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APPLICATION NUMBER:

22-554

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Lara Dimick, M.D., F.A.C.S.
Review Completion Date	March 10, 2010
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
older

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

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that rifaximin be approved for the indication of “reduction in risk of recurrence of overt hepatic encephalopathy (HE)”.

1.2 Risk Benefit Assessment

Although, there is only one randomized controlled trial, results of this trial are robust with a very low p-value in primary and key secondary evaluations. The review team had concern about the use of Conn scores for determining the primary endpoint outcome, and thus the validity of the results. However, in light of the lack of validated endpoint measures in hepatic encephalopathy (HE), and the wide spread clinical acceptance of use of the Conn score, I conclude, that the results meet the criteria of “substantial evidence of effectiveness or clinical benefit” as per the Orphan Drug Act. In addition, the clinically important, key secondary end-point, time to HE-related hospitalizations, confirms the robustness of the trial. Decreasing hospitalizations is important, both for the impact on morbidity and decreasing the cost to society.

The trial was conducted with 91% of the subjects receiving concomitant lactulose. The efficacy has not been established as a stand alone drug, which should be reflected in the labeling.

The dose of rifaximin used was selected by the sponsor based on one small trial in the treatment of HE, a different indication. The trial tested three dose levels, 600mg, 1200mg and 2400mg per day. Dose relationship in relation to the main objective parameter was not established. In my opinion, a lower dose may be efficacious, and should be tested.

The safety of rifaximin in the target population appears to be acceptable. However the trial enrolled a relatively healthy population of cirrhotic patients, in that it limited the Model for End stage Liver Disease (MELD) score to 25 and below and enrolled only a small number of patients with higher (>19) MELD scores. In addition, there were very few Child Class C subjects enrolled. The pharmacodynamic results showed increased systemic exposures with increasing MELD score or Child Class. Thus the safety of rifaximin in patients with the most severe liver disease has not been studied.

The development program did not include ECG evaluations in any phase 3 trials. Our tQT team recommends post-marketing requirements for ECGs. These should be done

at t-max and in patients with more severe levels of hepatic impairment, and thus higher systemic exposures.

The protocol excluded patients with creatinine levels > 2, therefore rifaximin has not been studied in severe renal insufficiency or renal failure patients.

Issues that are raised by the long-term use of an antibiotic include development of cross resistant strains of bacteria and mycobacterium. These issues need to be adequately addressed. In addition, long term effects on the gastrointestinal flora and the colon are not known and need to be studied.

The preclinical review by the pharmacology-toxicology reviewer, revealed inconsistencies in the preclinical study reports with some liver and small bowel toxicity seen at lower doses in older pre-GLP studies, but no toxicity seen in more recent, higher dose studies. In the more recent studies (done under GLP) the range of plasma drug values were lower than the range of plasma drug values seen in cirrhotic patients. Thus, animal toxicity studies don't provide assurance of safety for rifaximin use in cirrhotic patients. This deficiency should be addressed with a Post Marketing Requirement.

The overall risk-benefit analysis allows the conclusion that rifaximin is likely effective and safe in the population studied. However further trials may be needed to clarify the risk/benefit in other types of patients, such as those with more severe liver impairment.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Post-market Requirements and Commitments

The following Post-marketing Requirements (PMR) and Commitments (PMC) are recommended by the Agency. They have not been presented to the Applicant and will be modified after discussions between the Applicant and the Agency.

Clinical - PMR

- 1) A randomized controlled clinical trial to evaluate safety in patients classified as Child-Pugh Class C, MELD >19 and MELD >25 hepatic impairment.

A sub-study should obtain additional PK data in patients with MELD 19 - 25 and MELD > 25.

A additional sub-study should evaluate the effect of long term treatment with rifaximin on the gut flora and in vitro susceptibility to rifaximin and other rifamycin

antimicrobial drugs, and depending on the outcome of such studies, consideration may need to be given to evaluating the clinical significance of in vitro “resistance” on the efficacy of rifaximin.

Another sub-study should be performed to assess potential effect of concurrent renal insufficiency on the systemic exposure to rifaximin in cirrhotic patient; sparse blood samples should be collected for a population pharmacokinetic analysis. The PK data should be analyzed by renal insufficiency (e.g. creatinine clearance) within a Child-Pugh class/and by MELD score.

Rational:

The drug appears to be safe in the population studied, however there is little data in patients with higher levels of hepatic impairment (i.e., Child Class C, MELD score > 19). There are some safety signals in this population (i.e., increased mortality in Child C patients in RCT), but the numbers are too small to permit conclusions, with the known increased systemic exposures in this population and the unknown toxicity of the drug when it is absorbed at these levels, additional safety data is necessary. Drugs in this class (rifampin) are known to have increased incidence of renal failure, hepatitis and immune reactions. This population is likely to be given the drug in the clinical setting, as there are few other treatment options. This would need to have a control arm because of the difficulty in evaluating AE's in this very ill population.

The microbiology reviewer, found that no microbiology information was collected in the 6 month HE study or reported in the literature publications submitted by the applicant. In the absence of any microbiological data, the long term effects of rifaximin on gut flora and any change in the in vitro susceptibility of gut flora to rifaximin and other antimicrobial drugs within the rifamycin class cannot be evaluated.

Microorganisms can develop drug resistance during treatment (i.e., under drug pressure), and the same possibility exists with the use of rifaximin. It is important to note, however, that there are several drugs of the rifamycin class (e.g., rifampin, rifabutin, and rifapentine) that are currently approved, marketed and used in combination with other drugs for the long term treatment of tuberculosis. The role of these products on in vitro susceptibility of gut flora, and the additional impact of the long term use of rifaximin on gut flora have not been evaluated.

The trial protocol excluded patients with creatinine >2, therefore, rifaximin has not been studied in patients with significant renal insufficiency.

- 2) Perform ECG evaluations in patients with a level of severity of hepatic impairment that results in the highest systemic exposure to Xifaxan. This may be performed as a sub study in the ongoing Phase 3 trial, or as part of additional safety trials (PMR)

Rational:

Rifaximin is low risk for QT prolongation, however no ECG's were collected in phase 3 trials and no ECG's have been done at t_{max} in any trial. This is safety issue in that inadequate data exists.

Clinical - PMC

- 3) Randomized Controlled Clinical Trial to evaluate whether lactulose is required in combination with rifaximin to delay time to onset of episode of overt HE

Rational:

Lactulose was used in 91% of the patients in the controlled trial, therefore the efficacy of rifaximin as a stand alone product has not been established

Clinical Pharmacology - PMC

- 4) In vivo drug interaction study to evaluate the effect of P-glycoprotein inhibitor(s) on rifaximin pharmacokinetics.

Rational:

In vitro study showed that there is a potential for increased systemic exposure of rifaximin when a p-glycoprotein inhibitor is co-administered. This potential was not evaluated in vivo.

This study will answer if a concomitant p-gp inhibitor can increase the systemic exposure to rifaximin in vivo. Based on the study result, adequate labeling language will be provided to avoid a potential drug interaction via P-gp.

- 5) In vitro study to evaluate the potential for rifaximin to inhibit P-glycoprotein transporter

Rational:

In vitro study indicates that rifaximin can inhibit p-glycoprotein and thus can increase the systemic exposure of concomitant medications which are p-gp substrates. The inhibition potential at the clinically relevant concentrations is unknown. This issue for now will be addressed by appropriate labeling language.

Although a positive inhibitory effect of rifaximin on p-gp was observed in vitro, the study was conducted only at one concentration; therefore the utility of the results was limited. In this study, effect of rifaximin on efflux of p-gp substrate will be studied at a wider range of concentrations to determine the K_i value. This will clarify the inhibition potential of rifaximin at the clinically relevant concentrations.

Preclinical Toxicology - PMR

- 6) Conduct a chronic oral toxicology study that evaluates AUC exposure in animals that are comparable the highest AUC's observed in cirrhotic patients. These AUC values must be achieved and maintained throughout the duration of the chronic toxicity study. In the event that sufficiently high AUC levels cannot be achieved from oral dosing, alternative routes of administration may be used.

Rational:

Although prior clinical experience and nonclinical toxicity studies suggest that rifaximin is probably safe, the higher levels of systemic exposure in cirrhotic patients compared to systemic exposures in healthy subjects is a key area of concern. In order to address the safety concern about higher AUC levels in cirrhotic patients, the Applicant must conduct an oral toxicity study of least 3 months duration in rats. The objective of this study is to evaluate the toxicity of rifaximin at AUC values equal to or greater than the highest AUC values observed in cirrhotic patients (approximately 400 ng•hr/ml).

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 patients ≥ 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.

Rifaximin is also being investigated under multiple INDs for different indications: IND 72-757 for irritable bowel syndrome; IND 71-425 for pediatric bacterial diarrhea; and IND 52-980 for the prevention of travelers' diarrhea.

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 patients ≥ 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 as 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	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-L-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

2.3 Availability of Proposed Active Ingredient in the United States

Rifaximin is currently marketed in the United States by Salix Pharmaceuticals Inc. under the trade name Xifaxan® as 200mg tablets for the indication of treatment and prevention of Travelers Diarrhea.

Medical Officer's Comment:

Rifaximin is used off label in the United States for HE, dosed at 400mg three times daily.

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

Please refer to the complete clinical microbiology review by Dr Purfield.

The applicant had tested *in vitro* activity against a wide range of Gram positive and Gram negative bacterial pathogens. Rifaximin stays predominantly intraluminally. This makes it challenging to evaluate MICs in the usual fashion. The clinical trial results in patients with Traveler's diarrhea, supported efficacy against *Escherichia coli* (enterotoxigenic and enteroaggregative strains) only. The information from the clinical studies was not sufficient to interpret the *in vitro* susceptibility results for the other pathogens. Also, interpretative criteria and breakpoints could not be established for any of the pathogens in part because this is an intraluminal agent and stool cultures are difficult to work with for microbiologic evaluations. In the absence of interpretative criteria and breakpoints, the results of *in vitro* susceptibility (MIC) should be interpreted with caution. Although the word "resistance" is used below, this word is meant to denote an MIC value determined from susceptibility testing, but should be correlated with clinical outcome (i.e., failure) before the results can be interpreted that the organism is resistant to therapy. On the basis of the preclinical and clinical information reviewed by microbiology reviewers (for details see microbiology reviews dated March 14, 2002 and April 13, 2004) the following information was incorporated in the approved rifaximin package insert, including an acknowledgement that the clinical significance of the *in vitro* finding has not been studied:

In Microbiology section:

"*Escherichia coli* has been shown to develop resistance to rifaximin *in vitro*. However, the clinical significance of such an effect has not been studied."

"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."

In "Warnings and Precautions" section (Development of Drug Resistant

Bacteria): “Prescribing XIFAXAN Tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.”

As noted above, the significance of an *in vitro* finding of “resistance” to an organism that is found in the gut lumen and acted upon by a product with low systemic absorption in the fasting and fed state (as noted in the XIFAXAN package insert) is unknown.

Long Term Safety:

There was no information on the long term safety of rifaximin available from the clinical studies reviewed previously for the treatment of travelers’ diarrhea; these studies were of 3 days duration.

Effects of long term treatment on gut flora:

For the treatment of hepatic encephalopathy (HE), the applicant is proposing a higher dose and duration (550 mg, b.i.d. for about 6 months) of rifaximin. The currently approved regimen is short, only 3 days, and Dr. Anne Purfield, the Microbiology reviewer found that no microbiology information was collected in the 6 month HE study or reported in the literature publications submitted by the applicant. In the absence of any microbiological data, the long term effects of rifaximin on gut flora and any change in the *in vitro* susceptibility of gut flora to rifaximin and other antimicrobial drugs within the rifamycin class cannot be evaluated.

Microorganisms can develop drug resistance during treatment (i.e., under drug pressure), and the same possibility exists with the use of rifaximin. It is important to note, however, that there are several drugs of the rifamycin class (e.g., rifampin, rifabutin, and rifapentine) that are currently approved, marketed and used in combination with other drugs for the long term treatment of tuberculosis. The role of these products on *in vitro* susceptibility of gut flora, and the additional impact of the long term use of rifaximin on gut flora have not been evaluated.

The clinical Microbiologist had the following recommendation:

If rifaximin is approved for the treatment of HE, post marketing studies should be considered to evaluate the effect of long term treatment with rifaximin on the gut flora and *in vitro* susceptibility to rifaximin and other rifamycin antimicrobial drugs, and depending on the outcome of such studies, consideration may need to be given to evaluating the clinical significance of *in vitro* “resistance” on the efficacy of rifaximin.

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. Rifaximin was studied at doses greater than 25 mg/kg/day and produced hepatotoxicity in rats and dogs when administered orally for 3-6 months; however plasma drug levels were not measured in these studies. Subsequently, rifaximin was studied at doses as high as 300 mg/kg/day in rats for 6 months, and 1000 mg/kg/day in dogs for 9 months, showed no signs of hepatotoxicity.

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 mean and maximum AUC values that occurred in the toxicity studies (42 to 127 ng·hr/ml) were generally lower than the mean and maximum AUC values 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. See Table 8

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.

Table 8: Rifaximin PK by Degree of Hepatic Impairment

	Healthy subjects (n=12) ¹	Child-Pugh A (n=18) ²	Child-Pugh B (n=7) ²	Child-Pugh C (n=4) ³
AUC _{tau} (ng·h/ml)	12.3 (4.76)	118 (67.8)	161 (101)	245.9 (119.6)
C _{max} (ng/ml)	3.41 (1.62)	19.5 (11.4)	25.1 (12.6)	35.5 (12.5)
T _{max} (h)	0.76 (0.5, 4)	1 (0.9, 10)	1 (0.97, 1)	1 (0, 2)
CL/F (L/min)	863 (364)	122 (101)	70.6 (29.2)	--

Mean (SD) PK parameters at steady-state after 550 mg BID

1 Study RFPK1007

2 Study RFHE3002PK

3 Amendment on 1/26/10

4.4 Clinical Pharmacology

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 and Pharmacokinetics

See complete Clinical Pharmacology review by Insook Kim, PhD. The conclusions are summarized below;

- 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; these evaluations were in the treatment of HE, which is a different indication than the one being evaluated in NDA 22-554
- A concomitant high fat meal delayed oral absorption of rifaximin and increased the mean AUC by 2 fold

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 9 was conducted for other indications. They are relevant only as part of the integrated safety data in Section 7.

Table 9: 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 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

Study ID	Trial Type	Trial Design	Number Centers	Number subjects	Dosage	Duration
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
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 9). 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).

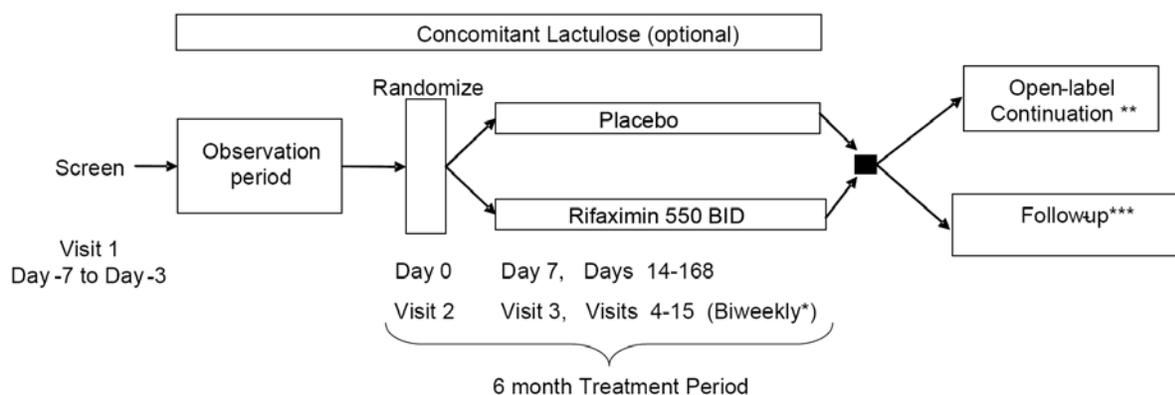
The primary efficacy endpoint was the time to first breakthrough overt HE episode. A breakthrough overt HE episode was defined as an increase of Conn score to Grade ≥ 2 (i.e., from 0 or 1) or an increase in Conn and asterixis score of 1 grade each for those subjects who entered the study with a Conn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

5.3.3.2 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 10: 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 11: 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%)
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 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]).

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.

Table 12: 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)

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 13: 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%)
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%)

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 14.

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

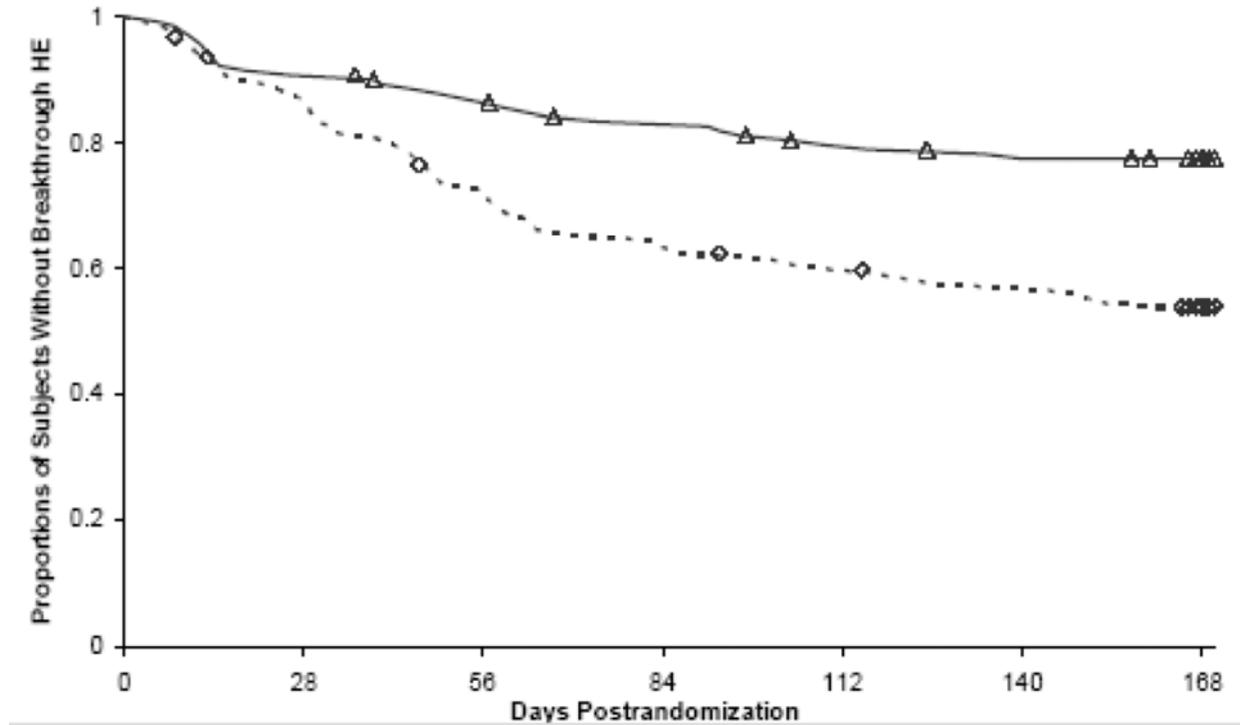


Table 14: Study RFHE3001: Kaplan-Meier Estimates and Statistical Analyses of Time to First Breakthrough Overt HE (up to 6 Months of Treatment, Day 170) (ITT Population)

Treatment interval (days)	Placebo (N = 159)					Rifaximin (N = 140)				
	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 ^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 15.

Table 15: 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 16 the non-responders are all patients who discontinued for any reason. Table 17 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 16: 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 17: 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 18. This was captured on the CRF page 118 Breakthrough episodes.

**Table 18: 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 19: 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 20: 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 21.

Table 21: 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. No validated endpoints have been established for clinical trials in Hepatic Encephalopathy

6.1.5 Analysis of Secondary Endpoints(s)

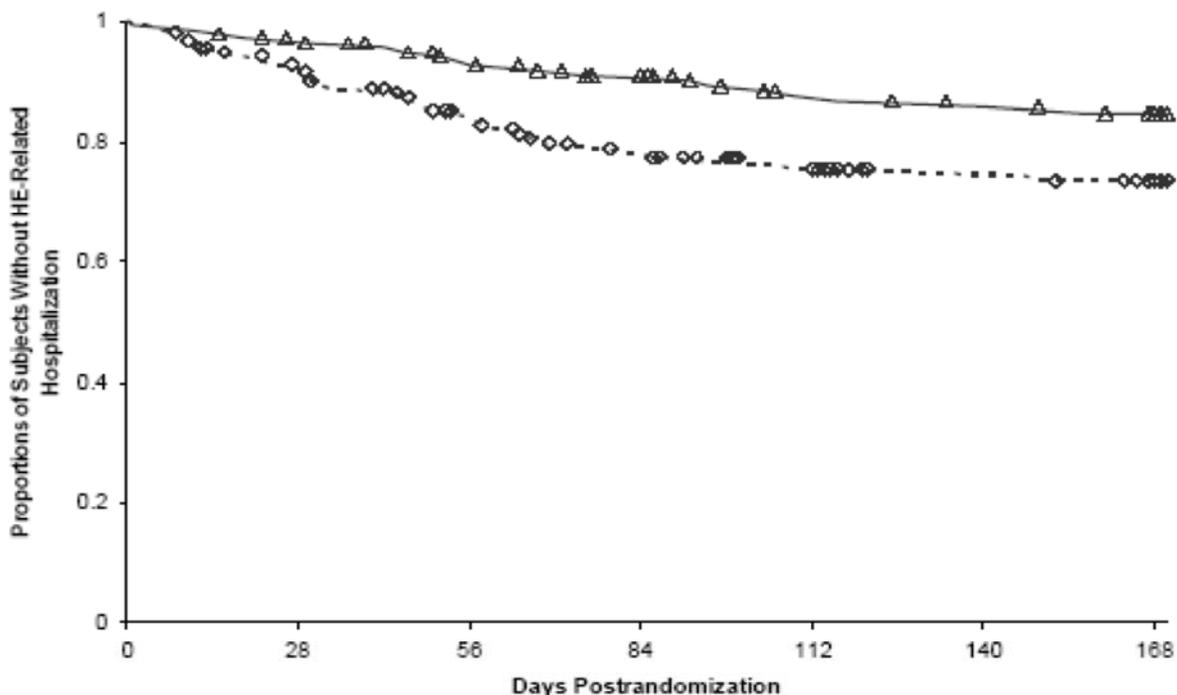
Key secondary endpoints were prospectively placed in hierarchical order as shown below and statistical testing was performed according to this order.

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

Treatment interval (days)	Placebo (N = 159)					Rifaximin (N = 140)				
	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:		0.500 ^e								
95% CI:		(0.287, 0.873)								
p-value		0.0129								

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 23: 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.

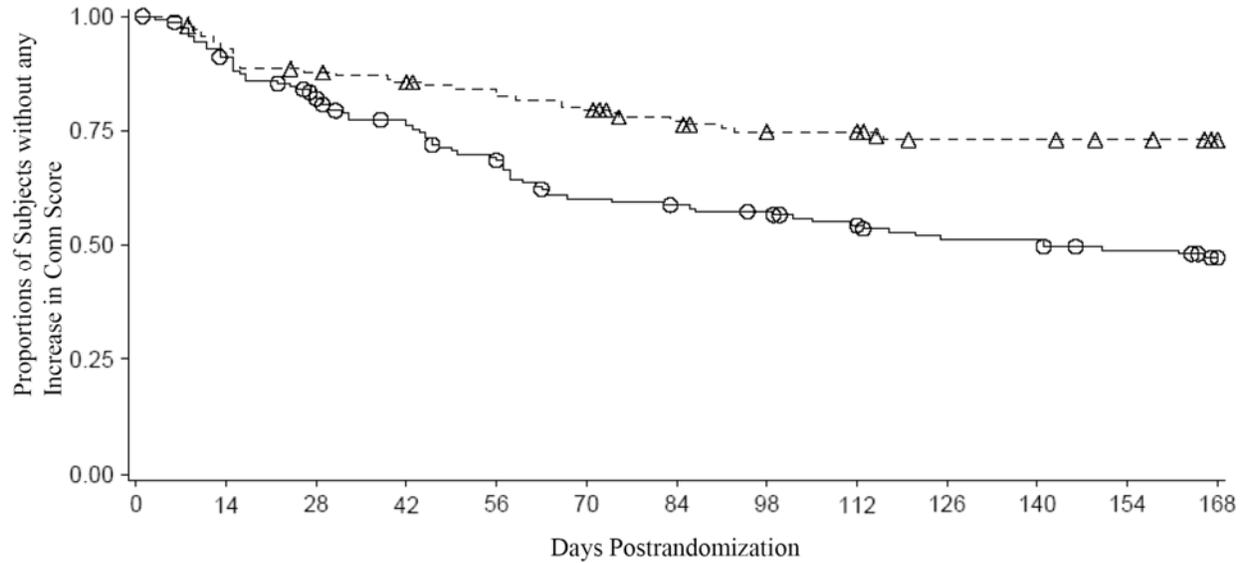
Medical Officer's Comment:

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

Treatment interval (days)	Placebo (N = 159)					Rifaximin (N = 140)				
	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:		0.463 ^e								
95% CI:		(0.312, 0.685)								
p-value		< 0.0001								

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

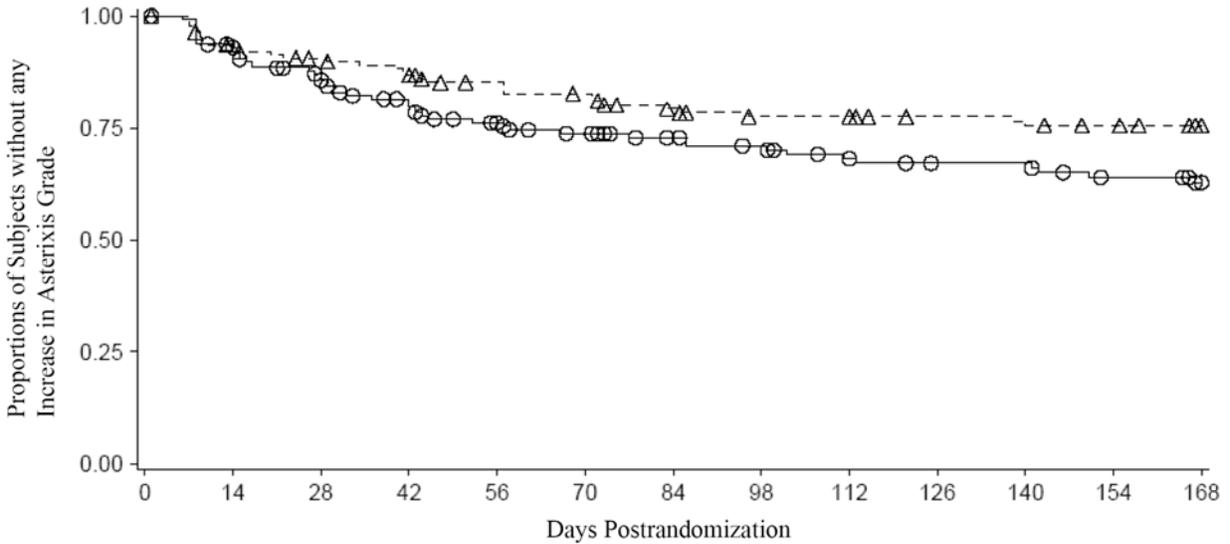
Abbreviations: CI = confidence interval; SE = standard error.

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

Treatment interval (days)	Placebo (N = 159)					Rifaximin (N = 140)				
	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 26: 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, 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 27: 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 28: 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 29). 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 (± 2.096) cups/day in the rifaximin group and 3.51 (± 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 (± 0.03767) and 0.0076 (± 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

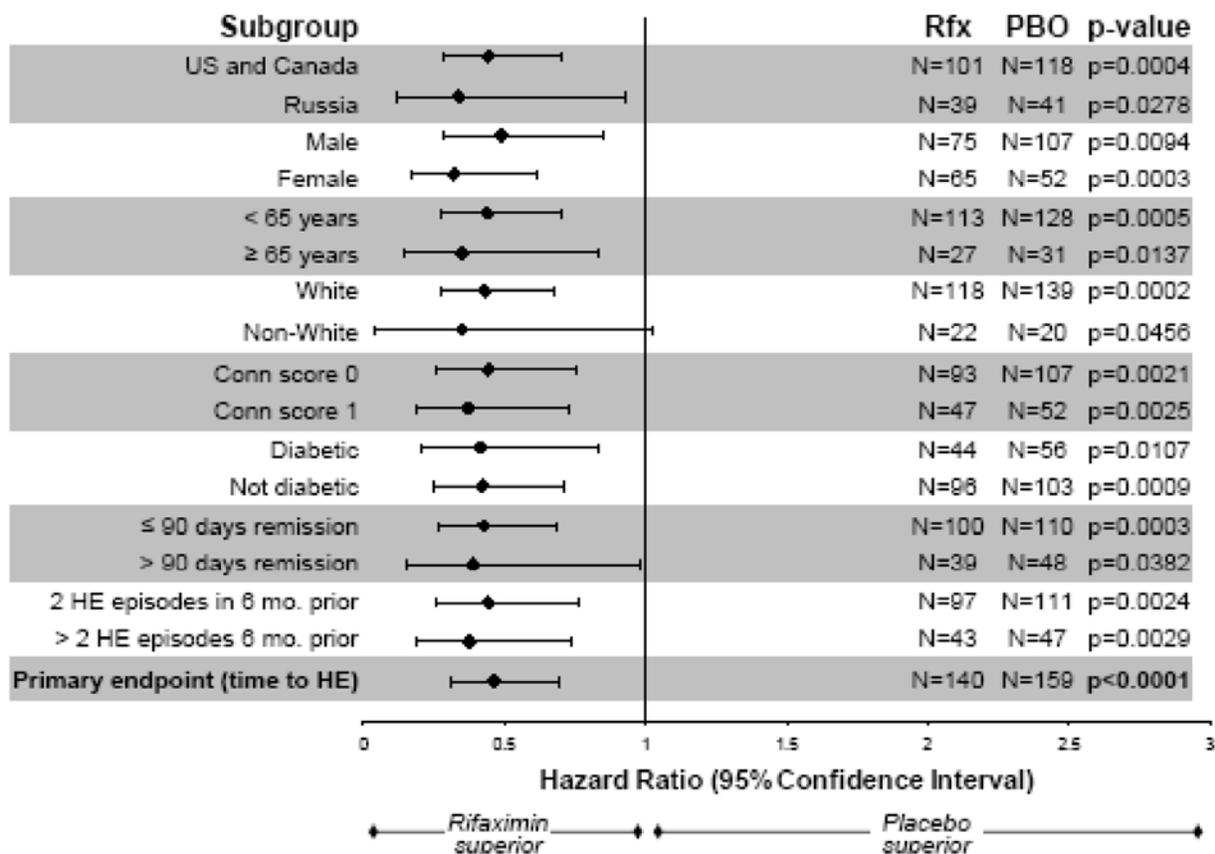
Subgroup analyses were conducted to determine the robustness of the observed rifaximin treatment effect for the primary efficacy endpoint. Outcomes for the primary efficacy endpoint were evaluated in the following subgroups: geographic analysis region (North America versus Russia), sex, age (< 65 versus ≥ 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

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.

The dose ranging trials were performed in **Treatment** of HE, for only a short duration, and did not show significant differences in the response to different doses, and the onset of treatment effect may be delayed by as much as four weeks, as seen in the RCT. Therefore, a lower dose may be efficacious, and should be studied.

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).

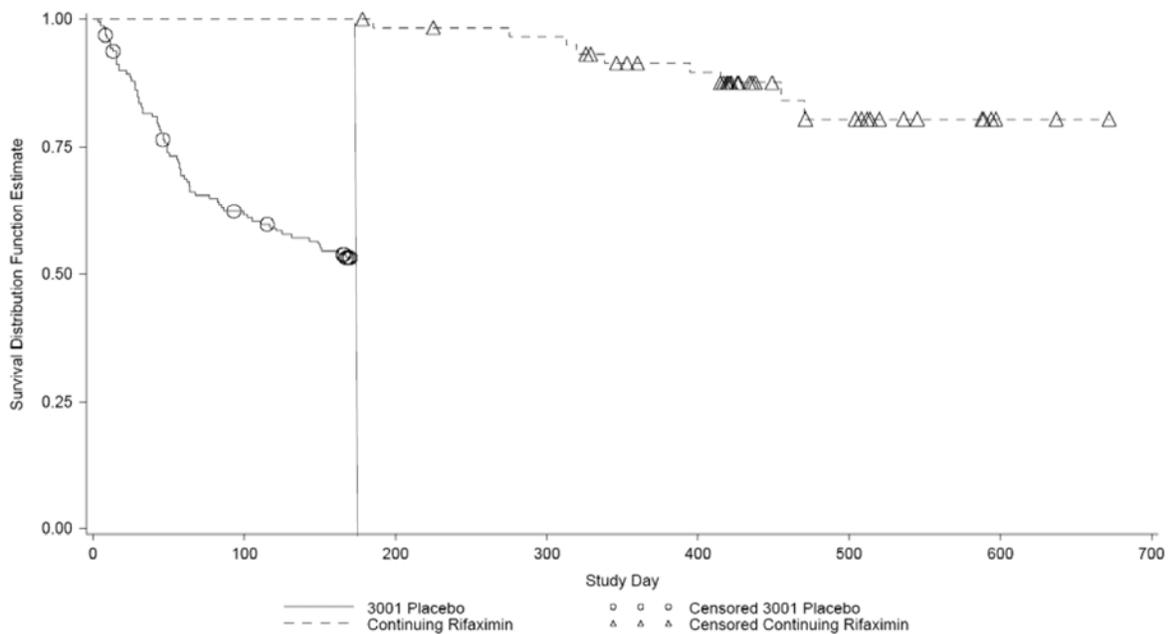
The Applicant reports that data from RFHE3002 provide information on the long-term durability of rifaximin for the protection against breakthrough overt HE episodes. Rifaximin treated subjects from RFHE3001 who were in remission at the end of RFHE3001 (6 months treatment) were followed during open-label 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 29). 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 29) 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 29: Daily Lactulose Use during the Treatment Period by Treatment Group (ITT Population)

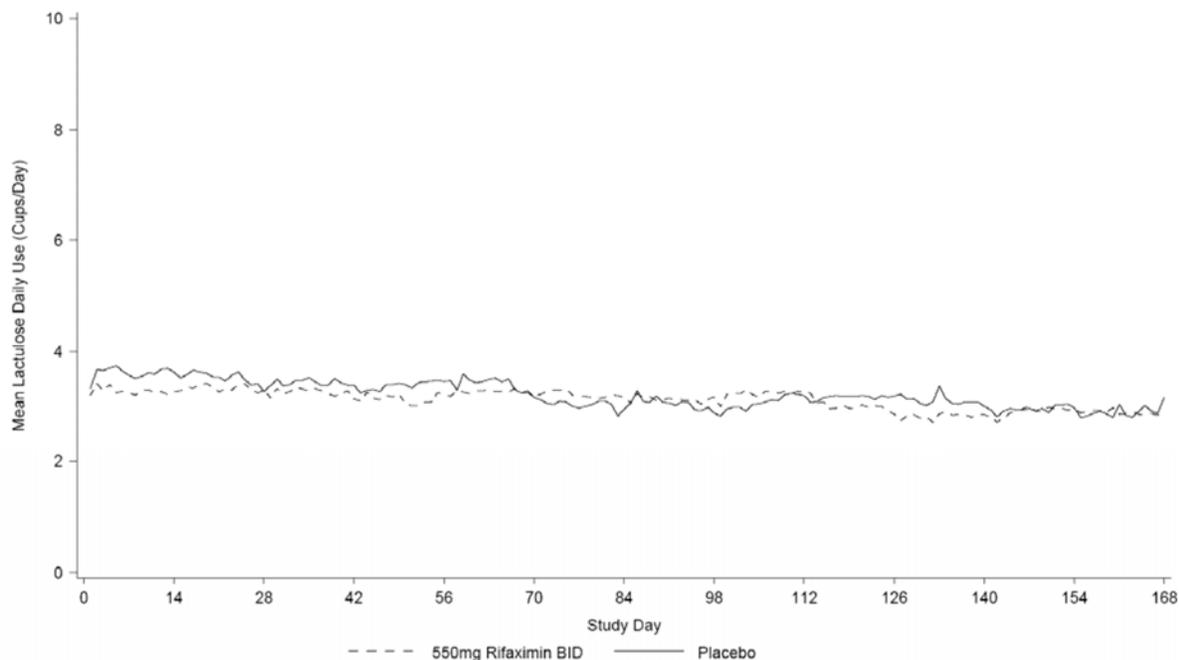
	Placebo N = 159	Rifaximin N = 140
Average daily lactulose use during the treatment period – (cups/day)^a		
n	142	132
Mean (SD)	3.51 (2.592)	3.14 (2.096)
Median (min, max)	2.82 (0, 11.8)	2.82 (0, 9.0)
Lactulose use change rate – (cups/day)^a		
n	142	132
Mean (SD)	0.0076 (0.10595)	0.0030 (0.03767)
Median (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 RFHE3002
 - **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 their dosing regimen.

Table 30: Rifaximin Exposure ^a

Exposure duration	RFHE3001		Long Term Exposure – RFHE 3001 & RFHE3002		
	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 31: 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 \geq 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 31: 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		

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	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 32

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 32: 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 Special Animal and/or In Vitro Testing

7.2.4 Routine Clinical Testing

Medical Officer's Comments:

Adverse event reporting was lower in Russia than at United States and Canadian sites. This is likely due to decrease reporting of adverse events in Russia though this was not apparent on site inspection. Since patients were discontinued from the study at the time of development of HE; there was poor data collection on these patients for final endpoint evaluation. Frequently, lab values were not located for patients who were discontinued at hospital admission for HE. When the data was examined 44% of the rifaximin subjects that were discontinued for any reason did not have lab values in the data base from 3 days prior to discontinuation through 30 days after discontinuation.

The Neurological and Psychological evaluations used to establish baseline and subsequent Conn scores was not fully recorded in the Case Report Forms and was frequently assigned by retrospective analysis and by non-medical personnel. A Consult was obtained from Dr. Ranjit Mani from the Department of Neurology and is summarized below. The conclusion of the consult was that study RFHE3001 is

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer the Clinical Pharmacology Summary Review under Tab 4

7.2.6 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 33: 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 34: 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 34 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 34: 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

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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 35). 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 35: 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=12	n=17
n (%)	2 (16.7)	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 35). 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 35 and Table 36).

Table 36: Deaths by Child-Pugh Classification (baseline) - RFHE3002

Child-Pugh classification	Placebo crossover ^b	Rifaximin rollover ^c
	N =82	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 37: 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)

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 38 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 38: 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 39: TEAEs Resulting in Study Discontinuation in ≥ 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 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 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 40 and Table 41 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 40: 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 41: 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 42. 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 42. 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 42); with the exception of hepatic failure, which occurred at a lower event rate in RFHE3001 than in the RFHE3002 rifaximin groups.

Table 42: 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 43: 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 (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 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 38

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 [REDACTED] (b) (6), 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 44: 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 45 and Table 46

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 45: 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 (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 (%)			
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 46: 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 47

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 47: 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 n (%)		Rifaximin 550 mg BID n (%)		Cumulative 120-Day Results n (%)	
	N→H EOT	N→L EOT	N→H EOT	N→L EOT	N→H Last Value	N→L 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 48: 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 EOT	N→L EOT	N→H EOT	N→L EOT	N→H Last Value	N→L 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 49: 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.

Medical Officers Comments:

During review of the case report forms it was noted that lab values were not in the data sets for many of the patients at the time of discontinuation, subsequent analysis revealed that there were no lab values in the data sets for patients who were discontinued from 2 days prior through 30 days after the discontinuation in 44% of the

rifaximin patients, and 32% of the placebo patients. This makes it difficult to do an adequate safety evaluation.

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.

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. 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

Refer to Pharmacology Review Summary in Tab 4.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No studies or trials have been performed.

7.6.2 Human Reproduction and Pregnancy Data

No data is available in humans. Rifaximin is categorized as Class C for use in pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

No trials in pediatrics have been performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no known abuse potential in this drug, no trials have been performed.

7.7 Additional Submissions / Safety Issues

7.7.1 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 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 Travelers' Diarrhea Safety Studies

In the treatment of Travelers' Diarrhea 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. 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.

7.7.2 120-day Safety Update

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

- Data from the ongoing treatment extension safety trial
- 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 trail RFHE3001 were 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 50: 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 51: 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 51.

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 \geq 3 months (303/348 subjects). A total of 265 subjects had received rifaximin for \geq 6 months and 202 subjects for \geq 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.

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.

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. Conclusions with respect to safety therefore remain unchanged from the original ISS.

7.7.3 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, 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, 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 composite 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, 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

Refer to full reviews by the Office of Surveillance and Epidemiology Review (OSE), Ann Corken Mackey, RPh, MPH, and Patty Greene, PharmD, which are summarized below

Summary

Post marketing analysis recommends adding **Anaphylaxis** to the **Warning section** of the label. In addition, cases of rifaximin-induced *C. difficile* colitis have been reported (including one death), and should be included in the **Adverse Events Postmarketing section** of the label (in addition to the Warnings section).

Distribution Data

In the US, rifaximin 200 mg tablets were approved for marketing in May 2004 for the treatment of travelers' diarrhea. Rifaximin has been marketed in Italy since 1987. Marketing authorizations have been granted to Alfa Wasserman and others for rifaximin tablets (200 mg) and a cherry granulate for oral suspension in Italy and a number of other countries worldwide. Currently, one or both pharmaceutical forms of rifaximin are approved outside the US in 24 countries.

Globally, patients have received approximately 221,958,261 days of rifaximin tablet treatment and approximately 7,398,610 months of treatment during the post-marketing periods. Total worldwide distribution of rifaximin as oral suspension during the approximated 10 year postmarketing window was 35,955,432 units (100mg/5mL). Globally, patients have received approximately 8,998,858 days of rifaximin treatment as oral suspension and approximately 299,963 months of treatment during the post marketing periods.

No regulatory actions (e.g., license application rejections or withdrawals from the market) have been reported since rifaximin was first approved for marketing.

Drug Use Data – From Division of Epidemiology

Total dispensed prescriptions for Xifaxan® (rifaximin) increased (b) (4) 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.

Postmarketing Clinical Data

From Sponsor

A total of 38 subjects have reported 113 post-marketing SAEs. Most SAEs were reported spontaneously. Almost half of the serious events were Gastrointestinal Disorders, Skin and Subcutaneous Tissue Disorders, or General Disorders and Administrative Site Conditions. The most frequently reported SAEs (≥ 4 events) in descending order of frequency were abdominal pain, diarrhea, vomiting, and rash. There were no SAE terms reported in ≥ 5 subjects.

Other post-marketing SAEs reported at a frequency of ≥ 2 and < 4 events, in descending order of frequency, were: condition aggravated, musculoskeletal pain,

headache, urticaria, vertigo, asthenia, drug ineffective, edema peripheral, clostridium difficile colitis, clostridium difficile toxin test positive, international normalized ratio increased, speech disorder, dyspnea, and pruritus.

Office of Surveillance and Epidemiology (OSE) Consult

A consult was obtained from OSE and is summarized below, for full report see consult in DARRTS.

Safety Evaluation - Division of Pharmacovigilance

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. 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 OSE 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.

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)

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.

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, and 1 case was reported as worsening HE

Eleven cases reported labeled events:

- Chest pain/pruritus (1)
- Fatigue (1)
- Frequent bowel movements (1)
- Respiratory problems (1)
- Vomiting (1)
- Anaphylaxis/angioedema [hypersensitivity reactions, but not anaphylaxis, are labeled)

- *C. difficile/campylobacter* (5; the label states that antibacterial agents alter normal flora of the colon)

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 (1)
- Increased blood glucose/ vomiting (1)
- Worsening chronic renal failure (1)
- Edema of lower extremities/scrotal swelling (1)
- Pancytopenia/worsening HE/skin disorder.

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).

Because of reports of *C. difficile* (including one fatality), it should be included 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.

Table 52: Serious Adverse Events during Postmarketing Use of Xifaxan by System Organ Class

System Organ Class	Total SAEs	Total Subjects
Blood and Lymphatic System Disorders	4	4
Cardiac Disorders	2	1
Congenital, Familial and Genetic Disorders	0	0
Ear and Labyrinth Disorders	4	2
Endocrine Disorders	0	0
Eye Disorders	1	1
Gastrointestinal Disorders	22	15
General Disorders and Administrative Site Conditions	14	12
Hepatobiliary Disorders	1	1
Immune System Disorders	2	2
Infections and Infestations	3	3
Injury, Poisoning and Procedural Complications	1	1
Investigations	9	8
Metabolism and Nutrition Disorders	3	3
Musculoskeletal and Connective Tissue Disorders	8	7
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	0	0
Nervous System Disorders	12	7
Pregnancy, Puerperium and Perinatal Conditions	1	1
Psychiatric Disorders	2	2
Renal and Urinary Disorders	3	2
Reproductive System and Breast Disorders	0	0
Respiratory, Thoracic and Mediastinal Disorders	6	4
Skin and Subcutaneous Tissue Disorders	14	10
Surgical and Medical Complications	0	0
Vascular Disorders	1	1
TOTAL	113	38

Source: Internal Salix ARISg Safety Database, Frequency Report for Serious Xifaxan Events from Spontaneous Sources and Literature, 20 May-2004 (earliest case) to 06 April 2009.

9 Appendices

9.1 Literature Review/References

See attached bibliography Section 9.4

9.2 Labeling Recommendations

The labeling review and negotiations are in progress; initial summary recommendations are listed below:

1. The wording of the indication requested by the applicant should be changed to better reflect the results of the pivotal trial performed. Discussion is underway in the Division at the time of this review finalization; however the wording should be similar to the following; reduction in risk of recurrence of overt hepatic encephalopathy in patients ≥ 18 years of age”.
2. The label should state that the efficacy of rifaximin has not been studied in patients who where not using lactulose as a concomitant drug.
3. Add anaphylaxis to the warning section of the labeling
4. Clinical Pharmacology: Increased systemic exposure in increasing Child Class or increased levels of hepatic impairment.
5. Preclinical: Concern about unknown toxicity profile at the AUC levels occurring in Child-Pugh Class C patients.
6. Not studies in renal failure patients.

9.3 Advisory Committee Meeting

From meeting minutes by **Designated Federal Official**: Kristine Khuc, Pharm.D.

The Gastrointestinal Drugs Advisory Committee (GIDAC) met on February 23rd 2010. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. The meeting was called to order by Jean-Pierre Raufman, M.D., (Acting Chair); the conflict of interest statement was read into the record by Kristine Khuc, Pharm.D. (Designated Federal Official). There were approximately 175 persons in attendance. There was one speaker for the Open Public Hearing session.

Attendance:

Gastrointestinal Drugs Advisory Committee Members Present (Voting):

William Hasler, M.D., Sunanda Kane, M.D., Jean-Pierre Raufman, M.D., Jill Sklar
(Consumer Representative)

Gastrointestinal Drugs Advisory Committee Member Present (Non-Voting):

Debra Silberg, M.D., Ph.D. (Industry Representative)

Special Government Employee Consultants Present (Temporary Voting Members):

Garnet Anderson, Ph.D., Steven Brass, M.D., Jeffrey Cohen, M.D., Donna Cryer J.D.
(Patient Representative); Srinivasan Dasarathy, M.D., Norman Gitlin, M.D., Richard
Haubrich, M.D., Steven Hersch, M.D., Joan Hilton, Sc.D., Atul Kumar, M.D., Alan
Lockwood, M.D., Celia Maxwell, M.D., Susan Rehm, M.D., Steven Solga, M.D.

FDA Participants Present (Non-Voting):

Donna Griebel, M.D., Joyce Korvick, M.D., Ruyi He, M.D., Lara Dimick, M.D.

Open Public Hearing Speaker:

Diane Dorman, National Organization for Rare Disorders

Designated Federal Official:

Kristine Khuc, Pharm.D.

The Applicant presented followed by questions. The FDA then presented followed by questions and discussion. The questions, as listed below, were then discussed and voted on. The results follow:

Questions to the Committee:

1. Study RFHE3001 enrolled a patient population with hepatic encephalopathy (HE). To be eligible patients had to have a history within the past 6 months prior to screening of ≥ 2 episodes of overt HE defined as Conn score ≥ 2 . At enrollment the patients were required to have Conn scores of 0 or 1. At least 1 of the prior episodes must have been verifiable from medical records. Hepatic encephalopathy episodes primarily attributed to GI hemorrhage requiring ≥ 2 units of blood, medications (e.g., narcotics), renal failure requiring dialysis, or CNS insult were not counted as a prior, qualifying episode of HE. Two thirds of patients in the trial had a baseline Conn Score of 0 and 1/3 had a baseline Conn Score of 1. Ninety one percent of patients were taking lactulose. (Discussion)

How should remission be defined in overt episodic HE? Should patients with a Conn score of 1 be considered to be in remission?

1. Committee members expressed that the Conn index is a simple and reasonably valid measure; however, it may not be adequate to address the syndrome over time. It is difficult to assess stability when a patient's mental status may be fluctuating between scores on a given day. The committee unanimously agreed that a Conn Score of 1 is not remission, based on the true definition of remission.

2. For future clinical trials, what clinically meaningful endpoints should be evaluated (as primary and key secondary endpoints), and how should they be measured for (Discussion):

decreasing the risk of episodes of overt HE
treatment of overt HE

Committee members commented that there is a need to:

- Better capture uniform assessment of endpoints through the use of blinded, independent reviewers;
- Obtain mean cumulative frequency of episodes of HE as an endpoint to obtain assessment of effect over time;
- Consider time to first hospitalization as an endpoint;
- Perform repeated measure analysis by measuring Conn score at specific points in time during treatment;
- Utilize neuro-imaging techniques;
- Utilize more sensitive neuro-psych testing in addition to the Conn score, including counts of Asterixis frequency.

3. Do the clinical data included in the rifaximin application provide substantial evidence of efficacy for an indication of maintenance of remission from HE (i.e., decreasing the risk for episodes of overt HE)? (Voting)

In your response, please discuss your thinking regarding the following issues:

Which clinical data, if any, provide substantial evidence of efficacy?

What, if any, are the deficiencies in the clinical data that make the evidence less than substantial?

Yes: 15 No: 3* Abstain: 0

The committee members who voted “Yes” expressed that the pivotal trial’s primary and secondary endpoints showed consistency of findings. The consensus among the committee members was that the drug labeling needs to include information that rifaximin is to be used as an adjunct to lactulose.

The committee members who voted “No” felt that the single study data was strong, but not compelling and that a second confirmatory study should have been conducted. There were concerns raised because of lack of clinical efficacy data for the product as a single agent, without accompanying use of lactulose. These members also were concerned that while the drug may have demonstrated maintenance of remission, it did not demonstrate remission because not all patients were in remission when they entered the trial. It was also suggested that the efficacy of the drug should be demonstrated in patients not using lactulose.

* A panel member placed a vote in the electronic voting system as “Yes”; however, the panel member verbally stated his vote as “No”.

4. Has the safety of rifaximin at the proposed dose and duration been adequately assessed? In answering this question please discuss whether additional analyses or trials are needed. (Voting)

Yes: 12 No: 6 Abstain: 0

A majority of the committee members commented that the safety of rifaximin has been adequately addressed. For those that voted “No”, the concern raised was related to the expected long term use of the drug, and the effects of the drug on the gut flora.

The panel members recommended that the Agency consider:

- The conduct of additional studies during Phase IV post-marketing;
- Need to further evaluate patients with more serious liver disease, MELD score greater than 25;
- Long-term effects on gut flora and gut flora change with use;
- Development of drug resistant organisms with use;
- Surveillance occurrence and susceptibility of *Clostridium difficile*;

The committee commented and recommended:

- A need to conduct Phase IV post-marketing studies;
- The conduct of further studies: on patients with MELD score of 25 or greater (the most ill patients) and for a longer duration;
- The clinical data supports the demonstration of significant improvement in patients with HE but does not support a finding of remission in patients with HE.

5. Is the safety of rifaximin at the proposed dose and duration acceptable? (Voting)

Yes: 13 No: 5 * Abstain: 0

* A panel member placed a vote in the electronic voting system as “Yes”; however, the panel member verbally stated her vote as “No”.

The majority of the committee members stressed the need for surveillance of infections with drug resistant organisms, Phase IV studies, and studies of longer duration.

6. In light of the safety and efficacy data presented in this application, does the risk benefit profile support approval of rifaximin for an indication of maintenance of remission from HE (i.e., decreasing the risk for episodes of overt HE)? (Voting)

Yes: 14 No: 4 Abstain: 0

The committee commented and recommended:

- A need to conduct Phase IV post-marketing studies;
- The conduct of further studies: on patients with MELD score of 25 or greater (the most ill patients) and for a longer duration;
- The clinical data supports the demonstration of significant improvement in patients with HE but does not support a finding of remission in patients with HE.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22554	ORIG-1	SALIX PHARMACEUTICA LS INC	XIFAXAN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LARA DIMICK-SANTOS
03/12/2010

HUGO E GALLO TORRES
03/12/2010

Excellent MO review of a complex but clinically important subject matter.

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION**

**Division of Neurology Products (HFD – 120)
Center for Drug Evaluation and Research**

Date: November 29, 2009

**From: Russell G. Katz, M.D.
Division Director**

**Subject: NDA 22554
Xifaxan®; Salix Pharmaceuticals
Hepatic Encephalopathy**

**To: Director
Division of Gastrointestinal Products**

Document Type: Consult

Enclosed is the Division's response to your request

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:	11/29/09
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. 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.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

6.1 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

6.2 Objectives

6.2.1 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.

6.2.2 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.

6.3 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.

6.4 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 6.8.1) 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 \geq 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 \leq 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.

6.5 Key Exclusion Criteria

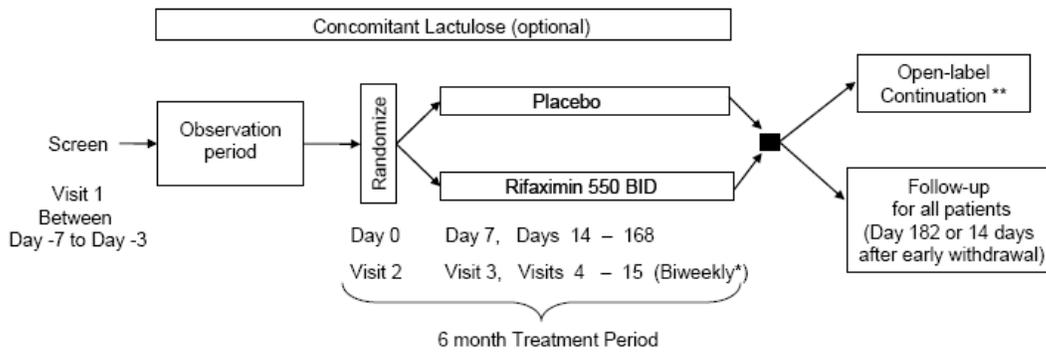
- Significant medical or psychiatric condition that, as per the investigator, precluded study participation
- Expected to receive a liver transplant within 1 month of screening
- History of lactulose intolerance and not willing to discontinue lactulose for the duration of the study
- History of allergy 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

6.6 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

6.7 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) ¹	Telephone Contacts 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161 (± 2)	EOS (Visit 15) ^f 168 ± 2	Follow-up (Visit 16) ^g 182 ± 2
STUDY ASSESSMENT						
Obtain Informed consent	X					
Assign Subject Screening Number	X					
Confirm eligibility	X					
Record medical history (with HE history) ^h	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 ⁴	X		X (Day 84 only)		X	
Record demographic characteristics	X					
Assign Randomization Number		X				
Dispense study drug		X	X			
Perform clinical laboratory tests ⁵	X	X	X (Days 28 and 84 only)		X	
Corn 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)	TREATMENT PERIOD				FOLLOW-UP PERIOD
		(Baseline) / Randomization (Visit 2)	Visits 3 to 14	Telephone Contacts	EOS (Visit 15) ^f	Follow-up (Visit 16) ^h
	-7 to -1	0 ^a (± 1)	7, 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, (± 2) ⁱ	21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161 (± 2)	168 ± 2	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 ^a	X ^a	X ^a	X ^a	
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

- a 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.
- b 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).
- c This is to be a symptom-directed physical examination only and to be performed only if necessary.
- d For females of childbearing potential only.
- e Includes hematology, coagulation (PT/INR), blood chemistry and urinalysis.
- f EOS visit may be Visit 1 (Screening) for an open-label continuation study (i.e., for all subjects, whether they complete RFHE3001 or not).
- g Mental status will be assessed at visits by determining Conn Score and will be assessed during telephone contacts by asking general health questions.
- h 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).
- i 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 7.7). 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 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. 18 DEC 2005	05	<input type="checkbox"/> 0 <input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

6.8 Description Of Efficacy-Related Assessments

6.8.1 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 asterixis 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 7.7).

6.8.2 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.

6.8.2.1 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.

6.8.2.2 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.

6.8.3 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 is 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.

6.8.4 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.

6.8.5 Venous Blood Ammonia Level

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

6.8.6 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”).

6.8.7 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.

6.8.8 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.

6.9 Outcome Measures

6.9.1 Efficacy Measures

6.9.1.1 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.

6.9.1.2 Secondary Efficacy Parameters

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

6.9.1.2.1 “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).

6.9.1.2.2 “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.

6.9.1.3 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.

6.9.2 Safety Measures

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

6.10 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.

6.10.1 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.

6.10.2 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.

6.10.3 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.

6.10.4 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.

6.10.5 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.

6.10.6 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.

6.11 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.

7. 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.

7.1 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.

7.2 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.

7.3 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.

7.4 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.

7.5 Demographic And Other Baseline Characteristics

7.5.1 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.

7.5.2 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)

Characteristic	Placebo N = 159	Rifaximin N = 140
≥ 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.

7.6 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)

7.7 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.

7.7.1 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.

7.7.2 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.

7.7.2.1 “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.

7.7.2.2 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.

7.7.3 Materials Provided To Study Sites To Help In Detecting And Documenting Episodes Of Hepatic Encephalopathy

These materials included the following:

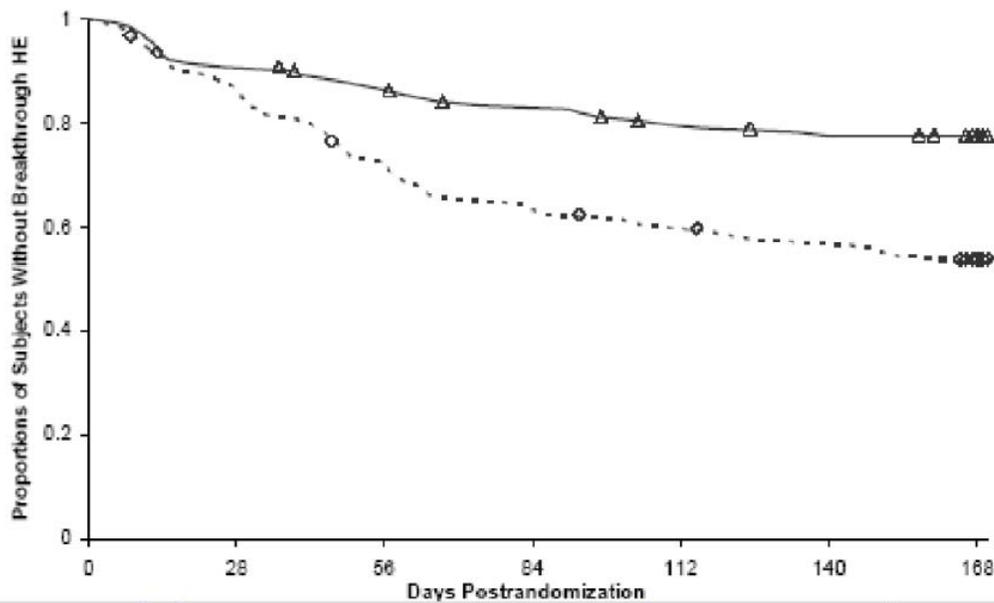
- Study-specific source documents to record Conn scores, asterixis grade and Hepatic Encephalopathy Scoring Algorithm evaluation
- Pocket guidelines for the documentation of breakthrough episodes of hepatic encephalopathy
- Hepatic encephalopathy breakthrough symptom checklist.

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.

7.8 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.

Treatment interval (days)	Placebo (N = 159)					Rifaximin (N = 140)				
	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 ^e									
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.

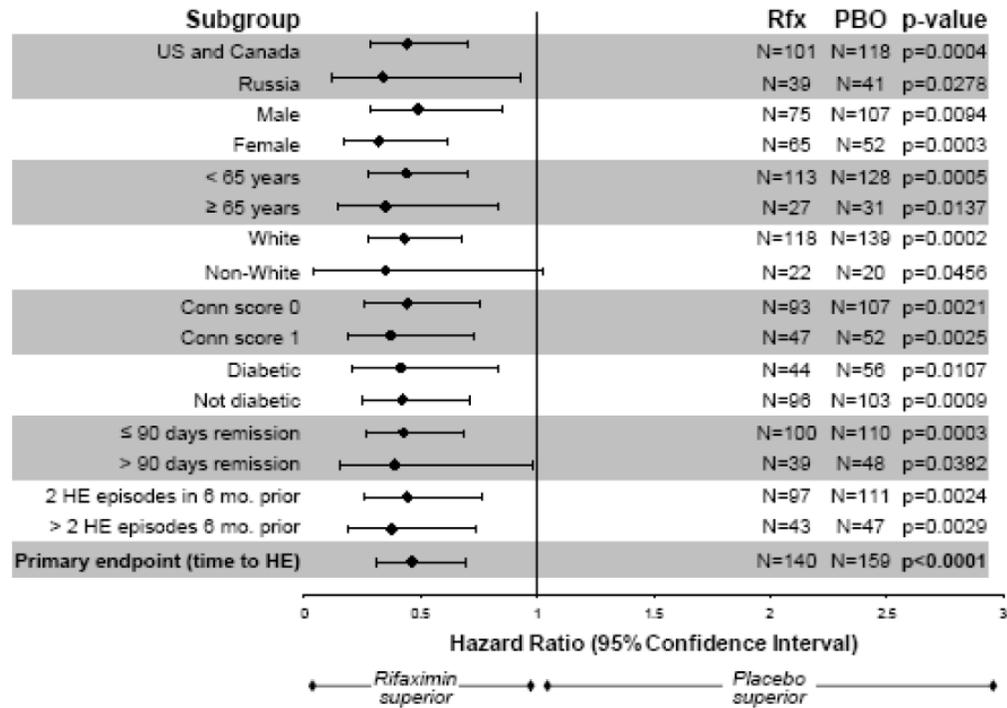
7.9 Additional Analyses On Primary Efficacy Parameter

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

7.10 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

Key Secondary Efficacy Parameter	Hazard Ratio* (95% CI)	p-value
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

7.11 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.

7.12 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 were also seen 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.

8. 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 [REDACTED] (b) (4) 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.

9. Reviewer’s Summary Comments

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 inhibiting the occurrence of episodes of hepatic encephalopathy is by inhibiting the division of intestinal urea-deaminating and

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 in the context of the sponsor-presented study results is also discussed.

9.1 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 by 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.

9.2 Discussion Of Study (Efficacy) Results

Despite the results of this study, as presented by the sponsor in the study report, ostensibly providing unequivocal evidence that rifaximin reduces the risk of developing relapses of more overt hepatic encephalopathy in patients with cirrhosis and/or portal hypertension, 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) as already outlined in the body of this review. 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 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, as described by Hassanein et al, would appear suitable 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 may be only preliminary

The Hepatic Encephalopathy Scoring Algorithm 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 Hepatic Encephalopathy Scoring Algorithm 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. A review of source documents, which are reported to include the Hepatic Encephalopathy Scoring Algorithm score sheets and final grades, in a sufficiently large sample of patients may be the only means of providing better clarification of how Conn grades were actually assigned during this study.

More importantly, in an uncertain proportion of 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. The reliability of determining the occurrence of breakthrough episodes of hepatic encephalopathy 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, unless the sponsor can confirm to the Agency's satisfaction that the means used were, in fact, accurate.

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; that 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 (See Section 6.7) 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.

9.3 Discussion Of Text Of Proposed New Indication

The sponsor is seeking the approval of rifaximin for "*maintenance of remission of hepatic encephalopathy in patients 18 years of age or older*" (emphasis mine).

Assuming that Study RFHE3001 does indeed provided evidence for the efficacy of rifaximin, based on the results of the primary efficacy analysis (evidence that is at present questionable), the term "maintenance of remission" implies that rifaximin entirely prevents relapses of hepatic encephalopathy, a conclusion that the study results cannot support even if sponsor's conclusions are entirely accepted at their face value. The phrase "reducing the frequency of relapses" may then be more appropriate, instead of "maintenance of remission."

The question of whether the term "hepatic encephalopathy" as used in the currently-proposed indication is specific enough to describe the hepatic encephalopathy subset (Type C) actually studied in the INDICATIONS AND USAGE section of the product label is a matter that is more appropriately addressed by the primary reviewing division.

10. Conclusion

The report of Study RFHE3001 does **not** provide enough evidence for this reviewer 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 fulfilled.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 11/29/09
cc:
HFD-120
NDA 22554

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22554	ORIG-1	SALIX PHARMACEUTICA LS INC	XIFAXAN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RANJIT B MANI
01/05/2010

RUSSELL G KATZ
01/13/2010

Miskala, Paivi

From: Miskala, Paivi
Sent: Wednesday, August 05, 2009 12:41 PM
To: Dimick, Lara L
Cc: Burke, Laurie B; Snow, Nancy; Shiley, Kimberly; Lianos, Hee S
Subject: RE: NDA 22-554 Rifaximin

Hi Lara,

As I mentioned on the phone, SEALD will not be able to review content validity (i.e., whether the scale is adequately measuring what it is suppose to measure) of the West Haven criteria and neuropsychological testing because it requires specific clinical expertise in that field. These are not subjective assessments of patient reported symptoms, functioning etc that the SEALD group generally reviews and SEALD group does not have clinical expertise in neurology to evaluate content validity of neurology clinical rating scales or neuropsych tests. We recommend that you consult Ranjit Mani in the neurology division regarding these instruments.

Please note that SEALD group has previously reviewed at least 2 DGP submissions related to hepatic encephalopathy which may be helpful to you:

1) Please see my review under IND (b) (4) -- I made some methodological comments related to the West Haven criteria. Ranjit Mani's neurology review is also filed under that IND.

2) I also suggest you take a look at Elektra Papadopoulos' review under IND (b) (4) I think Dr Mani's neurology review is also under that IND.

I feel that neurology division's clinical expertise related to content validity and clinical appropriateness of these instruments will be the most useful for your interpretation of the findings. If you need our assistance on any methodological issues after consulting with neurology, please contact us to discuss.

Thank you.

Best,
Paivi

From: Dimick, Lara L
Sent: Wednesday, August 05, 2009 9:09 AM
To: Miskala, Paivi
Subject: NDA 22-554 Rifaximin

Paivi,

The Conn score or West Haven Criteria, which are the same is completely subjective, based on evaluator review. They also do some neuropsych testing to help differentiate the lower levels, stage 0,1 and 2 from each other, but rely on the Conn score as the final determinant. In addition, they frequently relay on history as given by the patients caregiver or hospital records to stage the patient. I attached a copy of the west haven criteria and a review article on Hepatic Encephalopathy. This is a paper submission, I have 42 boxes outside my office. But I have scanned in a few things, and have a desk copy of a summary you can have.

Lara

*Lara Dimick, MD, FACS
Medical Officer - CDER - GDP
WO - 22, Room 5439
Ph - 301-796-4843
Lara.Dimick@fda.hhs.gov*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22554	ORIG-1	SALIX PHARMACEUTICA LS INC	XIFAXAN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PAIVI H MISKALA
11/13/2009

LAURIE B BURKE
11/13/2009

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 22-554 Applicant: Salix

Stamp Date: June 24, 2009

Drug Name: Rifaximin

NDA/BLA Type: 505(b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Paper CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?			N/A	
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1) NDA 21-361 Xifaxan®/Rifaximin
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: RFHE9701,9702, 9901 & RFPK 1007 RFPK 9801 Sample Size: _____ Arms: _____ Location in submission: Module 2.4.2.1.1	X			No studies in Child's Class C patient's
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 RFHE 3001 Hepatic Encephalopathy Indication: remission of		X		Only one placebo controlled small study. Second pivotal study is open label treatment.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 RFHE 3002 Indication: remission of HE - ongon open label treatment extension study				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?		X		Only one placebo controlled study. End point questionable
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.		X		The primary endpoint is subjective and can vary through out the day, not validated. The endpoint was agreed to by FDA Dec 2004, No SPA obtained
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		?		Pivotal trials conducted in the USA & Canada(R-101, P-118) and Russia(R-39, P-41) see analysis by geographic region but do not see <i>rationale</i> . See CFR 314.06
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?		X		Not tested at this dose, clin-pharm will address
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?		X		At indicated dose: 297 > 3 months 257 > 6 months 114 > 1 year
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			N/A	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			Was sent on request
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?		X		Will need micro/ID consult re long term exposure risks (done)
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Has not been tested in sever hepatic impairment, no PK studies. Clinical studies in mild and moderate cirrhosis only
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			N/A	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver under Orphan Drug
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			N/A	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		?		Not able to locate a <i>rational</i> , there is data analysis by geographic region. See CFR 314.06
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			N/A	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			JMP files appear to be working and adequate
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			N/A	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Some early foreign data not done under CMP

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Is there a rational for acceptability of foreign data? If not please submit See CFR 314.106

Lara Dimick, MD, FACS 7/21/2009

 Reviewing Medical Officer Date

Hugo Gallo-Torres, MD, PhD, PNS 7/21/2009

 Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LARA DIMICK-SANTOS
08/18/2009