety population for the RFIB2001 study, mean duration of exposure was 27.5 days (range: 1 to 57 days). Most (616/674, 91.4%) of the subjects received study drug for at least 22 days. For the 2-week rifaximin regimens, subjects were to receive active drug for 2 weeks and then placebo for 2 weeks.

Demographics and Baseline Characteristics

Demographics and baseline characteristics were not changed significantly in the update. Data from an additional 18 additional patients were included in the update. The additional data from the IBS trials is not applicable to this application; however the placebo and treatment groups were well matched in these trials.

Adverse Events

In general, slight increases were observed compared with original ISS results in the proportion of All Rifaximin subjects experiencing each common ($\geq 5\%$) TEAE. This was consistent with the increased duration of study RFHE3002 included in the analysis. Overall, the pattern of TEAEs remained consistent with the original ISS and event rates for most common ($\geq 5\%$) TEAEs, by individual preferred term, actually declined with increased exposure to rifaximin (347 PEY vs. 252 PEY).

As with the RCT Study groups, the most common TEAEs among All Rifaximin subjects in the Long Term Rifaximin Experience population were disorders and events often observed in the subject population, i.e., subjects with advanced liver disease and a history of overt HE. For All Rifaximin subjects in the primary analysis studies, the most frequent TEAEs (i.e., $\geq 10\%$ of subjects) at the time of this 120-day Safety Update were nausea (19.0%), peripheral edema (18.4%), ascites (15.8%), urinary tract infections (15.2%), abdominal pain (13.5%), vomiting (12.4%), muscle spasms (12.1%), anemia (11.8%), diarrhea (11.8%), fatigue (11.5%), dizziness (11.2%), and constipation (10.1%). This pattern of TEAEs was consistent with findings observed in the original ISS and with the RCT Study groups. In addition, HE episodes that satisfied protocol-defined criteria for an SAE (e.g., due to hospitalization) were recorded for 86 rifaximin treated subjects (24.7%).

The overall percentage of All Rifaximin subjects in the primary analysis studies who experienced at least 1 TEAE at the time of this 120-day Safety Update (88.2%) was higher than the placebo (79.9%) and rifaximin (80.0%) groups in the RCT Study population. However, event rates for subjects experiencing TEAEs were comparable between populations, indicating that the higher percentage in the Long Term population was attributable to the increased time on the open-label study and the increased duration of observation.

One notable TEAE preferred term with a higher event rate in the Long Term Experience Population compared with the RCT Study population was hepatic failure (5.5/100 PEY vs. 2.1/100 PEY). Of the 19 subjects in the Long Term population with SAEs of hepatic failure, 10 died as a result of hepatic failure, and 4 experienced hepatic failures related to disease progression and had liver transplants. None of the events of hepatic failure in rifaximin-treated subjects were judged by the assessing investigator to be related to study medication. Other preferred terms used by investigators to denote the progression of underlying liver disease in rifaximin-treated subjects in the HE program included hepatic cirrhosis (17 subjects), liver disorder (5 subjects), and cirrhosis alcoholic (2 subjects). Overall, the incidence of TEAEs in subjects was similar during each exposure window. In this analysis, TEAEs were more common among rifaximin-treated subjects during the first 6 months of exposure. The pattern of types and frequencies of TEAEs was similar for each exposure window. The most frequent events in each exposure window were generally those common in patients with a history of overt HE.

No new subjects have experienced events of *Clostridium colitis* (*C. difficile*) in the HE program since the original ISS. The pattern and frequency of most special interest TEAEs in All Rifaximin subjects at the time of this 120-day Safety Update was comparable to placebo-treated subjects in the RCT Study and consistent with the population under study.

Deaths

In the Long Term Rifaximin Experience population, a total of 52 subject deaths (14.9%) were recorded for All Rifaximin subjects up to the time of the 120-day Safety Update, inclusive of the 10 deaths in the rifaximin group in the RCT Study. This total for the 120-day update included 16 new subject deaths in the RFHE3002 study recorded since the time of the original ISS. In total, 28 rifaximin treated subjects (8.0%) died while on drug (including through 5 days after last dose) in the primary analysis studies. Among the new or revised deaths for the 120-day update, the following SAE terms were recorded for multiple subjects: hepatic failure (3 subjects), GI hemorrhage (2 subjects), hepatic neoplasm malignant (2 subjects), septic shock (2 subjects), renal failure acute (2 subjects), and respiratory failure (2 subjects). As with the subject deaths previously reported in the original ISS, the majority of new subject deaths occurring since the original ISS were attributed to worsening hepatic function and underlying disease progression.

In the RFHE3001 and RFHE3002 study cohorts, SAEs with fatal outcomes were examined in the clinical setting of the natural history of cirrhosis (from compensated to a decompensated disease) and the subject's MELD score at baseline to evaluate the survival patterns according to short term survival estimates described in the published literature. Assuming patients start out with compensated cirrhosis, clinical deterioration and worsening of liver disease in the absence of surgical intervention or liver transplant tends to involve certain signs/complications that are encapsulated under the term "decompensated." Signs of liver decompensation include: ammonia retention/HE, high bilirubin/jaundice, fluid accumulation/ascites, and portal hypertension/ variceal bleeding. Based on a review of medical history, of the 52 rifaximin-treated subjects who died during or after the study, all but 5 had additional evidence (besides HE) of hepatic decompensation at baseline. Two of these 5 subjects had other baseline conditions associated with short term survival in cirrhotic patients (i.e., TIPS, coagulopathy) and 3 of 5 died due to hepatic neoplasm malignant, hepatic cirrhosis, or hepatic failure.

The event rate for deaths per 100 PEY for the primary analysis populations for the 120-day Safety Update was lower for All Rifaximin subjects in the Long Term Rifaximin Experience population (15.0) compared with RCT Study rifaximin group (20.0) and the RCT Study placebo group (23.9).

In the RCT Study population, serious TEAEs were experienced by a higher proportion of subjects in the placebo group (39.6% vs. 36.4%). The incidence of SAEs of anemia (2.9% vs. 0%), esophageal varices hemorrhage (2.9% vs. 1.3%), pneumonia (2.9% vs. 0.6%), and vomiting (2.1% vs. 0%) were at least 2-fold higher in the rifaximin group compared with the placebo group. Serious TEAEs which occurred in at least 3% of All Rifaximin subjects were HE (24.4%), renal failure acute (6.3%), hepatic failure (5.5%), anemia (4.6%), hepatic cirrhosis (4.3%), liver transplant (4.3%), ascites (4.0%), cellulitis (4.0%), gastrointestinal hemorrhage (3.4%), and pneumonia (3.2%).

Discontinuations

Most of the TEAEs resulting in study discontinuation were events related to hepatic function and progression of underlying disease (e.g., alcoholic cirrhosis, hepatic cirrhosis, hepatic failure, liver disorder, hepatic neoplasm malignant, hepatic encephalopathy).

With respect to safety in other special groups and populations, no other clinically meaningful trends were observed based on intrinsic factors in this update.

Summary

In summary, the new data collected from additional exposure in the RFHE3002 study were consistent with findings reported from the original ISS. Safety data compiled to date from studies RFHE3001 and RFHE3002 appear to support a favorable safety profile of rifaximin 550 mg BID for the maintenance of remission from HE. Conclusions with respect to safety therefore remain unchanged from the original ISS.

7.6.3 Supportive Published Studies

The following bullet points summarize results from 3 published studies that investigated the effectiveness of interventional treatment with rifaximin in subjects with active HE over chronic durations of therapy (3 months or 6 months).

- In a 3-month study published Loguercio et al,^{xxii} the proportion of subjects who achieved normalization of blood ammonia levels and the proportion of subjects who achieved complete normalization in mental status (Conn score = 0) by end of treatment were higher in the groups treated with rifaximin compared with lactitol ($p < 0.05$ in favor of the rifaximin groups in pairwise comparison to lactitol alone).
- In a 3-month study published by Fera et al,^{xxiii} rifaximin was more effective than lactulose in decreasing the severity of PSE, decreasing electroencephalogram (EEG) irregularities, and improving the subjects' mental states (The PSE index was a component score that included scores for mental state [Conn score], asterixis, venous ammonia levels, number connection test [NCT], and EEG).
- In a 6-month study published by Miglio et al,^{xxiv} of rifaximin (1200 mg/day) versus neomycin (3 g/day) (Miglio et al), subjects in both treatment groups (rifaximin 1200 mg/day or neomycin 3 g/day) experienced decreases from baseline in HE grade and in blood ammonia levels.

8 Postmarket Experience

Summary

Refer to Office of Surveillance and Epidemiology Review (OSE)

9 Appendices

9.1 Literature Review/References

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Review and Evaluation of Clinical Data

NDA (Serial Number)	22554
Sponsor:	Salix Pharmaceuticals
Drug:	Xifaxan®
Proposed Indication:	Hepatic Encephalopathy*
Material Submitted:	New Drug Application
Correspondence Date:	6/24/09
Date Received By Reviewer:	8/10/09
Date Review Completed:	1/21/10
Reviewer:	Ranjit B. Mani, M.D.

*The full proposed orphan drug indication for Xifaxan® is the "maintenance of remission of hepatic encephalopathy in patients 18 years of age or older."

1. Review Summary and Conclusions

This submission, a Type 6 New Drug Application (NDA) for Xifaxan®, has been received as a consultation from the Division of Gastroenterology Products. The sponsor is seeking the approval of Xifaxan® (rifaximin) in a 550 mg tablet strength for the "*maintenance of remission of hepatic encephalopathy in patients 18 years of age or older.*"

Xifaxan® is currently approved in this country, in a 200 mg tablet strength, for the "*treatment of patients (≥ 12 years of age) with travelers' diarrhea caused by non-invasive strains of Escherichia coli.*" This drug is a broad-spectrum antibiotic whose putative mode of action in reducing the occurrence of episodes of hepatic encephalopathy is by inhibiting the division of intestinal urea-deaminating and other bacteria that are responsible for the formation of ammonia and other compounds considered to be important to the pathogenesis of hepatic encephalopathy.

This consultation addresses only the design and (efficacy) results of the single major Phase III study (Study RFHE3001) that the sponsor contends as principally establishing the efficacy of Xifaxan® for the proposed new indication. That study and its results are summarized and discussed below. The text of the proposed new indication is also discussed in the context of the sponsor-presented study results.

Summary Of Study RFHE3001

The primary objective of the study was to compare the effects of rifaximin against placebo in "maintaining remission" in patients who previously had episodes of hepatic encephalopathy, but were judged to be in remission at study entry.

This was a randomized, double-blind, placebo-controlled, parallel-arm study of 6 months' duration.

250 patients satisfying the selection criteria for the study were to be randomized (1:1) to treatment with either Rifaximin 550 mg BID or matching placebo BID. A total of 299 patients were eventually randomized and assigned to the two treatment groups, so that 159 patients were in the placebo group and 140 patients were in the rifaximin group.

Key inclusion criteria were as follows.

- Male or female; if female, was to be of non-childbearing-potential or practicing adequate birth control. Age ≥ 18 years
- Conn score (grade) of 0 or 1 at entry, indicating that the patient was in remission from hepatic encephalopathy
- Two or more episodes of hepatic encephalopathy associated with cirrhosis or portal hypertension equivalent to a Conn score ≥ 2 within 6 months prior to screening. An episode of hepatic encephalopathy was defined as a Conn score rising from 0 or 1 to ≥ 2 and returning to a score of 0 or 1; at least one episode of hepatic encephalopathy must have been confirmed by reviewing medical records from a treating physician, clinic, or hospital, while other episodes could have been documented from descriptions given by the subject's caregiver. Episodes of hepatic encephalopathy primarily attributable to the following were excluded: gastrointestinal hemorrhage requiring ≥ 2 units of blood by transfusion; medications such as narcotics, tranquilizers, and sedatives; renal failure requiring dialysis; or a central nervous system insult such as a subdural hematoma. Patients should have continued to be in remission during the observation period, lasting a maximum of 6 days between screening and baseline
- Model for End-Stage Liver Disease score ≤ 25 .

The primary efficacy parameter was the time to the first breakthrough episode of hepatic encephalopathy. A breakthrough episode of hepatic encephalopathy was defined as either of the following 2 circumstances:

- An increase in Conn score from Grade 0 or 1 (the entry score) to Grade ≥ 2
- An increase in Conn score and asterixis score (grade) of one grade each for those with a baseline Conn score of 0.

The assignment of Conn scores was to be guided, in a manner not clearly outlined in the study protocol or report, by Hepatic Encephalopathy Scoring Algorithm grades (the Hepatic Encephalopathy Scoring Algorithm has been proposed as a structured means of assigning Conn scores, thereby making the latter assignment more precise).

The diagnosis of a breakthrough episode of hepatic encephalopathy was to be made either by direct assessment of the patient by study personnel or indirectly through information obtained – partly retrospectively – from hospital or emergency room medical records or treating physicians, caregivers, and other sources.

The time to the first breakthrough episode of hepatic encephalopathy was defined as the duration between the date of the first dose of study drug and the date of commencement of the first breakthrough episode of hepatic encephalopathy.

Patients who had a breakthrough episode of hepatic encephalopathy as defined above were to be withdrawn from the study (but were also to have the option of continuing in an open-label uncontrolled study). Patients who completed the entire 6-month treatment period without experiencing a breakthrough episode of hepatic encephalopathy were to be censored at the time of the final study visit.

The primary efficacy analysis was performed on the intent-to-treat population and involved a comparison of the two treatment groups on the primary efficacy parameter using the Cox proportional hazards model with a two-sided test at a significance level of 0.05 under the proportional hazards assumption.

Episodes of breakthrough overt hepatic encephalopathy occurred in 31/140 patients treated with rifaximin and in 73/159 patients treated with placebo during the period from randomization until Month 6. The primary efficacy analysis, using the prospectively stipulated Cox proportional hazards model, indicated that the hazard ratio for the risk of experiencing breakthrough episodes of overt hepatic encephalopathy was 0.421 (95% confidence interval: 0.276 to 0.641; p-value < 0.0001), for the rifaximin group versus the placebo group, during the 6 month period of the trial. Various sensitivity analyses tended to support these results.

Analyses based on the Cox proportional hazards model yielded at least nominally statistically significant results favoring rifaximin over placebo for two secondary efficacy that were prospectively stipulated as being “key”: the time to the first hepatic encephalopathy-related hospitalization and the time to any increase from baseline in Conn score.

Discussion Of Study (Efficacy) Results

There are several serious concerns as to the validity of how such relapses (breakthrough episodes) were actually delineated during the study. These concerns are further explained below.

The primary efficacy parameter for this study was the time to the first breakthrough episode of hepatic encephalopathy. A breakthrough episode of hepatic encephalopathy was defined as either of the following 2 circumstances:

- An increase in Conn score from Grade 0 or 1 (the entry score) to Grade ≥ 2
- An increase in Conn score and asterixis score (grade) of one grade each for those with a baseline Conn score of 0.

Thus, a key component in deciding whether an episode of breakthrough hepatic encephalopathy had occurred during this study was the Conn (West Haven) grade in each patient during the episode, as determined either by direct assessment by study personnel at visits to the study site, or indirectly (i.e., through information obtained, sometimes retrospectively, from medical records, hospital or emergency room physician, caregiver or other sources). An assessment of the severity of asterixis, either by direct observation or by the indirect means already alluded to in the previous sentence, was also an element in determining whether an episode of breakthrough hepatic encephalopathy had occurred.

It appears to be widely recognized that the terms used to define each stage of the standard Conn grading system for hepatic encephalopathy are imprecise and dependent on a clinician's judgment. The Conn grading system is also insufficiently sensitive at differentiating milder levels of severity of hepatic encephalopathy. (Hassanein TI et al. Introduction to the Hepatic Encephalopathy Scoring Algorithm. Dig Dis Sci 2008;53: 529-538)

The Hepatic Encephalopathy Scoring Algorithm, as described by Hassanein et al, has been proposed as a structured means of assigning Conn grades in an effort to make that assignment more precise, and on face, the algorithm, appears suitable to this reviewer for that purpose. However, as the same authors make clear, such information as is currently available regarding the validity of the Hepatic Encephalopathy Scoring Algorithm is only preliminary.

The Hepatic Encephalopathy Scoring Algorithm (HESA) was to be applied to each patient in this study at each in-person visit during the treatment period and a score assigned, but the final score derived from the use of that algorithm was not recorded in the patient's Case Report Form. Although the protocol and study report suggest that the HESA was to be utilized as a guide to help assign a Conn grade, the manner in, and extent to, which that was actually accomplished during the study are unclear. Thus it is unclear as to how structured – and therefore precise – the assignment of Conn grade was in this study, even by direct observation. The HESA score was apparently recorded in the source documents, which were not submitted with this NDA. This reviewer may have more confidence in the Conn scores if the source documents from a sufficiently large sample of patients were provided as a means of better clarification.

More importantly, in many patients who were judged to have developed breakthrough episodes of hepatic encephalopathy during the study, that determination was based on Conn grades and asterixis scores derived not from direct observation, but indirectly – and sometimes retrospectively - from hospital

medical records, treating physicians, caregivers, and other sources. In the rifaximin group, 8 patients were determined to have breakthrough episodes of hepatic encephalopathy based on direct observation by study site personnel, while 22 patients were diagnosed to have such episodes by indirect means; thus, only 26% of patients in that treatment group who were diagnosed to have breakthrough episodes of hepatic encephalopathy had that determination made by direct observation. In the placebo group, 30 patients were determined to have breakthrough episodes of hepatic encephalopathy based on direct observation, while 40 patients were diagnosed to have such episodes by indirect means; thus, in that placebo group, 42% of patients were diagnosed to have breakthrough episodes of hepatic encephalopathy by direct observation.

Table 1: Method of Diagnosing Breakthrough Hepatic Encephalopathy

	Placebo N = 70	Rifaximin N = 30	Total N = 100
Direct (at site)	30 (42.8%)	8 (26.6%)	38 (30%)
Indirect Hospitalized	22 (31.4%)	12 (40%)	34 (34%)
Indirect - Other	18 (25.7%)	10 (33.3%)	28 (28%)

Of patients with data available from CRF

When the patients who were indirectly diagnosed were analyzed by numbers admitted to the hospital with a diagnosis of HE (Breakthrough HE Hospitalization), which would likely provide greater accuracy, see Table 1, it is apparent that approximately 30% of patients in each group were diagnosed without direct observation from either a hospital visit or a site visit.

The reliability of determining the occurrence of breakthrough episodes of hepatic encephalopathy and assigning a specific Conn score by such indirect, and especially retrospective, means must be considered questionable at best. It is thus necessary for the sponsor to provide more compelling evidence that those patients who were indirectly diagnosed to have breakthrough episodes of hepatic encephalopathy in this study either did indeed have such episodes as defined by the criteria stipulated in the protocol or were otherwise not critical to the overall conclusions of the study.

A related concern is whether a specific and key inclusion criterion for this study could have been accurately applied. Under that particular criterion, all patients enrolled in the study should have had two or more episodes of hepatic encephalopathy equivalent to a Conn score ≥ 2 within 6 months of screening. In fulfilling that criterion: an episode of hepatic encephalopathy was defined as a Conn score rising from 0 or 1 to ≥ 2 and returning to a score of 0 or 1; and at least one episode of hepatic encephalopathy should have been confirmed by reviewing medical records from a treating physician, clinic, or hospital, with other episodes being documented based on descriptions provided by a caregiver. Here

again, the reliability of diagnosing episodes of hepatic encephalopathy, and especially those of a specific severity, by retrospective means is open to question.

A further concern pertaining to the accuracy with which breakthrough episodes of (overt) hepatic encephalopathy were diagnosed is the extent to which such episodes may have been missed in between study visits and phone contacts with the patient, particularly since such episodes can be both frequent and short-lived, as well as associated with only a subtle change in mental state. (Mullen, KD et. al. An Algorithm for the Management of Hepatic Encephalopathy. Semin Liver Dis. 1999; 2007;27(suppl 2):32-47). This concern exists despite a study visit or phone contact with the patient occurring as frequently as every week throughout the study. While the study protocol indicates that patients were required to complete a structured daily diary that included an assessment of mental status, those with cognitive impairment, a *sine qua non* of having a Conn grade ≥ 1 , cannot be assumed to have been capable of reliably evaluating their own mental state. In fact, it is questionable, whether those who were even mildly cognitively impaired were capable of reliably completing other elements of the daily diary, either. At the same time, the degree to which patients were under observation by their caregivers (for example, were they required to spend a specified proportion of each day with the patient?), and the extent to which caregivers recorded their own daily observations of the patient, were required to assist patients in completing the daily diary, and participated in phone contacts between the patient and study site is unclear and should be further clarified by the sponsor. Section 9.3.3 of the study report entitled Caregiver Responsibilities does not address those uncertainties adequately, and even indicates that caregivers were not required to attend all study visits.

CONCLUSION

It is this reviewer's opinion that the data submitted in this NDA do not provide enough evidence to conclude that Xifaxan® administered in a dose of 550 mg BID over 6 months has efficacy, in comparison with placebo, in reducing the risk of relapse of hepatic encephalopathy in patients with cirrhosis of the liver and/or portal hypertension. More specifically, evidence is lacking in this submission that the main component of the primary efficacy parameter, breakthrough episodes of hepatic encephalopathy while on treatment with study drug, were accurately recorded. There is also insufficient evidence that the occurrence, or lack thereof, of episodes of hepatic encephalopathy in the months prior to study entry was accurately recorded, either; an accurate recording of the frequency and severity of such episodes was needed for one of the main inclusion criteria for this study to be satisfied.

2. Background

This submission, a Type 6 New Drug Application (NDA) for Xifaxan®, has been received as a consultation from the Division of Gastroenterology Products.

In submitting this application, the sponsor is seeking the approval of Xifaxan® (rifaximin) for the *“maintenance of remission of hepatic encephalopathy in patients 18 years of age or older.”*

Xifaxan® is currently approved in this country, in a 200 mg tablet strength, for the *“treatment of patients (≥ 12 years of age) with travelers’ diarrhea caused by non-invasive strains of Escherichia coli.”*

(In the current application, the sponsor seeks to also market a 550 mg tablet strength of Xifaxan®, since the proposed dose for the presently-sought indication is 550 mg BID).

This application has been granted Priority Review status by the Agency, as sought by the sponsor.

The formal consultation request asked this Division to “review and comment on Salix’s proposed primary efficacy endpoints that pertain to the neurological assessment in their proposed target population.” Clarification of the nature of the consultation request that was then provided to this reviewer by the Division of Gastroenterology Products indicated that the Division of Neurology Products had been asked to review the design and results of the major Phase III randomized, double-blind controlled efficacy study (Study RFHE3001) that the sponsor contends is the key to establishing the efficacy of Xifaxan® for the proposed new indication.

In the cover letter to this submission, the sponsor states that Study RFHE3001 was designed and conducted in accordance with discussions at an End-of-Phase II meeting held with the Agency on December 14, 2004 (note that the Agency’s own minutes indicate that the meeting was held on December 13, 2004).

This application was also discussed between the sponsor and Agency at a pre-NDA meeting held on December 16, 2008. The Division of Neurology Products has not, however, been consulted regarding the development of Xifaxan® for the currently-proposed indication until the present time.

Xifaxan® has been developed under IND 59133.

In this consultation, “Xifaxan®” and “rifaximin” are used interchangeably.

3. Contents Of Submission

This submission, which is primarily in paper format and consists of 331 volumes, has the standard components of a NDA.

Section 5.3.5.1.1 (comprising Volumes 25 to 152) of the application has the report of Study RFHE3001.

An electronic version of the report for Study RFHE3001 has also been made available, and has been used for my review.

4. Contents Of Review

In accordance with the consultation request, this review will be confined to a description and discussion of the design and efficacy results of Study RFHE3001. Please note that no attempt has, however, been made by this reviewer to independently confirm the results of the sponsor's efficacy analyses using the statistical datasets supplied by the sponsor; that task has been entirely deferred to the Agency Biometrics reviewer for this application.

Studies of Xifaxan® contained in this submission other than RFHE3001 while designated by the sponsor as being "supportive" are incapable by design of providing evidence for the efficacy of Xifaxan® for "*maintenance of remission of hepatic encephalopathy in patients 18 years of age or older*" or for any other related indication. They have therefore not been reviewed as part of this consultation.

Safety data for Xifaxan® will not be reviewed, as they are beyond the remit of this consultation.

The contents of the submission will be reviewed under the following principal headings, and in the same order as below:

- Proposed mechanism of action of Xifaxan® in hepatic encephalopathy
- Nomenclature of hepatic encephalopathy as related to Protocol RFHE3001
- Protocol RFHE3001
- Efficacy results of Study RFHE3001
- Pertinent agreements reached at End-of-Phase II Meeting (December 13, 2004)
- Reviewer's summary comments
- Conclusion.

5. Proposed Mechanism Of Action Of Xifaxan® In Hepatic Encephalopathy

Broad-spectrum antibiotics, e.g., neomycin and vancomycin, hitherto used to treat hepatic encephalopathy, are presumed to act by inhibiting the division of urea-deaminating bacteria, thereby reducing the production of ammonia and other compounds that are believed to be important to the pathogenesis of hepatic encephalopathy.

Xifaxan® (rifaximin) is also a broad-spectrum antibiotic which is reported to act by inhibiting a bacterial deoxyribonucleic acid-dependent ribonucleic acid polymerase, thus inhibiting ribonucleic acid synthesis. Its proposed mode of action in hepatic encephalopathy is presumably the same as that of other broad-spectrum antibiotics used to treat the same condition; however, according to the sponsor, rifaximin has negligible systemic absorption in contrast to the other broad-spectrum antibiotics referred to above.

6. Nomenclature Of Hepatic Encephalopathy As Related To Protocol RFHE3001

The nomenclature of hepatic encephalopathy presented by the sponsor is summarized in the following table, which I have copied from the submission. Hepatic encephalopathy is abbreviated as "HE" in the table.

Type	Description	Subcategory	Subdivision
A	Encephalopathy associated with acute liver failure	–	–
B	Encephalopathy with portosystemic bypass and no intrinsic hepatocellular disease	–	–
C	Encephalopathy associated with cirrhosis or portal hypertension/portosystemic shunts	• Overt, episodic HE	Precipitated Spontaneous Recurrent (relapsing)
		• Persistent HE	Mild Severe Treatment dependent
		• Minimal HE	

Protocol RFHE3001 is directed at evaluating the efficacy of Xifaxan® as a treatment for Type C hepatic encephalopathy of the overt, episodic sub-category in whom episodes of neurological dysfunction (characterized by a deterioration in mental state and by motor disturbances such as asterixis) lasting hours to days are followed by remission to baseline.

7. Protocol RFHE3001

The protocol summarized below is that contained as an appendix to the report of Study RFHE3001 after its final amendment (Amendment #5) on September 4, 2008.

7.1 Title

A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial To Evaluate The Efficacy, Safety, And Tolerability Of Rifaximin 550 Mg BID For 6 Months In Preventing Hepatic Encephalopathy

7.2 Objectives

7.2.1 Primary Objective

To compare the effects of rifaximin (in a dose of 550 mg BID) and placebo in maintaining remission (over 6 months of treatment) from previously-demonstrated hepatic encephalopathy.

7.2.2 Secondary Objectives

To compare the safety, tolerability, and quality-of-life during treatment with rifaximin, as compared with placebo, while being used to maintain remission from hepatic encephalopathy.

7.3 Design, Dose, Sample Size, And Duration

This was a randomized, double-blind, placebo-controlled, parallel-arm study.

The study was designated as being of 6 months' duration.

250 patients were to be randomized (1:1) to treatment with either:

- Rifaximin 550 mg BID
- Placebo BID.

7.4 Key Inclusion Criteria

- Age \geq 18 years
- Male or female. If female, were to be of non-childbearing-potential or practicing adequate birth control
- Conn score (see Section 7.8.1) of 0 or 1 at entry (ostensibly indicating that the patient was in remission from hepatic encephalopathy)
- Two or more episodes of hepatic encephalopathy associated with cirrhosis or portal hypertension equivalent to a Conn score \geq 2 within 6 months prior to screening. Note the following regarding this criterion:
 - An episode of hepatic encephalopathy was defined as the a Conn score rising from 0 or 1 to \geq 2 and returning to a score of 0 or 1

- At least one episode of hepatic encephalopathy must be confirmed by reviewing medical records from a treating physician, clinic, or hospital. Other episodes may be documented from descriptions given by the subject's caregiver.
 - Episodes of hepatic encephalopathy primarily attributable to the following are excluded: gastrointestinal hemorrhage requiring ≥ 2 units of blood by transfusion; medications such as narcotics, tranquilizers, and sedatives; renal failure requiring dialysis; or a central nervous system insult such as a subdural hematoma.
- Model for End-Stage Liver Disease score ≤ 25
 - If a patient has a history of a portal-systemic shunt, transjugular intrahepatic portosystemic shunt placement (TIPS) must have been > 3 months prior to screening
 - Family member or other individual who can provide oversight for and be available to the patient during the conduct of the trial.
 - Informed consent

Note that patients were to be considered to be in remission from hepatic encephalopathy at the time of randomization if they had an Conn score of 0 or 1 at screening, and no episodes of hepatic encephalopathy (based on the patient-recorded daily diary) during the observation period lasting a maximum of 6 days between screening and baseline, and, presumably, at baseline as well.

7.5 Key Exclusion Criteria

- Significant medical or psychiatric condition that, as per the investigator, precluded study participation
- Expected to receive a liver transplant within 1 month of screening
- History of lactulose intolerance and not willing to discontinue lactulose for the duration of the study
- History of allergy to rifampin or rifaximin
- Participation in an investigational drug or device study within 30 days prior to screening
- Pregnant or at risk of pregnancy; lactating
- Consumption of an alcoholic beverage within 14 days of screening; evidence of drug dependence
- Diagnosis of human immunodeficiency virus infection
- History of tuberculosis.
- Diagnosis of chronic renal and/or respiratory insufficiency, or of an intercurrent infection
- Active spontaneous bacterial peritonitis or requiring daily prophylactic antibiotic treatment
- Treatment with sedatives within 7 days prior to screening
- Presence of intestinal obstruction; inflammatory bowel disease
- Visual or neurological disorder that the investigator believed could have an effect on the patient's performance on neuropsychological testing
- Active malignancy in the last 5 years, except basal cell carcinoma of the skin, or *in situ* cancer of that cervix that has been surgically excised
- Any condition that the investigator believes would prevent study completion or proper analysis of the study results

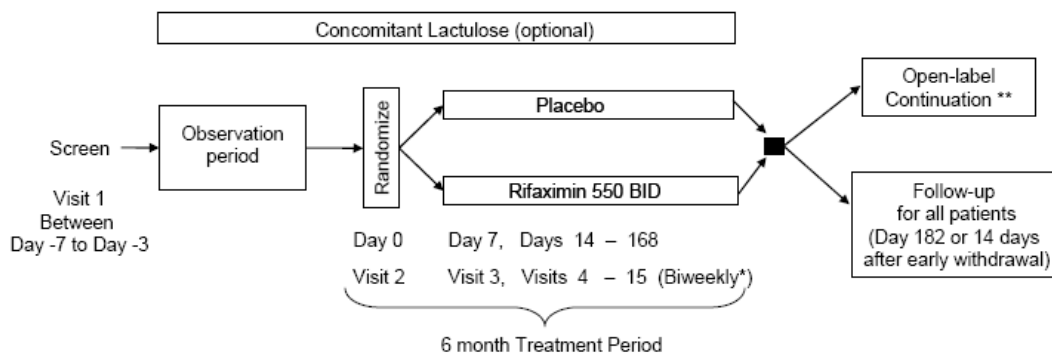
- Ongoing gastrointestinal bleeding or a history of gastrointestinal bleeding sufficient to require hospitalization and a transfusion of ≥ 2 units of blood within 3 months of screening
- Serum creatinine > 2.0 mg/dL
- Hemoglobin < 8 mg/dL
- Significant hypovolemia
- Any electrolyte abnormality that can affect mental function
- Serum potassium < 2.5 mEq/L
- Requires medications are on the list of prohibited medications for this study

7.6 Prohibited Concomitant Medications

- Benzodiazepines, or other drugs with benzodiazepine-like effects
- Experimental drugs
- Non-absorbable disaccharides, except lactulose
- Psyllium-containing preparations
- Narcotics, psychotropic drugs, and other drugs with effects on the central nervous system
- Warfarin-type anticoagulants
- Elemental zinc
- Sodium benzoate
- Milk thistle
- SAM-E
- Rifampin
- Alternative, herbal, or complementary therapies for hepatic encephalopathy, other than those required to manage fluid and electrolyte homeostasis
- Antibiotic therapy other than that used to treat active spontaneous bacterial peritonitis or prevent that condition
- Branched-chain amino acids and L-ornithine-L-aspartate

7.7 Schedule

A schematic illustration of the overall study schedule is copied below from this submission.



* Visits 6, 8, 10, 12, & 14 on Days 42, 70, 98, 126, and 154 are OPTIONAL

**All Subjects may enroll into the open-label continuation study

The full study schedule is in the next table, which I have also copied from the submission.

Study Day(s)	SCREENING /OBSERVATION PERIOD (Visit 1)	(Baseline) / Randomization (Visit 2)	TREATMENT PERIOD			FOLLOW-UP PERIOD
	~7 to ~1	0 ^a (± 1)	Visits 3 to 14 7, 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, (± 2) ⁱ	Telephone Contacts 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161 (± 2)	EOS (Visit 15) ^f 168 ± 2	Follow-up (Visit 16) ^h 182 ± 2
STUDY ASSESSMENT						
Obtain Informed consent	X					
Assign Subject Screening Number	X					
Confirm eligibility	X					
Record medical history (with HE history) ^a	X					
Dispense lactulose (if needed)	X	X	X			
Document number of bowel movements during the 2 days before Screening	X					
Record prior medications taken within 30 days of screening	X					
Record concomitant medications	X	X	X	X	X	X
Perform serum pregnancy test ^g	X		X (Day 84 only)		X	
Record demographic characteristics	X					
Assign Randomization Number		X				
Dispense study drug		X	X			
Perform clinical laboratory tests ^a	X	X	X (Days 28 and 84 only)		X	
Conn score, HESA score, asterixis score, and CFF	X	X	X		X	
SF-36 (optional), CLDQ, and Epworth Sleepiness Scale		X	X (Days 28, 56, 84, 112, and 140 only)		X	
Discuss dietary requirements	X					
Dispense Observation Period symptom diary	X					
Review Observation Period symptom diary		X				

(Continued)

Study Day(s)	SCREENING /OBSERVATION PERIOD (Visit 1)	(Baseline) / Randomization (Visit 2)	TREATMENT PERIOD			FOLLOW-UP PERIOD
	~7 to ~1	0 ^a (± 1)	Visits 3 to 14 7, 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, (± 2) ⁱ	Telephone Contacts 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161 (± 2)	EOS (Visit 15) ^f 168 ± 2	Follow-up (Visit 16) ^h 182 ± 2
Assess and record AEs	X	X	X	X	X	X
Obtain venous blood ammonia level		X	X (Days 28 and 84 only)		X	
Assess any change in mental status		X ^g	X ^g	X ^g	X ^g	
Perform physical examination	X	X ^c	X ^c		X	X ^c
Obtain vital signs (including weight)	X	X	X		X	X
Dispense AE/con med diaries		X	X			
Retrieve and review AE/con med diaries		X	X		X	
Schedule/confirm next visit/phone contact	X	X	X	X	X	
Collect study drug; determine compliance			X		X	
Consent patients for open-label continuation study					X	

Abbreviations: EOS = end of study; HE = hepatic encephalopathy; CLDQ = Chronic Liver Disease Questionnaire; AEs = adverse events; con med = concomitant medications; CFF = critical flicker frequency; HESA = Hepatic Encephalopathy Scoring Algorithm

- Return appointments must always be scheduled relative to Day 0 of the study. For scheduling purposes, Day 1 is the day study drug is started, regardless of the number of doses taken that day. It is imperative that all visits occur within the specified windows. The baseline visit may occur from 3 to 7 days after screening.
- HE history is to include documentation of date of first diagnosis of advanced liver disease, current MELD score, date of first diagnosis of HE, diagnosis of previous episodes of HE within 6 months with severity equivalent to a Conn score of 2 or greater, including factors contributing to the episodes (if any), the source of the episodes (i.e., physician or subject reported), and the dates of relapse, diagnosis of current remission, requirement of lactulose to achieve remission, and current regimen of lactulose used for remission maintenance (if the subject uses lactulose).
- This is to be a symptom-directed physical examination only and to be performed only if necessary.
- For females of childbearing potential only.
- Includes hematology, coagulation (PT/INR), blood chemistry and urinalysis.
- EOS visit may be Visit 1 (Screening) for an open-label continuation study (i.e., for all subjects, whether they complete RFHE3001 or not).
- Mental status will be assessed at visits by determining Conn Score and will be assessed during telephone contacts by asking general health questions.
- The Follow-up visit may not be required for subjects who roll-over directly to the extension study (i.e., within 16 days of the EOS/early termination visit from this double-blind study).
- In-clinic Treatment Visits 6, 8, 10, 12, and 14 (i.e., on Days 42, 70, 98, 126, and 154) are OPTIONAL but should be conducted if deemed necessary by the investigator. If an in-clinic Treatment Visit is not conducted on Days 42, 70, 98, 126, or 154 then the site will telephone the subject on these days (± 2 days) to monitor their health, mental status, and concomitant medications, and schedule the next study visit/phone contact.

Note the following:

- During the Observation Period, lasting a maximum of 6 days, prior to baseline, patients were to be observed for episodes of breakthrough hepatic encephalopathy (see Section 8.7). A symptom diary (see below) was to be maintained during that period. Patients who developed episodes of breakthrough hepatic encephalopathy during that period were not to be randomized.
- Concomitant medication and adverse event diaries (see below) were also to be maintained during the treatment period.

- Telephone contacts were to be made between the study site and patient in between study visits, according to the schedule above. At those contacts, the following were to be assessed: adverse events; concomitant medications; and changes in mental status. The date of the next study visit was also to be confirmed.
- The following is stated in the study protocol regarding the diary: *"A diary will be maintained by the subject during the observation period. An adverse event and concomitant medication diary will be used during the treatment period of the study. Subjects will be encouraged to complete the diary to the best of their ability and will be instructed on the importance of diary compliance."*

An example of an entry from the patient diary is below, copied from the submission. It appears that such entries needed to be made daily during the treatment period for the study.

DATE (Day/Month/Year)	# OF UNITS OF LACTULOSE (Total for Day) Dose 1 = 2 units Dose 2 = 3 units Total for day = 5 units	MENTAL STATUS (Check All Symptoms That Apply) Symptoms for Mental Status: 0=No Problems 1=Distracted 2=Sluggish (Lethargic) 3=Confused (Disoriented) 4=Change in Personality/ Inappropriate Behavior 5=Very Sluggish (Very Lethargic) 6=Very Confused (Very Disoriented) 7=Bizarre (Weird) Behavior 8=Not Responsive	ANY CHANGES IN YOUR HEALTH SINCE YESTERDAY?	ANY CHANGES IN YOUR MEDICATION USE SINCE YESTERDAY? (Other Than Lactulose)
1. 1 8 D E C 2005	0 5	<div>0 <input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/></div> <div>3 <input checked="" type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/></div> <div>6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/></div>	1 <input type="checkbox"/> Yes 2 <input checked="" type="checkbox"/> No	1 <input checked="" type="checkbox"/> Yes 2 <input type="checkbox"/> No

7.8 Description Of Efficacy-Related Assessments

7.8.1 Conn Score (West Haven Score)

The Conn score, also known as the West Haven score, is used to grade the mental status of patients with hepatic encephalopathy.

The scale used by the sponsor to assign a Conn Score was as follows.

Grade	Manifestations
0	No personality or behavioral abnormality detected
1	Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired ability to add or subtract
2	Lethargy; disorientation for time; obvious personality change; inappropriate behavior
3	Somnolence to semi-stupor, but with response to stimuli; confusion; gross disorientation; bizarre behavior
4	Coma; unable to test mental state

Note that the presence or absence of asterix was not a criterion used to assign a Conn score in this study.

The Conn score was to be assigned based on assessments performed at study visits, both scheduled and unscheduled. Conn scores were also to be assigned based on indirect assessments (see Section 8.7).

7.8.2 Hepatic Encephalopathy Scoring Algorithm

The sponsor has provided only a brief description of this measure in the final study protocol, but a more detailed description of this measure is contained in the final study report. Both descriptions are provided below.

7.8.2.1 Description In Final Study Protocol

The following is how the Hepatic Encephalopathy Scoring Algorithm was described in the study protocol.

- This is a method that uses both clinical and neuropsychological assessments to evaluate mental status
- The algorithm has been validated previously and correlated with the Conn score
- The algorithm will be evaluated at screening and throughout the treatment period
- The algorithm is to be used for exploratory purposes.

7.8.2.2 Description In Study Report

A more detailed description of the algorithm actually used in this study and how it was scored is in the body of the study report. Further details are below.

The components of the Hepatic Encephalopathy Scoring Algorithm consisted of 2 sets of assessments: clinical and neuropsychological. Each set of assessments was scored separately and an overall Hepatic Encephalopathy Scoring Algorithm score derived from both assessments.

The clinical assessments performed and the methods for scoring them are in the following table, which I have copied from the submission.

Clinical Assessments (O)	Description
Grade 4	
No eyes opening	Subject does not open eyes upon attempts to awaken (e.g. pinch)
No reaction to simple commands	Subject does not react to simple commands, no motor responses
No verbal response	No verbal communication to commands
Grade 3	
Somnolence	Subject has extremely difficult time staying awake through assessments; difficult to re-awaken
Confusion	Marked confusion; subject does not orient to testing
Disoriented to Place	Subject unable to state his/her location despite orienting them
Bizarre Behavior/Anger/Rage	Displays strange behavior, voices; very angry outbursts
Clonus/Rigidity/ Nystagmus/Babinsky	Clonus/Rigidity: Hand on calf muscle and flex foot up = repeatedly contracting muscle Nystagmus: Hold pen out in front of eyes: Eyes appear "shaky" Babinsky: Toes flair out
Grade 2	
Lethargy	Subject is very sleepy but is able to stay awake for testing
Loss of Time	Subject is unable to state correct date despite orienting them
Slurred Speech	Subject has slurred speech, difficult to understand
Hyperactive Reflexes	Fast up/down tendon response to hammer on elbow. Large response at knee
Inappropriate Behavior	Displays inappropriate behavior during testing
Grade 1	
Sleep Disorder	Subject sleep pattern is not consistent (sleeps during day/awake at night) or takes medicine to sleep
Tremor	With arms stretched out visible tremor (shaking) in hands

(Note that the word "Babinski" is spelt incorrectly in the table above)

The neuropsychological assessments performed were in the following categories

- Evaluation of mental control, based on counting numbers and listing the alphabet
- Assessment of vision (using a picture of a cross held 12 inches from the subject)
- Hopkins Verbal Learning Test (delayed recall and recognition components)
- Simple and complex computations
- Depression rating
- Anxiety and nervousness rating
- Digit span
- Figure copying.

Further details of each of the above assessments are in the submission. The scoring sheet used for neuropsychological assessments is copied below.

Neuropsychological Assessments (<input type="checkbox"/>)	IMPAIRED (Mark boxes)	Test Results
Grade 3		
Mental Control	Score = 0	
Grade 2		
Slow responses	Mental Control < 4	
Amnesia for recent events	HVLT < 100%	
Anxiety S	core > 4	
Simple computations	First 3 problems < 100%	
Grade 1		
Complex computations	Second 3 problems < 100%	
Shortened attention span	Digit Span < 5	
Construction ability	Copy Trial < 6 or cannot write name legibly	
Depression S	core > 4	

The overall Hepatic Encephalopathy Scoring Algorithm grading sheet is below, copied from the submission (squares represent neuropsychological tests; circles represent clinical assessments; circles and/or squares were checked if impaired)

Time __ : __ 24 Hour Clock	
4	<input type="radio"/> No eyes opening <input type="radio"/> No verbal/voice response <input type="radio"/> No reaction to simple commands
	All applicable ⇒ Grade 4 otherwise continue
3	<input type="radio"/> Somnolence <input type="radio"/> Confusion <input type="radio"/> Disoriented to place <input type="radio"/> Bizarre Behavior / Anger/Rage <input type="radio"/> Clonus/Rigidity / Nystagmus / Babinsky <input type="checkbox"/> Mental Control = 0
	3 or more applicable ⇒ Grade 3 otherwise continue
2	<input type="radio"/> Lethargy <input type="radio"/> Loss of time <input type="radio"/> Slurred Speech <input type="radio"/> Hyperactive Reflexes <input type="radio"/> Inappropriate Behavior <input type="checkbox"/> Slow responses <input type="checkbox"/> Amnesia of recent events <input type="checkbox"/> Anxiety <input type="checkbox"/> Impaired simple computations
	2 or more <input type="radio"/> and 3 or more <input type="checkbox"/> applicable ⇒ Grade 2 otherwise continue
1	<input type="radio"/> Sleep disorder / Impaired Sleep Pattern <input type="radio"/> Tremor <input type="checkbox"/> Impaired complex computations <input type="checkbox"/> Shortened attention span <input type="checkbox"/> Impaired construction ability <input type="checkbox"/> Depression
	4 or more applicable ⇒ Grade 1 otherwise Grade 0
Hepatic Encephalopathy Grade __	

The following is stated in the study report about the use of Hepatic Encephalopathy Scoring Algorithm (HESA) measurements in this study:

"Because HESA measurements are correlated with Conn score, the HESA worksheet and results of the HESA test were used as diagnostic tools to focus the clinical staff on HE clinical manifestations associated with the transitions from Conn scores of 0 through 4. Additionally, HESA worksheets were used in the evaluations of HE symptoms that were reported by caregivers and subjects."

The following publication is cited in support of the statement that Hepatic Encephalopathy Scoring Algorithm measurements are correlated with Conn score: *Hassanein TI et al. Introduction to the Hepatic Encephalopathy Scoring Algorithm. Dig Dis Sci 2008;53: 529-538.*

Grades for the Hepatic Encephalopathy Scoring Algorithm were to be assigned based on assessments performed at study visits. However, these grades were not recorded in individual Case Report Forms, which also did not contain the Hepatic Encephalopathy Scoring Algorithm scoring sheets; data from Hepatic

Encephalopathy Scoring Algorithm assessments were considered to be part of source documents.

7.8.3 Asterixis Grade

The presence of asterixis was to be evaluated by having the subject extend the upper arms and forearms, and dorsiflex the wrists while keeping the fingers open (spread) for ≥ 30 seconds.

The severity of asterixis was to be measured 5 grade levels, the criteria for each of which are in the following table.

Grade	Criterion
0	No tremors
1	Rare flapping motions
2	Occasional, irregular flaps
3	Frequent flaps
4	Almost continuous flapping motions

The asterixis grade was to be assigned based on assessments performed at study visits.

7.8.4 Critical Flicker Frequency Score

The term “critical flicker frequency” as used by the sponsor corresponds to the term “critical flicker fusion frequency,” as used more conventionally. The latter term refers to the frequency at which an intermittent light stimulus is perceived by an observer to be continuous. On the other hand, the term “critical flicker frequency” as described by the sponsor refers to the frequency at which a continuous stimulus becomes intermittent.

This measure is stated to be an objective means of assessing mental status, including that of patients with hepatic encephalopathy. The sponsor further states that a critical flicker frequency value of 39 Hz has been demonstrated to be the threshold for separation between those with overt hepatic encephalopathy (i.e., a Conn score ≥ 1) and those without symptoms of hepatic encephalopathy (i.e., a Conn score of 0).

In this protocol, critical flicker frequency (in Hz) was to be measured using an instrument specifically intended for that purpose. The ultimate single value for critical flicker frequency assigned to a patient at each timepoint was to be the mean of 8 separate fusion-to-flicker transition tests conducted in quick succession.

A lower critical flicker frequency score (in Hz) is considered to be indicative of greater impairment.

7.8.5 Venous Blood Ammonia Level

A further description of this measure is not necessary, as its title is self-explanatory.

7.8.6 Chronic Liver Disease Questionnaire (Health-Related Quality Of Life Measure)

This is a patient-completed instrument containing 29 questions addressing specific symptoms. Each question has a range of 7 possible responses with each response having a categorical score that ranges from 1 (“all of the time”) to 7 (“none of the time”).

7.8.7 Epworth Sleepiness Scale

The Epworth Sleepiness Scale is a patient-rated measure of daytime sleepiness. Patients are asked to rate their chances of dozing during each of the following 8 circumstances, on a scale from 0-3 (0=never; 1=slight; 2=moderate; 3=high): sitting and reading; watching television; sitting inactive in a public place; being a passenger in a car for an hour without a break; lying down to rest in the afternoon when circumstances permit; sitting and talking to someone; sitting quietly after a lunch without alcohol; and stopped for a few minutes in traffic while driving.

7.8.8 The Short-Form 36 (SF-36)

This is a standard measure of health-related quality of life consisting of 36 items administered through a questionnaire directed at the patient. The scale assesses the following domains: physical functioning, role limitations due to physical problems, bodily pain, general health perception, energy/vitality, social functioning, role limitations due to emotional problems and mental health. Higher scores are reputed to indicate better health-related quality of life.

7.9 Outcome Measures

7.9.1 Efficacy Measures

7.9.1.1 Primary Efficacy Parameter

The primary efficacy parameter was to be the time to the first breakthrough episode of hepatic encephalopathy.

A breakthrough episode of hepatic encephalopathy was defined as either of the following 2 circumstances:

- An increase in Conn score from Grade 0 or 1 (the entry score) to Grade ≥ 2

- An increase in Conn score and asterixis score (grade) of one grade each for those with a baseline Conn score of 0.

The time to the first breakthrough episode of hepatic encephalopathy was defined as the duration between the date of the first dose of study drug and the date of commencement of the first breakthrough episode of hepatic encephalopathy.

Patients who completed the entire 6-month treatment period without experiencing a breakthrough episode of hepatic encephalopathy were to be censored at the time of the final study visit.

Patients who withdrew early from the study for reasons other than a breakthrough episode of hepatic encephalopathy were to be contacted 6 months or later from the date of randomization to assess if they have experienced a breakthrough episode of hepatic encephalopathy or other outcome (e.g., death, presumably as determined through an individual other than a patient such as a caregiver). Those who did not experience a breakthrough episode of hepatic encephalopathy were to be censored at the time of contact or death, whichever was earlier.

Note that patients who had a breakthrough episode of hepatic encephalopathy as defined above were to be withdrawn from Study RFHE3001, but were also to have the option of continuing in an open-label uncontrolled study.

7.9.1.2 Secondary Efficacy Parameters

The sponsor divided these into “key” secondary efficacy endpoints and “other” endpoints. They are listed below.

7.9.1.2.1 “Key” Secondary Efficacy Parameters

- Time to first hepatic encephalopathy-related hospitalization
- Time to any increase from baseline in Conn score
- Time to any increase from baseline in asterixis grade
- Mean change from baseline in the fatigue domain score of the Chronic Liver Disease Questionnaire at end of treatment.
- Mean change from baseline in blood ammonia concentration at end of treatment.

(For the first three of the above parameters, those who completed the study or terminated early from the study without the event occurring were to be censored at the time of study completion or early termination).

7.9.1.2.2 “Other” Secondary Efficacy Parameters

- Time to diagnosis of spontaneous bacterial peritonitis

- Mean change from baseline at each post-baseline timepoint and end of treatment in critical flicker frequency
- Mean change from baseline at each post-baseline timepoint in blood ammonia concentration
- Number and proportion of subjects at each level of change from baseline at each post-baseline timepoint and end of treatment in Conn score
- Number and proportion of subjects at each level of change from baseline at each post-baseline timepoint and end of treatment in asterixis grade.

7.9.1.3 Tertiary Efficacy Parameters

- Mean change from baseline at each post-baseline timepoint and end of treatment in Chronic Liver Disease Questionnaire
- Mean change from baseline at each post-baseline timepoint and end of treatment in Epworth Sleepiness Scale total score
- Proportion of subjects who have an Epworth Sleepiness Score ≥ 10 at each post-baseline timepoint and end of treatment
- Mean change from baseline at each post-baseline timepoint and end of treatment in Short Form-36
- Total average daily lactulose usage (cup/day)
- Duration (in days) of hepatic encephalopathy-related serious adverse events leading to hospitalization.

7.9.2 Safety Measures

- Adverse events
- Physical examination findings
- Vital signs
- Laboratory tests (hematology, clinical chemistry, and urinalysis)
- Coagulation tests.

7.10 Analysis Plan

Note that only those aspects of the analysis plan that are pertinent to the primary efficacy analysis or to the analysis of the key secondary efficacy parameters are summarized below.

7.10.1 General

Statistical testing was to be two-sided, in general, with the alpha at a 0.05 level of significance.

The statistical analysis for efficacy was to be stratified by analysis region (the analysis regions were Russia and North America [United States and Canada])

Patients who discontinued early were not to be replaced, but data from these subjects were to be included in the efficacy and safety analyses.

7.10.2 Analysis Populations

The analysis populations were to be as follows:

- The intent-to-treat population, consisting of all randomized patients who received at least one dose of study drug
- The safety population, including all randomized subjects who ingested at least one dose of study medication and provided at least one post-baseline safety assessment.

7.10.3 Demographic And Other Baseline Characteristics

The following demographic and other baseline characteristics were to be summarized descriptively for the intent-to-treat and safety populations:

- Age, gender, race, ethnicity, and weight
- Model End Stage Liver Disease Score
- Conn score
- Asterixis grade
- Lactulose dose for maintenance of remission at screening
- Duration of current remission
- Time since diagnosis of advanced liver disease
- Time since first diagnosis of hepatic encephalopathy
- Average of stool count during the 2 days prior to screening
- Number of hepatic encephalopathy episodes within the past 6 months
- Factors contributing to hepatic encephalopathy episodes
- Average critical flicker frequency
- Diabetes mellitus at screening.

7.10.4 Primary Efficacy Analysis

The primary efficacy parameter is the time to the first breakthrough episode of hepatic encephalopathy, as already noted above.

The primary efficacy analysis was to be performed on the intent-to-treat population.

The primary efficacy analysis was to be based on a comparison of the primary efficacy parameter between the two treatment groups using the Cox proportional hazards model, with a two-sided test at a significance level of 0.05 under the proportional hazards assumption. If the proportional hazards assumption was violated, an alternative method such as a Cox model with non-proportional hazards was to be used. In addition, the Kaplan-Meier method was to be used to estimate the proportions of subjects experiencing a breakthrough episode of hepatic encephalopathy on Days 28, 56, 84, 140 and 168 for each treatment group; a plot containing the Kaplan-Meier estimators of the survival curves for each treatment group was to be provided. Additional covariates were to be fitted into the model if there was an imbalance at baseline for a clinically important variable.

Two sensitivity analyses were also to be conducted.

- One sensitivity analysis was to exclude from the intent-to-treat population those who had known precipitating factors (for hepatic encephalopathy) at the time of randomization
- The other sensitivity analysis was to exclude from the intent-to-treat population those who took prohibited medications during the treatment phase.

7.10.5 Analysis Of Key Secondary Efficacy Parameters

The methods of analysis to be used for the key secondary efficacy parameters are summarized in the following table.

Key Secondary Efficacy Parameter	Method(s) Of Analysis
Time to first hepatic encephalopathy-related hospitalization	Survival analysis methods as for primary efficacy parameter
Time to any increase from baseline in Conn score	Survival analysis methods as for primary efficacy parameter
Time to any increase from baseline in asterixis grade	Survival analysis methods as for primary efficacy parameter
Mean change from baseline in the fatigue domain score of the Chronic Liver Disease Questionnaire at end of treatment.	Analysis of covariance model with effects for treatment and analysis region, and baseline value as a covariate
Mean change from baseline in blood ammonia concentration at end of treatment.	Analysis of covariance model with effects for treatment and analysis region, and baseline value as a covariate

The plan for statistical analysis of the above secondary efficacy parameters, as contained in the final study protocol, did not include a method of adjusting the Type I error for multiple comparisons.

7.10.6 Sample Size Estimate

The basis for the sponsor's sample size estimate has been explained as follows.

The sample size (125 patients per treatment group) is based on an analysis of the relative risk of experiencing breakthrough hepatic encephalopathy based on Cox regression analysis of the time to the first breakthrough episode hepatic encephalopathy.

The null and alternative hypotheses are the following:

$$H_0: \beta_{\text{rifaximin}} = 0$$

$$H_A: \beta_{\text{rifaximin}} \neq 0$$

$\beta_{\text{rifaximin}}$ is defined as the coefficient of the active treatment arm in a Cox proportional hazards regression model compared with the placebo group; according to the sponsor, it is considered to represent the log of the hazard ratio for comparing rifaximin to placebo and is equivalent to testing that the hazard ratio for the occurrence of a hepatic encephalopathy breakthrough event is significantly different from 1.

The sample size estimate is based on the following:

- About 50% of those assigned to rifaximin and 70% of those assigned to placebo will experience breakthrough hepatic encephalopathy over the course of the 6-month treatment period. On that basis the hazard ratio for rifaximin relative to placebo can be estimated at about 0.58 ($\beta_{\text{rifaximin}} = -0.54$) for comparing time to first breakthrough hepatic encephalopathy episode in the two treatment groups
- A Type I error of 0.05 (two-sided).

Using the above, the sponsor estimated that a sample size of about 100 subjects per treatment group provided > 80% power to demonstrate the superiority of rifaximin to placebo.

7.11 Rationale For Dose Selection

The selection of the dose used in Study RFHE3001 appears to have been based on the results of previous clinical trials of rifaximin in the treatment of hepatic encephalopathy, included several small, short-duration randomized controlled trials.

8. Efficacy Results Of Study RFHE3001

This study was conducted at a total of 70 sites in the United States, Canada, and Russia, between December 2005 and August 2008.

The main efficacy results of the study are further described below.

8.1 Changes In Planned Efficacy Analysis

The following were the key aspects of the efficacy analysis that differed from the final plan described in the study protocol, and thus appear to have been post-hoc.

- Two non-primary efficacy endpoints, the time to diagnosis of spontaneous bacterial peritonitis and the duration of hepatic encephalopathy-related serious adverse events leading to hospitalization – were not analyzed, as the available data in each instance were deemed inadequate to conduct such analyses.
- According to the study protocol, a sensitivity analysis was to be conducted on the primary efficacy parameter after excluding from the intent-to-treat population those who took prohibited medications during the treatment phase. However, the

actual sensitivity analysis only excluded those received medications for the treatment or prevention of hepatic encephalopathy (other than lactulose).

- For tabular presentations of time-to-event analyses, the number of subjects at risk during each treatment interval were calculated using the life table method, rather than by using Kaplan-Meier estimates.
- The key secondary efficacy parameters were analyzed in a hierarchical manner, in the same sequence as below, at a level of significance of 0.05 until a p-value > 0.05 was reached; any subsequent results were considered exploratory only.

Order Of Analysis	Key Secondary Efficacy Parameter
1	Time to first hepatic encephalopathy-related hospitalization
2	Time to any increase from baseline in Conn score
3	Time to any increase from baseline in asterixis grade
4	Mean change from baseline in the fatigue domain score of the Chronic Liver Disease Questionnaire at end of treatment.
5	Mean change from baseline in blood ammonia concentration at end of treatment.

8.2 Patient Disposition

A total of 299 patients were randomized: 219 were randomized at centers in North America, and 80 were randomized at centers in Russia. Of the 219 patients randomized at centers in North America, the vast majority (205 patients) were at centers in the United States.

Of the 299 patients randomized, 159 patients were randomized to receive placebo and 140 patients were randomized to receive rifaximin. All randomized patients received at least one dose of study drug.

The disposition of those randomized is further summarized in the next table, which I have copied from the submission.

Category	Placebo n (%)	Rifaximin n (%)	Total n (%)
Randomized	159 (100.0)	140 (100.0)	299 (100.0)
Completed 6 months of treatment	66 (41.5)	88 (62.9)	154 (51.5)
Discontinuation due to breakthrough hepatic encephalopathy event	69 (43.4)	28 (20.0)	97 (32.4)
Discontinuation due to non-breakthrough hepatic encephalopathy event	19 (11.9)	17 (12.1)	36 (12.0)
Discontinuation due to adverse event	7 (4.4)	8 (5.7)	15 (5.0)
Discontinuation due to subject request	9 (5.7)	6 (4.3)	9 (3.0)
Discontinuation due to development of any exclusion criterion	3 (1.9)	1 (0.7)	4 (1.3)
Discontinuation due to liver transplant	1 (0.6)	0 (0.0)	1 (0.3)
Death	3 (1.9)	6 (4.3)	9 (3.0)
Discontinuation for other reason	1 (0.6)	3 (2.1)	4 (1.3)

Based on the above table, a total of 135 patients (84.9%) in the placebo group, and 116 patients (82.9%) in the rifaximin group, completed the study as stipulated in the protocol; they included those who completed treatment and those who discontinued treatment on account of a breakthrough hepatic encephalopathy event.

8.3 Protocol Deviations

The number and proportion of subjects in each treatment group with major protocol deviations (in 3 different categories) are summarized in the following table.

Category	Placebo n (%)	Rifaximin n (%)
Randomized	159 (100.0)	140 (100.0)
More than one deviation from the stipulated inclusion and exclusion criteria	13 (8.2)	14 (10.0)
Use of concomitant medications for the prevention or treatment of hepatic encephalopathy	3 (1.9)	3 (2.1)
Incorrectly dispensed study drug*	2 (1.3)	2 (1.4)

*Only 1 patient in each treatment group actually took incorrectly dispensed study drug and for 2 weeks in each instance.

8.4 Study Populations

The intent-to-treat and safety populations corresponded precisely to the randomized populations, i.e., 159 patients in the placebo group and 140 patients in the rifaximin group.

8.5 Demographic And Other Baseline Characteristics

8.5.1 Demographic Characteristics

These are summarized in the following table, which I have copied from the submission.

Characteristic Category or statistic	Placebo N = 159	Rifaximin N = 140	Total N = 299
Age (years)			
n	159	140	299
Mean (SD)	56.8 (9.18)	55.5 (9.57)	56.2 (9.38)
Median (Min, max)	57.0 (21, 78)	55.0 (26, 82)	56.0 (21, 82)
Age group – n (%)			
< 65	128 (80.5)	113 (80.7)	241 (80.6)
≥ 65	31 (19.5)	27 (19.3)	58 (19.4)
Sex – n (%)			
Male	107 (67.3)	75 (53.6)	182 (60.9)
Female	52 (32.7)	65 (46.4)	117 (39.1)
Ethnicity – n (%)			
Hispanic or Latino	28 (17.6)	21 (15.0)	49 (16.4)
Not Hispanic or Latino	131 (82.4)	119 (85.0)	250 (83.6)
Race			
American Indian/Alaskan native	3 (1.9)	5 (3.6)	8 (2.7)
Asian	8 (5.0)	4 (2.9)	12 (4.0)
Black/African American	5 (3.1)	7 (5.0)	12 (4.0)
Native Hawaiian/Pacific islander	1 (0.6)	2 (1.4)	3 (1.0)
White	139 (87.4)	118 (84.3)	257 (86.0)
Other	3 (1.9)	3 (2.1)	6 (2.0)
Missing	0	1 (0.7)	1 (0.3)
Country – n (%)			
United States	112 (70.4)	93 (66.4)	205 (68.6)
Canada	6 (3.8)	8 (5.7)	14 (4.7)
Russia	41 (25.8)	39 (27.9)	80 (26.8)

While the majority of demographic characteristics may have been broadly comparable between treatment groups, the proportion of men was considerably higher (and the proportion of women thus considerably lower) in the placebo group as compared with the rifaximin group.

8.5.2 Baseline Disease Characteristics

Selected baseline disease characteristics in each treatment group are summarized in the following table.

Characteristic	Placebo N = 159	Rifaximin N = 140
Conn Score At Baseline N (%)		
Grade 0	107 (67.3)	93 (66.4)
Grade 1	52 (32.7)	47 (33.6)
Asterixis Grade At Baseline N (%)		
Grade 0	108 (67.9)	96 (68.6)
Grade 1	45 (28.3)	41 (29.3)
Grade 2	5 (3.1)	2 (1.4)
Grade 3	1 (0.6)	1 (0.7)
Number Of Episodes Of Hepatic Encephalopathy During The Previous 6 Months N (%)		
2	111 (69.8)	97 (69.3)
3	35 (22.0)	29 (20.7)
4	8 (5.0)	5 (3.6)
5	1 (0.6)	7 (5.0)
≥ 6	3 (1.9)	2 (1.4)
Missing	1 (0.6)	0 (0.0)
Model For End-Stage Liver Disease Score		
N	158	140
Mean (standard deviation)	12.7 (3, 94)	13.1 (3, 64)
Median (minimum, maximum)	12.4 (6, 23)	13.1 (6, 24)
Model For End-Stage Liver Disease Score Category N (%)		
≤ 10	48 (30.2)	34 (24.3)
11-18	96 (60.4)	94 (67.1)
19-24	14 (8.8)	12 (8.6)
≥ 25	0 (0.0)	0 (0.0)
Missing	1 (0.6)	0 (0.0)

As the above table indicates, the majority of, but not all, disease characteristics were comparable between the treatment groups at baseline.

Note that the above table presents a comparison of only a select group of baseline disease characteristics that this reviewer felt might be particularly important. A table comparing a larger set of baseline disease characteristics is in the study report; the parameters compared by the sponsor that are not in the above table are listed below; the parameters listed below were also broadly comparable between treatment groups on review of the sponsor's table.

- Time since the first diagnosis of hepatic encephalopathy
- Past severity of hepatic encephalopathy (based on the Conn score during the episode of hepatic encephalopathy prior to the most recent one)
- Duration of current remission
- Average critical flicker frequency
- Average venous ammonia concentration

- Daily dose of lactulose at baseline
- Average daily stool count during the 2 days prior to screening.

8.6 Lactulose Use

A comparison of concomitant lactulose use between the treatment groups is in the following table.

Characteristic	Placebo N = 159	Rifaximin N = 140
Prior Lactulose Use With Continuation During Study N (%)		
Yes	145 (91.2)	128 (91.4)
No	14 (8.8)	12 (8.6)
Lactulose Use Newly Initiated During Study N (%)		
Yes	2 (1.3)	1 (0.7)
No	157 (98.7)	139 (99.3)

8.7 Methods Used In Detecting And Documenting Episodes Of Breakthrough Overt Hepatic Encephalopathy

The following is a summary of what is stated in an attachment to the study report, although not stipulated in the study protocol.

8.7.1 Qualifications And Training Of Study Personnel

All Principal Investigators who participated in Study RFHE3001 were board-certified physicians working at a hepatology center or a tertiary care clinic for liver transplant patients.

Most study personnel were familiar with the symptoms and signs of cirrhosis of the liver and associated medical conditions as well as with the use of the West Haven (Conn) criteria for assessing the severity of hepatic encephalopathy.

The following aspects of hepatic encephalopathy were covered by experts at an investigator meeting: etiology; symptoms; diagnosis (including the use of Conn scores and asterixis grading); sub-clinical manifestations; treatments; and precipitating factors. Those attending the meeting included investigators, site staff, and site management personnel. A copy of the (PowerPoint) expert presentation is contained in this submission.

Training and certification in the use of the Hepatic Encephalopathy Scoring Algorithm was provided to investigators and site staff. A copy of the (PowerPoint) training presentation is contained in this submission.

8.7.2 Detection And Documentation Of Episodes Of Breakthrough Hepatic Encephalopathy

The detection and documentation of episodes of breakthrough hepatic encephalopathy (as defined in the study protocol) was conducted either “in person” or retrospectively. Further details are below.

8.7.2.1 “In-Person” Assessment

This assessment was made in either one of the following circumstances:

- During a clinic visit by the patient
- During a stay in an emergency room or while a hospital inpatient.

Detection and documentation (by the investigator or study personnel) of an episode of breakthrough hepatic encephalopathy during a clinic visit was based on:

- Assessment of the patient
- Information from the caregiver
- Patient diary
- Asterixis grade
- Hepatic Encephalopathy Scoring Algorithm grade.

Detection and documentation of an episode of breakthrough hepatic encephalopathy during a stay in an emergency room or while a hospital inpatient was based on:

- Patient’s medical record, including neurological signs and symptoms
- Discussion with a doctor who evaluated the patient
- Information from a caregiver or from another individual not involved in medical care.

8.7.2.2 Retrospective Assessment

This assessment was made based on the following

- Caregiver description of signs and symptoms
- Patient diary
- Patient’s medical record, including the description of neurological signs and symptoms
- Discussion with a clinician who may have evaluated the patient during the episode
- Information from an individual not involved in medical care.

8.7.3 Materials Provided To Study Sites To Help In Detecting And Documenting Episodes Of Hepatic Encephalopathy

These materials included the following:

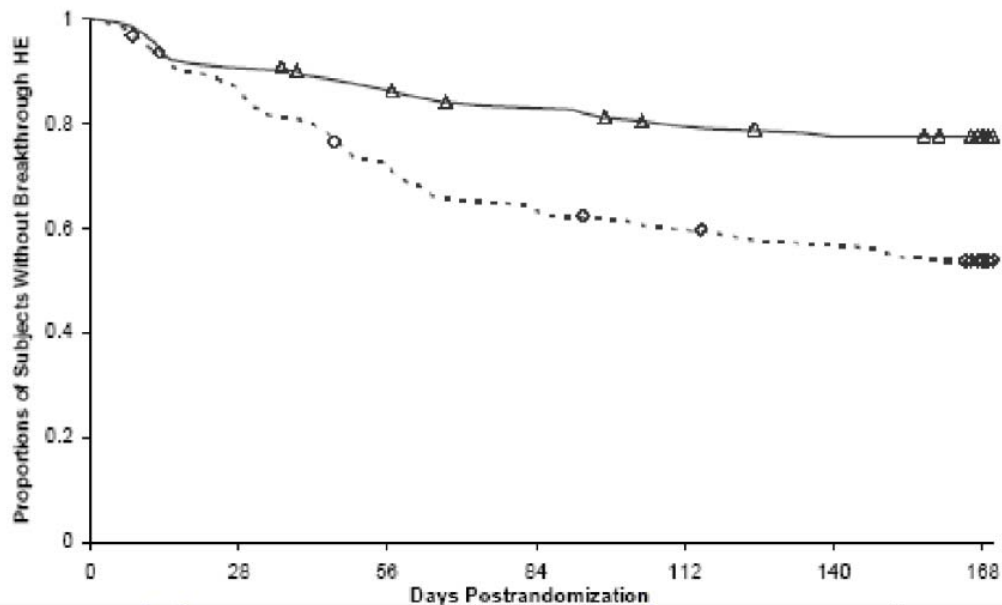
- Study-specific source documents to record Conn scores, asterixis grade and Hepatic Encephalopathy Scoring Algorithm evaluation
- Pocket guidelines for the documentation of breakthrough episodes of hepatic encephalopathy
- Hepatic encephalopathy breakthrough symptom checklist.

Note that none of these materials, which I have read in detail, provides specific instructions as to how the Conn score was to be assigned.

8.8 Results Of Primary Efficacy Analysis

Episodes of breakthrough overt hepatic encephalopathy occurred in 31/140 patients treated with rifaximin and in 73/159 patients treated with placebo during the period from randomization until Day 170.

Kaplan-Meier estimates of the time to the first breakthrough episode of overt hepatic encephalopathy up to Day 170 (Month 6) in the intent-to-treat population are in the following figure, which I have copied from the submission.



Note: Dashed line represents rifaximin group and solid line represents placebo group. Open circles and open triangles represent censored subjects. Subjects who discontinued prior to a breakthrough overt HE episode and prior to completion of the 6-month treatment period (discontinuation reasons = death, withdrawal of consent [subject withdrawal], or withdrawal due to development of exclusion criteria) were censored at the time of discontinuation.

The table below presents the same estimates as above together with the results of the related statistical analysis.

Placebo (N = 159)						Rifaximin (N = 140)				
Treatment interval (days)	At risk ^a	Number of events ^b	Cumulative number of events	Event probability (SE) ^c	Probability of no breakthrough overt HE ^d	At risk ^a	Number of events ^b	Cumulative number of events	Event probability (SE) ^c	Probability of no breakthrough overt HE ^d
0 to <28	158	20	20	0.13 (0.03)	1.0000	140	13	13	0.09 (0.02)	1.0000
28 to <56	137	23	43	0.17 (0.03)	0.8734	126	4	17	0.03 (0.02)	0.9071
56 to <84	113	14	57	0.12 (0.03)	0.7262	120	6	23	0.05 (0.02)	0.8783
84 to <140	98	10	67	0.10 (0.03)	0.6363	112	7	30	0.06 (0.02)	0.8344
140 to <168	84	6	73	0.07 (0.03)	0.5713	98	1	31	0.01 (0.01)	0.7820
≥168	38	0	73	0	0.5305	46	0	31	0	0.7740
Hazard ratio: 0.421*										
95% CI: (0.276, 0.641)										
p-value < 0.0001										

Abbreviations: CI = confidence interval, SE = standard error.

- a Number of subjects at risk during the treatment interval, estimated using the life table method. Assuming that censored cases were at risk for half of the interval, they only counted for half in figuring the number at risk.
- b Number of events occurring during the treatment interval.
- c Kaplan-Meier estimate of the probability of experiencing breakthrough overt HE during the treatment interval. Standard error estimated by using Greenwood's formula.
- d Estimate of the probability of no breakthrough overt HE until at least the beginning of the next treatment interval.
- e Hazard ratio estimate (hazard of breakthrough overt HE in the rifaximin group compared with the placebo group) determined from the Cox proportional hazards model. P-value based on the Score statistic.

As the table above indicates, a comparison of the 2 treatment groups showed that the hazard ratio for the risk of experiencing breakthrough episodes of overt hepatic encephalopathy was 0.421 (95% confidence interval: 0.276 to 0.641; p-value < 0.0001) for the rifaximin group, versus the placebo group, during the 6 month period of the trial.

8.9 Additional Analyses On Primary Efficacy Parameter

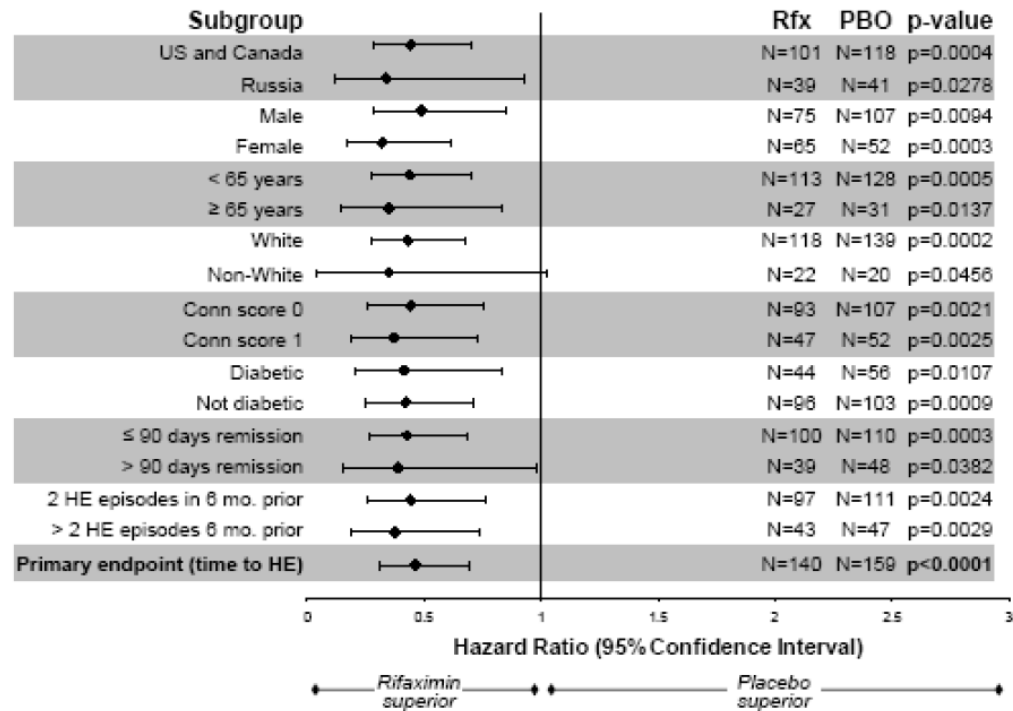
Additional analyses performed by the sponsor on the primary efficacy parameter included the following:

- A protocol-specified sensitivity analysis of the primary efficacy parameter was conducted after excluding those patients who had known precipitating factors for hepatic encephalopathy at the time of randomization; the population for this sensitivity analysis included 120 patients in the placebo group and 110 patients in the rifaximin group. A hazard ratio of 0.512 (95% confidence interval of 0.3137 to 0.839; p = 0.0068) for rifaximin versus placebo was seen in this population. A further analysis of the primary efficacy parameter using the excluded patients only (39 in the placebo group and 30 in the rifaximin group) yielded a hazard ratio of 0.248 (p = 0.0004) for rifaximin versus placebo. Both analyses otherwise used the same statistical method as that used for the primary efficacy analysis.
- A further sensitivity analysis of the primary efficacy parameter excluded 4 patients – all in the placebo group – who had used concomitant medication other than lactulose for the treatment of hepatic encephalopathy. This analysis, which

was also otherwise similar to the primary efficacy analysis, yielded a hazard ratio of 0.419 (95% confidence interval: 0.275 to 0.640; p-value < 0.0001) for rifaximin versus placebo.

- An analysis of the primary efficacy parameter up to the time of last contact (for patients who did not experience an episode of hepatic encephalopathy during the 6-month period of the study – these patients were followed after the end of the study) revealed a hazard ratio of 0.461 (95% confidence interval of 0.307 to 0.693; p = 0.0001) for rifaximin versus placebo, using the same statistical model as for the primary efficacy analysis.
- Analyses examined the effects of the following covariates (potential prognostic factors) on the primary efficacy parameter, using the log rank test stratified for each covariate: sex; age; race; geographic region; Model for End-Stage Liver Disease (MELD) score at entry; Conn score at entry; diabetes mellitus at baseline; duration of remission at entry; and number of episodes of hepatic encephalopathy within 6 months prior to randomization. Covariates that were strong independent predictors of breakthrough episodes of hepatic encephalopathy included age, MELD score at entry, duration of remission at entry, and number of episodes of hepatic encephalopathy within 6 months prior to randomization. To control for the effects of these factors on the outcome of the primary efficacy analysis, a multivariate analysis was then performed on the primary efficacy parameter using the Cox proportional hazards model specified for the primary efficacy analysis and including age, MELD score at entry, duration of remission at entry, and number of episodes of hepatic encephalopathy within 6 months prior to randomization. The latter analysis revealed a hazard ratio of 0.403 (95% confidence interval of 0.264 to 0.617; p < 0.0001) for rifaximin versus placebo.

- Analyses of the time to the first breakthrough episode of overt hepatic encephalopathy through Day 170 in a number of subgroups in the intent-to-treat population, using the same statistical model as for the primary efficacy analysis yielded the results displayed in the sponsor's figure below.



In the above figure:

HE: Hepatic Encephalopathy
RFX: Rifaximin
PBO: Placebo

8.10 Analysis Of Key Secondary Efficacy Parameters

The results of the sponsor's analysis of the first 3 key secondary efficacy parameters are in the following table. In each instance, the results are based on a Cox proportional hazards model applied to the intent-to-treat population using data collected up to Day 170, and methods of censoring described in the analysis plan. In the first 2 instances, a nominally statistically significant result favoring rifaximin was reported to have been seen.

Key Secondary Efficacy Parameter	Hazard Ratio* (95% CI)	p-value
Time to first hepatic encephalopathy-related hospitalization	0.500 (0.287 to 0.873)	0.0129
Time to any increase from baseline in Conn score	0.463 (0.312 to 0.685)	< 0.0001
Time to any increase from baseline in asterixis grade	0.646 (0.414 to 1.008)	0.0523

*Rifaximin relative to placebo
CI: Confidence Interval

The results of analysis of the remaining two secondary efficacy parameters are in the next table, and are self-explanatory.

Key Secondary Efficacy Parameter	Mean Change From Baseline (SD)		p-value
	Placebo N = 159	Rifaximin N = 140	
Mean change from baseline in the fatigue domain score of the Chronic Liver Disease Questionnaire at end of treatment.	0.11 (1.319)	0.30 (1.262)	0.9877
Mean change from baseline in venous blood ammonia concentration (µg/dL) at end of treatment.	-1.2 (60.98)	-5.7 (46.77)	0.0391

SD: Standard Deviation

8.11 Analysis Of Other Secondary Efficacy And Tertiary Efficacy Parameters

The change from baseline to end of treatment, or to assessment at breakthrough overt hepatic encephalopathy episode, in Conn score and asterixis grade was considered to be at least nominally statistically significant and favorable to rifaximin over placebo by the sponsor as indicated in the following table.

Change from baseline to end of treatment or to assessment at breakthrough overt HE episode ^a	Placebo N = 159 n (%)	Rifaximin N = 140 n (%)	Odds Ratio ^b of rifaximin to placebo (95% CI)	P-value ^b
Conn score				
n	152	135	2.46 (1.56, 3.87)	< 0.0001
-1	14 (9.2)	24 (17.8)		
0	68 (44.7)	80 (59.3)		
1	38 (25.0)	13 (9.6)		
2	19 (12.5)	15 (11.1)		
3	11 (7.2)	2 (1.5)		
4	2 (1.3)	1 (0.7)		
Asterixis grade				
n	117	121	1.92 (1.08, 3.42)	0.0262
-2	1 (0.9)	1 (0.8)		
-1	9 (7.7)	15 (12.4)		
0	80 (68.4)	91 (75.2)		
1	18 (15.4)	9 (7.4)		
2	7 (6.0)	3 (2.5)		
3	1 (0.9)	2 (1.7)		
4	1 (0.9)	0		

Abbreviations: CI = confidence interval.

- a Baseline value was the last available value prior to first dose of study drug, and end of treatment value was the assessment at breakthrough overt HE episode for subjects who had breakthrough HE and the last available postbaseline value for subjects without breakthrough HE during the treatment period.
- b P-value was calculated using proportional odds model with effects for treatment and geographic analysis region.

A nominally statistically significant treatment effect favoring rifaximin over placebo was also seen on the critical flicker frequency test as per the sponsor; the results are displayed in the next table.

	Placebo N = 159 (Hz)	Rifaximin N = 140 (Hz)	P-Value ^a
Baseline	n = 159	n = 140	
Mean (SD) CFF result	37.41 (6.03)	36.90 (5.47)	
End of treatment	n = 155	n = 139	
Mean (SD) CFF result	37.60 (5.98)	37.81 (4.88)	
Change from baseline to end of treatment	n = 155	n = 139	
Mean (SD) change in CFF result	0.355 (4.70)	0.945 (4.75)	p = 0.0320

Note: Baseline value was the last available value prior to first dose of study drug, and end of treatment value was the last available postbaseline value during the treatment period.

a P-value was calculated using analysis of covariance with effects for treatment and geographic analysis region, and baseline as a covariate.

8.12 Sponsor's Main Conclusions Regarding Efficacy Results Of Study RFHE3001

The sponsor's main conclusions regarding the efficacy results of Study RFHE3001 may be summarized as follows:

- Rifaximin had a highly significant protective effect against breakthrough overt hepatic encephalopathy over a 6-month treatment period compared with placebo in patients in remission from overt hepatic encephalopathy. These results were also seen in covariate analyses, sensitivity analyses and in analyses of population subgroups.
- Statistically significant results in favor of the rifaximin group were seen for key secondary efficacy endpoints including protection against hepatic encephalopathy-related hospitalization and increases in Conn score.

9. Pertinent Agreements Reached At End-of-Phase II Meeting (December 13, 2004)

Based on the meeting minutes, the following appear to have been the key agreements pertaining to the pivotal Phase III efficacy study RFHE3001 – as then proposed- that were reached between the Division of Gastrointestinal and Coagulation Drug Products (as it was then known) and the sponsor at the End-of-Phase II Meeting held on December 13, 2004.

- A placebo-controlled superiority design would be acceptable for the key Phase III efficacy study.
- The following text was acceptable for the primary efficacy endpoint for the proposed Phase III study: "*The primary endpoint is the proportion of*

treatment failures by treatment group at Day 56. Treatment failure is defined as an increase in the Conn score to Grade ≥ 2 (i.e., 0 or 1 to Grade ≥ 2) or a Conn and asterixis score increase of 1 grade each. Early study termination will be considered a treatment failure."

Note that a Xifaxan® dose of 400 mg BID and a duration of 8 weeks of double-blind, placebo-controlled treatment was proposed for Study RFHE3001 at the time of the End-of-Phase II meeting, whereas a Xifaxan® dose of 550 mg BID and a duration of 6 months (of double-blind, placebo-controlled treatment) was eventually used for that study.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 1/21/10
cc:
HFD-120
NDA 22554

CLINICAL PHARMACOLOGY REVIEW SUMMARY

<i>NDA</i>	22-554	<i>Submission Date(s)</i>	6/24/09, 8/4/09, 8/7/09, 8/11/09, 9/17/09, 11/06/09, 12/21/09
<i>Brand Name</i>	Xifaxan®		
<i>Generic Name</i>	Rifaximin		
<i>PDUFA goal date</i>	March 24, 2010		
<i>Reviewer</i>	Insook Kim, Ph.D.		
<i>Team Leader</i>	Sue-Chih Lee, Ph.D.		
<i>OCP Division</i>	Division of Clinical Pharmacology III		
<i>OND Division</i>	Division of Gastroenterology Products		
<i>Sponsor</i>	Salix		
<i>Relevant IND(s)</i>	59,133		
<i>Submission Type; Code</i>	Type 6 - Efficacy Supplement		
<i>Formulation; Strengths; Regimen</i>	<p>Immediate release oral tablet Two 550 mg oral tablet twice daily</p> <p>200 mg tablet approved under NDA 21-361* in May 2004</p> <p>* Due to an issue during DARRTS migration, a new NDA number was granted to the current supplement.</p>		
<i>Indication</i>	Maintenance of remission of Hepatic Encephalopathy in patients \geq 18 years of age		

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1. Overview

Rifaximin (Xifaxan®) was approved in 2004 for the treatment of patients with traveler's diarrhea using a dosing regimen of 200 mg three times daily for 3 days. In this application, the sponsor is pursuing the use of rifaximin 550 mg BID for maintenance of remission of hepatic encephalopathy in patients ≥ 18 years of age.

The systemic absorption of oral rifaximin was shown to be limited in a previous mass balance study conducted in healthy volunteers. When radiolabeled rifaximin was orally administered, 97% of the administered dose was recovered in feces as the unchanged drug. Only about 0.32% of the administered dose was recovered in urine, of which 0.03% of the administered dose was present as the unchanged drug, suggesting that absorbed rifaximin underwent metabolism. It is unknown which enzymes are responsible for the metabolism of rifaximin. In a separate study, rifaximin was detected in the bile in patients with intact GI mucosa who were administered oral rifaximin prior to cholecystectomy. The concentration of rifaximin in the bile ranged from non-detectable to 16.5 $\mu\text{g/mL}$ after 400 mg twice a day for 2 days, suggesting biliary excretion of rifaximin.

For the proposed indication, the patients are expected to have hepatic impairment, which could lead to increased systemic exposure of rifaximin. In support of the proposed indication, the sponsor submitted three in vivo and two in vitro clinical pharmacology related studies. The three in vivo studies are (1) Study RFPK1007 to characterize single dose and multiple dose pharmacokinetics and to evaluate food effect in healthy subjects, (2) Study RFPK1008 to assess drug interaction with midazolam in healthy volunteers, and (3) Study RFHE3002PK to determine the effect of different degrees of hepatic impairment on the pharmacokinetics of rifaximin. The two in vitro studies were conducted to evaluate if rifaximin is a substrate and/or inhibitor of efflux transporter(s) and to evaluate protein binding in blood samples from PK studies.

2. Conclusion

- Systemic exposure (mean AUC) to rifaximin at the proposed dosing regimen in patients with hepatic encephalopathy (550 mg twice a day) was more than 10 -fold higher than that for the approved dose to treat traveler's diarrhea (200 mg three times a day) and that in healthy subjects at the proposed dosing regimen (550 mg twice a day).
- There is no PK information in patients with Child-Pugh C category of hepatic impairment
- The drug interaction potential with concomitant medications has not been adequately characterized.
- No thorough QT study was conducted for this drug.
- The dosing regimen selected was based on the results from a Phase 2 trial in which the trial design was not optimal for dose selection.

3. Clinical Pharmacology and Biopharmaceutics Summary

Pharmacokinetic/ Biopharmaceutics Properties in healthy subjects

Single dose and multiple dose PK

Pharmacokinetics following a single dose and at steady-state after multiple doses of 550 mg twice daily for 7 days were characterized in healthy subjects (RFPK1007). After a single dose and after multiple doses, the median time to peak plasma concentration was 0.75 hours (Table 1). The mean C_{max} was 4.04 ng/ml and 3.41 ng/ml after a single dose and multiple doses of rifaximin, respectively. After multiple doses, the accumulation ratio was 1.37. The mean half-life was 1.83 and 4.17 hours after a single dose and multiple doses of rifaximin, respectively. The half-life at steady-state was comparable to that under fed conditions, while it was longer than that under fasting conditions. The shorter t_{1/2} after a single-dose administration under fasting condition is likely due to the low plasma concentrations during the elimination phase.

Table 1. Mean ± SD (%CV) Pharmacokinetic Parameters After a Single Dose and Multiple Doses of 550 mg Rifaximin in Healthy Subjects Under Fasting Condition

	Single dose Under fasting condition (n=12)	Single dose Under fed condition (n=12)	Multiple doses 550 mg twice daily for 7 days (n=14)
C _{max} (ng/mL)	4.04 ± 1.51 (37%)	4.76 ± 4.25 (89%)	3.41 ± 1.62 (47.5%)
T _{max} ¹	0.75 (0.5-2.05)	1.50 (0.5-4.08)	0.76 (0.5-4.0)
AUC _{tau} (ng·h/mL)	--	--	12.3 ± 4.76 (38.6%)
AUC _∞ (ng·h/mL)	11.1 ± 4.15 (37%)	22.5 ± 12.0 (53%)	--
CL/F (L/min)	959 ± 411 (42.8%)	--	863 ± 364 (42%)
T _{1/2} (h)	1.83 ± 1.38	4.84 ± 1.34	4.17 ± 3.3

¹Median (range)

Reviewer's comments: *The dose-proportionality of rifaximin PK was not formally studied.*

Gender effect:

The AUC and C_{max} were slightly higher in healthy female subjects than in healthy male subjects (Table 2). It may be due to a lower body weight for females than for males.

Table 2. PK parameters in healthy subjects by gender

	550 mg single dose ¹		at steady-state 550 mg BID	
	Cmax (ng/ml)	AUCi (ng·h/mL)	Cmax (ng/ml)	AUCtau (ng·h/mL)
Male (n=6)	3.12 ± 1.19	9.73 ± 4.27	2.95 ± 1.63	10.71 ± 4.13
Female (n=8)	4.70 ± 1.55	11.53 ± 4.32	3.67 ± 1.54	13.07 ± 5.33

¹Male (n=5), Female (n=7)

Food effect:

A concomitant high fat meal delayed oral absorption of rifaximin and increased the mean AUC by 2 fold (see Table 1).

The mean AUC was increased by 2 fold when rifaximin was administered within 30 min after a high fat meal. The median Tmax was delayed by 0.75 hours with a high fat meal and the mean Cmax was not significantly different. The Cmax with a concomitant high fat meal was more variable than without a high fat meal. The similar food effect on AUC was observed in the application for treatment of patients with travelers' diarrhea, after administration of two 200 mg tablets which are compositionally proportional to the proposed 550 mg tablet.

Reviewer's comments: During the Phase 3 trials, no specific instruction as to the meal intake was given and during the PK study in patients, a light meal was taken 1 hour after the dose and immediately after the 1 hour blood sampling.

Pharmacokinetics in patients with hepatic impairment (comparison to healthy subjects):

Systemic exposure to rifaximin was significantly higher in the target patient population (who had hepatic impairment) than in healthy subjects.

The pharmacokinetics of rifaximin was evaluated in the target patient population during the open-label Phase 3 trial RFHE3002. PK blood samples were collected after dosing for 7 consecutive days in patients with Child-Pugh A and Child-Pugh B class hepatic impairment. Note that PK blood samples were collected after confirmation of 100% compliance of at least 7 days of dosing. Because the PK study was done during any time of trial 3002, the total days of dosing for patients were ≥ 7 days.

Overall, in patients with hepatic impairment the mean apparent oral clearance was reduced by 88% and the half-life was increased by 2 fold compared in healthy subjects. The mean Cmax and AUCtau were 6 fold- and 11 fold higher, respectively, than in healthy subjects (Table 3, Figure 1).

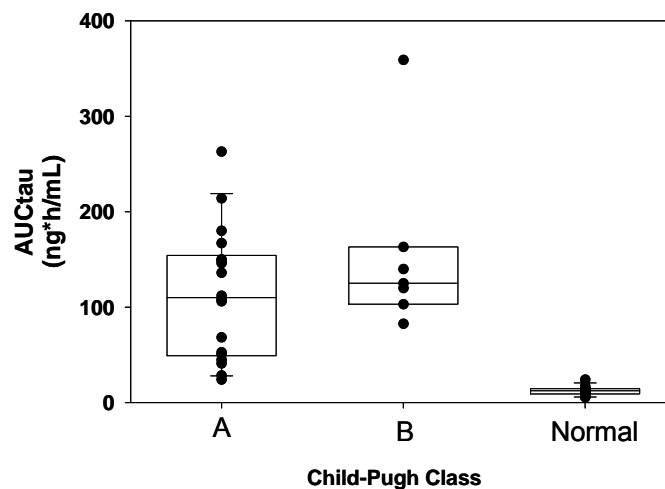
When the PK parameters were analyzed by liver function, the mean Cmax and AUCtau in patients in moderate (Child-Pugh B) hepatic impairment were 28% and 36% higher than in patients with mild (Child-Pugh A) hepatic impairment (Table 3). The mean Cmax and AUCtau in patients increased as MELD (Model of End Stage Liver Diseases) score increased (Figure 2).

Table 3: Mean \pm SD (%CV) Pharmacokinetic Parameters After Multiple Doses of 550 mg Rifaximin Twice Daily

Liver function	Mild impairment Child-Pugh A (n=18)	Moderate impairment Child-Pugh B (n=7)	Overall (n=25)	Normal (n=14) ¹
C _{max} (ng/ml)	19.5 \pm 11.4 (58.5%)	25.1 \pm 12.6 (50.2%)	21.1 \pm 11.8 (56%)	3.41 \pm 1.62 (47.5%)
C _{min} (ng/ml)	5.13 \pm 4.01 (78%)	7.90 \pm 5.35 (67.7%)	5.91 \pm 4.49 (76%)	0.275 \pm 0.333 (121%)
T _{max} (h)	1 (0.9-10)	1 (0.97-1)	1 (0.9-10)	0.76 (0.5-4)
AUC _{tau} (ng·h/mL)	118 \pm 67.8 (57%)	161 \pm 101 (62.7%)	130 \pm 77.6 (59.7%)	12.3 \pm 4.76 (38.6%)
CL/F (L/min)	122 \pm 101 (82.8%)	70.6 \pm 29.2 (41.4%)	109 \pm 90.1 (82.7%)	863 \pm 364 (42%)
T _{1/2} (h)	8.12 \pm 3.58 (44.1%)	10.5 \pm 1.5 (14.3%)	8.64 \pm 3.63 (42%)	4.17 \pm 3.3 (79%)

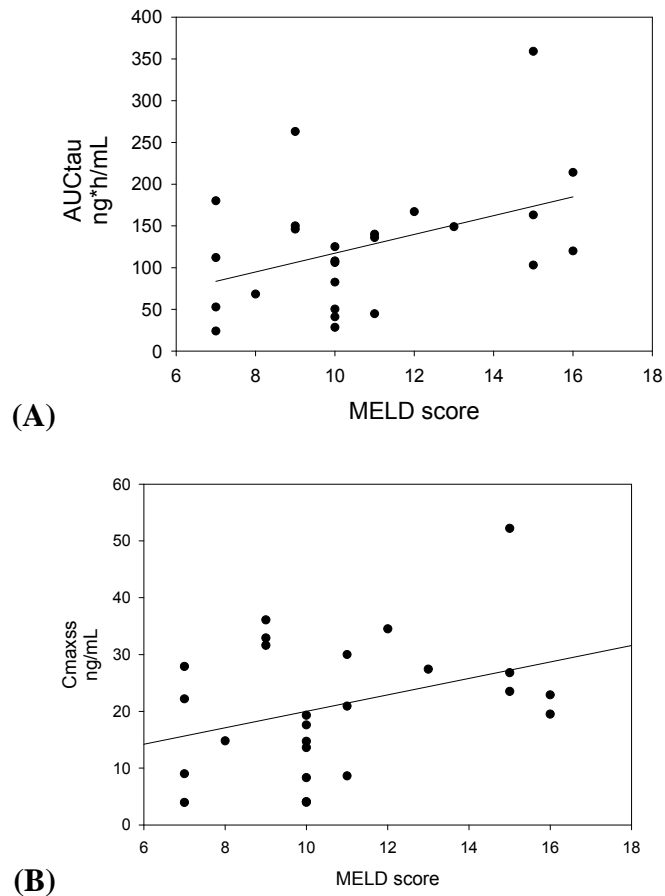
¹ RFPK1007 Cross-study comparison

Figure 1. AUC_{tau} in patients with liver function impairment and in healthy subject from study 1007



Reviewer's comments: The PK was not evaluated in hepatic impairment patients of Child-Pugh class C. The sponsor initially planned to study PK in patients in Child-Pugh class C, yet could not enroll patients for the PK sub-study. In RFHE3001 (the pivotal phase 3 study), there were a total of 31 patients in Child-Pugh class C and 17 of them were randomized to rifaximin treatment arm, while 14 patients were randomized in the control arm. Because both safety and efficacy were evaluated in patients with mild and moderate hepatic impairment receiving rifaximin at the proposed dosing regimen, no dosage adjustment is needed based on the systemic exposure.

Figure 2. (A) AUC and (B) Cmax increased with an increase in MELD score of patients



Protein Binding: hepatic encephalopathy patients vs. healthy subjects

Rifaximin is moderately protein bound and protein binding of rifaximin was about 9% lower in patients with hepatic impairment.

In healthy subjects, the average protein binding ratio after administration of 550 mg rifaximin twice daily was 67.5% ranging from 62.5% to 72.8%, with a coefficient of variation of 5.5%. As such, rifaximin is moderately protein bound. Rifampin, a structural analog of rifaximin, is about 80% protein bound.

On the other hand, the average ratio of protein binding in patients with hepatic impairment after administration of 550 mg rifaximin twice daily was 62% ranging from 55.3 to 68.2% with a coefficient of variation of 7.06%.

***Reviewer's comments:** This suggests that slightly more unbound drug is available in patients with hepatic impairment than in healthy subjects at given plasma concentrations. The lower protein binding in patients with hepatic impairment is likely attributed to a lower plasma protein due to reduced liver function.*

Drug interaction:

- *Effect of rifaximin on concomitant drugs which are substrates of CYP3A4:*

No clinically meaningful effect of rifaximin is expected on co-administered drugs which are metabolized by CYP3A4 in healthy subjects.

However, it is unknown if rifaximin in the target population, who have impaired liver function and consequently have elevated rifaximin systemic exposure, would cause clinically meaningful drug interaction with other drugs which are metabolized by CYP3A4 enzyme.

Rifaximin induces CYP3A4 enzyme activity in vitro. The in vivo drug interaction via CYP3A4 induction by rifaximin was studied in study RFPK1008 in healthy subjects. When Rifaximin 550 mg was administered three times daily for 7 days and 14 days, the AUC of midazolam, a probe substrate of CYP3A4 was 3.8% and 8.8% lower, respectively than when midazolam was administered alone, and Cmax of midazolam also decreased 4-5% when rifaximin was administered for 7-14 days prior to midazolam administration.

Reviewer's comments: *This degree of drug interaction is not considered clinically meaningful. However, the dosage regimen of rifaximin in this study i.e., three times a day, is different from the proposed dosage regime i.e. twice a day. Nonetheless the same conclusion is applicable to the proposed twice a day dosage regimen as this study was conducted under more stringent condition and resulted in no significant effect.*

Study RFDI1008 was intended to address the question about the effect of rifaximin on other CYP3A4 substrates. The induction of CYP3A4 by rifaximin may be dose- and treatment-duration dependent. The drug interaction study RFDI1008 which was conducted in healthy volunteers could not address the issue in the target population whose plasma concentration of rifaximin is ≥ 5 fold higher than healthy subjects (Table 4).

Table 4. Comparison of Mean Peak Plasma Concentrations

Study	Dosage regimen	Cmax (ng/mL)	Cmax (μM)	In vivo CYP3A4 induction
RFDI1002* ⁺	7 days 200 mg TID	1.21	0.00154	None
RFDI1008 ⁺	7 days 550 mg TID	3.61	0.00459	< 25%
	14 days 550 mg TID	3.89	0.00495	< 25%
RFHE3002PK	7+ days 550 mg BID			Not evaluated
	Child-Pugh A	19.5	0.0248	
	Child-Pugh B	25.1	0.0319	

**submitted in NDA 21-361 original submission*

⁺in healthy volunteers

Reviewer's comments: In the presence of 0.2 μM rifaximin, which is about 6-10 fold higher than the observed mean peak plasma concentration of rifaximin in patients, CYP3A4 enzyme activity was increased by 1.5 fold in vitro and the potency of induction was about 50% of rifampin, a strong CYP3A4 inducer (Table 5). The CYP3A4 induction was not studied at lower rifaximin concentrations.

Table 5. In vitro CYP3A4 Induction (fold increase in CYP3A4 activity) Based On Rate of Testosterone-6 β -hydroxylation (from Clinical Pharmacology review for NDA 21-361 original submission)

Conc. (μM)	Rifaximin	Rifampin
0.2	1.5	3
1.0	1.7	3.7
10	1.8	4
20	1.3	3
50	0.15#	3.2

Appeared to alter the morphology of the hepatocytes as observed by light microscopy. However, the sponsor stated that no clear signs of toxicity were observed. Taken from original Clinical Pharmacology review for NDA 21-361.

- **Effect of P-glycoprotein inhibitors on rifaximin permeability in vitro**
In the presence of P-glycoprotein (P-gp) inhibitors, the efflux ratio (ER) of rifaximin decreased by 2-12 fold. Other transporters are likely involved in efflux transport of rifaximin:

The membrane permeability of rifaximin was evaluated in Caco-2 cell monolayer system. The apparent permeability of rifaximin from apical to basolateral direction was about 1×10^{-6} cm/sec and it was comparable to that of Mannitol (1×10^{-6} cm/sec). Rifaximin was greatly more permeable from basolateral to apical side. The efflux ratio of rifaximin at 5 μM was 45-135 while the efflux ratio of digoxin, a substrate of P-gp was 11-12. This results show that one or more transporters may be involved in the transport of rifaximin through Caco-2 monolayers.

In the presence of P-gp inhibitors i.e. 60 μM verapamil and 0.5 μM GF120918, the efflux ratio of rifaximin decreased by 2-12 fold (Table 6).

Table 6. Inhibition of Rifaximin transport by P-gp inhibitors

	ER	ER _{Verapamil}	ER _{GF120918}
Round 1	134.54 \pm 0.1	10.89 \pm 0.2	16.48 \pm 0.17
Round 2	78.53 \pm 0.32	11.56 \pm 0.28	29.68 \pm 0.11

Round: Independent experiment on different days

- ***Effect of rifaximin on the permeability of P-gp substrate (digoxin) in vitro***
In the presence of Rifaximin at 50 μ M, the efflux ratio of digoxin decreased from 11-12 to 2-6. However, the inhibition potential of rifaximin at the therapeutic concentrations was not evaluated.

The efflux ratio of digoxin decreased from 11-12 to 2-6 in presence of rifaximin at 50 μ M. Known P-gp inhibitor, verapamil and GF120918 reduced the efflux ratio of digoxin to 1 (Table 7). This result suggests that rifaximin at 50 μ M has a potential to inhibit efflux transport of concomitant drugs which are P-gp substrates in vivo but its inhibitory potency is expected to be lower than that of verapamil.

Reviewer's comments: *Nevertheless, this effect was studied only at one concentration which was much higher than the highest C_{max} of 66 nM observed in a patient with moderate liver impairment. Additional study at lower concentrations of rifaximin will be helpful to determine if in vivo drug interaction study is warranted.*

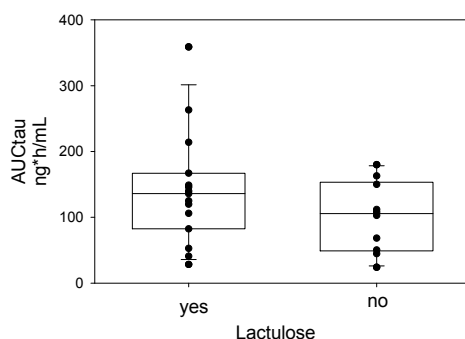
Table 7. Inhibition of Digoxin Transport by Rifaximin

	ER	ER _{Rifaximin}
Round 1	11.35 \pm 0.31	4.77 \pm 0.27
Round 2	11.74 \pm 0.32	1.99 \pm 0.44
Round 3	12.32 \pm 0.21	6.36 \pm 0.28

Effect of Concomitant Lactulose Use

Fifteen patients out of total 25 patients who participated in PK substudy were on concomitant lactulose therapy during the PK study. The mean systemic exposure in patients with concomitant lactulose use was higher than that in patients without concomitant lactulose regardless of liver function (Figure 3). The mean AUC in patients with concomitant lactulose was 142 ng*h/mL (61% CV) and that in patients without concomitant lactulose was 106 ng*h/mL (44% CV). Of note, 33% (5 out of 15) of patients who used lactulose concomitantly had moderate hepatic impairment and 20% (2 out of 10) of patients who did not use lactulose had moderate hepatic impairment. It is unknown if the slightly higher systemic exposure observed is due to an interaction between rifaximin and lactulose. During the pivotal RFHE3001 trial, 91% patients based on patient's diary used lactulose concomitantly.

Figure 3. Mean AUC in patients with a history of HE by concomitant lactulose use



Exposure (Dose)-Response Relationship

Rifaximin for the proposed indication is presumably acting locally in the intestine. As such the systemic exposure may be more relevant to safety than efficacy. Nevertheless, because only one dose level was studied in the target population for the proposed indication, there is insufficient information to draw a conclusion about the exposure-response relationship in terms of safety and efficacy.

• Effect of rifaximin on the QT prolongation

A thorough QT study was not conducted for rifaximin. Although the systemic absorption after oral administration is limited, rifaximin is systemically available to an appreciable degree. The systemic exposure to rifaximin in the new patient population after 550 mg twice daily dosing is about 16-20 times higher than that in healthy subjects after 200 mg three times a day dosing, which is the dosing regimen for the approved treatment of patients with traveler's diarrhea. The phase 3 trials did not collect ECG data.

Reviewer's comment: *As such, the current marketing experience with rifaximin can not reasonably allay the cardiac safety issue in terms of QT prolongation potential of rifaximin in the proposed patient population.*

Dose selection for the pivotal Phase 3 trials

Dose selection was based on results of a Phase 2 trial although the design of that trial was not optimal for the purpose.

The total daily dose of 1100 mg for Phase 3 trials was determined based on published literature and a supportive dose ranging study conducted in active HE patients with an endpoint of Portal Systemic Encephalopathy (PSE) Index (RFHE9702). In RFHE9702, daily dose of 600 mg, 1200 mg and 2400 mg in three divided doses were administered to patients with grade I, II, or III hepatic encephalopathy for 7 days and the efficacy was assessed by PSE Index which is a composite score of Mental State (Conn score), asterixis grade, Number Connection Test Score, Electroencephalography (EEG) score and venous ammonia levels.

While there was no statistically significant difference among three dose groups based on PSE Index at the end of the treatment (Table 8), the change of PSE Index from baseline

after 8 days of rifaximin dosing tended to be greater after 1200 mg and 2400 mg daily dosing than after 600 mg daily dosing. The mean change of PSE Index from baseline to end of treatment was -6.4%, -10.3%, and -10.7% in 600 mg, 1200 mg, and 2400 mg rifaximin daily dose groups, respectively. The total daily dose of 1200 mg was further studied in supportive Phase 3 trials in active HE patients (RFHE9702, 9701). Because there was no control group in the Phase 2 trial, it is unknown if the minimum effective dose was identified.

Table 8. Mean PSE Index at baseline and after 7 days of treatment

Rifaximin daily dose		PSE Index (%)					Adjusted mean from analysis of covariance	
		N	Mean	St dev	Min	Max	Mean	95% CI
600 mg	Day 1	14	37.8	11.4	25.0	64.3		
	Day 7 or withdrawal	17	31.9	16.9	3.6	67.9	32.4	22.9, 42.7
1200 mg	Day 1	16	38.4	13.8	21.4	75.0		
	Day 7 or withdrawal	18	28.2	18.9	7.1	82.1	30.8	22.7, 39.2
2400 mg	Day 1	16	41.7	8.5	17.9	50.0		
	Day 7 or withdrawal	16	31.0	14.2	7.1	57.1	25.8	18.8, 34.4

Nonetheless, the contribution of this information to the current dose rationale is limited due to differences in the target population, the primary efficacy endpoint and treatment duration (≤ 14 days versus 6 months) between these supportive studies and RFHE 3001 trial. In the pivotal Phase 3 trial (RFHE3001), patients had a history of ≥ 2 overt HE episodes with a documented severity equivalent to Conn score ≥ 2 within 6 months prior to screening and had a Conn score of 0 or 1 at the baseline assessment. The primary efficacy parameter for double-blind, placebo controlled study RFHE3001 was the occurrence of an episode of breakthrough overt HE during treatment. Breakthrough overt HE was defined as an increase of the Conn score to Grade ≥ 2 (i.e. 0 or 1 to ≥ 2) or an increase in Conn and asterixis score of 1 grade each for those subjects who entered the study with a Conn score of 0.

The sponsor also estimated the intestinal transit time of rifaximin 200 mg tablet from RFPK1002 and used it to support the twice daily dosing frequency.

SUMMARY OF OFFICE OF BIOSTATISTICS REVIEW

NDA/Serial Number: 22-554

Drug Name: XIFAXAN® (Rifaximin) 550mg Tablets BID

Indication(s): Maintenance of Remission of Hepatic Encephalopathy

Applicant: Salix Pharmaceuticals, Inc.

Date(s): Date submitted: June 24, 2009
PDUFA Goal date: March 24, 2010

Submission Type Type 6 NDA; 505(b)(1)

Review Priority: Priority with Amendment (3 month extension)

Office of Biostatistics Division: Division of Biometrics III

Statistical Reviewer: Behrang Vali M.S.

Team Leader: Mike Welch Ph.D.

Office of New Drugs Division: Division of Gastroenterology Products

Clinical Team: Medical Officer: Lara Dimick, M.D., FACS
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Cross Discipline Team Leader: Hugo Gallo-Torres, M.D.
Division Director: Donna Griebel, M.D.

Project Manager: Hee (Sheila) Lianos, RPh., PharmD.

I. Background

Pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, Salix Pharmaceuticals, Inc. (Salix), on June 24, 2009, submitted an efficacy supplement to the New Drug Application (NDA 021361) for XIFAXAN® (rifaximin) tablets regarding the proposed orphan drug indication of the maintenance of remission of hepatic encephalopathy (HE) in patients 18 years of age or older. This supplement was a Type 6 NDA (administratively filed under NDA 022554) which provided data for a new strength (550 mg BID) of the currently approved (200 mg) oral tablet dosage form. Rifaximin was granted orphan designation for the treatment of HE on February 10, 1998, which encompassed the proposed indication as confirmed with the Office of Orphan Products Development on November 24, 2008. This application consisted of data from a global clinical development program conducted under IND 59,133. Salix requested and was ultimately granted priority review status for this efficacy supplement by the Division of Gastroenterology Products (DGP), however due to a major amendment to the application during the review cycle, the PDUFA goal date was extended by three months.

HE is a serious, rare, complex, episodic, neuropsychiatric syndrome associated with advanced liver disease. HE is a formidable burden on the patient, his/her family, and the healthcare system. Overt HE episodes are debilitating, can present without warning, render the patient incapable of self-care, and frequently result in hospitalization. Overt, episodic HE is common among patients with liver cirrhosis; however, the condition is rare among individuals in the overall, general population.

II. Brief Overview and Summary of Relevant Trials

To establish clinical efficacy of rifaximin for the maintenance of remission of HE, Salix conducted one pivotal clinical trial, RFHE3001, which consequently serves as the principal source for any efficacy claim to be reflected in the labeling. RFHE3001 is a Phase 3, long term (6 month), randomized, double-blind, placebo-controlled, multicenter study. Salix has also conducted a subsequent open-label long term safety trial, RFHE3002, which is still ongoing. This roll-over protocol is comprised of patients who participated in the RFHE3001 study while also enrolling new patients for long-term rifaximin use. However, due to the principal objective and subsequent design of this follow-up study, any efficacy results are viewed as marginally supportive. Table 1 below contains further summary information for these relevant clinical trials submitted under this application.

Table 1 – Summary Information for Relevant Trials

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Subjects	Patient Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	RFHE3001	<i>Primary:</i> Compare the maintenance of remission from previously demonstrated recurrent episodic HE as measured by Conn score and Asterixis grade; <i>Secondary:</i> Safety and tolerability	Multinational, Multicenter, randomized, double-blind, placebo-controlled, parallel groups	Rifaximin 550mg and matching placebo; BID; 550mg tablets	Rifaximin: 140 Placebo: 159 Total: 299	Patients diagnosed with HE currently in remission	6 months	Complete; Full
Safety	RFHE3002	Long-term safety and tolerability	Multinational, Multicenter, open-label, single-arm	Rifaximin 550mg; BID; 550mg tablets	RFHE3001: 152 New: 115 Total: 267	Patients diagnosed with HE currently in remission	At least 24 months, regulatory approval, or sponsor termination	Ongoing; Interim

III. RFHE3001

A. Background Information

As stated and shown previously in Table 1, study RFHE3001 enrolled patients previously diagnosed with recurrent episodic HE who were currently in remission (per Inclusion/Exclusion Criteria defined to be a Conn Score of 0 or 1) at screening. Its primary objective was to compare the maintenance of this remission as measured by Conn score and asterixis grade (both of which are later defined below). The secondary objective of RFHE3001 was to assess the safety and tolerability of rifaximin usage. This was a Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study with patients being administered one 550mg rifaximin tablet (or corresponding matching placebo) to be taken BID.

The number of planned subjects was 250 (125 in each arm) which provides >80% power to demonstrate the superiority of rifaximin to placebo. The number of patients enrolled was 381, and 299 were subsequently randomized (1:1) with, ultimately, 140 patients to rifaximin and 159 to placebo.

The duration of treatment was to be for 6 months (with bi-weekly visits), and the overall trial lasted roughly two years and eight months with first-patient-first-visit on December 19, 2005, and last-patient-last-visit on August 15, 2008. There

were 70 sites in total with 14 in Russia (80 patients), 5 in Canada (14 patients), and 51 in the United States (205 patients). The disposition of all randomized subjects is presented in Table 2 below.

Table 2 – Disposition

	Placebo (N = 159) n (%)	550mg Rifaximin BID (N = 140) n (%)	Total (N = 299) n (%)
Subjects Treated	159 (100.0%)	140 (100.0%)	299 (100.0%)
Subjects Completed the Study	66 (41.5%)	88 (62.9%)	154 (51.5%)
Subjects Discontinued Early from the Study	93 (58.5%)	52 (37.1%)	145 (48.5%)
Primary Reason for Discontinuation			
Occurrence of an Adverse Event	7 (4.4%)	8 (5.7%)	15 (5.0%)
Development of any Exclusion Criteria	3 (1.9%)	1 (0.7%)	4 (1.3%)
Pregnancy	0	0	0
Subject Request to Withdraw	9 (5.7%)	6 (4.3%)	15 (5.0%)
Breakthrough HE episode	69 (43.4%)	28 (20.0%)	97 (32.4%)
Liver Transplant	1 (0.6%)	0	1 (0.3%)
Death	3 (1.9%)	6 (4.3%)	9 (3.0%)
Other	1 (0.6%)	3 (2.1%)	4 (1.3%)
Subjects Discontinued and Retrospectively Determined at Follow-Up to have experienced a Breakthrough HE episode	4 (2.5%)	2 (1.4%)	6 (2.0%)

There is a discrepancy in the number of patients who experienced breakthrough HE, which exists between those that were reported as discontinuations from breakthrough in Table 2 (28 rifaximin and 69 placebo) and what was recorded on the breakthrough HE CRF pages (31 rifaximin and 73 placebo) which were loaded into the datasets for the primary and secondary analyses. (Patients were supposed to discontinue from study due to breakthrough hence these numbers should have reconciled.)

As specified in the protocol, subjects were to be withdrawn from the study after experiencing a breakthrough overt HE episode. As one can see from Table 2, breakthrough overt HE episode was the primary reason for early study withdrawal for 28 of 140 subjects (20.0%) in the rifaximin group and 69 of 159 subjects (43.4%) in the placebo group. Of 48 subjects (24 in each group) who discontinued for reasons other than breakthrough overt HE episode, 36 subjects (17 and 19 in the rifaximin and placebo groups, respectively) were followed to determine if they would still experience a breakthrough overt HE episode or other outcome (i.e., mortality status). In addition, they were evaluated retrospectively to determine whether there had actually been a breakthrough HE event prior to

discontinuing treatment. This evaluation identified 2 additional patients in the rifaximin group and 4 additional patients in the placebo group who experienced breakthrough overt HE prior to or after discontinuing treatment. Furthermore, while on treatment one other rifaximin patient who, through a protocol deviation, continued treatment on study despite having experienced a breakthrough HE event.

The summary of all patients who were counted in the datasets as a breakthrough HE episode for the primary efficacy analysis is as follows:

- Breakthrough HE primary reason for discontinuation: 28 rifaximin, 69 placebo;
- One additional rifaximin subject (764-0002) completed the study although he/she experienced breakthrough HE during the study (a protocol deviation), therefore, $28 + 1 = 29$.
- 2 additional subjects determined retrospectively to have had breakthrough HE (30 rifaximin, 70 placebo):
 1. Rifaximin patient 478-0006 reason for discontinuation = other [cocaine abuse], with breakthrough experienced 36 days before discontinuation
 2. Placebo patient 761-0001 reason for discontinuation = subject request to withdraw, with breakthrough experienced 71 days before discontinuation
- 4 additional subjects experienced breakthrough HE after discontinuation (31 rifaximin, 73 placebo):
 1. Rifaximin patient 893-0005 reason for discontinuation = occurrence of an AE, with breakthrough experienced 70 days after discontinuation but still within six months of first dose
 2. Placebo patient 106-0003 reason for discontinuation = subject request to withdraw, with breakthrough experienced 52 days after discontinuation but still within six months of first dose
 3. Placebo patient 891-0003 reason for discontinuation = subject request to withdraw, with breakthrough experienced 104 days after discontinuation but still within six months of first dose
 4. Placebo patient 893-0004 reason for discontinuation = subject request to withdraw, with breakthrough experienced 85 days after discontinuation but still within six months of first dose

B. Statistical Analysis Information

The formal definitions of Conn Score and Asterixis Grade are respectively presented in Tables 3 and 4 below, and the first three key secondary efficacy endpoints in the RFHE3001 study subsequently follow.

Table 3 – Conn Score

Conn Score 0 = No personality or behavioral abnormality detected.
Conn Score 1 = Trivial lack of awareness, euphoria or anxiety; shortened attention span; impairment of addition or subtraction.
Conn Score 2 = Lethargy; disorientation for time; obvious personality change; inappropriate behavior.
Conn Score 3 = Somnolence to semi-stupor, responsive to stimuli; confused; gross disorientation; bizarre behavior.
Conn Score 4 = Coma; unable to test mental state.

Table 4 – Asterixis Grade

Asterixis Grade 0 = No tremors.
Asterixis Grade 1 = Rare flapping motions.
Asterixis Grade 2 = Occasional, irregular flaps.
Asterixis Grade 3 = Frequent flaps.
Asterixis Grade 4 = Almost continuous flapping motions.

- **Primary Endpoint**
 - Time to first breakthrough HE Episode defined as an increase in Conn score to Grade ≥ 2 (i.e., 0 or 1 to ≥ 2) or a Conn score and Asterixis grade increase of 1 point each
- **Key Secondary Endpoints**
 - Time to first HE-Related Hospitalization
 - Hospitalization directly resulting from breakthrough HE or hospitalization later complicated by breakthrough HE
 - Time to any increase from baseline in Conn Score
 - Time to any increase from baseline in Asterixis Grade

Please note that the sponsor designated these three secondary endpoints as most clinically important, and consequently pre-specified the order, as presented, in which they would be analyzed. Two additional key secondary endpoints that were designated as lower priority will not be discussed in this review.

The statistical analysis methodology was a traditional survival analysis using Kaplan-Meier curve estimation. Cox Proportional Hazards modeling was also administered with effect for treatment and stratification/adjustment by region (North America and Russia). Unless specified, all analyses were conducted under the Intent-to-Treat (ITT) analysis set (defined as all randomized subjects who ingested at least one dose of study drug).

The initial Missing Data handling strategy is consistent with what is common in survival analysis in that for all of the 'Time to Event' analyses for the endpoints previously presented, subjects who did not complete the 6 month treatment period and did not experience the event of interest were censored at the time of last available assessment and consequently dropped for any analysis at time points following the censoring time point. This is an anti-conservative approach

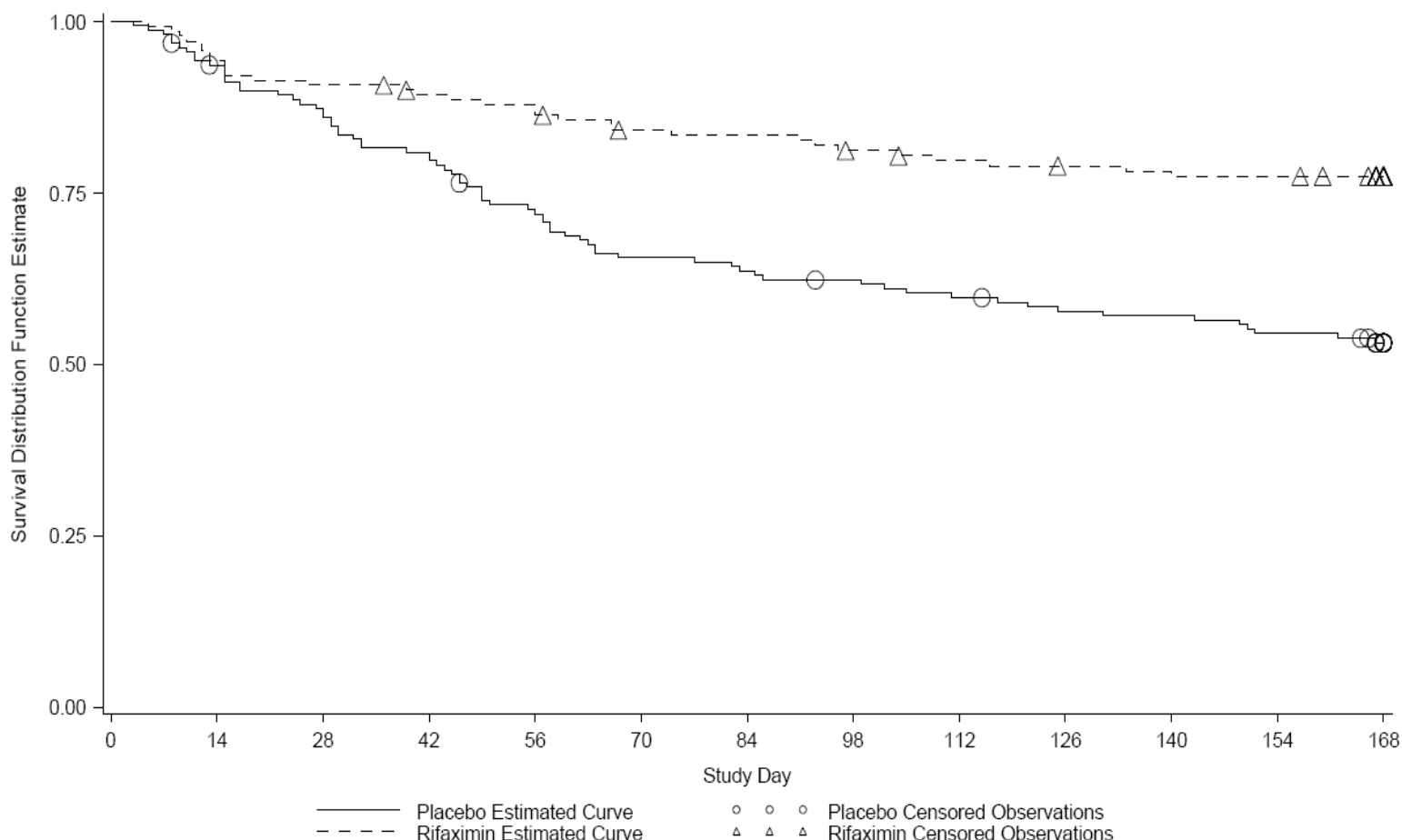
to handling missing/censored data in this context, and, consequently, two sensitivity analyses are presented below regarding more conservative missing data handling strategies.

The pre-specified Multiplicity Adjustment strategy for testing the key secondary endpoints used a standard gate-keeping approach (formally testing the next endpoint at $\alpha = 0.05$ if and only if the result of the test for the current endpoint is found to be significant at $\alpha = 0.05$). It is important to note that the p-values and confidence intervals reported in this briefing document corresponding to all other analyses are presented with no adjustment for multiplicity. These nominal p-values and confidence intervals are presented as part of the overall exploratory assessment of the efficacy of rifaximin and are not viewed as providing evidence of efficacy.

C. Primary Efficacy Analysis

1. Time to First Breakthrough HE Episode (up to Month Six)

Figure 1 - Kaplan-Meier Plot for Time to First Breakthrough HE Episode (up to Month Six)



The Cox Proportional Hazards model, stratified by region, produced a hazard ratio (hazard of breakthrough HE in the rifaximin group ÷ hazard of breakthrough HE in the placebo group) point estimate of 0.421 along with corresponding 95% Confidence Interval (CI) (0.276, 0.641). The p-value corresponding to the test for treatment effect was less than 0.0001. Although there is distinct separation between the two treatment groups at Month Six (shown in Figure 1 above), it appears that this separation was established between the beginning of Month Two and the end of Month Three. These two months are the major contributors to the overall six month results. During the last half of the study, the rate at which patients experienced breakthrough HE events began to converge between the rifaximin and placebo groups. Note that this relative behavior of the survival curves representing both treatment groups is fairly consistent throughout all of the subsequent analyses pertaining to the key secondary endpoints as well.

Table 5 below shows the numbers of breakthrough HE episodes experienced in this study. It is clear that the change in Conn Score is responsible for the majority of these episodes, rather than Asterixis Grade.

Table 5 – Breakthrough HE Episodes by Category

	Placebo (N = 159) n (%)	550mg Rifaximin BID (N = 140) n (%)	Total (N = 299) n (%)
Breakthrough HE Episodes	73 (45.9%)	31 (22.1%)	104 (34.8%)
Conn \geq 2	56 (35.2%)	28 (20.0%)	84 (28.1%)
Concurrent Increase in both Conn Score and Asterixis Grade of 1 each from Baseline	17 (10.7%)	3 (2.1%)	20 (6.7%)

2. Sensitivity Analyses

The following sensitivity analyses were conducted:

- Excluded the six patients previously presented who were diagnosed to have experienced breakthrough HE retrospectively or after discontinuation but before Month Six
- Time to first breakthrough HE episode up to last contact (includes data from beyond Month Six)
- Excluding subjects who took prohibited medications
- Whether patients had a concomitant comorbidity at baseline (analgesic use, constipation, infection, and portal shunt surgery)
- Two separate analyses, each corresponding to a different approach to handling the missing/censored data
 1. All non-breakthrough HE subjects who discontinue due to AE, liver transplant, or death prior to the completion of the six month treatment period are categorized as if they experienced a breakthrough HE at that discontinuation time point.
 2. Worst case scenario: All non-breakthrough HE subjects who discontinue due to any reason prior to the completion of the six month treatment period are categorized as if they experienced a breakthrough HE at that discontinuation time point.

The principal results of these sensitivity analyses are presented in Table 6 below. Keep in mind the results in this and the following sections pertaining to the primary efficacy analysis are exploratory in nature and not for confirmation of a statistical hypothesis.

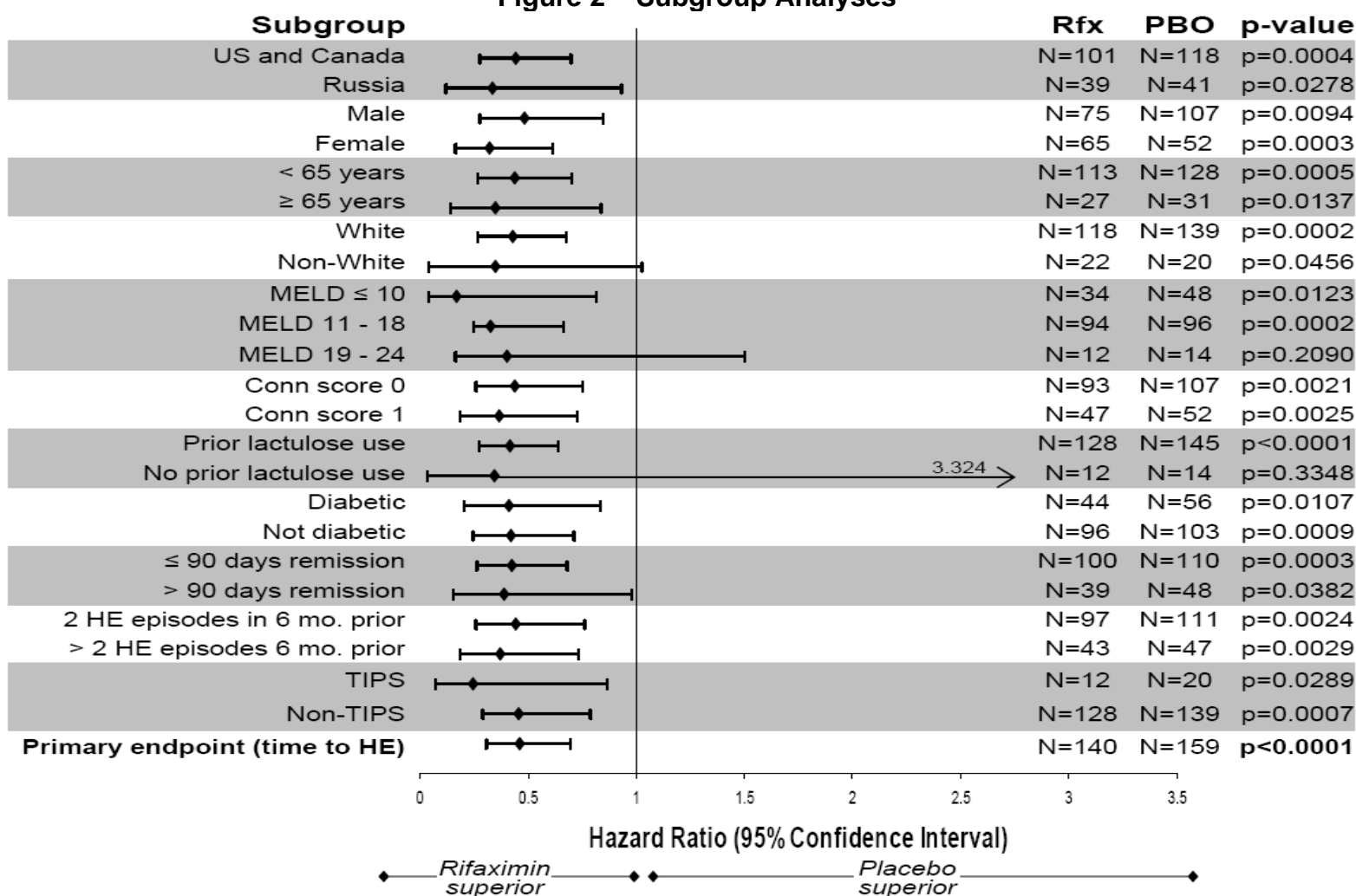
Table 6 – Principal Results for Sensitivity Analyses

Sensitivity Analysis	Placebo N =	550mg Rifaximin BID N =	Hazard Ratio Point Estimate	Hazard Ratio 95% CI	Treatment Effect p-value
Time to First Breakthrough HE (Exclusion of Six Patients)	159	140	0.419	(0.271, 0.647)	<0.0001
Time to First Breakthrough HE Episode up to Last Contact	159	140	0.461	(0.307, 0.693)	0.0001
Excluding Subjects who took Prohibited Medications	155	140	0.419	(0.275, 0.640)	<0.0001
Concomitant Comorbidity at Baseline					
Yes	39	30	0.248	(0.108, 0.571)	0.0004
No	120	110	0.512	(0.313, 0.839)	0.0068
Missing Data Strategy I	159	140	0.495	(0.342, 0.715)	0.0001
Missing Data Strategy II/Worst Case	159	140	0.533	(0.379, 0.749)	0.0002

3. Subgroup Analysis

A series of subgroup analyses were administered pertaining to region, gender, age, race, baseline Model End Stage Liver Disease (MELD) Score, baseline Conn Score, prior lactulose usage, baseline diabetes status, number of days in HE remission prior to study participation, number of HE episodes in the six months prior to study participation, and transjugular intrahepatic portal-systemic shunt (TIPS) procedures ongoing at the time of randomization. The principal results (with comparison to the primary endpoint result on the last row) are presented respectively in Figure 2 below.

Figure 2 – Subgroup Analyses



4. Per-Protocol Analysis

All previous primary analyses were then conducted on a Per-Protocol (PP) analysis set of patients defined to be ITT subjects with no major protocol violations (e.g. Inclusion/Exclusion violations). The PP definition often includes a treatment compliance requirement as well (e.g. pill consumption compliance between 80% and 120%), but this was not included for the RFHE3001 PP analysis set. The resulting patient counts were as follows:

- Rifaximin: 128
- Placebo: 149
- Total: 277

Results from each analysis re-administered under the PP analysis set were consistent with the previous corresponding results under the ITT analysis set. Consequently, reporting the results under the PP analysis set is not necessary,

and we will use the ITT analysis set of patients for all remaining analysis presentations.

5. Responder Analysis

For all 'Time to Event' analyses, in general, a corresponding responder analysis can be determined by defining a responder (or a failure) as a patient who experiences the event of interest before, after or directly at a clinically relevant time point. During the course of the review cycle, the FDA requested that the applicant conduct a responder analysis by month. A responder was defined as a patient who had not experienced breakthrough HE by each month sequentially for six months.

Two different presentations of this responder analysis are given below in Tables 7 and 8 respectively, and each presentation pertains to how censored patient data are handled. In Table 7 (Responder Analysis I), subjects who discontinued the study due to any reason other than Breakthrough HE were excluded altogether from the analysis for that specified time period. Hence this presentation reconciles directly with the original primary efficacy analysis [Time to first Breakthrough HE episode (up to Month Six)]. In Table 8 (Responder Analysis II), subjects were classified as non-responders if they discontinued for any reason or had Breakthrough HE. Thus this presentation reconciles directly with the Missing Data Sensitivity Analysis II (Worst Case). P-values were calculated using the Cochran-Mantel-Haenszel (CMH) Test, adjusted by analysis region. As stated previously, please note that rifaximin's separation from placebo primarily occurs between the beginning of Month Two and the end of Month Three.

Table 7 – Responder Analyses I

	Placebo (N = 159) n/n' (%)	550mg Rifaximin BID (N = 140) n/n' (%)	p-value
Responder Throughout Entire 6 Months	80/153 (52.3%)	100/131 (76.3%)	<0.0001
Responder Throughout First 5 Months	87/154 (56.5%)	102/133 (76.7%)	0.0003
Responder Throughout First 4 Months	92/155 (59.4%)	106/134 (79.1%)	0.0003
Responder Throughout First 3 Months	99/156 (63.5%)	113/136 (83.1%)	0.0002
Responder Throughout First 2 Months	112/156 (71.8%)	119/138 (86.2%)	0.0028
Responder Throughout First 1 Month	135/157 (86.0%)	127/140 (90.7%)	0.2230

Note: n' regards the number of patients at risk during the specified time period.

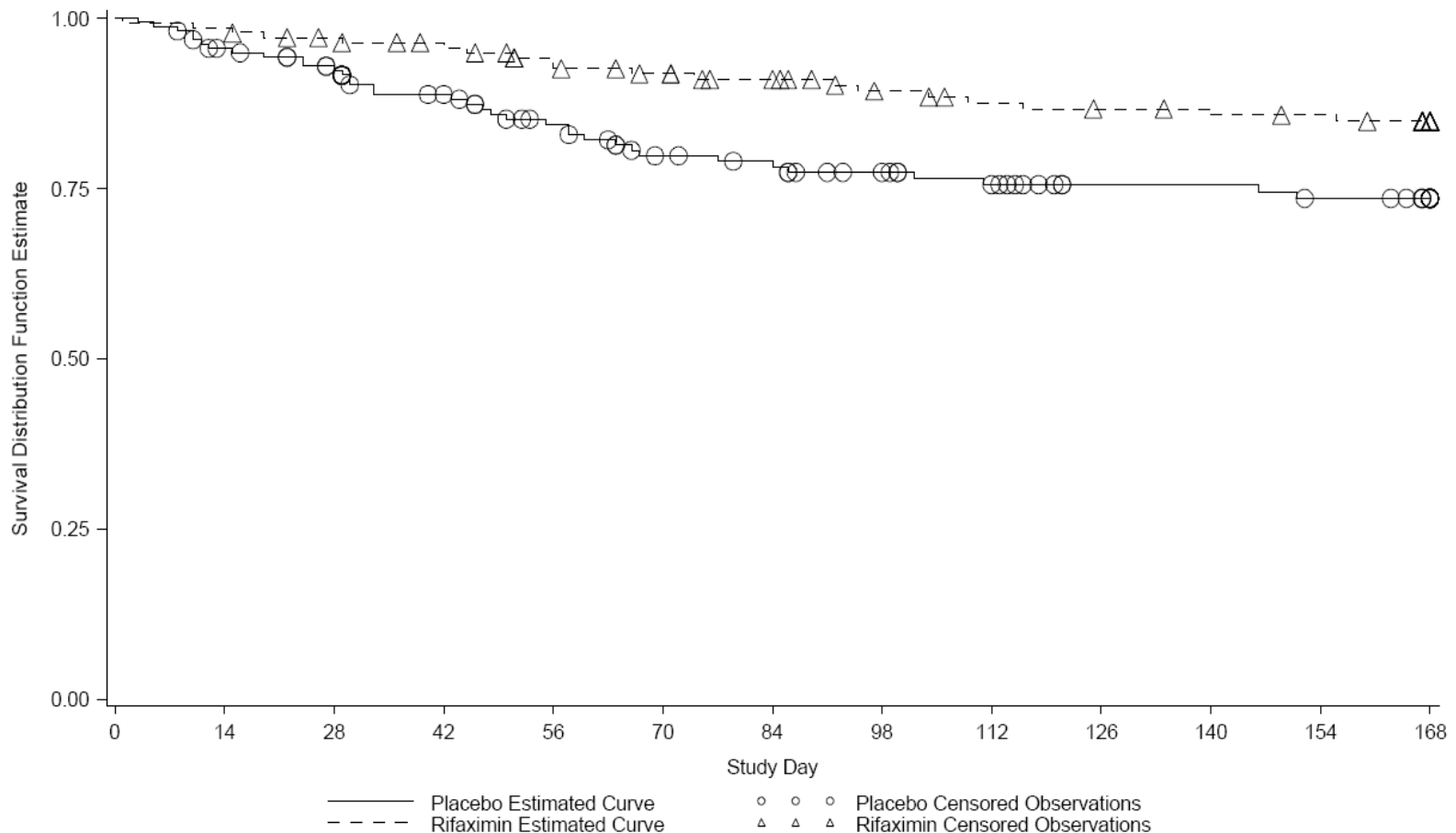
Table 8 – Responder Analyses II

	Placebo (N = 159) n/N (%)	550mg Rifaximin BID (N = 140) n/N (%)	p-value
Responder Throughout Entire 6 Months	80/159 (50.3%)	100/140 (71.4%)	0.0002
Responder Throughout First 5 Months	87/159 (54.7%)	102/140 (72.9%)	0.0013
Responder Throughout First 4 Months	92/159 (57.9%)	106/140 (75.7%)	0.0012
Responder Throughout First 3 Months	99/159 (62.3%)	113/140 (80.7%)	0.0005
Responder Throughout First 2 Months	112/159 (70.4%)	119/140 (85.0%)	0.0030
Responder Throughout First 1 Month	135/159 (84.9%)	127/140 (90.7%)	0.1414

D. Secondary Efficacy Analysis

1. Time to First HE-Related Hospitalization (up to Month Six)

Figure 3 - Kaplan-Meier Plot for Time to First HE-Related Hospitalization (up to Month Six)



The Cox Proportional Hazards model, stratified by region, produced a hazard ratio point estimate of 0.500 along with corresponding 95% CI (0.287, 0.873). The p-value corresponding to the test for treatment effect was 0.0129. The formal test for this endpoint was found to be significant at $\alpha = 0.05$ hence the hypothesis for the next secondary endpoint can be formally tested.

The clinical team felt that the time to first HE related hospitalization might be more reflective of clinical benefit than a 1 or 2 point change in Conn Score because the need for hospitalization may better reflect the clinical impact of severe HE episodes.

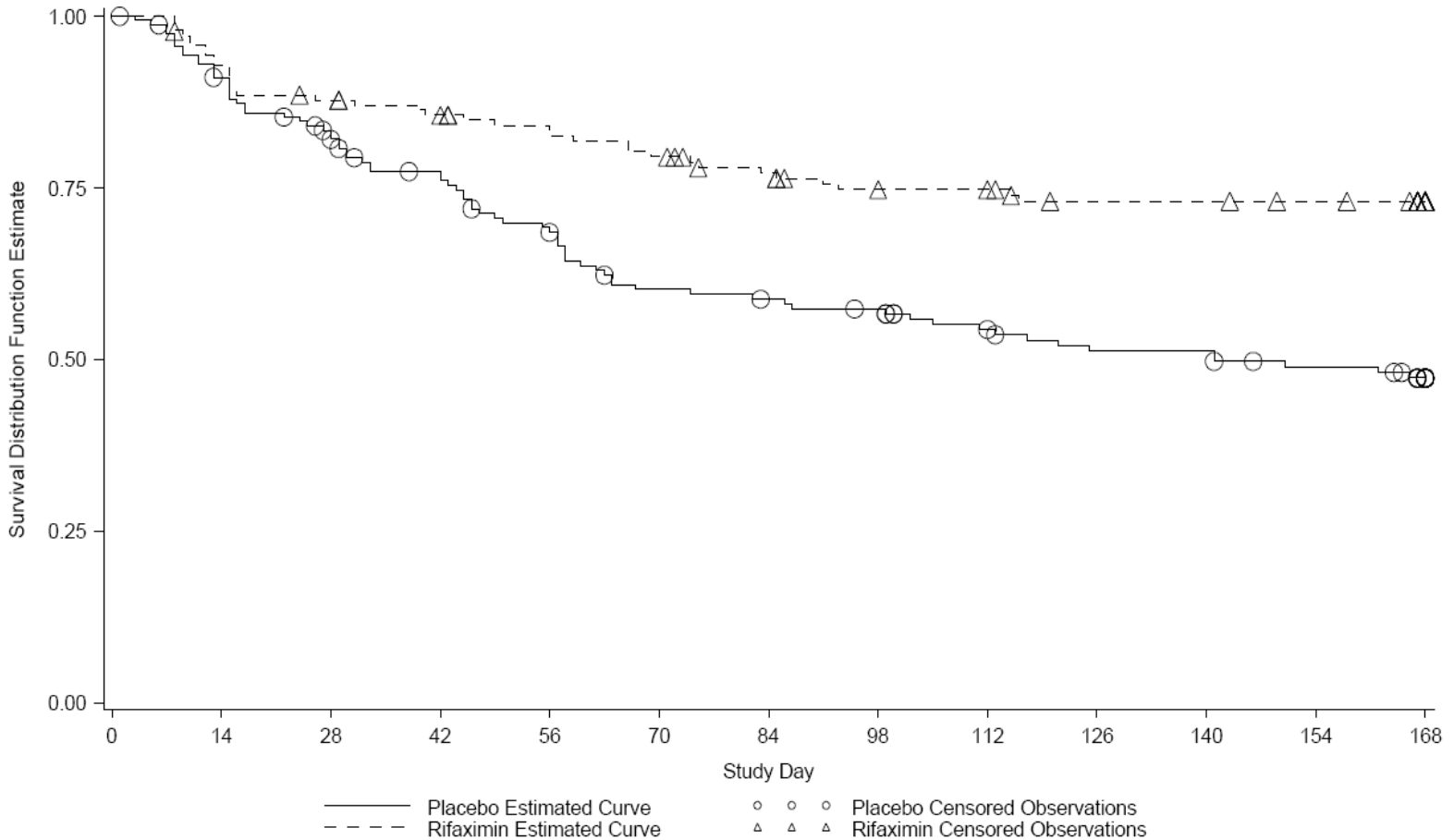
DGP subsequently requested further information from the sponsor with analysis of whether the breakthrough-HE episode resulted in any hospitalization (and the duration of this hospitalization) or not. The sponsor replied that data were not

collected and not available for duration of breakthrough HE episodes. They, however, provided the frequency data below regarding breakthrough HE hospitalizations.

- Breakthrough HE hospitalization: Forty-four (15 rifaximin, 29 placebo) of the 104 subjects diagnosed with a protocol-defined breakthrough HE episode were hospitalized specifically due to the breakthrough HE episode.
- HE-caused hospitalization: In addition to the 44 patients in bullet 1, there were four patients in the placebo group who were hospitalized with a diagnosis of HE, however, the site investigator felt that they did not meet breakthrough criteria. When those patients were included in the analysis, forty-eight (15 rifaximin; 33 placebo) of the 299 subjects had HE-caused hospitalization (i.e., hospitalization directly resulting from breakthrough HE or HE symptoms not meeting breakthrough criteria).
- HE-related hospitalization: In addition to the 44 patients in bullet 1, there were four rifaximin patients and 7 placebo patients who were hospitalized for other reasons but subsequently developed HE while in the hospital. Hence fifty-five (19 rifaximin; 36 placebo) of the 299 subjects had HE-related hospitalization (i.e., hospitalization directly resulting from HE or hospitalization complicated by HE).
- All-cause hospitalization: One hundred six subjects (46 rifaximin; 60 placebo) of the 299 subjects were hospitalized for any reason.

2. Time to Any Increase from Baseline in Conn Score (up to Month Six)

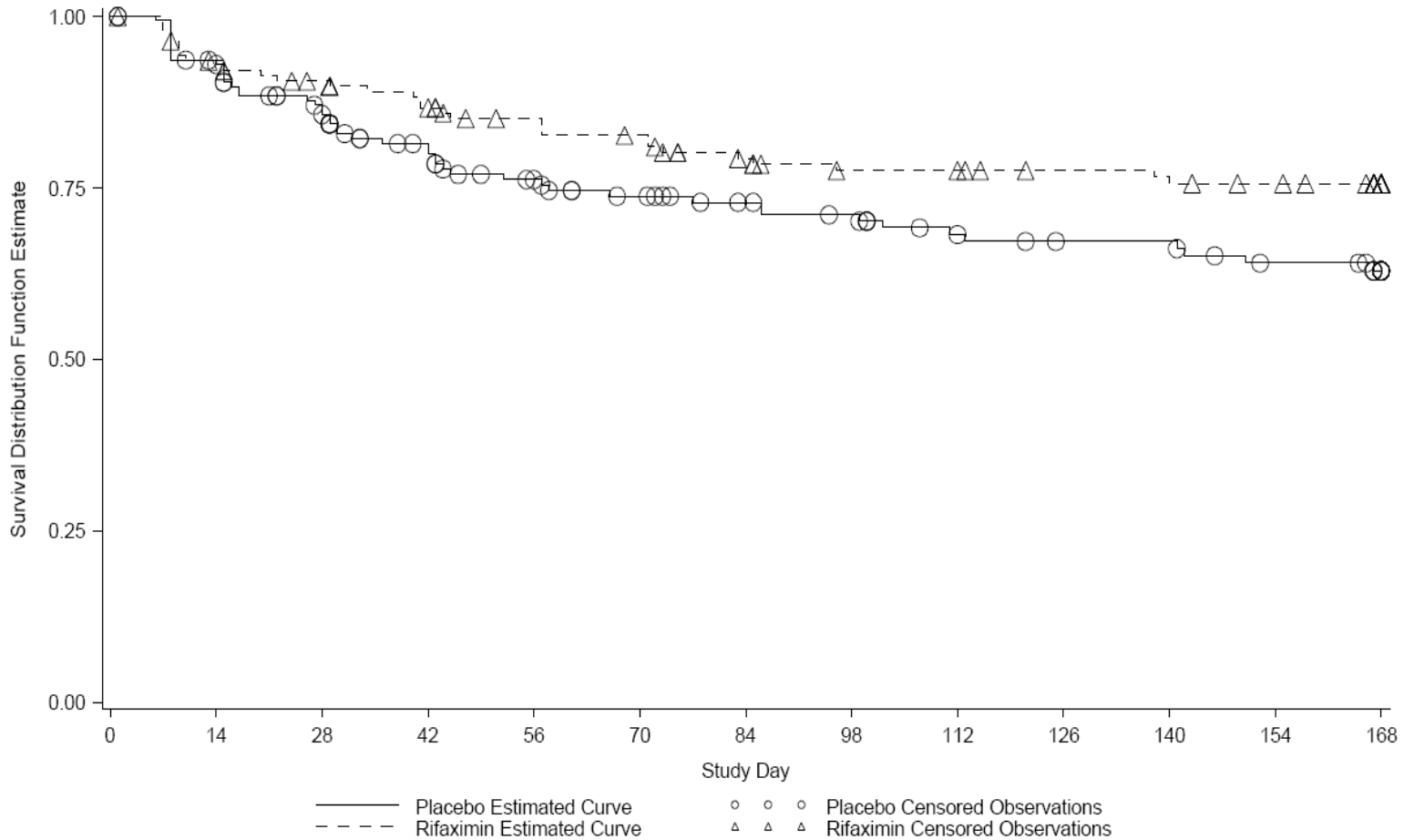
Figure 4 - Kaplan-Meier Plot for Time to Any Increase from Baseline in Conn Score (up to Month Six)



A hazard ratio point estimate of 0.463 was determined along with corresponding 95% CI (0.312, 0.685). The p-value corresponding to the test for treatment effect was <0.0001 . The formal test for this endpoint was found to be significant at $\alpha = 0.05$ hence the hypothesis for the next secondary endpoint can be formally tested.

3. Time to Any Increase from Baseline in Asterixis Grade (up to Month Six)

Figure 5 - Kaplan-Meier Plot for Time to Any Increase from Baseline in Asterixis Grade (up to Month Six)



A hazard ratio point estimate of 0.646 was determined along with corresponding 95% CI (0.414, 1.008). The p-value corresponding to the test for treatment effect was 0.0523. The formal test for this endpoint was not found to be significant at $\alpha = 0.05$ hence we stopped any formal analysis on further secondary efficacy endpoints.

E. Lactulose Usage and its Effect on Interpretability

According to Section 5.6.2 of the finalized (04SEP2008) RFHE3001 protocol, 'Lactulose use is optional for subjects during the study, if lactulose is present at baseline. Lactulose will be available to subjects throughout the study (i.e., from screening through EOS) and, for subjects who use lactulose, it will be titrated to a dose during the 3-to-7-day observation period according to accepted medical practice for this unapproved HE medication. If the subject does not use lactulose then lactulose therapy may not be initiated after baseline unless the subject is withdrawn from the study. Subjects who do not use lactulose prior to screening should not start lactulose during the 3-to-7-day observation period unless the investigator believes there is an immediate need for this concomitant therapy. If lactulose is present at baseline then its use will be permitted as needed throughout the study.'

It was ultimately determined that out of the 299 randomized subjects, 273 of them (128 with rifaximin and 145 with placebo) concurrently used lactulose throughout the treatment period. Based on the previously given protocol passage, one could certainly surmise that of the 273 patients (128 with rifaximin and 145 with placebo) who had prior lactulose use, that none of them would actually take the option of dropping lactulose before study drug initiation. However, this did indeed occur. Three prior-use subjects (762-0002 [rifaximin], 799-0016 [placebo], and 897-0003 [placebo]) declined concurrent use of lactulose during the treatment period. Two of the three, one rifaximin subject and one placebo subject, experienced an overt HE event on study. Furthermore, via a protocol deviation, three non-prior-use subjects (547-0006 [placebo], 882-0003 [placebo], and 905-0002 [rifaximin]) had lactulose newly initiated for concurrent use. These changes offset each other resulting in, as previously indicated, 273 total patients (128 with rifaximin and 145 with placebo) who concurrently took lactulose during the trial.

It was also determined that lactulose usage was balanced across the rifaximin and placebo groups for this 273 patient subset as evidenced by Figure 6 below. Hence based on these joint findings, pivotal study RFHE3001 was technically an add-on study of rifaximin+lactulose vs. placebo+lactulose. (Note that the primary efficacy results using the 26 patients [12 with rifaximin and 14 with placebo] who did not partake in concurrent lactulose usage [regardless of the nature of these results; in this case, not compelling] are technically not generalizable due to the relatively small set of patients.) As a consequence, the primary efficacy analysis and all secondary efficacy analyses were re-administered by FDA on this 273 patient subset who did take lactulose while on study. The principal results of this exploratory analysis are presented in Table 9 below. The only change in results for a re-tested endpoint pertained to the time to increase from baseline in asterixis grade.

Figure 6 – Average Daily Lactulose Use

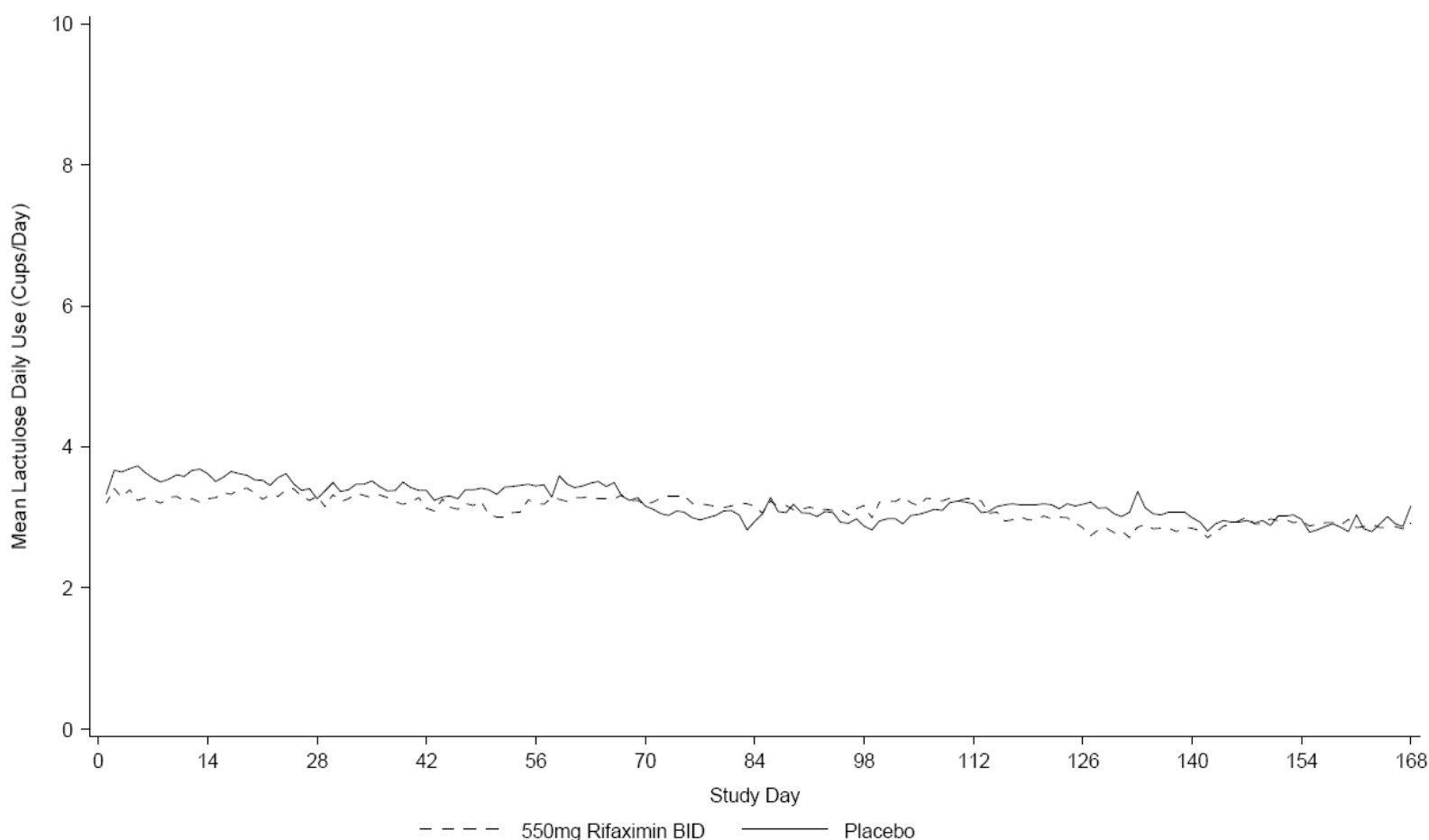


Table 9 – Principal Results for All Re-Administered Efficacy Endpoint Analyses

Efficacy Endpoint Analysis	Hazard Ratio Point Estimate	Hazard Ratio 95% CI	Treatment Effect p-value
Time to First Breakthrough HE Episode (up to Month Six)	0.417	(0.272, 0.639)	<0.0001
Time to First HE-Related Hospitalization (up to Month Six)	0.501	(0.283, 0.888)	0.0158
Time to Any Increase from Baseline in Conn Score (up to Month Six)	0.439	(0.292, 0.660)	<0.0001
Time to Any Increase from Baseline in Asterixis Grade (up to Month Six)	0.575	(0.363, 0.909)	0.0166

F. Conn Score and Asterixis Grade Assessments

Breakthrough HE episodes were either evaluated in-person by trained study personnel or retrospectively reviewed (i.e. not done or evaluated at a study visit). The evaluation type (i.e., direct by site personnel or indirect) was only recorded for 100 of the 104 total patients in the study who had breakthrough HE episodes. The evaluation type was not recorded for the four patients (1 rifaximin and 3 placebo) who experienced breakthrough HE after discontinuation but within six months of first dose. In addition, the evaluation type (direct or indirect) was not recorded at site visits for patients who did not have breakthrough HE episodes. Of the 100 patients for which these data were accessible, 38 were evaluated in-person by trained study personnel (8 rifaximin and 30 placebo), and 62 were retrospectively reviewed (22 rifaximin and 40 placebo).



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date:

To:

Donna Griebel, MD, Director
Division of Gastrointestinal Products (DGP)

Through:

Mark Avigan, MD, CM, Director
Division of Pharmacovigilance I (DPV I)
Lanh Green, PharmD, MPH
Safety Evaluator Team Leader DPV I

From:

Ann Corken Mackey, RPh, MPH
Safety Evaluator, DPV I
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Drug Use Data Analyst
Division of Epidemiology

Subject:

Safety profile

Drug Name(s):

Rifaximin (Xifaxan)

Application

22-554

Type/Number:

Applicant/sponsor:

Salix Pharmaceuticals, Inc.

OSE RCM #:

2009-1407

1 INTRODUCTION

DGP has requested that DPV identify any safety signals associated with rifaximin (Xifaxan) use, a locally-acting antibiotic (rifamycin class) approved by the Division of Special Pathogens in May 2004 for the short-term treatment (3 days) of Traveler's diarrhea caused by noninvasive strains of *Escherichia coli* in patients ≥ 12 years of age.¹ The sponsor, Salix Pharmaceuticals, is proposing an additional indication of "maintenance of remission of hepatic encephalopathy," an indication that may involve long-term use; their supporting data include one placebo-controlled 6 month study (review ongoing) and one ongoing 2-year safety study. Rifaximin is approved in ten other countries for the treatment or maintenance of remission of hepatic encephalopathy (HE). Salix Pharmaceuticals has obtained Orphan Designation for this application.

Systemic absorption of oral rifaximin is 0.4%. Labeled adverse events include gastrointestinal disorders (e.g., abdominal distension, diarrhea), general disorders (e.g., chest pain, fatigue, malaise), nervous system disorders (e.g., abnormal dreams, dizziness, syncope), renal and urinary disorders (e.g., hematuria, dysuria, urinary frequency), respiratory disorders (e.g., dyspnea, pharyngitis), and skin disorders (e.g., rash, increased sweating). The Postmarketing adverse events section includes hypersensitivity reactions (e.g., exfoliative dermatitis, rash, angioneurotic edema, urticaria, pruritus).¹ (See Appendix 1 for the Warnings and Adverse Reactions sections of the rifaximin label.)

On March 7, 2006, an OSE review was performed due to receipt of an AERS report of eosinophilia, an unlabeled event, associated with rifaximin use.² The review described cases of eosinophilia as well as other allergic phenomena. The patient who developed eosinophilia continued rifaximin therapy and eosinophilia resolved. In addition to the hypersensitivity adverse events listed in the Postmarketing section of the label, based on two confounded cases, the review recommended that anaphylaxis be added; despite the review conclusion, it appears that anaphylaxis was not added to the January 2007 version of the rifaximin label.

2 MATERIAL REVIEWED

Adverse Event Reporting System (AERS): AERS was searched from May 2004 (approval of rifaximin to treat Traveler's diarrhea) to August 31, 2009 using the drug name rifaximin (Xifaxan). Three separate searches were performed as follows:

1. All adverse events (involves all reasons for use),
2. Adverse events related to rifaximin use to treat or prevent HE using the search strategy specified above along with the reported indications of *hepatic encephalopathy* and *hepatic encephalopathy prophylaxis* using MedDRA Preferred Terms [PTs], and
3. All deaths (all adverse events with the outcome of death).

All adverse events (all reported indications for use; n=173 [note raw data, duplicates could exist]): A PT printout was generated to identify adverse events reported for rifaximin. The top 21 reported MedDRA Preferred Terms (n ≥ 5) included the following:

¹ Xifaxan (rifaximin) product label, Salix Pharmaceuticals, revised January 30, 2007.

² Gish P. Rifaximin: eosinophilia and other allergic phenomena, March 7, 2006, PID# D050716.

Diarrhea* (n=30)	Pyrexia* (n=7)
Abdominal pain* (n=15)	Asthenia (n=6)
Condition aggravated (n=15)	Dyspnoea* (n=6)
Drug ineffective (n=14)	Malaise* (n=6)
Headache* (n=12)	Rash* (n=6)
Nausea* (n=12)	Abdominal pain upper* (n=5)
Flatulence* (n=9)	Anemia (n=5; these cases are described below)
Abdominal distension* (n=8)	<i>Clostridium difficile</i> colitis* (n=5)
Myalgia* (n=8)	Insomnia* (n=5)
Vomiting* (n=8)	Oedema peripheral (n=5)
Dehydration* (n=7)	

* Labeled events for rifaximin (see Appendix 1 for the Warnings and Adverse Reactions sections of the label)

Because of a potential safety signal for **anemia**, these 5 cases were reviewed separately. Of the 5 cases, 2 patients were using rifaximin to treat bacterial overgrowth (a 9-year-old female developed "bloody G-tube output" [patient also was receiving warfarin] and a 67-year-old female had underlying acute kidney failure and anemia resulting from interstitial nephritis due to rifampin use [consumer reporter who listed Xifaxan as suspect drug, but discussed rifampin in narrative]). The 3 remaining patients were using rifaximin to treat HE (these reports are described below as well): a 53-year-old male developed numerous adverse events including anemia due to underlying conditions including HE, a 50-year-old female developed anemia and thrombocytopenia secondary to cirrhosis per discharge summary, and a 59-year-old male developed complications including anemia due to infectious colitis from *Campylobacter* (reporter suspected that rifaximin altered intestinal flora). It appears that most of these cases were confounded by the patients' underlying medical condition and/or concomitant medications.

In addition, a line listing report found that uses for rifaximin, other than Traveler's diarrhea, included HE (not a labeled indication in the US), Crohn's disease, irritable bowel syndrome, ulcerative colitis, and colitis. A separate search found that the duration of use for rifaximin was reported for 118 out of 173 reports; 64 of the 118 reports stated a duration of use > 3 days (mean=25 days, range=4 to 369 days). Note that these are raw data, duplicates could exist. The majority of the 64 reports mentioned nonserious events (e.g., GI symptoms, rash); adverse events such as pancytopenia, anaphylaxis, thrombocytopenia, and *Campylobacter* infection occurred in patients using rifaximin to treat HE and are described below. Of the 64 cases, 5 cases were reviewed because they described serious events: thrombocytopenia (reporter felt the event could have been due to concomitant vancomycin or metronidazole), thrombocytopenia/cerebral hemorrhage (87 yo male with infectious colitis, reporter suspected post transfusion purpura and was awaiting test results), rectal hemorrhage/pleural effusion (patient with underlying Crohn's disease; source of bleeding not identified [consumer report]), dyspnea/edema/atrial fibrillation/myocarditis (12yo female hospitalized because of dyspnea found to have myocarditis; little information provided in this foreign case), and amoebic colitis/GI necrosis (foreign patient developed amoebic colitis that progressed to megacolon and perforation; she required colectomy).

Adverse events associated with prevention/treatment of HE (n=21 [deduplicated cases]): Since rifaximin is not approved domestically for this indication, at least 6 of these reports involved study patients and one case involved a foreign patient. The mean duration for patients using rifaximin to prevent or treat HE was 32 days; the range was 2 to 180 days (duration of use reported for 17 patients; 16 out of 17 patients used rifaximin > 3 days). All 21 cases are described below.

Of the 21 cases, 2 cases provided little information to determine causality (reported as tongue discoloration and ataxia) and 1 case was reported as worsening HE (patient had additional adverse events, but all were related to worsening HE).

Eleven cases reported labeled events: chest pain/pruritus (1), fatigue (1), frequent bowel movements (1), respiratory problems (1), vomiting (1), anaphylaxis/angioedema (1; the time to onset was 2 weeks; the patient was also receiving ramipril for 3-4 months [page 2 of this report was missing making it difficult to evaluate the case]; hypersensitivity reactions, but not anaphylaxis, are labeled), *C. difficile/campylobacter* (5; the label states that antibacterial agents alter normal flora of the colon; one reporter felt that the patient's infections were related to changes in gut flora). Of these 11 cases, 1 patient died (patient developed *C. difficile*; see description below) and 5 patients were hospitalized because of their adverse events (I.e., respiratory problems [1], anaphylaxis/angioedema [1], *C. difficile* [3]).

Two cases reported bleeding disorders due to thrombocytopenia; one reporter stated that thrombocytopenia was secondary to cirrhosis (both patients were hospitalized).

The remaining 5 cases reported the following adverse events: suicidal ideation/increased eosinophil count (1; eosinophilia was an incidental finding; his count was 5000, but resolved while the patient continued rifaximin therapy; little information was provided), increased blood glucose/vomiting (1; the reporter felt that patient may have had underlying pancreatic dysfunction), worsening chronic renal failure (1), edema of lower extremities/scrotal swelling (1), and pancytopenia/worsening HE/skin disorder (1; this patient's WBC, RBC, platelets, hemoglobin, and hematocrit were decreased before initiating rifaximin; little information was provided). Of these 5 cases, 4 patients were hospitalized for their events (i.e., suicidal ideation, increased blood glucose, edema of lower extremities, pancytopenia).

All deaths (n=2 [deduplicated cases]): The search identified two fatalities involving patients using rifaximin to prevent HE (n=1) or to treat small intestinal bacterial overgrowth (1). The former patient (62-year-old male) used 1200 mg of rifaximin a day for 30 days (ceftriaxome listed as concomitant medication, but dates of administration were not reported); he developed *C. difficile* diarrhea and died 22 days later due to "complications of liver disease worsened by *C. difficile* diarrhea." The later patient (85-year-old female with end-stage renal failure) used 600 mg of rifaximin a day for 7 days; she hit her head and was found dead in the bathroom (exact cause of death not known, the reporter did not feel that it was related to rifaximin).

Literature: A review article summarizing studies in which rifaximin was used to treat HE found that only minor gastrointestinal (GI) adverse events were reported (approximately 180 patients in seven studies; exact number of patients who developed GI adverse events was not reported).³

Drug use: There was an increase in the rifaximin market from 2004 to 2007; use has been the same from 2007 to 2009. Gastroenterologists were the primary prescribers for rifaximin. See Appendix 2 for information on number of prescriptions dispensed, prescribing specialties, and diagnosis for use.

³ Maclayton DO, Eaton-Maxwell A. Rifaximin for treatment of hepatic encephalopathy. *Ann Pharmacother* 2009; 43: 77-84.

4. DISCUSSION

Rifaximin is an locally-acting, broad-spectrum antibiotic with a specific domestic indication for treatment of Travelers diarrhea caused by noninvasive strains of *Escherichia coli* in patients ≥ 12 years of age.¹ Its use in the prevention/treatment of HE is based on the drug's ability to reduce the concentration of urease-bacteria in the colon (with severe liver impairment, toxic substances such as urease-bacteria which are normally removed by the liver accumulate in the blood and impair cerebral function).³

Overall, most of the adverse events associated with rifaximin use identified in AERS are labeled or possibly related to the patients' underlying conditions. Most of the adverse events that have been reported reported for patients receiving rifaximin to treat HE are labeled (some of these patients were in studies and the events reported are not considered spontaneous). In addition, antibiotics such as rifaximin, are known to cause changes in gut flora possibly leading to infection. No new safety signals were found in AERS or the literature in patients using rifaximin. There was one death described as possibly related to rifaximin use in a patient who developed *C. difficile* (the Warnings section of the product label discusses overgrowth of gut flora associated with antibiotic use with *C. difficile* as the primary cause). Note that rifaximin has been also been used to treat *C. difficile*; however, strains with decreased susceptibility have been identified.⁴ Given that the systemic absorption of rifaximin after oral administration is 0.4%, few adverse events would be expected.

The current domestic label recommends use of rifaximin for 3 days only to treat Traveler's diarrhea. It appears that many patients in this case series used rifaximin beyond 3 days and for treatment of conditions other than Traveler's diarrhea (e.g., HE [not an approved indication in the US], Crohn's disease, irritable bowel syndrome, bacterial overgrowth). Based on AERS data in this case series, no conclusions can be made regarding safety for short-term (3 day) versus long-term use for most of the adverse events identified; events such as bacterial overgrowth are known to occur with antibiotic use.

5. CONCLUSIONS AND RECOMMENDATIONS

Overall, many of the adverse events identified in this review are labeled (e.g., hypersensitivity reactions, gastrointestinal complications); other adverse events may be related to the patients' underlying conditions. Most of the adverse events reported for patients receiving rifaximin to treat HE are labeled (some of these patients were in studies and the events reported are not considered spontaneous). There are no new safety signals associated with rifaximin use. Based on AERS data in this case series, no conclusions can be made regarding safety for short-term (3 day) versus long-term use for most of the adverse events identified; events such as bacterial overgrowth are associated with antibiotics and are a concern for long term use of rifaximin.

Because of reports of *C. difficile* (including one fatality), DGP should consider including in the Adverse Events Postmarketing section of the label (in addition to the Warnings section) that cases of rifaximin-induced *C. difficile* colitis have been reported.

⁴ O'Connor JR, Galand MA, Sambol SP et al. Rifampin and rifaximin resistance in clinical isolates of *Clostridium difficile*. Antimicrob Agents Chemother 2008; 52(8): 2813-7.

Appendix 1

Warnings and Adverse Reactions Sections of the Rifaximin Label¹

WARNINGS

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of “antibiotic-associated colitis.”

ADVERSE REACTIONS

The safety of XIFAXAN® Tablets 200 mg taken three times a day (TID) was evaluated in 320 patients in two placebo-controlled clinical trials with 95% of patients receiving at least three days of treatment with XIFAXAN® Tablets. All adverse events for XIFAXAN® Tablets 200 mg TID that occurred at a frequency $\geq 2\%$ in the two placebo-controlled trials combined are provided in Table 2. (These include adverse events that may be attributable to the underlying disease.)

The following adverse events, presented by body system, have also been reported in $<2\%$ of patients taking XIFAXAN® Tablets in the two placebo-controlled clinical trials where the 200 mg taken three times a day dose was used.

Table 2. All Adverse Events With an Incidence $\geq 2\%$ Among Patients Receiving XIFAXAN™ Tablets, 600 mg/day, in Placebo-Controlled Studies

	Number (%) of Patients	
	XIFAXAN™ Tablets, 600 mg/day (N = 320)	Placebo N = 228
MedDRA Preferred Term		
Flatulence	36 (11.3%)	45 (19.7%)
Headache	31 (9.7%)	21 (9.2%)
Abdominal Pain NOS	23 (7.2%)	23 (10.1%)
Rectal Tenesmus	23 (7.2%)	20 (8.8%)
Defecation Urgency	19 (5.9%)	21 (9.2%)
Nausea	17 (5.3%)	19 (8.3%)
Constipation	12 (3.8%)	8 (3.5%)
Pyrexia	10 (3.1%)	10 (4.4%)

The following includes adverse events regardless of causal relationship to drug exposure.

Blood and Lymphatic System Disorders: lymphocytosis, monocytosis, neutropenia

Ear and Labyrinth Disorders: ear pain, motion sickness, tinnitus

Gastrointestinal Disorders: abdominal distension, diarrhea NOS, dry throat, fecal abnormality

NOS, gingival disorder NOS, inguinal hernia NOS, dry lips, stomach discomfort

General Disorders and Administration Site Conditions: chest pain, fatigue, malaise, pain NOS, weakness

Infections and Infestations: dysentery NOS, respiratory tract infection NOS, upper respiratory tract infection NOS

Injury and Poisoning: sunburn

Investigations: aspartate aminotransferase increased, blood in stool, blood in urine, weight decreased

Metabolic and Nutritional Disorders: anorexia, dehydration

Musculoskeletal, Connective Tissue, and Bone Disorders: arthralgia, muscle spasms, myalgia, neck pain

Nervous System Disorders: abnormal dreams, dizziness, migraine NOS, syncope, loss of taste

Psychiatric Disorders: insomnia

Renal and Urinary Disorders: choluria, dysuria, hematuria, polyuria, proteinuria, urinary frequency

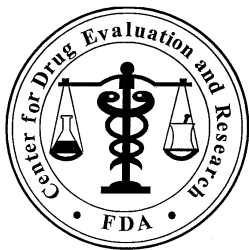
Respiratory, Thoracic, and Mediastinal Disorders: dyspnea NOS, nasal passage irritation, nasopharyngitis, pharyngitis, pharyngolaryngeal pain, rhinitis NOS, rhinorrhea

Skin and Subcutaneous Tissue Disorders: clamminess, rash NOS, sweating increased

Vascular Disorders: hot flashes NOS

Postmarketing Experience

The following events: hypersensitivity reactions, including exfoliative dermatitis, rash, angioneurotic edema (swelling of face and tongue and difficulty swallowing), urticaria, flushing, and pruritus; have been identified during post-approval use of XIFAXAN® Tablets. These events occurred as early as within 15 minutes of drug administration.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date:

To:

Donna Griebel, MD, Director
Division of Gastrointestinal Products (DGP)

Through:

Mark Avigan, MD, CM, Director
Division of Pharmacovigilance I (DPV I)
Lanh Green, PharmD, MPH
Safety Evaluator Team Leader DPV I

From:

Ann Corken Mackey, RPh, MPH
Safety Evaluator, DPV I
Patty Greene, PharmD
Drug Use Data Analyst
Division of Epidemiology

Subject:

Safety profile

Drug Name(s):

Rifaximin (Xifaxan)

Application

22-554

Type/Number:

Applicant/sponsor:

Salix Pharmaceuticals, Inc.

OSE RCM #:

2009-1407

3 INTRODUCTION

The Division of Gastroenterology Products (DGP) is evaluating safety signals associated with the use of Xifaxan[®] (rifaximin) for the indication of maintenance therapy for the remission of hepatic encephalopathy. In support of that assessment, the Division of Epidemiology (DEPI) has been requested to provide total dispensed prescription, prescribing specialty, and diagnosis data for rifaximin from July 1, 2004 to June 30, 2009.

4 METHODS AND MATERIAL

4.1 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives[™] data (*see Appendix 2*) were used to determine the setting in which rifaximin tablets were sold. Sales of these products by number of bottles (eaches) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for year 2008 (*data not provided*).⁵ During this period, retail pharmacy settings (chain stores, independent pharmacies, and food stores) accounted for the majority of rifaximin sales (76%). Non-retail and mail order pharmacy accounted for 12% and 11%, respectively, of rifaximin sales. Thus, the examination of rifaximin utilization patterns focused on the outpatient setting.

4.2 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

We examined total outpatient dispensed prescriptions by quarter and prescribing specialty for rifaximin using the SDI: Vector One[®]: National (VONA) (see Appendix 2 for full description) from July 2004 to June 2009. Diagnosis associated with the use of these products, as reported by office-based physicians, were determined using SDI's Physician Drug and Diagnosis Audit (PDDA) for the same period.

5 RESULTS

Figure 1/Table 1 (*Appendix 1*) provides the total number of dispensed prescriptions for rifaximin by quarter in U.S. outpatient retail pharmacies from July 1, 2004 to June 30, 2009. For the entire review period, nearly 860,000 total prescriptions were dispensed in outpatient retail pharmacy settings. Overall, prescription utilization increased by 108%, a 2-fold increase, from 4th quarter 2005 to 4th quarter 2008. By 1st quarter 2007, dispensed prescriptions for rifaximin reached its highest point during this study period at approximately 61,000 prescriptions. However, a 7% decline in prescription utilization was noted between 2nd quarter 2007 through 2nd quarter 2009.

⁵ IMS Health, IMS Nationals Sales Perspectives[™], Year 2008 Data extracted 09-08-2009 Source file: 0909rifa.DVR

Table 2 (*Appendix 1*) provides the total number of dispensed prescriptions for rifaximin in outpatient retail pharmacies by the top 10 prescribing specialties. From July 2004 to June 2009, Gastroenterology was the top prescribing specialty for rifaximin with approximately 55% of total dispensed prescriptions. Internal Medicine was the second most common prescribing specialty with approximately 14% of total dispensed prescriptions. Infectious Disease specialists accounted for approximately 2% of total dispensed prescription over the entire review period.

Based upon a survey of U.S. office-based physician practices from July 2004 to June 2009, diagnosis codes associated with the use of rifaximin are provided in Table 3 (*Appendix 1*). “GI System Symptoms NEC” (ICD-9 787.9) was the most common diagnosis code associated with the use of rifaximin at approximately 29% followed by “Infectious diarrhea NOS” (ICD-9 009.2) at 16% and “Irritable colon” (ICD-9 564.1) at 15%. All other diagnoses were below the acceptable count allowable to provide a reliable estimate of use. For the entire review period, the diagnosis code for “Hepatic Coma” (ICD-9 572.2) was mentioned approximately 1% of the time by physician survey for rifaximin. “Hepatic Coma” (ICD-9 code 572.2) includes the following diagnosis codes: hepatic encephalopathy, hepatocerebral intoxication and portal-systemic encephalopathy.⁶

6 LIMITATIONS

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated rifaximin tablets are distributed primarily to outpatient settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these channels may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Indications for use were obtained using SDI’s PDDA, a monthly survey of 3,200 office-based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for the products in clinical practice, and the VONA outpatient prescription data to evaluate trends over time.

7 CONCLUSIONS

Total dispensed prescriptions for Xifaxan® (rifaximin) increased 108% from quarter 4 2005 to quarter 4 2008. The top prescribing specialty for rifaximin is Gastroenterology. The most common diagnoses associated with the use of rifaximin were “GI System Symptoms NEC” (ICD-9 787.9), “Infectious diarrhea NOS” (ICD-9 009.2), and “Irritable colon” (ICD-9 564.1). The diagnosis code for “Hepatic Coma” (ICD-9 572.2) was mentioned approximately 1% of the time by physician survey for rifaximin.

⁶ Website: www.ICD9.chrisendres.com Year 2009

Appendix 1 – Figure and Tables

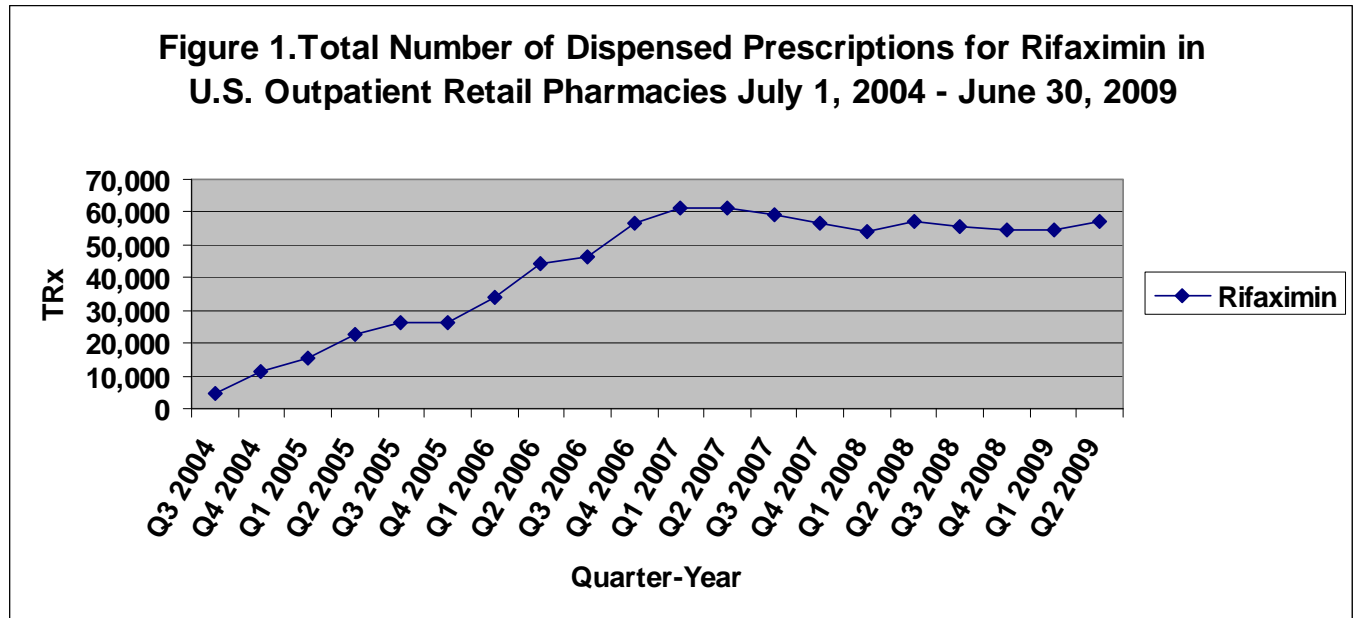


Table 1. Total number of dispensed prescriptions by quarter for Rifaximin in U.S. outpatient retail pharmacies, July 1, 2004 - June 30, 2009

	JUL - DEC 2004		2005				2006				2007				2008				JAN - JUN 2009	
	Q3 2004	Q4 2004	Q1 2005	Q2 2005	Q3 2005	Q4 2005	Q1 2006	Q2 2006	Q3 2006	Q4 2006	Q1 2007	Q2 2007	Q3 2007	Q4 2007	Q1 2008	Q2 2008	Q3 2008	Q4 2008	Q1 2009	Q2 2009
Rifaximin	4,440	11,549	15,698	22,765	26,075	26,285	33,823	44,117	46,568	56,467	61,333	61,283	59,092	56,400	53,881	56,929	55,376	54,661	54,502	57,035

Source: SDI Vector One®: National, Data Extracted 9-2009. File: VONA 2009-1407 Rifaximin 09-08-09.xls

Table 2. Total number of dispensed prescriptions for Rifaximin in outpatient retail pharmacies by top 10 prescribing specialties, July 1, 2004 to June 30, 2009

	7/2004-6/2009	
	TRxs	Share %
Rifaximin	858,281	100.0%
GASTROENTEROLOGY	470,548	54.8%
INTERNAL MEDICINE	119,802	14.0%
GP/FM/DO	60,181	7.0%
UNSPEC	58,080	6.8%
HOSPITAL	20,062	2.3%
INFECTIOUS DISEASES	19,792	2.3%
NURSE PRACTITIONER	18,077	2.1%
PHYSICIAN ASSISTANT	13,312	1.6%
PEDIATRICS	12,714	1.5%
ALL OTHER SURGERY	11,991	1.4%
All Others	53,722	6.3%

Source: SDI Vector One®: National, Data Extracted 9-2009. File: VONA 2009-1407 Rifaximin MD 09-08-09.xls

*GP/FM/DO – General Practice, Family Medicine, Doctor of Osteopathy

Table 3. Diagnoses associated with the use* of Rifaximin as reported by office-based physician practices, July 1, 2004 to June 30, 2009

	7/2004-6/2009	
	Uses (000)	Share %
Rifaximin	713	100.0%
7879 GI SYSTEM SYMPTOMS NEC	209	29.3%
0092 INFECTIOUS DIARRHEA NOS	112	15.8%
5641 IRRITABLE COLON	106	14.8%
7873 FLATUL/ERUCTAT/GAS PAIN	70	9.7%
5715 CIRRHOSIS OF LIVER NOS	27	3.8%
5589 NONINF GASTROENTERIT NEC	24	3.3%
0084 BACTERIAL ENTERITIS NEC	23	3.2%
5559 REGIONAL ENTERITIS NOS	14	2.0%
7890 ABDOMINAL PAIN	13	1.8%
5621 DIVERTICULA OF COLON	12	1.6%
V728 EXAMINATION NEC	10	1.4%
3483 ENCEPHALOPATHY NEC	10	1.4%
5308 ESOPHAGEAL DISORDER NEC	10	1.4%
5368 STOMACH FUNCTION DIS NEC	9	1.2%
5722 HEPATIC COMA	8	1.1%
5569 ULCERATIVE COLITIS NOS	7	1.0%
5712 ALCOHOL CIRRHOSIS LIVER	7	0.9%
0707 VIRAL HEPATITIS C UNSPEC	6	0.9%
7872 DYSPHAGIA	5	0.8%
5660 ANAL & RECTAL ABSCESS	5	0.7%
V078 PROPHYLACTIC MEASURE NEC	5	0.7%
1539 MALIGNANT NEO COLON NOS	5	0.7%
2113 BENIGN NEOPLASM LG BOWEL	4	0.5%
5640 CONSTIPATION	4	0.5%
1369 INFECT/PARASITE DIS NOS	3	0.5%
5609 INTESTINAL OBSTRUCT NOS	3	0.5%
7870 NAUSEA AND VOMITING	3	0.5%

Source: SDI Physician Drug and Diagnosis Audit, Extracted September 2009. File: PDDA 2009-1407 Rifaximin 09-08-09.xls

* Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease.

Appendix 2 – Description of all data sources used

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002, Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the database account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Physician Drug & Diagnosis Audit (PDDA)

SDI's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS

NDA #: 21361 (S-011, SDN #100)
and 22554 (S-06, SDN #1)

REVIEWER : Anne Purfield
CORRESPONDENCE DATE : 7-21-09; 6-24-09
CDER RECEIPT DATE : 7-22-09; 6-26-09
REVIEW ASSIGN DATE : 8-25-09
REVIEW COMPLETE DATE: 10-07-09

APPLICANT: Salix Pharmaceuticals, Inc.
1700 Perimeter Dr
Morrisville, NC 27560

DRUG CATEGORY: Antibacterial

INDICATION: Treatment of travelers' diarrhea
Treatment of hepatic encephalopathy (NDA #22554 under review in
Division of Gastroenterology Products)

DOSAGE FORM: Tablet for oral administration

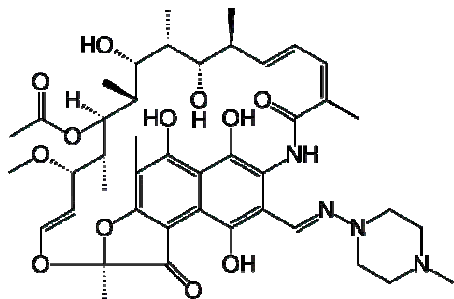
PRODUCT NAMES:

a. **PROPRIETARY:** Xifaxan®

b. **NONPROPRIETARY:** Rifaximin

c. **CHEMICAL:** (2S,16Z,18E,20S,21S,22R,23R,24R,25S,26S,27S,28E)-
5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-
octamethyl-2,7-(epoxypentadeca-[1,11,13]trienimino)benzofuro
[4,5-e]pyrido[1,2-a]-benzimidazole-1,15(2H)-dione,25-acetate

STRUCTURAL FORMULA:



Molecular weight: 785.879
Molecular formula: C₄₃H₅₁N₃O₁₁

SUPPORTING DOCUMENTS: NDA #22554, NDA #21361

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1. Executive Summary

Rifaximin (Xifaxan®) is approved for the treatment of patients (≥ 12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli*. In this submission, the applicant has included three nonclinical and two clinical studies to support the above statements. The applicant is seeking approval for changes to the label that include PLR formatting and add additional information to the Microbiology Section 12.4 that include

- rifaximin has a unique mechanism of action which results in a lower rate of pathogen eradication and a lack of alteration of the gut flora in patients treated with rifaximin compared to fluoroquinolones and aminoglycosides.
- rifaximin may alter virulence factors of enteric bacterial pathogens without killing them, which has been seen with subtherapeutic levels of drugs and colonization fimbriae of enterotoxigenic *E. coli*.
- morphological changes are observed when susceptible or resistant bacteria are exposed to low concentrations of rifaximin.
- rifaximin reduces the viability and virulence of resistant bacteria.

Of the 3 nonclinical studies, one study by Debbia *et al.*, 2008³, describe the effects of bacterial exposure to sub-inhibitory rifaximin concentrations in vitro, including induced resistance and virulence mechanisms such as plasmid stability and frequency of plasmid transfer. However, the description of methods and results are inadequate to support the applicant's statements. For example, colonization of fimbriae was not described in this study and appropriate controls for virulence factors and morphological changes were not included. Fimbriae are external structures of Gram negative bacteria which enable the bacteria to adhere to host cells and promotes persistence of infection. The other two studies either did not include testing of rifaximin (Vosbeck *et al.*, 2008) or the method used was not specified (Jiang *et al.*, 2005).

Two clinical trials by Dupont *et al.*, 1998⁴, and 2001⁵, describe the efficacy of rifaximin treatment for traveler's diarrhea. DuPont *et al.*, 1998⁴, show that patients with traveler's diarrhea have a lower rate of treatment failure when treated with rifaximin compared to TMP/SMX; however the duration of diarrhea is not statistically different. However, an aminoglycoside was not used as a comparator in either trial, as the applicant proposes to state in the labeling. Similarly, the other study by Dupont *et al.*, 2001⁵ shows that clinical outcome, microbiologic cure, and the number of treatment failure were not statistically different for patients treated with rifaximin or ciprofloxacin. The two clinical studies (DuPont *et al.*, 1998⁴ and DuPont *et al.*, 2001⁵) did not compare the rate of pathogen eradication between rifaximin and an aminoglycoside, nor did either study correlate such changes with significant alteration of gut flora or describe a unique mechanism of action.

In summary, the referenced publications included for review do not support the applicant's proposed changes to the microbiology section of the rifaximin labeling.

2. Introduction and Background

Rifaximin (Xifaxan®) is approved by FDA for treatment of patients (≥ 12 years of age) with travelers' diarrhea caused by noninvasive strains of *E. coli*. Rifaximin is approved for use in 27 countries, including Mexico and countries in Europe, Northern Africa and Asia. In this submission, the applicant is seeking approval of changes to the label that include PLR formatting and changes to the Microbiology Section 12.4.

3. Preclinical/Nonclinical Microbiology

Preclinical studies were previously reviewed (NDA #21-361 Microbiology Reviews by Mr. Peter Dionne and Dr. Avery Goodwin dated 3/14/02 and 4/13/04, respectively). In this submission, the applicant includes three non-clinical studies (Jiang *et al.*, 2005⁶, Vosbeck *et al.*, 1979⁹, and Debbia *et al.*, 2008³), to support statements made in the label. The studies are summarized below.

3.1. Jiang *et al.*, 2005⁶

The study included a summary of in vitro susceptibility data from multiple studies without including methods (Table 1).

Table 1: In vitro susceptibility (MIC) to rifaximin of enteric pathogens isolated from patients with bacterial diarrhea from multiple areas of the world

Species	Number of isolates	MIC ₅₀ µg/ml	MIC ₉₀ µg/ml	MIC range µg/ml
<i>Aeromonas</i> spp.	27	16	128	16 to >256
<i>Campylobacter jejuni</i>	54	12.5	>100	0.78 to >100
<i>Campylobacter</i> spp.	35	32	128	0.25 to >256
Enterococci	50	64	128	16 to >256
Enterohemorrhagic <i>E. coli</i>	17	64	>256	32 to >256
Enteroinvasive <i>E. coli</i>	20	64	128	8 to >256
ETEC	153	64	128	8 to 256
ETEC with LT	50	64	256	8 to >256
ETEC with ST	76	64	128	8 to >256
ETEC with ST and LT	27	64	128	32 to >256
<i>Plesiomonas shigelloides</i>	25	64	256	16 to >256
<i>Salmonella</i> spp.	53	64	128	8 to >256
<i>Shigella</i> spp.	88	64	128	32 to >256
<i>Vibrio</i> spp. ¹	25	128	128	8 to 128
<i>Yersinia</i> spp.	91	12.5	25	0.2 to 25

LT = Heat-labile toxin; ST = heat-stable toxin.
¹ *Vibrio* spp. include non-cholera-causing vibrios.

Note: Clinical trials with contributing data: Mathewson *et al.*, unpublished data, Sierra *et al.*, 2001⁸ (previously reviewed by Dr. Avery Goodwin in Microbiology Review dated 4/13/04 for NDA 21-361), and Mignini *et al.*, 1989⁷.

Note: Adapted from Jiang *et al.*, 2005⁶, Table 1

Note: Interpretive criteria for susceptibility have not been established

3.2. Vosbeck *et al.*, 1979⁹

The study did not include testing of effect of sub-inhibitory levels of rifaximin on the adhesive properties of bacteria and therefore was not relevant for this review.

3.3. Debbia *et al.*, 2008³

The effects of exposure to sub-inhibitory concentrations of rifaximin on induced resistance and susceptibility virulence mechanisms, such as plasmid stability and frequency of plasmid transfer, were evaluated for strains with low MIC (8 µg/mL; stated to be rifaximin susceptible) and high MIC (≥ 512 µg/mL; stated to be resistant) in vitro by Debbia *et al.*, 2008³. Rifaximin resistant *E. coli* strains were selected for in vitro and the frequency of spontaneous rifaximin-resistant mutant strains was determined in the presence of rifaximin concentrations below the minimum inhibitory concentration (MIC) (sub-inhibitory). The authors state Clinical Laboratory of Standards Institute (CLSI) standardized methods for MIC determination for enterobacteria using broth microdilution (M2-A8; M100-S15). *E. coli* (ATCC 25922 standard reference strain) cultures were cultured for 18-24 hours in the presence of 0.06x, 0.12x, 0.25x and 0.5x MIC of rifaximin (MIC = 4 mg/L) or ciprofloxacin (MIC = 0.004 mg/L). Approximately 10^7 CFU/mL were seeded onto agar plates containing either 40 µg/mL (10xMIC) rifaximin or 0.04 mg/mL (10xMIC) ciprofloxacin and incubated for 48 hours at 37°C to select for resistant mutants that were then evaluated for in vitro susceptibility.

Table 2 shows that *E. coli* cultured in the presence of rifaximin induces a higher rate of spontaneous mutations than ciprofloxacin or bacteria cultured in the absence of drug. The resulting mutants were resistant to >512 µg/mL rifaximin compared to 8 µg/mL for the sensitive strains. It is unclear if a mutant “strain” was sequenced to show clonality or if “strain” refers to a single colony on the agar plate. Also, the range and or confidence intervals were not included to show experiment to experiment variability for five experiments.

The morphology of the resistant and sensitive strains was assessed microscopically. A change in morphology is observed in rifaximin susceptible (MIC = 4 µg/mL) and resistant (MIC >512 µg/mL) strains in the presence of drug. When either strain was cultured in the presence of very low levels of rifaximin (0.008 x MIC), the morphology appears the same as controls (rods). The “control” was not described. As the concentration of rifaximin is increased, changes in morphology are noted; and the morphologies are described the same for susceptible and resistant strains.

Table 2: The emergence of spontaneous resistant-mutants to rifaximin and ciprofloxacin in drug free medium (control) or sub-inhibitory concentrations of rifaximin and ciprofloxacin.

Antibiotic	MIC (mg/L)	Used dose (xMIC)	Number of spontaneous resistant strains /10 ⁸ CFU/mL
Rifaximin ¹	4	0.5	569
		0.25	1447
		0.125	0
		0.06	0
		Control	27
Ciprofloxacin ²	0.004	0.5	21
		0.25	0
		0.125	0
		0.06	0
		Control	0

¹Selection on plates containing rifaximin (40 mg/L)
²Selection on plates containing ciprofloxacin (0.04 mg/L)
Average from 5 separate experiments

Note: Adapted from Debbia *et al.*, 2008³, Table 2

The segregational plasmid stability was evaluated in bacteria carrying plasmids when cultured in sub-inhibitory rifaximin or ciprofloxacin concentrations. Plasmid stability was determined in enterobacteria carrying plasmids encoding antibiotic resistance, including *E. coli*, *Staphylococcus aureus*, *Morganella morganii*, *Citrobacter freundii*, *Proteus mirabilis*, and *Klebsiella pneumoniae*. For this, bacteria (starting inoculum $\leq 10^3$ CFU/mL) were cultured for 20-24 generations at 37°C in the presence of drug. Bacteria were diluted 100-fold with “warm broth” and incubated an additional 90 minutes. It is unclear what “warm broth” refers to (drug-free media or media with drug). Cultures were diluted further and plated on Mueller-Hinton agar plates. The dilution factor or amount of bacteria plated is unclear. Plates were incubated for 18 to 20 hours and colonies were replicated onto medium with antibiotic or without. Bacterial growth on agar containing antibiotic indicated the presence of plasmid and successful transfer of plasmids to daughter cells (stability). The number of colonies was counted and the proportion of cells that lost the plasmid (cells cured) was determined by the number of colonies growing on medium with antibiotic relative to the number grown on antibiotic-free medium. It is not clear if transmission efficiency (plasmid stability in bacteria grown in the absence of antibiotic) was determined. Select bacteria were plated on McConkey’s agar plates and plasmid stability was identified by the use of lactose.

Table 3 shows the range of “percent cells cured” (plasmid-free) following bacterial culture in sub-inhibitory drug concentrations. The percent of cured cells was higher in bacteria containing a high molecular weight, low copy plasmid (*Flac*) compared to low molecular weight, high copy plasmids (p507). In many cases, the cells cultured with rifaximin had a wider range of percent cells cured compared to ciprofloxacin; however the drugs elicited a similar percentage of cells

cured (Table 3). The mean, median or statistical significance of this range from five separate experiments was not included, thus it is difficult to interpret the relevance of the results.

Table 3: Plasmid elimination from different bacterial hosts exposed to sub-inhibitory concentrations of rifaximin and ciprofloxacin

Bacterial Host (Plasmid)	Antibiotic	MIC (mg/L)	Sub-MIC Used (mg/L)	Cells Cured* (%)
ATCC25922 (Flac)	rifaximin	4	2	4.5-70
	ciprofloxacin	0.004	0.002	5.7-47.6
ATCC25922 (P507)	rifaximin	4	2	0-18
	ciprofloxacin	0.004	0.002	1.3-10.2
<i>S. aureus</i> I Pen-R Oxa-S	rifaximin	0.004	0.002	8.4-18.2
	ciprofloxacin	0.25	0.125	12.5-33.7
<i>S. aureus</i> II Pen-R Oxa-S	rifaximin	0.008	8	<0.1-18
	ciprofloxacin	0.01	0.005	23-36.2
<i>M. morgani</i> ESBL33	rifaximin	8	4	9.5-58.6
	ciprofloxacin	0.015	0.008	17.4-37.9
<i>C. freundii</i> ESBL33	rifaximin	32	16	10.6-47.1
	ciprofloxacin	0.03	0.015	22.3-40.2
<i>P. mirabilis</i> ESBL33	rifaximin	8	4	2.3-38.7
	ciprofloxacin	0.06	0.03	11.6-61.2
<i>K. pneumoniae</i> ESBL33	rifaximin	8	4	14.3-66.6
	ciprofloxacin	0.06	0.03	31.8-42.6
<i>E. coli</i> ESBL 33	rifaximin	8	4	7.7-43.8
	ciprofloxacin	0.01	0.005	3.4-52.4
<i>E. coli</i> ETEC Mex 264	rifaximin	16	8	22.4-46.1
	ciprofloxacin	0.03	0.015	19.7-55.2

*range from five separate experiments
Note: Adapted from Debbia *et al.*, 2008³, Table 4
Note: Reported "Sub MIC" values are only 0.5 x MIC with the exception of "*S. aureus* II" which has a rifaximin Sub-MIC value of MICx1000. It is unclear if this is a typo. Additional "Sub-MIC" concentrations are not included.

The effect of rifaximin on bacterial conjugation, as measured by the frequency of plasmid transfer, was measured. Actively growing donor strain (2×10^3 CFU/mL) and recipient strain (4×10^3 CFU/mL) were mixed in Luria Broth (LB) medium (Table 4). Cells were harvested, diluted and plated on selective media after 90 minutes of incubation. It is unclear when bacteria were exposed to sub-inhibitory concentrations of ciprofloxacin or rifaximin. Control cells were not exposed to ciprofloxacin or rifaximin; however it is unclear if control cells were cultured with selective media. The authors report rifaximin inhibits transfer of genetic material by at least 100-fold when ATCC 29922 (*Flac* TcR) donor and ATCC25922 AzdIR strains are used, and results were comparable to ciprofloxacin. A 20-fold reduction of conjugation was observed with the *E. coli* clinical isolate carrying the conjugative plasmid ESBL33. The results are difficult to interpret because the methods are unclear.

Table 4: Effect of rifaximin and ciprofloxacin on plasmid transfer in *E. coli*

Donator	Recipient	Antibiotic (mg/L)	N. recombinants/10 ⁵ recipients
ATCC29922 (Flac TcR)	ATCC25922 AzdR*	rifaximin(40)	4
		ciprofloxacin(0.2)	3.4
		control	630
ESBL33		rifaximin	21
		ciprofloxacin	12
		control	430

AzdR, Spontaneous sodium azide-resistant (200 mg/L) strain

4. Clinical Microbiology

4.1. Description of clinical studies

The applicant includes two publications to support changes in the label to suggest rifaximin has a unique mechanism of action based on pathogen eradication or alterations in the gut flora.

4.1.1. DuPont *et al.*, 1998⁴

A randomized, prospective, double-blind clinical trial was conducted to determine the efficacy of rifaximin for the treatment of traveler's diarrhea in 72 adults visiting Mexico from the U.S. Participants were randomized to receive rifaximin (200, 400 or 600 mg, t.i.d. for 5 days) or trimethoprim/sulfamethoxazole (160 mg TMP/ 800 mg SMX, b.i.d. for 5 days). Stool was collected pre-treatment and at 24 hours after the end of therapy. Stool was assessed for presence of enteropathogens; however the methods were not included. The test of cure was the passage of formed stool and expressed as "time to last unformed stool" (TLUS) which was defined as the hours elapsed after the first dose of medication until passage of the last unformed stool. Table 5 shows the TLUS for all treatment groups. Participants who were administered the lowest rifaximin dose had the shortest duration of diarrhea. The differences in duration of diarrhea were not statistically significant. Participants were classified as "well" after passage of the last unformed stool. It is unclear if "well" is equivalent to "cure" or considered a successful treatment and whether microbiological cure (pathogen eradication) is included. The rate of reported treatment failure was lower in patients administered rifaximin treatment (6/55, 11%) compared to TMP/SMX (5/17, 29%). Four of six rifaximin treatment failures occurred in the highest dosing arm (600 mg rifaximin, t.i.d.).

Table 5: Time to last unformed stool

Drug group	Number	Duration of posttreatment diarrhea, h	
		median	mean
Rif 200	18	26.3	36.9
Rif 400	18	40.5	38.6
Rif 600	19	35.0	53.0
Rif total	55	35.0	43.1
TMP/SMX	17	47.0	55.7
p		N/S	N/S

Rif 200 = Rifaximin 200 mg p.o. t.i.d.; Rif 400 = rifaximin 400 mg p.o. t.i.d.; Rif 600 = rifaximin 600 mg p.o. t.i.d.; Rif total = all rifaximin-treated subjects; TMP/SMX = 160 mg trimethoprim/800 mg sulfamethoxazole p.o. b.i.d.

Adapted from DuPont *et al.*, 1998⁴, Table 1

Results in Table 6 show 27 enteropathogens identified from 26 of the 72 pre-treatment stool samples. In one stool sample, two pathogens were identified, including enteric *E. coli* (ETEC) and *Campylobacter jejuni*. Of the 26 patients, twenty patients were from rifaximin arm and six patients were from TMP/SMX arm. Following treatment, 16 of 20 (80%) pathogens in the rifaximin group were eradicated. Two ETEC isolates in the 400 mg t.i.d. rifaximin group and one *Shigella* isolate and one *Salmonella* isolate in the 600 mg t.i.d. rifaximin group were not eradicated. Seven pathogens identified from pre-treatment stool of 6 patients in the TMP/SMX arm were eradicated. It is unclear if patients with persisting pathogens achieved clinical cure because it is unclear if “cure” (Table 6) refers to microbiological eradication or clinical cure (not defined in methods). From results in Table 6, it is unclear if “cure” refers to microbiological eradication or clinical cure.

Table 6: Enteropathogens identified in pre-treatment samples and eradication during therapy

Drug group	ETEC	Shigella, Salm, Campy	Crypto	Total pathogens	Cure
Rif 200	7	4	0	11	11 (100%)
Rif 400	3	1	1	5	3 (60%)
Rif 600	2	2	0	4	2 (50%)
Rif total	12 ^a	7 ^a	1	20	16 (80%)
TMP/SMX	6	1	0	7	7 (100%)

Salm = *Salmonella* spp; Campy = *C. jejuni*; Crypto = *Cryptosporidium*; Rif 200 = rifaximin 200 mg p.o. t.i.d.; Rif 400 = rifaximin 400 mg p.o. t.i.d.; Rif 600 = rifaximin 600 mg p.o. t.i.d.; Rif total = all rifaximin-treated subjects; TMP/SMX = 160 mg trimethoprim/800 mg sulfamethoxazole p.o. b.i.d.

^a ETEC plus *C. jejuni* on pretreatment sample in 1 subject.

Note: Green boxes surround pathogens that were not eradicated completely

Adapted from DuPont *et al.*, 1998⁴, Table 3

All non-Campylobacter pathogens (n=24) identified from pre-treatment samples were tested for susceptibility to rifaximin and TMP by “dilutional minimum inhibitory concentration (MIC)” testing or “disc testing”, respectively. Further details of the susceptibility testing methods were not included. Table 7 shows the susceptibility of pathogens to both drugs. Note that rifaximin susceptibility breakpoints have not been established. MIC interpretive criteria/breakpoints for trimethoprim are <8 µg/mL for “Susceptible” and >16 µg/mL for “Resistant”².

Table 7: Susceptibility of bacterial enteropathogens to trimethoprim by disc testing and rifaximin by dilutional MIC

Enteropathogen	Number	Trimethoprim susceptible	Median rifaximin MIC (range)
ETEC	18	11 (61%)	12.5 (0.098–25)
<i>Salmonella</i>	4	4 (100%)	18.8 (12.5–50)
<i>Shigella</i>	2	1 (50%)	0.57 (0.39–0.75)

Note: methods are not described in detail and different methods were used to determine susceptibility to trimethoprim and rifaximin

The four enteropathogens that were not eradicated following rifaximin treatment were evaluated for susceptibility to rifaximin. Susceptibility of two ETEC isolates from the 400 mg rifaximin group did not change after treatment (<0.098 and 25 µg/mL). However, the post-treatment *Shigella* isolate from the 600 mg rifaximin group was 0.39 µg/mL before treatment and <0.098 µg/mL post treatment. Likewise, the *Salmonella* isolate, from one patient, in the 600 mg group was 6.25 µg/mL before and 3.125 µg/mL after treatment. It is difficult to interpret the results without knowing the method used.

4.1.2. DuPont *et al.*, 2001⁵

A randomized, double-blind, double-dummy clinical trial was conducted to determine the efficacy of rifaximin for the treatment of traveler’s diarrhea in 187 adults visiting Mexico or Jamaica from the U.S. Participants were randomized to receive rifaximin (200 mg, b.i.d. for three days) or ciprofloxacin (500 mg, b.i.d. for 3 days). The test of cure was determined by consistency of stool and clinical symptoms in a 24 hour (no watery stools and no fever) or 48 hour (no unformed stools and no fever) period. The primary endpoint was resolution of diarrhea and modification of stools. The time to last unformed stool (TLUS) was defined as the interval from initiation of therapy until passage of the last unformed stool, after which subjects were declared healthy. Microbiologic cure was a secondary endpoint and defined by a negative post-treatment sample (pathogen eradication).

Table 8 shows clinical efficacy results as measured by total number unformed stools. Note that Table 8 shows “n=3” in the Rifaximin treatment arm, but the text describes 93 subjects. It is unclear if the data described in Table 7 is calculated from n=3 or n=93. The treatment groups did not differ significantly in the total number of unformed stools or the duration of illness. However, “duration of illness” (Table 8, green box) was not defined. It is unclear if the duration of illness refers to the time to test of cure or time to when patients are declared “healthy” (TLUS); however the duration of illness is longer than the reported TLUS for each treatment

group, which is 25.7 hours (95% CI, 20.9-38.0) for rifaximin-treated participants and 25.0 hours (95% CI, 18.5 – 35.2) for ciprofloxacin treated participants. Eighty-one of 93 (87%) participants that received rifaximin therapy and 83 of 94 (88%) in the ciprofloxacin treatment group were considered cured. Nine (10%) subjects in the rifaximin treatment group and five (6%) subjects in the ciprofloxacin treatment group failed treatment (“did not become healthy”). It is unclear how 3 participants in the rifaximin treatment group and six participants in the ciprofloxacin treatment group were classified.

Table 8: Measurements of efficacy for participants treated with rifaximin or ciprofloxacin

Disease characteristics	Treatment group		P
	Rifaximin (n = 3)	Ciprofloxacin (n = 94)	
Total no. of unformed stools			
Mean ± SD	6.0 ± 3.1	6.1 ± 3.7	.793 ^a
Median (range)	5.0 (3-15)	5.0 (3-23)	
Duration of illness, h			
Mean ± SD	30.4 ± 21.2	27.2 ± 18.3	.466 ^a
Median (range)	27.0 (2.5-71.5)	23.3 (3-68.5)	

^a Determined by analysis of variance
Note: Rifaximin (n=3) likely a typo from the publication. 93 subjects were evaluated from the Rifaximin treatment group for efficacy.

Stool was collected pre-treatment and at day four or five after initiation of therapy and assessed for presence of enteropathogens. The methods were not described for identification of bacterial species including *Shigella*, *Salmonella*, *Aeromonas*, *Vibrio* spp., and *Plesiomonas* spp., *Campylobacter jejuni*, and *Yersinia enterocolitica*. ELISA was used to identify protozoa, including *Entamoeba histolytica*, *Cryptosporidium* spp., and *Giardia* spp. *E. coli*-like colonies were isolated and transported on peptone stabs to a different laboratory where enterotoxigenic *E. coli* was identified by the production of heat-labile and heat-stable enterotoxin confirmed with a DNA hybridization/probe technique. Enteroadhesive *E. coli* was confirmed using the HEp-2 cell assay for adherence. Details of the methods were not included.

Pathogens were identified from paired pre-treatment and post-treatment samples for participants treated with rifaximin (n=33) or ciprofloxacin (n=30). Table 9 shows the pathogens identified in pre-treatment stool samples and the eradication of those samples after treatment. Pathogens were eradicated in 29 of 39 (74%) participants who received rifaximin and 38 of 43 (88%) in the ciprofloxacin therapy group. ETEC was eradicated in 23 of 33 (70%) rifaximin-treated participants and 28 of 32 (88%) ciprofloxacin-treated participants. A statistical analysis of eradication rates was not included.

Table 9: Pathogens identified pre-treatment from stool of patients administered rifaximin or ciprofloxacin						
Pathogen	No. (%) of patients who received					
	Rifaximin treatment			Ciprofloxacin treatment		
	All	Microbiological		All	Microbiological	
		Cure	Failure		Cure	Failure
ETEC only	30	20 (67)	10 (33)	31	27 (87)	3 (10)
<i>Shigella</i> species	3	3 (100)	0 (0)	5	5 (100)	0 (0)
<i>Salmonella</i> species	2	2 (100)	0 (0)	3	3 (100)	0 (0)
<i>Shigella</i> species and ETEC	1	1 (100)	0 (0)	0	0 (0)	0 (0)
<i>Salmonella</i> species and ETEC	0	0 (0)	0 (0)	2	2 (100)	0 (0)
<i>Campylobacter jejuni</i>	1	1 (100)	0 (0)	0	0 (0)	0 (0)
<i>Cryptosporidium</i> species	0	0 (0)	0 (0)	1	1 (100)	0 (0)
<i>Cryptosporidium</i> species and ETEC	1	1 (100)	0 (0)	1	0 (0)	1 (100)
<i>C. jejuni</i> and ETEC	1	1 (100)	0 (0)	0	0 (0)	0 (0)
In pretreatment stool samples	39	29 (74)	10 (26)	43	38 (88)	4 (9)
<p>NOTE. ETEC, enterotoxigenic <i>Escherichia coli</i>.</p> <p>Note: only participants who provided a pre-treatment and post-treatment stool sample are included, 33 paired samples from the rifaximin group and 30 paired samples from the ciprofloxacin group</p> <p>Adapted from DuPont <i>et al.</i>, 2001⁵, Table 2</p>						

Bacterial enteropathogens were evaluated for in vitro susceptibility to rifaximin and ciprofloxacin before treatment and after treatment if eradication was not achieved. Standardized agar dilution methods described by the National Committee of Clinical Laboratory Standards (NCCLS) were used to determine the minimal inhibitory concentration (MIC). It is unclear what methods from NCCLS were followed because the authors cite the CLSI method, M27-A¹, which is incorrect. M27-A¹ describes susceptibility testing methods for yeast and not bacteria. All pathogens isolated from pre-treatment stool were evaluated for in vitro susceptibility to both drugs. Table 10 shows the MIC values of bacterial isolates obtained before treatment with rifaximin (n=44) or ciprofloxacin (n=48). The MIC₉₀ was 0.25 to 32 µg/mL for rifaximin and <0.016 to 0.125 µg/mL for ciprofloxacin.

Table 10: MIC values for bacterial isolates from stool samples before treatment with rifamoxacin or ciprofloxacin

Treatment group, isolate	No. of isolates	Rifaximin, µg/mL			Ciprofloxacin, µg/mL		
		MIC ₅₀	MIC ₉₀	MIC range	MIC ₅₀	MIC ₉₀	MIC range
Rifaximin							
ETEC	36	16	32	0.5–128	<0.016	0.016	0.016–0.3125
<i>Shigella</i> species	5	64	64	16–256	<0.016	<0.016	<0.016–32
<i>Salmonella</i> species	3	16	16	16	<0.016	<0.016	<0.016
Ciprofloxacin							
ETEC	36	16	32	8–64	<0.016	<0.016	<0.016
<i>Shigella</i> species	6	32	32	8–64	<0.016	<0.016	<0.016
<i>Salmonella</i> species	6 ^a	32	32	16–64	<0.016	<0.016	<0.016

NOTE. ETEC, enterotoxigenic *Escherichia coli*.

^a One *Salmonella* strain did not grow.

Adapted from DuPont *et al.*, 2001⁵, Table 4

Pathogens that were not eradicated were evaluated for susceptibility to rifaximin and ciprofloxacin. Table 11 shows differences in MIC values for paired pre- and post-treatment pathogens. Of 10 microbiological treatment failures in the rifaximin group, the MIC value of one *E. coli* isolate increased by three 2-fold dilutions (0.5 µg/mL to 4 µg/mL). The MIC value decreased by one 2-fold dilution in three and the MIC value was unchanged in five. Of the four microbiological treatment failures in the ciprofloxacin group, one had a lower MIC value in the post-treatment sample (0.5 µg/mL to <0.016 µg/mL) and three were unchanged.

Table 11: MIC values of paired pre- and post-treatment pathogens isolated from the stool of participants treated with rifaximin or ciprofloxacin

Subject number	Treatment group	MIC of rifaximin, $\mu\text{g/mL}$		MIC of ciprofloxacin, $\mu\text{g/mL}$	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
37-021 ^a	Rifaximin	16	8	<0.016	<0.016
37-064	Rifaximin	No growth	8	No growth	<0.016
37-085	Rifaximin	16	16	<0.016	<0.016
37-137 ^a	Rifaximin	32	16	<0.016	<0.016
37-139 ^b	Rifaximin	0.5	4	<0.016	<0.016
37-185	Rifaximin	16	16	<0.016	0.03125
37-194	Rifaximin	16	16	<0.016	<0.016
37-196	Rifaximin	16	16	<0.016	<0.016
37-207	Rifaximin	4	4	<0.016	<0.016
37-209 ^a	Rifaximin	16	8	<0.016	<0.016
37-191	Ciprofloxacin	16	16	<0.016	<0.016
37-094 ^c	Ciprofloxacin	32	32	0.5	<0.016
37-183	Ciprofloxacin	16	16	<0.016	<0.016
37-192	Ciprofloxacin	16	0.25	<0.016	<0.016

^a Rifaximin-treated subjects for whom MICs of rifaximin were lower in the posttreatment samples.
^b Only rifaximin-treated subject for whom the MIC of rifaximin was higher in the post-treatment sample.
^c Ciprofloxacin-treated subject for whom the MIC of ciprofloxacin was lower in the posttreatment sample.

Adapted from DuPont *et al.*, 2001⁵, Table 5

4.2. Interpretive Criteria

Standardized breakpoints for rifaximin have not been established and the applicant does not propose interpretive criteria in this submission.

5. Discussion

The applicant has submitted 3 nonclinical microbiology studies and 2 clinical studies to support changes in the labeling.

The nonclinical study by Debbia *et al.*, 2008³, showed the effects of sub-inhibitory levels of rifaximin on bacterial virulence mechanisms, such as cell morphology, plasmid stability and frequency of plasmid transfer, in bacterial strains with low or high susceptibility to rifaximin. Resistant mutants were selected for and evaluated for susceptibility to rifaximin. Characterization of the mutant's genotype would be helpful to show whether culture with drug induces specific mutations affecting drug transport, DNA repair mechanisms or drug target. Also, the viability of the resulting mutants was not assessed to support the applicant's proposed statement that viability and virulence are reduced with rifaximin exposure.

Morphological changes were observed in both rifaximin resistant and susceptible strains at sub-inhibitory concentrations; however it is unclear if the morphological changes observed are

reversible or affect cell viability. The morphological changes were noted in parallel for rifaximin susceptible and resistant *E. coli* strains as the concentration of drug was increased; however changes in morphology were not correlated with functional changes that may affect virulence or viability. Since both susceptible and resistant strains had similar morphologies, it is unlikely that the changes are associated with drug susceptibility and are, perhaps, a temporal condition in response to environmental stimuli.

Plasmid stability was influenced by sub-inhibitory concentrations of rifaximin. Stability is the successful distribution of at least one plasmid in each daughter cell during division. The development of plasmid free cells can affect bacterial viability and productivity. The authors did not include studies to determine the effects of plasmid loss or viability or drug susceptibility. Also, appropriate controls that show plasmid stability in the absence of drug were not included.

DuPont *et al.*, 1998⁴, show that patients with traveler's diarrhea have a lower rate of treatment failure when treated with rifaximin compared to TMP/SMX; however the duration of diarrhea is not statistically different. The rate of reported treatment failure was lower in patients administered rifaximin treatment (6/55, 11%) compared to TMP/SMX (5/17, 29%). The sample size was too small to show statistical differences between treatment groups. Following treatment, four of 20 pathogens were not eradicated in the rifaximin treatment arm compared to all pathogens (7) in the comparator arm. Pathogens were tested for susceptibility to TMP and rifaximin. The results from the clinical study are inadequate to support the applicant's proposed changes to the label for a comparison of rifaximin to aminoglycosides or fluoroquinolones because the comparator drug in this trial was TMP/SMX (DHFR inhibitor/sulfonamide). Also, no studies were conducted to evaluate a "unique mechanism of action", as cited by the applicant; and the methods for susceptibility testing are not described in detail.

DuPont *et al.*, 2001⁵, show there was no significant difference in the proportion of subjects with traveler's diarrhea that were treated with rifaximin or ciprofloxacin with respect to duration of clinical illness, treatment failure or microbiologic cure. Based on a small number of observations regarding pathogen eradication no reference to alteration in gut flora or eradication rate should be made in the labeling. No studies were conducted to evaluate a unique mechanism of action for rifaximin.

6. References

1. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard. M27-A. 1997. National Committee for Clinical Laboratory Standards (NCCLS).
Ref Type: Report
2. Performance Standards for Antimicrobial Susceptibility Testing; Nineteenth Informational Supplement. M100-S19. 1-1-2009. Clinical and Laboratory Standards Institute (CLSI).
Ref Type: Report

3. **Debbia, E. A., E. Maioli, S. Roveta, and A. Marchese.** 2008. Effects of rifaximin on bacterial virulence mechanisms at supra- and sub-inhibitory concentrations. *J Chemother.* **20**:186-194.
4. **DuPont, H. L., C. D. Ericsson, J. J. Mathewson, E. Palazzini, M. W. DuPont, Z. D. Jiang, A. Mosavi, and F. J. de la Cabada.** 1998. Rifaximin: a nonabsorbed antimicrobial in the therapy of travelers' diarrhea. *Digestion* **59**:708-714.
5. **DuPont, H. L., Z. D. Jiang, C. D. Ericsson, J. A. Adachi, J. J. Mathewson, M. W. DuPont, E. Palazzini, L. M. Riopel, D. Ashley, and F. Martinez-Sandoval.** 2001. Rifaximin versus ciprofloxacin for the treatment of traveler's diarrhea: a randomized, double-blind clinical trial. *Clin Infect.Dis* **33**:1807-1815.
6. **Jiang, Z. D. and H. L. DuPont.** 2005. Rifaximin: in vitro and in vivo antibacterial activity--a review. *Chemotherapy* **51 Suppl 1**:67-72.
7. **Mignini, F., E. Falcioni, M. Prenna, F. Santacroce, and S. Ripa.** 1989. Antibacterial activity of rifaximin against *Clostridium difficile*, *Campylobacter jejuni* and *Yersinia* spp. *J Chemother.* **1**:220-222.
8. **Sierra, J. M., J. Ruiz, M. M. Navia, M. Vargas, and J. Vila.** 2001. In vitro activity of rifaximin against enteropathogens producing traveler's diarrhea. *Antimicrob Agents Chemother.* **45**:643-644.
9. **Vosbeck, K., H. Handschin, E. B. Menge, and O. Zak.** 1979. Effects of subminimal inhibitory concentrations of antibiotics on adhesiveness of *Escherichia coli* in vitro. *Rev Infect.Dis* **1**:845-851.

7. The Label

7.1. Applicant's version of the label

Additions to the approved label are underlined. This version has been formatted for PLR.

12.1 Mechanism of Action

Rifaximin is an anti-bacterial drug (see 12.4 Microbiology).

12.4 Microbiology

Mechanism of Action

Rifaximin is a non-aminoglycoside semi-synthetic antibiotic derived from rifamycin SV; it is a structural analog of rifampin. The mechanism of action of rifaximin depends on the inhibition of DNA-dependent RNA polymerase of the target microorganisms, leading to the suppression of initiation of chain formation in RNA synthesis.

The lower rate of eradication of fecal pathogens in patients treated with rifaximin compared with fluoroquinolones and aminoglycosides and lack of alteration of gut flora indicate a unique mechanism of action. Rifaximin may alter virulence factors of enteric bacterial pathogens without killing them, as has been seen with subtherapeutic levels of drugs and colonization fimbriae of enterotoxigenic *E. coli*. Rifaximin caused morphological alterations in both susceptible and resistant bacterial strains at concentrations as low as 1/32 of the MIC.¹ Rifaximin reduced the viability and virulence of resistant bacteria, suggesting that if *in vivo* pathogens are

exposed to sub-MICs of the drug, not only are their physiological functions compromised, but gene virulence and antibiotic resistance are not fully expressed.

Rifaximin has in vitro antimicrobial activity against numerous Gram-positive and Gram-negative bacteria, such as *Escherichia coli*. Animal and human studies demonstrate negligible systemic rifaximin absorption (< 1%) after oral administration. The negligible systemic absorption of rifaximin from the gastrointestinal tract minimizes the potential adverse events associated with systemically absorbed antibiotics. Rifaximin is delivered at high concentrations to the gastrointestinal tract, which is the therapeutic site of action.

Rifaximin acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis.

Escherichia coli has been shown to develop resistance to rifaximin *in vitro*. However, the clinical significance of such an effect has not been studied.

Rifaximin is a structural analog of rifampin. Organisms with high rifaximin minimum inhibitory concentration (MIC) values also have elevated MIC values against rifampin. Cross-resistance between rifaximin and other classes of antimicrobials has not been studied.

Rifaximin has been shown to be active against the following pathogen in clinical studies of infectious diarrhea as described in the **INDICATIONS AND USAGE** section: *Escherichia coli* (enterotoxigenic and enteroaggregative strains).

Susceptibility Tests

In vitro susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) agar dilution method M7-A6¹². However, the correlation between susceptibility testing and clinical outcome has not been determined.

Escherichia coli has been shown to develop resistance to rifaximin *in vitro*. However, the clinical significance of such an effect has not been studied. Rifaximin is a structural analog of rifampin. Organisms with high rifaximin minimum inhibitory concentration (MIC) values also have elevated MIC values against rifampin. Cross-resistance between rifaximin and other classes of antimicrobials has not been studied.

15 REFERENCES

1. Debbia EA, Maioli E, Roveta S, Marchese A. Effects of rifaximin on bacterial virulence mechanisms at supra- and sub-inhibitory concentrations. *J Chemother.* 2008 Apr;20(2):186-94.
2. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. National Committee for Clinical Laboratory Standards, Sixth Edition, Wayne PA. *Approved Standard NCCLS Document M7-A6* January 2003; 23 (2).

7.2. Comments

1. Applicant proposes to add a description of the derivation or rifaximin and structural similarity to rifamycin. This comment is more appropriate for the Chemistry section.
2. Applicant proposes that the unique mechanism of action of rifaximin is supported by evidence that treatment results in a lower rate of pathogen eradication than fluorquinolones and aminoglycosides and a lack of alteration of the gut flora. The applicant cites two studies (DuPont *et al.*, 1998⁴ and DuPont *et al.*, 2001⁵) for supporting this statement. Neither reference compared the rate of pathogen eradication between rifaximin and an aminoglycoside nor did either study correlate these changes with

alteration of gut flora. DuPont *et al.*, 2001, showed that treatment of diarrhea with rifaximin had a lower, yet comparable, rate of pathogen eradication (29 of 39, 74%) compared to ciprofloxacin (38 of 43, 88%) from approximately one-third of patients for who paired pre- and post-treatment stool samples collected. The authors do not address important alterations of gut flora in participants treated with rifaximin or ciprofloxacin as suggested in the proposed labeling; however a review of the study results for enteropathogen eradication suggests it is comparable between treatment groups. DuPont *et al.*, 1998, report that five different enteropathogens were detected in the 20 pre-treatment stool samples of participants receiving rifaximin (200, 400 or 600 mg t.i.d.) and three pathogens (*E. coli*, *Shigella* and *Samonella*) from four participants were detected post-treatment. Two enteropathogens were detected in stool of seven participants treated with TMP/SMX and both pathogens were eradicated. DuPont *et al.*, 2001, reports that six enteropathogens were identified in pre-treatment stool of rifaximin-treated participants and one pathogen, *E. coli*, was identified in post-treatment stool samples. Four enteropathogens were identified in ciprofloxacin pre-treated participants stool, and two pathogens (*E. coli* and *Cryptosporidium*) were identified in post-treatment samples. This evidence does not support the applicant's statement that treatment with rifaximin results in a lack of alteration in gut flora.

3. The applicant proposes that "Rifaximin may alter virulence factors of enteric bacterial pathogens without killing them, as has been seen with subtherapeutic levels of drugs and colonization fimbriae of enterotoxigenic *E. coli*." The applicant cites Vosbeck *et al.*, 1979⁹, and Debbia *et al.*, 2008³, to support this statement. Rifaximin was not used in the Vosbeck *et al.*, 1979, study and therefore this study was not included in this review. Debbia *et al.*, 2008, did not investigate colonization fimbriae of *E. coli* when exposed to rifaximin. The methods to support experiments that evaluated virulence factors, such as the source of isolates, methods for culture with drug to select for resistance and morphological changes, and susceptibility testing were not included with appropriate detail to support the applicant's claims.
4. Applicant proposes to state that morphological changes are observed when susceptible or resistant bacteria are exposed to low concentrations of rifaximin. The normal morphology of *E. coli* are rods. Debbia *et al.*, 2008, report the morphology is altered as observed by microscopy following exposure to sub-inhibitory concentrations of rifaximin for 18 to 24 hours and then grown on selective agar containing 10x MIC rifaximin (40 mg/L). As the concentration of drug increases (0.008x MIC to 0.5x MIC), the morphohology is reported to be rods → short rods mixed with rods → short rods → very rare filaments mixed with short rods → rare filaments mixed with short rods → filaments mixed with short rods. The same morphological descriptions are provided for *E. coli* with rifaximin MIC values of 4 µg/mL or >512 µg/mL. This suggests that the morphological changes may not be related to susceptibility. The methods were not adequately described for an independent review and inclusion in labeling. Additional studies to determine the functional effect or reversibility of the morphological changes were not included.

5. Applicant states rifaximin reduces the viability and virulence of resistant bacteria. Debbia *et al.*, 2008³, show frequency of plasmid transfer and plasmid stability is reduced in the presence of sub-inhibitory levels of rifaximin. The frequency of plasmid transfer and plasmid stability are considered virulence factors because (1) they increase the genetic variability of bacteria and (2) genes encoding resistance to antibiotics are frequently encoded on plasmids. The methods and results included in the publication are unclear and inadequate for an independent review and therefore do not support inclusion of this statement in the label. In addition, the clinical relevance of such an effect is not known.
6. The applicant includes a statement that describes rifaximin activity in vitro against broad spectrum bacteria. Rifaximin is approved for treatment of *E. coli* and inclusion of such a statement may be misleading.
7. The applicant includes several statements regarding systemic absorption, adverse events associated with systemic absorption and drug concentrations in the gut. These statements are inappropriate for Section 12.4.
8. The applicant includes a statement regarding cross resistance with other antimicrobial agents. This sentence was relocated to coincide with rifaximin resistance.
9. The applicant includes repeated statements about resistance in the last paragraph of Section 12.4. To avoid redundancy, these statements should be deleted.

7.3. FDA's version of the label

Additions to the applicant's proposed label are double underlined, deletions are struck through.

12.1 Mechanism of Action

Rifaximin is an anti-bacterial drug [see Clinical Pharmacology (12.4)].

12.2 Microbiology

Mechanism of Action

~~— Rifaximin is a non-aminoglycoside semi-synthetic antibiotic derived from rifamycin SV; it is a structural analog of rifampin. The mechanism of action of rifaximin depends on the inhibition of DNA dependent RNA polymerase of the target microorganisms, leading to the suppression of initiation of chain formation in RNA synthesis.~~

~~The lower rate of eradication of fecal pathogens in patients treated with rifaximin compared with fluoroquinolones and aminoglycosides and lack of alteration of gut flora indicate a unique mechanism of action. Rifaximin may alter virulence factors of enteric bacterial pathogens without killing them, as has been seen with subtherapeutic levels of drugs and colonization fimbriae of enterotoxigenic *E. coli*.⁻ Rifaximin caused morphological alterations in both susceptible and resistant bacterial strains at concentrations as low as 1/32 of the MIC.⁴ Rifaximin reduced the viability and virulence of resistant bacteria, suggesting that if *in vivo* pathogens are exposed to sub-MICs of the drug, not only are their physiological functions compromised, but gene virulence and antibiotic resistance are not fully expressed.~~

~~Rifaximin has in vitro antimicrobial activity against numerous Gram positive and Gram negative bacteria, such as *Escherichia coli*. Animal and human studies demonstrate negligible systemic rifaximin absorption (<1%) after oral administration. The negligible systemic absorption of rifaximin from the gastrointestinal tract minimizes the~~

~~potential adverse events associated with systemically absorbed antibiotics. Rifaximin is delivered at high concentrations to the gastrointestinal tract, which is the therapeutic site of action.~~

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Rifaximin has been shown to be active against the following pathogen in clinical studies of infectious diarrhea as described in the **INDICATIONS AND USAGE** section: *Escherichia coli* (enterotoxigenic and enteroaggregative strains).

Susceptibility Tests

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~~*Escherichia coli* has been shown to develop resistance to rifaximin *in vitro*. However, the clinical significance of such an effect has not been studied. Rifaximin is a structural analog of rifampin. Organisms with high rifaximin minimum inhibitory concentration (MIC) values also have elevated MIC values against rifampin. Cross resistance between rifaximin and other classes of antimicrobials has not been studied.~~

15 REFERENCES

1. Debbia EA, Maioli E, Roveta S, Marchese A. Effects of rifaximin on bacterial virulence mechanisms at supra- and sub-inhibitory concentrations. *J Chemother.* 2008 Apr;20(2):186-94.

1-2. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. National Committee for Clinical Laboratory Standards, Sixth Edition, Wayne PA. *Approved Standard NCCLS Document M7-A6* January 2003; 23 (2).

8. Recommendations:

The citations included for review do not support the applicant's proposed changes to the microbiology section of the rifaximin labeling.

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CONCURRENCES:

DSPTP /Microbiology Team Leader Shukal Bala Signature 12/8/09 Date
CC:
DSPTP/Original NDA
DSPTP/PM/June Germain

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22554	ORIG-1	SALIX PHARMACEUTICA LS INC	XIFAXAN

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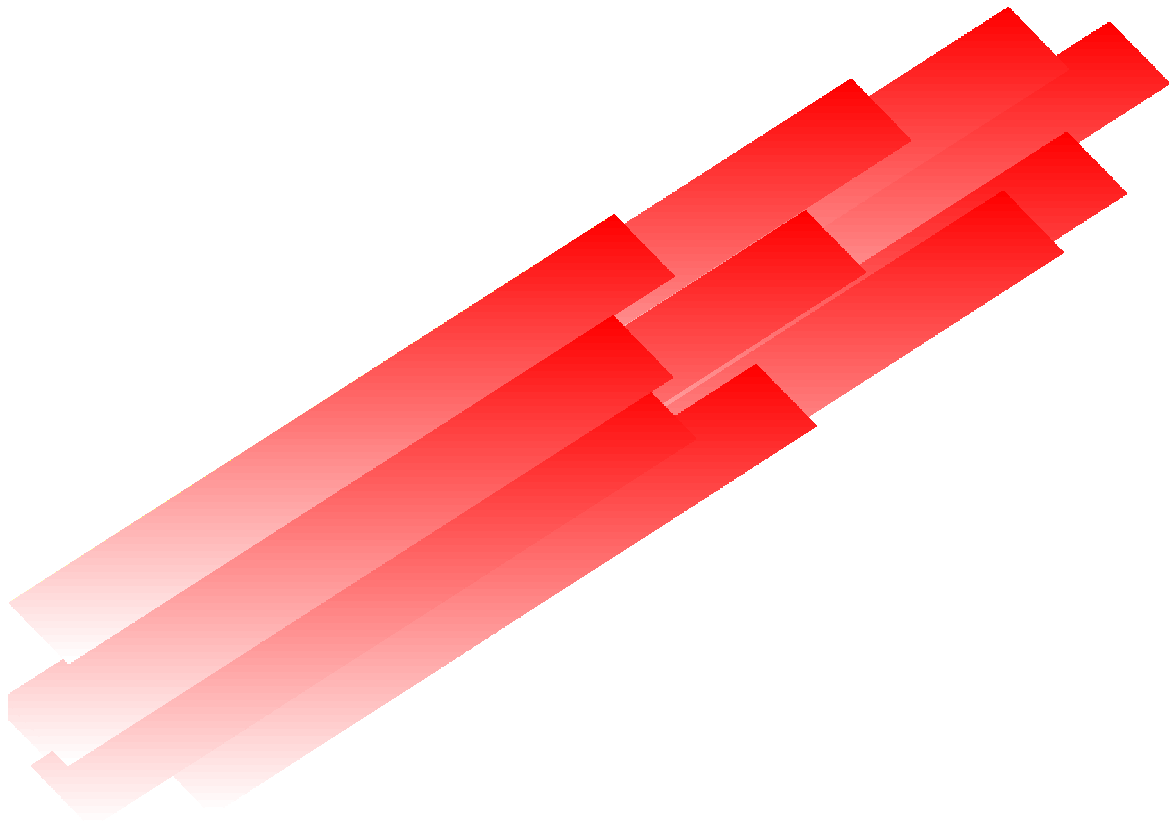
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Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products



**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
Clinical 6**

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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May 1998
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GUIDANCE FOR INDUSTRY¹

Providing Clinical Evidence of Effectiveness² for Human Drug and Biological Products

I. INTRODUCTION

This document is intended to provide guidance to applicants planning to file new drug applications (NDAs), biologics license applications (BLAs), or applications for supplemental indications on the evidence to be provided to demonstrate effectiveness.

This document is also intended to meet the requirements of subsections 403(b)(1) and (2) of the Food and Drug Administration Modernization Act (the Modernization Act) of 1997 for human drug and biological products (P.L. 105-115).³ Subsection 403(b)(1) directs FDA to provide guidance on the circumstances in which published matter may be the basis for approval of a supplemental application for a new indication. Section III of this guidance satisfies this requirement by describing circumstances in which published matter may partially or entirely support approval of a supplemental application. Subsection 403(b)(2) directs FDA to provide guidance on data requirements that will avoid duplication of previously submitted data by recognizing the availability of data previously submitted in support of an original application to support approval of a supplemental application. Section II of this guidance satisfies this requirement by describing a range of circumstances in which related existing data, whether from an original application or other sources, may be used to support approval of a supplemental application.

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that, to obtain marketing approval, manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies. Since then, the issue of what constitutes sufficient evidence of effectiveness has been debated by the Agency, the scientific community, industry, and others. Sound evidence of effectiveness is a crucial component of the Agency's benefit-risk assessment of a new product or use. At the same time, the demonstration of effectiveness represents a major component of drug development time and cost; the amount

¹ This guidance document represents the agency's current thinking on providing clinical evidence of effectiveness for human drug and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

² As used in this guidance, the term efficacy refers to the findings in an adequate and well-controlled clinical trial or the intent of conducting such a trial and the term effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data.

³ The Modernization Act requirements in Section 403 also apply to animal drugs and medical devices. These products will be addressed in separate guidances.

and nature of the evidence needed can therefore be an important determinant of when and whether new therapies become available to the public. The public health is best served by the development of sound evidence of effectiveness in an efficient manner.

The science and practice of drug development and clinical evaluation have evolved significantly since the effectiveness requirement for drugs was established, and this evolution has implications for the amount and type of data needed to support effectiveness in certain cases. As a result of medical advances in the understanding of pathogenesis and disease staging, it is increasingly likely that clinical studies of drugs will be more narrowly defined to focus, for example, on a more specific disease stage or clinically distinct subpopulation. As a consequence, product indications are often narrower, the universe of possible indications is larger, and data may be available from a number of studies of a drug in closely related indications that bear on a determination of its effectiveness for a new use. Similarly, there may be studies of a drug in different populations, studies of a drug alone or in combination, and studies of different doses and dosage forms, all of which may support a particular new use of a drug. At the same time, progress in clinical evaluation and clinical pharmacology have resulted in more rigorously designed and conducted clinical efficacy trials, which are ordinarily conducted at more than one clinical site. This added rigor and scope has implications for a study's reliability, generalizability, and capacity to substantiate effectiveness.

Given this evolution, the Agency has determined that it would be appropriate to articulate its current thinking concerning the quantitative and qualitative standards for demonstrating effectiveness of drugs and biologics. FDA hopes that this guidance will enable sponsors to plan drug development programs that are sufficient to establish effectiveness without being excessive in scope. The guidance should also bring greater consistency and predictability to FDA's assessment of the clinical trial data needed to support drug effectiveness.

Another major goal of this guidance is to encourage the submission of supplemental applications to add new uses to the labeling of approved drugs. By articulating how it currently views the quantity and quality of evidence necessary to support approval of a new use of a drug, FDA hopes to illustrate that the submission of supplements for new uses need not be unduly burdensome.

II. QUANTITY OF EVIDENCE NECESSARY TO SUPPORT EFFECTIVENESS

A. Legal Standards for Drug and Biological Products

Drugs: The effectiveness requirement for drug approval was added to the Federal Food, Drug, and Cosmetic Act (the Act or the FDC Act) in 1962. Between passage of the Act in 1938 and the 1962 amendments, drug manufacturers were required to show only that their drugs were safe. The original impetus for the effectiveness requirement was Congress's growing concern about the misleading and unsupported claims being made by pharmaceutical companies about their drug products coupled with high drug prices. After two years of hearings on these issues, Congress adopted the 1962 Drug Amendments,

which included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence." *Substantial evidence* was defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Since the 1962 Amendments added this provision to the statute, discussions have ensued regarding the quantity and quality of the evidence needed to establish effectiveness. With regard to quantity, it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. (See e.g., Final Decision on Benylin, 44 FR 51512, 518 (August 31, 1979); *Warner-Lambert Co. V. Heckler*, 787 F. 2d 147 (3d Cir. 1986)). FDA's position is based on the language in the statute⁴ and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase "adequate and well-controlled investigations" was designed not only to describe the quality of the required data but the "quantum" of required evidence. (S. Rep. No. 1744, Part 2, 87th Cong. 2d Sess. 6 (1962))

Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing. In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness. In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval — generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.

In section 115(a) of the Modernization Act, Congress amended section 505(d) of the Act to make it clear that the Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial

⁴ Section 505(d) of the Act uses the plural form in defining "substantial evidence" as "adequate and well-controlled investigations, including clinical investigations." See also use of "investigations" in section 505(b) of the Act, which lists the contents of a new drug application.

evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. In making this clarification, Congress confirmed FDA's interpretation of the statutory requirements for approval and acknowledged the Agency's position that there has been substantial progress in the science of drug development resulting in higher quality clinical trial data.

Biologics. Biological products are approved under authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. § 262). Under section 351, as in effect since 1944, licenses for biologics have been issued only upon a showing that the products meet standards designed to ensure the "continued safety, purity, and potency" of the products. *Potency* has long been interpreted to include effectiveness (21 CFR 600.3(s)). In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would consist of controlled clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25 (d) (2)). One such adequate alternative was identified to be serological response data where a previously accepted correlation with clinical effectiveness exists. As with nonbiological drug products, FDA has approved biological products based on single, multicenter studies with strong results.

Although section 123(a) of the Modernization Act amended section 351 of the PHS Act to make it clear that separate licenses are not required for biological products and the establishments at which the products are made, the evidentiary standard for a biological product was not changed: the product must be shown to be "safe, pure, and potent" (section 351 (a)(2) of the PHS Act as amended). In the Modernization Act (section 123(f)) Congress also directed the agency to take measures to "minimize differences in the review and approval" of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved NDAs under section 505(b)(1) of the FDC Act.

B. Scientific Basis for the Legal Standard

The usual requirement for more than one adequate and well-controlled investigation reflects the need for *independent substantiation* of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness. The reasons for this include the following.

- Any clinical trial may be subject to unanticipated, undetected, systematic biases. These biases may operate despite the best intentions of sponsors and investigators, and may lead to flawed conclusions. In addition, some investigators may bring conscious biases to evaluations.

- The inherent variability in biological systems may produce a positive trial result by chance alone. This possibility is acknowledged, and quantified to some extent, in the statistical evaluation of the result of a single efficacy trial. It should be noted, however, that hundreds of randomized clinical efficacy trials are conducted each year with the intent of submitting favorable results to FDA. Even if all drugs tested in such trials were ineffective, one would expect one in forty of those trials to “demonstrate” efficacy by chance alone at conventional levels of statistical significance.⁵ It is probable, therefore, that false positive findings (i.e., the chance appearance of efficacy with an ineffective drug) will occur and be submitted to FDA as evidence of effectiveness. Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.
- Results obtained in a single center may be dependent on site or investigator specific factors (e.g., disease definition, concomitant treatment, diet). In such cases, the results, although correct, may not be generalizable to the intended population. This possibility is the primary basis for emphasizing the need for independence in substantiating studies.
- Rarely, favorable efficacy results are the product of scientific fraud.

Although there are statistical, methodologic, and other safeguards to address the identified problems, they are often inadequate to address these problems in a single trial. Independent substantiation of experimental results addresses such problems by providing consistency across more than one study, thus greatly reducing the possibility that a biased, chance, site-specific, or fraudulent result will lead to an erroneous conclusion that a drug is effective.

The need for independent substantiation has often been referred to as the need for replication of the finding. Replication may not be the best term, however, as it may imply that precise repetition of the same experiment in other patients by other investigators is the only means to substantiate a conclusion. Precise replication of a trial is only one of a number of possible means of obtaining independent substantiation of a clinical finding and, at times, can be less than optimal as it could leave the conclusions vulnerable to any systematic biases inherent to the particular study design. Results that are obtained from studies that are of different design and independent in execution, perhaps evaluating different populations, endpoints, or dosage forms, may provide support for a conclusion of effectiveness that is as convincing as, or more convincing than, a repetition of the same study.

⁵ p-value = 0.05, two-tailed, which implies an error rate in the efficacy (false positive) tail of 0.025 or one in forty.

C. The Quantity of Evidence to Support Effectiveness

The following three sections provide guidance on the quantity of evidence needed in particular circumstances to establish substantial evidence of effectiveness. Section 1 addresses situations in which effectiveness of a new use may be extrapolated entirely from existing efficacy studies. Section 2 addresses situations in which a single adequate and well-controlled study of a specific new use can be supported by information from other related adequate and well-controlled studies, such as studies in other phases of a disease, in closely related diseases, of other conditions of use (different dose, duration of use, regimen), of different dosage forms, or of different endpoints. Section 3 addresses situations in which a single multicenter study, without supporting information from other adequate and well-controlled studies, may provide evidence that a use is effective.

In each of these situations, it is assumed that any studies relied on to support effectiveness meet the requirements for adequate and well-controlled studies in 21 CFR 314.126. It should also be appreciated that reliance on a single study of a given use, whether alone or with substantiation from related trial data, leaves little room for study imperfections or contradictory (non-supportive) information. In all cases, it is presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal, and that the results reflect a clear prior hypothesis documented in the protocol. Moreover, a single favorable study among several similar attempts that failed to support a finding of effectiveness would not constitute persuasive support for a product use unless there were a strong argument for discounting the outcomes in the studies that failed to show effectiveness (e.g., study obviously inadequately powered or lack of assay sensitivity as demonstrated in a three-arm study by failure of the study to show efficacy of a known active agent).

Whether to rely on a single study to support an effectiveness determination is not often an issue in contemporary drug development. In most drug development situations, the need to find an appropriate dose, to study patients of greater and lesser complexity or severity of disease, to compare the drug to other therapy, to study an adequate number of patients for safety purposes, and to otherwise know what needs to be known about a drug before it is marketed will result in more than one adequate and well-controlled study upon which to base an effectiveness determination.

This guidance is not intended to provide a complete listing of the circumstances in which existing efficacy data may provide independent substantiation of related claims; rather, it provides examples of the reasoning that may be employed. The examples are applicable whether the claim arises in the original filing of an NDA or BLA, or in a supplemental application.

1. Extrapolation from Existing Studies

In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form. The following are examples of situations in which effectiveness might be extrapolated from efficacy data for another claim or product.

a. Pediatric uses

The rule revising the Pediatric Use section of product labeling (21 CFR 201.57(f)(9)(iv)) makes allowance for inclusion of pediatric use information in labeling without controlled clinical trials of the use in children. In such cases, a sponsor must provide other information to support pediatric use, and the Agency must conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients. Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions. Examples in which pediatric use labeling information has been extrapolated from adult efficacy data include ibuprofen for pain and loratidine for seasonal allergic rhinitis.

b. Bioequivalence

The effectiveness of alternative formulations and new dosage strengths may be assessed on the basis of evidence of bioequivalence.

c. Modified-release dosage forms

In some cases, modified release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to a previously studied immediate-release dosage form. Because the pharmacokinetic patterns of modified-release and immediate-release dosage forms are not identical, it is generally important to have some understanding of the relationship of blood concentration to response, including an understanding of the time course of that relationship, to extrapolate the immediate-release

data to the modified-release dosage form.

d. Different doses, regimens, or dosage forms

Dose-response relationships are generally continuous such that information about the effectiveness of one dose, dosage regimen, or dosage form is relevant to the effectiveness of other doses, regimens, or dosage forms. Where blood levels and exposure are not very different, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data alone. Even if blood levels are quite different, if there is a well-understood relationship between blood concentration and response, including an understanding of the time course of that relationship, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial. In this situation, pharmacokinetic data, together with the well-defined pharmacokinetic/pharmacodynamic (PK/PD) relationship, are used to translate the controlled trial results from one dose, regimen, or dosage form to a new dose, regimen, or dosage form (See also section II.C.2.a).

2. Demonstration of Effectiveness by a Single Study of a New Use, with Independent Substantiation From Related Study Data

The discussion that follows describes specific examples in which a single study of a new use, with independent substantiation from study data in related uses, could provide evidence of effectiveness. In these cases, the study in the new use and the related studies support the conclusion that the drug has the effect it is purported to have. Whether related studies are capable of substantiating a single study of a new use is a matter of judgment and depends on the quality and outcomes of the studies and the degree of relatedness to the new use.

a. Different doses, regimens, or dosage forms

As discussed in Sections II.C.1.d, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial where blood levels and exposure are not very different or, even if quite different, there is a well-understood relationship between blood concentration and response. Where the relationship between blood concentration and response is not so well understood and the pharmacokinetics of the new dose, regimen, or dosage form differ from the previous one, clinical efficacy data will likely be necessary to support effectiveness of a new regimen. In this case, a single additional efficacy study should ordinarily be sufficient. For example, a single controlled trial was needed to support the recent approval of a once

daily dose of risperidone because the once daily and twice daily regimens had different pharmacokinetics and risperidone's PK/PD relationship was not well understood.

b. Studies in other phases of the disease

In many cases, therapies that are effective in one phase of a disease are effective in other disease phases, although the magnitude of the benefit and benefit-to-risk relationship may differ in these other phases. For example, if a drug is known to be effective in patients with a refractory stage of a particular cancer, a single adequate and well-controlled study of the drug in an earlier stage of the same tumor will generally be sufficient evidence of effectiveness to support the new use.

c. Studies in other populations

Often, responses in subsets of a particular patient population are qualitatively similar to those in the whole population. In most cases, separate studies of effectiveness in demographic subsets are not needed (see also discussion of the pediatric population in section II.C.1.a). However, where further studies are needed, a single study would ordinarily suffice to support effectiveness in age, race, gender, concomitant disease, or other subsets for a drug already shown to be generally effective in a condition or to be effective in one population. For example, a single study was sufficient to support tamoxifen use in breast cancer in males.

d. Studies in combination or as monotherapy

For a drug known to be effective as monotherapy, a single adequate and well-controlled study is usually sufficient to support effectiveness of the drug when combined with other therapy (as part of a multidrug regimen or in a fixed-dose combination). Similarly, known effectiveness of a drug as part of a combination (i.e., its contribution to the effect of the combination is known) would usually permit reliance on a single study of appropriate design to support its use as monotherapy, or as part of a different combination, for the same use. For example, a single study of a new combination vaccine designed to demonstrate adequate immune response will ordinarily provide sufficient evidence of effectiveness if the new combination contains products or antigens already proven to be effective alone or in other combinations. These situations are common for oncologic and antihypertensive drugs, but occur elsewhere as well.

e. Studies in a closely related disease

Studies in etiologically or pathophysiologically related conditions, or studies of a symptom common to several diseases (e.g., pain) can support each other, allowing initial approval of several uses or allowing additional claims based on a single adequate and well-controlled study. For example, certain anti-coagulant or anti-platelet therapies could be approved for use in two different settings based on individual studies in unstable angina/acute coronary syndrome and in the postangioplasty state. Because the endpoints studied and the theoretical basis for use of an anti-coagulant or anti-platelet drug are similar, each study supports the other for each claim. Similarly, single analgesic studies in several painful conditions would ordinarily be sufficient to support either a general analgesic indication or multiple specific indications. The recent approval of lamotrigine for treatment of Lennox-Gastaut Syndrome (a rare, largely pediatric, generalized seizure disorder) was based on a single adequate and well-controlled trial, due in part to related data showing efficacy of the drug in partial-onset seizures in adults.

f. Studies in less closely related diseases, but where the general purpose of therapy is similar

Certain classes of drug therapy, such as antimicrobials and antineoplastics, are appropriate interventions across a range of different diseases. For therapies of this type, evidence of effectiveness in one disease could provide independent substantiation of effectiveness in a quite different disease. For example, it is possible to argue that evidence of effectiveness of an antimicrobial in one infectious disease setting may support reliance on a single study showing effectiveness in other settings where the causative pathogens, characteristics of the site of infection that affect the disease process (e.g., structure and immunology) and patient population are similar.⁶ Similarly, for an oncologic drug, evidence of effectiveness in one or more tumor types may support reliance on a single study showing effectiveness against a different kind of tumor, especially if the tumor types have a common biological origin.

g. Studies of different clinical endpoints

Demonstration of a beneficial effect in different studies on two different clinically meaningful endpoints could cross-substantiate a claim for

⁶ See Division of Anti-Infective Drug Products: Points to Consider in the Clinical Development and Labeling of Anti-Infective Drug Products, October 1992.

effectiveness for each outcome. For example, the initial claim for effectiveness of enalapril for heart failure was supported by one study showing symptom improvement over several months and a second study showing improved survival in a more severely ill population. The two different findings, each from an adequate and well-controlled study, led to the conclusion that enalapril was effective in both treating symptoms and improving survival.

h. Pharmacologic/pathophysiologic endpoints

When the pathophysiology of a disease and the mechanism of action of a therapy are very well understood, it may be possible to link specific pharmacologic effects to a strong likelihood of clinical effectiveness. A pharmacologic effect that is accepted as a validated surrogate endpoint can support ordinary approval (e.g., blood pressure effects, cholesterol-lowering effects) and a pharmacologic effect that is considered reasonably likely to predict clinical benefit can support accelerated approval under the conditions described in 21 CFR 314 Subpart H and 21 CFR 601 Subpart E (e.g., CD4 count and viral load effects to support effectiveness of anti-viral drugs for HIV infection). When the pharmacologic effect is not considered an acceptable effectiveness endpoint, but the linkage between it and the clinical outcome is strong, not merely on theoretical grounds but based on prior therapeutic experience or well-understood pathophysiology, a single adequate and well-controlled study showing clinical efficacy can sometimes be substantiated by persuasive data from a well-controlled study or studies showing the related pharmacologic effect.

For example, a single clearly positive trial can be sufficient to support approval of a replacement therapy such as a coagulation factor, when it is combined with clear evidence that the condition being treated is caused by a deficiency of that factor. Demonstration of physical replacement of the deficient factor or restoration of the missing physiologic activity provides strong substantiation of the clinical effect. The corrective treatment of an inborn error of metabolism could be viewed similarly. In the case of preventive vaccines, one adequate and well-controlled clinical trial may be supported by compelling animal challenge/protection models, human serological data, passive antibody data, or pathogenesis information. The more evidence there is linking effects on the pharmacologic endpoint to improvement or prevention of the disease, the more persuasive the argument for reliance on a single clinical efficacy study.

Note, however, that plausible beneficial pharmacologic effects have often not correlated with clinical benefit, and, therefore, caution must be observed in relying on a pharmacologic effect as contributing to evidence

of effectiveness. For example, pharmacologic effects such as arrhythmia suppression by Type 1 antiarrhythmics and increased cardiac output by phosphodiesterase inhibitors or beta adrenergic inotropes resulted in increased mortality, rather than, as was expected, decreased sudden death and improved outcome in heart failure. The reasons for the absence of an expected correlation between pharmacologic and clinical effects are diverse and can include an incompletely understood relationship between the pharmacologic effect and the clinical benefit and the presence of other pharmacologic effects attributable to a drug in addition to the effect being measured and thought to be beneficial. Generally, the utility of pharmacologic outcomes in providing independent substantiation will be greatest where there is prior experience with the pharmacologic class. Even in this case, however, it is difficult to be certain that a pharmacologic effect that correlates with a clinical benefit accounts for all the clinical benefit or that other effects are not present and relevant.

3. Evidence of Effectiveness from a Single Study

When the effectiveness requirement was originally implemented in 1962, the prevailing efficacy study model was a single institution, single investigator, relatively small trial with relatively loose blinding procedures, and little attention to prospective study design and identification of outcomes and analyses. At present, major clinical efficacy studies are typically multicentered, with clear, prospectively determined clinical and statistical analytic criteria. These studies are less vulnerable to certain biases, are often more generalizable, may achieve very convincing statistical results, and can often be evaluated for internal consistency across subgroups, centers, and multiple endpoints.

The added rigor and size of contemporary clinical trials have made it possible to rely, in certain circumstances, on a single adequate and well-controlled study, without independent substantiation from another controlled trial, as a sufficient scientific and legal basis for approval. For example, the approval of timolol for reduction of post-infarction mortality was based on a single, particularly persuasive (low p-value), internally consistent, multicenter study that demonstrated a major effect on mortality and reinfarction rate. For ethical reasons, the study was considered unrepeatable. The Center for Biologics Evaluation and Research has also approved a number of products based upon a single persuasive study. The Agency provided a general statement in 1995 describing when a single, multicenter study may suffice (60 FR 39181; August 1, 1995), but the Agency has not comprehensively described the situations in which a single adequate and well-controlled study might be considered adequate support for an effectiveness claim, or the characteristics of a single study that could make it adequate support for an effectiveness claim.

Whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. For example, sequential repetition of strongly positive trials that demonstrated a decrease in post-infarction mortality, prevention of osteoporotic fractures, or prevention of pertussis would present significant ethical concerns. Repetition of positive trials showing only symptomatic benefit would generally not present the same ethical concerns.

The discussion that follows identifies the characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim. Although no one of these characteristics is necessarily determinative, the presence of one or more in a study can contribute to a conclusion that the study would be adequate to support an effectiveness claim.

a. Large multicenter study

In a large multicenter study in which (1) no single study site provided an unusually large fraction of the patients and (2) no single investigator or site was disproportionately responsible for the favorable effect seen, the study's internal consistency lessens concerns about lack of generalizability of the finding or an inexplicable result attributable only to the practice of a single investigator. If analysis shows that a single site is largely responsible for the effect, the credibility of a multicenter study is diminished.

b. Consistency across study subsets

Frequently, large trials have relatively broad entry criteria and the study populations may be diverse with regard to important covariates such as concomitant or prior therapy, disease stage, age, gender or race. Analysis of the results of such trials for consistency across key patient subsets addresses concerns about generalizability of findings to various populations in a manner that may not be possible with smaller trials or trials with more narrow entry criteria. For example, the timolol postinfarction study randomized patients separately within three severity strata. The study showed positive effects on survival in each stratum supporting a conclusion that the drug's utility was not limited to a particular disease stage (e.g., relatively low or high severity).

c. Multiple *studies* in a single study

Properly designed factorial studies may be analyzed as a series of pairwise comparisons, representing, within a single study, separate demonstrations of activity of a drug as monotherapy and in combination with another drug. This model was successfully used in ISIS II, which showed that for patients with a myocardial infarction both aspirin and streptokinase had favorable effects on survival when used alone and when combined (aspirin alone and streptokinase alone were each superior to placebo; aspirin and streptokinase in combination were superior to aspirin alone and to streptokinase alone). This represented two separate (but not completely independent) demonstrations of the effectiveness of aspirin and streptokinase.

d. Multiple endpoints involving different events

In some cases, a single study will include several important, prospectively identified primary or secondary endpoints, each of which represents a beneficial, but different, effect. Where a study shows statistically persuasive evidence of an effect on more than one of such endpoints, the internal weight of evidence of the study is enhanced. For example, the approval of beta-interferon (Betaseron) for prevention of exacerbations in multiple sclerosis was based on a single multicenter study, at least partly because there were both a decreased rate of exacerbations and a decrease in MRI-demonstrated disease activity — two entirely different, but logically related, endpoints.

Similarly, favorable effects on both death and nonfatal myocardial infarctions in a lipid-lowering, postangioplasty, or postinfarction study would, in effect, represent different, but consistent, demonstrations of effectiveness, greatly reducing the possibility that a finding of reduced mortality was a chance occurrence. For example, approval of abciximab as adjunctive treatment for patients undergoing complicated angioplasty or atherectomy was supported by a single study with a strong overall result on the combined endpoint (decreased the combined total of deaths, new infarctions, and need for urgent interventions) and statistically significant effects in separate evaluations of two components of the combined endpoint (decreased new infarctions and decreased need for urgent interventions). In contrast, a beneficial effect on multiple endpoints that evaluate essentially the same phenomenon and correlate strongly, such as mood change on two different depression scales or SGOT and CPK levels postinfarction, does not significantly enhance the internal weight of the evidence from a single trial.

Although two consistent findings within a single study usually provide reassurance that a positive treatment effect is not due to chance, they do not protect against bias in study conduct or biased analyses. For example, a treatment assignment not well balanced for important prognostic variables could lead to an apparent effect on both endpoints. Thus, close scrutiny of study design and conduct are critical to evaluating this type of study.

e. Statistically very persuasive finding

In a multicenter study, a very low p-value indicates that the result is highly inconsistent with the null hypothesis of no treatment effect. In some studies it is possible to detect nominally statistically significant results in data from several centers, but, even where that is not possible, an overall extreme result and significance level means that most study centers had similar findings. For example, the thrombolysis trials of streptokinase (ISIS II, GISSI) had very sizable treatment effects and very low p-values, greatly adding to their persuasiveness. Preventive vaccines for infectious disease indications with a high efficacy rate (e.g., point estimate of efficacy of 80% or higher and a reasonably narrow 95% confidence interval) have been approved based on a single adequate and well-controlled trial.

4. Reliance on a Single, Multicenter Study — Caveats

While acknowledging the persuasiveness of a single, internally consistent, strong multicenter study, it must be appreciated that even a strong result can represent an isolated or biased result, especially if that study is the only study suggesting efficacy among similar studies. Recently, the apparent highly favorable effect of vesnarinone, an inotropic agent, in heart failure (60% reduction of mortality in what appeared to be a well-designed, placebo-controlled, multicenter trial with an extreme p-value) has proven to be unrepeatable. In an attempt to substantiate the finding, the same dose of the drug that seemed lifesaving in the earlier study significantly increased mortality (by 26%), and a lower dose also appeared to have a detrimental effect on survival. Although the population in the second study was, on the whole, a sicker population than in the first, the outcomes in similarly sick patients in each study were inconsistent so this factor does not explain the contradictory results.

When considering whether to rely on a single multicenter trial, it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single multicenter trial. In the case of vesnarinone, there were other data that were not consistent with the dramatically favorable outcome in the multicenter study. These data seemed to show an inverse dose-response relationship, showed no suggestion

of symptomatic benefit, and showed no effect on hemodynamic endpoints. These inconsistencies led the Agency, with the advice of its Cardio-Renal Advisory Committee, to refuse approval — a decision borne out by the results of the subsequent study.

This example illustrates how inadequacies and inconsistencies in the data, such as lack of pharmacologic rationale and lack of expected other effects accompanying a critical outcome, can weaken the persuasiveness of a single trial. Although an unexplained failure to substantiate the results of a favorable study in a second controlled trial is not proof that the favorable study was in error — studies of effective agents can fail to show efficacy for a variety of reasons — it is often reason not to rely on the single favorable study.

III. DOCUMENTATION OF THE QUALITY OF EVIDENCE SUPPORTING AN EFFECTIVENESS CLAIM

When submitting the requisite quantity of data to support approval of a new product or new use of an approved product, sponsors must also document that the studies were adequately designed and conducted. Essential characteristics of adequate and well-controlled trials are described in 21 CFR 314.126. To demonstrate that a trial supporting an effectiveness claim is adequate and well-controlled, extensive documentation of trial planning, protocols, conduct, and data handling is usually submitted to the Agency, and detailed patient records are made available at the clinical sites.

From a scientific standpoint, however, it is recognized that the extent of documentation necessary depends on the particular study, the types of data involved, and the other evidence available to support the claim. Therefore, the Agency is able to accept different levels of documentation of data quality, as long as the adequacy of the scientific evidence can be assured. This section discusses the factors that influence the extent of documentation needed, with particular emphasis on studies evaluating new uses of approved drugs.

For the purposes of this section, the phrase *documentation of the quality of evidence* refers to (1) the completeness of the documentation and (2) the ability to access the primary study data and the original study-related records (e.g., subjects' medical records, drug accountability records) for the purposes of verifying the data submitted as evidence. These interrelated elements bear on a determination of whether a study is adequate and well-controlled.

In practice, to achieve a high level of documentation, studies supporting claims are ordinarily conducted in accordance with good clinical practices (GCPs). Sponsors routinely monitor all clinical sites, and FDA routinely has access to the original clinical protocols, primary data, clinical site source documents for on-site audits, and complete study reports.

However, situations often arise in which studies that evaluate the efficacy of a drug product lack the full documentation described above (for example, full patient records may not be available) or in which the study was conducted with less monitoring than is ordinarily seen in commercially sponsored trials. Such situations are more common for supplemental indications because postapproval studies are more likely to be conducted by parties other than the drug sponsor and those parties may employ less extensive monitoring and data-gathering procedures than a sponsor. Under certain circumstances, it is possible for sponsors to rely on such studies to support effectiveness claims, despite less than usual documentation or monitoring. Some of those circumstances are described below.

A. Reliance on Less Than Usual Access to Clinical Data or Detailed Study Reports

FDA's access to primary data has proven to be important in many regulatory decisions. There are also reasons to be skeptical of the conclusions of published reports of studies. Experience has shown that such study reports do not always contain a complete, or entirely accurate, representation of study plans, conduct and outcomes. Outright fraud (i.e., deliberate deception) is unusual. However, incompleteness, lack of clarity, unmentioned deviation from prospectively planned analyses, or an inadequate description of how critical endpoint judgments or assessments were made are common flaws. Typically, journal article peer reviewers only have access to a limited data set and analyses, do not see the original protocol and amendments, may not know what happened to study subjects that investigators determined to be non-evaluable, and thus may lack sufficient information to detect critical omissions and problems. The utility of peer review can also be affected by variability in the relevant experience and expertise of peer reviewers. FDA's experiences with the Anturane Reinfarction Trial, as well as literature reports of the efficacy of tacrine and the anti-sepsis HA-1A antibody, illustrate its concerns with reliance on the published medical literature.

Notwithstanding these concerns, the presence of some of the factors discussed below can make it possible for FDA to rely on studies for which it has less than usual access to data or detailed study reports to partially or entirely (the so-called *paper* filing) support an effectiveness claim. FDA's reliance on a literature report to support an effectiveness claim is more likely if FDA can obtain additional critical study details. Section 1 below describes additional information that, if available, would increase the likelihood that a study could be relied on to support an effectiveness claim. Section 2 describes factors that may make efficacy findings sufficiently persuasive to permit reliance on the published literature alone. Note that the factors outlined in Section 2 are relevant to an assessment of the reliability of literature reports generally, whether alone, or accompanied by other important information as discussed in Section 1.

1. Submission of Published Literature or Other Reports in Conjunction with Other Important Information that Enhances the Reliability of the Data

If a sponsor wishes to rely on a study conducted by another party and cannot obtain the primary data from the study, for most well-conducted studies it is possible to obtain other important information, such as a protocol documenting the prospective plans for the trial, records of trial conduct and procedures, patient data listings for important variables, and documentation of the statistical analysis. FDA has considerable experience evaluating large multicenter outcome studies sponsored by U.S. and European government agencies (NIH, British Medical Research Council) and private organizations (the ISIS studies, the SAVE study) for which there was limited access to primary study data, but for which other critical information was available. Providing as many as possible of the following important pieces of information about a study, in conjunction with the published report, can increase the likelihood that the study can be relied on to support an effectiveness claim:

- a. The protocol used for the study, as well as any important protocol amendments that were implemented during the study and their relation to study accrual or randomization.
- b. The prospective statistical analysis plan and any changes from the original plan that occurred during or after the study, with particular note of which analyses were performed pre- and post-unblinding.
- c. Randomization codes and documented study entry dates for the subjects.
- d. Full accounting of all study subjects, including identification of any subjects with on-treatment data who have been omitted from analysis and the reasons for omissions, and an analysis of results using all subjects with on-study data.
- e. Electronic or paper record of each subject's data for critical variables and pertinent baseline characteristics. Where individual subject responses are a critical variable (e.g., objective responses in cancer patients, clinical cures and microbial eradications in infectious disease patients, death from a particular cause), detailed bases for the assessment, such as the case report, hospital records, and narratives, should be provided when possible.
- f. Where safety is a major issue, complete information for all deaths and drop-outs due to toxicity. For postapproval supplemental uses, however, there is generally less need for the results of lab tests or for details of adverse event reports and, consequently, much more limited documentation may be sufficient (e.g., only for unexpected deaths and previously undescribed serious adverse effects). Exceptions to this

approach would include situations in which the population for the supplemental use is so different that existing safety information has limited application (e.g., thrombolysis in stroke patients versus myocardial infarction patients) or where the new population presents serious safety concerns (e.g., extension of a preventive vaccine indication from young children to infants).

2. Submission of Published Literature Reports Alone

The following factors increase the possibility of reliance on published reports alone to support approval of a new product or new use:

- a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.
- b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.
- c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.
- d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or "evaluable" subset).
- e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

There have been approvals based primarily or exclusively on published reports. Examples include the initial approval of secretin for evaluation of pancreatic function and recent approvals of bleomycin and talc for malignant pleural effusion and doxycycline for malaria.

B. Reliance on Studies with Alternative, Less Intensive Quality Control/On-Site Monitoring

Industry-sponsored studies typically use extensive on-site and central monitoring and auditing procedures to assure data quality. Studies supported by other sponsors may employ less stringent procedures and may use no on-site monitoring at all. An International Conference on Harmonisation guideline on good clinical practices,⁷ recently accepted internationally, emphasizes that the extent of monitoring in a trial should be based on trial-specific factors (e.g., design, complexity, size, and type of study outcome measures) and that different degrees of on-site monitoring can be appropriate. In recent years, many credible and valuable studies conducted by government or independent study groups, often with important mortality outcomes, had very little on-site monitoring. These studies have addressed quality control in other ways, such as by close control and review of documentation and extensive guidance and planning efforts with investigators. There is a long history of reliance on such studies for initial approval of drugs as well as for additional indications. Factors that influence whether studies with limited or no monitoring may be relied on include the following:

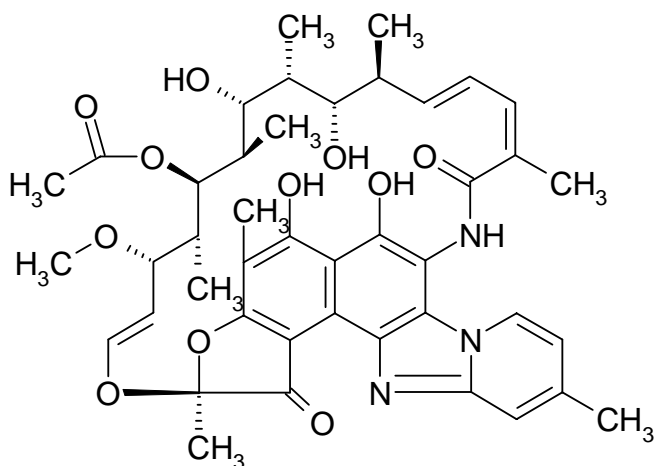
1. The existence of a prospective plan to assure data quality.
2. Studies that have features that make them inherently less susceptible to bias, such as those with relatively simple procedures, noncritical entry criteria, and readily assessed outcomes.
3. The ability to sample critical data and make comparisons to supporting records (e.g., hospital records).
4. Conduct of the study by a group with established operating procedures and a history of implementing such procedures effectively.

⁷ International Conference on Harmonisation Guidance for Industry E6, *Good Clinical Practice: Consolidated Guideline*, April 1996.

XIFAXAN[®] (rifaximin) Tablets
(zuh FAX in)

DESCRIPTION

XIFAXAN[®] Tablets contain rifaximin, a semi-synthetic, nonsystemic antibiotic. The chemical name for rifaximin is (2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca-[1,11,13]trienimino)benzofuro[4,5-*e*]pyrido[1,2-*a*]-benzimidazole-1,15(2*H*)-dione,25-acetate. The empirical formula is C₄₃H₅₁N₃O₁₁ and its molecular weight is 785.9. The chemical structure is represented below:



XIFAXAN® Tablets for oral administration are film-coated and contain 200 mg of rifaximin. Inactive ingredients are colloidal silicon dioxide, disodium edetate, glycerol palmitostearate, hypromellose, microcrystalline cellulose, propylene glycol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: The mean pharmacokinetic parameters of rifaximin in 14 healthy subjects after a single oral 400-mg dose given as 2 x 200 mg doses under fed and fasting conditions are summarized in Table 1.

Table 1. Effect of Food on the Mean \pm S.D. Pharmacokinetic Parameters Following a Single 400-mg Dose of Rifaximin (N = 14)

Parameter	Fasting	Fed
C _{max} (ng/mL)	3.80 \pm 1.32	9.63 \pm 5.93
T _{max} (h)	1.21 \pm 0.47	1.90 \pm 1.52
Half-Life (h)	5.85 \pm 4.34	5.95 \pm 1.88
AUC (ng·h/mL)	18.35 \pm 9.48	34.70 \pm 9.23
% Excreted in Urine	0.023 \pm 0.009	0.051 \pm 0.017

Rifaximin can be administered with or without food. Systemic absorption of rifaximin was low in both the fasting state and when administered within 30 minutes of a high-fat breakfast.

¹⁴C-Rifaximin was administered as a single dose to 4 healthy male subjects. The mean overall recovery of radioactivity in the urine and feces of 3 subjects during the 168 hours after administration was 96.94 \pm 5.64% of the dose. Radioactivity was excreted almost exclusively in the feces (96.62 \pm 5.67% of the dose), with only a small proportion of the dose (mean 0.32% of the dose) excreted in urine. Analysis of fecal extracts indicated that rifaximin was being excreted as unchanged drug. The amount of radioactivity in urine (<0.4% of the dose) suggests that rifaximin is poorly absorbed from the gastrointestinal tract and is almost exclusively and completely excreted in feces as unchanged drug. Mean rifaximin pharmacokinetic parameters were C_{max} 4.3 \pm 2.8 ng/mL and AUC_t 19.5 \pm 16.5 ng·h/mL with a median T_{max} of 1.25 hours.

Systemic absorption of rifaximin (200 mg three times daily) was also evaluated in 13 subjects with shigellosis on Days 1 and 3 of a three-day course of treatment. Rifaximin concentrations and exposures were low and variable. There was no evidence of accumulation of rifaximin following repeated administration for 3 days (9 doses). Peak plasma rifaximin concentrations after 3 and 9

consecutive doses ranged from 0.81 to 3.4 ng/mL on Day 1 and 0.68 to 2.26 ng/mL on Day 3.

Similarly, AUC_{0-last} estimates were 6.95 ± 5.15 ng•h/mL on Day 1 and 7.83 ± 4.94 ng•h/mL on Day

3. Rifaximin is not suitable for treating systemic bacterial infections because less than 0.4% of the drug is absorbed after oral administration (see **WARNINGS**).

Distribution: Animal pharmacokinetic studies have demonstrated that 80% to 90% of orally administered rifaximin is concentrated in the gut with less than 0.2% in the liver and kidney, and less than 0.01% in other tissues. In adults with infectious diarrhea treated with rifaximin 800 mg daily for three days, concentrations of rifaximin in stools averaged ~8000 µg/g the day after treatment ended.

Metabolism: *In vitro* drug interactions studies have shown that rifaximin, at concentrations ranging from 2 to 200 ng/mL, did not inhibit human hepatic cytochrome P450 isoenzymes: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4. In an *in vitro* hepatocyte induction model, rifaximin was shown to induce cytochrome P450 3A4 (CYP3A4), an isoenzyme which rifampin is known to induce. Two clinical drug-drug interaction studies using midazolam and an oral contraceptive containing ethinyl estradiol and norgestimate demonstrated that rifaximin did not alter the pharmacokinetics of these drugs (see **Drug-Drug Interactions**).

Excretion: Rifaximin is excreted primarily in the feces. After oral administration of 400 mg ¹⁴C-rifaximin to healthy volunteers, approximately 97% of the dose was recovered in feces, almost entirely as unchanged drug, and 0.32% was recovered in the urine.

Special Populations

Geriatric: The pharmacokinetics of rifaximin in patients ≥ 65 years of age has not been studied.

Pediatric: The pharmacokinetics of rifaximin has not been studied in pediatric patients of any age.

Gender: The effect of gender on the pharmacokinetics of rifaximin has not been studied.

Renal Insufficiency: The pharmacokinetics of rifaximin in patients with impaired renal function has not been studied.

Hepatic Insufficiency: Mean peak rifaximin plasma concentrations of 13.5 µg/mL were detected in hepatic encephalopathy patients administered rifaximin 800 mg three times daily for 7 days. Less than 0.1% of the administered dose was recovered after 7 days. Because of the limited systemic absorption of rifaximin, no specific dosing adjustments are recommended for patients with hepatic insufficiency.

Drug-Drug Interactions

In an *in vitro* hepatocyte induction model, rifaximin was shown to induce cytochrome P450 3A4 (CYP3A4), an isoenzyme which rifampin is known to induce. Two clinical drug-drug interaction studies were conducted using midazolam and an oral contraceptive containing ethinyl estradiol and norgestimate to assess the effect of rifaximin on the pharmacokinetics of these drugs.

The midazolam study was an open-label, randomized, crossover, drug-interaction trial designed to assess the effect of rifaximin 200 mg administered orally (PO) every 8 hours (Q8H) for 3 days and every 8 hours for 7 days, on the pharmacokinetics of a single dose of either midazolam 2 mg intravenous (IV) or midazolam 6 mg PO. No significant difference was observed in the metrics of systemic exposure or elimination of IV or PO midazolam or its major metabolite, 1'-hydroxymidazolam, between midazolam alone or together with rifaximin. Therefore, rifaximin was not shown to significantly affect intestinal or hepatic CYP3A4 activity.

The oral contraceptive study utilized an open-label, crossover design in 28 healthy female subjects to determine if rifaximin 200 mg PO administered Q8H for 3 days altered the pharmacokinetics of a single dose of an oral contraceptive containing 0.07 mg ethinyl estradiol and 0.50 mg norgestimate. Results showed that the pharmacokinetics of single doses of ethinyl estradiol and norgestimate were not altered by rifaximin.

Microbiology

Rifaximin acts by binding to the beta-subunit of bacterial DNAdependent RNA polymerase resulting in inhibition of bacterial RNA synthesis.

Escherichia coli has been shown to develop resistance to rifaximin *in vitro*. However, the clinical significance of such an effect has not been studied. Rifaximin is a structural analog of rifampin. Organisms with high rifaximin minimum inhibitory concentration (MIC) values also have elevated MIC values against rifampin. Cross-resistance between rifaximin and other classes of antimicrobials has not been studied.

Rifaximin has been shown to be active against the following pathogen in clinical studies of infectious diarrhea as described in the **INDICATIONS AND USAGE** section: *Escherichia coli* (enterotoxigenic and enteroaggregative strains).

Susceptibility Tests

In vitro susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) agar dilution method M7-A61. However, the correlation between susceptibility testing and clinical outcome has not been determined.

INDICATIONS AND USAGE

XIFAXAN[®] Tablets are indicated for the treatment of patients (≥ 12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* (see **WARNINGS**, **Microbiology**, and **CLINICAL STUDIES**).

XIFAXAN[®] Tablets should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*.

CONTRAINDICATIONS

XIFAXAN[®] Tablets are contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN[®] Tablets.

WARNINGS

XIFAXAN[®] Tablets were not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*.

XIFAXAN[®] Tablets are not effective in cases of travelers' diarrhea due to *Campylobacter jejuni*. The effectiveness of XIFAXAN[®] Tablets in travelers' diarrhea caused by *Shigella* spp. and *Salmonella* spp. has not been proven. XIFAXAN[®] Tablets should not be used in patients where *Campylobacter jejuni*, *Shigella* spp., or *Salmonella* spp. may be suspected as causative pathogens.

XIFAXAN[®] Tablets should be discontinued if diarrhea symptoms get worse or persist more than 24-48 hours and alternative antibiotic therapy should be considered.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of “antibiotic-associated colitis.”

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug

discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile*.

PRECAUTIONS

General

The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Information for Patients

Patients should be advised that XIFAXAN[®] Tablets may be taken with or without food. Patients should be advised that XIFAXAN[®] Tablets should be discontinued if their diarrhea persists

more than 24-48 hours or worsens, or if they have fever and/or blood in the stool that they should seek medical care (see **Patient Information**).

Drug-Drug Interactions

Although *in vitro* studies demonstrated the potential of rifaximin to interact with cytochrome P450 3A4 (CYP3A4), a clinical drug-drug interaction study demonstrated that rifaximin did not significantly affect the pharmacokinetics of midazolam either presystemically or systemically. An additional clinical drug-drug interaction study showed no effect of rifaximin on the presystemic metabolism of an oral contraceptive containing ethinyl estradiol and norgestimate. Therefore, clinical interactions with drugs metabolized by human cytochrome P450 isoenzymes are not expected (see **Pharmacokinetics** and **Drug-Drug Interactions**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were not conducted. Rifaximin was not genotoxic in the bacterial reverse mutation assay, chromosomal aberration assay, rat bone marrow micronucleus assay, and the CHO/HGPRT mutation assay. There was no effect on fertility in male or female rats following the administration of rifaximin at doses up to 300 mg/kg (approximately 5 times the clinical dose, adjusted for body surface area).

Pregnancy—Teratogenic Effects (Pregnancy Category C)

Pregnancy

Pregnancy category C: Rifaximin was teratogenic in rats at doses of 150 to 300 mg/kg (approximately 2.5 to 5 times the clinical dose, adjusted for body surface area) and in rabbits at doses of 62.5 to 1000 mg/kg (approximately 2 to 33 times the clinical dose, adjusted for body surface area). These effects include cleft palate, agnathia, jaw shortening, hemorrhage, eye

partially open, small eyes, brachygnathia, incomplete ossification, and increased thoracolumbar vertebrae. There are no adequate and well controlled studies in pregnant women. XIFAXAN[®] Tablets should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Use during lactation

It is not known whether rifaximin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from XIFAXAN[®] Tablets, a decision should be made whether to dis-continue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of XIFAXAN[®] Tablets in pediatric patients less than 12 years of age have not been established.

Geriatric Use

Clinical studies of XIFAXAN[®] Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects.

ADVERSE REACTIONS

The safety of XIFAXAN[®] Tablets 200 mg taken three times a day (TID) was evaluated in 320 patients in two placebo-controlled clinical trials with 95% of patients receiving at least three days of treatment with XIFAXAN[®] Tablets. All adverse events for XIFAXAN[®] Tablets 200 mg TID that occurred at a frequency $\geq 2\%$ in the two placebo-controlled trials combined are provided in Table 2. (These include adverse events that may be attributable to the underlying disease.)

Table 2. All Adverse Events With an Incidence $\geq 2\%$ Among Patients Receiving XIFAXANTM Tablets, 600 mg/day, in Placebo-Controlled Studies

MedDRA Preferred Term	Number (%) of Patients	
	XIFAXANTM Tablets, 600 mg/day (N = 320)	Placebo N = 228
Flatulence	36 (11.3%)	45 (19.7%)
Headache	31 (9.7%)	21 (9.2%)
Abdominal Pain NOS	23 (7.2%)	23 (10.1%)
Rectal Tenesmus	23 (7.2%)	20 (8.8%)
Defecation Urgency	19 (5.9%)	21 (9.2%)
Nausea	17 (5.3%)	19 (8.3%)
Constipation	12 (3.8%)	8 (3.5%)
Pyrexia	10 (3.1%)	10 (4.4%)
Vomiting NOS	7 (2.2%)	4 (1.8%)

The following adverse events, presented by body system, have also been reported in $<2\%$ of patients taking XIFAXAN[®] Tablets in the two placebo-controlled clinical trials where the 200 mg taken three times a day dose was used. The following includes adverse events regardless of causal relationship to drug exposure.

Blood and Lymphatic System Disorders: lymphocytosis, monocytosis, neutropenia

Ear and Labyrinth Disorders: ear pain, motion sickness, tinnitus

Gastrointestinal Disorders: abdominal distension, diarrhea NOS, dry throat, fecal abnormality NOS, gingival disorder NOS, inguinal hernia NOS, dry lips, stomach discomfort

General Disorders and Administration Site Conditions: chest pain, fatigue, malaise, pain NOS, weakness

Infections and Infestations: dysentery NOS, respiratory tract infection NOS, upper respiratory tract infection NOS

Injury and Poisoning: sunburn

Investigations: aspartate aminotransferase increased, blood in stool, blood in urine, weight decreased

Metabolic and Nutritional Disorders: anorexia, dehydration

Musculoskeletal, Connective Tissue, and Bone Disorders: arthralgia, muscle spasms, myalgia, neck pain

Nervous System Disorders: abnormal dreams, dizziness, migraine NOS, syncope, loss of taste

Psychiatric Disorders: insomnia

Renal and Urinary Disorders: choluria, dysuria, hematuria, polyuria, proteinuria, urinary frequency

Respiratory, Thoracic, and Mediastinal Disorders: dyspnea NOS, nasal passage irritation,

nasopharyngitis, pharyngitis, pharyngolaryngeal pain, rhinitis NOS, rhinorrhea

Skin and Subcutaneous Tissue Disorders: clamminess, rash NOS, sweating increased

Vascular Disorders: hot flashes NOS

Postmarketing Experience

The following events: hypersensitivity reactions, including exfoliative dermatitis, rash, angioneurotic edema (swelling of face and tongue and difficulty swallowing), urticaria, flushing, and pruritus; have been identified during post-approval use of XIFAXAN[®] Tablets. These events occurred as early as within 15 minutes of drug administration.

DRUG ABUSE AND DEPENDENCY

Abuse

None reported.

Dependency

None reported.

OVERDOSAGE

No specific information is available on the treatment of overdose with XIFAXAN[®] Tablets. In clinical studies at doses higher than the recommended dose (> 600 mg/day), adverse events were similar to the recommended dose (200 mg taken three times a day) and to placebo. In the case of overdose, discontinue XIFAXAN[®] Tablets, treat symptomatically, and institute supportive measures as required.

DOSAGE AND ADMINISTRATION

XIFAXAN[®] Tablets can be administered orally with or without food. For travelers' diarrhea, the recommended dose is one 200 mg tablet taken three times a day for 3 days.

HOW SUPPLIED

XIFAXAN[®] Tablets are available as circular, pink-colored, biconvex tablets containing 200 mg rifaximin, debossed with "Sx" on one side.

NDC 65649-301-03 Bottles of 30 tablets

NDC 65649-301-41 Bottles of 100 tablets

NDC 65649-301-05 Carton of 100 Tablets, Unit Dose

Store XIFAXAN[®] Tablets at 20–25°C (68–77°F); excursions permitted to 15–30°C (59–86°F). See USP Controlled Room Temperature.

CLINICAL STUDIES

The efficacy of rifaximin (200 mg orally taken three times a day for 3 days) was evaluated in two-randomized, multi-center, double-blind, placebo controlled studies in adult subjects with travelers' diarrhea. One study was conducted at clinical sites in Mexico, Guatemala, and Kenya (Study 1). The other study was conducted in Mexico, Guatemala, Peru, and India (Study 2).

Stool specimens were collected before treatment and 1 to 3 days following the end of treatment to identify enteric pathogens. The predominant pathogen in both studies was *Escherichia coli*.

The clinical efficacy of rifaximin was assessed by the time to return to normal, formed stools and resolution of symptoms. The primary efficacy endpoint was time to last unformed stool (TLUS) which is defined as the time to the last unformed stool passed, after which clinical cure was declared. Table 3 displays the median TLUS and the number of patients who achieved clinical cure for the intent to treat population (ITT) of Study 1. The duration of diarrhea was significantly shorter in patients treated with rifaximin than in the placebo group. More rifaximin-treated patients were classified as clinical cures than were those in the placebo group.

Table 3 - Clinical Response in Study 1 (ITT population)

	Rifaximin (n=125)	Placebo (n=129)	Estimate (97.5% CI)	P-Value
Median TLUS (hours)	32.5	58.6	1.78 ^a (1.26, 2.50)	0.0002
<u>Clinical cure</u> , n (%)	99 (79.2)	78 (60.5)	18.7 ^b (5.3, 32.1)	0.001

^a Hazard Ratio

^b Difference in rates

Microbiological eradication (defined as the absence of a baseline pathogen in culture of stool after 72 hours of therapy) rates for Study 1 are presented in Table 4 for patients with any pathogen at baseline and for the subset of patients with *Escherichia coli* at baseline. *Escherichia coli* was the only pathogen with sufficient numbers to allow comparisons between treatment groups.

Even though rifaximin had microbiologic activity similar to placebo, it demonstrated a clinically significant reduction in duration of diarrhea and a higher clinical cure rate than placebo. Therefore, patients should be managed based on clinical response to therapy rather than microbiologic response.

**Table 4 - Microbiologic Eradication Rates in Study 1
Subjects with a Baseline Pathogen**

	Rifaximin	Placebo
Overall	48/70 (68.6)	41/61 (67.2)
<i>E. coli</i>	38/53 (71.7)	40/54 (74.1)

Study 2 provided additional information to support the results presented for Study 1. This study also provided evidence that rifaximin-treated subjects with fever and/or blood in the stool at baseline had prolonged TLUS. These subjects had lower clinical cure rates than those without fever or blood in the stool at baseline. Many of the patients with fever and/or blood in the stool (dysentery-like diarrheal syndromes) had invasive pathogens, primarily *Campylobacter jejuni*, isolated in the baseline stool.

Also in this study, the majority of the rifaximin-treated subjects who had *Campylobacter jejuni* isolated as a sole pathogen at baseline failed treatment and the resulting clinical cure rate for these patients was 23.5% (4/17). In addition to not being different from placebo, the microbiologic eradication rates for subjects with *Campylobacter jejuni* isolated at baseline were much lower than the eradication rates seen for *Escherichia coli*.

In an unrelated Phase 1, open-label, pharmacokinetic study of oral XIFAXAN[®] Tablets 200 mg taken every 8 hours for 3 days, 15 adult subjects were challenged with *Shigella flexneri* 2a, of whom 13 developed diarrhea or dysentery and were treated with rifaximin. Although this open-label challenge trial was not adequate to assess the effectiveness of rifaximin in the treatment of shigellosis, the following observations were noted.

Eight subjects received rescue treatment with ciprofloxacin either because of lack of response to rifaximin treatment within 24 hours (2), or because they developed severe dysentery (5), or because of recurrence of *Shigella flexneri* in the stool (1). Five of the 13 subjects received ciprofloxacin although they did not have evidence of severe disease or relapse.

REFERENCES

1. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. National Committee for Clinical Laboratory Standards, Sixth Edition, Wayne PA.

Approved Standard NCCLS Document M7-A6 January 2003; 23 (2).

Rx Only

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Part #

Revision Date

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XIFAXAN safely and effectively. See full prescribing information for XIFAXAN.

XIFAXAN® (rifaximin) Tablets

Initial U.S. Approval: 2004

INDICATIONS AND USAGE

XIFAXAN is a nonsystemic antibiotic indicated for:

- The treatment of patients (≥ 12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* (1.1)
- XIFAXAN Tablets, 550 mg are indicated for the maintenance of remission of hepatic encephalopathy in patients ≥ 18 years of age. (1.2)

DOSAGE AND ADMINISTRATION

XIFAXAN can be taken with or without food.

- Travelers' diarrhea: one 200 mg tablet taken three times a day for 3 days (2.1)
- Hepatic encephalopathy: one 550 mg tablet taken two times a day (2.2)

DOSAGE FORMS AND STRENGTHS

- 200 and 550 mg tablets (3)

CONTRAINDICATIONS

- History of hypersensitivity to rifaximin, and of the or to rifamycin antimicrobial agents, or any of the components of XIFAXAN (4)

WARNINGS AND PRECAUTIONS

- XIFAXAN was not found effective in Diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*. If diarrhea symptoms get worse or persist for more than 24-48 hours, discontinue treatment with XIFAXAN (5.1)
- XIFAXAN was not proven effective in Travelers' diarrhea due to *Campylobacter jejuni*, and *Salmonella* spp. (5.2)
- Pseudomembranous colitis has been reported in nearly all antibiotic agents (5.4) Clostridium difficile-associated diarrhea has been reported in all antibiotic agents (5.3)

ADVERSE REACTIONS

Most common adverse reactions are: peripheral edema, nausea, flatulence, headache (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-866-669-7597 and www.Salix.com) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- No clinically relevant drug interactions with XIFAXAN are anticipated (7)

USE IN SPECIFIC POPULATIONS

- Pediatrics: Use of XIFAXAN Tablets, 200 mg in patients under 12 years of age and use of XIFAXAN Tablets, 550 mg in patients under 18 years of age has not been established (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: xxx/20xx

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- Hepatic encephalopathy

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- Hepatic encephalopathy

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1 FULL PRESCRIBING INFORMATION

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3

1 INDICATIONS AND USAGE

1.1 Travelers' diarrhea

XIFAXAN® Tablets, 200 mg are indicated for the treatment of patients (≥12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* (see WARNINGS, Microbiology, and CLINICAL STUDIES).

XIFAXAN Tablets should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*.

1.2 Hepatic encephalopathy

XIFAXAN Tablets, 550 mg are indicated for the maintenance of remission of hepatic encephalopathy in patients ≥ 18 years of age.

2 DOSAGE AND ADMINISTRATION

XIFAXAN Tablets can be administered orally with or without food.

2.1 Travelers' diarrhea:

The recommended dose is one 200 mg tablet taken orally three times a day for 3 days.

2.2 Hepatic encephalopathy:

The recommended dose is one 550 mg tablet taken orally two times a day.

3 DOSAGE FORMS AND STRENGTHS

XIFAXAN Tablets are pink-colored biconvex tablets and are available in the following strengths:

- 200 mg – a round tablet debossed with “Sx” on one side.
- 550 mg – an oval tablet debossed with “rfx” on one side.

4 CONTRAINDICATIONS

XIFAXAN Tablets are contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN Tablets.

5 WARNINGS AND PRECAUTIONS

5.1 Travelers' Diarrhea with fever and/or blood in stool

XIFAXAN Tablets were not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*.

XIFAXAN Tablets should be discontinued if diarrhea symptoms get worse or persist more than 24-48 hours and alternative antibiotic therapy should be considered.

5.2 Traveler's Diarrhea caused by *Campylobacter jejuni*, *Shigella* spp., or *Salmonella* spp.

XIFAXAN Tablets are not effective in cases of travelers' diarrhea due to *Campylobacter jejuni*. The effectiveness of XIFAXAN Tablets in travelers' diarrhea caused by *Shigella* spp. and *Salmonella* spp. has not been proven. XIFAXAN[®] Tablets should not be used in patients where *Campylobacter jejuni*, *Shigella* spp., or *Salmonella* spp. may be suspected as causative pathogens.

5.3 Pseudomembranous colitis *Clostridium difficile*-Associated Diarrhea

~~Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.~~

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile*.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon which may lead to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of XIFAXAN and other antibacterial drugs, XIFAXAN should be used only to treat or prevent infections or conditions that are proven or strongly suspected to be caused by bacteria.

~~The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should super infection occur during therapy, appropriate measures should be taken.~~

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Travelers' Diarrhea

The safety of XIFAXAN Tablets 200 mg taken three times a day (TID) was evaluated in 320 patients in two placebo-controlled clinical trials with 95% of patients receiving at least three days of treatment with XIFAXAN Tablets. All adverse events for XIFAXAN Tablets 200 mg TID that occurred at a frequency $\geq 2\%$ in the two placebo-controlled trials combined are provided in Table 1. (These include adverse events that may be attributable to the underlying disease.)

Table 1. All Adverse Events With an Incidence $\geq 2\%$ Among Patients Receiving XIFAXAN Tablets, 600 mg/day, in Placebo-Controlled Studies

MedDRA Preferred Term	Number (%) of Patients	
	XIFAXAN Tablets, 600 mg/day (N = 320)	Placebo N = 228
Flatulence	36 (11.3%)	45 (19.7%)
Headache	31 (9.7%)	21 (9.2%)
Abdominal Pain NOS	23 (7.2%)	23 (10.1%)
Rectal Tenesmus	23 (7.2%)	20 (8.8%)
Defecation Urgency	19 (5.9%)	21 (9.2%)
Nausea	17 (5.3%)	19 (8.3%)
Constipation	12 (3.8%)	8 (3.5%)
Pyrexia	10 (3.1%)	10 (4.4%)
Vomiting NOS	7 (2.2%)	4 (1.8%)

The following adverse events, presented by body system, have also been reported in <2% of patients taking XIFAXAN[®] Tablets in the two placebo-controlled clinical trials where the 200 mg was taken three times a day for travelers' diarrhea was used. The following includes adverse events regardless of causal relationship to drug exposure.

Blood and Lymphatic System Disorders: lymphocytosis, monocytosis, neutropenia
Ear and Labyrinth Disorders: ear pain, motion sickness, tinnitus
Gastrointestinal Disorders: abdominal distension, diarrhea NOS, dry throat, fecal abnormality NOS, gingival disorder NOS, inguinal hernia NOS, dry lips, stomach discomfort
General Disorders and Administration Site Conditions: chest pain, fatigue, malaise, pain NOS, weakness
Infections and Infestations: dysentery NOS, respiratory tract infection NOS, upper respiratory tract infection NOS
Injury and Poisoning: sunburn
Investigations: aspartate aminotransferase increased, blood in stool, blood in urine, weight decreased
Metabolic and Nutritional Disorders: anorexia, dehydration
Musculoskeletal, Connective Tissue, and Bone Disorders: arthralgia, muscle spasms, myalgia, neck pain
Nervous System Disorders: abnormal dreams, dizziness, migraine NOS, syncope, loss of taste
Psychiatric Disorders: insomnia
Renal and Urinary Disorders: choluria, dysuria, hematuria, polyuria, proteinuria, urinary frequency
Respiratory, Thoracic, and Mediastinal Disorders: dyspnea NOS, nasal passage irritation, nasopharyngitis, pharyngitis, pharyngolaryngeal pain, rhinitis NOS, rhinorrhea
Skin and Subcutaneous Tissue Disorders: clamminess, rash NOS, sweating increased
Vascular Disorders: hot flashes NOS

Hepatic Encephalopathy

A total of 336 patients were exposed to XIFAXAN in clinical studies (mean exposure was 274 days). The safety of XIFAXAN 550 mg taken two times a day for the maintenance of remission from hepatic encephalopathy in adult patients was evaluated in a 6-month placebo-controlled clinical trial. All adverse events that occurred at an incidence ≥ 5% and at a higher incidence in XIFAXAN-treated subjects than in the placebo group in this trial are provided in Table 2. (These include adverse events that may be attributable to the underlying disease.)

142 **Table 2: Adverse Events Occurring in $\geq 5\%$ of Patients Receiving XIFAXAN**
143 **and at a Higher Incidence Than Placebo**

MedDRA Preferred Term	Number (%) of Patients	
	XIFAXAN Tablets 550 mg BID N = 140	Placebo N = 159
Edema peripheral	21 (15.0%)	13 (8.2%)
Nausea	20 (14.3%)	21 (13.2%)
Dizziness	18 (12.9%)	13 (8.2%)
Fatigue	17 (12.1%)	18 (11.3%)
Ascites	16 (11.4%)	15 (9.4%)
Muscle spasms	13 (9.3%)	11 (6.9%)
Pruritus	13 (9.3%)	10 (6.3%)
Abdominal pain	12 (8.6%)	13 (8.2%)
Abdominal distension	11 (7.9%)	12 (7.5%)
Anemia	11 (7.9%)	6 (3.8%)
Cough	10 (7.1%)	11 (6.9%)
Depression	10 (7.1%)	8 (5.0%)
Insomnia	10 (7.1%)	11 (6.9%)
Nasopharyngitis	10 (7.1%)	10 (6.3%)
Abdominal pain upper	9 (6.4%)	8 (5.0%)
Arthralgia	9 (6.4%)	4 (2.5%)
Back pain	9 (6.4%)	10 (6.3%)
Constipation	9 (6.4%)	10 (6.3%)
Dyspnea	9 (6.4%)	7 (4.4%)
Pyrexia	9 (6.4%)	5 (3.1%)
Rash	7 (5.0%)	6 (3.8%)

144 The following adverse events, presented by body system, have also been reported in the
145 placebo-controlled clinical trial in greater than 2 % but less than 5% of patients taking
146 XIFAXAN[®] Tablets, 550 mg taken two times a day for hepatic encephalopathy. The following
147 includes adverse events occurring at a greater incidence than placebo, regardless of causal
148 relationship to drug exposure.

149 Ear and Labyrinth Disorders: vertigo

150 Gastrointestinal Disorders: abdominal pain lower, abdominal tenderness, dry mouth,
151 esophageal variceal bleed, stomach discomfort

152 General Disorders and Administration Site Conditions: chest pain, generalized edema,
153 influenza like illness, pain NOS

154 Infections and Infestations: cellulitis, pneumonia, rhinitis, upper respiratory tract infection
155 NOS

156 Injury, Poisoning and Procedural Complications: contusion, fall, procedural pain

157 Investigations: weight increased

158 Metabolic and Nutritional Disorders: anorexia, dehydration, hyperglycemia,
159 hyperkalemia, hypoglycemia, hyponatremia

160 Musculoskeletal, Connective Tissue, and Bone Disorders: myalgia, pain in extremity

161 Nervous System Disorders: amnesia, disturbance in attention, hypoesthesia, memory
162 impairment, tremor

163 Psychiatric Disorders: confusional state

164 Respiratory, Thoracic, and Mediastinal Disorders: epistaxis

165 Vascular Disorders: hypotension
166
167
168

6.2 Postmarketing Experience

The following events: adverse events have been identified during post approval use of XIFAXAN. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting or causal connection to XIFAXAN.

General: hypersensitivity reactions, including exfoliative dermatitis, rash, angioneurotic edema (swelling of face and tongue and difficulty swallowing), urticaria, flushing, and pruritus; ~~have been identified during postapproval use of XIFAXAN® Tablets.~~ These events occurred as early as within 15 minutes of drug administration.

7 DRUG INTERACTIONS

~~In an *in vitro* hepatocyte induction model, rifaximin was shown to induce cytochrome P450 3A4 (CYP3A4) an isoenzyme which rifampin is known to induce. Two clinical drug-drug interaction studies were conducted with the rifaximin 200 mg tablet and one drug-drug interaction study with the 550 mg tablet. Two studies using midazolam, a known substrate for CYP3A4, and 1 study using an oral contraceptive containing ethinyl estradiol and norgestimate were conducted to assess the effect of rifaximin on the pharmacokinetics of these drugs. Based on the results of these studies and *in vitro* induction and inhibition studies using human liver fractions, no clinically relevant drug interactions are anticipated with XIFAXAN.~~

~~Although *in vitro* studies demonstrated the potential of rifaximin to interact with cytochrome P450 3A4 (CYP3A4), a clinical drug-drug interaction study demonstrated that rifaximin did not significantly affect the pharmacokinetics of midazolam either presystemically or systemically. An additional clinical drug-drug interaction study showed no effect of rifaximin on the presystemic metabolism of an oral contraceptive containing ethinyl estradiol and norgestimate. Therefore, clinical interactions with drugs metabolized by human cytochrome P450 isoenzymes are not expected (see **Pharmacokinetics and Drug-Drug Interactions**).~~

7.1 Midazolam

Two studies have been performed to evaluate the potential for drug interactions with midazolam. ~~The midazolam study was~~ The first was an open-label, randomized, crossover, drug-interaction trial designed to assess the effect of rifaximin 200 mg administered orally (PO) every 8 hours (Q8H) for 3 days and ~~every 8 hours~~ Q8H for 7 days, on the pharmacokinetics of a single dose of either midazolam 2 mg intravenous (IV) or midazolam 6 mg PO. No significant difference was observed in the metrics of systemic exposure or elimination of IV or PO midazolam or its major metabolite, 1'-hydroxymidazolam, between midazolam alone or together with rifaximin. Therefore, rifaximin was not shown to significantly affect intestinal or hepatic CYP3A4 activity.

The second study, an open-label, drug-interaction study examined the effect of rifaximin, 550 mg three times daily, on orally administered (PO) midazolam 2 mg when dosed for 7 and 14 consecutive days. In this study rifaximin was shown to be a weak inducer of CYP3A4; given the low systemic exposure of rifaximin, this interaction is believed to be limited to the gastrointestinal tract. This induction is both dose- and dosing-duration dependent. When rifaximin was orally administered at high doses (1650 mg/day) for at least 7 days, the mean C_{max} , AUC_{0-t_2} and $AUC_{0-\infty}$ of midazolam were reduced by < 25%.

7.2 Oral Contraceptives

The oral contraceptive study utilized an open-label, crossover design in 28 healthy female subjects to determine if rifaximin 200 mg PO administered Q8H for 3 days altered the pharmacokinetics of a single dose of an oral contraceptive containing 0.07 mg ethinyl estradiol and 0.50 mg norgestimate. Results showed that the pharmacokinetics of single doses of ethinyl estradiol and norgestimate were not altered by rifaximin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

~~Pregnancy Category C: Rifaximin was teratogenic in rats at doses of 150 to 300 mg/kg (approximately 2.5 to 5 times the clinical dose for travelers' diarrhea [600 mg/day], adjusted for body surface area) and in rabbits at doses of 62.5 to 1000 mg/kg (approximately 2 to 33 times the clinical dose for travelers' diarrhea [600 mg/day], adjusted for body surface area). These effects include cleft palate, agnathia, jaw shortening, hemorrhage, eye partially open, small eyes, brachygnathia, incomplete ossification, and increased thoracolumbar vertebrae. There are no adequate and well controlled studies in pregnant women. XIFAXAN Tablets should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.~~

Pregnancy Category B: Reproduction studies have been performed in rats at doses up to 2.5 to 5.0 times (adjusted for body surface area) the human dose, and in rabbits at doses up to 2.0 to 33.0 times (adjusted for body surface area) the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to rifaximin. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.2 Nursing Mothers

It is not known whether rifaximin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from XIFAXAN Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Pediatric Use

The safety and effectiveness of XIFAXAN Tablets, 200 mg in pediatric patients less than 12 years of age have not been established. There has been no evaluation of XIFAXAN Tablets, 550 mg in patients less than 18 years of age.

8.4 Geriatric Use

Clinical studies of XIFAXAN Tablets 200 mg or 550 mg did not include sufficient numbers of patients subjects aged 65 and over to determine whether they respond differently than younger subjects.

8.5 Renal Insufficiency

The pharmacokinetics of rifaximin in patients with impaired renal function has not been studied.

8.6 Hepatic Insufficiency

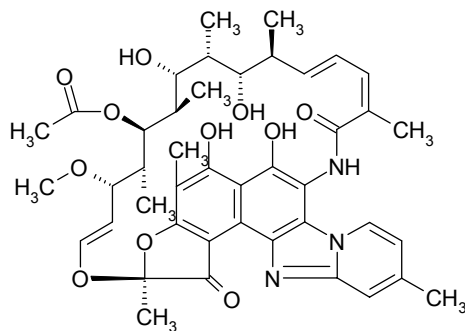
Two studies evaluated the pharmacokinetics of rifaximin in patients with hepatic impairment. In the first study, Mean (SD) peak rifaximin plasma concentrations of 13.5 (14.8) ng/mL were detected in hepatic encephalopathy patients 3 hours after administration of the first dose of administered rifaximin 800 mg three times daily for 7 days; Less than 0.1% of the administered dose was recovered in urine after 7 days. Because of the limited systemic absorption of rifaximin, no specific dosing adjustments are recommended for patients with hepatic insufficiency. In the second study, patients were administered rifaximin 550 mg two times a day. Mean (SD) rifaximin steady-state systemic exposure values (C_{max}) in those with hepatic impairment grades of Child-Pugh A and Child-Pugh B were 19.5 (11.4) ng/mL and 25.1 (12.6) ng.h/mL (approximately 5.7- and 7.4-fold higher, respectively, than steady-state C_{max} values observed in healthy individuals). This increase in systemic exposure to rifaximin in patients with hepatic impairment does not require a dosing adjustment with rifaximin due to its gastrointestinal local action and low systemic bioavailability.

10 OVERDOSAGE

No specific information is available on the treatment of overdose with XIFAXAN Tablets. In clinical studies at doses higher than the recommended dose (> 600 mg/day for travelers' diarrhea or >1100 mg/day for hepatic encephalopathy), adverse events were similar in subjects who received doses higher than the recommended dose and placebo. In the case of overdose, discontinue XIFAXAN Tablets, treat symptomatically, and institute supportive measures as required.

11 DESCRIPTION

XIFAXAN Tablets contain rifaximin, a semi-synthetic, nonsystemic antibiotic. The chemical name for rifaximin is (2S,16Z,18E,20S,21S,22R,23R,24R,25S,26S,27S,28E)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca-[1,11,13]trienimino)benzofuro[4,5-e]pyrido[1,2-a]benzimidazole-1,15(2H)-dione,25-acetate. The empirical formula is $C_{43}H_{51}N_3O_{11}$ and its molecular weight is 785.9. The chemical structure is represented below:



XIFAXAN Tablets for oral administration are film-coated and contain 200 mg or 550 mg of rifaximin.

Inactive ingredients: Each tablet contains colloidal silicon dioxide, disodium edetate, glycerol palmitostearate, hypromellose, microcrystalline cellulose, propylene glycol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rifaximin is an anti-bacterial drug (see 12.4 Microbiology).

12.2 Pharmacodynamics

The dose-response relationship for rifaximin efficacy in reducing the severity of hepatic encephalopathy (HE) was established in a double-blind dose-ranging study (600, 1200, or 2400 mg total daily dose for 7 days) in patients with Grade 1, 2, or 3 HE, improvements from baseline were observed in all groups, as measured by an index measuring multiple HE symptoms; mean changes (improvements) in symptom index scores were -0.064, -0.103, and -0.107 in groups receiving total daily doses of 600 mg, 1200 mg, and 2400 mg, respectively.

12.3 Pharmacokinetics

Absorption

The mean plasma pharmacokinetic parameters of rifaximin in 14 healthy subjects after a single oral 400 mg dose given as 2 x 200 mg doses and a single 550 mg dose in 12 healthy subjects under fed and fasting conditions are summarized in Table 3.

Table 3. Effect of Food on the Mean \pm S.D. Pharmacokinetic Parameters

Parameter	Single 400 mg Dose of Rifaximin (N = 14)		Single 550 mg Dose of Rifaximin (N= 12)	
	Fasting	Fed	Fasting	Fed
C _{max} (ng/mL)	3.80 \pm 1.32	9.63 \pm 5.93	4.04 \pm 1.51	4.76 \pm 4.25
T _{max} (h)	1.21 \pm 0.47	1.90 \pm 1.52	0.75 (0.50-2.05)*	1.50 (0.50-4.08)*
Half-Life (h)	5.85 \pm 4.34	5.95 \pm 1.88	1.83 \pm 1.38	4.84 \pm 1.34
AUC (ng·h/mL)	18.35 \pm 9.48	34.70 \pm 9.23	11.1 \pm 4.15	22.5 \pm 12.0
% Excreted in Urine	0.023 \pm 0.009	0.051 \pm 0.017		

*Median (range)

~~Rifaximin can be administered with or without food.~~ Because systemic absorption of rifaximin was low, minimal in both the fasting state and when administered within 30 minutes of a high-fat breakfast, XIFAXAN can be administered with or without food.

¹⁴C-Rifaximin was administered as a single dose to 4 healthy male subjects. The mean overall recovery of radioactivity in the urine and feces of 3 subjects during the 168 hours after administration was 96.94 \pm 5.64% of the dose. Radioactivity was excreted almost exclusively in the feces (96.62 \pm 5.67% of the dose), with only a small proportion of the dose (mean 0.32% of the dose) excreted in urine. Analysis of fecal extracts indicated that rifaximin was being excreted as unchanged drug. The amount of radioactivity in urine (<0.4% of the dose) suggests that rifaximin is poorly absorbed from the gastrointestinal tract and is almost exclusively and completely excreted in feces as unchanged drug. Mean rifaximin pharmacokinetic parameters were C_{max} 4.3 \pm 2.8 ng/mL and AUC_t 19.5 \pm 16.5 ng·h/mL with a median T_{max} of 1.25 hours.

Special Populations

Systemic absorption of rifaximin (XIFAXAN 200 mg three times daily) was also evaluated in 13 subjects challenged with shigellosis on Days 1 and 3 of a three-day course of treatment. Rifaximin plasma concentrations and exposures were low and variable. There was no evidence of accumulation of rifaximin following repeated administration for 3 days (9 doses). Peak plasma rifaximin concentrations after 3 and 9 consecutive doses ranged from 0.81 to 3.4 ng/mL on Day 1 and 0.68 to 2.26 ng/mL on Day 3. Similarly, AUC_{0-last} estimates were 6.95 ± 5.15 ng•h/mL on Day 1 and 7.83 ± 4.94 ng•h/mL on Day 3. Rifaximin is not suitable for treating systemic bacterial infections because less than 0.4% ~~1%~~ of the drug is absorbed after oral administration (see **WARNINGS AND PRECAUTIONS**).

The pharmacokinetics of patients with hepatic impairment (hepatic impairment grades of Child-Pugh A and Child-Pugh B) taking XIFAXAN 550 mg two times a day were evaluated in an open-label rifaximin study. Rifaximin exposure values (AUC_T) in subjects with Child-Pugh score A and B (118 and 161 ng•h/mL, respectively) were approximately 9.6- and 13.1-fold higher than that observed in healthy subjects following two times a day oral doses of 550 mg (12.3 ng•h/mL), respectively. Intersubject variabilites in the pharmacokinetics of healthy subjects were generally similar to those measured in subjects with hepatic impairment.

Distribution

Animal pharmacokinetic studies have demonstrated that 80% to 90% of orally administered rifaximin is concentrated in the gut with less than 0.2% in the liver and kidney, and less than 0.01% in other tissues. In adults with infectious diarrhea treated with rifaximin 800 mg daily for three days, concentrations of rifaximin in stools averaged ~8000 µg/g the day after treatment ended.

Metabolism

In vitro drug interactions studies have shown that rifaximin, at concentrations ranging from 2 to 200 ng/mL, did not inhibit human hepatic cytochrome P450 isoenzymes: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4. In an *in vitro* hepatocyte induction model, rifaximin was shown to induce cytochrome P450 3A4 (CYP3A4), an isoenzyme which rifampin is known to induce. Two clinical drug-drug interaction studies using midazolam and an oral contraceptive containing ethinyl estradiol and norgestimate demonstrated that rifaximin (200 mg TID for 3 days) did not alter the pharmacokinetics of these drugs, and rifaximin 550 mg TID for 7 or 14 days resulted in only slightly reduced exposure to midazolam following a single oral midazolam dose.(see **DRUG INTERACTIONS**).

In vitro study data suggest that rifaximin is a substrate for P-glycoprotein. Rifaximin is a weak inhibitor of P-gp; at concentrations (50 µM) significantly higher than those anticipated in plasma following oral dose administration, rifaximin only partially inhibited transport of a model P-gp substrate. Therefore, no clinically significant interactions with other drugs affected by P-glycoprotein are anticipated.

Excretion

Rifaximin is excreted primarily in the feces. After oral administration of 400 mg ¹⁴C-rifaximin to healthy volunteers, approximately 97% of the dose was recovered in feces, almost entirely as unchanged drug, and 0.32% was recovered in the urine (see **Clinical Pharmacology**).

12.4 Microbiology

Mechanism of Action

Rifaximin is a non-aminoglycoside semi-synthetic antibiotic derived from rifamycin SV; it is a structural analog of rifampin. The mechanism of action of rifaximin depends on the inhibition of DNA-dependent RNA polymerase of the target microorganisms, leading to the suppression of initiation of chain formation in RNA synthesis.

The lower rate of eradication of fecal pathogens in patients treated with rifaximin compared with fluoroquinolones and aminoglycosides and lack of alteration of gut flora indicate a unique mechanism of action. Rifaximin may alter virulence factors of enteric bacterial pathogens without killing them, as has been seen with subtherapeutic levels of drugs and colonization fimbriae of enterotoxigenic *E. coli*. Rifaximin caused morphological alterations in both susceptible and resistant bacterial strains at concentrations as low as 1/32 of the MIC.¹ Rifaximin reduced the viability and virulence of resistant bacteria, suggesting that if *in vivo* pathogens are exposed to sub-MICs of the drug, not only are their physiological functions compromised, but gene virulence and antibiotic resistance are not fully expressed.

Rifaximin has *in vitro* antimicrobial activity against numerous Gram-positive and Gram-negative bacteria, such as *Escherichia coli*. Animal and human studies demonstrate negligible systemic rifaximin absorption (< 1%) after oral administration. The negligible systemic absorption of rifaximin from the gastrointestinal tract minimizes the potential adverse events associated with systemically absorbed antibiotics. Rifaximin is delivered at high concentrations to the gastrointestinal tract, which is the therapeutic site of action.

Rifaximin acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis.

Escherichia coli has been shown to develop resistance to rifaximin *in vitro*. However, the clinical significance of such an effect has not been studied.

Rifaximin is a structural analog of rifampin. Organisms with high rifaximin minimum inhibitory concentration (MIC) values also have elevated MIC values against rifampin. Cross-resistance between rifaximin and other classes of antimicrobials has not been studied.

Rifaximin has been shown to be active against the following pathogen in clinical studies of infectious diarrhea as described in the **INDICATIONS AND USAGE** section: *Escherichia coli* (enterotoxigenic and enteroaggregative strains).

Susceptibility Tests

In vitro susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) agar dilution method M7-A6¹². However, the correlation between susceptibility testing and clinical outcome has not been determined.

Escherichia coli has been shown to develop resistance to rifaximin *in vitro*. However, the clinical significance of such an effect has not been studied. Rifaximin is a structural analog of rifampin. Organisms with high rifaximin minimum inhibitory

concentration (MIC) values also have elevated MIC values against rifampin. Cross-resistance between rifaximin and other classes of antimicrobials has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of rifaximin was examined in a 2 year study with CD rats. Daily oral administration of at dose levels ranging from 20, 50, to 250 mg/kg/day produced no evidence of a carcinogenic effect.

Similarly, in a study with Tg.rasH2 mice daily oral administration by gavage with rifaximin at doses up to 1500 mg/kg/day (males) and 2000 mg/kg/day (females) for 26-weeks did not increase the incidence of tumors when compared to vehicle control.

Rifaximin was not genotoxic in the bacterial reverse mutation assay, chromosomal aberration assay, rat bone marrow micronucleus assay, rat hepatocyte unscheduled DNA synthesis assay, and the CHO/HGPRT mutation assay. There was no effect on fertility in male or female rats following the administration of rifaximin at doses up to 300 mg/kg (approximately 5 times the clinical dose of 600 mg/day, adjusted for body surface area). ~~Rifaximin was teratogenic in rats at doses of 150 to 300 mg/kg and in rabbits at doses of 62.5 to 1000 mg/kg (see Pregnancy).~~

13.2 Animal Toxicology

Results from multiple-dose oral toxicity studies in rats, rabbits, and dogs showed negligible toxic effects of rifaximin at doses ranging from 6 to 68 times the clinical dose for travelers' diarrhea (600 mg/day) for durations of up to 39 weeks.

In a 26-week study with Tg.rasH2 mice orally administered rifaximin at doses up to 1500 mg/kg/day (males) and 2000 mg/kg/day (females) 2/25 female mice at 2000 mg/kg day presented ruffled fur and hunched appearance in low incidence that did not reach statistical significance.

14 CLINICAL STUDIES

14.1 Travelers' Diarrhea

The efficacy of ~~rifaximin~~ XIFAXAN (200 mg orally taken three times a day for 3 days) was evaluated in 2 randomized, multi-center, double-blind, placebo-controlled studies in adult subjects with travelers' diarrhea. One study was conducted at clinical sites in Mexico, Guatemala, and Kenya (Study 1). The other study was conducted in Mexico, Guatemala, Peru, and India (Study 2). Stool specimens were collected before treatment and 1 to 3 days following the end of treatment to identify enteric pathogens. The predominant pathogen in both studies was *Escherichia coli*.

The clinical efficacy of ~~rifaximin~~ XIFAXAN was assessed by the time to return to normal, formed stools and resolution of symptoms. The primary efficacy endpoint was time to last unformed stool (TLUS) which was defined as the time to the last unformed stool passed, after which clinical cure was declared. Table ~~3~~ 4 displays the median TLUS and the number of patients who achieved clinical cure for the intent to treat population (ITT) of Study 1. The duration of diarrhea was significantly shorter in patients treated

with rifaximin-**XIFAXAN** than in the placebo group. More rifaximin-**XIFAXAN**-treated patients were classified as clinical cures than were those in the placebo group.

Table 4. Clinical Response in Study 1 (ITT population)

	Rifaximin XIFAXAN (n=125)	Placebo (n=129)	Estimate (97.5% CI)	P-Value
Median TLUS (hours)	32.5	58.6	1.78 ^a (1.26, 2.50)	0.0002
Clinical cure, n (%)	99 (79.2)	78 (60.5)	18.7 ^b (5.3, 32.1)	0.001

^a Hazard Ratio

^b Difference in rates

Microbiological eradication (defined as the absence of a baseline pathogen in culture of stool after 72 hours of therapy) rates for Study 1 are presented in Table 5 for patients with any pathogen at baseline and for the subset of patients with *Escherichia coli* at baseline. *Escherichia coli* was the only pathogen with sufficient numbers to allow comparisons between treatment groups.

Even though rifaximin-**XIFAXAN** had microbiologic activity similar to placebo, it demonstrated a clinically significant reduction in duration of diarrhea and a higher clinical cure rate than placebo. Therefore, patients should be managed based on clinical response to therapy rather than microbiologic response.

**Table 5. Microbiologic Eradication Rates in Study 1
Subjects with a Baseline Pathogen**

	Rifaximin	Placebo
Overall	48/70 (68.6)	41/61 (67.2)
<i>E. coli</i>	38/53 (71.7)	40/54 (74.1)

Study 2 provided additional information to support the results presented for Study 1. This study also provided evidence that rifaximin-**XIFAXAN**-treated subjects with fever and/or blood in the stool at baseline had prolonged TLUS. These subjects had lower clinical cure rates than those without fever or blood in the stool at baseline. Many of the patients with fever and/or blood in the stool (dysentery-like diarrheal syndromes) had invasive pathogens, primarily *Campylobacter jejuni*, isolated in the baseline stool.

Also in this study, the majority of the rifaximin-**XIFAXAN**-treated subjects who had *Campylobacter jejuni* isolated as a sole pathogen at baseline failed treatment and the resulting clinical cure rate for these patients was 23.5% (4/17). In addition to not being different from placebo, the microbiologic eradication rates for subjects with *Campylobacter jejuni* isolated at baseline were much lower than the eradication rates seen for *Escherichia coli*.

In an unrelated Phase 1, open-label, pharmacokinetic study of oral **XIFAXAN**[®] Tablets 200 mg taken every 8 hours for 3 days, 15 adult subjects were challenged with *Shigella flexneri* 2a, of whom 13 developed diarrhea or dysentery and were treated with rifaximin-**XIFAXAN**. Although this open-label challenge trial was not adequate to assess the effectiveness of rifaximin-**XIFAXAN** in the treatment of shigellosis, the following observations were noted.

Eight subjects received rescue treatment with ciprofloxacin either because of lack of response to ~~rifaximin~~-XIFAXAN treatment within 24 hours (2), or because they developed severe dysentery (5), or because of recurrence of *Shigella flexneri* in the stool (1). Five of the 13 subjects received ciprofloxacin although they did not have evidence of severe disease or relapse.

14.2 Hepatic Encephalopathy

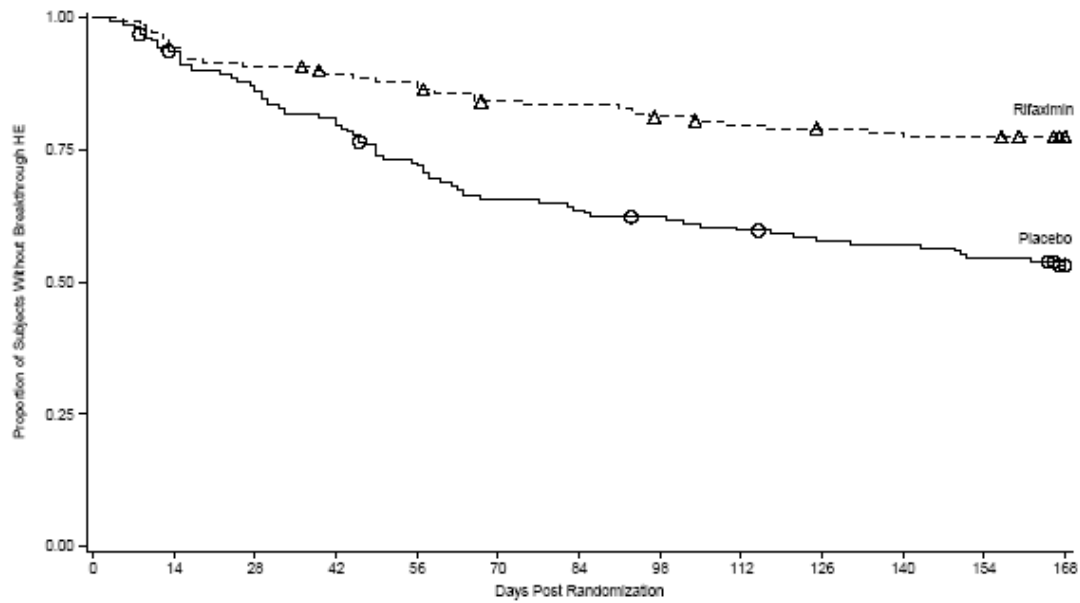
The efficacy of XIFAXAN 550 mg taken orally two times a day was evaluated in a randomized, placebo-controlled, double-blind, multi-center 6-month study of adult subjects from the US, Canada and Russia who were currently in remission (Conn score of 0 or 1) from hepatic encephalopathy (HE). Eligible subjects had ≥ 2 episodes of HE associated with chronic liver disease in the previous 6 months.

A total of 299 subjects were randomized to receive XIFAXAN (140 subjects) or placebo (159 subjects) in this study. Patients had a mean age of 56 years (range, 21-82 years), 81% < 65 years of age, 61% were male and 86% Caucasian. At baseline 67% of patients had a Conn score of 0 and 68% had an Asterixis grade of 0. The majority of subjects had MELD scores of either ≤ 10 (27.4%) or 11 to 18 (63.5%) at baseline. Lactulose was concomitantly used by 91% of the patients in each treatment arm of the study. Per the study protocol, subjects were withdrawn from the study after experiencing a breakthrough HE episode. Adverse events (rifaximin 5.7%; placebo 4.4%), patient request to withdraw (rifaximin 4.3%; placebo 5.7%) and other (rifaximin 7.1%; placebo 5.0%) were the primary reasons for early study discontinuation.

The primary endpoint was the time to first breakthrough HE episode. A breakthrough HE episode was a marked deterioration in neurological function and defined as an increase of Conn score to Grade ≥ 2 or an increase in Conn score and asterixis grade of 1 grade each for those subjects who entered the study with a Conn score of 0.

Breakthrough HE episodes were experienced by 31 of 140 subjects (22%) in the XIFAXAN group and by 73 of 159 subjects (46%) in the placebo group during the 6-month treatment period. Comparison of Kaplan-Meier estimates of time to breakthrough HE for XIFAXAN versus placebo showed a highly statistically significant reduction in risk of HE breakthrough ($p < 0.0001$). Subjects in the XIFAXAN group had a 58% reduction in the risk of overt HE breakthrough during the 6-month treatment period when compared to placebo.

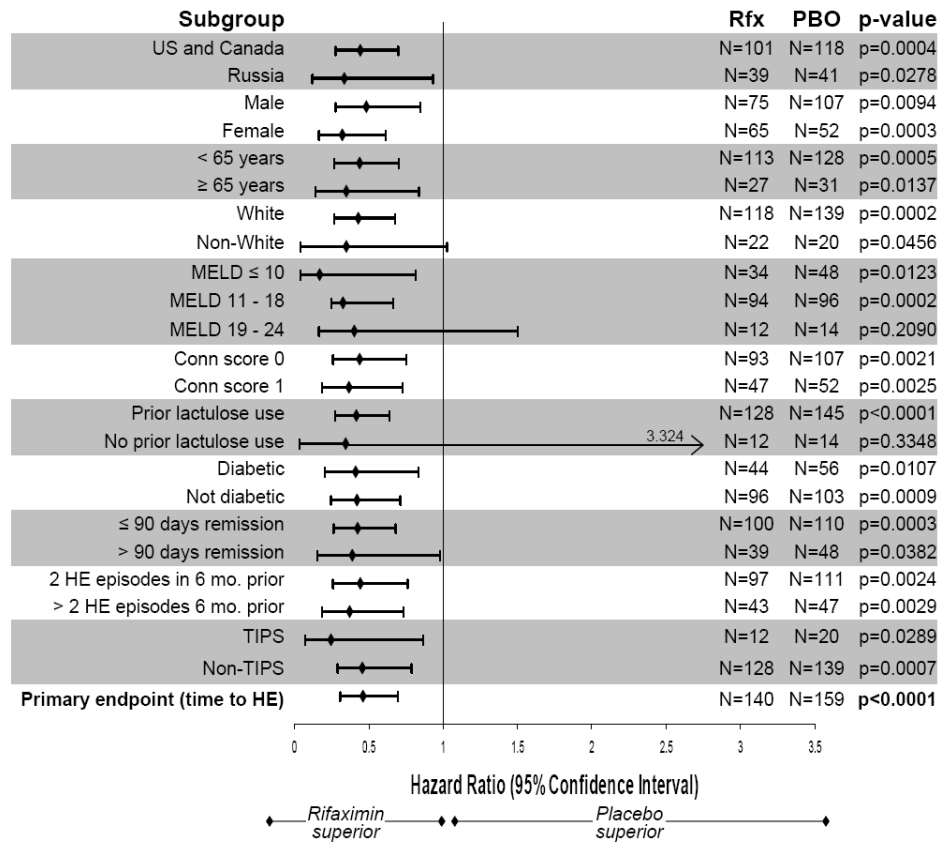
Figure 1: Time to First Breakthrough HE Episode (up to 6 Months of Treatment, Day 170) HE Study (ITT Population)



Note: Open circles and open triangles represent censored subjects..

Outcomes for the primary efficacy endpoint were evaluated in the following subgroups: region, sex, age, race, baseline MELD score, baseline Conn score, diabetes, duration of current remission, and the number of HE episodes within the 6 months prior to randomization. The effect of XIFAXAN treatment in reducing the risk of experiencing breakthrough overt HE episodes during the 6-month treatment period was consistent across all subgroups. There were too few subjects with MELD >19 (n=26) and subjects without concomitant lactulose use (n=26) to assess differences in these populations.

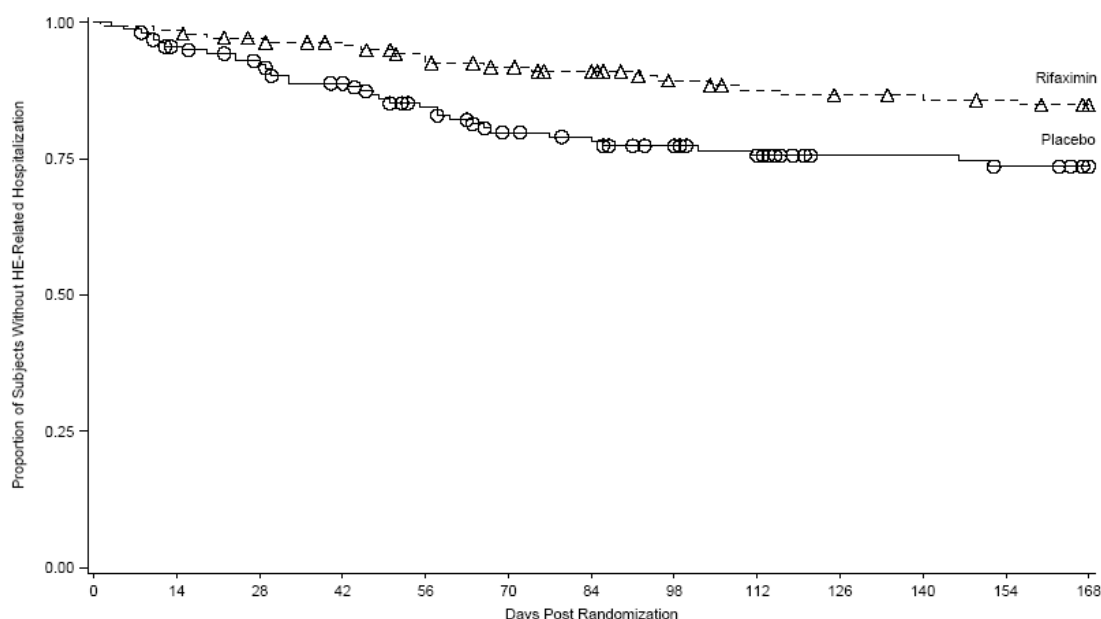
Figure 2: Hazard Ratio for all Subgroups in HE Study



Note: This figure shows hazard ratios for the risk of experiencing breakthrough overt HE (rifaximin group divided by placebo group) for each subgroup. 95% confidence intervals as determined by the Cox proportional hazards model. P-values for differences between the rifaximin and placebo groups were determined by log rank test.

HE-related hospitalizations were reported for 19 of 140 subjects (14%) and 36 of 159 subjects (23%) in the XIFAXAN and placebo groups, respectively. XIFAXAN had a significant reduction of risk against HE-related hospitalization during the 6-month treatment period; hazard ratio in the XIFAXAN group relative to placebo was 0.500 (95% CI: 0.287 to 0.873) (p = 0.0129). Subjects in the XIFAXAN group had a 50% reduction in the risk of hospitalization due to HE during the 6-month treatment period when compared with placebo.

Figure 3: Time to First HE-Related Hospitalization in HE Study (up to 6 Months of Treatment, Day 170) (ITT Population)



Note: Open circles and open triangles represent censored subjects.

Highly significant protective effects of XIFAXAN were observed with respect to time to any increase from baseline in Conn score and time to any increase from baseline in asterixis grade when analyzed independently; hazard ratio in the rifaximin group relative to placebo was 0.463 (95% CI: 0.312 to 0.685) ($p < 0.0001$) for the risk of experiencing an increase in Conn score (ie, worsening in mental status) and 0.646 (95% CI: 0.414 to 1.008) ($p = 0.0523$) for the risk of experiencing an increase in asterixis grade (ie, worsening in neuromotor functioning) during the 6-month treatment period.

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16 HOW SUPPLIED/STORAGE AND HANDLING

200 mg

- NDC 65649-301-04, single blister unit (Professional Sample)
- NDC 65649-301-03, bottles of 30 tablets
- NDC 65649-301-41 bottles of 100 tablets
- NDC 65649-301-05 carton of 100 tablets, Unit Dose

550 mg

- NDC 65649-303-01, bottles of 6 tablets (Professional Sample)
- NDC 65649-303-02, bottles of 60 tablets
- NDC 65649-302-03, carton of 60 tablets, Unit Dose

Storage

Store XIFAXAN Tablets at 20–25°C (68–77°F); excursions permitted to 15–30°C (59–86°F). See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

17.1 Administration with Food

Patients should be informed that XIFAXAN may be taken with or without food.

17.2 Persistent Diarrhea

For those patients being treated for travelers' diarrhea, XIFAXAN tablets should be discontinued if diarrhea persists **more than 24-48 hours** or worsens, or if the patient has fever and/or blood in the stool the patient should seek medical care.

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June 2009

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Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis

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CASE REPORT

Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis

M I Prince, A D Burt, D E J Jones

Gut 2002;**50**:436–439

There is evidence to suggest that rifampicin is an effective second line therapy for controlling pruritus in patients with chronic cholestatic liver disease. It is most widely used as an antipruritic agent in the autoimmune cholestatic liver disease, primary biliary cirrhosis (PBC). Rifampicin has been reported as causing hepatitis in patients being treated for tuberculosis. Most reports of this have been confounded however by the concurrent use of other hepatotoxic antitubercular therapy. Here we report a single centre experience of the use of rifampicin in PBC, and describe three cases of significant hepatitis associated with rifampicin therapy. Two of these patients had significant impairment of liver synthetic function (necessitating liver transplantation in one case). These are the first reports of impaired hepatic synthetic function due to rifampicin monotherapy. Rifampicin caused significant hepatitis in 7.3% (95% confidence interval 2.5–19.4%) of patients treated for cholestatic liver disease in our centre.

Primary biliary cirrhosis (PBC) is a chronic autoimmune liver disorder characterised by slowly progressive destruction of intrahepatic bile ducts.¹ Pruritus is one of the commonest symptoms experienced by patients, and one that can significantly impair quality of life.² Pruritus is present in up to 33% of patients at the time of diagnosis of PBC and in up to 58% of patients at 10 years following diagnosis.³ The pruritus of PBC is generally unresponsive to antihistamines and often responds only poorly to bile sequestrants (which have entered widespread clinical use as first line treatment⁴ despite limited trial evidence⁵). There is little evidence to suggest that the hydrophilic bile acid ursodeoxycholic acid (UDCA) is effective in reducing pruritus, with benefit only being reported in two of 11 trials reviewed in a recent meta-analysis.⁶ There is increasing evidence (both in terms of subjective improvement in the sensation of itching and objective reduction in scratching activity) to suggest that opiate antagonist agents (such as naltrexone administered orally or naloxone administered parenterally) are effective for the management of pruritus in cholestasis.^{7–9}

A number of relatively short term clinical trials have suggested that rifampicin is effective in controlling pruritus in PBC,^{10–13} and this agent is frequently used as second line treatment in specialist clinics. Although there have been no published reports of significant additional liver dysfunction in PBC patients treated with rifampicin, concerns remain regarding its safety in PBC, given the described incidence of de novo hepatotoxicity when this agent is used as an antimicrobial.^{14–17} Following a case of severe rifampicin hepatotoxicity in our patient cohort, we reviewed the notes of all patients in our practice who had been treated with rifampicin (n=41) to study the frequency of rifampicin induced hepatotoxicity. We examined patient records to identify individuals with a 50% increase in their liver function tests

(bilirubin, alanine transaminase, or alkaline phosphatase) following commencement of rifampicin therapy. Using this approach we identified three cases of rifampicin hepatotoxicity, which are presented below.

CASE REPORTS

Case No 1

A 42 year old female company director presented to her general practitioner with a four week history of generalised pruritus. Her general practitioner initially prescribed chlorpheniramine and when this led to no improvement in her symptoms he performed a full blood count, electrolyte screen, and thyroid and liver function tests. Liver function tests (LFTs) were abnormal (albumin 40 g/l, bilirubin 17 µmol/l (normal range <17), alanine transaminase (ALT) 110 IU/l (<35), alkaline phosphatase (ALP) 610 IU/l (<120), and γ-glutamyl transferase 428 (<55)), and she was referred to secondary care.

A further clinical history gave no risk factors for liver disease. An abdominal ultrasound was normal. Further investigation revealed an elevated antimitochondrial antibody (titre 1 in 160) and a raised IgM level of 5.8 g/l (<2.8). Albumin and prothrombin time were normal. Liver biopsy showed a ductopenic process with portal fibrosis, consistent with PBC (Scheuer stage 3). She was initially treated with UDCA at doses of up to 13 mg/kg with no symptomatic improvement. She was subsequently commenced on cholestyramine therapy but could not tolerate doses above 2 g/day due to constipation while lower doses did not relieve pruritus.

Rifampicin was started at a dose of 600 mg at night. Her itch resolved in the first 10 days of therapy but four weeks after starting rifampicin she developed nausea, jaundice, discolouration of urine and stool, and a worsening of pruritus. Her LFTs had significantly deteriorated (bilirubin 103 µmol/l, ALT 544 IU/l, ALP 400 IU/l). Her prothrombin time increased to 18 seconds (control 15 seconds) and albumin fell to 34 g/l. Rifampicin was immediately stopped and her LFTs and prothrombin time returned to their previous levels over the next six weeks. Her itch recurred over the next month and was eventually treated with the oral opiate antagonist naltrexone with an excellent response.

Case No 2

A 58 year old woman consulted her general practitioner with a two year history of progressively worsening pruritus. Her general practitioner performed LFTs which revealed elevated ALP (621 IU/l) and ALT (95 IU/l) and an autoantibody screen which showed a positive antimitochondrial antibody. Bilirubin, albumin, and prothrombin time were normal. She was commenced on cholestyramine (4 g/day) and referred for further investigation.

Abbreviations: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid; LFTs, liver function tests; ALT, alanine transaminase; ALP, alkaline phosphatase.

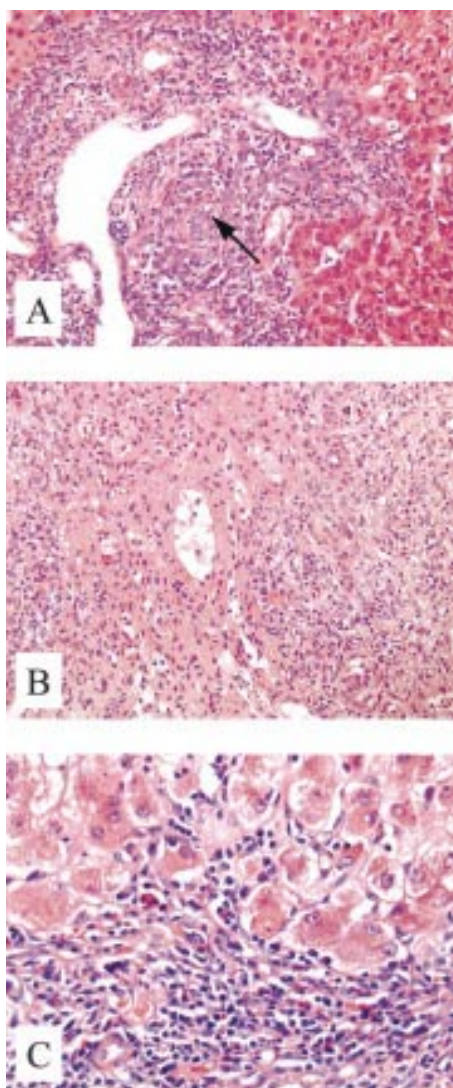


Figure 1 (A) Initial biopsy of patient No 3. Portal tract inflammation with infiltration of the bile duct by lymphocytes is evident; there is a ductular reaction and mild (lymphocytic) interface hepatitis. (B) Second biopsy (after rifampicin). Area of confluent necrosis with a prominent inflammatory infiltrate is seen. (C) Explant liver specimen. Note the marked interface hepatitis (all photomicrographs, haematoxylin-eosin stained).

A liver biopsy confirmed the diagnosis of PBC (stage 1) and she was commenced on UDCA (gradually increased to 12 mg/kg) with no improvement in her symptoms. Her pruritus responded to an increased dose of cholestyramine (6 g/day). Her itch recurred two years later despite continuing on this regimen. This symptomatic relapse was not associated with deterioration of LFTs (bilirubin 8 $\mu\text{mol/l}$, ALP 592 IU/l, ALT 51 IU/l, albumin 43 g/l). Rifampicin was introduced at 150 mg at night. The patient was reviewed fortnightly and reported a significant improvement in pruritus. Seven weeks after commencing therapy her LFTs deteriorated (bilirubin 8 $\mu\text{mol/l}$, ALP 537 IU/l, ALT 353 IU/l). Her prothrombin time and albumin remained normal. These results were discussed with the patient who elected to continue with rifampicin given her symptomatic improvement. She was monitored closely for signs of further deterioration. Her LFTs were stable for eight more months (ALT 303–385 IU/l with bilirubin level and synthetic function remaining normal).

The patient self presented to clinic 11 months after starting rifampicin complaining of jaundice and nausea. Her LFTs had

deteriorated (bilirubin 116 $\mu\text{mol/l}$, ALP 142 IU/l, ALT 419 IU/l, albumin 29 g/l). Her prothrombin time was elevated to 19 seconds. Rifampicin was stopped and her LFTs returned to their previous levels within seven weeks (bilirubin 12 $\mu\text{mol/l}$, ALP 154 IU/l, ALT 52 IU/l, albumin 35 g/l). Her pruritus remains under control seven months after stopping rifampicin.

Case No 3

A 39 year old women presented to her general practitioner with an eight month history of pruritus and dry mouth and eyes. Her mother had been diagnosed as having PBC six years earlier. Initial LFTs confirmed a combined cholestatic and hepatitic abnormality (bilirubin 31 $\mu\text{mol/l}$, ALP 258 IU/l, ALT 311 IU/l, albumin 40 g/l, prothrombin time 16 seconds). PBC was confirmed by an antimitochondrial antibody (titre 1 in 640) and liver biopsy (stage 3). Her liver biopsy showed lymphocytic destruction of medium sized bile ducts and a moderate ductular reaction with minimal fibrosis. Portal tract inflammation included lymphocytes, eosinophils, and epithelioid macrophages; there was mild interface hepatitis but negligible intra-acinar hepatitis (fig 1A). The appearances were those of PBC stage 2 (Scheuer). There were no serological features suggestive of an autoimmune hepatitis crossover syndrome (IgG levels were normal and the patient was antinuclear and smooth muscle antibody negative). She was treated with cholestyramine and UDCA (10 mg/kg) with good control of her pruritus.

Despite continued therapy, a distressing level of pruritus returned three years later. Her LFTs had improved on UDCA (bilirubin 27 $\mu\text{mol/l}$, ALP 288 IU/l, ALT 149 IU/l, albumin 40 g/l, prothrombin time 15 seconds). The patient was already on the maximum tolerated dose of cholestyramine. UDCA was increased to 13 mg/kg with no improvement in symptoms. Rifampicin was started at 150 mg at night which controlled her itch within six weeks. Fourteen months after starting rifampicin her LFTs deteriorated again (bilirubin 91 $\mu\text{mol/l}$, ALP 151 IU/l, ALT 389 IU/l, albumin 38 g/l, prothrombin time 18 seconds). Repeat liver biopsy showed progression to stage 4 disease but, in addition, severe interface hepatitis and a marked intra-acinar hepatitis with areas of confluent and bridging necrosis were found (fig 1B). The patient was unable to tolerate withdrawal of rifampicin because of severe recurrent pruritus. Her LFTs deteriorated (bilirubin 120 $\mu\text{mol/l}$ and prothrombin time 22 seconds). She was assessed for transplantation on the grounds of severe liver impairment with uncontrollable symptoms off rifampicin. She underwent liver transplantation and made a good recovery. Histological examination of the explanted tissue confirmed the presence of an established biliary type cirrhosis but again showed severe interface hepatitis and intra-acinar inflammation (fig 1C)

DISCUSSION

Rifampicin is a semisynthetic antibiotic derived from the rifamycins, a group of antibacterials produced by *Streptomyces mediterranei*. Rifampicin was initially developed to treat tuberculosis but more recently has been used against other bacteria. The beneficial effect of rifampicin on pruritus was initially discovered serendipitously. Four formal studies (three of which were randomised controlled trials) have suggested a subjective effect of rifampicin on itch severity.^{10–13} These studies also suggested that rifampicin was better at relieving itch than other hepatic enzyme inducing agents such as phenobarbitone.¹⁰ A single small study failed to confirm the effectiveness of rifampicin for subjective itching in cholestatic liver disease (including three patients with PBC).¹⁸ All of these studies used subjective measures of itch severity (for example, visual analogue scales). To our knowledge no trial of rifampicin in cholestasis has examined efficacy in terms of objective changes in scratching activity,¹⁹ an outcome measure which should now be regarded as the “gold standard” for

assessment of pruritus in cholestasis.² None of the patients in these studies of rifampicin (total n=64) developed drug induced hepatitis although treatment was not continued for a prolonged period (range seven days to eight months). In all studies the majority of patients showed an improvement in alkaline phosphatase levels during therapy.

The mechanism by which rifampicin alleviates pruritus is unknown; two mechanisms have been postulated although conclusive data supporting either are limited. The first suggests that rifampicin acts as an inducer of microsomal enzymes leading to increased metabolism of endogenous pruritogenic compounds.²⁰ Intriguingly, it has been reported that introduction of rifampicin can induce a withdrawal reaction in individuals taking methadone.²¹ One interpretation of this observation is that endogenous opiates are among the "pruritogens" retained in cholestasis whose metabolism is increased by rifampicin. If this were the case it would suggest that rifampicin and opiate antagonists mediate their therapeutic effects through interaction on the same endogenous opiate pathway. The second postulated mechanism of action of rifampicin is by inhibition of bile salt uptake by hepatocytes leading to a reduction in bile salt mediated disruption of hepatocyte membranes causing release of "pruritogens".²²

"Rifampicin hepatitis" was originally described by Scheuer *et al* in 1974 in a case series of 11 patients.¹⁴ Ten of these patients developed abnormal LFTs within six weeks of starting rifampicin therapy. These patients were found to have a wide range of histological changes ranging from isolated steatosis through varying degrees of portal inflammation with a neutrophil or mononuclear infiltrate, to confluent necrosis. All 11 of these patients however had received rifampicin for tuberculosis, and were also treated with other antibiotics which are also known to be hepatotoxic (isoniazid and streptomycin in all patients and p-aminosalicylic acid in three patients). It is therefore difficult to distinguish the potentially toxic effects of rifampicin from those of other drugs. Indeed, eight of the 10 patients who survived the initial hepatotoxicity were rechallenged with rifampicin and only two of these developed further liver problems (both of whom were also rechallenged with isoniazid). It is therefore possible that some or most of these cases of "rifampicin hepatitis" were in fact due to the effects of isoniazid. Other case series of possible rifampicin induced hepatotoxicity have also been confounded by use of other antitubercular agents.^{15, 16} Rothwell and Richmond described one case of renal failure and jaundice occurring in a patient taking rifampicin intermittently (three doses of 450 mg over five weeks) for tuberculosis.¹⁷ Although the patient suffered symptoms of nausea and "chills" immediately following rifampicin, it is not clear whether the patient also took PAS which had been coprescribed.

A Medline literature search identified only two previous cases of hepatitis occurring in patients treated with rifampicin in the absence of other hepatotoxic agents. Bachs *et al* described two cases of rifampicin hepatitis in women treated for PBC.²³ These cases were drawn from a cohort of 16 PBC patients who were treated with rifampicin for a mean of 12 months. Their incidence of rifampicin hepatitis (12.5% (95% confidence interval (CI) 3.5–36.0)) was therefore not dissimilar to ours (7.3% (95% CI 2.5–19.4)). In common with cases 1 and 2 above (and 10 of the cases reported by Scheuer), both patients reported by Bachs *et al* developed problems within two months of starting therapy. Although both cases reported by Bachs *et al* developed elevated ALT levels (1624 IU/l and 819 IU/l) and jaundice (maximum bilirubin 162 µmol/l and 64 µmol), neither was reported to suffer deterioration in hepatic synthetic function.

The importance of rifampicin dose on the frequency and severity of hepatic side effects is not clear. The first patient described above, who suffered the most severe reaction, was

started on what we would now consider to be a high initial dose of rifampicin. All 11 patients in the series described by Scheuer *et al* were prescribed 450–600 mg daily.¹⁴ The two patients described by Bachs *et al* received an initial dose of 10 mg/kg/day.²³ To our knowledge there have been no reports of the effect of rifampicin dose on hepatotoxicity in monotherapy. In the absence of a clear evidence basis for dosing of rifampicin in PBC, and given the fact that a significant proportion of cases of hepatotoxicity appear to have occurred in patients taking relatively high doses of rifampicin, we consider it prudent to start patients on a daily dose of 150 mg with subsequent increase in the dose to a daily maximum of 600 mg based on clinical need.

To our knowledge the cases described here are the first reports of significant impairment of hepatic synthetic function associated with rifampicin monotherapy. In each case of impairment of synthetic function, rifampicin was continued after the onset of abnormal LFTs because of the presence of otherwise uncontrollable severe pruritus; a factor which may explain the severe clinical pattern. Case No 3 presented unusually late after starting rifampicin. Scheuer *et al* described one case of "rifampicin hepatitis" starting 52 weeks after transplantation.

Only a limited number of patients receiving rifampicin therapy for pruritus in PBC appear to develop significant hepatotoxicity. However, the cases described here clearly demonstrate that the process of liver damage induced by rifampicin can progress from the stage of the previously described elevation in transaminases to significant impairment of liver synthetic function. The majority of patients who develop hepatotoxicity will probably do so in the first two months of therapy and LFTs should be monitored regularly during this period. Continuation of rifampicin therapy after the initial development of a transaminitis can result, as the cases described here demonstrate, in the development of progressive liver dysfunction with impairment of synthetic capacity. If rifampicin hepatitis develops this will usually resolve with cessation of therapy.

There is however a broader issue to be addressed. Given the potential for rifampicin to induce significant hepatotoxicity, and the advent of seemingly more effective (and better characterised) second line antipruritic agents such as the oral opiate antagonists, it is unclear whether the use of rifampicin should still be recommended, other than perhaps as an agent of last resort in patients who have failed to respond to or tolerate all other agents (including oral opiate antagonists).

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