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**XIFAXAN<sup>®</sup> (rifaximin) Tablets, 550 mg**  
**NDA 22-554**

**Briefing Document for Gastrointestinal Drugs Advisory Committee Meeting**  
**23 February 2010**

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## 1. Executive Summary

### Introduction

Hepatic encephalopathy (HE) is a serious and progressive complication that occurs in patients with advanced liver disease. The impairment of liver function and the presence of porto-systemic shunting leads to highly elevated levels of gut-derived toxins in systemic circulation which then cross the blood brain barrier producing the deleterious effects on brain function. Once the toxic substances are in neural tissues, a number of neurochemical changes occur that affect neurocognitive and neuromuscular function.<sup>7,70</sup> Therapeutic approaches for the treatment of HE are directed at reducing production and absorption of gut-derived toxins therefore decreasing the concentration of toxins affecting brain function.

Rifaximin is a gut-targeted, minimally absorbed, broad-spectrum, oral antibiotic that is well suited for the treatment of gastrointestinal (GI)-based conditions and is ineffective for the treatment of existing systemic infections due to its low systemic exposure and high concentration in the GI tract.<sup>1,2,3</sup> Rifaximin is believed to affect gut bacteria resulting in a decrease in production and/or absorption of bacterial derived toxins responsible for the neurocognitive and neuromuscular dysfunction seen in patients with HE.

Rifaximin 200 mg tablets (XIFAXAN<sup>®</sup>) were approved for marketing in the United States (US) in May 2004 for the treatment of travelers' diarrhea (TD) caused by noninvasive strains of *E. coli* in patients 12 years of age or older at a dosage of 200 mg 3 times daily (TID) for 3 days.

Rifaximin has also been studied in the US for the treatment of conditions including: TD prophylaxis (600 mg once daily for 14 days), irritable bowel syndrome (IBS) (550 mg TID for 14 days), *Clostridium difficile* (*C. difficile*)-associated diarrhea (400 mg TID for 10 days), and HE.

Rifaximin was first approved in 1985 in Italy and is currently approved in 33 countries for various gastrointestinal indications; including 11 countries for the treatment of HE and 11 countries as adjunctive therapy for the treatment of hyperammonemia.

**Proposed Indication:** The maintenance of remission of HE in patients  $\geq$  18 years of age.

**Dosage and Administration:** One 550 mg tablet taken orally 2 times daily (BID).

### Clinical Pharmacology

**Mechanism of Action:** Rifaximin acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis.<sup>1,2,3</sup> In vitro, rifaximin has a broad spectrum of antibacterial activity against both aerobic and anaerobic Gram-positive and Gram-negative organisms. Rifaximin is believed to affect gut bacteria resulting in a decreased production and/or absorption of bacterial derived neurotoxins, including ammonia, responsible for the neurocognitive and neuromuscular dysfunction seen in patients with HE.

**Absorption:** Rifaximin's minimal oral systemic availability is consistent with its low intestinal permeability and low aqueous solubility (Biopharmaceutics Classification System [BCS] IV Classification); its oral absorption is limited further by efflux transport by P-glycoprotein (P-gp).

**Distribution:** Animal studies demonstrate that 80% to 90% of orally administered rifaximin is concentrated in the gut with less than 0.2% in the liver and kidney, and less than 0.01% in other tissues. In adults, rifaximin 800 mg/day for 3 days resulted in concentrations of about 8000 µg/g in stools.<sup>4</sup> Plasma protein binding is 68% in healthy subjects and 62% in subjects with hepatic impairment.

**Metabolism and Excretion:** In healthy volunteers, oral administration of 400 mg <sup>14</sup>C-rifaximin resulted in recovery of 96.94% of the total radioactive dose: 96.62% in feces almost entirely as unchanged drug; and 0.32% in the urine.<sup>55</sup> Only 1 metabolite has been identified, 25-desacetyl-rifaximin. In a second study, following a dose of 400 mg in healthy volunteers, 0.02% and 0.0002% of the total dose was recovered in the urine as rifaximin and 25-desacetyl-rifaximin, respectively.<sup>5</sup> In HE subjects receiving 600, 1200, and 2400 mg/day of rifaximin for 7 days, 24-hour urine collection resulted in 0.061%, 0.1%, and 0.056% of the total daily dose excreted renally as unchanged drug, respectively.<sup>14</sup> Human and animal studies demonstrate that rifaximin is excreted in bile.

**Pharmacokinetics:** Systemic exposure of rifaximin following oral administration is minimal in all populations studied to date. While exposures are elevated in subjects with hepatic impairment, they are low compared with those achieved following oral administration of systemic antibiotics or other nonabsorbed antibiotics.<sup>58,59</sup> Given the low plasma exposures and overall safety profile in these subjects, no dose adjustment is recommended in hepatic impairment.

**Drug Interactions:** In vitro: rifaximin does not inhibit human hepatic cytochrome P450 (CYP) isoenzymes: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4 at concentrations of 2 to 200 ng/mL, and induces CYP3A4.<sup>65</sup> Two drug-drug interactions studies have been conducted in healthy volunteers: rifaximin (550 mg TID) with midazolam and rifaximin (550 mg TID) with an oral contraceptive.<sup>66,67</sup> In vitro, rifaximin is a P-gp efflux substrate, a weak P-gp inhibitor,<sup>56</sup> and does not inhibit hERG. No dose adjustment is recommended when co-administering rifaximin with other drugs based on the in vivo and in vitro profile of rifaximin.

### Disease Background and Medical Need

Hepatic encephalopathy is a serious, episodic, and neuropsychiatric syndrome associated with advanced liver disease. Overt HE episodes are debilitating, can present without warning, render the patient incapable of self-care, frequently result in hospitalization, and can result in coma and even death.<sup>8,73</sup> A history of overt HE episodes and the severity of HE episodes were found to be predictive of diminished survival in patients with advanced liver disease.<sup>6,7</sup> Hepatic encephalopathy is therefore a formidable burden on the patient, his/her family, and the healthcare system.<sup>8,73</sup>

While currently existing therapies may be effective, there remains an unmet medical need for a treatment conducive to safe and effective long-term therapy for patients with HE. Currently available therapies present a challenge for the patient, their caregiver and physician due to poor tolerability, compliance and toxicity issues.

Rifaximin has antimicrobial, pharmacological, and physicochemical properties that make it well suited for long term, daily use in preventing overt HE. Rifaximin's properties include: gut targeted distribution with negligible systemic exposure, no drug-drug interactions, no reports of stable microbial resistance, and a strong tolerability profile. The use of rifaximin for the

treatment of HE has been demonstrated over many years as cited in published clinical studies and sponsor-initiated, randomized, controlled clinical studies.<sup>13,14,15,16,23,74,99,100,109,110</sup> These properties as well as the magnitude of beneficial effect differentiate rifaximin from other therapies and represents a new treatment option for patients with HE.

### **Clinical Efficacy**

The efficacy of rifaximin in maintaining remission in subjects diagnosed with episodic, overt HE is primarily based on the results of a large (299 subjects), double-blind, placebo controlled, multinational, phase 3 study (RFHE3001) and supporting evidence from a long-term, open-label, Phase 3 study RFHE3002. Additional evidence is derived from clinical studies in acute HE, 3- and 6-month studies from the published literature, and meta-analyses.

RFHE3001 demonstrated a clinically meaningful reduction in the risk of recurrent overt HE in a statistically very persuasive manner. The following findings from this study substantiate this claim of effectiveness:

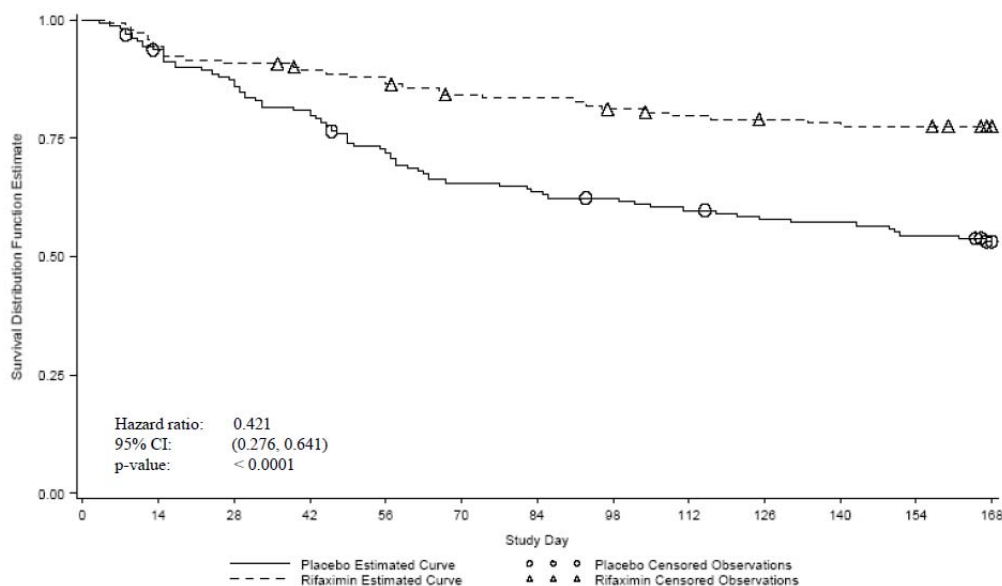
- The risk of experiencing a breakthrough overt HE episode was reduced by 58% in rifaximin-treated subjects compared with placebo (primary endpoint). This reduction in risk was clinically (22% of rifaximin vs. 46% of placebo experience overt HE) and statistically ( $p < 0.0001$ ) significant. (See figure below.)
- Consistency across important subgroups emphasizes the generalizability of the findings of the primary efficacy endpoint. RFHE3001 allowed for a relatively diverse patient population to be enrolled. The analysis of the response across important subgroups at baseline such as presenting HE severity, concomitant therapy, disease stage, age, gender, race and geographic location demonstrates consistency of the estimate of risk reduction and almost always results in statistical significance. This finding provides confidence that the effect seen in the primary endpoint is based upon homogeneity of effect and is not the result of tremendous benefit being conferred to a select population. (See figure below.)
- The risk of experiencing an HE-related hospitalization was reduced by 50% in rifaximin-treated subjects compared with placebo (key secondary endpoint). (See figure below.) The reduced risk of HE-related hospitalization, defined as hospitalizations either directly caused by HE or complicated by HE, was clinically (19 rifaximin vs. 36 placebo subjects) and statistically ( $p = 0.0129$ ) significant. In addition, breakthrough overt HE hospitalization (15 rifaximin vs. 29 placebo, 51% risk reduction,  $p = 0.0225$ ) and all-cause hospitalization (46 rifaximin vs. 60 placebo, 30% risk reduction,  $p = 0.0793$ ) reflect the benefit of reduced healthcare utilization.
- Additionally, secondary endpoints provide clinically and statistically significant support for the use of rifaximin in HE as demonstrated by the reduction in the risk of time to first worsening in Conn score (mental status) and asterixis grade (neuromuscular function); improvement in all domains of a validated disease-specific, quality-of-life questionnaire; and improvements in pharmacological effects associated with HE (blood ammonia and Critical Flicker Frequency [CFF]).
- In RFHE3001, the pharmacological effect of rifaximin correlates to the clinical benefit. Ammonia is the best characterized neurotoxin that precipitates HE and CFF is a sensitive method for measuring neurotoxin-induced retinal gliopathy in patients with HE. The

reliability, responsiveness and utility of the primary efficacy endpoint was demonstrated by association with ammonia and CFF.<sup>9,10,11,12,76,79,80,96</sup> Both the reduction in ammonia and the increase in CFF seen in the rifaximin group were shown to be predictive of reduced risk of breakthrough overt HE episodes, underscoring that the pharmacological mechanism by which rifaximin is believed to work is statistically correlated to the outcome observed in the primary endpoint, as expected based on the pathogenesis of HE as described in the literature.

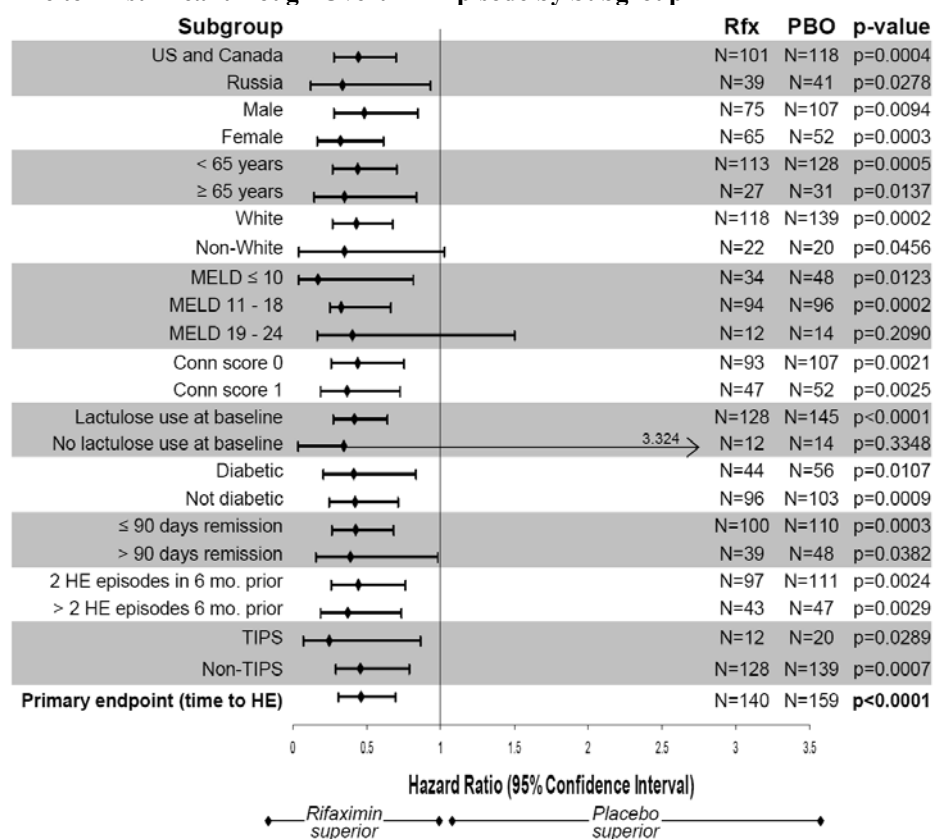
- Durability of the effect of rifaximin on maintaining subjects free from breakthrough overt HE episodes is observed in subjects who continued rifaximin therapy in RFHE3002 after maintaining remission in RFHE3001. Treatment for periods longer than 6 months does not result in loss of effect.
- Repeatability of the rifaximin treatment effect was observed in subjects who crossed over from placebo in RFHE3001 to rifaximin treatment in RFHE3002.
- Supportive efficacy: Rifaximin was effective in long-term, HE treatment studies<sup>13,100,131</sup> and short-term (acute), HE treatment studies.<sup>14,15,16</sup> Published literature have demonstrated the therapeutic benefit of rifaximin treatment in patients with HE.<sup>109,110</sup>

The efficacy results demonstrate that rifaximin treatment maintains remission from breakthrough overt HE episodes, reduces hospitalization, and improves quality-of-life and functional status, thereby reducing the disease burden on the patient, his/her caregivers, and the healthcare system.<sup>8,73</sup>

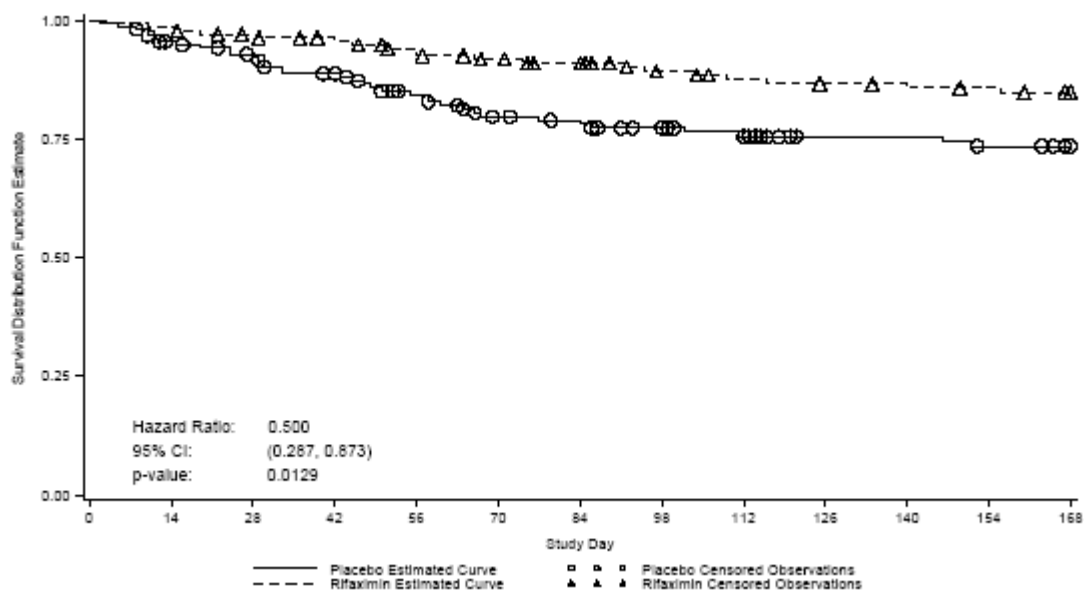
#### Study RFHE3001: Time to First Breakthrough Overt HE Episode



### Time to First Breakthrough Overt HE Episode by Subgroup



### Study RFHE3001: Time to First HE-Related Hospitalization



### Clinical Safety

The safety of rifaximin has been established through experience in multiple clinical studies in HE and other indications with approximately 5000 subjects, as well as extensive postmarketing

exposure (20+ years).<sup>17,18</sup> Subjects in rifaximin clinical studies included HE subjects (N=757), IBS or TD subjects (N=4089), and healthy volunteers in clinical pharmacology studies (N=237). The patterns of adverse events (AEs) experienced by rifaximin-treated subjects in these various indications were reflective of expected AEs in the populations under study (HE, IBS, or TD).

The primary safety analysis for maintenance of remission from HE consists of 348 unique subjects in RFHE3001/RFHE3002 with a maximum exposure of up to 1008 days (mean: 364 days). In accord with the population at risk, the safety review contained herein focuses on frequent, serious, mortal events with special attention to areas of primary concern to this patient population namely, events involving: blood and lymphatics, gastrointestinal disorders, hepatobiliary disorders, and infections.

Analysis of the safety database supports a positive benefit/risk ratio for rifaximin therapy in this patient population. The key safety findings during the randomized control study and the long-term study are described below.

- The overall profile of AEs in the primary studies is consistent with the population under study, ie, subjects with advanced liver disease and a history of overt HE. The most frequent events are those typically expected in patients with advanced liver disease. The most common AEs occurring in >10% of subjects were peripheral edema, nausea, dizziness, fatigue, ascites, diarrhea, and headache.
- In RFHE3001, treatment-emergent AEs (TEAEs) occurred in 80% of subjects in each group. Serious AEs (40% placebo vs. 36% rifaximin), and TEAEs leading to discontinuation (28% placebo vs. 21% rifaximin) were experienced by a higher percentage of placebo subjects.
- Rifaximin treatment did not adversely affect mortality, 6% of subjects in the rifaximin group and 7% in the placebo group died in study RFHE3001. The observed death rate and causes of death are reflective of what is described in the literature for patients with advanced liver disease.<sup>6,7,86</sup>
- Adverse events related to areas of primary concern in this patient population including blood and lymphatics, gastrointestinal disorders, hepatobiliary disorders, and infections were comparable and consistent with the known incidence in the same population and recorded in their medical history.
- Clinical laboratory evaluations revealed no notable imbalances between rifaximin and placebo.
- Long-term rifaximin treatment in RFHE3002 did not impact the overall safety profile.

### **Benefits and Risks Conclusions**

Rifaximin provided clinical benefit to patients with HE. All relevant and clinically meaningful analyses demonstrate that administration of rifaximin 550 mg BID is an effective treatment for the maintenance of remission from HE episodes in patients with advanced liver disease. This conclusion is supported by the robustness of the efficacy findings in RFHE3001; supportive results in RFHE3002; and published literature of both long term and short term studies in subjects with acute HE.<sup>13,14,15,16,19,23,74,99,100,109,110</sup>

There is a significant unmet medical need for patients with HE as current therapies leave patients needing substantial improvement in efficacy, safety, and tolerability.<sup>22,27,28,101,116,117</sup> Rifaximin therapy demonstrates substantial clinical benefits for this population of patients with advanced liver disease as it significantly reduces the incidence of breakthrough overt HE episodes, thereby reducing the burden on patients, their families, the caregivers, and the healthcare system.

Analysis of the safety database supports a positive benefit/risk ratio for rifaximin therapy in this patient population. In comparison to placebo, and during long-term therapy, rifaximin showed a favorable safety profile. The pattern of AEs, deaths, and laboratory findings was consistent with the population studied. Long-term treatment with rifaximin in the target population did not have an adverse impact on the safety profile. The primary safety analysis, safety data in other indications, published literature, and postmarketing surveillance, support the use of rifaximin for the maintenance of remission of HE.

In summary, rifaximin was effective and safe in the patient population studied. Rifaximin represents the first significant therapeutic advancement in the treatment of HE in over 30 years for patients in the US.



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## LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC <sub>tau</sub>	AUC from time 0 to end of the dosing interval, tau
BCS	Biopharmaceutics Classification System
BID	2 times daily or twice daily
BSEP	bile salt export pump
<i>C. difficile</i>	<i>Clostridium difficile</i>
CFF	critical flicker frequency
CI	confidence interval
CLDQ	Chronic Liver Disease Questionnaire
C <sub>max</sub>	maximum observed plasma concentration
C <sub>min</sub>	minimum observed plasma concentration
CNS	central nervous system
CYP	cytochrome P-450
DSMB	data and safety monitoring board
EAEC	enteroaggregative <i>Escherichia coli</i>
EEG	electroencephalogram
<i>E. coli</i>	<i>Escherichia coli</i>
EOS	end-of-study
FU	follow-up
ETEC	enterotoxigenic <i>E. coli</i>
FDA	Food and Drug Administration
GI	gastrointestinal
HCT	hematocrit
Hgb	hemoglobin
HE	hepatic encephalopathy
IBS	irritable bowel syndrome
IC <sub>50</sub>	50% inhibitory concentration
IND	Investigational New Drug Application
INR	international normalized ratio
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	intent-to-treat
LFT	liver function test

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MELD	Model End Stage Liver Disease
MELD UNOS	MELD United Network for Organ Sharing
MIC	minimal inhibitory concentration
MIC <sub>50</sub>	MIC that inhibits 50% of microorganism growth
MIC <sub>90</sub>	MIC that inhibits 90% of microorganism growth
NCT	number connection test
NDA	New Drug Application
PEY	person exposure years
P-gp	P-glycoprotein
PSE	portal-systemic encephalopathy
PT	prothrombin time
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
SAE	serious adverse event
SD	standard deviation
SIBO	small-intestinal bacterial overgrowth
TD	travelers' diarrhea
TEAE	treatment-emergent AE
TID	3 times daily
t <sub>1/2</sub>	terminal or disposition half-life
T <sub>max</sub>	time to C <sub>max</sub>
TIPS	transjugular intrahepatic portosystemic shunt
T <sub>wa</sub>	time-weighted average
ULN	upper limit of normal
US	United States



## 2. Regulatory Background

### 2.1. Product Information

Rifaximin is a semi-synthetic, nonsystemic antibiotic. Rifaximin is currently approved in the United States (US) for the treatment of patients ( $\geq 12$  years of age) with travelers' diarrhea (TD) caused by noninvasive strains of *Escherichia coli* (*E. coli*). The chemical name for rifaximin is (2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca-[1,11,13]trienimino)benzofuro[4,5-*e*]pyrido[1,2-*a*]-benzimidazole-1,15(2*H*)-dione,25-acetate. The empirical formula is  $C_{43}H_{51}N_3O_{11}$  and its molecular weight is 785.9.

### 2.2. Currently Approved Treatments in the United States for Hepatic Encephalopathy

The most common treatment options for hepatic encephalopathy (HE) aim to lower the production and absorption of ammonia from the gut.<sup>76</sup> Nonabsorbable disaccharides, eg, lactulose or lactitol, are widely used in the treatment of HE.<sup>19,23,24,25</sup> There is evidence that nonabsorbable disaccharides lower plasma levels of ammonia by acidification of stools, which prevents the production of ammonia and purging which increases the fecal excretion of nitrogen.<sup>70</sup>

In the United States, lactulose is widely used and approved for the treatment and prevention of HE. Lactulose is thought to lower plasma levels of ammonia by acidification of stools, which prevents the production of ammonia, and purging, which increases the fecal excretion of nitrogen.<sup>70</sup> The recommended dose is 15-60 mL, 3-4 times daily, and is self-titrated by the patient to produce 2-3 soft stools to achieve efficacy.<sup>20</sup> Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy (ie, HE).<sup>20</sup> While deemed effective, the side effects of lactulose therapy include bloating, abdominal cramps, diarrhea, an unpleasant taste, resulting in low tolerability and poor adherence to long term treatment.<sup>21,22,97,101,117</sup> Additionally, it should be recognized that in patients with underlying advanced liver disease, complications such as dehydration and electrolyte disturbances (eg, hypokalemia) may occur for which other specific therapy may be required.<sup>20</sup>

Antibiotics appear to act indirectly by reducing the number of deaminating bacteria and urease producing bacteria, thus reducing the production of ammonia and other potential toxins. Broad-spectrum, gastrointestinal (GI)-active antibiotics including neomycin have demonstrated efficacy and have been used with or without lactulose.<sup>13,23,24,25,26,72,74</sup>

Neomycin sulfate is not approved for the prevention of HE. Neomycin is approved for acute use as adjunctive therapy in hepatic coma.<sup>27</sup> The long-term use of neomycin in the treatment of HE is limited by nephrotoxicity and ototoxicity.<sup>27,28</sup> Additionally, aminoglycosides are used cautiously in patients with advanced liver disease due to increased risk of aminoglycoside-induced nephrotoxicity in this patient population.<sup>29,30,31</sup>

There are no other approved therapies for HE. While currently existing therapies may be effective, there remains an unmet medical need for a treatment conducive to safe and effective long-term therapy for patients with HE.

### 2.3. Availability of Proposed Active Ingredient in the United States

Rifaximin was approved by the Food and Drug Administration (FDA) in 2004 as described above (Section 2.1). The approved dosage is one 200 mg tablet taken 3 times daily (TID) for 3 days.

Current XIFAXAN product labeling is included in Section 11.

### 2.4. Summary of Regulatory History

Table 1 identifies the ongoing development activities in the US.

**Table 1 Rifaximin Drug Development Programs**

IND/ODA	Regulatory Status	Dosage	Indication
IND 52,980	NDA 21-361 Approved May, 2004	XIFAXAN <sup>®</sup> 200 mg tablets 3 times daily for 3 days	Traveler's diarrhea
IND 59,133	NDA 22-554 PDUFA date March 24, 2010	550 mg tablets twice daily	Hepatic encephalopathy
ODA 97-1094	Orphan drug status Granted 1998	n/a	Hepatic encephalopathy
IND 72,757	Phase 3 complete NDA: 2Q 2010	550 mg tablets 3 times daily	Irritable bowel syndrome
IND 71,425	to be determined	to be determined	Pediatric acute diarrhea

Orphan drug status for rifaximin for the treatment of HE was granted by FDA to Salix in 1998.

Based upon FDA recommendations from the pre-Investigational New Drug application (IND) meeting, Salix initiated one 14-day study in subjects with acute HE (RFHE9901).

Following completion of RFHE9901, Salix met with the FDA in December of 2004 to discuss the possibility of developing rifaximin to be used for the maintenance of remission in patients with HE. At the time of the meeting, there were 19 published clinical studies and 1 meta-analysis (Cochrane group) which provided a basis for the potential of rifaximin in HE. Notable takeaways from that meeting included:

- That an NDA submission involving the available clinical reports, available published studies and meta-analysis would most likely not be adequate to support marketing approval.
- The FDA Division of Gastroenterology Products (Division) raised the possibility of performing 1 definitive study in the maintenance of remission of HE along with all previous, supportive data by citing the May 1998 guidance on 'Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.' Specifically, the guidance cites that although usually 2 adequate and well controlled studies are necessary, a single large study which is well designed and well executed may suffice.

Salix, in consultation with the Division, developed the RFHE3001 protocol with a primary endpoint based on clinically relevant changes in thinking and behavior as assessed by the Conn score.<sup>70,84</sup> Additionally, use of the Conn score to grade patients' presenting severity of HE and to score changes in HE was endorsed as the most clinically relevant endpoint by the Working Party

on Hepatic Encephalopathy.<sup>93,94,95</sup> This committee reported its results to the World Congress of Gastroenterology and published their report in *Hepatology* in 2002.<sup>94</sup>

The Conn score, also known as the West Haven Criteria, is a 5-point scale based upon neurocognitive function that ranges in severity from normal (Grade 0), to euphoria or anxiety (Grade 1), to subtle personality change and inappropriate behavior (Grade 2), to somnolence and confusion (Grade 3), to coma (Grade 4). Originally, Salix proposed that subjects reaching a Conn score of 2 from a baseline of 0 or 1 would meet the criteria of breakthrough HE. Based upon previous data from rifaximin in acute HE (RFHE9901), the FDA recommended the use of a neuromuscular assessment, namely asterixis, as a component of the primary endpoint as well. Asterixis, commonly seen in liver impaired patients, is defined as bilateral but asynchronous flapping motions of the outstretched, dorsiflexed hands.<sup>14,85</sup> Since the scoring for Conn is based on changes in consciousness, intellectual function, and behavior, the addition of asterixis grading allowed for the inclusion of neuromuscular changes to assist with a more sensitive and specific diagnosis and assessment of change, particularly near the lower spectrum of Conn scores (ie, Conn score of 0 moving to a Conn score of 1).

Following the recommendation of the Division, Salix proposed that the use of asterixis in the primary endpoint comprises a second definition for clinically relevant change, and that this criteria be applied only to changes that occur in subjects presenting with a Conn score of 0. The Division concurred with this approach of using the composite endpoint. RFHE3001 was designed to enroll HE subjects with prior history of overt HE that present at baseline with a Conn score of 0 or 1. The primary endpoint was defined as the time to breakthrough overt HE, defined as the time until a subject reaches a Conn score of 2 or the time until the subjects with a baseline Conn score of 0 increase their Conn score by 1 and increase their baseline asterixis grade by 1. The protocol design, agreed to by the FDA, including key inclusion and exclusion criteria as well as the efficacy measures of Conn, asterixis, hospitalizations, critical flicker frequency (CFF), and ammonia levels, and the definition of the primary endpoint, is reflected in the completed study RFHE3001.

Following completion of RFHE3001, Salix held a pre-New Drug Application (NDA) meeting with the FDA in December 2008 to discuss the clinical development program and NDA submission. In June 2009, Salix filed an NDA for the maintenance of remission of HE containing RFHE3001 as the pivotal study, with supporting efficacy from open-label study RFHE3002 and additional short-term studies RFHE9702, RFHE9701, and RFHE9901, along with the available literature.

The FDA accepted the NDA and granted priority review in August 2009.

## **2.5 Regulatory Considerations – Determination of Clinical Effectiveness**

RFHE3001 is a pivotal phase 3 study sufficient to grant approval and fulfills the requirements set forth in FDA guidance “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products”, May 1998, specifically, the reliance on a single study to support effectiveness.<sup>32</sup>

Per FDA guidance, reliance on a single study is generally limited to situations in which a study has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome. There are 5 criteria required to support effectiveness per guidance:

large multicenter study, consistency across study subgroups, multiple *studies* in a single study, multiple endpoints involving different events, and a statistically very persuasive finding.

Each of these criteria was satisfied by the results of study RFHE3001 as described below.

- Large multicenter study: RFHE3001 was a large (N=299), phase 3, multi-center, placebo-controlled study. A total of 70 sites in North America and Russia enrolled subjects. A by-center analysis determined that no single site or investigator was disproportionately responsible for the favorable effect seen in the study.
- Consistency across subgroups: The effect of rifaximin treatment in reducing the risk of experiencing breakthrough overt HE episodes over the treatment period was consistent across all prespecified subgroups defined by geographic region, demographics, and baseline characteristics.
- Multiple *studies* in a single study: Analyses of the primary endpoint by geographic regions, North America (n=219) and Russia (n=80), showed independent and statistically significant demonstrations of efficacy (p=0.0004 North America and p=0.0278 Russia).
- Multiple endpoints involving different events: There were multiple endpoints involving different clinically relevant events, including the primary efficacy endpoint (Conn and asterixis), which showed a 58% reduction in the risk of a breakthrough overt HE episode (p < 0.0001).
  - The key secondary endpoint of HE-related hospitalizations also showed a highly significant effect (p = 0.0129) in favor of rifaximin treatment.
  - Key secondary endpoint: time to any increase from baseline in Conn score, demonstrated a significant protective effect of rifaximin relative to placebo of 0.463 (95% confidence interval [CI]: 0.312 to 0.685) (p < 0.0001) for the risk of experiencing any worsening in mental status during the treatment period. A third key secondary endpoint was time to any increase from baseline in asterixis grade (ie, worsening in neuromuscular status); and results showed a strong trend toward a protective effect of rifaximin with a hazard ratio in the rifaximin group relative to placebo of 0.646 (95% CI: 0.414 to 1.008) (p = 0.0523).
  - Health-related quality of life: Subjects in the rifaximin group had significantly less fatigue (p = 0.0087) and significantly better overall quality of life (p = 0.0093) than subjects in the placebo group. Fatigue and other functional status/quality-of-life data were collected by using the Chronic Liver Disease Questionnaire (CLDQ), a health-related quality-of-life tool that is validated and specific for subjects with advanced liver disease.<sup>33</sup> Significant differences in CLDQ results in favor of the rifaximin group were also observed for each of the other component domains of the CLDQ.
  - Results for additional objective measures of clinical activity, venous ammonia level and CFF results, also showed significant improvements from baseline in the rifaximin group when compared with the placebo group (p = 0.0391 [venous ammonia level] and p = 0.0320 [CFF test results]).
- Statistically very persuasive finding: As described in the above 4 criteria and elsewhere in this briefing document, there is sufficient statistically very persuasive data in support of the efficacy of rifaximin. The primary endpoint resulted in a reduction in the risk of a breakthrough overt HE episode by 58% with p = 0.000032, denoted as p < 0.0001.

Prognostic factor analyses, subgroup analyses, and key secondary endpoint results demonstrated a consistent, statistically significant rifaximin treatment effect.

To summarize, all relevant and clinically meaningful analyses consistently demonstrate that long term administration of rifaximin 550 mg BID is an effective treatment for the maintenance of remission from breakthrough overt HE episodes. All data from the RFHE3001 pivotal study, as well as supportive data from other clinical studies performed and those reported in the literature, support the conclusion that rifaximin has a positive risk-benefit ratio in the maintenance of remission from overt HE episodes.

## **2.5. Other Relevant Background Information**

First marketed in 1987, rifaximin is now currently approved and available in 33 countries for various GI conditions. Rifaximin is approved in 11 countries for the treatment of HE and in 11 countries as adjunctive therapy for the treatment of hyperammonemia. Rifaximin has never been withdrawn from any country for safety concerns.

### 3. Overview of Rifaximin Clinical Pharmacology

#### 3.1. Mechanism of Action and Microbiology

While the spectrum of mechanisms contributing to the effects of rifaximin in chronic GI disorders is not fully understood, the antimicrobial mechanism of action of rifaximin depends on the inhibition of RNA synthesis.<sup>1,2,3</sup> Since rifaximin is poorly absorbed after oral administration, the drug is active in the GI tract. This gut-targeted localization is beneficial in the treatment of HE in that gut bacteria, implicated in HE pathogenesis, are altered by rifaximin without systemic effects.

Rifaximin is believed to affect gut bacteria, resulting in a decrease in production and/or absorption of bacterial derived neurotoxins, including ammonia, responsible for the neurocognitive and neuromuscular dysfunction seen in patients with HE. This mechanism is supported by data (Section 6.2.4) from study RFHE3001 including rifaximin's effect on lowering systemic ammonia exposure in HE subjects and its effect on increasing CFF, a method of measuring neurotoxin-induced retinal gliopathy in HE patents.

Rifaximin has a lower rate of fecal eradication of pathogens compared with other commonly used antibacterial drugs and causes minimal alterations in colonic flora, suggesting that rifaximin has a different mechanism of action than other commonly used drugs in treating enteric bacterial infection, such as the fluoroquinolones, which are known to deplete colonic flora.<sup>34,35</sup> The antibacterial properties of rifaximin include bactericidal activity at rifaximin concentrations greater than or equal to the minimal inhibitory concentration (MIC), and from alterations in bacterial virulence<sup>36</sup> and physiological functioning of epithelial cells,<sup>37</sup> which have been observed at sub-MIC concentrations.

Extraintestinal flora resistance should be uncommon with rifaximin treatment due to its intraluminal activity and low levels of absorption. Characteristics that may reduce the incidence of resistance are rifaximin localization to the GI tract, which reduces selective pressure at sites outside of the GI tract and limits dissemination of resistant bacteria; a resistance mechanism that requires mutation in host cell DNA and is not plasmid based; the instability of resistant bacteria in vivo; and the observation that rifaximin has bacteriostatic properties and inhibition of virulence against sensitive and resistant bacteria.<sup>38,39,40,41</sup>

Ranges for the rifaximin concentration that inhibits 50% of microorganism growth (MIC<sub>50</sub>), and MIC that inhibits 90% of microorganism growth (MIC<sub>90</sub>) have been established for 1607 clinical isolate pathogens associated with infectious diarrhea.<sup>42,43,44,45</sup> The highest MIC established was 1024 µg/mL. From a clinical pharmacokinetic study, the fecal concentration of rifaximin was determined to be almost 8-fold higher than the highest MIC established for these clinical pathogens.<sup>46</sup> *Clostridium* species were found to be some of the most sensitive organisms to rifaximin, with MIC<sub>90</sub> = 0.005 through 2 µg/mL; rifaximin activity against *Clostridium difficile* (*C. difficile*) was comparable to that of metronidazole and vancomycin.<sup>43</sup> When the antimicrobial activity against enteroaggregative *E. coli* (EAEC) and enterotoxigenic *E. coli* (ETEC), the major causes of TD, was compared between rifaximin and 6 standard antimicrobial agents, rifaximin had better or comparable activity to most of the agents evaluated, including ampicillin, chloramphenicol, tetracycline, and trimethoprim.<sup>47,48,49,50</sup>

Jiang and DuPont studied 590 *C. difficile* isolates collected from consecutive patients studied from August 2006 to August 2009 at St. Luke's Episcopal Hospital in the Texas Medical Center in Houston, Texas.<sup>51</sup> The in vitro susceptibility of *C. difficile* isolates and the emergence of resistant organisms were compared between rifaximin and rifampin. Approximately 95% of *C. difficile* isolates collected over the 3-year period were susceptible to rifaximin. Low MIC values were observed for rifaximin against *C. difficile* isolates in this study (MIC<sub>50</sub> of < 0.01 µg/mL; MIC<sub>90</sub> of 0.25 µg/mL). Results of testing for 359 of the 590 *C. difficile* isolates were recently reported by Jiang et al.<sup>52</sup>

Development of resistance to rifaximin may be primarily due to a chromosomal 1-step alteration in the drug target, DNA-dependent RNA polymerase.<sup>2</sup> This mechanism differs from the plasmid-mediated resistance that is easily acquired by susceptible bacteria rendering them resistant to aminoglycosides, sulfonamides, and macrolides. Rifaximin shortens the duration of TD and non-dysenteric diarrheal illness due to EAEC and ETEC without major alteration of aerobic fecal flora and without important side effects.<sup>34,35</sup> In at least 2 clinical studies, there appears to be a rapid return to sensitive bacterial strains, especially in aerobic species, after rifaximin treatment ends.<sup>53,54,121</sup>

### 3.2. Absorption

Rifaximin's gut-specific activity is a result of poor oral absorption and poor solubility, resulting in the majority of the dose residing in the gastrointestinal tract lumen. Following a single 400 mg <sup>14</sup>C-rifaximin dose in healthy subjects, of a total of approximately 97% of recovered radioactivity, >96% was present in the feces; the remaining fraction (0.32%) was recovered in the urine.<sup>55</sup> In vitro, rifaximin showed very low apical→basolateral permeability in Caco-2 cells.<sup>56</sup> In addition, data in Caco-2 cells<sup>56</sup> indicated that rifaximin is a substrate for P-glycoprotein (P-gp), an active efflux transporter expressed in gut wall that limits oral absorption by transporting rifaximin out of enterocytes into the gut lumen.

### 3.3. Pharmacokinetics

Systemic exposure to rifaximin following oral administration is extremely low regardless of dose, disease state, or feeding state. Following a single 400-mg oral dose in fasted and fed healthy subjects, mean area under the plasma concentration-time curve (AUC) values were 18.4 ng.h/mL and 34.7 ng.h/mL, respectively.<sup>57</sup> Administration of a single 550-mg oral dose to fasted and fed healthy subjects resulted in mean AUC values of 11.1 ng.h/mL and 22.5 ng.h/mL, respectively.<sup>58</sup> These data, showing that rifaximin pharmacokinetics are nonlinear with respect to dose (ie, increasing dose resulting in less-than-proportional plasma exposure), are typical of compounds with solubility- or permeability-limited oral absorption.

In subjects with liver impairment, systemic exposure is higher than that observed in healthy subjects, but low nonetheless (Table 2). Following repeat dosing at 550 mg BID in liver-impaired subjects, mean steady-state AUC from time 0 to the end of the dosing interval, tau (AUC<sub>tau</sub>), values of 118, 161, and 246 ng.h/mL were observed in Child-Pugh A, Child-Pugh B and Child-Pugh C subjects, respectively.<sup>59</sup> Respective mean maximum observed plasma concentration (C<sub>max</sub>) values were 19.5, 25.1, and 35.5 ng/mL, compared with a mean C<sub>max</sub> of 3.41 ng/mL in healthy subjects. These exposure elevations in subjects with hepatic impairment are consistent with liver disease mediated reductions in liver blood flow (due to development of

porto-systemic shunts) and impairment in drug-metabolizing enzymes, resulting in reduced hepatic first-pass and systemic clearance.<sup>60</sup>

While subjects' maximum plasma exposure is increased by approximately 10-fold in subjects with liver impairment as compared with healthy subjects, this exposure is low compared with  $C_{\max}$  values in subjects receiving systemic or nonabsorbed antibiotics (Figure 1). For example, rifampin, a systemic antibiotic that is a structural analog of rifaximin, is associated with  $C_{\max}$  values of approximately 11000 ng/mL (approximately 200-fold greater than rifaximin) in healthy subjects at its therapeutic dose; administration of oral neomycin, approved for adjunctive treatment of hepatic coma, results in a plasma  $C_{\max}$  of 590 ng/mL in healthy subjects at a dosage regimen lower than that recommended in HE.<sup>61</sup> Furthermore, the circulating free fraction of neomycin (70%-100%) is substantially greater than that of rifaximin (32%-38%). Given rifaximin's relatively low exposures, combined with the favorable safety profiles in this population, no dosage adjustment is recommended in patients with hepatic impairment. Plasma concentrations of rifaximin (500 mg BID), rifampin (600 mg daily), and neomycin (1 g  $\times$  2 doses) are illustrated in Figure 1.

**Figure 1 Plasma Concentrations of Rifaximin, Rifampin, and Neomycin**

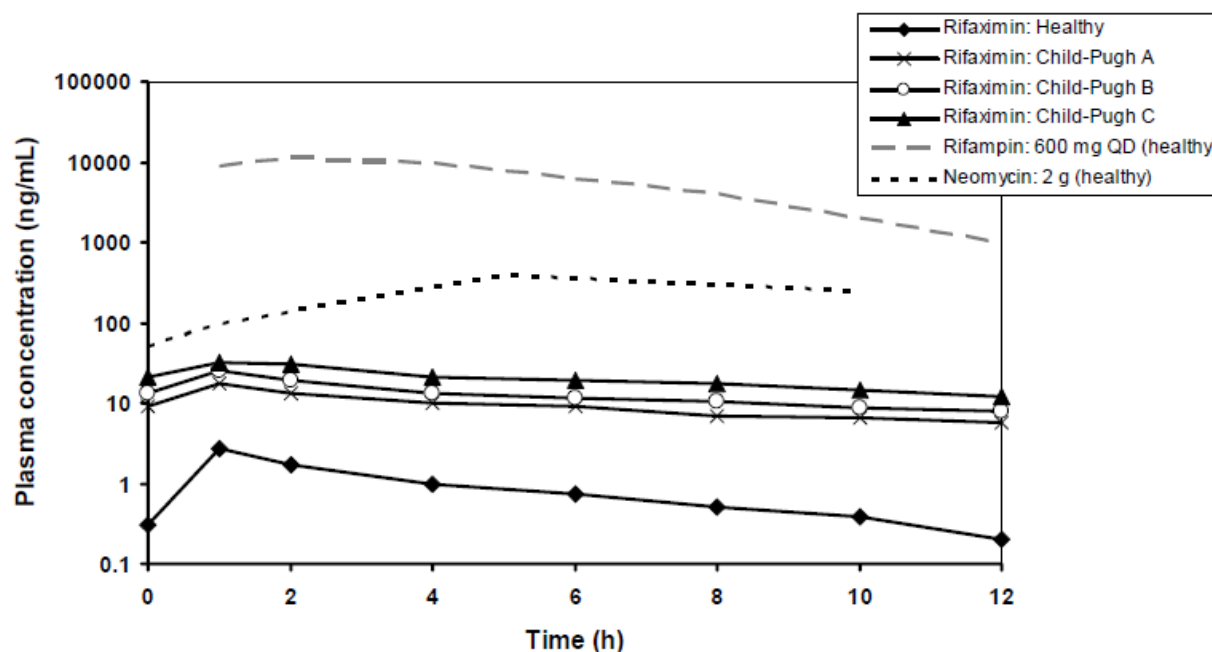


Table 2 presents a comparison of rifaximin pharmacokinetic parameters in subjects with hepatic impairment (RFHE3002PK) and healthy volunteers (RFPK1007).



**Table 2: Arithmetic Mean ( $\pm$  SD) Pharmacokinetic Parameters of Rifaximin 550 mg Multiple-Dose BID in Subjects with Hepatic Impairment (RFHE3002PK) and in Healthy Subjects (RFPK1007)**

Parameters	RFHE3002PK			RFPK1007
	Child-Pugh A (Mild) N = 18	Child-Pugh B (Moderate) N = 7	Child-Pugh C (Severe) N = 4	Healthy Volunteers N = 14
AUC <sub>tau</sub> (ng•h/mL)	118 (67.8)	161 (101)	246 (119)	12.3 (4.76)
C <sub>max</sub> (ng/mL)	19.5 (11.4)	25.1 (12.6)	35.5 (12.5)	3.41 (1.62)
C <sub>min</sub> (ng/mL)	5.13 (4.01)	7.90 (5.35)	11.5 (5.46)	0.275 (0.333)
T <sub>max</sub> (h)	1.00 (0.933, 10.0)	1.00 (0.967, 1.00)	1.00 (0, 2)	0.76 (0.50-4.00)
t <sub>1/2</sub> (h)	8.12 (3.58)	10.5 (1.50)	6.55 (1.64)	4.17 (3.30)

Source: Table 9 in Module 2.7.2 and current clinical database (Child-Pugh C data).

AUC<sub>tau</sub>=area under the concentration-time curve (AUC) from time 0 (predose) to the end of the dosing interval, tau;  
C<sub>max</sub>=maximum observed plasma concentration; C<sub>min</sub>=minimum observed plasma concentration; SD=standard deviation; t<sub>1/2</sub> = terminal or disposition half-life; T<sub>max</sub> = time to C<sub>max</sub>.

### 3.4. Distribution

Animal pharmacokinetic studies demonstrate that, at 4 hours following a 24 mg/kg oral dose in rats, less than 0.2% of the dose is distributed into the liver and kidney, and less than 0.01% in other tissues. The plasma protein binding of rifaximin, evaluated ex vivo in healthy volunteers as well as in subjects with liver impairment, was moderate in both populations (mean bound fraction: healthy: 68%; liver impairment: 62%), indicating that the alteration in plasma exposure in subjects with liver impairment was not attributable to protein binding.

Results from a scintigraphy study confirmed that the rifaximin is retained primarily in the gastrointestinal tract after oral administration in healthy subjects.<sup>62</sup> Following a single 200 mg oral dose, the rifaximin tablet rapidly disintegrated in the stomach (within 6 through 23 minutes) after oral administration, and moved through the small intestine within 3.82 through 6.25 h post dose, and through the colon within 3.94 through 7.28 h post dose.

### 3.5. Metabolism and Excretion

In healthy subjects receiving a single 400-mg <sup>14</sup>C-rifaximin dose, 96.94% of the total radioactive dose was recovered; 0.32% of the dose was excreted in the urine, and 96.62% of the radioactivity was excreted in feces (almost entirely as unchanged drug). Of the dose recovered in urine, 0.025% was recovered as rifaximin and <0.01% as 25-desacetyl-rifaximin, the only rifaximin metabolite that has been identified in humans. In a second study, healthy subjects received a single 400-mg rifaximin dose; 0.02% of the dose was recovered as rifaximin parent drug, and 0.0002% as 25-desacetyl-rifaximin.<sup>5</sup> In HE subjects receiving 600, 1200, and 2400 mg rifaximin daily for 7 days, a 24-h urine collection on Day 7 resulted in 0.061%, 0.1%, and 0.056% of the total daily dose excreted renally as unchanged drug, respectively.<sup>14</sup> The following table summarizes renal excretion data for rifaximin.

**Table 3: Rifaximin Renal Excretion Results in Healthy Volunteers and in Subjects with Liver Impairment**

Study population	Dose	Urinary Rifaximin (% of dose)	Urinary 25-Desacetylriifaximin (% of dose)
Healthy	400 mg single dose ( <sup>14</sup> C)	0.025	< 0.01
Healthy	400 mg single dose	0.020	0.0002
Liver impairment	600 mg x 7 d	0.061	Not determined
Liver impairment	1200 mg x 7 d	0.1	Not determined
Liver impairment	2400 mg x 7 d	0.053	Not determined

Source: references 5, 14, and 55.

Rifaximin appears in low concentrations in human bile following oral administration. In a study in cholecystectomy patients receiving multiple rifaximin doses, bile concentrations were too low for quantitation in 7 of the 13 subjects; in the remaining 6, the median bile concentration was 6.4 µg/mL.<sup>63</sup> In bile duct cannulated rats, approximately 1.1% of an oral <sup>14</sup>C-rifaximin dose was excreted in the bile. The rate of systemic clearance by metabolism, as predicted by human liver microsomes and human hepatocytes in vitro, is low (<30% of hepatic blood flow in microsomes, and no detectable turnover in hepatocytes), suggesting that rifaximin metabolic clearance is limited by hepatocellular permeability.

### 3.6. Drug Interactions

In vitro and in vivo studies indicate that the risk of clinically significant drug interactions with rifaximin is minimal. Rifaximin is a substrate for P-gp and potentially for other efflux transport proteins; its substrate status likely is a contributor to its minimal systemic exposure following oral administration. Furthermore, rifaximin appears to be a weak inhibitor of P-gp; at high concentrations (50 µM), rifaximin only partially inhibited transport of P-gp substrate digoxin,<sup>56</sup> suggesting that a clinical interaction between rifaximin and other compounds that undergo efflux via P-gp is unlikely. The potential for rifaximin to inhibit the human bile salt export pump (BSEP) was evaluated in vitro; its 50% inhibitory concentration (IC<sub>50</sub>) was 83 µM. No significant BSEP-mediated drug interactions are anticipated.

Rifaximin did not inhibit the major cytochrome P-450 (CYP) drug metabolizing enzymes (CYPs 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4) at concentrations up to 200 ng/mL in a human liver microsome assay.<sup>64</sup> In cultured human hepatocytes, the maximal ability of rifaximin to induce CYP3A4 activity was approximately half that of prototypical inducer rifampin at equivalent incubation concentrations (10 µM).<sup>65</sup> In vivo, rifaximin 200 mg TID x 3 days did not significantly affect the pharmacokinetics of single doses of oral midazolam, intravenous midazolam, or oral Ortho-Cyclen<sup>®</sup>.<sup>66,67</sup> Rifaximin 550 mg TID for 7 or 14 days resulted in only slightly reduced exposure to midazolam (approximately 10%) following a single oral midazolam dose.<sup>68</sup> By comparison, rifampin (600 mg daily for 5 days) was reported to reduce the AUC of oral midazolam by 95%, indicating that rifaximin's minimal effects on midazolam are related both to its intrinsically low induction potential in vitro and its limited distribution in vivo.<sup>69</sup> Thus, based on in vitro and in vivo data, no dose adjustment is recommended when rifaximin is co-administered with other drugs.

The unique properties of rifaximin, namely its poor oral absorption, minimal systemic exposure in both healthy individuals and those with advanced liver disease, high concentration in the gut lumen following oral administration, and minimal risk of drug interactions, contribute favorably to its efficacy and safety profiles.

## 4. Hepatic Encephalopathy - A Progressive, Debilitating Condition

Hepatic encephalopathy reflects a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known brain disease.<sup>94</sup> Hepatic encephalopathy manifests as a continuum of mental status deterioration, that may be observable in the patients' consciousness, intellect, personality and behavior, and neuromuscular function.<sup>7,70</sup> Hepatic encephalopathy can occur at any age, and both sexes are affected in roughly equal proportions. Patients at risk for occurrence of overt HE episodes have 2 fundamental conditions: portal-systemic shunting and advanced liver cirrhosis;<sup>71,72,73,74</sup> however, the etiology of cirrhosis is not predictive of HE episodes or the severity of HE episodes.<sup>75</sup> Hepatic encephalopathy episodes are debilitating, can present without warning, render the patient incapable of self-care, frequently result in hospitalization, and can result in coma and even death.

The neurological symptoms of hepatic encephalopathy are attributed to global central nervous system (CNS) depression from nitrogenous compounds (eg, ammonia) that result in excitation of GABAergic receptors and decreased neurotransmission of glutamate.<sup>71,76,77,78,79,80,81</sup> Normally, these nitrogenous compounds are eliminated in the liver, but in patients with cirrhosis, these compounds bypass the liver due to portal-systemic shunts, pass into general circulation and exert a direct or indirect influence on the CNS system. Gut-derived neurotoxins, including, ammonia, mercaptans, phenols, manganese, short chain fatty acids, bilirubin and a variety of neuroactive medications, have also been implicated.<sup>76,81</sup>

### 4.1. Definition and Nomenclature

Hepatic encephalopathy has been classified into 3 types (A, B, or C). Hepatic encephalopathy associated with cirrhosis is categorized as type C (see Table 4).<sup>94,95,82,83,93</sup>

In recurrent, overt, episodic HE, which is the most common subcategory, patients experience episodes of neuropsychiatric dysfunction lasting up to several days followed by remission to baseline neurological function. Subjects in RFHE3001 and RFHE3002 had type C, overt, episodic HE, and this is the classification under study for the phase 3 development program (see shaded region in Table 4).

**Table 4 Nomenclature for Classification of HE**

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	• Episodic HE	Precipitated Spontaneous Recurrent (relapsing)	} Overt
		• Resistant (persistent) HE	Mild Severe Treatment dependent	
		• Minimal		

Taken from references 84,94,95,82,83.

Note: In episodes of overt HE, the observed neurological dysfunction is characterized by clinical symptoms of mental status deterioration as defined by Conn<sup>84</sup> (see Table 5 in Section 4.3) and the presence of neuromuscular disturbances such as asterixis<sup>14,85</sup> (see Table 6 in Section 4.3).

#### 4.2. Impact of HE

The seriousness of HE is due to the chronic debilitating effects of recurrent episodes of overt HE, as described above. Hepatic encephalopathy is associated with a low quality of life compared to age-matched patients without HE.<sup>86,87,88,89</sup> Patients with HE experience symptoms including fatigue, daytime sleepiness, and lack of awareness (Conn score 1); and confusion and disorientation (Conn score 2) that significantly interfere with day-to-day function and decreased ability for self care. Often, this lack of self care can lead to improper nutrition and non-adherence to therapy and can further escalate into more severe symptoms such as increased somnolence, gross disorientation and stupor, which require hospitalization. The frequency of hospitalizations due to HE increased since 1993 from 27,368 to over 200,000 patients in 2007.<sup>90</sup> HE-associated hospitalizations are prolonged and costly, the mean length of stay in 2007 was 6.0 days with a mean cost per stay of about \$30,000.<sup>90</sup>

A history of overt HE episodes and the severity of HE episodes were found to be predictive of diminished survival in patients with advanced liver disease.<sup>91,92</sup> In patients with advanced liver disease and a history of overt HE episodes, survival probability was 42% at 1 year and 23% at 3 years after experiencing an HE episode.<sup>6</sup> Hepatic encephalopathy is therefore a formidable burden on the patient, his/her family, and the healthcare system.

#### 4.3. Clinical Diagnosis of HE

The clinical diagnosis of episodic HE in patients with advanced liver disease and portal-systemic shunting is based on the observation of impairments in consciousness, intellectual function, personality and behavior, and neuromuscular function in the absence of other etiologies.<sup>70,93,94,95</sup> Diagnosis is further confirmed by the frequent recurrence of HE episodes, with normal mental status between episodes. Elevated blood ammonia and the involvement of precipitating factors/comorbid conditions are also indicative.<sup>79,80</sup> Known precipitating factors/comorbid conditions include azotemia; sedatives, tranquilizers, or analgesics; GI bleeding; excess dietary protein; metabolic alkalosis; infection; constipation; dehydration; and sometimes the precipitating factor is unknown (ie, spontaneous).<sup>70,72,76</sup> Also, surgery, particularly the transjugular intrahepatic portosystemic shunt (TIPS) procedure, which increases portal-systemic shunting of blood, may precipitate HE.

The severity of the neuropsychiatric impairment associated with HE is measured by the West-Haven or Conn criteria (Table 5).<sup>84</sup> The Conn score describes 4 progressive stages (0=no impairment to 4= coma) of neurologic impairment associated with consciousness, intellectual function, and personality and behavior. These criteria are widely used and recommended by the World Congress of Gastroenterology Working Party on HE in 1998 to diagnose and determine the severity of overt episodes of HE.<sup>93,94,95</sup> Symptoms of neuromuscular dysfunction are also commonly used for diagnosis, and asterixis or “flapping” tremor<sup>14,85</sup> can also be graded (Table 6) to assess severity.

The CFF assessment,<sup>9,10,11,12,96</sup> a recognized quantitative measure of CNS dysfunction, is shown to be strongly correlated to the neurological impairment due to HE and may be used to confirm HE diagnosis and measure severity.

Often, due to the wide spectrum of cognitive impairment manifested in HE, the use of more than one diagnostic tool to clinically diagnose and measure the severity of HE is warranted.

**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 status.

Taken from references 70, 84.

**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.

Taken from reference 14, 85

#### 4.4. Current Treatment for HE

The most common treatment options for HE aim to lower the production and absorption of ammonia from the gut, often by using nonabsorbable disaccharides (eg, lactulose or lactitol), and/or antibiotics.<sup>19,23,24,26,76</sup> The commonly used disaccharides and antibiotics are compared in Table 8, and discussed below.

In the United States, lactulose is widely used and approved for the treatment and prevention of HE. Lactulose is thought to lower plasma levels of ammonia by acidification of stools, which prevents the production of ammonia, and purging, which increases the fecal excretion of nitrogen.<sup>70</sup> The recommended dose is 15-60 mL, 3-4 times daily, and is self-titrated by the patient to produce 2-3 soft stools to achieve efficacy.<sup>20</sup> Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy (ie, HE).<sup>20</sup> While deemed effective, the side effects of lactulose therapy include bloating, abdominal cramps, diarrhea, an unpleasant taste, resulting in low tolerability and poor adherence to long term treatment.<sup>20,22,101,97,117</sup> Additionally, it should be recognized that in patients with underlying advanced liver disease, complications such as dehydration and electrolyte disturbances (eg, hypokalemia) may occur for which other specific therapy may be required.<sup>20</sup>

Antibiotics appear to act indirectly by reducing the number of deaminating bacteria and urease producing bacteria, thus reducing the production of ammonia and other potential toxins. Antibiotics such as neomycin and metronidazole have demonstrated efficacy and have been used with or without lactulose.<sup>13,23,24,25,26,72,74</sup>

Neomycin sulfate is an aminoglycoside antibiotic that is approved for acute treatment as adjunctive therapy in hepatic coma at total daily doses of 4 to 12 g.<sup>27</sup> However, neomycin use is only recommended for short-term therapy in the treatment of HE due to the risk of nephrotoxicity and ototoxicity.<sup>27,28</sup> Furthermore, even though oral neomycin is commonly

considered a nonabsorbed antibiotic, it has significant oral absorption (approximately 3%)<sup>27</sup> and systemic exposure, especially in patients with renal insufficiency. Systemically absorbed neomycin accumulates in soft tissues after repeated dosings, particularly in the renal cortex and inner ear. Neomycin is effective primarily against Gram-negative bacilli with some activity against Gram-positive organisms, and no activity against anaerobic bowel flora.<sup>27</sup> Mainly due to this latter limitation, and because Gram-negative anaerobic bacteria are major contributors to ammonia generation in the gut, metronidazole, an antibiotic that is effective against anaerobic bacteria has been considered and used in the treatment of HE.<sup>26,98</sup> However, metronidazole is not approved for the treatment of HE and is not recommended for long term treatment due to CNS toxicity and a risk of convulsive seizures and peripheral neuropathy, particularly in patients with severe hepatic disease.<sup>116</sup>

Therefore, while current treatments are effective in treating acute HE in the short term, their use as long term continuous therapy in the prevention of recurrent episodes of HE is limited by side effects, lack of tolerance and poor adherence. There remains an unmet medical need for a treatment conducive to safe and effective long-term therapy for patients with HE.

An antibiotic with low systemic absorption and a broad spectrum of activity against Gram-positive and Gram-negative, as well as against aerobic and anaerobic bacteria that is conducive for continuous long term use would fulfill this unmet medical need.

#### **4.5. Rifaximin in the Treatment of Hepatic Encephalopathy Addresses an Unmet Medical Need**

There is no currently approved drug in the US for the indication of the maintenance of remission of HE.

Rifaximin is an attractive therapy to fulfill this unmet medical need for the treatment of patients with HE. Rifaximin has a low systemic bioavailability and high concentration in the GI tract, broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria and against aerobic and anaerobic isolates, low potential risk of development of antibiotic resistance, and a low risk of clinically relevant drug-drug interactions (see discussion of clinical pharmacology and microbiology of rifaximin in Sections 3.1 through 3.6).<sup>2</sup>

Rifaximin has been previously investigated in numerous clinical studies of subjects with HE.<sup>13,14,15,16,23,74,,99,100,109,110</sup> Studies conducted have demonstrated short- and long-term efficacy following treatment regimens of  $\leq 21$  days (ie, acute treatment) or longer treatment durations of 3 months and 6 months (described in Table 7 below).<sup>13,100,131</sup> Results of these studies demonstrated efficacy and a favorable safety profile for rifaximin in patients with HE. The clinical studies are discussed in Sections 6.4 through 6.6 and Table 43.<sup>109,110</sup> Further, 2 studies demonstrated a significant reduction in hospitalizations due to HE during rifaximin therapy, as compared to lactulose treatment, over 6 months.<sup>101,102</sup>

**Table 7: Long- and Short-Term Efficacy Studies of Rifaximin Treatment in Subjects with HE**

Study # or Publication (# study sites)/ Location	Study Design	Subject Population	Treatment Dose	Pts per Treatment Group	Treatment Duration
RFHE9702 Williams et al. <sup>14</sup> (4)/ UK	R, DB, P, DR	HE Gr 1-3 (Conn)	<ul style="list-style-type: none"> <li>• RFX 200 mg TID</li> <li>• RFX 400 mg TID</li> <li>• RFX 800 mg TID</li> </ul>	18 19 17	7 days
RFHE9701 Mas et al. <sup>15</sup> (13)/ Spain	R, DB, AC, P	Recurrent HE Gr 1 to 3 acute (Conn)	<ul style="list-style-type: none"> <li>• RFX 400 mg TID</li> <li>• Lactitol 20 g TID</li> </ul>	50 53	5-10 days
RFHE9901 Bass et al. <sup>16</sup> (11)/ Poland, Hungary, Scotland, US	R, DB, PBC	Chronic, mild to moderate HE & intolerant to lactulose or lactitol.	<ul style="list-style-type: none"> <li>• RFX 400 mg TID</li> <li>• Pbo matching TID</li> </ul>	48 45	14 days
Loguercio et al. <sup>131</sup> (1)/Italy	R, DB, P	HE Gr 1 to 2 (Conn)	<ul style="list-style-type: none"> <li>• RFX 400 mg + sorbitol 20 g TID</li> <li>• lactitol 20 g + Pbo TID</li> <li>• RFX 400 mg + lactitol 20 g TID</li> </ul>	14 13 13	15 consecutive days / month for 3 months
Fera et al. <sup>100</sup> (1)/Italy	R, DB, AC	PSE Gr 1& liver cirrhosis	<ul style="list-style-type: none"> <li>• RFX 400 mg TID</li> <li>• lactulose 40 mg TID</li> </ul>	20 20	1st 2 wks of each month for 3 months
Miglio et al. <sup>13</sup> (3)/Italy	R, DB, AC	HE Gr 1 to 2 (Conn) & liver cirrhosis	<ul style="list-style-type: none"> <li>• RFX 400 mg TID</li> <li>• neomycin 1 g TID</li> </ul>	30 30	14 consecutive days / month for 6 months
Als-Nielson et al. <sup>109</sup>	Meta-analysis 22 published R studies	Acute, chronic, or minimal HE	<ul style="list-style-type: none"> <li>• lactulose/lactitol (mean 30-84g) vs Pbo or no intervention</li> <li>• lactulose/lactitol (mean 30-120 g) vs antibiotics, including RFX 400 mg TID</li> </ul>	280 (10 studies)  698 (12 studies)	median 15 days (5-360 days)  median 15 days (5-90 days)
Lawrence and Klee <sup>110</sup>	Review 1966 – 2007 R, DB, PBC, AC, OL	HE G 1-3 (Conn)	<ul style="list-style-type: none"> <li>• RFX 200, 400, or 800 mg TID</li> <li>• paromomycin 500 mg TID</li> <li>• neomycin 1 g TID</li> <li>• lactulose (30-60 g/day) or lactitol 60 g/day</li> </ul>	20 to 103	Majority 7 to 21 days;

KEY: AC = Active controlled, DB = Double-blind, DR = Dose-ranging, Gr = Grade, HE = Hepatic encephalopathy, OL = Open label, P = Parallel, PBC = Placebo-controlled, Pbo Placebo, PSE = Portal systemic encephalopathy, R = Randomized; RFX = Rifaximin

Rifaximin has advantages in the treatment of HE relative to other commonly used current therapies in that it is nonsystemic; with low absorption from the GI tract, has demonstrated efficacy, and a favorable safety profile for the short- and long-term treatment of HE. This differentiates rifaximin from other therapies and represents a new treatment option for patients with HE.

Table 8 summarizes commonly used disaccharides and antibiotics in patients with HE.



**Table 8: Nonabsorbable Disaccharides and Antibiotics Used in Patients with HE**

	Lactulose <sup>a</sup>	Neomycin <sup>b</sup>	Metronidazole <sup>c</sup>	Rifaximin <sup>d</sup>
Description	Non-absorbable disaccharide	Aminoglycoside antibiotic	Nitroimidazole antibiotic	Rifamycin antibiotic
Indication	For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma. Continuous long-term therapy to lessen the severity and prevent the recurrence of portal-systemic encephalopathy	Effective adjunctive therapy in hepatic coma by reduction of the ammonia forming bacteria in the intestinal tract. The subsequent reduction in blood ammonia has resulted in neurologic improvement.	No indication for HE	Proposed: The maintenance of remission of HE in patients $\geq 18$ years of age
Dosage	30 to 45 mL, (20 g to 30 g) 3-4 times daily. Dosage adjusted to produce 2 - 3 soft stools daily. Same dose for long-term, preventive therapy.	4-12 g per day in divided doses over 5-6 days Treatment for periods longer than two weeks is not recommended.	500-800 mg/day divided doses <sup>103</sup> Not recommended for long term therapy in patients with advanced liver disease. <sup>104</sup>	550 mg twice daily
Activity	Lowers plasma levels of ammonia by acidification of stools, and converting $\text{NH}_3$ to $\text{NH}_4^+$ , which is trapped and purged	Bactericidal, mainly against Gram-negative aerobes. Not active against anaerobic bowel flora	Antibacterial against a broad spectrum of Gram-negative and Gram-positive anaerobic bacteria	Antibacterial activity against a broad-spectrum of both Gram-positive and Gram-negative aerobic and anaerobic bacteria
Pharmacology	<ul style="list-style-type: none"> <li>Poorly absorbed.</li> <li>Only small amounts reaching the blood.</li> <li>Urinary excretion <math>\leq 3</math> % (within 24h)</li> </ul>	<ul style="list-style-type: none"> <li>Poorly absorbed</li> <li><math>\text{C}_{\text{max}}</math> 590 ng/mL after 3g total dose.<sup>61</sup></li> <li>Approximately 97 % is eliminated unchanged in the feces, metabolite excreted by the kidney</li> <li>Progressive tissue binding and accumulation in kidneys, inner ear.</li> <li>Plasma protein binding 0-30%</li> </ul>	<ul style="list-style-type: none"> <li>Well absorbed</li> <li>250 - 2,000 mg dose <math>\text{C}_{\text{max}}</math> 6,000 - 40,000 ng/mL 1-2h after oral dosing.</li> <li>Elimination is via urine (60-80%), feces ( 6 to 15%).</li> <li>Plasma protein binding <math>&lt;20\%</math></li> </ul>	<ul style="list-style-type: none"> <li>Poorly absorbed (highly concentrated in gut).</li> <li><math>\text{C}_{\text{max, steady-state}}</math> = 3 to 52.2 ng/mL (healthy to patients with hepatic impairment) with 550 mg twice daily oral dose</li> <li>Of <math>\approx 97\%</math> recovered dose, 96.62 % eliminated unchanged in the feces; 0.03% in urine</li> <li>Plasma protein binding 62-68%</li> </ul>

	Lactulose <sup>a</sup>	Neomycin <sup>b</sup>	Metronidazole <sup>c</sup>	Rifaximin <sup>d</sup>
AE	Nausea and vomiting, bloating, abdominal cramps, flatulence, diarrhea with dehydration, hypokalemia, hypernatremia.	Nephrotoxicity, ototoxicity, neuromuscular blockage, nausea and vomiting, diarrhea, Malabsorption Syndrome	Not indicated in HE convulsive seizures, peripheral neuropathy, nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation.	(Most common in HE patients) peripheral edema, nausea, dizziness, fatigue, ascites, diarrhea, and headache
Label highlights: potential limitations in patients with HE	Other specific therapy may be required for electrolyte disturbance (e.g., hypokalemia) in patients with underlying liver disease.	Contraindicated in patients with IBD and in patients with impaired renal function.	Potential for accumulation of drug and metabolites in patients with severe hepatic disease	Labeling for antibiotic-associated <i>Clostridium difficile</i> -associated diarrhea.

a Lactulose solution [package insert]. Toronto, Ontario, Canada and Weston, FL; Apotex Inc: 2005.

b Neo-Fradin<sup>®</sup> [package insert]. Big Flats, NY; X-Gen Pharmaceuticals, Inc: 2005.

c Flagyl<sup>®</sup> [package insert]. New York, NY; G.D. Searle, LLC, Division of Pfizer, Inc: 2006, and see references 26,103,104,122

d XIFAXAN<sup>®</sup> [package insert]. Morrisville, NC; Salix Pharmaceuticals, Inc: 2008

## 5. Clinical Overview

The studies represented in Table 7 showed effectiveness and safety of rifaximin for the treatment of HE. However, collectively these studies covered treatment durations of various length, and differing endpoints and comparators. A robust, long term, double blind, placebo-controlled study evaluating rifaximin in the prevention of HE in patients with advanced liver disease was required to firmly establish efficacy and safety. To address this requirement, studies RFHE3001 and RFHE3002 were designed as described in Table 9.

**Table 9: Primary Efficacy Studies Evaluating Rifaximin for the Maintenance of Remission of HE**

Study # or Publication (# study sites)/ Location	Study Design	Subject Population	Treatment Dose	Pts per Treatment Group	Treatment Duration
RFHE3001 (70)/ US, Canada, and Russia	R, DB, PBC	Overt episodic HE Gr 0 or 1 (Conn)	<ul style="list-style-type: none"> <li>• RFX 550 mg BID</li> <li>• Plc matching BID</li> </ul>	140 159	6 months
RFHE3002 (57)/ US, Canada, and Russia	OL	Overt episodic HE Gr 0 or 1 (Conn)	<ul style="list-style-type: none"> <li>• RFX 550 mg BID</li> </ul>	267	ongoing

KEY: DB = Double-blind, Gr = Grade, HE = Hepatic encephalopathy OL = Open label, PBC = Placebo-controlled, PBO = Placebo, R = Randomized; RFX = Rifaximin

### 5.1. Rationale for Rifaximin Dose

The dosage regimen used (550 mg BID) in the phase 3 studies was based on past clinical experience with rifaximin in patients with HE and other patient populations. In several previous studies (see Section 6.6 and Section 9 [Table 43]), rifaximin was safe and effective in subjects with HE at a dose of 1200 mg per day (2 × 200 mg tablets TID) with or without concomitant lactulose. In a 6-month study of rifaximin vs. neomycin,<sup>13</sup> rifaximin 1200 mg/day and neomycin (3 g/day) had comparable efficacy in patients with HE (see Section 6.5). In the 3-month studies of rifaximin vs. lactitol, subjects who received rifaximin 1200 mg daily (2 × 200 mg tablets TID) showed significant improvements in HE endpoints (Section 6.5).<sup>100,131</sup>

In dose-ranging study RFHE9702 in subjects with active symptoms of HE, there was a dose-dependent trend in improvement in the portal-systemic encephalopathy (PSE) index up to 1200 mg (2 × 200 mg tablets TID). Similar results were observed for the 1200 mg and 2400 mg doses (4 × 200 mg tablets TID) (Table 10). In a dose-response analysis, the Jonckheere-Terpstra test indicated a trend in improvements in PSE index across dose groups (p = 0.0586).

**Table 10 RFHE9702: Change from Baseline in PSE Index (ITT population)**

PSE index <sup>a</sup>	RFHE9702 (N=54)		
	Rifaximin		
	600 mg/day N=18	1200 mg/day N=18	2400 mg/day N=18
End-of-treatment (Day 7) minus baseline			
n	14	16	16
Mean (standard deviation)	-0.064 (0.137)	-0.103 (0.137)	-0.107 (0.149)

Source: RFHE9702 study report

Abbreviations: PSE: portal systemic encephalopathy; EEG: electroencephalogram.

a PSE index was calculated as follows: [Mental status (Conn score) × 3 + asterixis grade × 1 + number connection test (NCT) grade × 1 + ammonia grade × 1 + EEG grade × 1 (if available) / 24 (or 28 if EEG is available)]. (24 [or 28 if EEG results are included] is the highest possible score and higher scores are indicative of worse symptoms of HE.)

The 1200 mg daily dose (2 × 200 mg tablets TID) was also effective in the phase 3, short-term treatment studies RFHE9701 and RFHE9901.<sup>15,16</sup>

A scintigraphy study revealed a rapid GI transit time of rifaximin 200 mg tablets (marketed dosage form). Initial disintegration of the tablets occurred in the stomach between 6 and 23 minutes post dose while the initial small intestinal transit time was between 3.82 and 6.25 hours. Average time for 50% of the tablet contents to arrive in the colon was approximately 5 hours, with the total dose reaching the colon at an average time of approximately 7 hours. Considering this transit time, BID dosing was chosen in order to maintain high rifaximin concentration in the gut. Finally, dose-dependent reductions in small intestinal bacterial overgrowth (SIBO) of 17%, 26%, 60%, and 80% were reported at daily doses of 600, 800, 1200, and 1600 mg per day, respectively, suggesting that the 1200 mg dose level would be effective in the reduction of gut flora in patients with HE.<sup>105,106</sup> These SIBO data are relevant to studies of patients with HE since studies indicate that SIBO may be common in cirrhotic patients with HE and/or portal hypertension.<sup>107</sup> Although it appeared that the 1200-mg daily dose was optimal, the rifaximin tablet was limited to 550 mg due to physical limitations on tablet size, and 1100 mg of rifaximin per day (550 mg BID) was tested in the pivotal studies.

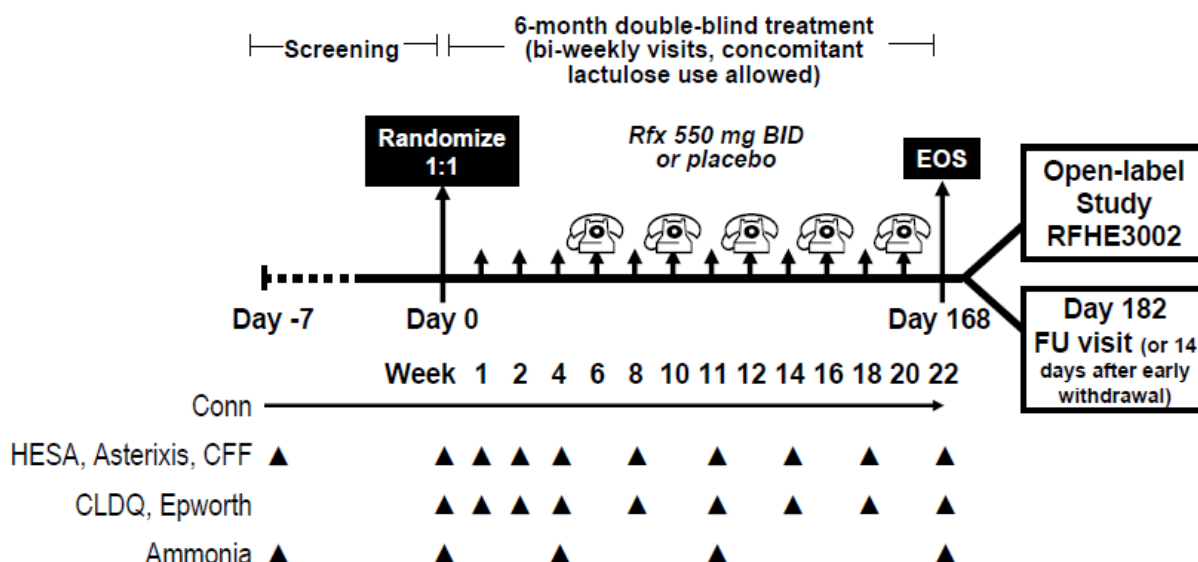
## **5.2. Primary Studies (RFHE3001 and RFHE3002)**

### **5.2.1. RFHE3001**

#### **5.2.1.1. Study Design**

RFHE3001 was a phase 3 randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of rifaximin in subjects currently in remission from demonstrated HE (see Table 44 in Section 10). The study consisted of a screening period (4 days), observation period (3 days), baseline visit, and treatment period (6 months). After determining eligibility, subjects underwent a baseline assessment period prior to randomization. This 7-day period was used to determine the subject's eligibility, to provide adequate instructions to patients and caregivers, and to establish baseline mental status and neuromuscular function before entering the double-blind period. Patients were randomized to receive rifaximin 550-mg tablet BID or matching placebo tablet BID for 6 months. Subjects had the option to use lactulose as a concomitant medication, and 91% of subjects in both groups were taking lactulose during the course of the study. Subjects underwent evaluations of mental status (Conn score) and neuromuscular functioning (asterixis grade) for determination of the occurrence of a breakthrough overt HE episode by the investigators and site personnel at each in-person study visit. Telephone interviews, caregiver reports, and subject diaries were also used to establish if a breakthrough overt HE episode occurred. Per the protocol, subjects were discontinued from the study at the time of breakthrough overt HE episode. After participation in study RFHE3001, subjects had the option to enroll in the open-label, treatment-extension study (RFHE3002).

**Figure 2 RFHE3001: Study Design**



#### 5.2.1.2. Study Population

Males or females subjects aged 18 years and older were eligible for the study if they met the following key inclusion criteria:

- Conn score 0 or 1
- History within 6 months of  $\geq 2$  episodes of overt HE associated with advanced liver disease (eg, cirrhosis or portal hypertension) with a documented severity equivalent to Conn score  $\geq 2$  prior to screening (ie, subjects had documented recurrent, overt HE). At least 1 prior episode was verified from medical records. Hepatic encephalopathy episodes primarily attributed to GI hemorrhage, medications (eg, narcotics, tranquilizers, sedatives), renal failures requiring dialysis, or CNS insult such as a subdural hematoma were not counted as prior, qualifying episodes of HE.
- Model End-State Liver Disease (MELD) score of  $\leq 25$
- TIPS placement or revision  $> 3$  months prior to screening (if present) and
- Had a close family member or other caregiver providing oversight who was available to the subject during the study.

Subjects were excluded from the study if the following key exclusion criteria applied:

- Expected to receive a liver transplant within 1 month of screening
- Consume alcohol within 14 days of screening, sedatives within 7 days or evidence of drug dependence
- Human immunodeficiency virus as determined by medical history
- History of tuberculosis infection or treatment for a tuberculosis infection

- Active spontaneous bacterial peritonitis or daily prophylactic antibiotic therapy
- GI bleeding requiring hospitalization and blood transfusion  $\leq 3$  months of screening
- Presence of intestinal obstruction or had inflammatory bowel disease
- Renal insufficiency (serum creatinine  $> 2.0$  mg/dL)
- Anemia (hemoglobin [Hgb]  $< 8$  gm/dL)
- Hypovolemia or electrolyte abnormality ( $\text{Na}^+ < 125$  mEq/L,  $\text{Ca}^{++} > 10$  mg/dL,  $\text{K}^+ < 2.5$  mEq/L)
- Neurological disease other than HE, that in the opinion of the Investigator, could impact the subjects' performance on study assessments

#### **5.2.1.3. Efficacy Endpoints**

The primary 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  $\geq 2$  (ie, 0 or 1 to  $\geq 2$ ) 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 breakthrough overt HE episode was the duration from first dose of study drug to the first breakthrough overt HE episode.

Key secondary endpoints are listed below:

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

#### **5.2.1.4. Statistical Methods**

Efficacy data were analyzed using the intent-to-treat (ITT) population. The ITT population included all randomized subjects who received at least 1 dose of study drug.

The analysis of the primary efficacy endpoint was based on the comparison of time to the first breakthrough overt HE episode between rifaximin and placebo groups. The analysis utilized the Cox proportional hazards model (Score test, [ie, Log rank test stratified by analysis region, where analysis region refers to Russia and North America (US and Canada)]) with a 2-sided test at a significance level of 0.05 under the proportional hazards assumption.

Censoring: 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 breakthrough overt HE were contacted at 6 months from randomization. If the subject had no breakthrough overt HE episode prior to contact, he/she was censored at the time of contact. Therefore, complete capture was achieved for breakthrough overt HE episodes up to 6 months postrandomization.

Key secondary endpoints were tested in sequential order after establishing statistical significance in the primary efficacy analysis, each at a 5% level of significance.

### 5.2.1.5. Data and Safety Monitoring Board

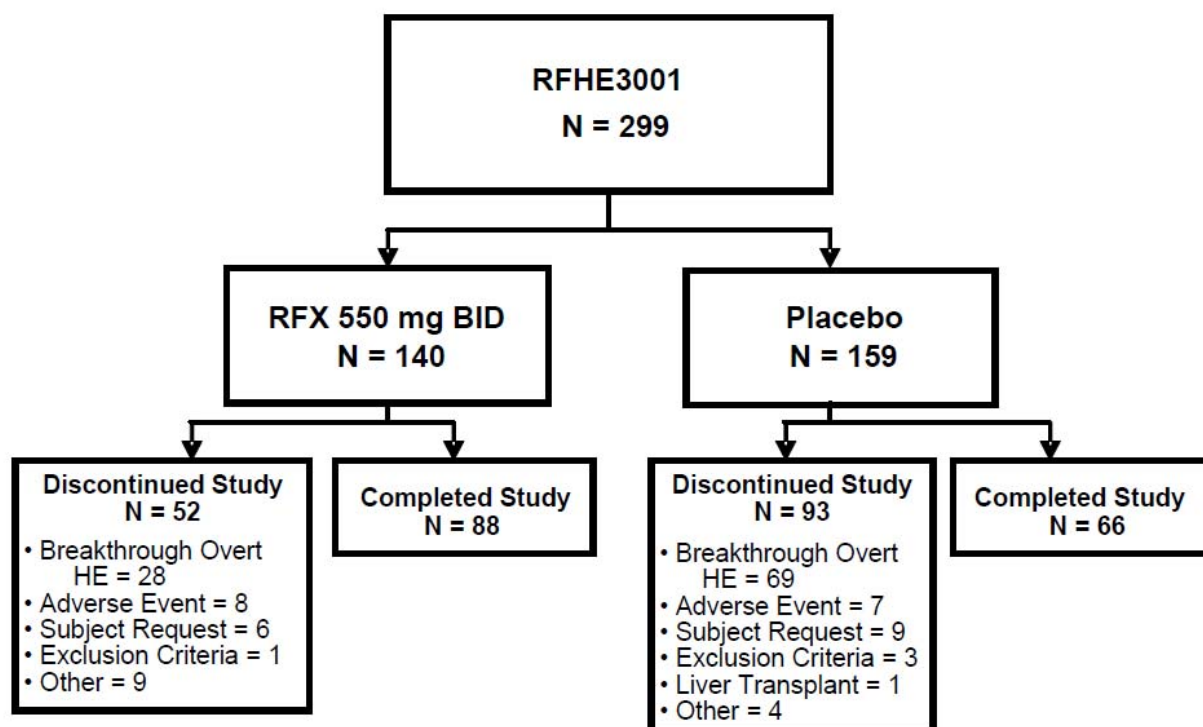
An independent data and safety monitoring board (DSMB) periodically reviewed and evaluated accumulated study data for subject safety, study conduct and progress toward achieving predefined objectives. The DSMB members (E.R. Schiff [chair], F. Wong, J. Borer and L. LaVange) and DSMB proceedings were independent from participation in the study and from the analyses of study results. The DSMB met on four different occasions. In addition, the DSMB reviewed serious adverse events (SAEs) reports on an ongoing basis throughout the duration of the study.

### 5.2.1.6. Subject Disposition

A total of 299 subjects were randomized to placebo (159 subjects) or rifaximin (140 subjects) in the study (Figure 3).

As specified in the protocol, subjects were withdrawn from the study after experiencing a breakthrough overt HE episode.<sup>108</sup>

**Figure 3 Subject Disposition in Study RFHE3001**



Source: RFHE3001 study report. Abbreviations: RFX=rifaximin, HE=hepatic encephalopathy.

Note: Subjects may have discontinued early for more than 1 reason; the primary reason is given here.

### 5.2.1.7. Demographics

Demographic characteristics are summarized for the ITT population in Table 11.

The relative distributions of subjects by demographic characteristic were comparable between treatment groups in the ITT population.

**Table 11 RFHE3001: Demographics by Treatment Group (ITT Population)**

Characteristic Category or statistic	Placebo N = 159	Rifaximin N = 140	Total N = 299
<b>Age (years)</b>			
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)
<b>Age group – n (%)</b>			
< 65	128 (80.5)	113 (80.7)	241 (80.6)
≥ 65	31 (19.5)	27 (19.3)	58 (19.4)
<b>Sex – n (%)</b>			
Male	107 (67.3)	75 (53.6)	182 (60.9)
Female	52 (32.7)	65 (46.4)	117 (39.1)
<b>Ethnicity – n (%)</b>			
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)
<b>Race</b>			
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)
<b>Country – n (%)</b>			
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)

Source: RFHE3001 study report.

Abbreviation: SD=standard deviation

#### 5.2.1.8. Baseline Characteristics

Hepatic encephalopathy baseline characteristics in the ITT population such as HE severity for recent episodes of overt HE (Conn scores and asterixis grades) and time since last HE episode are summarized in Table 12. Liver disease characteristics and other characteristics of subjects at baseline in the ITT population such as disease severity (MELD score), time since first diagnosis of advanced liver disease and etiology of advanced liver disease are summarized in Table 13 and Table 14. Baseline characteristics were generally comparable across the treatment groups.

There were no notable differences in baseline characteristics between placebo and rifaximin groups by geographic analysis region, by sex, by age group, and by race.



**Table 12 RFHE3001: Hepatic Encephalopathy Baseline Characteristics by Treatment Group (ITT Population)**

Characteristic	Placebo N = 159	Rifaximin N = 140	Total N = 299
<b>Time since first diagnosis of hepatic encephalopathy (months)</b>			
n	159	139	298
Mean (SD)	21.9 (26.4)	20.8 (23.13)	21.4 (24.9)
Median (min, max)	11.0 (0.6, 179.4)	11.8 (0.5, 125.1)	11.5 (0.5, 179.4)
<b>Number of HE episodes within the past 6 months - n (%)</b>			
2	111 (69.8)	97 (69.3)	208 (69.6)
3	35 (22.0)	29 (20.7)	64 (21.4)
4	8 (5.0)	5 (3.6)	13 (4.3)
5	1 (0.6)	7 (5.0)	8 (2.7)
≥6	3 (1.9)	2 (1.4)	5 (1.6)
Missing	1 (0.6)	0	1 (0.3)
<b>Past HE severity (Conn score at most recent episode prior to study) - n (%)</b>			
Grade 1	2 (1.3)	1 (0.7)	3 (1.0)
Grade 2	130 (81.8)	115 (82.1)	245 (81.9)
Grade 3	24 (15.1)	20 (14.3)	44 (14.7)
Grade 4	2 (1.3)	3 (2.1)	5 (1.7)
Missing	1 (0.6)	1 (0.7)	2 (0.7)
<b>Duration of verified current remission (taking qualifying HE episodes into account) (days)</b>			
n	158	139	297
Mean (SD)	73.1 (51.33)	68.8 (47.68)	71.1 (49.62)
Median (min, max)	61.0 (12, 205)	55.0 (8, 222)	57.0 (8, 222)
<b>Duration of verified current remission categories - n (%)</b>			
≤ 90 days	110 (69.2)	100 (71.4)	210 (70.2)
> 90 days	48 (30.2)	39 (27.9)	87 (29.1)
Missing	1 (0.6)	1 (0.7)	2 (0.7)
<b>Conn score - n (%) (at Baseline, subjects were in remission)</b>			
Grade 0	107 (67.3)	93 (66.4)	200 (66.9)
Grade 1	52 (32.7)	47 (33.6)	99 (33.1)
<b>Asterixis grade - n (%)</b>			
Grade 0	108 (67.9)	96 (68.6)	204 (68.2)
Grade 1	45 (28.3)	41 (29.3)	86 (28.8)
Grade 2	5 (3.1)	2 (1.4)	7 (2.3)
Grade 3	1 (0.6)	1 (0.7)	2 (0.7)
<b>Average critical flicker frequency (Hz)</b>			
n	159	140	299
Mean (SD)	37.4 (6.03)	36.9 (5.47)	37.2 (5.77)
Median (min, max)	37.5 (15, 50)	37.2 (18, 48)	37.3 (15, 50)
<b>Average Venous Ammonia Concentration (μmol/L)</b>			
n	146	132	278
Mean (SD)	90.3 (52.48)	87.9 (47.76)	89.2 (50.22)
Median (min, max)	84 (20, 465)	76.5 (20, 290)	79.5 (20, 465)
<b>Prior lactulose use- n (%)</b>			
Yes	145 (91.2)	128 (91.4)	273 (91.3)
No	14 (8.8)	12 (8.6)	26 (8.7)
<b>Lactulose daily dose at Baseline (cups/day)<sup>a</sup></b>			
n	145	128	273
Mean (SD)	3.7 (2.54)	3.5 (3.24)	3.6 (2.88)
Median (min, max)	3.0 (0, 13)	2.8 (0, 30)	2.9 (0, 30)

Source: RFHE3001 study report. Abbreviations: HE=hepatic encephalopathy; SD=standard deviation.

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

Note: Values for lower case 'n' are the numbers of subjects with available data for the individual parameter at baseline.

**Table 13 RFHE3001: Advanced Liver Disease and Other Characteristics at Baseline by Treatment Group (ITT Population)**

Characteristic	Placebo N = 159	Rifaximin N = 140	Total N = 299
<b>Time since first diagnosis of advanced liver disease (months)</b>			
n	159	140	299
Mean (SD)	60.5 (64.89)	51.2 (49.2)	56.2 (58.2)
Median (min, max)	39.0 (2, 323.4)	38.0 (1.7, 260.5)	38.3 (1.7, 323.4)
<b>Model end-stage liver disease (MELD) score</b>			
n	158	140	298
Mean (SD)	12.7 (3.94)	13.1 (3.64)	12.9 (3.80)
Median (min, max)	12.4 (6, 23)	13.1 (6, 24)	12.6 (6, 24)
<b>MELD United Network for Organ Sharing (UNOS) category - n (%)</b>			
≤ 10	48 (30.2)	34 (24.3)	82 (27.4)
11 - 18	96 (60.4)	94 (67.1)	190 (63.5)
19 - 24	14 (8.8)	12 (8.6)	26 (8.7)
≥ 25	0	0	0
Missing	1 (0.6)	0	1 (0.3)
<b>Child-Pugh classification<sup>a</sup></b>			
n	142	124	266
Mean (SD)	7.2 (1.87)	7.5 (1.93)	7.3 (1.90)
Median (min, max)	7.0 (3, 13)	7.0 (5, 14)	7.0 (3, 14)
<b>Child-Pugh classification<sup>a</sup> - n (%)</b>			
A (5-6)	56 (35.2)	46 (32.9)	102 (34.1)
B (7-9)	72 (45.3)	65 (46.4)	137 (45.8)
C (10-15)	14 (8.8)	17 (12.1)	31 (10.4)
Missing	17 (10.7)	12 (8.6)	29 (9.7)
<b>Diabetes at baseline - n (%)</b>			
Yes	56 (35.2)	44 (31.4)	100 (33.4)
No	103 (64.8)	96 (68.6)	199 (66.6)

Source: RFHE3001 study report.

Abbreviations: MELD UNOS=Model End-Stage Liver Disease United Network for Organ Sharing; SD=standard deviation.

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

**Table 14 RFHE3001: Etiology of Advanced Liver Disease**

System Organ Class	RCT Study Population (RFHE3001)	
	Placebo (N = 159)	Rifaximin 550 mg BID (N = 140)
	n (%)	n (%)
Etiology		
Hepatitis C	67 (42)	61 (44)
Alcohol	57 (36)	47 (34)
Hepatitis C + Alcohol	10 (6)	18 (13)
Other:		
NAFLD/NASH	17 (11)	13 (9)
Hepatitis B	13 (8)	11 (8)
Cryptogenic	11 (7)	9 (6)
Autoimmune Hepatitis	1 (1)	9 (6)
Primary Biliary cirrhosis	5 (3)	4 (3)
Drug/chemical induced	1 (1)	2 (1)

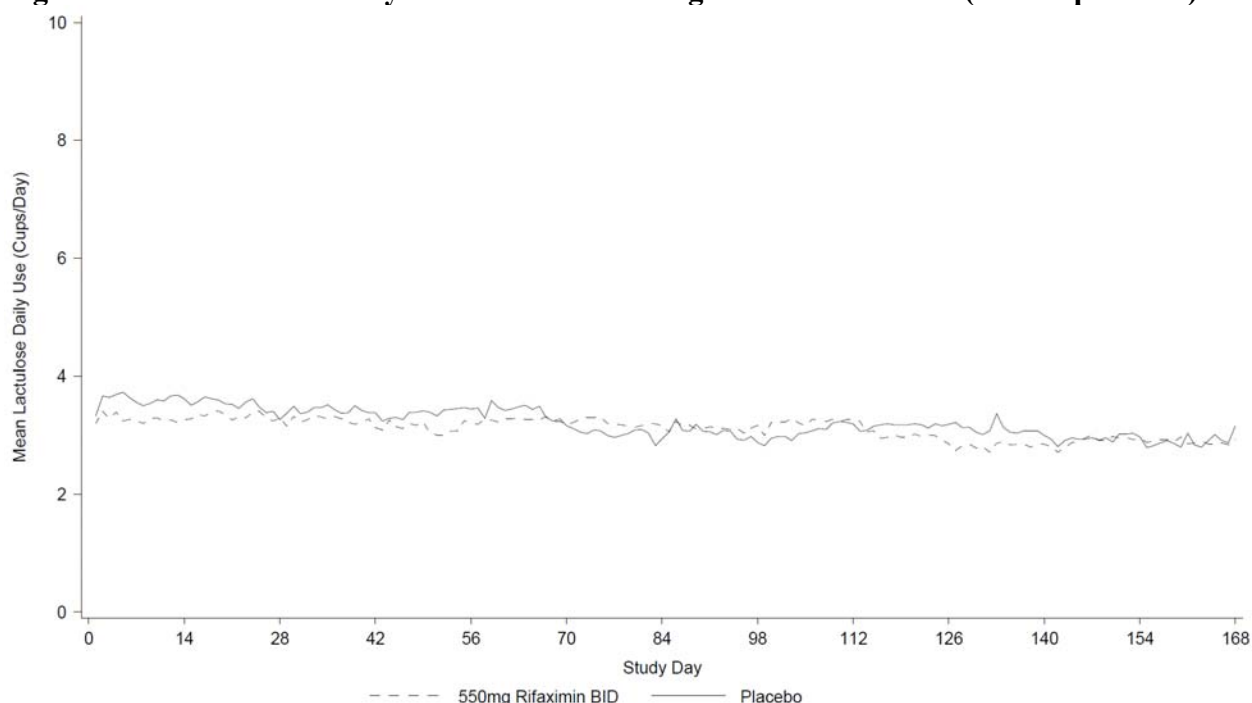
System Organ Class	RCT Study Population (RFHE3001)	
	Placebo (N = 159)	Rifaximin 550 mg BID (N = 140)
	n (%)	n (%)
Genetic	2 (1)	0

Source: Integrated Summary of Safety (ISS) 120-Day Update database.

Abbreviations: RCT=randomized control trial; NAFLD/NASH=nonalcoholic fatty liver disease/nonalcoholic steatohepatitis

It is important to note that most subjects received concomitant lactulose during the course of studies RFHE3001 (91% in each group) and RFHE3002 (approximately 75%). Daily lactulose use in RFHE3001 is illustrated in Figure 4. These data show that there was no between-group difference in daily doses of lactulose and lactulose doses were stable during the study.

**Figure 4 RFHE3001: Daily Lactulose Use During Treatment Period (ITT Population)**



Source: RFHE3001 study report.

## 5.2.2. RFHE3002

### 5.2.2.1. Study design

Study RFHE3002 is an ongoing phase 3, multicenter, open-label, treatment-extension study evaluating the long-term safety of rifaximin 550 mg BID in subjects with a history of recurrent, episodic, overt HE. All eligible subjects had a history of overt HE episodes with a documented severity of Conn score  $\geq 2$  within 12 months prior to screening, a Conn score of  $\leq 2$  at enrollment, and either had participated in RFHE3001 or were new subjects. Treatment with rifaximin 550 mg tablet BID is planned for at least 24 months or until regulatory approval. Concomitant therapy with lactulose is optional.

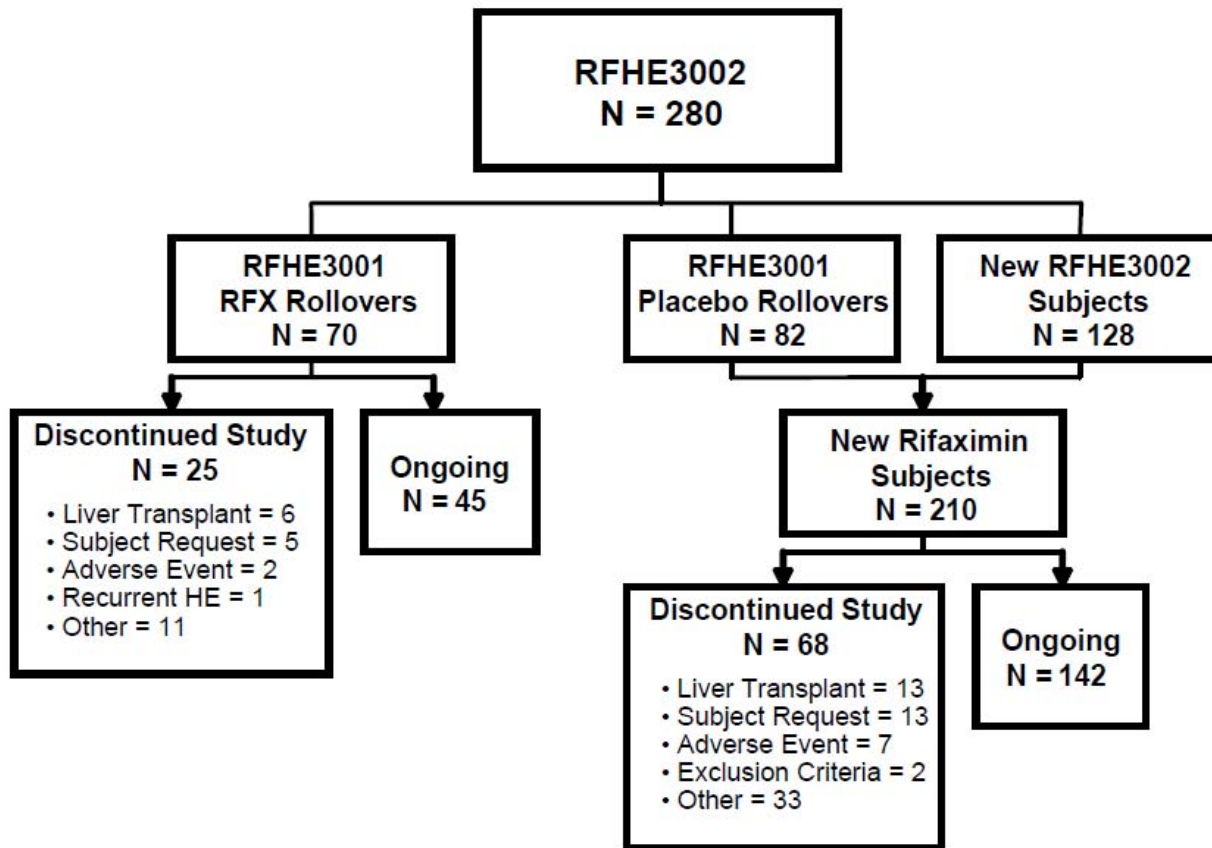
Although RFHE3002 was primarily designed to evaluate the long-term safety of rifaximin 550 mg, additional efficacy assessments of Conn score and asterixis grade were collected during the study. In RFHE3002, breakthrough overt HE was defined as an increase of Conn score to Grade  $\geq 2$ , an increase 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  $\geq 3$  for subjects who had a Conn score of 2 at study entry.

#### 5.2.2.2. Subject Disposition

Subject disposition is summarized below in Figure 5.

A total of 280 subjects were enrolled at 60 study sites. A total of 152 (54.3%) of these subjects rolled over from the lead-in study (RFHE3001) and 128 (45.7%) were new subjects. A total of 187 subjects (66.8%) are still ongoing in the study. Ninety-three subjects (33.2%) discontinued treatment early, and primary reasons are shown in Figure 5.

**Figure 5 Subject Disposition in RFHE3002**



Source: ISS 120-day update, Figure 1. Abbreviations: RFX=rifaximin, HE=hepatic encephalopathy.

Note: Subjects may have discontinued early for more than 1 reason; the primary reason is given here.

Two subjects entered RFHE3002 and were not included in safety analyses because they had no postbaseline safety data.

### **5.2.2.3. Demographics and Baseline Characteristics**

Differences between baseline characteristics between RFHE3001 subjects and RFHE3002 were related to differences in entry criteria. Subjects had  $\geq 1$  verifiable episode of HE within 12 months prior to screening for study RFHE3002 vs.  $\geq 2$  HE episodes within 6 months prior to screening for RFHE3001. Consistent with these differences, when compared with study RFHE3001, subjects in RFHE3002 had longer durations of current verified remission from HE and lower proportions of subjects with 2 or 3 verifiable HE episodes prior to study entry.

## **5.3. Supportive Efficacy Studies RFHE9702, RFHE9701, and RFHE9901 - Study Design, Demographics, and Baseline Characteristics**

### **5.3.1. Study design**

Study RFHE9702 was a double-blind, dose-ranging study in subjects with Grade 1-3 HE enrolled at 5 centers in the United Kingdom. Subjects were randomized to rifaximin at daily doses of 600 mg (200 mg TID), 1200 mg (400 mg TID), or 2400 mg (800 mg TID) for 7 days. Planned enrollment was 54 subjects (18 per group).

Study RFHE9701 was a double-blind, double-dummy, comparative, phase 3 study of rifaximin 1200 mg/day and lactitol 60 g/day for up to 10 days of treatment in hyperammonemic, cirrhotic subjects with Grade 1-3 HE enrolled at 16 centers in Spain. Planned enrollment was 120 subjects (60 per group).

Study RFHE9901 was a phase 3, international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing 14 days of rifaximin 400 mg TID to placebo in cirrhotic subjects with mild to moderate HE who were intolerant to the GI side effects of lactulose or lactitol. The study was conducted in the US, Poland, Hungary, and the United Kingdom. Planned enrollment was 112 subjects (56 per group).

#### **5.3.1.1. Primary efficacy endpoint**

Mental status (Conn score) and neuromuscular function (asterixis grade) were assessed in studies RFHE9702, RFHE9701 and RFHE9901 using the same criteria as described above for studies RFHE3001 and RFHE3002 (see Table 5 and Table 6 in Section 4.3).

Venous ammonia levels, number connection test (NCT) scores, and EEG (electroencephalogram) results were graded according to increasing severity.

**Study RFHE9702:** The primary efficacy endpoint for study RFHE9702 was the PSE index at the end of study. The PSE index was a component score that included scores for mental status (Conn score), asterixis, venous ammonia levels, NCT, and EEG.

The differences in PSE index at end of study across rifaximin 600 mg, 1200 mg, and 2400 mg daily treatment groups were evaluated by analysis of covariance.

**Study RFHE9701:** Four primary efficacy endpoints were defined:

1. Improvement in mental status (Conn score)
2. PSE index
3. Decrease in venous ammonia levels
4. Decrease in PSE index

**Study RFHE9901:** The primary efficacy endpoint was the overall response rate, defined as the proportions of subjects who showed improvement in mental status (Conn score) by at least 1 level (eg, change from Conn score 2 to Conn score 1 or 0) after completing treatment when compared to baseline.

### 5.3.1.2. Demographics and Baseline Characteristics

In study RFHE9702, mean ages were 55.2 years, 52.3 years, and 55.3 years in the 600 mg, 1200 mg, and 2400 mg groups, respectively. In study RFHE9701, mean ages were 61.6 years and 62.9 years in the rifaximin and lactitol groups, respectively. In study RFHE9901, mean ages were 53.6 years and 53.3 years in the rifaximin and placebo groups, respectively.

Demographic characteristics were generally similar across treatment groups in studies RFHE9702, RFHE9701, and RFHE9901.<sup>14, 15, 16</sup>

Table 15 presents a summary of baseline characteristics for studies RFHE9702, RFHE9701, and RFHE9901. Subjects in study RFHE9701 had more severe HE symptoms, as measured by mental status/Conn scores, asterixis grades, and PSE index, than subjects in study RFHE9901. Also, disease severity was greater in RFHE9701 compared with RFHE9702. For example, the proportions of subjects with mental status/Conn scores of  $\geq 2$  at baseline were 70% (rifaximin) and 60.3% (lactitol) in RFHE9701, 14.6% (rifaximin) and 4.4% in RFHE9901, and 16.7%, 31.6%, and 23.5% in the 600 mg, 1200 mg, and 2400 mg groups in RFHE9702. Time since diagnosis of the HE condition (ie, duration of HE) was substantially longer in the RFHE9701 than in RFHE9901 and RFHE9702 (see Table 15).

**Table 15 RFHE9702, RFHE9701, and RFHE9901: Summary of Baseline Characteristics (ITT population)**

	RFHE9702 (N=54) n (%)			RFHE9701 (N=103) n (%)		RFHE9901 (N=93) n (%)	
	Rifaximin			Rifaximin	Lactitol	Rifaximin	placebo
Category	600 mg/day	1200 mg/day	2400 mg/day	1200 mg/day	60 g/day	1200 mg/day	
<b>Duration of hepatic encephalopathy (years)</b>							
n	18	19	17	46	49	48	45
Mean (SD)	0.4 (0.9)	0.9 (2.1)	0.8 (2.9)	3.7 (4.3)	4.4 (5.0)	1.49 (1.82)	1.56 (2.20)
Min, max	0, 18	8, 19	12, 17	0.003, 15	0, 20	0, 7.3	0, 9.0
<b>Mental status/Conn score – n (%)</b>							
0	1 (5.6)	1 (5.3)	0	0	1 (1.9)	5 (10.4%)	3 (6.7%)
1	14 (77.8)	12 (63.2)	13 (76.5)	15 (30.0)	20 (37.7)	36 (75.0%)	40 (88.9%)
2	3 (16.7)	5 (26.3)	4 (23.5)	29 (58.0)	20 (37.7)	7 (14.6%)	2 (4.4%)
3	0	1 (5.3)	0	6 (12.0)	12 (22.6)	0	0
<b>Asterixis grade – n (%)</b>							
0	2 (11.1)	4 (21.1)	3 (17.7)	5 (10.2)	1 (1.9)	19 (39.6%)	22 (48.9%)
1	10 (55.6)	10 (52.6)	5 (29.4)	5 (10.2)	8 (15.4)	21 (43.6%)	18 (40.0%)
2	3 (16.7)	4 (21.1)	8 (47.1)	10 (20.4)	17 (32.7)	5 (10.4%)	5 (11.1%)
3	3 (16.7)	0	1 (5.9)	18 (36.7)	14 (26.9)	2 (4.2%)	0
4	0	1 (5.3)	0	11 (22.5)	12 (23.1)	1 (2.1%)	0

	RFHE9702 (N=54) n (%)			RFHE9701 (N=103) n (%)		RFHE9901 (N=93) n (%)	
Category	Rifaximin			Rifaximin	Lactitol	Rifaximin	placebo
	600 mg/day	1200 mg/day	2400 mg/day	1200 mg/day	60 g/day	1200 mg/day	
<b>PSE index</b>							
n	14	16	16	43	38	46	43
Mean (SD)	0.38 (0.11)	0.38 (0.14)	0.42 (0.085)	0.56 (0.13)	0.56 (0.16)	0.30 (0.14)	0.29 (0.10)
<b>Venous ammonia level (μmol/L)<sup>a</sup></b>							
n	14	16	16	50	51	48	44
Mean (SD)	77.2 (63.2)	83.2 (81.1)	106.3 (90.4)	76.3 (40.0)	87.4 (60.3)	55.2 (35.2)	49.4 (21.8)

Source: RFHE9702, RFHE9701, and RFHE9901 study reports and Integrated Summary of Efficacy (ISE) Supplemental Tables 1, 2, 4, 9-1, 9-2, and 9-3 from the ISE.

Note: Details of criteria for mental status/Conn score, asterixis grade, PSE index, and ammonia grade are presented in Sections 4.3 and 5.3.1.1.

a Venous ammonia levels were reported in μg/dL for RFHE9702, RFHE9701, and RFHE9901. For consistency with Table 12 and Table 18, ammonia values were multiplied by 0.58 to convert from μg/dL to μmol/L.

## 6. Clinical Efficacy

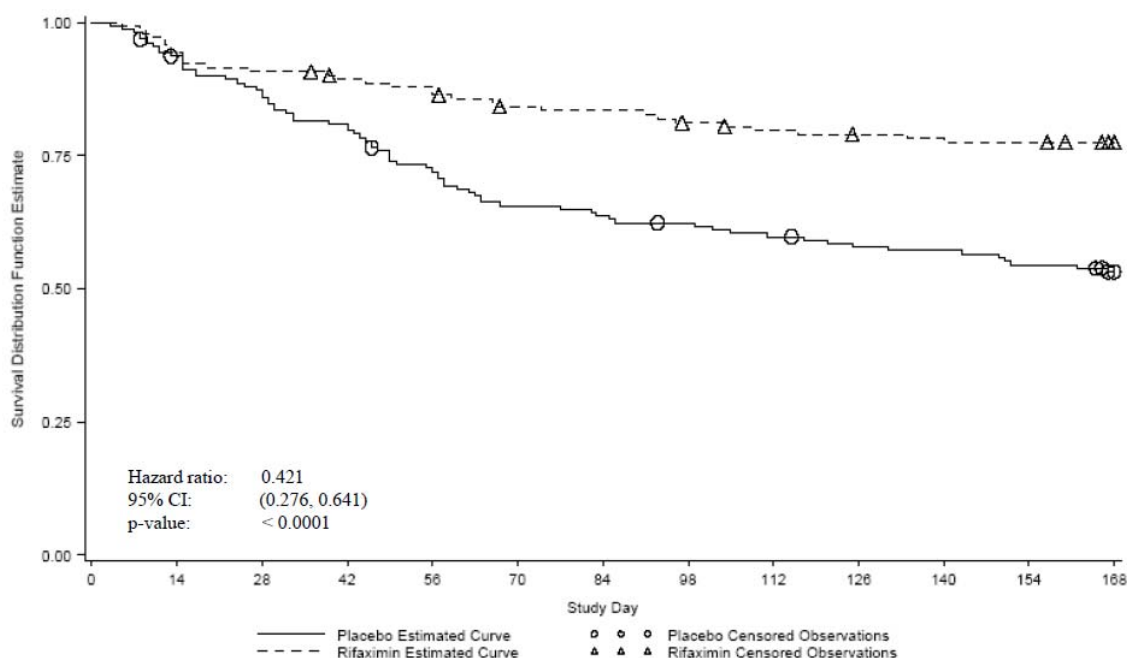
The primary evidence for the efficacy of rifaximin in the maintenance of remission of HE is based on highly clinically relevant and statistically significant results in favor of rifaximin in placebo-controlled phase 3 study RFHE3001 and additional efficacy data from the open-label phase 3 study RFHE3002.

### 6.1. RFHE3001 Primary Efficacy Analyses

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

Rifaximin treatment resulted in a 58% reduction, when compared with placebo, in the risk of experiencing breakthrough overt HE during the course of this study ( $p < 0.0001$ ) (Figure 6). 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 to 0.641) during the 6-month treatment period. Breakthrough overt HE episodes were experienced by 31 of 140 subjects (22%) in the rifaximin group and by 73 of 159 subjects (46%) in the placebo group during the 6-month period since randomization (up to Day 170).

**Figure 6 RFHE3001: Time to First Breakthrough Overt HE Episode (ITT Population)**



Source: RFHE3001 study report.

Note: Survival distribution estimate on y-axis represents the proportion of subjects without breakthrough overt HE. 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.



### 6.1.1. Treatment Effect Adjusted for Prognostic Factors by Covariate Analyses

Rifaximin treatment, after adjusting for significant prognostic factors, resulted in a 60% reduction in the risk of experiencing a breakthrough overt HE episode during the course of this study, when compared with placebo. The results indicate that rifaximin significantly prevented breakthrough overt HE episodes when compared with placebo ( $p < 0.0001$ ) in the presence of statistically significant competing factors.

To investigate the potential effect of prognostic factors on breakthrough overt HE episode, a log rank test stratified on each covariate was performed. The following prognostic factors were examined:

- Sex (male vs. female)
- Age
- Race (white vs. non-white)
- Analysis Region (North America vs. Russia)
- MELD United Network for Organ Sharing (UNOS) category
- Conn Score (0 vs. 1)
- Diabetes at Baseline (Yes vs. No)
- Duration of current verified remission
- Number of HE Episodes within the past 6 months prior to randomization

Strong independent predictors of breakthrough overt HE episodes were the baseline age ( $p = 0.0160$ ), MELD UNOS category ( $p = 0.0003$ ), duration of current verified remission ( $p = 0.1089$ ), and number of prior HE episodes ( $p = 0.0022$ ). Using these significant factors together with treatment group in a Cox proportional hazards model, a hazard ratio (rifaximin to placebo) of 0.403 (95% CI: 0.264 to 0.617) ( $p < 0.0001$ ) was noted.

### 6.1.2. Components of the Primary Endpoint

Although the study was not powered for between-group differences in the individual components of the definition of breakthrough overt HE, component results shown in the table below support overall results for time to breakthrough overt HE.

**Table 16 RFHE3001: Components of the Primary Efficacy Endpoint**

Breakthrough Criteria	Placebo N = 159 n (%)	Rifaximin N = 140 n (%)	Hazard ratios (95% CI)	p-value <sup>a</sup>
Overall Breakthrough Overt HE	73 (45.9%)	31 (22.1%)	0.421 (0.276,0.641)	<0.0001 <sup>a</sup>
Conn Score $\geq 2$	58 (36.5%)	28 (20.0%)		0.0019 <sup>b</sup>
Concurrent Increase in Conn and Asterixis Grade of 1 each from Baseline if Baseline Conn Score=0	15 (9.4%)	3 (2.1%)		0.0088 <sup>b</sup>

Source: ADC Table 1.2; Abbreviations: BID = twice daily; CI=confidence interval.

<sup>a</sup> Hazard ratio estimate (hazard of breakthrough overt HE for rifaximin compared to placebo) obtained from Cox proportional hazards model with effect for treatment and stratified by analysis region. P-value based on the Score statistic.

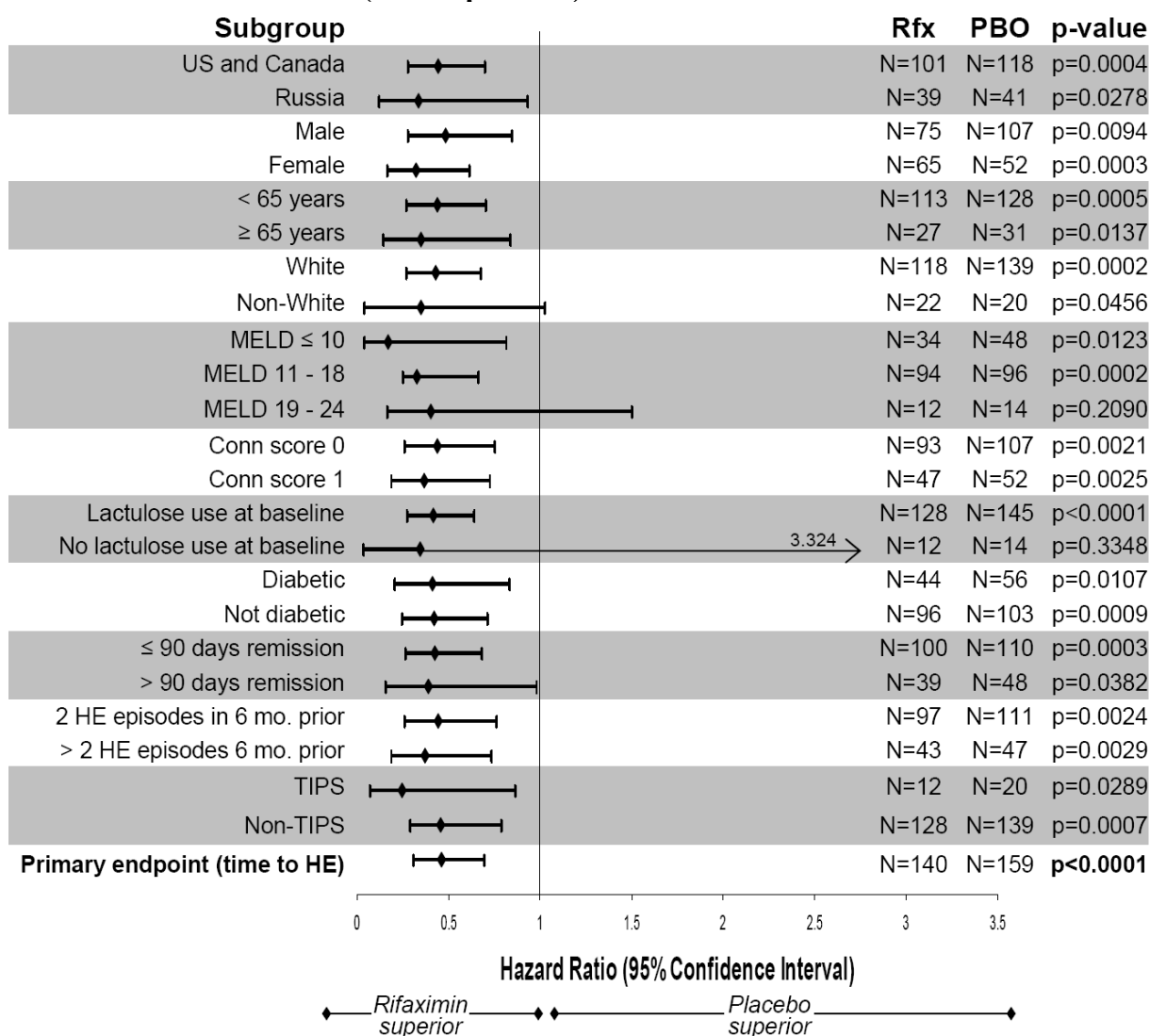
<sup>b</sup> P-value was calculated using Cochran-Mantel-Haenszel Test, adjusted by analysis region.

### 6.1.3. RFHE3001: Subgroup Analyses for Time to Breakthrough Overt HE

Rifaximin treatment reduced the risk of experiencing breakthrough overt HE episodes in a consistent manner across all subgroups examined, supporting the generalizability of the primary efficacy endpoint results.

Hazard ratios for the risk of experiencing breakthrough overt HE in the rifaximin group relative to the placebo group (primary efficacy endpoint), 95% CIs, and p-values from the Cox proportional hazards model are presented in Figure 7 below. Hazard ratios of less than 1 indicate that the outcome favors rifaximin and greater than 1 favors placebo.

**Figure 7 Time to First Breakthrough Overt HE Episode by Subgroup During the Treatment Period (ITT Population)**



Source: RFHE3001 study report.

Note: This figure shows hazard ratios for the risk of experiencing breakthrough overt HE (rifaximin group divided by placebo group) for each subgroup. Hazard ratio, 95% CI determined from time to breakthrough overt HE analysis using Cox proportional hazards model with effect for treatment and stratified by analysis region. P-value determined from the Score statistic.

### 6.1.3.1. Analysis by Child-Pugh Class

The FDA Division of Gastroenterology Products requested subgroup analysis of the primary endpoint by Child-Pugh class.

Rifaximin treatment resulted in significant reductions in the risk of experiencing breakthrough overt HE episode when compared to placebo, across Child-Pugh A, B, or C classes. A statistically significant rifaximin treatment effect in reducing the risk of experiencing breakthrough overt HE was observed in Child-Pugh A (5-6), B (7-9), and C (10-15) classifications.

Time to first breakthrough overt HE episode results across Child-Pugh classifications at baseline are presented in Table 17. The Child-Pugh subscores, total scores and classifications were obtained post study.

**Table 17 RFHE3001: Breakthrough Overt HE Episodes by Child-Pugh Class**

Classification (score)	Placebo N = 159 n (%)	Rifaximin N = 140 n (%)	Hazard ratios (95% CI) <sup>a</sup>	p-value <sup>a</sup>
Child-Pugh A (5-6), n	56	46		
Breakthrough overt HE, n (%)	26 (46.4)	8 (17.4)	0.339 (0.153, 0.749)	0.0050
No breakthrough overt HE, n (%)	30 (53.6)	38 (82.6)		
Child-Pugh B (7-9), n	72	65		
Breakthrough overt HE, n (%)	32 (44.4)	15 (23.1)	0.442 (0.239, 0.816)	0.0073
No breakthrough overt HE, n (%)	40 (55.6)	50 (76.9)		
Child-Pugh C (10-15), n	14	17		
Breakthrough overt HE, n (%)	9 (64.3)	5 (29.4)	0.345 (0.115, 1.037)	0.0474
No breakthrough overt HE, n (%)	5 (35.7)	12 (70.6)		
Missing, n	17	12		
Breakthrough overt HE, n (%)	6 (35)	3 (25)		
No breakthrough overt HE, n (%)	11 (65)	9 (75)		

Source: Table 2 - analysis by Child-Pugh class (18 Dec 2009 submission to FDA); Abbreviations: BID = twice daily; CI=confidence interval.

<sup>a</sup> Hazard ratio, 95% CI determined from time to breakthrough overt HE analysis using Cox proportional hazards model with effect for treatment and stratified by analysis region. P-value determined from Log Rank test stratified by analysis region.

## 6.2. Secondary Efficacy Analyses (RFHE3001)

### 6.2.1. Time to Hospitalization

#### 6.2.1.1. Time to HE-Related Hospitalization (key secondary efficacy endpoint)

Rifaximin treatment resulted in a 50% reduction, when compared with placebo, in the risk of HE-related hospitalization (ie, hospitalization directly resulting from HE or HE events occurring during hospitalization) during the 6-month treatment period (hazard ratio=0.500, 95% CI: 0.287 to 0.873, p=0.0129) (see Figure 8). Hepatic encephalopathy-related hospitalizations were reported for 19 of 140 subjects and 36 of 159 subjects in the rifaximin and placebo groups, respectively. After normalization to exposure, the HE-related hospitalization rate was 51% lower (0.38 event/person exposure year [PEY], rifaximin vs. 0.78 event/PEY, placebo) in the rifaximin group.

The figure is a Kaplan-Meier survival plot comparing the survival distribution function estimate over time (Study Day) for two treatment groups: Placebo and Ritaximin. The y-axis represents the Survival Distribution Function Estimate, ranging from 0.00 to 1.00. The x-axis represents Study Day, ranging from 0 to 168.

**Legend:**

- Solid line: Placebo Estimated Curve
- Dashed line: Ritaximin Estimated Curve
- Open squares: Placebo Censored Observations
- Open triangles: Ritaximin Censored Observations

**Hazard Ratio:** 0.500  
**95% CI:** (0.287, 0.873)  
**p-value:** 0.0129

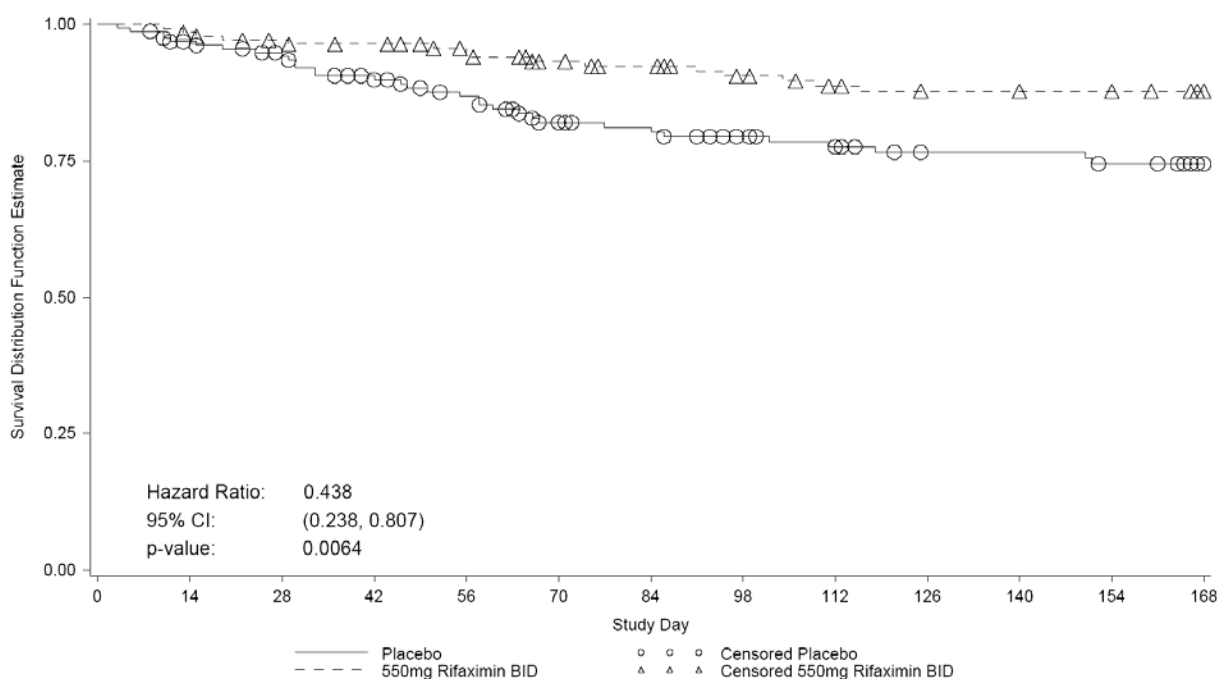
The plot shows that the Ritaximin group has a significantly higher survival probability compared to the Placebo group throughout the study period. The Ritaximin curve starts at 1.00 and remains relatively stable until around day 112, after which it begins to decline, reaching approximately 0.85 by day 168. The Placebo curve starts at 1.00 and declines more rapidly, reaching approximately 0.75 by day 168.

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.

- *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. The risk of breakthrough HE hospitalization was reduced by 51% in the rifaximin group when compared with placebo (p = 0.0225 for between-group difference in relative risk).

Subjects in the rifaximin group had a 56% reduction in the risk of HE-caused hospitalization (ie, hospitalization directly resulting from HE only) during the 6-month treatment period when compared with placebo (hazard ratio=0.438, 95% CI: 0.238 to 0.807, p = 0.0064) (Figure 9). HE-caused hospitalizations were reported for 15 of 140 subjects and 33 of 159 subjects in the rifaximin and placebo groups, respectively. The HE-caused hospitalization rate was 0.30 events/PEY in the rifaximin group vs. 0.72 event/PEY in the placebo group.

**Figure 9 Study RFHE3001: Time to First HE-Caused Hospitalization (ITT Population)**



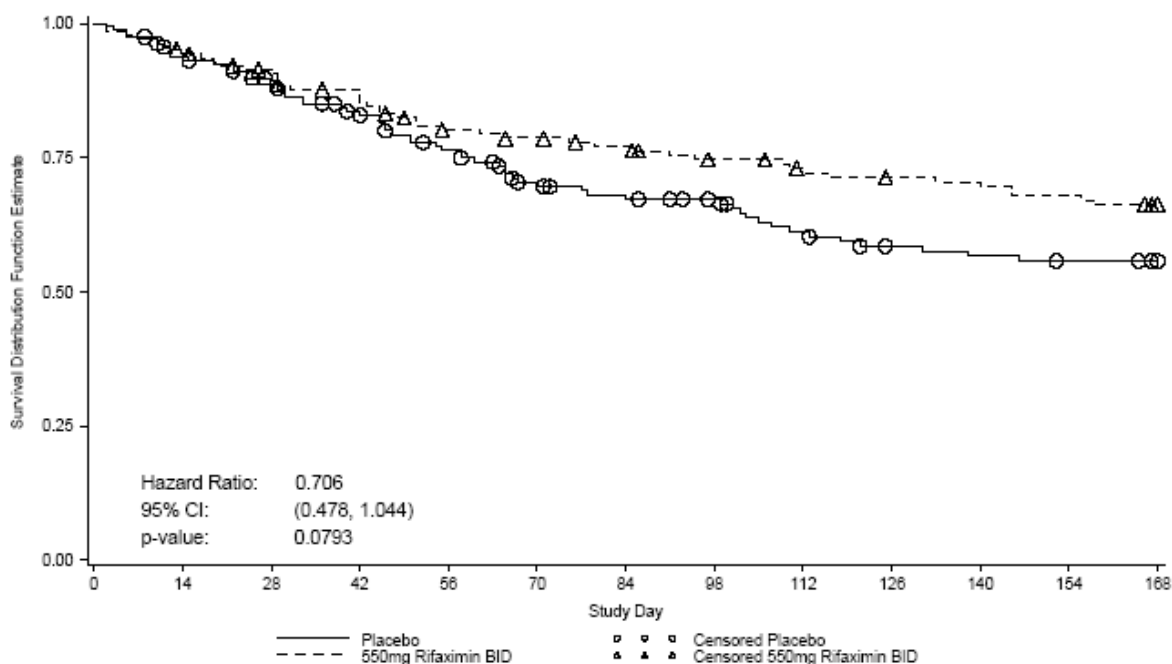
Source: Table 2.1 and Figure 2.1 from the ISE.

Note: Survival distribution estimate on y-axis represents the proportion of subjects without HE-caused hospitalizations. Open circles and open triangles represent censored subjects. Subjects who discontinued prior to hospitalization were censored at the time of discontinuation.

### 6.2.1.3. All-Cause Hospitalization

The risk of all-cause hospitalization was 30% lower in the rifaximin group when compared to placebo ( $p = 0.0793$  for between-group difference in relative risk) (Figure 10). Forty-six of 140 rifaximin subjects and 60 of 159 placebo subjects were hospitalized due to any SAE. The all-cause hospitalization rate was 0.92 events/PEY in the rifaximin group vs. 1.31 event/PEY in the placebo group.

**Figure 10 Study RFHE3001: Time to First All-Cause Hospitalization (Safety Population)**



Source: ISE Figure 2.2.

Note: Survival distribution estimate on y-axis represents the proportion of subjects without all-cause hospitalization.

Open circles and open triangles represent censored subjects. Subjects who discontinued prior to hospitalization were censored at the time of discontinuation.

### 6.2.2. RFHE3001: Time to Any Increase from Baseline in Conn Score

Rifaximin treatment resulted in a 54% reduction, when compared with placebo, in the risk of experiencing an increase in Conn score (ie, worsening in mental status) during the course of this study; hazard ratio in the rifaximin group relative to placebo was 0.463 (95% CI: 0.312 to 0.685) ( $p < 0.0001$ ) (Figure 11). Increases in Conn score from baseline were reported for 37 of 140 subjects and 77 of 159 subjects in the rifaximin and placebo groups, respectively.

**Survival Distribution Function Estimate**

**Hazard Ratio:** 0.463  
**95% CI:** (0.312, 0.685)  
**p-value:** <.0001

**Study Day**

— Placebo Estimated Curve  
 - - - Rifaximin Estimated Curve  
 ○ ○ ○ Placebo Censored Observations  
 ▲ ▲ ▲ Rifaximin Censored Observations

Note: Survival distribution estimate on y-axis represents the proportion of subjects without any increase in Conn score. 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.

Rifaximin treatment resulted in a 35% reduction, when compared with placebo, in the risk of experiencing an increase in asterixis grade (ie, worsening in neuromuscular functioning) during the course of this study; hazard ratio in the rifaximin group relative to placebo was 0.646 (95% CI: 0.414 to 1.008) (p = 0.0523) (Figure 12). Increases in asterixis grade were reported for 32 of 140 rifaximin subjects and 50 of 159 placebo subjects.

Survival Distribution Function Estimate

Hazard Ratio: 0.646  
95% CI: (0.414, 1.008)  
p-value: 0.0523

Study Day

— Placebo Estimated Curve  
- - - Rifaximin Estimated Curve  
○ ○ ○ Placebo Censored Observations  
△ △ △ Rifaximin Censored Observations

Note: Survival distribution estimate on y-axis represents the proportion of subjects without any increase in asterixis grade. Dashed line represents rifaximin group and solid line represents placebo group. 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.

Results for changes from baseline in venous ammonia levels (a quantitative assessment associated with the CNS effects underlying HE) and CFF (a quantitative measure of CNS function) results show a positive rifaximin treatment effect, consistent with the primary efficacy endpoint.

Subjects in the rifaximin group had significantly greater reductions in venous ammonia levels when compared to placebo-treated subjects ( $p = 0.0391$ ) (Table 18). Also subjects in the rifaximin group had significantly greater increases in CFF results from baseline to end of treatment, indicating improvement in their CNS function, when compared with placebo ( $p=0.032$ ) (Table 18).



**Table 18 RFHE3001: Changes from Baseline in Venous Ammonia Levels and CFF Results (ITT population)**

Changes from baseline	Rifaximin n = 140	Placebo n = 159	p-value
Ammonia concentration, µg/dL	n = 125	n = 133	
Mean	-5.7	-1.2	0.0391
Min - max	-156 - 236	-334 - 189	
Critical flicker frequency test, Hz	n = 139	n = 155	
Mean	0.945	0.355	0.0320
Min - max	-13.88 - 11.30	-12.43 - 15.84	

Source: RFHE3001 study report.

#### 6.2.4.1. Association between Breakthrough Overt HE Episodes, CFF Results, and Venous Ammonia Levels

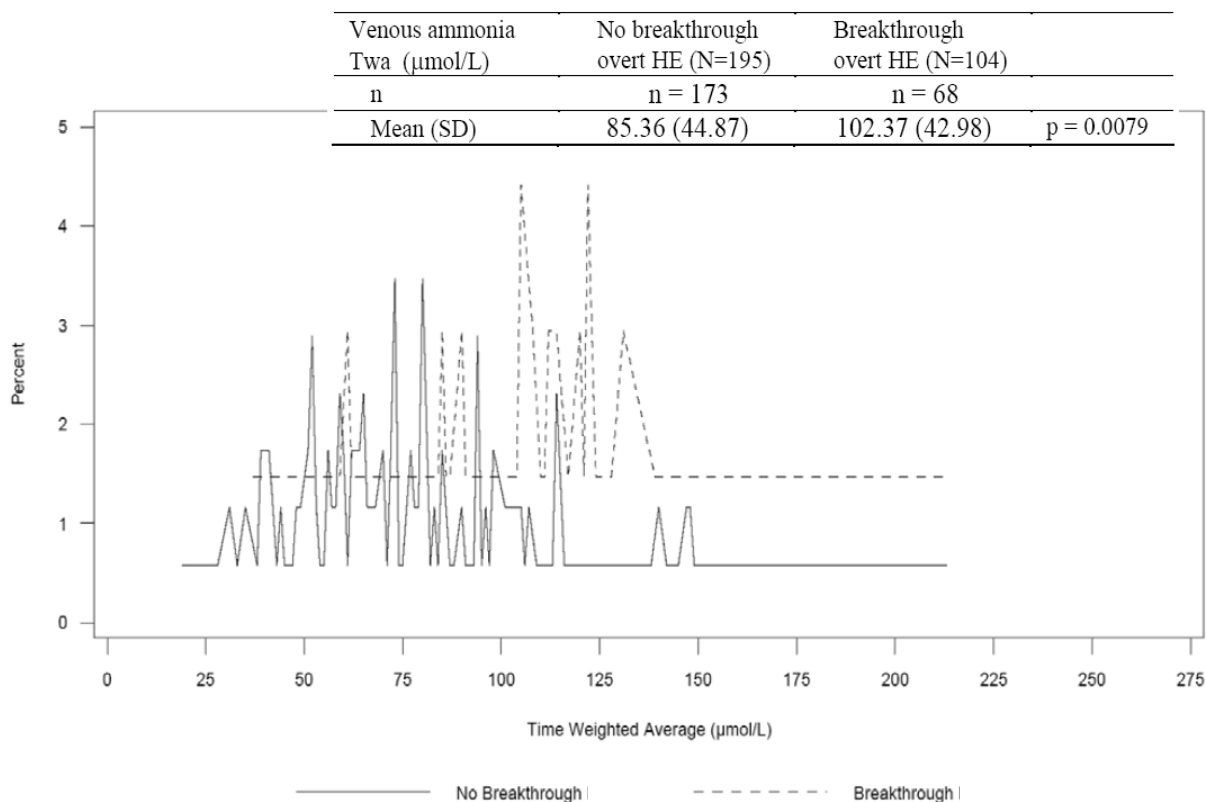
Venous ammonia levels and CFF results were shown to be highly predictive of breakthrough overt HE. The fact that these quantitative measures discriminate the presence or absence of a breakthrough overt HE episode in a highly statistically significant manner attests to the reliability and clinical relevance of the primary efficacy endpoint.

The quantitative results for ammonia levels and CFF were tested for correlation to the occurrence of breakthrough overt HE episode (primary efficacy endpoint).

Venous ammonia levels, expressed as time weighted average ( $T_{wa}$ , that is, AUC of venous ammonia levels over the course of the study normalized by exposure time), were shown to be predictive of breakthrough overt HE episodes as defined by the primary endpoint (Figure 13). Significantly higher venous ammonia levels were found in subjects with breakthrough overt HE (mean=102.4 µmol/L), and this group of subjects separated from subjects without breakthrough overt HE (mean = 85.4 µmol/L) at a high level of significance ( $p = 0.0079$ ). Time-weighted average correlated with presence or absence of breakthrough overt HE episode (Spearman correlation coefficient of 0.22,  $p = 0.0005$ ). The receiver operating characteristic (ROC) curves for sensitivity and specificity of venous ammonia levels in the diagnosis of breakthrough overt HE episodes as defined by the primary endpoint showed an area under the curve value of 0.64 (95% CI 0.57-0.72). Values close to 1 are considered diagnostically excellent.

Similar to the correlation for venous ammonia levels, there was a strong correlation between CFF results and the occurrence of breakthrough overt HE episodes. Figure 14 shows that the difference between the frequency distributions of  $T_{wa}$  corresponding to the presence (mean=12.5 Hz) and absence of breakthrough overt HE events (mean = 32.7 Hz) was statistically significant ( $p < 0.0001$ ). The mean  $T_{wa}$  correlated with presence or absence of breakthrough overt HE episodes (Spearman correlation coefficient = -0.62;  $p < 0.0001$ ). The ROC curve analysis of  $T_{wa}$  for the diagnosis of breakthrough overt HE by CFF showed an area under the curve value of 0.88 (95% CI 0.84-0.92).

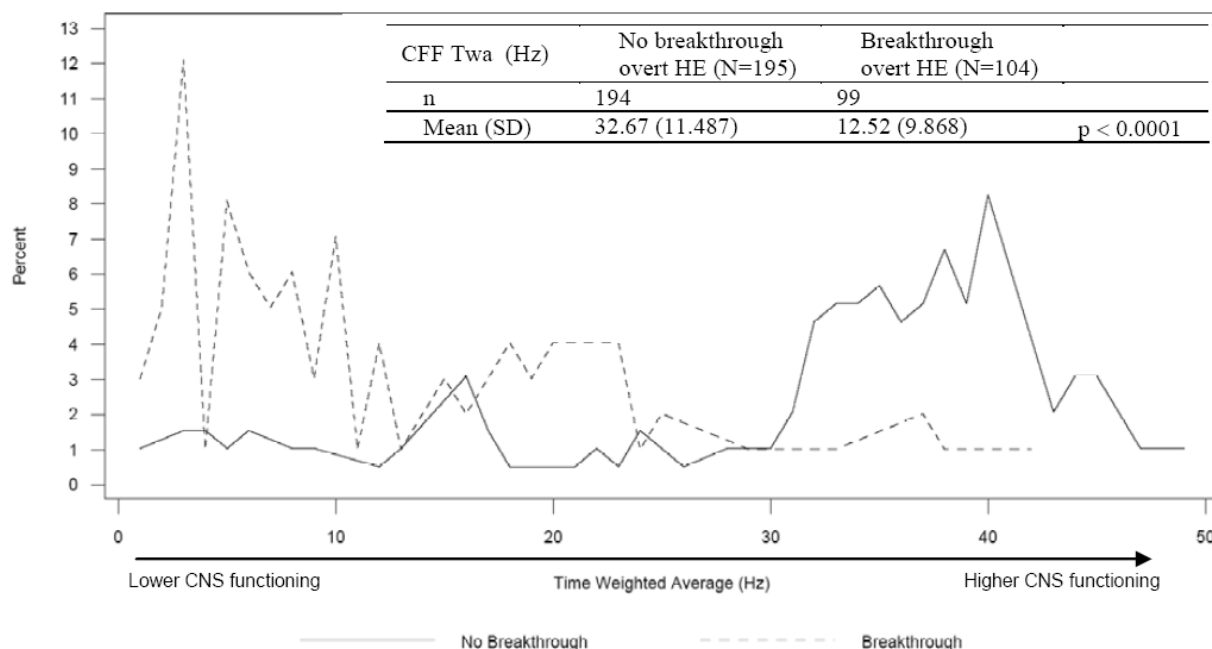
**Figure 13 Distribution and Comparison of T<sub>wa</sub> Ammonia Results by Breakthrough Overt HE Status (ITT Population)**



Source: ISE Figure 3.3 and Table 4.3.

Notes: p-value from analysis of covariance (ANCOVA) model with effects for treatment and analysis region as covariates. Spearman's correlation for T<sub>wa</sub> to presence or absence of breakthrough overt HE equals 0.22; p = 0.0005.

**Figure 14 Distribution and Comparison of T<sub>wa</sub> CFF Results by Breakthrough Overt HE Status (ITT Population)**



Source: ISE Figure 4.3 and Table 5.1.

Notes: p-value from ANCOVA model with effects for treatment and analysis region as covariates.

Spearman's correlation for Twa to presence or absence of breakthrough overt HE equals -0.62; p < 0.0001

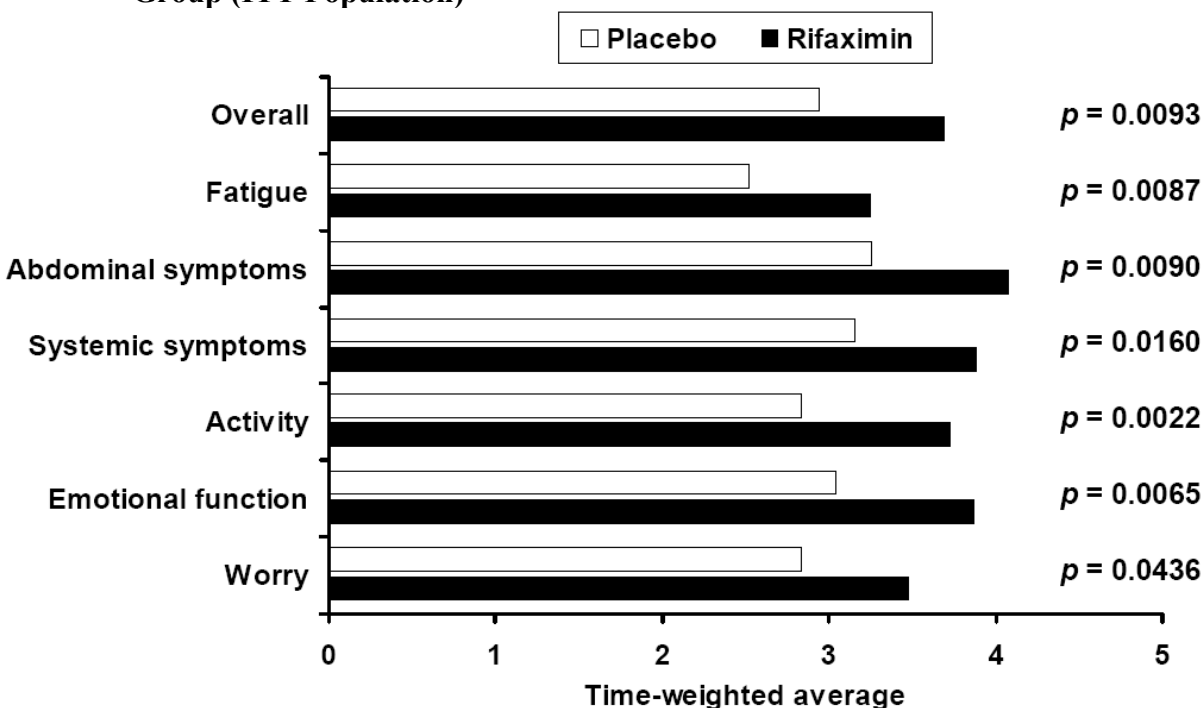
#### 6.2.5. Changes from baseline in CLDQ fatigue domain scores at end of treatment (RFHE3001)

Health related quality of life assessments were performed through the use of the validated CLDQ for subjects with advanced liver disease.<sup>33</sup>

Traditionally, CLDQ analyses are performed by comparing the changes from baseline to the last assessment in CLDQ overall and domain scores between the 2 treatment groups. However, in this study using a simple change from baseline analysis has the following limitations. Firstly, the questionnaire measures the subject's quality of life status over the 2 weeks prior to completing the questionnaire. By comparing results in the 2 weeks prior to last assessment to the 2 weeks prior to baseline (change from baseline analysis), changes over the entire course of the study are not captured in the analysis. Secondly, most subjects in the study also had comorbidities associated with advanced liver disease that can potentially skew results, depending on the timing of complication, and if it occurred at or near the first or last assessment. Finally, subjects who experienced a breakthrough overt HE episode were withdrawn from the study per protocol, and completed the last CLDQ assessment during the end of study visit, which often occurred after the resolution of the HE event. Therefore, for these subjects, the CLDQ results may have been similar to baseline levels. To address these limitations an AUC analysis using a T<sub>wa</sub> (AUC adjusted for exposure time in study) was performed since it allows for inclusion of CLDQ results over the subject's complete time of participation in the study especially prior to breakthrough overt HE episode (if applicable).

When CLDQ results were analyzed using the  $T_{wa}$ , subjects in the rifaximin group had significantly less fatigue and significantly greater overall quality of life than subjects in the placebo group (Figure 15). Chronic Liver Disease Questionnaire results in favor of the rifaximin group were also observed for the overall CLDQ domain score ( $p = 0.0093$ ), and for each of the other component domains of the CLDQ, including abdominal symptoms ( $p = 0.0090$ ), systemic symptoms ( $p = 0.0160$ ), activity ( $p = 0.0022$ ), emotional function ( $p = 0.0065$ ), and worry ( $p = 0.0436$ ).

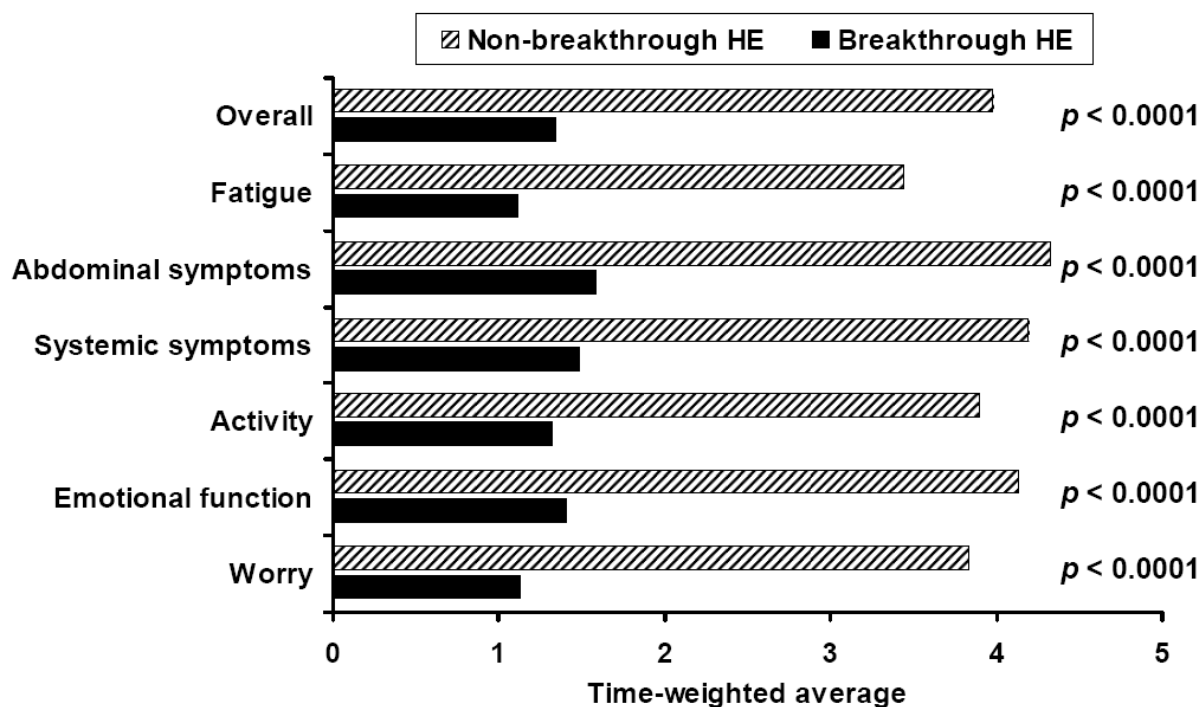
**Figure 15: RFHE3001: CLDQ Overall and Individual Domain  $T_{wa}$  Results by Treatment Group (ITT Population)**



Source: Table 2.2 (Efficacy Supplement - 24 Nov 2009 submission to FDA)

The CLDQ results were shown to be predictive of breakthrough overt HE episodes as defined by the primary endpoint (Figure 16). There were significant differences in frequency distributions of  $T_{wa}$  (AUC normalized by exposure time) for all domains of the CLDQ between subjects who had breakthrough overt HE and subjects without breakthrough overt HE (Figure 16). The mean  $T_{wa}$  for each domain and overall correlated with presence or absence of a breakthrough overt HE episode.

**Figure 16: RFHE3001: CLDQ Overall and Individual Domain T<sub>wa</sub> Results by Breakthrough Overt HE Status (ITT Population)**



Source: Table 2.3 (Efficacy Supplement - 24 Nov 2009 submission to FDA)

These findings demonstrate the clinical significance and personal impact on quality of life associated with the prevention of breakthrough overt HE in patients with advanced liver disease. The data also suggest that prevention of breakthrough overt HE is critical in patients with advanced liver disease, and would positively impact their quality of life.

### 6.3. Long-Term Efficacy (RFHE3001 and RFHE3002)

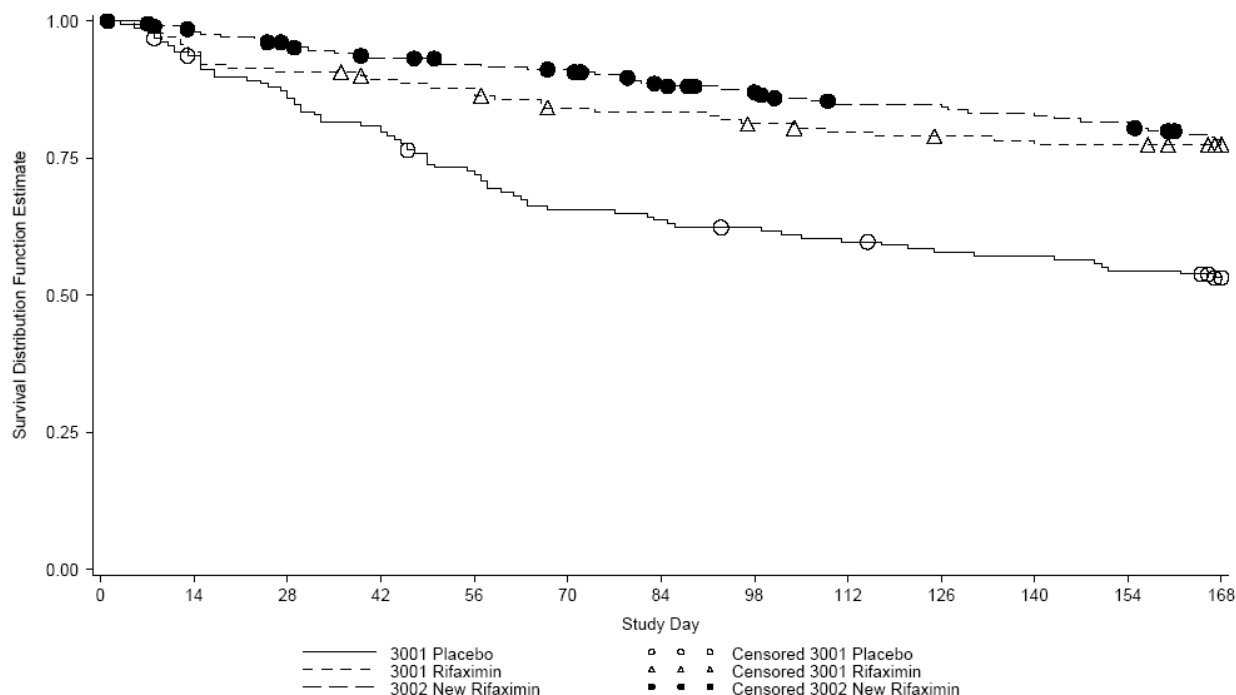
Although RFHE3002 was primarily designed to evaluate the long-term safety of rifaximin 550 mg additional efficacy assessments of Conn score and asterixis grade were collected at each visit and at the time of breakthrough overt HE. Kaplan Meier analyses of time to first breakthrough overt HE episode demonstrated consistency, durability, and repeatability of the protective effect of rifaximin compared with placebo as noted in RFHE3001.

#### 6.3.1. Time to First Breakthrough Overt HE in RFHE3002 - Consistency with RFHE3001 Results

Time to first breakthrough overt HE episode was similar between the rifaximin group in study RFHE3001 (rifaximin PEY=53) and new rifaximin subjects in RFHE3002 (rifaximin PEY=80) ( $p=0.3487$  for difference in relative risk) (Figure 17). Also, similar proportions of subjects had breakthrough overt HE episodes in the rifaximin group of RFHE3001 (22%, 31 of 140 [rifaximin group]) and in the new rifaximin group of RFHE3002 (20.5%, 43 of 210). Adjusted for exposure, rates of breakthrough overt HE episodes were 0.62 events/PEY in the rifaximin group from RFHE3001 compared to 0.5 events/PEY for new rifaximin subjects in RFHE3002.

These data demonstrate that protection against breakthrough overt HE in subjects who received rifaximin was consistent between the 2 studies.

**Figure 17: Comparison of Time to First Breakthrough Overt HE Episode in Study RFHE3001 (rifaximin vs. placebo groups) and in Study RFHE3002 (new to rifaximin group)**



Source: Figure 1.4 and Table 1.3. The figure above was submitted in the efficacy amendment (24 Nov 2009) and is updated from the figure in the original NDA.

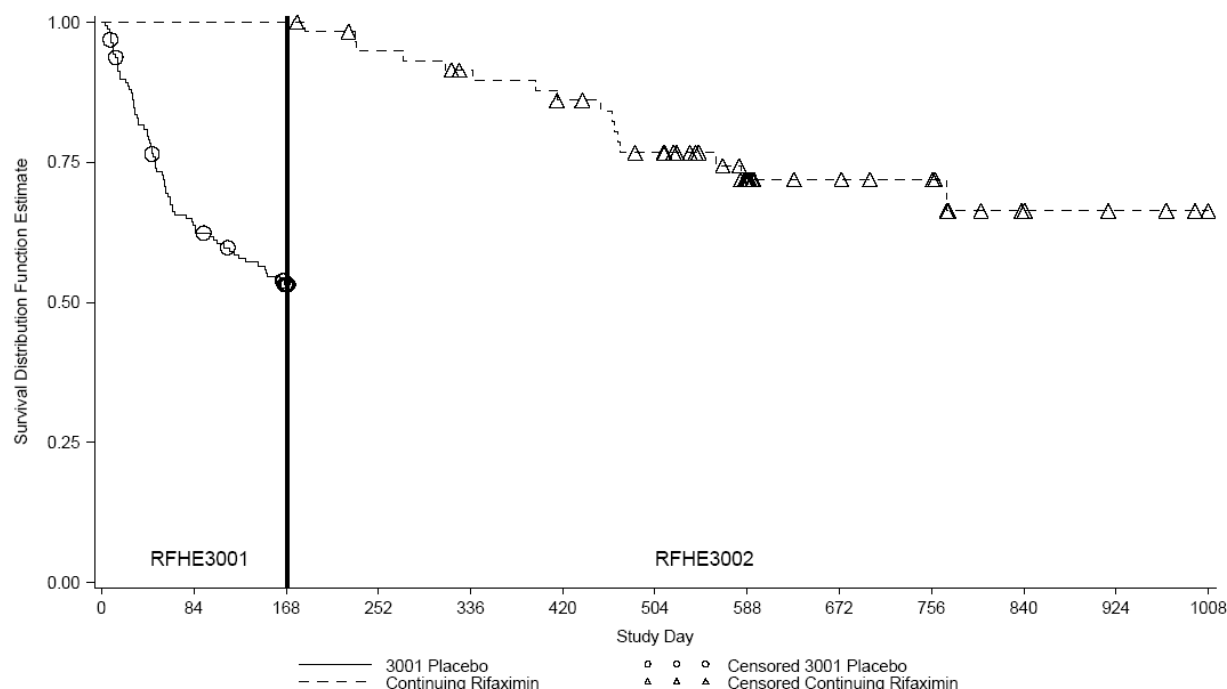
Notes: Survival distribution estimate on y-axis represents the proportion of subjects without breakthrough overt HE.

### 6.3.2. Durability of Rifaximin Treatment Effect in Subjects Who Received Rifaximin in RFHE3001 and RFHE3002

Rifaximin treated subjects from RFHE3001 who were in remission at the end of RFHE3001 (6 months treatment) and enrolled into RFHE3002 were followed during open-label study (n=60, rifaximin PEY=95). Time to first breakthrough overt HE episode is shown for these continuing rifaximin subjects and RFHE3001 placebo subjects in Figure 18.

The risk of time to first breakthrough overt HE episode for rifaximin subjects was lower than the RFHE3001 placebo group despite > 2-fold longer exposure in the continuing rifaximin group (hazard ratio of continuing rifaximin to placebo was 0.1110 [95% CI= 0.0655 - 0.1882] after adjusting for exposure time,  $p < 0.0001$  for difference between rifaximin and placebo). Person exposure years in the continuing rifaximin group was 95 vs. 45 in the RFHE3001 placebo group. Adjusted for exposure, rates of breakthrough overt HE episodes were 0.2 events/PEY in the continuing rifaximin group (n=60) vs. 1.6 events/PEY in the RFHE3001 placebo group. Of note, 43 of the 60 subjects in the continuing rifaximin group had not experienced breakthrough overt HE during rifaximin treatment in RFHE3001 and RFHE3002 at the time of interim analysis, including up to 1008 days of exposure (average exposure ~ 630 days).

**Figure 18 Kaplan Meier Estimates of Distribution of Time to First Breakthrough Overt HE for Continuing Rifaximin Subjects Who Did Not Have an HE Episode in RFHE3001 vs Placebo**



Source: Figure 1.2 and Table 1.4. The figure above was submitted in the efficacy amendment (24 Nov 2009) and is updated from the figure in the original NDA.

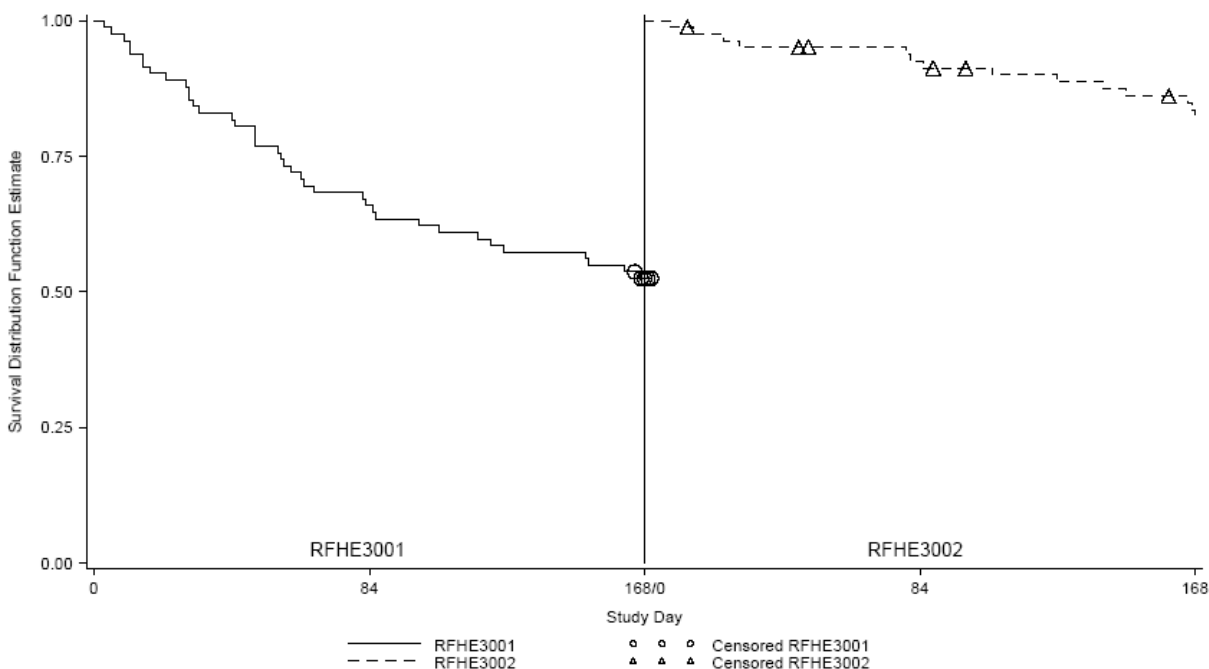
Note: Survival distribution estimate on y-axis represents the proportion of subjects without breakthrough overt HE. The vertical line marks the end of the double-blind study and start of the open-label study. Open circles represent censored subjects in the RFHE3001 placebo group and open triangles represent censored subjects in the continuing rifaximin group. Subjects who discontinued prior to the first breakthrough overt HE episode were censored at the time of discontinuation.

### **6.3.3. Time to Breakthrough Overt HE Episode in Placebo Subjects in RFHE3001 Who Crossed Over to Rifaximin Therapy in RFHE3002**

Placebo treated subjects from RFHE3001 who crossed over into RFHE3002 were followed during open-label study (n=82). The comparison of Kaplan Meier estimates of time to first breakthrough overt HE episode between the placebo experience in RFHE3001 and during the first 6 months of rifaximin treatment in RFHE3002 is shown in Figure 19. The ratio of the incidence of breakthrough overt HE episode for rifaximin treatment relative to placebo treatment was 0.2112 (95% CI: 0.1006 to 0.4432,  $p < 0.0001$  for between group difference in relative risk). This result represents a 79% reduction in the risk of experiencing breakthrough overt HE during rifaximin treatment in RFHE3002 when compared with their prior placebo experience in RFHE3001. Breakthrough overt HE was experienced by 14 of 82 during 6 months of rifaximin treatment in RFHE3002 vs. 39 of 82 during placebo treatment in RFHE3001. Rates of breakthrough HE episodes were 1.5 events/PEY during placebo experience in RFHE3001 and 0.4 events/PEY during rifaximin experience in RFHE3002.

Collectively these results demonstrate that the placebo crossover subjects in RFHE3002 experienced a similar protective effect against breakthrough overt HE episodes compared with rifaximin-treated subjects in RFHE3001 and the continuing rifaximin group in RFHE3002.

**Figure 19: Kaplan-Meier Estimates of Time to First Breakthrough Overt HE Episode: Placebo Experience in RFHE3001 vs. Rifaximin Experience in RFHE3002 for Placebo Crossover Subjects up to 6 Months of Treatment**



Source: Figure 1.3 and Table 1.3. The figure above was submitted in the efficacy amendment (24 Nov 2009) and is updated from the figure in the original NDA.

Notes: Survival distribution estimate on y-axis represents the proportion of subjects without breakthrough overt HE. RFHE3001 data on time to first breakthrough overt HE episode are shown in the left panel for the placebo group. The right panel shows time to first breakthrough overt HE in RFHE3002 among RFHE3001 placebo subjects (n=82) who crossed over to rifaximin therapy in RFHE3002. The vertical line between the left and right panels marks the end of the double-blind study and start of the open-label study.

#### 6.4. Supportive Studies of Short-Term Treatment in Subjects with Acute HE (RFHE9702, RFHE9701, and RFHE9901)

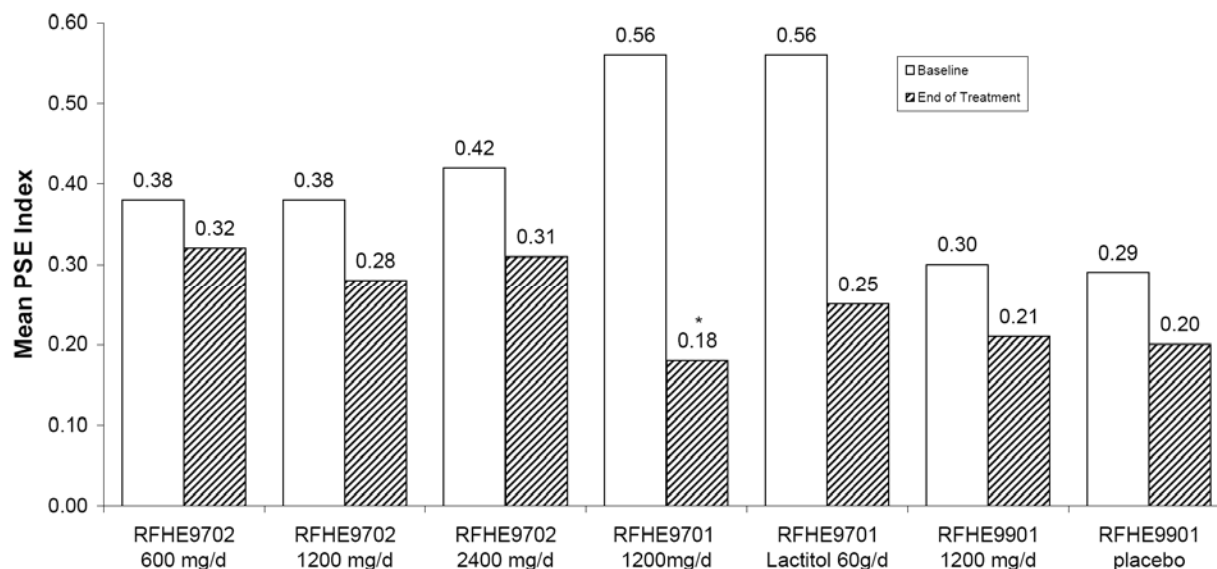
##### 6.4.1. PSE Index during Short-Term Treatment

Improvements (ie, decreases) in PSE index were observed in all treatment groups from baseline to end of treatment in the dose-ranging study, RFHE9702. Mean changes from baseline in PSE index at end of treatment was -6.4%, -10.3%, and -10.7% in the 600 mg, 1200 mg, and 2400 mg rifaximin daily dose groups, respectively. In study RFHE9701, which compared rifaximin 1200 mg daily to lactitol, there was a significant reduction in PSE index in the rifaximin group when compared with lactitol group ( $p = 0.0103$ ). Also in study RFHE9701, the PSE efficacy index showed significant improvements in the rifaximin group compared to the lactitol group ( $p = 0.0083$ ). Changes in PSE index were similar between rifaximin and placebo groups in study RFHE9901.



Figure 20 illustrates PSE index results at baseline and at end of studies RFHE9702, RFHE9701, and RFHE9901.

**Figure 20 Mean PSE Values at Baseline and at End-of-Treatment in Studies RFHE9702, RFHE9701, and RFHE9901**



#### 6.4.2. Improvements in Conn Score during Short-Term Treatment

In study RFHE9702 (dose-ranging study), there was evidence of a statistical trend showing greater proportions of subjects who had improvements in mental status (Conn score) in the 1200 mg group when compared with the 600 mg group ( $p = 0.099$  by using the proportional odds model). Additionally, at the 2400 mg daily dose, a higher proportion of subjects had improvements in Conn score when compared to the 600 mg daily dose (31.3% vs. 26.7% had Conn score changes of -1 or -2).

Improvements in mental status (Conn score), were not notably different between rifaximin and lactitol groups in RFHE9701; however, 3 of the RFHE9701 primary efficacy endpoints: decrease in PSE index, improvement in PSE efficacy index, and decrease in venous ammonia levels, showed significant, favorable effects of rifaximin. The absence of a significant rifaximin effect in improvements in Conn score in RFHE9701 may have been due to the short duration of study drug therapy (10 days).

In RFHE9901, the lack of a rifaximin effect on improvements in Conn score may have been due to short duration of therapy in this study (15 days) and the mild HE symptoms at baseline. Subjects in study RFHE9901 had mild HE symptoms, as measured by mental status/Conn scores, asterixis grades, and PSE index, when compared with subjects in study RFHE9701 or study RFHE9702 (see Section 6.5).

#### 6.4.3. Decreases in Venous Ammonia Levels during Short-Term Treatment

In study RFHE9701, venous ammonia levels decreased at a faster rate in the rifaximin group than in the lactitol group. In rifaximin-treated subjects, mean venous ammonia concentrations decreased from 131.5 to 85.7  $\mu\text{g/dL}$  over the course of treatment; in the lactitol-treated group,

concentrations decreased from 150.7 to 126.0 µg/dL ( $p=0.0084$  for between-treatment difference).

#### **6.4.4. Asterixis Grade, NCT Results, and Global Response During Short-Term Treatment**

The percentages of subjects who had improvements in asterixis grade while on drug increased with higher rifaximin doses in RFHE9702. In RFHE9701 (rifaximin vs. lactitol), the proportions of subjects who had improvements in asterixis grade were similar between groups. In the rifaximin vs. placebo study, RFHE9901, a greater frequency of subjects had improvements in asterixis grade in the rifaximin group compared to the lactitol group (39.1% vs. 9.3%;  $p = 0.0097$  for between-group difference in favor of rifaximin).

The changes in NCT scores were generally similar across groups in each of the 3 studies.

The overall global response to treatment was evaluated in RFHE9701. The percentages of subjects who were considered cured (venous ammonia normalized and mental status/Conn score of 0) by end of study were higher in the rifaximin group when compared with the lactitol group (53.1% vs. 39.2%).

#### **6.4.5. Summary of Results for Short-Term Treatment Studies RFHE9702, RFHE9701, and RFHE9901**

In RFHE9702, a dose-dependent trend in improvement of PSE index ( $p = 0.056$ ) and mental status/Conn score were observed, and results from this study showed the effectiveness of 1200 mg rifaximin daily dose (400 mg TID). These data, together with results from published studies of rifaximin 1200 mg/day in the treatment of HE (see Section 6.6 and Table 43 [Section 9]), provided a rationale for dose selection for the phase 3 studies RFHE3001 and RFHE3002 (see Section 5.1).

In RFHE9701, there were significant between-group differences in the changes in PSE index and venous ammonia levels (both of which were primary endpoints) in favor of the rifaximin group when compared with lactitol; and higher proportion of rifaximin subjects were considered cured at end of treatment (venous ammonia normalized and mental status/Conn score of 0).

In RFHE9901, a significant larger proportion of rifaximin subjects had improvements in asterixis grade when compared with placebo subjects; however, results for the primary endpoint, the proportion of subjects who had improvements in Conn score, were not significantly different between groups. Subjects in study RFHE9901 had mild HE symptoms when compared with subjects in study RFHE9701 (see Section 5.3.1.2).

### **6.5. Supportive Published Studies of Long Term Treatment in Subjects with Acute HE**

Three published studies, reported by Loguercio et al,<sup>131</sup> Fera et al,<sup>100</sup> and Miglio et al,<sup>13</sup> investigated the effectiveness of interventional treatment with rifaximin in subjects with acute HE over long term durations of therapy (3 months or 6 months) (Table 7 above summarizes study design).

In the Loguercio et al. study,<sup>131</sup> treatment with rifaximin or rifaximin with lactitol was more effective than lactitol alone as measured by normalization of blood ammonia levels by end of

treatment ( $p < 0.05$  in favor of the rifaximin groups) and normalization in mental status (defined as Conn score = 0) by end of treatment ( $p < 0.05$  in favor of the rifaximin groups).

Table 19 presents numbers and proportions of subjects who had normalized mental status (Conn score = 0) and who had normalized arterial ammonia levels ( $< 110 \mu\text{g/mL}$ ) by end of treatment.

**Table 19 Proportions of Subjects Who Had Normalized Mental Status (Conn score = 0) or Normalized Arterial Ammonia Levels ( $< 110 \mu\text{g/mL}$ ) by End of Treatment (Loguerico et al, 2003)**

	<b>Rifaximin</b> <b>N = 12</b> <b>n (%)</b>	<b>Lactitol</b> <b>N = 10</b> <b>n (%)</b>	<b>Rifaximin plus Lactitol</b> <b>N = 11</b> <b>n (%)</b>	<b>P-Value<sup>a</sup></b>
Mental status normalized (Conn score = 0)	8 (66.7)	2 (20.0)	6 (54.6)	$p < 0.05$
Ammonia level normalized ( $< 110 \mu\text{g/mL}$ )	11 (91.7)	4 (40.0)	10 (90.9)	$p < 0.05$

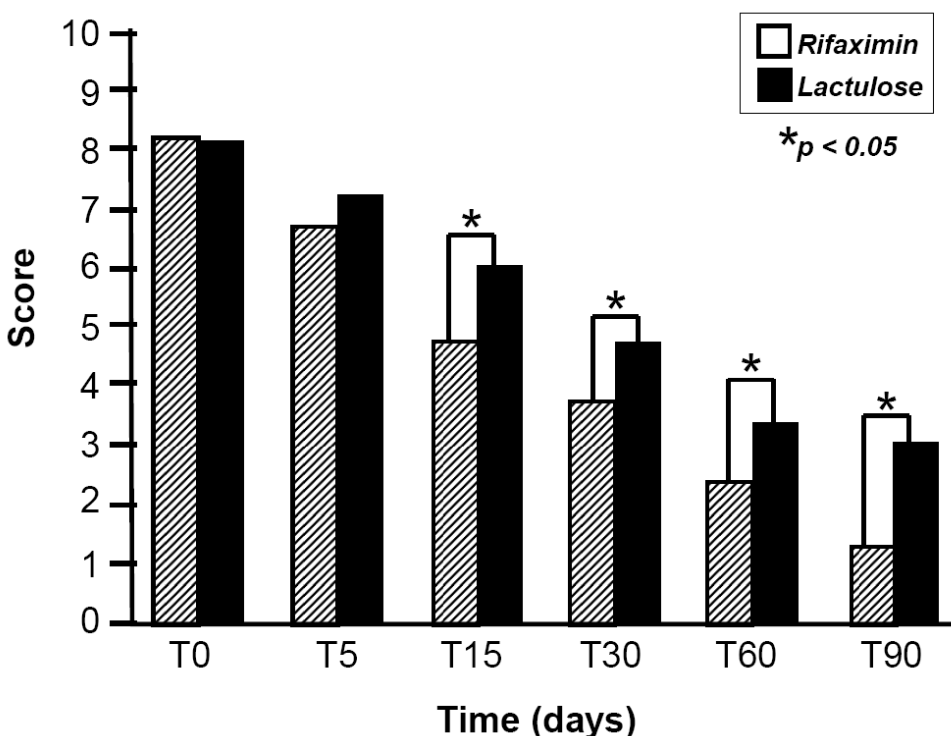
Source: Table 2 in Loguerico et al, 2003 (131).

a P-value was calculated for comparison to lactitol alone using Fisher's Exact test.

Results of the 3-month study (Fera et al.) of rifaximin plus lactulose vs. lactulose alone showed improvements in HE endpoints in both groups during the course of treatment,<sup>100</sup> and significantly greater improvements and/or more rapid improvements in the rifaximin group than in lactulose groups. Rifaximin was significantly more effective than lactulose in decreasing the severity of PSE ( $p < 0.05$  after 2 weeks), decreasing electroencephalogram irregularities ( $p < 0.01$  after 15 days and  $p < 0.05$  after 30 days), and improving the subjects' mental status ( $p < 0.05$  after 60 days and  $p < 0.02$  after 90 days of therapy).

Figure 21 illustrates mean PSE index values during the course of the study.<sup>100</sup> By 2 weeks after the start of treatment, the rifaximin group showed significant improvements in PSE index compared to the lactulose group.

**Figure 21 Mean PSE Index Values Over 3 Month Treatment with Rifaximin or Lactulose (Fera et al, 1993)**



Source: Figure 5 in Fera et al, 1993 (100).

PSE index was the sum of the individual severity grades for each of the endpoints measured (Conn score, asterixis grade, A cancellation test score, trailmaking [Reitan] test score, and EEG grade)

In the 6-month study (Miglio et al),<sup>13</sup> subjects in both treatment groups experienced significant decreases from baseline in HE grade and in blood ammonia levels. There were no significant differences between groups in HE endpoints in this study. Among 49 evaluable subjects (25 rifaximin, 24 neomycin), significant reductions in HE grade from baseline, beginning on Day 30 ( $p < 0.001$ ) were experienced in both treatment groups. Significant decreases in blood ammonia levels ( $p < 0.001$ ) occurred after rifaximin (from  $210.2 \pm 65.6$  to  $88.9 \pm 39.6$   $\mu\text{g/mL}$ ) and after neomycin (from  $202.1 \pm 60.1$  to  $86.2 \pm 42.9$   $\mu\text{g/mL}$ ).

The effectiveness of rifaximin in these 3 long-term studies is consistent with the efficacy of rifaximin in the maintenance of remission of overt HE as shown in study RFHE3001.

## 6.6. Published Studies of Rifaximin in the Treatment of Hepatic Encephalopathy

### Individual clinical studies

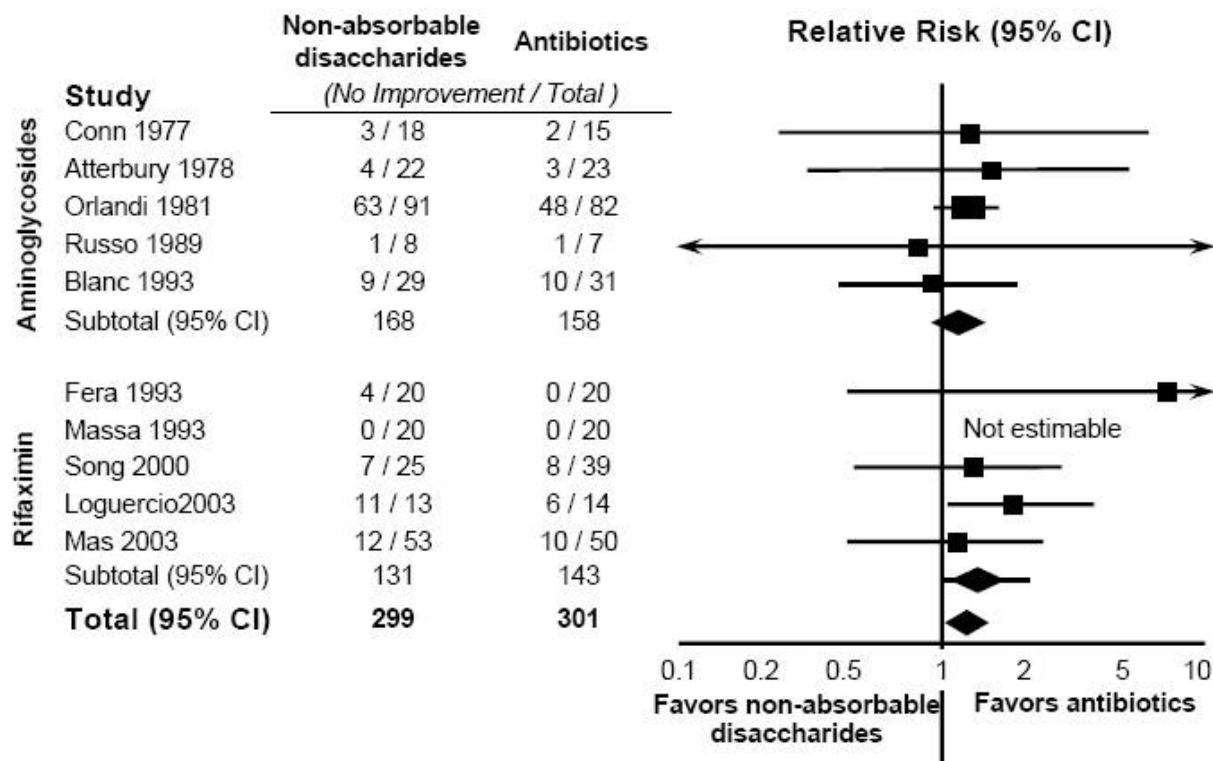
Most of the studies in the published literature followed treatment regimens of  $\leq 21$  days (ie, acute treatment). Longer treatment durations of 3 months and 6 months were investigated in 3 studies (ie, long term treatment).<sup>13,100,131</sup>

Table 43 (see Section 9) presents brief summaries of the acute treatment regimen studies and the long term treatment regimen studies.

### Meta-analyses

In the meta-analysis reported by Als-Nielsen, et al (2004)<sup>109</sup>, consisting of data from 22 clinical studies of lactulose or lactitol, antibiotics, no intervention, or placebo in the treatment of patients with HE, antibiotics (aminoglycosides or rifaximin) were superior to lactulose/lactitol in the treatment of HE (see Figure 22).

**Figure 22: Comparison of Studies in Non-Absorbable Disaccharides vs. Antibiotics**



Source: Als-Nielsen, Gluud, Gluud BMJ. 2004 May 1;328 (7447): 1046:1-6.

In a meta-analysis conducted by Lawrence and Klee (2008),<sup>110</sup> 17 clinical studies using rifaximin in patients with HE were reviewed for effectiveness in improving behavioral, laboratory, mental status and intellectual abnormalities associated with HE. The meta-analysis concluded that rifaximin was as effective, and in some studies, superior, to comparators such as lactulose, lactitol, neomycin, and paromomycin in reducing symptoms of HE.

In summary, results in published literature demonstrated the therapeutic benefit of rifaximin treatment in patients with HE.

## 7. Clinical Safety

The primary safety data for the HE indication consists of 348 subjects exposed to the dose and dosing regimen of rifaximin being proposed for approval, and these data are summarized in Sections 7.2 through 7.9.

### 7.1. Summary of Supportive Safety Data

The safety profile of rifaximin for the HE indication has been well established by the nonclinical and clinical pharmacology, pharmacokinetics (Section 3), and toxicology (Section 7.10); clinical data from ~5000 subjects enrolled in clinical studies across a range of indications; the current XIFAXAN<sup>®</sup> package insert;<sup>18</sup> and postmarketing surveillance from 33 countries including the US. Rifaximin has never been removed from marketing for safety reasons. In vitro and in vivo data from pharmacology, toxicology, drug interaction, and pharmacokinetics studies indicate no safety concerns. Data from other clinical studies conducted in indications such as irritable bowel syndrome (IBS), TD prophylaxis, etc, support the tolerability and safety of rifaximin in keeping with the current label for XIFAXAN.<sup>18</sup> The current US label reinforces the tolerability of rifaximin during short-term use, with frequencies of AEs comparable to placebo.

### 7.2. Evaluation of Safety Data in Patients with Advanced Liver Disease and HE

Rifaximin is currently being proposed for maintenance of remission of HE associated with advanced liver disease. In accord with the population at risk, the safety review contained herein focuses on frequent, serious, mortal events with special attention to areas of primary concern to this patient population. Namely, events involving the following system organ classes: blood and lymphatics, gastrointestinal disorders, hepatobiliary disorders, and infections. These are the areas of greatest clinical interest in treating this population due to the proposed long term use of this antibiotic in patients that are predisposed to clinical complications of coagulopathy, bleeding from the GI tract, liver function test (LFT) fluctuations, and immunosuppression due to the natural course of advanced liver disease.

The primary evidence for the safety of rifaximin 550 mg tablets in the maintenance of remission of HE was derived from an integrated safety analysis of phase 3 studies RFHE3001 and RFHE3002 (N=348). Two analysis populations were used for rifaximin in the maintenance of remission of HE: the Randomized Controlled Trial (RCT) Study population and the Long Term Rifaximin Experience population. These populations are defined below:

**RCT Study Population:** data from the double-blind, randomized, controlled study, RFHE3001 (N=159 in the placebo group and N=140 in the rifaximin group). This controlled, double-blind efficacy and safety comparison represented the main safety analysis for rifaximin in the maintenance of remission of HE.

**Long Term Rifaximin Experience Population:** subjects who received at least 1 dose of rifaximin in RFHE3001 or extension study RFHE3002 were pooled for the long term rifaximin experience analysis (All Rifaximin Subjects, N=348).

### 7.3. Overall Extent of Exposure

Table 20 summarizes subject exposure to rifaximin. In the RCT Study population (RFHE3001), the duration of exposure expressed as PEY, was ~9% longer, 50 vs. 46 PEY, in the rifaximin vs. the placebo treated group, respectively. This additional safety exposure for the RCT rifaximin group was consistent with the finding that more subjects in the rifaximin group completed the study, even though there were 19 more subjects enrolled in the placebo group.

Mean ( $\pm$ SD) exposure for All Rifaximin Subjects (RFHE3001 and RFHE3002) was 363.9 (226.19) days (approximately 1 year). The mean duration of exposure in All Rifaximin Subjects was approximately 3-fold longer than treatment durations in the RCT Study Groups.

Combined data represent approximately 347 PEYs to rifaximin 550 mg tablets BID in the All Rifaximin Group in primary analysis studies. In the RCT Study, rifaximin subjects had 50 PEYs and placebo had 46 PEYs. Total rifaximin exposure was approximately 7-fold longer in the All Rifaximin Subjects (RFHE3001+RFHE3002 experience) than in each of the treatment groups in RFHE3001.

**Table 20 Extent of Exposure to Rifaximin in the Primary Analysis Populations**

Category	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348)
	Placebo (PEY = 46.0) (N = 159)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140)	
Exposure duration (days)			
Mean (SD)	105.7 (62.71)	130.3 (56.47)	363.9 (226.19)
Median (Min, Max)	110.0 (6, 176)	168.0 (10, 178)	403.0 (7, 1008)

Source: Tables 3.1 and 3.2 in the ISS 120-Day Update.

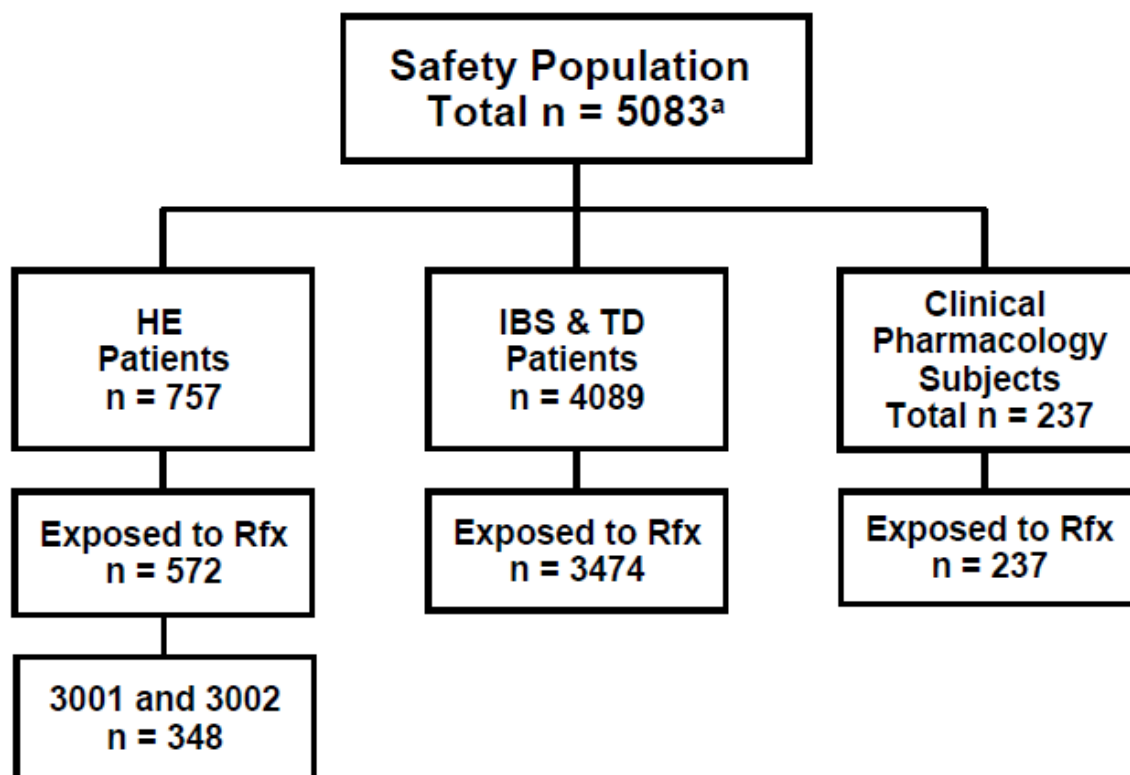
Abbreviations: PEY=person exposure year; SD=standard deviation

### 7.4. Subject Disposition

Figure 23 outlines the overall safety database of subjects in clinical studies of rifaximin across several indications. Subjects in rifaximin clinical studies included HE subjects (N=757), IBS or TD (N=4089), and healthy volunteers in clinical pharmacology studies (N=237). Treatment durations were 3 days to 2 weeks for the IBS, TD and clinical pharmacology studies.

Figure 24 shows disposition of subjects in studies RFHE3001 and RFHE3002, which provide the primary evidence for the safety of rifaximin 550 mg tablets in the maintenance of remission of HE. Results for the placebo group (N=159) and rifaximin group (N=140) in RFHE3001 (RCT Study Population) and for subjects who received rifaximin in RFHE3001 and/or RFHE3002, All Rifaximin Subjects (N=348), are described in the following sections. All Rifaximin Subjects includes: 140 subjects who received rifaximin in RFHE3001, 82 subjects new to rifaximin who rolled over from RFHE3001 placebo to RFHE3002, and 128 new subjects who received rifaximin in RFHE3002 only.

**Figure 23: Safety Population of Subjects in Rifaximin Clinical Studies Across Indications**

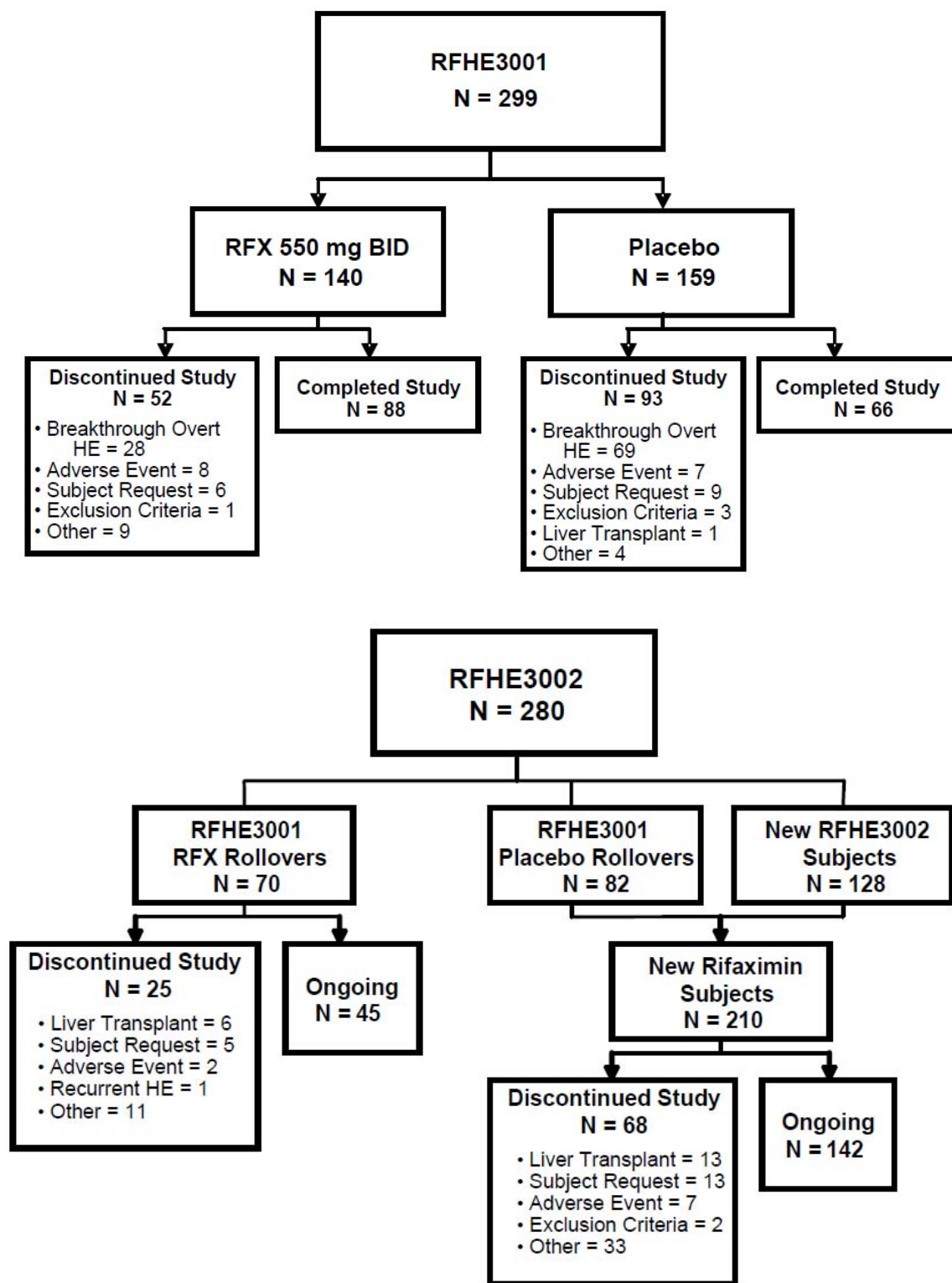


Abbreviations: IBS=irritable bowel syndrome; TD=travelers' diarrhea.

a Rifaximin all doses tested or placebo as of September 14, 2009.



**Figure 24: Subject Disposition in Studies RFHE3001 and RFHE3002**



Source: ISS 120-day update, Figure 1.

Abbreviations: RFX=rifaximin, HE=hepatic encephalopathy.

## 7.5. Demographics and Baseline Characteristics

Demographics, baseline HE characteristics, baseline advanced liver disease characteristics, baseline renal function, baseline laboratory parameters associated with liver disease, etiology of advanced liver disease, and medical history in RFHE3001 or RFHE3002 are presented in the tables below (Table 21 through Table 26).

Overall, the demographics, liver disease histories, and medical histories of subjects enrolled into the RFHE3001 and RFHE3002 studies were generally similar to those exposed to placebo. There were slightly more female subjects in the rifaximin group than placebo group in RFHE3001. Because over 70% of the safety data are from the US, the etiology of advanced liver disease strongly reflects the common etiologies for advanced liver disease in the US, with hepatitis C etiology for approximately 40% of subjects and alcohol etiology for 35%. As expected, frequently reported conditions in subjects' medical histories were hepatobiliary ( $\geq 94\%$  of subjects), gastrointestinal ( $\geq 85\%$ ), infections ( $\geq 61\%$ ), and blood and lymphatic ( $\geq 37\%$ ) disorders.

**Table 21 Demographics in RFHE3001 or RFHE3002**

Category	RCT Study Population (RFHE3001)		Long Term Rifaximin Experience Population (RFHE3001+RFHE3002)
	Placebo (N = 159) n (%)	Rifaximin 550 mg BID (N = 140) n (%)	All Rifaximin Subjects (N = 348) n (%)
Sex, n (%)			
Male	107 (67)	75 (54)	203 (58)
Female	52 (33)	65 (46)	145 (42)
Age, yr			
Mean (SD)	57 (9.2)	56 (9.6)	57 (9.3)
< 65 yr, n (%)	128 (81)	113 (81)	277 (80)
$\geq 65$ yr, n (%)	31 (20)	27 (19)	71 (20)
Race (n, %)			
Asian	8 (5)	4 (3)	9 (3)
Black/African-American	5 (3)	7 (5)	16 (5)
White	139 (87)	118 (84)	310 (89)
Ethnicity, n (%)			
Hispanic or Latino	28 (18)	21 (15)	45 (13)
Not Hispanic or Latino	131 (82)	119 (85)	303 (87)
Geographic region, n (%)			
United States	112 (70)	93 (66)	269 (77)
Canada	6 (4)	8 (6)	15 (4)
Russia	41 (26)	39 (28)	64 (18)

Source: Tables 2.1.1 and 2.1.2 in the ISS 120-Day Update.

**Table 22 Baseline Hepatic Encephalopathy Characteristics**

Baseline characteristic	RCT Study Population (RFHE3001)		Long Term Rifaximin Experience Population (RFHE3001+RFHE3002)
	Placebo (N = 159) n (%)	Rifaximin 550 mg BID (N = 140) n (%)	All Rifaximin Subjects (N = 348) n (%)
Time since last HE, days (SD)	73 (51)	69 (48)	98 (95)
Time since first HE, months (SD)	21.85 (26.41)	20.84 (23.13)	21.21 (25.1)
HE Episodes in Past 6 Months, n (%)			
1	0	0	62 (18)
2	111 (70)	97 (69)	177 (51)
> 2	47 (30)	43 (31)	105 (30)
Conn Score at study entry, n (%)			
Grade 0	107 (67)	93 (66)	223 (64)
Grade 1	52 (33)	47 (34)	114 (33)
Grade ≥ 2	0	0	11 (3)

Source: Tables 2.2.1 and 2.2.2 in the ISS 120-Day Update.

**Table 23 Baseline Liver Disease Characteristics and Renal Function**

Baseline characteristic	RCT Study Population (RFHE3001)		Long Term Rifaximin Experience Population (RFHE3001+RFHE3002)
	Placebo (N = 159) n (%)	Rifaximin 550 mg BID (N = 140) n (%)	All Rifaximin Subjects (N = 348) n (%)
Mean months since diagnosis of advanced liver disease (min, max)	61 (2, 323.4)	51 (1.7, 260.5)	66 (1.7, 515.8)
MELD score, mean (min, max)	12.7 (6, 23)	13.1 (6, 24)	12.7 (6, 24)
MELD UNOS category, n (%)			
≤ 10	48 (30)	34 (24)	109 (31)
11 – 18	96 (60)	94 (67)	208 (60)
≥ 19	14 (9)	12 (9)	29 (8)
Child-Pugh subscore, mean (min, max)	7.2 (3, 13)	7.5 (5, 14)	--
Child-Pugh classification, – n (%)			
A (5-6)	56 (35.2)	46 (32.9)	--
B (7-9)	72 (45.3)	65 (46.4)	--
C (10-15)	14 (8.8)	17 (12.1)	--
Renal impairment (serum creatinine) ≥ 1.5 ULN, n (%)	3 (1.9)	4 (2.9)	7 (2.0)

Source: Tables 2.2.1 and 2.2.2 in the ISS 120-Day Update.

Abbreviations: MELD UNOS=Model End-Stage Liver Disease United Network for Organ Sharing; SD=standard deviation; ULN=upper limit of normal.

**Table 24 Baseline Laboratory Parameters Associated with Advanced Liver Disease**

Laboratory Parameter	RCT Study Population (RFHE3001)		Long Term Rifaximin Experience Population (RFHE3001+RFHE3002)
	Placebo (N = 159) n (%)	Rifaximin 550 mg BID (N = 140) n (%)	All Rifaximin Subjects (N = 348) n (%)
<b>Hgb (g/dL)</b>			
n	159	138	346
Mean (SD)	13.0 (1.9)	12.3 (1.8)	12.4 (1.9)
Median (Min, max)	12.8 (8, 18)	12.4 (8, 17)	12.4 (8, 17)
<b>HCT (RATIO)</b>			
n	159	138	346
Mean (SD)	0.4 (0.05)	0.4 (0.05)	0.4 (0.05)
Median (Min, max)	0.4 (0, 1)	0.4 (0, 0)	0.4 (0, 1)
<b>PLATELETS (x10<sup>9</sup>/L)</b>			
n	157	138	341
Mean (SD)	117.3 (64.77)	114.7 (61.40)	116.1 (59.46)
Median (Min, max)	104.0 (29, 475)	99.0 (34, 321)	102.0 (32, 491)
<b>PROTHROMBIN TIME (PT) (seconds)</b>			
n	149	132	339
Mean (SD)	17.1 (4.15)	17.0 (3.29)	16.9 (3.54)
Median (Min, max)	16.5 (10, 47)	16.8 (10, 29)	16.4 (10, 38)
<b>INR (RATIO)</b>			
n	149	132	339
Mean (SD)	1.4 (0.35)	1.4 (0.28)	1.4 (0.28)
Median (Min, max)	1.4 (1, 4)	1.4 (1, 2)	1.3 (1, 3)
<b>CREATININE (umol/L)</b>			
n	159	140	347
Mean (SD)	82.6 (28.21)	84.7 (26.52)	85.3 (27.11)
Median (Min, max)	71.0 (41, 195)	80.0 (44, 168)	80.0 (34, 204)
<b>ALKALINE PHOSPHATASE (U/L)</b>			
n	159	140	348
Mean (SD)	140.4 (68.07)	158.0 (104.31)	146.9 (82.07)
Median (Min, max)	122.0 (35, 581)	138.5 (38, 1079)	131.5 (38, 1079)
<b>AST (U/L)</b>			
n	159	140	348
Mean (SD)	67.8 (46.22)	64.0 (35.00)	66.6 (41.16)
Median (Min, max)	52.0 (15, 274)	53.5 (11, 231)	54.0 (11, 311)
<b>ALT (U/L)</b>			
n	159	140	348
Mean (SD)	45.9 (31.30)	41.5 (25.74)	45.7 (32.63)
Median (Min, max)	35.0 (10, 216)	35.0 (7, 178)	36.5 (7, 238)
<b>TOTAL BILIRUBIN (umol/L)</b>			
n	159	140	348
Mean (SD)	32.2 (23.43)	34.4 (27.66)	34.6 (30.80)
Median (Min, max)	27.0 (4, 133)	27.0 (4, 210)	26.5 (3, 287)

Normal ranges: Hgb g/dL (Female:11.5-15.5; Male: 13.2 - 17); HCT (Female:0.35 - 0.47; Male:0.40 - 0.54); Platelets x10<sup>9</sup>/L (150 - 400); PT sec (8.9 - 16.3); INR (0.8 - 1.4); Creatinine umol/L (Female:44 - 89; Male:53-124); Alkaline Phosphatase U/L (40 - 135); AST U/L (0-37); ALT U/L (0 - 47); Total Bilirubin umol/L (0 - 19).

**Table 25 Etiology of Advanced Liver Disease in RFHE3001**

System Organ Class	RCT Study Population (RFHE3001)	
	Placebo (N = 159) n (%)	Rifaximin 550 mg BID (N = 140) n (%)
Etiology		
Hepatitis C	67 (42)	61 (44)
Alcohol	57 (36)	47 (34)
Hepatitis C + Alcohol	10 (6)	18 (13)
Other:		
NAFLD/NASH	17 (11)	13 (9)
Hepatitis B	13 (8)	11 (8)
Cryptogenic	11 (7)	9 (6)
Autoimmune Hepatitis	1 (1)	9 (6)
Primary Biliary cirrhosis	5 (3)	4 (3)
Drug/chemical induced	1 (1)	2 (1)
Genetic	2 (1)	0

Source: ISS 120-Day Update database.

**Table 26 Medical History in RFHE3001 or RFHE3002**

System Organ Class	RCT Study Population (RFHE3001)		Long Term Rifaximin Experience Population (RFHE3001+RFHE3002)
	Placebo (N = 159) n (%)	Rifaximin 550 mg BID (N = 140) n (%)	All Rifaximin Subjects (N = 348) n (%)
Any Organ Class	159 (100)	140 (100)	348 (100)
Blood and lymphatic system	59 (37)	63 (45)	176 (51)
Cardiac	35 (22)	34 (24)	80 (23)
Endocrine	11 (7)	18 (13)	39 (11)
Gastrointestinal	145 (91)	122 (87)	324 (93)
Hepatobiliary	152 (96)	132 (94)	342 (98)
Infections and infestations	97 (61)	93 (66)	240 (69)
Metabolism and nutrition	82 (52)	72 (51)	201 (58)
Musculoskeletal and connective tissue	59 (37)	48 (34)	152 (44)
Neoplasms benign, malignant and unspecified	18 (11)	17 (12)	51 (15)
Nervous system	36 (23)	38 (27)	140 (40)
Psychiatric	74 (47)	57 (41)	172 (49)
Renal and urinary	30 (19)	37 (26)	100 (29)
Skin and subcutaneous tissue	47 (30)	41 (29)	121 (35)
Vascular	68 (43)	64 (46)	165 (47)

Source: ISS 120-Day Update database (ADC Table 5).

## 7.6. Concomitant Medications

Table 27 presents concomitant medications by anatomic therapeutic chemical class (WHO dictionary).

Concomitant medication use was generally balanced between groups during double-blind treatment, with the exception of anti-anemic agents (placebo 15% vs. rifaximin 29%). The 2 most frequently used anti-anemic agents were ferrous sulfate (placebo 6.3% vs. rifaximin 7.9%) and folic acid (placebo 5.7% vs. rifaximin 14.3%).

All subjects received at least 1 concomitant medication during the studies. In RFHE3001, diuretics were often used in each treatment group (placebo 77% vs. rifaximin 84%); the most common diuretics were spironolactone (placebo 62.9% vs. rifaximin 71.4%) and furosemide (placebo 59.1% vs. rifaximin 60.0%).

The most frequently used beta blocking agent was propranolol (placebo 22% vs. rifaximin 25%); beta blocking agents are often prescribed for patients with advanced liver disease and associated portal hypertension for the prevention of variceal bleeding.

Lactulose was the most common concomitant medication, taken by 91% of subjects in RFHE3001 and by 75% in RFHE3002.

**Table 27 Concomitant Medication Use in RFHE3001 or RFHE3002**

Anatomical Therapeutic Chemical Class	RCT Study Population (RFHE3001)		Long Term Rifaximin Experience Population (RFHE3001+RFHE3002)
	Placebo (N = 159) n (%)	Rifaximin 550 mg BID (N = 140) n (%)	All Rifaximin Subjects (N = 348) n (%)
Any concomitant medication	159 (100)	140 (100)	343 (99)
Renin-angiotensin agents	25 (16)	26 (19)	57 (16)
Analgesics	39 (25)	36 (26)	125 (36)
Antianemic agents	24 (15)	41 (29)	108 (31)
Antibacterials (systemic)	45 (28)	35 (25)	167 (48)
Antiinflammatory/antirheumatic	14 (9)	10 (7)	24 (7)
Antithrombotics	12 (8)	16 (11)	51 (15)
Antivirals (systemic)	7 (4)	5 (4)	21 (6)
β-blocking agents	79 (50)	68 (49)	170 (49)
Bile and liver therapy	22 (14)	27 (19)	61 (18)
Cardiac	8 (5)	13 (9)	36 (10)
Corticosteroids (systemic)	6 (4)	12 (9)	42 (12)
Diuretics	123 (77)	118 (84)	278 (80)
Drugs for acid disorders	97 (61)	82 (59)	209 (60)
Drugs used in diabetes	56 (35)	37 (26)	106 (30)
Immunostimulants	2 (1)	6 (4)	12 (3)
Psychoanaleptics	45 (28)	34 (24)	105 (30)

Source: Tables 4.1 and 4.2 in the ISS 120-Day Update.

## 7.7. Summary of Adverse Events

An overall summary of treatment-emergent AEs (TEAEs) for the primary analysis populations is presented in Table 28.

During blinded treatment (RCT), the proportion of subjects with TEAEs was similar between the rifaximin group (80.0%) and placebo group (79.9%). Severe TEAEs (26% rifaximin vs. 31% placebo), drug-related TEAEs (19% vs. 21%), SAEs (36% vs. 40%), and TEAEs leading to

discontinuation (21% vs. 28%) were experienced by generally comparable percentages of subjects between treatment groups.

RFHE3001 was designed to assess the outcome of overt HE. As such, only events of HE that were greater in severity, required hospitalization, or otherwise were believed by the investigator to constitute AEs, required reporting as AEs. However, HE is a serious, debilitating event. The efficacy results indicate that 73/159 placebo and 31/140 rifaximin treated subjects experienced breakthrough overt HE episodes (46% vs. 22%, respectively). The most commonly occurring SAEs that occurred in the RCT were anemia, ascites, esophageal varices hemorrhage, and pneumonia. These events were expected in this patient population.

Mortality between the treatment groups was comparable; 6% in the rifaximin group and 7% in the placebo group died during treatment or within 30 days of discontinuing study medication. The long-term extension study, RFHE3002, had a lower death rate (death/PEY) than the blinded treatment groups. Death rates for subjects were 14 deaths/100 PEY in All Rifaximin Subjects compared to 18 and 24 deaths/100 PEY for rifaximin- and placebo-treated subjects in RFHE3001. These findings suggest that long-term treatment with rifaximin does not have a deleterious effect on the death rate in patients with end-stage liver disease.

**Table 28 Overall Summary of TEAE Incidence**

Category	RCT Study Population (RFHE3001)		Long Term Rifaximin Experience Population (RFHE3001+RFHE3002)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	All Rifaximin Subjects 550 mg BID (PEY = 346.7) (N = 348) n (%)
Any TEAEs	127 (79.9)	112 (80.0)	307 (88.2)
TEAEs by Intensity			
Severe	49 (30.8)	37 (26.4)	159 (45.7)
Moderate	54 (34.0)	52 (37.1)	111 (31.9)
Mild	24 (15.1)	23 (16.4)	37 (10.6)
TEAE Related to Study Drug	34 (21.4)	27 (19.3)	48 (13.8)
Serious TEAEs	63 (39.6)	51 (36.4)	190 (54.6)
TEAEs Resulting in Study Discontinuation	45 (28.3)	30 (21.4)	88 (25.3)
Liver transplants	1 (0.6)	0	23 (6.6)
Deaths <sup>a</sup>	11 (6.9)	9 (6.4)	47 (13.5)

Source: Tables 5.1.1b and 5.1.2 in the ISS 120-Day Update.

a Subjects who died during treatment or within 30 days of discontinuing study medication.

### 7.7.1. Common Adverse Events

Table 29 summarizes TEAEs that occurred in  $\geq 5\%$  of subjects in the RCT Study Population (RFHE3001) or in the Long Term Rifaximin Experience population (RFHE3001 plus RFHE3002).

The incidence of TEAEs was similar between treatment groups, and the most common events were disorders and events associated with advanced liver disease or overt HE. Among rifaximin subjects in the RCT Study population, the most common TEAEs (ie,  $\geq 10\%$  of rifaximin group) were the following (rifaximin vs. placebo): peripheral edema (15.0% vs. 8.2%), nausea (14.3%

vs. 13.2%), dizziness (12.9% vs. 8.2%), fatigue (12.1% vs. 11.3%), ascites (11.4% vs. 9.4%), diarrhea (10.7% vs. 13.2%), and headache (10.0% vs. 10.7%). Hepatic encephalopathy episodes that met the criteria for an SAE were recorded for 12.1% of rifaximin subjects vs. 21.4% of placebo subjects.

The percentage of subjects with TEAEs were marginally higher in the Long Term Experience Population (rifaximin experience in RFHE3001 plus RFHE3002) compared to double-blind treatment (RFHE3001). However, rifaximin exposure was >7-fold longer in the Long Term Experience Population. Therefore, the incidence of AEs, after adjustment for exposure duration (event/PEY), was lower than the incidence observed during double-blind treatment (RFHE3001).

The overall profile of common TEAEs in rifaximin-treated subjects during the primary studies was consistent with those observed in patients with advanced liver disease. There were few notable differences between rifaximin and placebo treatment groups, and long term exposure with rifaximin did not have a detrimental effect on the safety profile of the drug or increase the frequency of TEAEs.

**Table 29 TEAEs Occurring in ≥ 5% of Subjects in RFHE3001 or RFHE3002**

System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
Any TEAEs	127 (79.9)	112 (80.0)	307 (88.2)
<b>Blood and Lymphatic System Disorders</b>	<b>8 (5.0)</b>	<b>15 (10.7)</b>	<b>65 (18.7)</b>
Anemia	6 (3.8)	11 (7.9)	41 (11.8)
<b>Gastrointestinal System Disorders</b>	<b>67 (42.1)</b>	<b>72 (51.4)</b>	<b>224 (64.4)</b>
Nausea	21 (13.2)	20 (14.3)	66 (19.0)
Ascites	15 (9.4)	16 (11.4)	55 (15.8)
Abdominal pain	13 (8.2)	12 (8.6)	47 (13.5)
Vomiting	14 (8.8)	10 (7.1)	43 (12.4)
Diarrhea	21 (13.2)	15 (10.7)	41 (11.8)
Constipation	10 (6.3)	9 (6.4)	35 (10.1)
Abdominal pain upper	8 (5.0)	9 (6.4)	21 (6.0)
Abdominal distension	12 (7.5)	11 (7.9)	19 (5.5)
<b>General Disorders &amp; Administration Site Conditions</b>	<b>52 (32.7)</b>	<b>56 (40.0)</b>	<b>147 (42.2)</b>
Edema peripheral	13 (8.2)	21 (15.0)	64 (18.4)
Fatigue	18 (11.3)	17 (12.1)	40 (11.5)
Pyrexia	5 (3.1)	9 (6.4)	22 (6.3)
Asthenia	12 (7.5)	4 (2.9)	16 (4.6)
<b>Hepatobiliary Disorders</b>	<b>14 (8.8)</b>	<b>11 (7.9)</b>	<b>73 (21.0)</b>
Hepatic failure	1 (0.6)	1 (0.7)	19 (5.5)
<b>Infections and Infestations</b>	<b>49 (30.8)</b>	<b>46 (32.9)</b>	<b>163 (46.8)</b>
Urinary tract infection	14 (8.8)	8 (5.7)	53 (15.2)
Cellulitis	3 (1.9)	3 (2.1)	19 (5.5)
Nasopharyngitis	10 (6.3)	10 (7.1)	16 (4.6)
<b>Metabolism and Nutrition Disorders</b>	<b>21 (13.2)</b>	<b>28 (20.0)</b>	<b>108 (31.0)</b>
Dehydration	2 (1.3)	5 (3.6)	22 (6.3)



System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
Hypokalemia	3 (1.9)	2 (1.4)	26 (7.5)
<b>Musculoskeletal and Connective Tissue Disorders</b>	<b>32 (20.1)</b>	<b>31 (22.1)</b>	<b>108 (31.0)</b>
Muscle spasms	11 (6.9)	13 (9.3)	42 (12.1)
Arthralgia	4 (2.5)	9 (6.4)	23 (6.6)
Back pain	10 (6.3)	9 (6.4)	23 (6.6)
<b>Nervous System Disorders</b>	<b>64 (40.3)</b>	<b>53 (37.9)</b>	<b>158 (45.4)</b>
Hepatic encephalopathy <sup>a</sup>	34 (21.4)	17 (12.1)	86 (24.7)
Dizziness	13 (8.2)	18 (12.9)	39 (11.2)
Headache	17 (10.7)	14 (10.0)	31 (8.9)
<b>Psychiatric Disorders</b>	<b>29 (18.2)</b>	<b>27 (19.3)</b>	<b>78 (22.4)</b>
Depression	8 (5.0)	10 (7.1)	32 (9.2)
Insomnia	11 (6.9)	10 (7.1)	27 (7.8)
<b>Renal and Urinary Disorders</b>	<b>12 (7.5)</b>	<b>10 (7.1)</b>	<b>65 (18.7)</b>
Renal failure acute	5 (3.1)	2 (1.4)	27 (7.8)
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>	<b>39 (24.5)</b>	<b>36 (25.7)</b>	<b>99 (28.4)</b>
Dyspnea	7 (4.4)	9 (6.4)	30 (8.6)
Cough	11 (6.9)	10 (7.1)	20 (5.7)
<b>Skin and Subcutaneous Tissue Disorders</b>	<b>24 (15.1)</b>	<b>29 (20.7)</b>	<b>88 (25.3)</b>
Pruritus	10 (6.3)	13 (9.3)	29 (8.3)
Rash	6 (3.8)	7 (5.0)	24 (6.9)

Source: Tables 5.2.1.1b and 5.2.2.1 in the ISS 120-Day Update.

a Given that HE was the primary efficacy outcome, HE episodes recorded as nonserious AEs are excluded from this table. Serious AEs of HE are counted in this table.

### 7.7.2. Serious Adverse Events

Serious AEs experienced by rifaximin and placebo subjects during the primary studies were consistent with events observed in patients with advanced liver disease. Serious AEs in the blood and lymphatic, gastrointestinal disorders, hepatobiliary disorders, and infections system organ classes are described in Sections 7.7.4 through 7.7.4.3.

Serious AEs experienced by  $\geq 2\%$  of subjects are presented in Table 30.

**Table 30 Serious AEs Occurring in  $\geq 2\%$  of Subjects in RFHE3001 or RFHE3002**

System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
Any SAEs	63 (39.6)	51 (36.4)	190 (54.6)
<b>Blood and Lymphatic System Disorders</b>	<b>0</b>	<b>5 (3.6)</b>	<b>20 (5.7)</b>
Anemia	0	4 (2.9)	16 (4.6)
<b>Gastrointestinal System</b>	<b>11 (6.9)</b>	<b>16 (11.4)</b>	<b>68 (19.5)</b>

System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
<b>Disorders</b>			
Ascites	4 (2.5)	4 (2.9)	14 (4.0)
Gastrointestinal hemorrhage	3 (1.9)	1 (0.7)	12 (3.4)
Abdominal pain	1 (0.6)	2 (1.4)	10 (2.9)
Esophageal varices hemorrhage	2 (1.3)	4 (2.9)	8 (2.3)
Vomiting	0	3 (2.1)	6 (1.7)
<b>General Disorders &amp; Administration Site Conditions</b>	4 (2.5)	6 (4.3)	19 (5.5)
Generalized edema	2 (1.3)	3 (2.1)	6 (1.7)
<b>Hepatobiliary Disorders</b>	10 (6.3)	7 (5.0)	46 (13.2)
Hepatic failure	1 (0.6)	1 (0.7)	19 (5.5)
Hepatic cirrhosis	6 (3.8)	3 (2.1)	15 (4.3)
<b>Infections and Infestations</b>	9 (5.7)	11 (7.9)	59 (17.0)
Cellulitis	2 (1.3)	3 (2.1)	14 (4.0)
Pneumonia	1 (0.6)	4 (2.9)	11 (3.2)
Urinary tract infection	1 (0.6)	2 (1.4)	10 (2.9)
Peritonitis bacterial	3 (1.9)	1 (0.7)	7 (2.0)
<b>Metabolism and Connective Tissue Disorders</b>	4 (2.5)	7 (5.0)	30 (8.6)
Hyperkalemia	0	2 (1.4)	9 (2.6)
Hyponatremia	1 (0.6)	1 (0.7)	8 (2.3)
<b>Neoplasms Benign, Malignant and Unspecified</b>	3 (1.9)	3 (2.1)	12 (3.4)
Hepatic neoplasm malignant	2 (1.3)	2 (1.4)	9 (2.6)
<b>Nervous System Disorders</b>	36 (22.6)	18 (12.9)	91 (26.1)
Hepatic encephalopathy <sup>a</sup>	34 (21.4)	16 (11.4)	85 (24.4)
<b>Renal and Urinary Disorders</b>	6 (3.8)	2 (1.4)	29 (8.3)
Renal failure acute	4 (2.5)	2 (1.4)	22 (6.3)
Renal failure	2 (1.3)	0	7 (2.0)
<b>Surgical and Medical Procedures</b>	0	0	15 (4.3)
Liver transplant	0	0	15 (4.3)

Source: Tables 5.4.1.1 and 5.4.2.1 in the ISS 120-Day Update.

a Although HE was the primary efficacy outcome, HE episodes reported as SAEs were counted in this table.

A total of 23 rifaximin-treated subjects in RFHE3002 and 1 placebo-treated subject in RFHE3001 received a liver transplant. In RFHE3001 subjects were excluded from entering the study if a liver transplant was scheduled within 1 month of screening, to enable most subjects to complete the 6 months of treatment. However, subjects were not similarly restricted for entry in RFHE3002 which was designed as a long term study, and patients on the UNOS transplant list were permitted to enter the study. The expectation was that RFHE3002 would enroll many subjects who would discontinue the study due to liver transplants. Ten subjects were exposed to rifaximin for >300 days, 7 from 100-300 days; and 5 for <100 days prior to the liver transplant.

Most subjects who received a liver transplant had no significant change in MELD score from baseline to end of treatment. Mean baseline MELD scores for these 23 subjects was 15.43 (9.6 to 23.5), and their mean change from baseline to the subjects last study visit was -1.6 (-10.47 to 14).

### 7.7.3. Adverse Events Resulting in Study Discontinuation

Treatment-emergent AEs resulting in study discontinuation were experienced by 21.4% of rifaximin subjects and by 28.3% of placebo subjects in RFHE3001. The incidence of TEAEs resulting in study discontinuation in the All Rifaximin Subjects was 25.3%.

Treatment-emergent AEs resulting in study discontinuation occurring in  $\geq 2\%$  of subjects are presented in Table 31.

**Table 31 TEAEs Resulting in Study Discontinuation Occurring in  $\geq 2\%$  of Subjects in RFHE3001 or RFHE3002**

System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
Any AEs resulting in study discontinuation	45 (28.3)	30 (21.4)	88 (25.3)
<b>Hepatobiliary Disorders</b>	3 (1.9)	3 (2.1)	22 (6.3)
Hepatic failure	0	1 (0.7)	14 (4.0)
<b>Nervous System Disorders</b>	30 (18.9)	14 (10.0)	14 (4.0)
Hepatic encephalopathy <sup>a</sup>	30 (18.9)	14 (10.0)	14 (4.0)
<b>Surgical and Medical Procedures</b>	0	0	14 (4.0)
Liver transplant	0	0	14 (4.0)

Source: Tables 5.5.1.1b and 5.5.2.1 in the ISS 120-Day Update.

a Given that HE was the primary efficacy outcome, HE episodes recorded as nonserious AEs are excluded from this table. Serious AEs of HE are counted in this table.

### 7.7.4. Special Interest Adverse Events in Subjects with Hepatic Impairment - Blood System Disorders, Gastrointestinal Disorders, Infections, and Hepatic Events

Most subjects had medical histories significant for blood and lymphatic disorders, hepatobiliary and gastrointestinal conditions, and infections, as expected for subjects with advanced liver disease. Therefore, subjects entered studies RFHE3001 and RFHE3002 with a background risk for events related to hepatic function, blood disorders (eg, anemia and hemorrhage), gastrointestinal disorders (eg, nausea, ascites, and esophageal varices hemorrhage), and infection. Subjects in RFHE3001 and RFHE3002 were closely monitored for the emergence of infections due to their inherent predisposition and because the studies evaluated long term treatment with an antibiotic (rifaximin).

The occurrences of expected events for subjects with advanced liver disease: blood disorders, hepatic events, gastrointestinal events, and infection (ie, events of special interest), are described in detail in the following sections.

#### 7.7.4.1. Blood and Lymphatic System Disorders and Gastrointestinal Disorders

Blood and lymphatic system disorders and GI disorders are summarized in Table 32 (TEAEs) and Table 33 (SAEs). There were no remarkable between-group differences in blood and lymphatic system disorders and GI disorders in RFHE3001, with the exception of anemia (Table 32).

Anemia is an event often associated with advanced liver disease.<sup>111</sup> Anemia TEAEs were reported for 7.9% of rifaximin subjects compared with 3.8% of placebo subjects in RFHE3001. However, there was an imbalance of anemia history between groups at baseline; 30.7% of rifaximin subjects vs. 17% of placebo subjects had a previous medical history of anemia. Of the 11 rifaximin subjects who had anemia, 7 had a prior medical history of anemia. By contrast, only 1 of 6 placebo subjects who experienced anemia had a prior medical history of the event. Also, there was a higher proportion of rifaximin subjects who received anti-anemic concomitant medications compared with placebo subjects, which is consistent with the between-group difference in anemia history at baseline.

Serious AEs of anemia occurred in 4 rifaximin subjects and no placebo subjects in RFHE3001. Each of these 4 subjects were at risk for anemia due to mitigating causal factors, including acute blood loss related to esophageal variceal bleeding, longstanding medical history of anemia associated with chronic disease, and fluid overload secondary to low albumin. Three of the 4 subjects had a prior medical history of the event.

Gastrointestinal-related bleeding events (GI hemorrhage, esophageal varices hemorrhage, or upper GI hemorrhage) were the most frequently occurring blood or GI-related SAEs. Seven subjects in the placebo group and 5 subjects in the rifaximin group had hemorrhage SAEs during the double-blind study.

**Table 32 Blood and Lymphatic System and Gastrointestinal TEAEs Occurring in  $\geq 5\%$  of Subjects in RFHE3001 or RFHE3002**

System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
<b>Blood and Lymphatic System Disorders</b>	<b>8 (5.0)</b>	<b>15 (10.7)</b>	<b>65 (18.7)</b>
Anemia	6 (3.8)	11 (7.9)	41 (11.8)
<b>Gastrointestinal System Disorders</b>	<b>67 (42.1)</b>	<b>72 (51.4)</b>	<b>224 (64.4)</b>
Nausea	21 (13.2)	20 (14.3)	66 (19.0)
Ascites	15 (9.4)	16 (11.4)	55 (15.8)
Abdominal pain	13 (8.2)	12 (8.6)	47 (13.5)
Vomiting	14 (8.8)	10 (7.1)	43 (12.4)
Diarrhea	21 (13.2)	15 (10.7)	41 (11.8)
Constipation	10 (6.3)	9 (6.4)	35 (10.1)
Abdominal pain upper	8 (5.0)	9 (6.4)	21 (6.0)
Abdominal distension	12 (7.5)	11 (7.9)	19 (5.5)

Source: Tables 5.2.1.1b and 5.2.2.1 in the ISS 120-Day Update.

**Table 33 Blood and Lymphatic System and Gastrointestinal SAEs Occurring in  $\geq 1\%$  of Subjects in RFHE3001 or RFHE3002**

System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
<b>Blood and Lymphatic System Disorders</b>	<b>0</b>	<b>5 (3.6)</b>	<b>20 (5.7)</b>
Anemia	0	4 (2.9)	16 (4.6)
<b>Gastrointestinal System Disorders</b>	<b>11 (6.9)</b>	<b>16 (11.4)</b>	<b>68 (19.5)</b>
Ascites	4 (2.5)	4 (2.9)	14 (4.0)
Gastrointestinal hemorrhage	3 (1.9)	1 (0.7)	12 (3.4)
Abdominal pain	1 (0.6)	2 (1.4)	10 (2.9)
Esophageal varices hemorrhage	2 (1.3)	4 (2.9)	8 (2.3)
Vomiting	0	3 (2.1)	6 (1.7)
Upper gastrointestinal hemorrhage	2 (1.3)	0	5 (1.4)

Source: Tables 5.4.1.1 and 5.4.2.1 in the ISS 120-Day Update.

The incidences of hematology test results and SAEs related to GI hemorrhage are presented in Table 34. Potentially clinically significant changes in hematocrit (HCT) and Hgb are determined by change from baseline as well as change from previous visit; and international normalized ratio (INR) and prothrombin time (PT) are determined by change from baseline (see table footnote).

The long term use of rifaximin in this population had no apparent effect on bleeding, indices of blood loss, or clotting when compared to placebo.

**Table 34 Blood and Hemorrhage Related Hematology Results, AEs, and SAEs in RFHE3001 or RFHE3002**

Laboratory finding, <sup>a</sup> AE, or SAE	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
HCT ( $< 0.27$ or $\geq 0.10$ ↓ from prior visit or $\geq 0.15$ ↓ from baseline)	5 (3)	6 (4)	28 (8)
Hgb ( $< 9$ or $\geq 3$ ↓ from prior visit or $\geq 4$ ↓ from baseline)	8 (5)	8 (6)	43 (12)
INR ( $> 1.7$ )	21 (13)	20 (14)	56 (16)
PT (9 seconds $>$ baseline or ULN)	6 (4)	8 (6)	42 (12)
HCT decreased <sup>b</sup>	18 (11)	19 (14)	79 (23)
INR increased <sup>c</sup>	27 (17)	18 (13)	88 (25)
PT increased <sup>c</sup>	22 (14)	19 (14)	95 (27)
GI bleeding SAEs <sup>d</sup>	8 (5)	6 (4)	30 (9)

Source: ISS 120-Day Update database (ADC Table 7).

Abbreviations: GI=gastrointestinal; HCT=hematocrit; Hgb=hemoglobin; INR=international normalized ratio;

PT=prothrombin time; AE=adverse event; SAE=serious AEs; ULN=upper limit of normal.

a Parameters shown for HCT, Hgb, INR, and PT are protocol-defined criteria for potentially clinically significant findings.

	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
Laboratory finding, <sup>a</sup> AE, or SAE			

b HCT decreased is defined as shift from normal or high at baseline to low at postbaseline time point.

c INR or PT increased is defined as shift from normal or low at baseline to high at postbaseline time point.

d Gastrointestinal bleeding events included including gastroduodenal, gastrointestinal, lower gastrointestinal, oesophageal varices, peritoneal, rectal and upper gastrointestinal hemorrhage.

#### 7.7.4.2. Infections

In regards to infections, the current product labeling for XIFAXAN, which is indicated for the treatment of TD, has labeling information for physicians.<sup>18</sup> As is the case with all antibiotics, physicians are informed about the risk of *C. difficile* infection. As such, Salix believes the current label adequately informs physicians about the possibility of infections with rifaximin. The current XIFAXAN label has the following under ‘warning and precautions:’

##### ‘5.1 Travelers’ Diarrhea Not Caused by *Escherichia coli*’

‘XIFAXAN Tablets were not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*.

XIFAXAN Tablets should be discontinued if diarrhea symptoms get worse or persist more than 24-48 hours and alternative antibiotic therapy should be considered.

XIFAXAN Tablets are not effective in cases of travelers’ diarrhea due to *Campylobacter jejuni*. The effectiveness of XIFAXAN Tablets in travelers’ diarrhea caused by *Shigella spp.* and *Salmonella spp.* has not been proven. XIFAXAN Tablets should not be used in patients where *Campylobacter jejuni*, *Shigella spp.*, or *Salmonella spp.* may be suspected as causative pathogens.’

##### ‘5.2 *Clostridium difficile*-Associated Diarrhea’

“Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of “antibiotic-associated colitis.”

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile*.”

In the primary safety population, AEs related to infections are summarized in Table 35, and SAEs involving infections are presented in Table 36. The incidences of AEs related to infections were approximately 30% in the rifaximin and placebo groups in RFHE3001. This result is consistent with the reported expected frequency of infections (30-60%) in subjects with advanced liver disease,<sup>112</sup> as well as the reported incidence in the medical histories of RFHE3001/3002 subjects, where approximately 60% had a history of infection.

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.<sup>112</sup> The frequency of pneumonia SAEs (2.9% rifaximin and 0.6% placebo) is lower than the expected rate of 7-23%. In total, 17 rifaximin-treated subjects (4.9%) experienced pneumonia during the primary analysis studies. The event rate per 100 person years for pneumonia was lower during long-term therapy (All Rifaximin Group) (4.9/100 PEY) compared to the rifaximin group during double-blind treatment (8.0/100 PEY).

The total number of GI-derived infections (spontaneous bacterial peritonitis and *C. difficile*) was also comparable between groups in RFHE3001.

A total of 5 subjects (2 in RFHE3001 and 3 in RFHE3002) had *C. difficile* infection. At baseline, 6 subjects in RFHE3001/3002 had a medical history of *C. difficile* infection. Thus, the incidence in the studies appears equivalent to that seen in the medical history recorded at baseline (~1% in both) and the expected rate in subjects with advanced liver disease.<sup>113</sup>

*Clostridium difficile* infection resolved for each of the 5 subjects following either vancomycin or metronidazole therapy. Three of the 5 subjects remained on rifaximin or received off-study XIFAXAN following resolution of *C. difficile* infection. All 5 subjects had recent clinical histories that included several risk factors for infection, including hepatic cirrhosis, advanced age, hepatitis C, numerous hospitalizations that included treatment with multiple courses of antibiotics other than rifaximin, and concurrent use of proton pump inhibitors. Two of the 5 subjects were diagnosed with *C. difficile* infections > 20 days after last dose of rifaximin. Both of these *C. difficile* infections were diagnosed post study (ie, after discontinuation of rifaximin), and following hospitalization and the use of systemic antibiotics, making causal correlation difficult.

**Table 35 Infections TEAEs Occurring in ≥ 5% of Subjects in RFHE3001 or RFHE3002**

System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
<b>Infections and Infestations</b>	<b>49 (30.8)</b>	<b>46 (32.9)</b>	<b>163 (46.8)</b>
Urinary tract infection	14 (8.8)	8 (5.7)	53 (15.2)
Cellulitis	3 (1.9)	3 (2.1)	19 (5.5)
Nasopharyngitis	10 (6.3)	10 (7.1)	16 (4.6)

Source: Tables 5.2.1.1b and 5.2.2.1 in the ISS 120-Day Update.

**Table 36 Infections SAEs Occurring in ≥ 1% of Subjects in RFHE3001 or RFHE3002**

System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
<b>Infections and Infestations</b>	<b>9 (5.7)</b>	<b>11 (7.9)</b>	<b>59 (17.0)</b>
Cellulitis	2 (1.3)	3 (2.1)	14 (4.0)
Pneumonia	1 (0.6)	4 (2.9)	11 (3.2)

System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
Urinary tract infection	1 (0.6)	2 (1.4)	10 (2.9)
Peritonitis bacterial	3 (1.9)	1 (0.7)	7 (2.0)
Clostridium colitis	0	2 (1.4)	5 (1.4)
Lobar pneumonia	0	0	5 (1.4)
Septic shock	0	0	5 (1.4)
Sepsis	2 (1.3)	0	2 (0.6)

Source: Tables 5.4.1.1 and 5.4.2.1 in the ISS 120-Day Update.

### 7.7.4.3. Hepatic Events

Changes in MELD score were minimal during treatment with placebo or rifaximin in RFHE3001, indicating minimal deterioration in hepatic function during study RFHE3001. For example, in RFHE3001, mean MELD scores were 13.1 at baseline and 13.1 at last assessment in the rifaximin group and 12.7 at baseline and 12.8 at last assessment in the placebo group.

### Hepatobiliary SAEs

Hepatobiliary SAEs are presented in Table 37.

The incidence of hepatobiliary SAEs were comparable between rifaximin and placebo groups in RFHE3001 and between the All Rifaximin Group and placebo when exposure is taken into account (subjects in the Long Term population had ~ 7 times greater exposure [in PEY] compared to the RCT groups).

Of the 19 subjects in the Long Term Rifaximin Experience population with hepatic failure, 10 died as a result of hepatic failure, and 4 had liver transplants. Each of these subjects who died due to hepatic failure had conditions associated with hepatic decompensation at baseline, including HE, esophageal varices, ascites, portal hypertension, jaundice, edema, and GI hemorrhage. Hepatic decompensation is associated with a shorter survival rate, and according to D'Amico et al., the median survival of cirrhotic patients with hepatic decompensation decreases from > 8 years to approximately 2 years.<sup>114</sup>

**Table 37 Hepatobiliary SAEs Occurring in ≥ 1% of Subjects in RFHE3001 or RFHE3002**

System Organ Class Preferred Term	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
<b>Hepatobiliary Disorders</b>	<b>10 (6.3)</b>	<b>7 (5.0)</b>	<b>46 (13.2)</b>
Hepatic failure	1 (0.6)	1 (0.7)	19 (5.5)
Hepatic cirrhosis	6 (3.8)	3 (2.1)	15 (4.3)
Hepatorenal syndrome	0	0	4 (1.1)
Cirrhosis alcoholic	0	1 (0.7)	2 (0.6)

Source: Tables 5.4.1.1 and 5.4.2.1 in the ISS 120-Day Update.



### Clinical Laboratory Testing: Liver Function Tests

Liver function test results were analyzed for changes from baseline. Data were expressed as mean/median changes and frequencies of shifts from baseline, and outliers for alanine aminotransferase (ALT) and total bilirubin were compared between treatment groups. The observed changes from baseline were consistent with expected changes in LFTs for a population with pre-existing liver injury. Because this is an advanced liver disease population and subjects often had baseline values above the ULN, we evaluated changes that represented worsening from their already high baseline values or, for those subjects within the normal range at baseline, worsening to above normal postbaseline results were evaluated.

To evaluate outliers in RFHE3001, the incidences of subjects with postbaseline elevations in ALT, total bilirubin, alkaline phosphatase, and ALT > 3 × ULN concurrent with total bilirubin > 2 × ULN were investigated (Table 38). There were no remarkable between-group differences in postbaseline elevations of these LFTs.

**Table 38 Changes in LFT Results in RFHE3001 or RFHE3002**

Laboratory Variable Limit	Placebo (N = 159) n/N (%)	550mg Rifaximin	
		BID (N = 140) n/N (%)	All Rifaximin (N = 348) n/N (%)
<b>ALT &gt; 3x ULN concurrent with total bilirubin &gt; 2x ULN</b>	1/ 153 (1%)	2/ 137 (1%)	8/ 342 (2%)
<b>ALT</b>			
>3x ULN/BL	4/ 154 (3%)	2/ 138 (1%)	12/ 346 (3%)
>5x ULN/BL	0/ 154	0/ 138	7/ 346 (2%)
>8x ULN/BL	0/ 154	0/ 138	0/ 346
>10x ULN/BL	0/ 154	0/ 138	1/ 346 (<1%)
>20x ULN/BL	0/ 154	0/ 138	0/ 346
<b>Total bilirubin</b>			
>1.5x ULN/BL	12/ 154 (8%)	9/ 138 (7%)	33/ 346 (10%)
2x ULN/BL	18/ 154 (12%)	15/ 138 (11%)	45/ 346 (13%)
3x ULN/BL	8/ 154 (5%)	11/ 138 (8%)	35/ 346 (10%)
5x ULN/BL	5/ 154 (3%)	5/ 138 (4%)	15/ 346 (4%)
8x ULN/BL	3/ 154 (2%)	2/ 138 (1%)	11/ 346 (3%)
<b>Alkaline phosphatase</b>			
>2x ULN/BL	6/ 154 (4%)	5/ 138 (4%)	23/ 346 (7%)
>3x ULN/BL	0/ 154	1/ 138 (1%)	5/ 346 (1%)
>5x ULN/BL	0/ 154	0/ 138	0/ 346
>8x ULN/BL	0/ 154	0/ 138	0/ 346
>10x ULN/BL	0/ 154	0/ 138	0/ 346
>20x ULN/BL	0/ 154	0/ 138	0/ 346

### Clinical Laboratory Shift Analysis and Hepatic Function Adverse Events

Alanine aminotransferase and total bilirubin shift analysis reflecting a change from normal at baseline to high after initiation of study medication and AEs that reflect impaired hepatic function are summarized in Table 39. The hepatic function related AEs in RFHE3001 and RFHE3002 were ALT increased and total bilirubin increased; and AE terms combined under

gallbladder-related AEs, hepatic-related AEs, or portal-circulatory AEs. (The terms combined in these groups of AEs are listed in the footnote to Table 39).

There were no notable imbalances between rifaximin and placebo groups in postbaseline elevations in LFT increases (ALT and total bilirubin); or in AEs and SAEs that reflect impaired hepatic function such as gallbladder-related AEs, hepatic related AEs, and portal-circulatory AEs.

**Table 39 Hepatic Function Adverse Events in RFHE3001 or RFHE3002**

Hepatic Function AE	RCT Study Population		Long Term Rifaximin Experience Population
	Double-Blind Study Treatment		All Rifaximin Subjects (PEY = 346.7) (N = 348) n (%)
	Placebo (PEY = 46.0) (N = 159) n (%)	Rifaximin 550 mg BID (PEY = 50.0) (N = 140) n (%)	
ALT increased <sup>a</sup>	22 (14)	21 (15)	88 (25)
Total bilirubin increased <sup>a</sup>	24 (15)	24 (17)	83 (24)
Gallbladder-related AEs <sup>b</sup>	2 (1)	1 (1)	11 (3)
Hepatic-related AEs <sup>c</sup>	11 (7)	9 (6)	56 (16)
Portal-circulatory AEs <sup>d</sup>	1 (1)	3 (2)	10 (3)

Source: ISS 120-Day Update database (ADC Table 3.2).

Abbreviations: ALT=alanine aminotransferase; AE=adverse event.

- a ALT and total bilirubin increased are defined as either shift from baseline normal to postbaseline high or if baseline is already high, shift to postbaseline  $> 2 \times$  baseline value.
- b Gallbladder-related events include acute and chronic cholecystitis, cholelithiasis, cholestasis, cholangitis, gallbladder disorder, and biloma.
- c Hepatic-related events include hepatic cirrhosis, hepatic failure, cirrhosis alcoholic, jaundice, biliary cirrhosis primary, liver disorder, hepatorenal failure, hepatorenal syndrome, hepatic pain, and hepatomegaly.
- d Portal-circulatory AEs includes portal hypertension, portal hypertensive gastropathy, portal vein thrombosis, and hepatic vein thrombosis.

## 7.8. All-Cause Mortality

Twenty subjects died during the double-blind RFHE3001 study within 30 days of stopping study medication; 11 subjects (6.9%) in the placebo group and 9 subjects (6.4%) in the rifaximin group.

In RFHE3002, 38 subjects died during the study or within 30 days of stopping study medication. Therefore, a total of 47 rifaximin-treated subjects (9 in RFHE3001 and 38 in RFHE3002) died during the phase 3 program. Of these 47 subjects, 28 subjects died  $\leq 5$  days after last dose of rifaximin (ie, died on therapy).

None of the deaths in RFHE3001/3002 were considered by the investigator to be related to study drug and the vast majority of deaths in both the placebo group and the rifaximin group were related to the natural course of advanced liver disease and underlying disease progression.

Causes of death in RFHE3001 are shown in Table 40. The reported causes of deaths were balanced between treatment groups. This result provides further evidence that the majority of deaths in study RFHE3001 were probably related to the natural course of disease progression in subjects with advanced liver disease.

**Table 40 Causes of Death in RFHE3001**

Cause of death in RFHE3001	Rifaximin	Placebo
Liver decompensation/failure	3	4
Esophageal varices hemorrhage/coagulation	3	2
Liver transplant rejection	1	0
Acute renal failure	0	1
Infection/urosepsis	0	1
Cardiac	2	1
Hepatic neoplasms	0	2
Total	9	11

Source: ISS 120-Day Update database

In both studies, a large proportion of deaths were due to conditions associated with disease progression, including the following: hepatic neoplasm malignant, liver disorder, liver transplant rejection, hepatic cirrhosis, decompensated liver cirrhosis, hepatic failure, alcoholic cirrhosis, end-stage liver failure, hepatorenal failure/syndrome, multiple-organ failure, esophageal varices or esophageal varices hemorrhage, biliary cirrhosis primary, GI hemorrhage, acute/chronic renal failure, and HE.

Based on a review of medical history, of the 47 rifaximin-treated subjects who died during or after the study (9 subjects in RFHE3001 and 38 in RFHE3002), 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 patients with advanced liver disease (ie, TIPS, coagulopathy) and 3 of 5 died due to a hepatic malignancy, hepatic cirrhosis, or hepatic failure. Similarly, all placebo-treated subjects who died in study RFHE3001 also had additional evidence (besides HE) of hepatic decompensation at baseline.

Kamath et al.<sup>86</sup> performed a retrospective analysis of 2,278 patients to estimate survival probabilities among patients with cirrhosis. Survival probabilities were determined by MELD UNOS category in the following groups: patients hospitalized for TIPS procedures, ambulatory patients with noncholestatic liver disease, ambulatory patients with primary biliary cirrhosis, and a ‘historical group’ of cirrhotic subjects who were potentially at risk for death. Calculated probabilities of death at 3 months by MELD score across groups were 1% to 8% at MELD  $\leq$  9, 5.6% to 27% at MELD 10-19, and  $>$  50% at MELD score  $\geq$  20.

The death rate was comparable or lower in the rifaximin studies regardless of MELD UNOS category compared with the groups evaluated in the Kamath paper. Among All Rifaximin Subjects, deaths across baseline MELD categories were reported for 8 of 109 subjects (7.3%) for MELD score  $\leq$  10; 31 of 208 subjects (14.9%) for MELD score 11 to 18; and 8 of 29 subjects (27.6%) for MELD score  $\geq$  19 (deaths onstudy or within 30 days of last dose of study drug).

These observations, along with the review of evidence of hepatic decompensation at baseline, suggest that survival probability for subjects in the primary studies was consistent with the natural history of advanced liver disease, and that liver disease severity at baseline was the most important factor in determining the likelihood of survival for subjects in the study.

### 7.8.1. Survival Analysis

No difference in the survival probability (time-to-death) was observed in the Kaplan-Meier analysis shown Table 41. The risk of death was equivalent between groups.

**Table 41 RFHE3001: Survival Analysis for Subjects Who Died within 30 days of Last Dose**

Days	Placebo (N = 159)					550mg Rifaximin BID (N = 140)				
	At Risk <sup>1</sup>	Occurrences of Events <sup>2</sup>	Cumulative Occurrences of Events	Conditional Probability of Events (SE) <sup>3</sup>	Survival <sup>4</sup>	At Risk <sup>1</sup>	Occurrences of Events <sup>2</sup>	Cumulative Occurrences of Events	Conditional Probability of Events (SE) <sup>3</sup>	Survival <sup>4</sup>
[0-28)	153	2	2	0.01 (0.01)	1.0000	137	0	0	0.00 (0.00)	1.0000
[28-56)	135	2	4	0.01 (0.01)	0.9869	129	2	2	0.02 (0.01)	1.0000
[56-84)	115	2	6	0.02 (0.01)	0.9723	120	3	5	0.03 (0.01)	0.9844
[84-140)	98	2	8	0.02 (0.01)	0.9553	112	2	7	0.02 (0.01)	0.9598
[140-168)	85	0	8	0.00 (0.00)	0.9358	100	1	8	0.01 (0.01)	0.9426
≥168	42	3	11	0.07 (0.04)	0.9358	48	1	9	0.02 (0.02)	0.9332
Hazard Ratio <sup>5</sup> : 0.818										
95% CI: (0.339, 1.978)										
p-value: 0.6558										

[1] Number of subjects at risk in the interval for death, estimated using 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.

[2] Incidences of events occurring during the interval.

[3] Standard error (SE) estimated using Greenwood's formula.

[4] Estimate of survival function, that is, the probability of survival until the start time of each interval or later.

[5] Hazard ratio estimate (hazard of death 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.

The ratio of the incidence of death in All Rifaximin Subjects relative to placebo experience in RFHE3001 is 0.5825 with a 95% CI of 0.30 and 1.13 (Table 42). This implies that the incidence of death in the All Rifaximin Subjects (PEY=346.7) range from 70% less than, or up to 13% greater than that of subjects treated with placebo (PEY=46.0) in RFHE3001.

These findings suggest that long-term treatment with rifaximin does not have a deleterious effect on the death rate in patients with advanced liver disease.

**Table 42 Comparison of Death Rates (Deaths/PEY) Between Placebo in RFHE3001 and All Rifaximin Subjects**

Analysis Group	Total Number of Subjects with HE Event	Number of Subjects	Exposure Person-Year	Event Rate <sup>1</sup>	Ratio of Incidence <sup>2</sup>	95% CI	P-value
Placebo in 3001	11	159	46.0	0.2			
All Rifaximin	47	348	346.7	0.1	0.5825	(0.3003, 1.1296)	0.1097

1 Event rate is calculated as number of subjects who died within 30 days after last dose divided by total exposure year.

2 Ratio of incidences (death for rifaximin in RFHE3001 and RFHE3002 compared to placebo subjects in RFHE3001) and p value obtained from parameter estimates with effect for treatment and region.

## 7.9. Adverse Events in Special Populations

The influence of intrinsic and extrinsic factors on the AE profile of rifaximin in studies RFHE3001 and RFHE3002 was examined using race (white, nonwhite), age (< 65, ≥ 65), sex, baseline hepatic function (MELD UNOS score category: ≤ 10, 11-18, or ≥ 19), baseline renal

function (serum creatinine  $\geq 1.5 \times \text{ULN}$  and serum creatinine  $< 1.5 \times \text{ULN}$ ), and geographic region.

The AE profile was similar across intrinsic/extrinsic factor subgroups with the exceptions that there were higher incidences of TEAEs with increasing MELD score and there were lower incidences of TEAEs in Russia when compared with the North American geographic region. While differences were observed in these subgroups, the pattern and frequency of TEAEs was similar between rifaximin and placebo subjects regardless of MELD UNOS score category and regardless of analysis region in the RCT Study population.

#### **7.10. Supportive Safety Findings**

The nonclinical toxicology program for rifaximin included single-dose toxicology studies in mice and rats, repeat dose oral toxicology studies for up to 26 weeks in rats and up to 39 weeks in dogs; in vivo safety pharmacology, reproductive toxicity, genotoxicity, and carcinogenicity studies; and in vitro inhibition studies.

Single dose toxicology, safety pharmacology, reproductive toxicity, genotoxicity, and carcinogenicity studies resulted in no toxicities attributable to rifaximin exposure. In repeat dose toxicology studies, findings in rats at study durations up to 26 weeks were limited to decreases in weight gain and peripheral lymphocyte count. In dogs, at doses up to 3000 mg/kg/day (for 7 days) and 1000 mg/kg/day (for 39 weeks), orange feces/fur (attributed to the orange color of rifaximin) and nonspecific stress-induced thymic atrophy were reported; no consistent pathologic or histopathologic changes attributable to rifaximin were observed. Specific to the patient population under study in the current application, no histopathology suggesting hepatic effects of rifaximin was reported in rodent or nonrodent species.

In vitro, the effects of rifaximin on the human BSEP, the primary transporter regulating ATP-dependent bile salt translocation from the liver to the bile, was quantitated; it was a weak inhibitor with an  $\text{IC}_{50}$  of 83  $\mu\text{M}$ . This weak inhibition indicates a minimal risk of clinically significant BSEP inhibition.

Rifaximin concentrations up to 300  $\mu\text{M}$  failed to achieve 50% inhibition of the hERG potassium current in vitro, leading to an estimated  $\text{IC}_{50}$  of  $>100 \mu\text{M}$ . This value is more than 3000 times greater than the highest  $\text{C}_{\text{max}}$  observed in any rifaximin-treated subject to date, a safety margin that greatly exceeds the 30-fold separation that is commonly associated with minimization of risk of clinical QT interval prolongation.<sup>115</sup>

## 8. Benefits and Risks Summary

Rifaximin provided clinical benefit to patients with HE. All relevant and clinically meaningful analyses demonstrate that administration of rifaximin 550 mg BID is an effective treatment for the maintenance of remission from HE episodes in patients with advanced liver disease. This conclusion is supported by the robustness of the efficacy findings in RFHE3001; supportive results in RFHE3002; and published literature of both long term and short term studies in subjects with acute HE.<sup>13,14,15,16,19,23,74,99,100,109,110</sup>

There is an unmet medical need for patients with HE as current therapies leave patients needing substantial improvement in efficacy, safety, and tolerability.<sup>20,22,27,28,99,101,116,117</sup> In the absence of effective treatment, HE causes reduced health-related quality of life, an inability for self-care, and dependence on a caregiver for day-to-day functioning.<sup>86,87,88,89</sup> Hepatic encephalopathy episodes are evident across a spectrum of severity from fatigue, daytime sleepiness, and lack of awareness (Conn score 1); that significantly interfere with day-to-day function and decreased ability for self care. Often, this lack of self care can lead to improper nutrition and non-adherence to therapy and can further escalate into more severe symptoms such as confusion and disorientation, increased somnolence, and stupor (Conn score 2-4), which require hospitalization. In patients with cirrhosis, a history of overt HE episodes and the severity of HE episodes were found to be predictive of survival.<sup>91,92</sup> Bustamante et al,<sup>91</sup> reported that the probability of survival was 42% at 1 year and 23% at 3 years after experiencing an HE episode.

Rifaximin therapy has substantial benefits for this population of patients with advanced liver disease and recurrent HE. Rifaximin treatment results in fewer overt HE episodes that may otherwise incapacitate the patient, may alleviate the burden on family members who are required to care for the patient, and reduces the burden of hospitalization in this patient population and the healthcare system. Calculation of the number needed to treat, based on primary efficacy endpoint results, revealed that for every 4 subjects treated with rifaximin 1 less subject experienced breakthrough overt HE. Also, with respect to the key secondary efficacy endpoint of protection against HE-related hospitalization, the number needed to treat calculations showed that for every 9 subjects treated with rifaximin 1 less subject was hospitalized due to HE. The reduced risk of hospitalization due to HE in the rifaximin group compared with the placebo group underscores the clinical significance of efficacy findings in this study.

Results from the current safety database support a positive benefit/risk ratio for rifaximin therapy (550 mg BID, 1100 mg/day) in this patient population. In comparison to placebo, and during long-term therapy (median [minimum, maximum] exposure was 403.0 [7, 1008] days; and 347 PEY), rifaximin showed a favorable safety profile in the maintenance of remission of HE. The pattern of AEs, deaths, and laboratory findings was consistent with expectations for the population under study and comparable to placebo. Long term treatment with rifaximin in the target population did not appear to have an adverse impact on the safety profile of the drug. The primary safety analysis, along with compiled safety data for rifaximin in other indications, the published literature, and postmarketing surveillance, support the use of rifaximin for the maintenance of remission of HE.

## 9. Table of Published Studies of Rifaximin in the Treatment of HE

**Table 43 Published Studies of Rifaximin (Acute and Long Term Treatment Regimens) in Patients with Hepatic Encephalopathy**

Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
Lawrence and Klee <sup>110</sup>	<p>Review the effectiveness and safety of rifaximin for the treatment of hepatic encephalopathy</p> <p>Review based on literature search from 1966 – 2007, including placebo-controlled, treatment comparison, and open label studies</p> <p>Rifaximin 200 mg, 400 mg or 800 mg (primarily 400 mg) given TID for 5 to 21 days or 14 days each month for 6 months</p>	<ul style="list-style-type: none"> <li>• Paromomycin 500 mg TID</li> <li>• Neomycin 1 g TID</li> <li>• Lactulose 30 - 60 g or 90 mL per day</li> <li>• Lactitol 20 g TID</li> </ul> <p>N = 20 to 103</p>	<p>Rifaximin studies including patients with hepatic encephalopathy</p> <p>Studies published in the English-language</p>	<p>Rifaximin was at least as efficacious, and in some cases superior to nonabsorbable disaccharides and other antimicrobials in relieving the signs and symptoms in patients with mild-to-moderate HE. Rifaximin improved behavioral, laboratory, mental status and intellectual abnormalities commonly attributed to HE. Patients treated with rifaximin also required less hospitalization, had shorter hospital stays, and lower hospital costs compared to patients treated with lactulose.</p>	<p>Rifaximin was better tolerated than other HE treatments. Adverse events primarily consisted of minor gastrointestinal complaints.</p>
<b>Acute treatment regimens - other published studies</b>					
Bucci and Palmieri <sup>117</sup>	<p>Double-blind, double-dummy, randomized, controlled study of rifaximin 2 × 200 mg tablets 3 times/day + placebo vs. lactulose 10 g/day + placebo for 15 days</p>	<ul style="list-style-type: none"> <li>• 1200 mg rifaximin (2 × 200 mg tablets TID) plus a 10 g sachet of placebo (sorbitol) (N = 30)</li> <li>• 30 g lactulose (3 x 10 g sachets TID) plus placebo (N = 28)</li> </ul> <p>15 days treatment duration</p>	<ul style="list-style-type: none"> <li>• Patients with liver cirrhosis confirmed by liver biopsy and signs and symptoms of PSE</li> <li>• No severe psychiatric illnesses, renal insufficiency, chronic respiratory insufficiency, presence of tumors, hemoglobin &lt; 7 g/100 mL, or</li> </ul>	<p>Significant decreases in PSE index in both groups by Day 12 (<math>p &lt; 0.05</math>). Rifaximin group had significantly greater improvements than lactulose group at Day 12 and at end of treatment in PSE index (<math>p &lt; 0.05</math>).</p> <p>Other endpoints that showed significantly greater improvements in the rifaximin group than in the lactulose group were mental status, EEG irregularities, blood ammonia levels, and the A cancellation test</p>	<p>The incidence of adverse events was higher in patients treated with lactulose compared to rifaximin. Diarrhea, flatulence, and dyspepsia were reported in approximately half of the lactulose-treated patients; anorexia was reported in 39.3%, weight loss in 28.6%, and abdominal pain in</p>

Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
			potassium < 3.0 mEq/mL	score ( $p < 0.05$ ).	3.6% of lactulose patients. Flatulence (16.7%), abdominal pain (6.7%), and weight loss (6.7%) were the only events reported by rifaximin-treated patients.
Dal Monte et al. <sup>118</sup>	Open-label, uncontrolled trial to evaluate the effectiveness and tolerance of rifaximin in patients with diverticulitis of colon or HE	<ul style="list-style-type: none"> <li>1200 mg rifaximin (2× 200 mg tablets TID) for 14 days (N = 31 subjects with HE; and N = 56 subjects with diverticulitis)</li> </ul>	<ul style="list-style-type: none"> <li>Grade 1 or 2 hepatic encephalopathy as defined by Conn</li> <li>No patients suffering from serious ulcerative lesions of the intestine</li> </ul>	The course of the illness, evaluated as the sum of the scores according to the Conn classification, showed a reduction of 17.3% on Day 7 (from $3.8 \pm 0.4$ SD to $3.1 \pm 0.4$ SD) and 72% ( $1.1 \pm 0.3$ SD) at the end of treatment ( $p < 0.05$ ). At the follow-up, the score remained at values lower than the baseline values. Ammonia showed an overall statistically significant decrease from baseline ( $p < 0.01$ ).	Adverse events occurred in 7 subjects (8%), and these AEs were primarily GI events. The adverse events were all considered possibly related to study drug and mild to moderate in intensity. Precautionary suspension of treatment occurred in 2 patients (1 case of nausea and urticaria in a subject with HE, and 1 case of urticaria in a subject with diverticulitis), and a reduction of the dosage in 2 subjects, both with diverticulitis (1 case of nausea and 1 case of dyspepsia).
De Marco et al. <sup>119</sup>	Open-label, randomized, controlled trial to compare the effectiveness and tolerability of rifaximin to paromomycin in patients with PSE secondary to liver cirrhosis	<ul style="list-style-type: none"> <li>1200 mg rifaximin (2 × 200 mg tablets TID) for 6 - 12 days (N = 32)</li> <li>1500 mg paromomycin (2 × 250 mg tablets TID) for 6 - 15 days (N = 14).</li> </ul>	<ul style="list-style-type: none"> <li>Patients with PSE of different degrees, with or without ascites and splenomegaly, secondary to liver cirrhosis (as defined by Conn)</li> <li>No patients suffering</li> </ul>	Significant improvements in the patients' state of consciousness, intellectual function, behavior, and neurological signs were seen after 3 days of treatment, and significant decreases in blood ammonia levels after 3 - 5 days of treatment with rifaximin and with paromomycin ( $p < 0.05$ vs. baseline)	No AEs or significant changes in clinical laboratory parameters were recorded during the study. No subjects were reported to have experienced enterocolic disturbances.



Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
			from a concomitant primary or secondary disease of the central nervous system or acute forms of liver disease with a more severe course of transaminase levels not due to hyperammonemia that could cause CNS disturbances	for both treatments). Blood ammonia levels were lowered to a greater extent by rifaximin (-36.5 µg/dL) than by paromomycin (-29.7 µg/dL) after 3 - 5 days of treatment and at end of study (rifaximin:-54.55 µg/dL; paromomycin: -43.28 µg/dL), but these between-group differences were not statistically significant. Complete remissions were experienced by similar proportions of patients from each treatment group (77.7% for rifaximin and 78.5% for paromomycin), and all remaining patients experienced a partial submission. There were no statistically significant differences in efficacy parameters between groups.	
DiPiazza et al. <sup>120</sup>	Double-blind, crossover trial of rifaximin and neomycin to compare the effectiveness and tolerability of rifaximin/ lactulose to neomycin/ lactulose in patients with portal systemic encephalopathy secondary to liver cirrhosis	<ul style="list-style-type: none"> <li>• 1200 mg rifaximin (2 × 200 mg tablets TID) (N = 32)</li> <li>• 1500 mg neomycin (500 mg tablet TID) N = 14 for both treatments - crossover study</li> </ul> <p>Each drug was administered for 14 days (in two 7-day treatment periods), and treatment regimens were separated by a 7-day washout period.</p>	<ul style="list-style-type: none"> <li>• Patients with liver cirrhosis and chronic, permanent or recurrent PSE as defined by Zieve and Child</li> <li>• Good compliance with PSE medical treatment during the previous follow-up period of at least 8months</li> </ul>	All patients had grade I PSE at baseline, which remained unchanged during the entire study period. Compared to baseline, no significant improvements were seen in bradylalia, flapping tremor, and performance after both treatments (rifaximin and neomycin). In addition, no significant improvements occurred from baseline in the VEP or the trailmaking tests during the study period.	One patient withdrew because of bleeding of the esophageal varices after receiving one cycle of therapy (neomycin/rifaximin). The investigator determined that this was an “independent” event not related to treatment. No unpleasant, treatment-related side effects appeared during the study.
Eftimiadi et al. <sup>121</sup>  Also published		<ul style="list-style-type: none"> <li>• 1200 mg rifaximin (2 × 200 mg tablets TID) for 5 days (N = 20)</li> </ul>	<ul style="list-style-type: none"> <li>• Liver cirrhosis confirmed by laparobiopsy</li> </ul>	Both treatments (rifaximin and paromomycin) significantly decreased mean blood ammonia levels from baseline to the end of	There were no significant changes in hematologic, renal, or hepatic parameters

Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
as Testa et al <sup>122</sup>		<ul style="list-style-type: none"> <li>1500 mg paromomycin (2 × 250 mg tablets TID) for 5 days (N = 10).</li> </ul>	<ul style="list-style-type: none"> <li>Hepatic encephalopathy demonstrated by impaired number connection test or Retain Test II</li> <li>Elevated plasma levels of ammonia</li> <li>Lactulose (30 g/day for almost one week) within 2 weeks of study enrollment that did not produce a significant clinical improvement</li> <li>No antimicrobial agents within 4 weeks prior to enrollment</li> </ul>	treatment (from 95.1 ± 22.8 to 60.4 ± 32.5 µmol/L for rifaximin and ± 30.5 µmol/L for paromomycin; p<0.05). Both treatments also significantly reduced the time to take the number correction test (p < 0.05), which occurred after 2 days of treatment with paromomycin (from 135.5 ± 86.0 to 104.0 ± 81.2 msec) and after 3 days of treatment with rifaximin (from 75.4 ± 24.8 to 62.5 ± 12.8 msec).	following treatment with rifaximin and paromomycin.
Festi et al. <sup>123</sup> Combines results from 3 clinical studies.	Multi-center, open-label studies of rifaximin 1200 mg/day vs. lactulose (study 1), rifaximin 1200 mg/day vs. neomycin (study 2), and for 21 days, and rifaximin 1200 mg/day vs. no comparator (study 3)	<p>Treatment duration was 21 days for all 3 studies.</p> <p>Study 1: rifaximin 1200 mg/day (N = 30) vs. lactulose 40 g/day (N = 12)</p> <p>Study 2: rifaximin 1200 mg/day (N = 20) vs. neomycin (N = 15) 3000 mg/day</p> <p>Study 2: rifaximin 1200 mg/day (N=80)</p>	<p>For all 3 studies:</p> <ul style="list-style-type: none"> <li>Histologically confirmed liver cirrhosis</li> <li>Grade 1 HE as defined by Conn and identified by the presence of asterixis, difficulties in performing the Reitan test, EEG abnormalities (stages 1 and 2 of the Rhomer and Kutz classification), and blood ammonia levels &gt; 80 µg/dL</li> <li>No patients with</li> </ul>	<u>Study 1:</u> Both treatments (rifaximin and lactulose) were effective at reducing the neurological signs of hepatic encephalopathy in this study. Compared to baseline, significant reductions in the frequency of asterixis (p < 0.05) occurred after 3 days of therapy in both treatment groups, although the effect was more pronounced with rifaximin. In the rifaximin group, asterixis was reduced from 100% of patients at baseline to approximately 80% on Day 3, to 25% on Day 15, and to 0% on Day 21. In the lactulose group, asterixis was reduced from 100% of patients at baseline to approximately 90% on Day 3, to 58% on Day 15, and to 5% on Day 21. Both	<u>Study 1:</u> Mild side effects (nausea and abdominal cramps) were reported by some patients at the start of lactulose therapy, which disappeared by the end of the study. No side effects occurred during rifaximin administration. A significant increase in blood sodium levels, from 136.89 ± 3.69mEq/L at baseline to 140.11 ± 2.37 mEq/L (p<0.05), was seen at the end of the study in the rifaximin group. No significant changes in

Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
			more advanced stages of HE, psychiatric disorders, chronic renal, and/or respiratory failure, neoplasms, hemoglobin < 7 g/dL, or blood potassium < 3 mEq/L	<p>treatments also significantly reduced baseline ammonia blood levels after 3 days of treatment (<math>p &lt; 0.01</math>). In the rifaximin group, blood ammonia levels were reduced from approximately 114 <math>\mu\text{g}/100\text{ mL}</math> at baseline to 72 <math>\mu\text{g}/100\text{ mL}</math> on Day 7, and then to 46 <math>\mu\text{g}/100\text{ mL}</math> at the end of the study. In the lactulose group, blood ammonia levels were reduced from approximately 120 <math>\mu\text{g}/100\text{ mL}</math> at baseline to 80 <math>\mu\text{g}/100\text{ mL}</math> on Day 7, and then to 46 <math>\mu\text{g}/100\text{ mL}</math> at the end of the study. Significant reductions in EEG abnormalities also occurred during the study.</p> <p><u>Study 2:</u> Both treatments (rifaximin and neomycin) were effective at reducing the neurological signs of hepatic encephalopathy during the study, although at a faster rate after rifaximin than neomycin. Compared to baseline, significant reductions in the frequency of asterixis occurred after 3 days of rifaximin, from approximately 98% of patients at baseline to 80% on Day 3 (<math>p &lt; 0.001</math>). In contrast, significant reductions in asterixis at the <math>p &lt; 0.001</math> level were not observed until after 5 days of neomycin, from 98% of patients at baseline to approximately 60% of patients on Day 5. Asterixis was absent at the <math>p &lt; 0.001</math> level by Day 17 in all</p>	<p>the clinical laboratory parameters were reported with lactulose.</p> <p><u>Study 2:</u> Significant increases from baseline to the end of the study (<math>p &lt; 0.05</math>) were seen in blood sodium levels (from <math>134.75 \pm 5.38</math> to <math>138.70 \pm 3.69\text{ mEq/L}</math>) and albumin (from <math>48.55 \pm 5.92\%</math> to <math>51.94 \pm 3.30\%</math>) after rifaximin therapy. No significant increases in any of the laboratory parameters measured were reported for neomycin.</p>

Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
				<p>patients. A similar trend was observed in EEG abnormalities. Significant reductions occurred after 3 days of rifaximin, from 99% of patients at baseline to approximately 78% of patients on Day 3, but not until after 5 days of neomycin, from 99% of patients at baseline to approximately 70% of patients on Day 5. Rifaximin and neomycin also significantly reduced blood ammonia levels during the study (data not shown in publication), which had returned to normal by Day 7.</p> <p><u>Study 3:</u> Rifaximin significantly reduced the frequency of neurological signs of HE in all patients. Significant reductions occurred in the frequency of asterixis (<math>p &lt; 0.05</math>) after 5 days of treatment, from 98% of patients at baseline to approximately 58% of patients on Day 5. After 15 days of treatment, no patients exhibited asterixis. Blood ammonia levels returned to normal ranges (upper normal limit, 80 <math>\mu\text{g}/100\text{mL}</math>) after 5 days of rifaximin therapy; these reductions were significantly different (<math>p &lt; 0.01</math>) from the mean baseline level of 98 <math>\mu\text{g}/100\text{mL}</math>. Significant reductions also occurred in EEG abnormalities after 7 days of treatment (<math>p &lt; 0.01</math>); only a few patients had EEG abnormalities at the end of the treatment period.</p>	<p><u>Study 3:</u> No significant side effects were reported during the study. A significant decrease in bilirubin levels (<math>p &lt; 0.05</math>) was observed from baseline (<math>2.47 \pm 1.76 \text{ mg/dL}</math>) to the end of the study (<math>1.97 \pm 0.94 \text{ mg/dL}</math>). No other significant changes in biochemical parameters were observed during the study.</p>

Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
Massa et al <sup>124</sup>	Double-blind, double-dummy, randomized, controlled trial to compare the effectiveness of rifaximin to lactulose in cirrhotic patients with HE	<ul style="list-style-type: none"> <li>• 1200 mg rifaximin (2 × 200 mg tablets TID) plus lactulose placebo for 15 days (N = 20)</li> <li>• 60 mg lactulose (2 × 10 mg sachets TID) plus rifaximin placebo for 15 days (N = 20)</li> </ul>	<ul style="list-style-type: none"> <li>• Male or female patients with liver cirrhosis confirmed by clinical and laboratory data</li> <li>• Grade 1 to 3 hepatic encephalopathy according to West Haven criteria</li> <li>• No major psychiatric illness, chronic renal and/or respiratory insufficiency, tumors, intercurrent infection, hemoglobin &lt; 7 g/100 mL, potassium &lt; 3.0 mEq/L, or BUN &gt; 80 mg/dL</li> </ul>	At baseline, the two treatment groups were comparable; most patients had Grade 2 HE, while 3 had Grade 3 HE. Both treatments were effective at improving the signs and symptoms of hepatic encephalopathy, however, a significant difference was seen in favor of rifaximin compared to lactulose in the mean HE score on Day 6 (p < 0.01) and at the end of treatment (p < 0.05). Significant differences in favor of rifaximin were seen in the presence of asterixis on Day 6 (p < 0.05), in EEG anomalies on Day 6 (p < 0.01) and Day 9 (p < 0.05), in mental status from Day 12 through the end of treatment (p < 0.05), and in the time to take the Reitan test at the end of treatment (p < 0.001). Blood ammonia levels were also significantly decreased in favor of rifaximin after 15 days of treatment (from approximately 118 µg/100 mL to 62 µg/100 mL with rifaximin and from approximately 124 µg/100 mL to 72 µg/100 mL with lactulose) (p < 0.05). Overall, improvements in HE stage occurred in both treatment groups. Of the 20 rifaximin patients with HE at baseline (1 severe, 19 moderate), 6 had slight HE and 14 had no symptoms of HE after treatment. Of	Rifaximin was well tolerated and no undesired events were attributed to treatment with rifaximin. Flatulence, diarrhea, anorexia, nausea, abdominal cramps and burning sensation were reported with lactulose. Systemic tolerability was good with both treatments. Reductions in BUN and AST were more evident in the rifaximin group. BUN was reduced from 32.2 to 25.8 mg/dL after rifaximin while a slight increase from 38.7 to 40.4 mg/dL occurred with lactulose; this difference between the treatment groups was statistically significant (p < 0.001). Total bilirubin was reduced from 3.2 to 2.2 mg/dL after rifaximin and from 3.0 to 2.6 mg/dL after lactulose, and AST was reduced from 78.7 to 68.4 U/mL after rifaximin and 64.7 to 61 U/mL after lactulose.

Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
				the 20 lactulose patients with HE (2 severe, 18 moderate) at baseline, 2 patients had moderate HE, 7 patients had slight HE, and 11 patients had no symptoms of HE after treatment.	
Paik et al, <sup>125</sup>	Randomized study of rifaximin 2 × 200 mg tablets 3 times/day vs. lactulose 90 mL per day for 7 days (N=54)	<ul style="list-style-type: none"> <li>• 1200 mg rifaximin (2 × 200 mg tablets TID) plus lactulose placebo for 7 days (N = 32)</li> <li>• 90 mL lactulose (30 mL TID) for 7 days (N = 22)</li> </ul>	<ul style="list-style-type: none"> <li>• Liver cirrhosis diagnosed by clinical and laboratory data</li> <li>• Grades I to III HE as defined by Conn</li> <li>• Serum ammonia levels &gt; 75µmol/L</li> </ul>	Improvements in HE index were observed in 84% and 95% of rifaximin- and lactulose-treated patients, respectively. At the end of treatment, ammonia levels decreased in 25 (78.1%) of the 32 patients in the rifaximin group and 13 (59.1%) of the 22 lactulose group. Similarly, 26 (81.3%) out of 32 and 16 (72.7%) of 22 patients had improved HE grades in the rifaximin and lactulose groups, respectively.	One patient in the rifaximin group complained of abdominal pain and 1 patient experienced severe diarrhea in the lactulose group. No patients were withdrawn due to AEs.
Palmer <sup>126</sup>	Open-label, prospective, single-site, uncontrolled trial to evaluate the effectiveness and tolerability of rifaximin for the treatment of mild HE in patients with cirrhosis due to hepatitis C virus	<ul style="list-style-type: none"> <li>• 1200 mg rifaximin (2 × 200 mg tablets TID) for 14 days (N = 37)</li> </ul>	<ul style="list-style-type: none"> <li>• Liver cirrhosis due to hepatitis C virus</li> <li>• Grades I HE as defined by Conn</li> <li>• Not currently receiving HE treatment</li> </ul>	Overall, rifaximin treatment improved multiple clinical symptoms of HE. Rifaximin lowered serum ammonia levels in all 17 patients with available baseline data. Thirty-four of 35 patients had improved asterixis; 27 of 36 patients showed improvement in personality changes (irritability, anxiety and depression). Rifaximin also improved attention spans (26/31; 84%), reaction time (25/31; 81%), altered sleep patterns (20/30; 67%), slow or slurred speech (11/16; 69%) and the ability to perform mental tasks (addition/subtraction) (24/27; 89%) in the majority of patients.	Three patients (8%) reported mild bloating, and one each of the following: mild abdominal pain, diarrhea, nausea, flatulence, abdominal bloating, and headache.
Pedretti et al <sup>127</sup>	Randomized, double-blind, controlled trial to compare the effectiveness and safety	<ul style="list-style-type: none"> <li>• 1200 mg rifaximin (2 × 200 mg tablets TID) for 21 days (N = 15)</li> </ul>	<ul style="list-style-type: none"> <li>• Liver cirrhosis diagnosed by clinical and laboratory data</li> </ul>	At baseline, there were no significant differences in clinical and biochemical data, and the degree of	No side effects or changes in laboratory tests were reported after

Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
	of rifaximin to neomycin in patients with PSE secondary to liver cirrhosis	<ul style="list-style-type: none"> <li>3 g neomycin (1 g TID) for 21 days (N = 15)</li> </ul>	<p>and confirmed by liver biopsy and laparoscopy</p> <ul style="list-style-type: none"> <li>Grades I to III PSE as defined by West Haven and assessed by 2 independent observers</li> <li>No clinical, laboratory, or ultrasonographic data showing hepatocellular carcinoma and no GI bleeding on admission to the study</li> <li>No patients with grade IV PSE, hepatorenal syndrome, diabetes, chronic renal and pulmonary failure, or concomitant central nervous system diseases</li> <li>No concomitant medications that could interfere with the evaluation parameters (ie, lactulose or lactitol)</li> </ul>	<p>PSE between the treatment groups (rifaximin and neomycin). At the end of the study, the severity of PSE, EEG abnormalities, time to take the Reitan trail making test, and the presence of asterixis were significantly improved with both treatments (<math>p &lt; 0.05</math>) vs. baseline). The extent of improvements in these endpoints were numerically greater in the rifaximin group than in the neomycin group. Both treatments also significantly reduced baseline blood ammonia levels after 3 days of treatment (<math>p &lt; 0.001</math> for rifaximin and <math>p &lt; 0.005</math> for neomycin). However, rifaximin was more effective than neomycin at maintaining blood ammonia levels, and this difference was significant on days 14 and 21 (<math>p &lt; 0.005</math> for both days). Ammonia levels returned to normal by the end of the study only in the rifaximin group and to just above normal range in the neomycin group.</p>	<p>treatment with rifaximin. Twenty-six percent (n=4) of patients treated with neomycin had clinical laboratory abnormalities (increases in blood urea and plasma creatinine) during the study and 33% (n=5) reported adverse events (nausea, abdominal pain, vomiting).</p>
Puxxeddu et al. <sup>128</sup>	Open-label study of the efficacy and tolerability of short-term treatment of HE with rifaximin plus lactulose	<ul style="list-style-type: none"> <li>1200 mg rifaximin (2 × 200 mg tablets TID) + lactulose (sufficient dose to achieve 2-3 bowel movements/day) for 15 days (N = 55)</li> </ul>	<ul style="list-style-type: none"> <li>Liver cirrhosis confirmed by liver biopsy, and/or clinical, biochemical and instrumental signs</li> </ul>	<p>All patients had improvements in HE within 2-3 days of starting therapy. Improvements were seen in gait disturbances, behavior abnormalities, and results of the subtracting 7, 5-pointed star and</p>	<p>Rifaximin was well tolerated by all patients treated in this study. No significant side effects and no significant changes in chemistry</p>

Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
			<ul style="list-style-type: none"> <li>• Grade 1, 2 or 3 HE as defined by Conn</li> <li>• No patients with a GI hemorrhage, tumor, chronic renal and/or respiratory insufficiency, serious current psychiatric diseases, and serum levels of hemoglobin &lt; 7 g/100 mL, potassium &lt; 3.0 mEq/L, or BUN &gt; 80 mg/dL.</li> </ul>	<p>Reitan tests (<math>p &lt; 0.001</math>) after 2 days of rifaximin. Improvements were also seen in memory (<math>p = 0.001</math>), speech (<math>p = 0.002</math>), and writing abnormalities (<math>p &lt; 0.001</math>) after 3 days of treatment. Fifty percent of patients were free from asterixis after 3 days of treatment and this improvement was considered statistically significant (<math>p &lt; 0.020</math>). Asterixis was present in only 2 patients at the end of treatment. In addition, EEG abnormalities, present in 50% of patients at baseline, had returned to normal in all patients by the 8<sup>th</sup> day of treatment. Statistically significant reductions (<math>p &lt; 0.05</math>) in blood ammonia levels also occurred after 3 days of treatment (from approximately 160 <math>\mu\text{g}/100\text{ mL}</math> at baseline to approximately 140 <math>\mu\text{g}/100\text{ mL}</math>) and returned to values slightly above normal (&lt; 100 <math>\mu\text{g}/100\text{ mL}</math>) by the last day of treatment (15 days).</p>	and hematological parameters were observed during the study. All patients completed the study.
Riggio et al <sup>(129)</sup>	Open-label, randomized, controlled trial to compare two different treatments (lactitol or rifaximin) with no treatment in the prevention of post-TIPS HE	<ul style="list-style-type: none"> <li>• 1200 mg rifaximin (2 <math>\times</math> 200 mg tablets TID) (N = 25)</li> <li>• 60 g lactitol (20 g TID) (N = 25)</li> <li>• no treatment (N = 25)</li> </ul> <p>30-day treatment duration</p>	<ul style="list-style-type: none"> <li>• Patients with liver cirrhosis who underwent the TIPS procedure</li> </ul>	<p>There was no demonstrated difference in the incidence of overt (stage II or worse) HE in the month after TIPS placement with either rifaximin or lactitol prophylactic treatment. Twenty-five (33%) patients developed at least 1 episode of HE during the study period; 9 patients in the lactitol group, 8 in the rifaximin group, and 8 in the no treatment group. The 1-month</p>	<p>Five patients died (1 in no treatment, and 2 each in the lactitol and rifaximin groups. Causes of death were: 3 due to liver failure at 17, 18, and 20 days after TIPS; 1 due to cardiac failure; and 1 following surgery for strangulated hernial ring.</p>



Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
				cumulative incidence of HE observed in each group was similar ( $p = 0.97$ ). The number of severe episodes of HE (grade 3 – 4) in group was also similar (rifaximin and lactitol had 5 each; no treatment group had 3; $p = 0.71$ ). Most of the HE episodes were spontaneous without an evident precipitating event. Blood ammonia levels increased and the trail-making-test Part A score remained relatively unchanged from baseline in all groups in each group during the course of the study.	
Sama et al. <sup>130</sup>	Uncontrolled, open-label, pilot study to evaluate the effects of the rifaximin in patients with HE who were intolerant or nonresponsive to treatment with lactulose	<ul style="list-style-type: none"> <li>1200 mg rifaximin (<math>2 \times 200</math> mg tablets TID) for 10 days (N=26)</li> </ul>	<ul style="list-style-type: none"> <li>Subjects with liver cirrhosis or hepatic encephalopathy intolerant or nonresponsive to oral, nonabsorbable disaccharide (lactulose)</li> </ul>	Subjects split in groups of subjects intolerant to lactulose ( $n = 17$ ) or subjects who were nonresponders to lactulose ( $n = 9$ ). Mental status, asterixis, number-connection tests and arterial ammonia levels showed significant improvement after treatment with rifaximin in both groups. The mean (SD) PSE index significantly improved in both intolerant subjects (from 0.32 [0.07] to 0.22 [0.09]; $p < 0.01$ ) and in nonresponder subjects (from 0.38 [0.08] to 0.20 [0.11]; $p < 0.05$ ).	There was a slight increase in mean white blood cell count ( $p < 0.01$ vs baseline) and a slight decrease in mean serum creatinine concentration ( $p < 0.05$ vs baseline) in nonresponders. After treatment, the mean blood urea nitrogen level was significantly higher in nonresponders ( $p < 0.05$ vs intolerants).
<b>Long Term treatment regimens</b>					
Fera et al. <sup>100</sup>	Randomized, double-blind, double-dummy, controlled study of rifaximin vs. lactulose in cirrhotic patients with mild PSE 1200 mg/day or lactulose 120 mL/day during the first 2	<ul style="list-style-type: none"> <li>1200 mg rifaximin (<math>2 \times 200</math> mg tablets TID plus placebo sachets) (N = 20)</li> <li>120 mL/day lactulose (<math>2 \times 20</math> mg sachets TID plus placebo tablets)</li> </ul>	<ul style="list-style-type: none"> <li>Subjects with liver cirrhosis and Grade 1 portal systemic encephalopathy</li> <li>Ammonia blood levels up to 115 mg/100 mL without</li> </ul>	Both treatments (rifaximin and lactulose) were effective at improving the neurological signs and symptoms of hepatic encephalopathy. Asterixis decreased with both treatments, and the improvement was significant after 5 days of therapy ( $p$	Rifaximin was well tolerated in this study and no undesirable adverse events were attributed to rifaximin therapy. Moderate cases of meteorism and

Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
	weeks of each month for 3 months (N=40)	(N = 20) Subjects dosed first 2 weeks of each month for 3 months	evidence of neuropsychiatric disorders <ul style="list-style-type: none"> <li>No drugs capable of interfering with the evaluation parameters within 15 days of study entry</li> <li>No subjects with major psychiatric disorders, renal and/or chronic respiratory insufficiency, neoplasms, hemoglobin &lt;7 g/100 mL, and serum potassium &lt;3.0 mEq/L</li> </ul>	< 0.05) compared to baseline. Both treatments also reduced baseline serum ammonia concentrations to normal by the 10 <sup>th</sup> day of therapy (from approximately 124 to 80 µg/100 mL with rifaximin and from approximately 128 to 86 µg/100 mL with lactulose). Rifaximin was significantly more effective than lactulose in decreasing the severity of PSE (p < 0.05 after 2 weeks), decreasing EEG irregularities (p < 0.01 after 15 days and p < 0.05 after 30 days), and improving the subjects' mental status (p < 0.05 after 60 days and p < 0.02 after 90 days of therapy). Lactulose was significantly more effective than rifaximin at reducing the time for subjects to take the Reitan test (p < 0.01 after 60 days and p < 0.001 after 90 days of therapy).	abdominal pain (10 cases) and nausea (5 cases) occurred in association with lactulose therapy. Systemic tolerability was good with both treatments.
Loguercio et al. <sup>131</sup>	Double-blind, double-dummy, randomized, parallel group study to comparatively evaluate the effect of rifaximin, lactitol and their combination in treating chronic HE	<ul style="list-style-type: none"> <li>1200 mg RFX (2 × 200 mg tablets TID) + placebo (sorbitol) (N=14)</li> <li>60 g lactitol (20 g TID) + placebo (N=13)</li> <li>1200 mg RFX (2 × 200 mg tablets TID) + 60 g lactitol (20 g TID) (N=13)</li> </ul> 15 days each month for 3 months	<ul style="list-style-type: none"> <li>Male or female subjects with liver cirrhosis confirmed by clinical and laboratory data</li> <li>Grade 1 to 2 HE according to West Haven criteria</li> </ul>	Cyclic administration of rifaximin, alone or in combination with lactitol is more effective in the treatment of chronic HE than with lactitol alone. A significant improvement in mental status was observed from baseline in all treatments at the start of the 2 <sup>nd</sup> treatment cycle. However, 66.7% of rifaximin subjects achieved complete normalization in mental status (Conn score = 0), 54.6% in rifaximin/lactitol group and 20.0% in lactitol group by end of treatment (p < 0.05 in favor of the rifaximin groups in pairwise comparison to	No adverse events were reported for the study.

Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
				<p>lactitol alone).</p> <p>Asterixis significantly improved in all groups with no significant difference in any one group. The asterixis grade was normal in 75% of the subjects in the rifaximin group at the end of the study. Similar to the asterixis, the number connection test (NCT) showed no significant difference between groups; however, the rifaximin + lactitol and rifaximin groups improved sooner than the lactitol alone group. The proportions of subjects with normal blood ammonia levels was significantly higher in groups treated with rifaximin (<math>p &lt; 0.05</math>). Significant improvement in HE (based on improvement in mental status, asterixis, NCT and ammonia levels) was observed after the 1<sup>st</sup> cycle in the 2 rifaximin groups (<math>p &lt; 0.05</math>), while significant improvement in the lactitol group was not observed until the end of the 2<sup>nd</sup> cycle.</p>	

Reference	Study design	Treatment regimens and number of subjects	Inclusion Criteria	Efficacy Results	Safety Results
Miglio et al. <sup>13</sup>	Double-blind, multi-center, control study of rifaximin vs. neomycin in the treatment of grade 1 to 2 HE secondary to liver cirrhosis rifaximin 2 × 200 mg tablets 3 times/day vs. neomycin 1 g 3 times/day for 14 consecutive days per month (ie, 14 days on-treatment followed by 14 days off-treatment) for 6 months	<ul style="list-style-type: none"> <li>• 1200 mg RFX (2 × 200 mg tablets TID) + placebo (sorbitol) (N=30)</li> <li>• 3 g neomycin (1 g TID) + placebo (N=30)</li> </ul>	<ul style="list-style-type: none"> <li>• Subjects with liver cirrhosis confirmed by liver biopsy, laparoscopy with biopsy, ultrasonography alone or with clinical and laboratory data</li> <li>• Grade 1 to 2 hepatic encephalopathy defined using standardized and reproducible procedures that were established by all participating investigators</li> <li>• No subjects with neuropsychiatric disease, chronic renal or respiratory failure, neoplasms, levels of hemoglobin &lt; 7g/100 mL, potassium &lt; 3.0 mEq/L, and BUN &gt; 80 mg/100 mL</li> </ul>	Of the 60 subjects who were enrolled in the study, 11 (5 rifaximin, 6 neomycin) prematurely discontinued the study, 5 of whom were lost to follow-up and 6 because of adverse events. The remaining 49 evaluable subjects (25 rifaximin, 24 neomycin) experienced a statistically significant reduction in HE grade from baseline, beginning on Day 30 ( $p < 0.001$ ). No statistically significant differences were seen between the treatment groups. The greatest improvements occurred in neurological and neuropsychiatric signs (slurred or slowed speech, disturbances of memory and gait, abnormalities of behavior/mood and writing, asterixis, serial subtraction of 7s and 5-point star tests) for both treatment groups ( $p < 0.001$ ). Improvements in the Reitan test were also seen after both treatments ( $p < 0.02$ ). In addition, significant decreases in blood ammonia levels ( $p < 0.001$ ) occurred after rifaximin (from $210.2 \pm 65.6$ to $88.9 \pm 39.6$ $\mu\text{g/mL}$ ) and after neomycin (from $202.1 \pm 60.1$ to $86.2 \pm 42.9$ $\mu\text{g/mL}$ ).	Eleven subjects prematurely discontinued the study, 5 of whom were lost to follow-up and 6 because of AEs. Of the 6 subjects who discontinued due to an AE, 2 subjects (1 rifaximin, 1 neomycin) discontinued due to nausea; 2 subjects (1 rifaximin, 1 neomycin) discontinued due to dyspepsia; and 2 subjects (both neomycin) discontinued due to diarrhea.

a Portal-systemic encephalopathy (PSE) index is composed of 5 elements: mental status, presence and intensity of asterixis, time to complete tests of intellectual function (eg, number connection test), venous or arterial ammonia level, and EEG abnormalities (see reference 23).

## **10. Tabular Overviews of Maintenance of Remission Studies RFHE3001 and RFHE3001 and Supportive Efficacy Studies RFHE9702, RFHE9701, and RFHE9901.**

Table 44 below provides an overview of the primary efficacy study RFHE3001 and study RFHE3002. Table 45 provides an overview of supportive efficacy studies RFHE9702,<sup>14</sup> RFHE9701,<sup>15</sup> and RFHE9901.<sup>16</sup>

**Table 44 Overview of Studies in the Maintenance of Remission from HE**

Study Identifier	Study Description	Test Product; Dosage Regimen	Number of Subjects	Efficacy endpoints
RFHE3001 (Module 5.3.5.1.1)	<p>Phase 3, multi-center, 6-month, double-blind, randomized, placebo-controlled study of rifaximin vs. placebo in preventing HE episodes.</p> <p><u>Objectives:</u> Primary objective was to compare the maintenance of remission from previously demonstrated recurrent, overt, episodic HE as measured by Conn score and asterixis grade during 6 months of treatment with rifaximin at 550 mg BID or placebo. Secondary objectives were to compare safety, tolerability, and quality of life (ie, patient-reported outcomes) measurements using long-term dosing with rifaximin as compared to placebo in the maintenance of remission from HE.</p> <p><u>Subjects:</u> Eligible subjects had <math>\geq 2</math> episodes of overt HE associated with chronic hepatic cirrhosis with a documented severity equivalent to Conn score <math>\geq 2</math> within 6 months prior to screening (ie, subjects had documented recurrent, overt HE). At the baseline assessment, subjects were in remission (Conn score of 0 or 1) from previously demonstrated overt HE.</p> <p>Study was performed in the United States, Canada, and Russia.</p>	<p>Rifaximin 550-mg tablet BID or matching placebo tablet BID for 6 months.</p> <p>Most subjects (91.4% [rifaximin group] and 91.2% [placebo group]) received lactulose as a concomitant medication.</p>	<p>Planned: 125 subjects in each of the 2 treatment groups.</p> <p>Actual: 140 subjects in the rifaximin group and 159 subjects in the placebo group received at least 1 dose of study drug and were included in the ITT population.</p>	<p>The ITT population, defined as subjects who received at least 1 dose of study, was analyzed in this study.</p> <p><u>Primary efficacy endpoint</u> Primary efficacy endpoint was the time to first breakthrough overt HE episode.</p> <p>A breakthrough overt HE episode was defined as an increase of Conn score to Grade <math>\geq 2</math> (ie, 0 or 1 to <math>\geq 2</math>) 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 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 (ie, mortality status); and, if the subject had no breakthrough overt HE episode prior to contact, he/she was censored at the time of contact. Therefore, complete capture was achieved for breakthrough overt HE episodes up to 6 months postrandomization.</p> <p>The primary efficacy endpoint was analyzed using the Cox proportional hazards model. Covariate analyses were performed to evaluate the effect of prognostic factors. The highly significant protective effect of rifaximin was consistently observed in multivariate analysis and in subgroup analyses, in which the primary efficacy endpoint results were compared between the rifaximin and placebo groups across prespecified population subgroups.</p> <p><u>Key secondary efficacy endpoints</u></p> <ol style="list-style-type: none"> <li>1. Time to first HE-related hospitalization.</li> <li>2. Time to any increase from baseline in Conn score (mental status grade)</li> <li>3. Time to any increase from baseline in asterixis grade.</li> <li>4. Mean change from baseline in fatigue domain scores on the CLDQ at end of treatment.</li> <li>5. Mean change from baseline in venous ammonia concentration at end</li> </ol>

Study Identifier	Study Description	Test Product; Dosage Regimen	Number of Subjects	Efficacy endpoints
				of treatment.
RFHE3002 (Module 5.3.5.2.1)	<p>Ongoing phase 3, multicenter, open-label, treatment-extension study evaluating the long-term safety of rifaximin 550 mg BID in subjects with a history of recurrent, episodic, overt HE.</p> <p><u>Objective:</u> The primary objective of the study was to evaluate the long-term safety and tolerability of rifaximin treatment (550 mg BID) in subjects with a history of recurrent, overt, episodic HE.</p> <p><u>Subjects:</u> Eligible subjects had a history of overt HE episodes with a documented severity equivalent to Conn score <math>\geq 2</math> within 12 months prior to screening (<math>\geq 1</math> qualifying episode was required), a Conn score of <math>\leq 2</math> at the baseline assessment, and either participated in a previous HE study with rifaximin (ie, RFHE3001), or were new subjects. Study was performed in the United States, Canada, and Russia.</p>	<p>Rifaximin 550-mg tablet BID for <math>\geq 24</math> months, or until regulatory approval of rifaximin for HE, or until the sponsor closes the study, whichever comes first.</p> <p>A total of 75% of subjects received lactulose as a concomitant medication.</p>	<p>Planned: 500 subjects.</p> <p>Study is currently ongoing. 280 subjects were enrolled and 187 were active.</p>	<p>Conn scores and asterixis grades were assessed during the course of the study. Therefore, it was possible to determine time to breakthrough overt HE episodes for subjects who completed 6 months of rifaximin treatment in RFHE3001 and then entered RFHE3002, subjects who received placebo in RFHE3001 and then started rifaximin in RFHE3002, and in new subjects who started rifaximin therapy in RFHE3002. Unlike study RFHE3001, subjects were not required to withdraw from the study after experiencing a breakthrough overt HE episode.</p> <p>Efficacy assessments included the following:</p> <ul style="list-style-type: none"> <li>• Time to breakthrough overt HE. The definition for breakthrough overt HE was the same as described above for</li> <li>• Change from baseline in Conn scores over time.</li> <li>• Change from baseline in asterixis grades over time.</li> </ul>

**Table 45 Overview of Supportive Efficacy Studies in the Treatment of Subjects with HE**

Study Identifier	Study Description	Test Product; Dosage Regimen	Number of Subjects	Efficacy endpoints
RFHE9702 (study was published by Williams et al.) <sup>14</sup> (Module 5.3.5.4.1)	<p>Double-blind, dose-ranging study.</p> <p><u>Objectives:</u> To determine the safety and efficacy of rifaximin at 3 different doses in the treatment of HE.</p> <p><u>Subjects:</u> Subjects had Grade 1-3 HE at baseline. Study was performed at 4 centers in the United Kingdom.</p>	<p>Rifaximin 600 mg daily (200 mg TID). Rifaximin 1200 mg daily (400 mg TID). Rifaximin 2400 mg daily (800 mg TID). Duration of treatment was 7 days.</p>	<p>Planned: 54 subjects (18 per group). Actual: 54 subjects were randomized. 50 subjects completed (15, 19, and 16 subjects in the 600, 1200, and 2400 mg groups, respectively).</p>	<p>The ITT population, defined as subjects who received at least 1 dose of study drug, was analyzed in this study.</p> <p><u>Primary efficacy endpoint</u> The primary efficacy endpoint was the PSE index at the end of study. The PSE index was a component score that included scores for mental status, EEG, NCT, and venous ammonia levels. The PSE index was calculated as follows:  <math display="block">100 \times [\text{Mental status (Conn score)} \times 3 + \text{asterixis grade} \times 1 + \text{NCT grade} \times 1 + \text{ammonia grade} \times 1 + \text{EEG grade} \times 1 \text{ (if available)}] / 24 \text{ (or 28 if EEG is available)}].</math>                 (24 [or 28 if EEG results are included] is the highest possible score and higher scores are indicative of worse symptoms of HE.)                  Each of the PSE components was also assessed independently.</p>
RFHE9701 (study was published by Mas et al.) <sup>15</sup> (Module 5.3.5.4.2)	<p>Double-blind, double-dummy, comparative, phase 3 study.</p> <p><u>Objectives:</u> The objective of this study was to assess the efficacy and safety of rifaximin, in comparison to standard treatment with lactitol, in the treatment of hyperammonemic, cirrhotic patients with grade 1 to 3 acute or recurrent HE.</p> <p><u>Subjects:</u> Subjects had liver cirrhosis and grade 1 to 3 HE.  Study was performed at 14 centers in Spain.</p>	<p>Rifaximin 1200 mg daily (400 mg TID). Lactitol 60 g daily (20 g TID) Duration of treatment was 10 days</p>	<p>Planned: 120 subjects (60 per group). Actual: 104 subjects were randomized and 103 received at least 1 dose of study drug (50 and 53 subjects in the rifaximin and placebo groups, respectively)</p>	<p>The ITT population, defined as subjects who had at least 1 postbaseline assessment, was analyzed in this study.</p> <p><u>Primary efficacy endpoint</u> Four primary efficacy endpoints were defined:</p> <ol style="list-style-type: none"> <li>1. Improvement in mental status (Conn score)</li> <li>2. Therapeutic effect by using the PSE index (ie, change from baseline in PSE index)</li> <li>3. Decrease in venous ammonia levels</li> <li>4. Decrease in PSE index</li> </ol> <p>The PSE index in RFHE9701 is identical to the PSE index described above for RFHE9702. Therapeutic effect as measured by PSE efficacy index is calculated as follows:  <math display="block">[(\text{PSE index at baseline} - \text{PSE index at final assessment}) / \text{PSE index at baseline}] \times 100.</math></p> <p><u>Secondary efficacy endpoints</u> Secondary efficacy parameters were improvements in mental status (Conn score), asterixis grade, NCT score, EEG result, HE sum, number of bowel evaluations, and global response as determined by the investigator. The HE sum is the arithmetic sum of mental status/Conn score, asterixis grade, NCT score, venous ammonia grade, and EEG grade. Overall global response was categorized as cure, improvement, unchanged, and failure.</p>



Study Identifier	Study Description	Test Product; Dosage Regimen	Number of Subjects	Efficacy endpoints
RFHE9901 (study was published by Bass et al.) <sup>16</sup> (Module 5.3.5.4.3)	<p>Phase 3, international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study.</p> <p><u>Objectives:</u> The primary objective of this study was to investigate the efficacy and safety of a 14-day course of rifaximin in comparison with placebo in patients with chronic HE.</p> <p><u>Subjects:</u> Subjects had mild-to-moderate (mental status of grade 1 or 2) chronic HE and were intolerant to lactulose or lactitol.</p> <p>Study was performed at centers in Europe (8 centers) and in the United States (3 centers)</p>	<p>Rifaximin 1200 mg daily (400 mg TID). Placebo tablets.</p> <p>Duration of treatment was 14 days.</p>	<p>Planned: 112 subjects (56 per group). Actual: 93 subjects were randomized and received at least 1 dose of study drug (48 and 45 subjects in the rifaximin and placebo groups, respectively).</p>	<p>The ITT population, defined as subjects who received at least 1 dose of study drug, was analyzed in this study.</p> <p><u>Primary efficacy endpoint</u> The primary efficacy endpoint was the overall response rate, defined as the proportions of subjects who showed improvement in mental status (Conn score) by at least 1 level (eg, change from Conn score 2 to Conn score 1 or 0) after completing treatment when compared to baseline.</p> <p><u>Secondary efficacy endpoints</u> Secondary efficacy evaluations included changes from baseline in the PSE index; changes from baseline in the following PSE components: asterixis grade, NCT score, and EEG result; and changes from baseline in mini-mental status score.</p>

## **11. Current XIFAXAN Product Labeling**

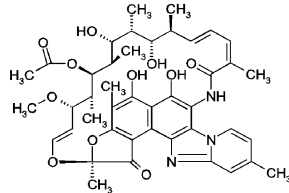
# XIFAXAN®

(rifaximin) tablets **200 mg**

**XIFAXAN® (rifaximin) Tablets**  
(zuh FAX in)

## DESCRIPTION

XIFAXAN® Tablets contain rifaximin, a semi-synthetic, non-systemic antibiotic. The chemical name for rifaximin is (2S,16Z,18E,20S,21S,22R,23R,24R,25S,26S,27S,28E)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca-[1,11,13]trien-imino)benzofuro[4,5-e]pyrido[1,2-α]-benzimidazole-1,15(2H)-dione,25-acetate. The empirical formula is C<sub>43</sub>H<sub>51</sub>N<sub>3</sub>O<sub>11</sub> and its molecular weight is 785.9. The chemical structure is represented below:



XIFAXAN® Tablets for oral administration are film-coated and contain 200 mg of rifaximin. Inactive ingredients are colloidal silicon dioxide, disodium edetate, glycerol palmitostearate, hypromellose, microcrystalline cellulose, propylene glycol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.

## CLINICAL PHARMACOLOGY

### Pharmacokinetics

**Absorption:** The mean pharmacokinetic parameters of rifaximin in 14 healthy subjects after a single oral 400-mg dose given as 2 x 200 mg doses under fed and fasting conditions are summarized in Table 1.

**Table 1. Effect of Food on the Mean ± S.D. Pharmacokinetic Parameters Following a Single 400-mg Dose of Rifaximin (N = 14)**

Parameter	Fasting	Fed
C <sub>max</sub> (ng/mL)	3.80 ± 1.32	9.63 ± 5.93
T <sub>max</sub> (h)	1.21 ± 0.47	1.90 ± 1.52
Half-Life (h)	5.85 ± 4.34	5.95 ± 1.88
AUC (ng•h/mL)	18.35 ± 9.48	34.70 ± 9.23
% Excreted in Urine	0.023 ± 0.009	0.051 ± 0.017

Rifaximin can be administered with or without food. Systemic absorption of rifaximin was low in both the fasting state and when administered within 30 minutes of a high-fat breakfast.

<sup>14</sup>C-Rifaximin was administered as a single dose to 4 healthy male subjects. The mean overall recovery of radioactivity in the urine and feces of 3 subjects during the 168 hours after administration was 96.94 ± 5.64% of the dose. Radioactivity was excreted almost exclusively in the feces (96.62 ± 5.67% of the dose), with only a small proportion of the dose (mean 0.32% of the dose) excreted in urine. Analysis of fecal extracts indicated that rifaximin was being excreted as unchanged drug. The amount of radioactivity in urine (<0.4% of the dose) suggests that rifaximin is poorly absorbed from the gastrointestinal tract and is almost exclusively and completely excreted in feces as unchanged drug. Mean rifaximin pharmacokinetic parameters were C<sub>max</sub> 4.3 ± 2.8 ng/mL and AUC<sub>0-12h</sub> 19.5 ± 16.5 ng•h/mL with a median T<sub>max</sub> of 1.25 hours.

Systemic absorption of rifaximin (200 mg three times daily) was also evaluated in 13 subjects with shigellosis on Days 1 and 3 of a three-day course of treatment. Rifaximin concentrations and exposures were low and variable. There was no evidence of accumulation of rifaximin following repeated administration for 3 days (9 doses). Peak plasma rifaximin concentrations after 3 and 9 consecutive doses ranged from 0.81 to 3.4 ng/mL on Day 1 and 0.68 to 2.26 ng/mL on Day 3. Similarly, AUC<sub>0-12h</sub> estimates were 6.95 ± 5.15 ng•h/mL on Day 1 and 7.83 ± 4.94 ng•h/mL on Day 3. Rifaximin is not suitable for treating systemic bacterial infections because less than 0.4% of the drug is absorbed after oral administration (see **WARNINGS**).

**Distribution:** Animal pharmacokinetic studies have demonstrated that 80% to 90% of orally administered rifaximin is concentrated in the gut with less than 0.2% in the liver and kidney, and less than 0.01% in other tissues. In adults with infectious diarrhea treated with rifaximin 800 mg daily for three days, concentrations of rifaximin in stools averaged ~8000 µg/g the day after treatment ended.

**Metabolism:** *In vitro* drug interaction studies have shown that rifaximin, at concentrations ranging from 2 to 200 ng/mL, did not inhibit human hepatic cytochrome P450 isoenzymes: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4. In an *in vitro* hepatocyte induction model, rifaximin was shown to induce cytochrome P450 3A4 (CYP3A4), an isoenzyme which rifampin is known to induce. Two clinical drug-drug interaction studies using midazolam and an oral contraceptive containing ethinyl estradiol and norgestimate demonstrated that rifaximin did not alter the pharmacokinetics of these drugs (see **Drug-Drug Interactions**).

**Excretion:** Rifaximin is excreted primarily in the feces. After oral administration of 400 mg <sup>14</sup>C-rifaximin to healthy volunteers, approximately 97% of the dose was recovered in feces, almost entirely as unchanged drug, and 0.32% was recovered in the urine.

### Special Populations

**Geriatric:** The pharmacokinetics of rifaximin in patients ≥65 years of age has not been studied.

**Pediatric:** The pharmacokinetics of rifaximin has not been studied in pediatric patients of any age.

**Gender:** The effect of gender on the pharmacokinetics of rifaximin has not been studied.

**Renal Insufficiency:** The pharmacokinetics of rifaximin in patients with impaired renal function has not been studied.

**Hepatic Insufficiency:** Mean peak rifaximin plasma concentrations of 13.5 µg/mL were detected in hepatic encephalopathy patients administered rifaximin 800 mg three times daily for 7 days. Less than 0.1% of the administered dose was recovered after 7 days. Because of the limited systemic absorption of rifaximin, no specific dosing adjustments are recommended for patients with hepatic insufficiency.

### Drug-Drug Interactions

In an *in vitro* hepatocyte induction model, rifaximin was shown to induce cytochrome P450 3A4 (CYP3A4), an isoenzyme which rifampin is known to induce. Two clinical drug-drug interaction studies were conducted using midazolam and an oral contraceptive containing ethinyl estradiol and norgestimate to assess the effect of rifaximin on the pharmacokinetics of these drugs.

The midazolam study was an open-label, randomized, crossover, drug-interaction trial designed to assess the effect of rifaximin 200 mg administered orally (PO) every 8 hours (Q8H)

for 3 days and every 8 hours for 7 days, on the pharmacokinetics of a single dose of either midazolam 2 mg intravenous (IV) or midazolam 6 mg PO. No significant difference was observed in the metrics of systemic exposure or elimination of IV or PO midazolam or its major metabolite, 1'-hydroxymidazolam, between midazolam alone or together with rifaximin. Therefore, rifaximin was not shown to significantly affect intestinal or hepatic CYP3A4 activity.

The oral contraceptive study utilized an open-label, crossover design in 28 healthy female subjects to determine if rifaximin 200 mg PO administered Q8H for 3 days altered the pharmacokinetics of a single dose of an oral contraceptive containing 0.07 mg ethinyl estradiol and 0.50 mg norgestimate. Results showed that the pharmacokinetics of single doses of ethinyl estradiol and norgestimate were not altered by rifaximin.

### Microbiology

Rifaximin acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis.

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

Rifaximin is a structural analog of rifampin. Organisms with high rifaximin minimum inhibitory concentration (MIC) values also have elevated MIC values against rifampin. Cross-resistance between rifaximin and other classes of antimicrobials has not been studied.

Rifaximin has been shown to be active against the following pathogen in clinical studies of infectious diarrhea as described in the **INDICATIONS AND USAGE** section: *Escherichia coli* (enterotoxigenic and enteroaggregative strains).

### Susceptibility Tests

*In vitro* susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) agar dilution method M7-A6<sup>1</sup>. However, the correlation between susceptibility testing and clinical outcome has not been determined.

### INDICATIONS AND USAGE

XIFAXAN® Tablets are indicated for the treatment of patients (≥12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* (see **WARNINGS, Microbiology, and CLINICAL STUDIES**).

XIFAXAN® Tablets should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*.

### CONTRAINDICATIONS

XIFAXAN® Tablets are contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN® Tablets.

### WARNINGS

XIFAXAN® Tablets were not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*. XIFAXAN® Tablets are not effective in cases of travelers' diarrhea due to *Campylobacter jejuni*. The effectiveness of XIFAXAN® Tablets in travelers' diarrhea caused by *Shigella* spp. and *Salmonella* spp. has not been proven. XIFAXAN® Tablets should not be used in patients where *Campylobacter jejuni*, *Shigella* spp., or *Salmonella* spp. may be suspected as causative pathogens.

XIFAXAN® Tablets should be discontinued if diarrhea symptoms get worse or persist more than 24-48 hours and alternative antibiotic therapy should be considered.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile*.

### PRECAUTIONS

#### General

The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

#### Information for Patients

Patients should be advised that XIFAXAN® Tablets may be taken with or without food. Patients should be advised that XIFAXAN® Tablets should be discontinued if their diarrhea persists **more than 24-48 hours** or worsens, or if they have fever and/or blood in the stool that they should seek medical care (see **Patient Information**).

#### Drug-Drug Interactions

Although *in vitro* studies demonstrated the potential of rifaximin to interact with cytochrome P450 3A4 (CYP3A4), a clinical drug-drug interaction study demonstrated that rifaximin did not significantly affect the pharmacokinetics of midazolam either presystemically or systemically. An additional clinical drug-drug interaction study showed no effect of rifaximin on the presystemic metabolism of an oral contraceptive containing ethinyl estradiol and norgestimate. Therefore, clinical interactions with drugs metabolized by human cytochrome P450 isoenzymes are not expected (see **Pharmacokinetics** and **Drug-Drug Interactions**).

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were not conducted. Rifaximin was not genotoxic in the bacterial reverse mutation assay, chromosomal aberration assay, rat bone marrow micronucleus assay, and the CHO/HGPRT mutation assay. There was no effect on fertility in male or female rats following the administration of rifaximin at doses up to 300 mg/kg (approximately 5 times the clinical dose, adjusted for body surface area).

#### Pregnancy—Teratogenic Effects (Pregnancy Category C)

##### Pregnancy

**Pregnancy category C:** Rifaximin was teratogenic in rats at doses of 150 to 300 mg/kg (approximately 2.5 to 5 times the clinical dose, adjusted for body surface area) and in rabbits at doses of 62.5 to 1000 mg/kg (approximately 2 to 33 times the clinical dose, adjusted for body surface area). These effects include cleft palate, agnathia, jaw shortening, hemorrhage, eye partially open, small eyes, brachygnathia, incomplete ossification, and increased thoracolumbar vertebrae.

There are no adequate and well controlled studies in pregnant women. XIFAXAN® Tablets should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

#### Use During Lactation

It is not known whether rifaximin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from XIFAXAN® Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

#### Pediatric Use

The safety and effectiveness of XIFAXAN® Tablets in pediatric patients less than 12 years of age have not been established.

#### Geriatric Use

Clinical studies of XIFAXAN® Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects.

#### ADVERSE REACTIONS

The safety of XIFAXAN® Tablets 200 mg taken three times a day (TID) was evaluated in 320 patients in two placebo-controlled clinical trials with 95% of patients receiving at least three days of treatment with XIFAXAN® Tablets. All adverse events for XIFAXAN® Tablets 200 mg TID that occurred at a frequency  $\geq 2\%$  in the two placebo-controlled trials combined are provided in Table 2. (These include adverse events that may be attributable to the underlying disease.)

**Table 2. All Adverse Events With an Incidence  $\geq 2\%$  Among Patients Receiving XIFAXAN® Tablets, 600 mg/day, in Placebo-Controlled Studies**

MedDRA Preferred Term	Number (%) of Patients	
	XIFAXAN® Tablets, 600 mg/day (N = 320)	Placebo N = 228
Flatulence	36 (11.3%)	45 (19.7%)
Headache	31 (9.7%)	21 (9.2%)
Abdominal Pain NOS	23 (7.2%)	23 (10.1%)
Rectal Tenesmus	23 (7.2%)	20 (8.8%)
Defecation Urgency	19 (5.9%)	21 (9.2%)
Nausea	17 (5.3%)	19 (8.3%)
Constipation	12 (3.8%)	8 (3.5%)
Pyrexia	10 (3.1%)	10 (4.4%)
Vomiting NOS	7 (2.2%)	4 (1.8%)

The following adverse events, presented by body system, have also been reported in  $<2\%$  of patients taking XIFAXAN® Tablets in the two placebo-controlled clinical trials where the 200 mg taken three times a day dose was used. The following includes adverse events regardless of causal relationship to drug exposure.

**Blood and Lymphatic System Disorders:** lymphocytosis, monocytosis, neutropenia

**Ear and Labyrinth Disorders:** ear pain, motion sickness, tinnitus

**Gastrointestinal Disorders:** abdominal distension, diarrhea NOS, dry throat, fecal abnormality NOS, gingival disorder NOS, inguinal hernia NOS, dry lips, stomach discomfort

**General Disorders and Administration Site Conditions:** chest pain, fatigue, malaise, pain NOS, weakness

**Infections and Infestations:** dysentery NOS, respiratory tract infection NOS, upper respiratory tract infection NOS

**Injury and Poisoning:** sunburn

**Investigations:** aspartate aminotransferase increased, blood in stool, blood in urine, weight decreased

**Metabolic and Nutritional Disorders:** anorexia, dehydration

**Musculoskeletal, Connective Tissue, and Bone Disorders:** arthralgia, muscle spasms, myalgia, neck pain

**Nervous System Disorders:** abnormal dreams, dizziness, migraine NOS, syncope, loss of taste

**Psychiatric Disorders:** insomnia

**Renal and Urinary Disorders:** choloria, dysuria, hematuria, polyuria, proteinuria, urinary frequency

**Respiratory, Thoracic, and Mediastinal Disorders:** dyspnea NOS, nasal passage irritation, nasopharyngitis, pharyngitis, pharyngolaryngeal pain, rhinitis NOS, rhinorrhea

**Skin and Subcutaneous Tissue Disorders:** clamminess, rash NOS, sweating increased

**Vascular Disorders:** hot flashes NOS

#### Postmarketing Experience

The following events: hypersensitivity reactions, including exfoliative dermatitis, rash, angioneurotic edema (swelling of face and tongue and difficulty swallowing), urticaria, flushing, and pruritus; have been identified during postapproval use of XIFAXAN® Tablets. These events occurred as early as within 15 minutes of drug administration.

#### DRUG ABUSE AND DEPENDENCY

##### Abuse

None reported.

##### Dependency

None reported.

#### OVERDOSAGE

No specific information is available on the treatment of overdosage with XIFAXAN® Tablets. In clinical studies at doses higher than the recommended dose ( $> 600$  mg/day), adverse events were similar to the recommended dose (200 mg taken three times a day) and to placebo. In the case of overdosage, discontinue XIFAXAN® Tablets, treat symptomatically, and institute supportive measures as required.

#### DOSEAGE AND ADMINISTRATION

XIFAXAN® Tablets can be administered orally with or without food. For travelers' diarrhea, the recommended dose is one 200 mg tablet taken three times a day for 3 days.

#### HOW SUPPLIED

XIFAXAN® Tablets are available as circular, pink-colored, biconvex tablets containing 200 mg rifaximin, debossed with "Sx" on one side.

NDC 65649-301-03	Bottles of 30 tablets
NDC 65649-301-41	Bottles of 100 tablets
NDC 65649-301-05	Carton of 100 Tablets, Unit Dose

Store XIFAXAN® Tablets at 20–25°C (68–77°F); excursions permitted to 15–30°C (59–86°F). See USP Controlled Room Temperature.

#### CLINICAL STUDIES

The efficacy of rifaximin (200 mg orally taken three times a day for 3 days) was evaluated in two randomized, multi-center, double-blind, placebo-controlled studies in adult subjects with travelers' diarrhea. One study was conducted at clinical sites in Mexico, Guatemala, and Kenya (Study 1). The other study was conducted in Mexico, Guatemala, Peru, and India (Study 2). Stool specimens were collected before treatment and 1 to 3 days following the end of treatment to identify enteric pathogens. The predominant pathogen in both studies was *Escherichia coli*.

The clinical efficacy of rifaximin was assessed by the time to return to normal, formed stools and resolution of symptoms. The primary efficacy endpoint was time to last unformed stool (TLUS) which is defined as the time to the last unformed stool passed, after which clinical cure was declared. Table 3 displays the median TLUS and the number of patients who achieved clinical cure for the intent to treat population (ITT) of Study 1. The duration of diarrhea was significantly shorter in patients treated with rifaximin than in the placebo group. More rifaximin-treated patients were classified as clinical cures than were those in the placebo group.

**Table 3. Clinical Response in Study 1 (ITT population)**

	Rifaximin (n=125)	Placebo (n=129)	Estimate (97.5% CI)	P-Value
Median TLUS (hours)	32.5	58.6	1.78* (1.26, 2.50)	0.0002
Clinical cure, n (%)	99 (79.2)	78 (60.5)	18.7* (5.3, 32.1)	0.001

a Hazard Ratio

b Difference in rates

Microbiological eradication (defined as the absence of a baseline pathogen in culture of stool after 72 hours of therapy) rates for Study 1 are presented in Table 4 for patients with any pathogen at baseline and for the subset of patients with *Escherichia coli* at baseline. *Escherichia coli* was the only pathogen with sufficient numbers to allow comparisons between treatment groups.

Even though rifaximin had microbiologic activity similar to placebo, it demonstrated a clinically significant reduction in duration of diarrhea and a higher clinical cure rate than placebo. Therefore, patients should be managed based on clinical response to therapy rather than microbiologic response.

**Table 4. Microbiologic Eradication Rates in Study 1 Subjects with a Baseline Pathogen**

	Rifaximin	Placebo
Overall	48/70 (68.6)	41/61 (67.2)
<i>E. coli</i>	38/53 (71.7)	40/54 (74.1)

Study 2 provided additional information to support the results presented for Study 1. This study also provided evidence that rifaximin-treated subjects with fever and/or blood in the stool at baseline had prolonged TLUS. These subjects had lower clinical cure rates than those without fever or blood in the stool at baseline. Many of the patients with fever and/or blood in the stool (dysentery-like diarrheal syndromes) had invasive pathogens, primarily *Campylobacter jejuni*, isolated in the baseline stool.

Also in this study, the majority of the rifaximin-treated subjects who had *Campylobacter jejuni* isolated as a sole pathogen at baseline failed treatment and the resulting clinical cure rate for these patients was 23.5% (4/17). In addition to not being different from placebo, the microbiologic eradication rates for subjects with *Campylobacter jejuni* isolated at baseline were much lower than the eradication rates seen for *Escherichia coli*.

In an unrelated Phase 1, open-label, pharmacokinetic study of oral XIFAXAN® Tablets 200 mg taken every 8 hours for 3 days, 15 adult subjects were challenged with *Shigella flexneri* 2a, of whom 13 developed diarrhea or dysentery and were treated with rifaximin. Although this open-label challenge trial was not adequate to assess the effectiveness of rifaximin in the treatment of shigellosis, the following observations were noted. Eight subjects received rescue treatment with ciprofloxacin either because of lack of response to rifaximin treatment within 24 hours (2), or because they developed severe dysentery (5), or because of recurrence of *Shigella flexneri* in the stool (1). Five of the 13 subjects received ciprofloxacin although they did not have evidence of severe disease or relapse.

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#### Rx Only

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VENART-65-1

March 2008

Product protected by US Patent No. 7,045,620 and other pending applications.

**Salix** 

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