CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-554

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 14, 2010
From	Hugo E Gallo-Torres, MD, PhD, PNS, Clinical Team Leader, DGP, HFD-180
Subject	Cross-Discipline Team Leader Review
NDA Supplement#	NDA 22-554
Applicant	Salix Pharmaceuticals, Inc.
Date of Submission	June 24, 2009
PDUFA Goal Date	December 24, 2009
Proprietary Name / Therapeutic class	XIFAXAN® [rifaximin] Rifaximin is an aminoglycoside semi-synthetic antibiotic derived from rifamycin
Dosage forms / Strength **Dosing regimen**	Immediate release tablet, 550 mg 550 mg orally twice per day
Proposed Indication	Maintenance of remission of Hepatic Encephalopathy [HE]
Intended Population	**Patients with cirrhosis or portal hypertension and history of Hepatic Encephalopathy**
Recommended:	Approval; with Post-Marketing Requirements

EXECUTIVE SUMMARY

Pursuant to Section 505(b)(l) of the Federal Food, Drug and Cosmetic Act, the applicant, Salix Pharmaceuticals, Inc. (Salix), on June 24, 2009, submitted an efficacy supplement to NDA 021361 for XIFAXAN® (rifaximin) tablets regarding the proposed orphan drug indication of the maintenance of remission of hepatic encephalopathy (HE) in patients 18 years of age or older. Rifaximin is a broad spectrum antibiotic whose putative mode of action in inhibiting the occurrence of episodes of HE is by inhibiting the division of intestinal urea-deaminating and bacteria that are responsible for the formation of ammonia and other compounds considered to be important to the pathogenesis of HE. This supplement was a Type 6 NDA, administratively filed under NDA 022554 that provided data for a new strength (550 mg BID) of the currently approved (200 mg) oral tablet dosage form.

Rifaximin was granted orphan designation for the treatment of HE on February 10, 1998. This designation encompasses the proposed indication as confirmed with the office of OPD on November 24, 2008. Application under NDA 22-554 consisted of data from a global clinical development program conducted under IND 59,133. Salix requested and was ultimately granted priority review status for the efficacy supplement by DGP[1].

HE is a condition difficult to treat and even more difficult to study. The CDTL has elected to introduce the subject matter addressing basic concepts related to HE[2] per se; this is followed by short summaries of the results of reviews and evaluations from different disciplines involved in the various aspects of NDA evaluation. Because we are dealing with a single pivotal trial approach to evaluate the efficacy of the drug, the emphasis is on the design,

[1] However due to a major amendment to the application during the review cycle, the PDUFA goal date was extended by three months

[2] To this purpose, the CDTL review makes use of gathered information from the recent annual meeting of the American Association for the Study of Liver Disease, November 2009, Boston, MASS.

detailed execution, collection of data, and proper interpretation of findings in Study RFHE3001 that support our conclusions and recommendations for regulatory action, which might include post-marketing requirements.

Key concepts on the pathogenesis of HE (Type C) are summarized first. HE in end-stage chronic liver failure has cognitive, psychiatric and motor components, high prevalence post-TIPS[3], major impact on Health-related Quality of Life. Both global and regional selected metabolic and functional changes in brain occur in Type C HE. Ammonia and glutamine concentrations increase throughout brain, manganese concentrations increase in globus pallidus leading to MRI signal hyperintensities[4]. Neurosteroids such as allopregnanolone result in "increased GABAergic tone" and neuroinhibition in type C HE[5]. Clinical trials in Type C HE demonstrate that prevention and treatment continues to rely upon ammonia-lowering strategies: -- Reduction of gut ammonia production by lactulose, rifaximin, or probiotics; -- Increased ammonia removal by residual hepatocytes, skeletal muscle using L-ornithine L aspartate [LOLA].

Practical issues in evaluation and management of subclinical and chronic encephalopathy are summarized next. The spectrum of HE ranges from minimal hepatic encephalopathy [MHE] to coma. *MHE adversely impacts quality of life, earning capacity and driving ability*. The differential diagnosis of HE is vast with several overlapping conditions that co-exist in the same patients. Clinical tools for the diagnosis of HE are often subjective while psychometric tools have yet to gain wide acceptance. An exhaustive search for a precipitating factor is essential for HE treatment. Although mentioned for completeness and academic purposes, there is no significant role of neomycin, flumazenil, metronidazole and zinc as stand-alone, therapies for HE[6]. Other drugs that have been used outside the U.S. are the already mentioned LOLA [L-ornithine L-aspartate] infusion and oral forms, acetyl carnitine and acarbose.

Table OES-1 summarizes the main findings, conclusions and recommendations from the multidisciplinary reviews and evaluations of NDA 22-554. All reviews primarily address issues related to the new HE indication and examine data from the pivotal Study RFHE30001 and its extension, RFHE3002. There is no separate Pharmacology/Toxicology review, but there are issues that need to be addressed via a PMR. Clinical Pharmacology notes that the efficacy supplement proposed a dose of XIFAXAN® [600 mg] that is higher than the currently approved dose [200 mg TID] and a longer duration in patients with chronic liver disease and HE. There are concerns about the higher bioavailability of XIFAXAN® in these HE patients[7] when compared to normals. The Clinical/Statistical/Neurologic evaluations of efficacy focused on results of RFHE3001 and also from Study RFHE3002, a treatment extension, open-label, non-comparative trial that enrolled patients that had participated in -3001. OSE performed a review of available post-marketing AE reporting data[8] but no signals of concern were found. Rifaximin has a broad spectrum of antimicrobial activity both against gram negative and gram positive organisms, but certain strains of each of these groups that colonize the gut lumen are not sensitive to this antibiotic. In particular, many strains of *Bacteroides fragilis,* anaerobic organisms that are major colonizers of the gut, are highly resistant to rifaximin. In addition, within a short time of rifaximin exposure many antimicrobial sensitive gram negative and gram positive luminal organisms develop significant resistance to the antibiotic; this issue needs to be further addressed. In the meantime, the microbiology assessment by the Division of Special pathogen and Transplant Products of publications describing results of in vitro studies and reports from two clinical trials for the short-term use in the treatment of traveler's diarrhea found results from these publications inadequate to support sponsor' s proposed labeling revisions. The in vitro data lacked information regarding specific methodology. Data from the two clinical trials were inadequate because these studies did not correlate changes in pathogen eradication with significant alteration of gut flora or describe a unique mechanism of action. Finally, at the end of Table OES-1 is a short summary of the Questions to and Answers from the GIDAC meeting of February 23, 2010 on the efficacy and safety of NDA 22-554 for XIFAXAN® [rifaximin) tables 550 mg for the indication maintenance of remission of HE. This use is for patients 18 y of age and older.

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[3] TIPS = Transjugular intrahepatic porto-systemic stent shunt. It is a metal prosthesis which functions like a side-to-side porto-caval shunt. It connects a branch of the hepatic vein to a branch of the portal vein, thereby allowing decompression of the portal venous system.

[4] Molecular neurobiology reveals altered expression of genes coding for key brain proteins involved in cell volume regulation, metabolism and neurotransmission.

[5] There is limited translational research involving the brain in type C HE.

[6] There are several other drugs in the pipeline for HE that are undergoing trials in the U.S.

[7] All in all, this issue of higher absorption in hepatic impairment patients with HE is incompletely addressed.

[8] Xifaxan® has been approved for marketing in the U.U. for over 6 years and is approved in other countries for HE and other indications.

When all things are considered, RFHE3001, a randomized, double blind, 2-arm, placebo control, multicenter, multi-country study was well designed and apparently well executed[9]. It is important to reiterate that HE is a serious, rare, complex, episodic, neuropsychiatric syndrome associated with advanced liver disease. Recruiting patients for these trials is a challenge and, during the review and evaluation of the submitted NDA 22-554, there have been questions and need for clarification about many aspects of trial design and execution. The primary objective of this study was to compare the effects of rifaximin against placebo in "maintenance of remission" in patients who previously had episodes of hepatic encephalopathy, but were judged to be in remission at study entry. No information was provided as to how "remission" was to be accomplished but the key inclusion criteria were: 1) Male or female [10]; 2) Age $\geq$ 18 years; 3) Conn score of 0 or 1 at entry, indicating that the patient was in remission from HE; 4) Two or more episodes of HE[11] associated with cirrhosis or portal hypertension equivalent to a Conn score of $\geq$ within 6 months prior to screening; 5) Model for End-Stage Liver Disease [MELD] $\leq$ 25; and 6) Exclusion of episodes of HE primarily attributable to the following: gastrointestinal hemorrhage requiring $\geq$ 2 Units of blood; medications such as narcotics, tranquilizers, and sedatives; renal failure requiring dialysis; or a central nervous system insult such as subdural hematoma. Patients should have continued to be in remission during the observation period, lasting a maximum of 6 days between screening and baseline.

All in all, primary and secondary efficacy parameters were adequately stipulated in the protocol. The primary efficacy parameter was the time to the first breakthrough episode of HE. A breakthrough episode of HE was defined as either a) An increase in Conn score from Grade 0 or 1 [the entry score] to Grade $\geq$ 2 or b) An increase in Conn score and asterixis grade of one each for those with a baseline Conn score of 0. The assignment of Conn scores was guided, in a manner not clearly outlined in the study protocol or report, by Hepatic Encephalopathy Scoring Algorithm grades [HESA][12]. HESA is one of the several approaches – none has been validated – that is used for this purpose. The diagnosis of a breakthrough episode of HE was made either by direct assessment of the patient by study personnel or by indirect means through information obtained – partly retrospectively – from hospital or emergency room medical records or treating physicians, caregivers, and other sources. The time to the first breakthrough episode of HE was defined as the duration between the date of the first dose of test medication and the date of commencement of the first breakthrough episode of HE (treatment failure = non-responder)[13]. Subjects who completed the study and did not experience a breakthrough overt HE (i.e., treatment success) were censored at the time of their 6-month visit. Subjects, or caregivers of subjects, who terminated early for reasons other than a breakthrough overt HE episode were contacted at 6 months from randomization to determine if subjects had experienced a breakthrough overt HE episode or other outcome (i.e., mortality status); and, if the subject had no breakthrough overt HE event prior to contact, he/she was censored at the time of contact. Therefore, it seems that complete capture was achieved for breakthrough overt episodes up to 6 months post-randomization. Patients who had a breakthrough episode of HE were withdrawn from the trial but also had the option of continuing in the open-label uncontrolled extension study [RFHE3002]. Patients who completed the entire 6-month treatment period without experiencing a breakthrough episode of HE were censored at the time of the final study visit. It is worth clarifying that enrollment into RFHE3002 included subjects who were withdrawn for a breakthrough overt HE episode as well as those who completed 6 months of double-blind treatment. The end-of-study visit was considered the screening visit for the continuation trial [-3002]. Subjects who did not enroll in the open-label continuation study within 16 days of the end-of-study/early termination visit completed a follow-up visit [Day 182 $\pm$ 2].

The first three key secondary endpoints designated by the applicant as the most clinically important were: time to first HE-related hospitalization; time to any increase from baseline in Conn score; and time to any increase from

[9] HE is a formidable burden on the patient, his/her family, and the healthcare system. Overt HE episodes are debilitating, can present without warning, render the patient incapable of self-care, and frequently result in hospitalization. Overt, episodic HE is common among patients with liver cirrhosis; however, the condition is rare among individuals in the overall, general population.

[10] If female, was to be of non-childbearing-potential or practicing adequate birth control.

[11] An episode of hepatic encephalopathy was defined as a Conn score rising from 0 or 1 to $\geq$ 2 and returning to a score of 0 or 1; at least one episode of hepatic encephalopathy must have been confirmed by reviewing medical records from a treating physician, clinic, or hospital, while other episodes could have been documented from descriptions given by the subject's caregiver.

[12] The Hepatic Encephalopathy Scoring Algorithm has been proposed as a structured means of assigning Conn scores, thereby making the latter assignment more precise.

[13] Because subjects discontinued at the time of breakthrough overt HE episode, the duration or severity of HE episodes was not captured in this study.

baseline in asterixis grade. The applicant pre-specified the order of analysis of these and two additional secondary endpoints, using a gate keeping procedure for multiplicity adjustment.

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

- In the rifaximin group, 8 patients were determined to have breakthrough episodes of HE based on direct observation by study site personnel, while 22 patients were diagnosed to have such episodes by indirect means; thus, only 27.7% of patients in the treatment group diagnosed with breakthrough episodes of HE had that determination made by direct observation.
- In the placebo group, 30 patients were determined to have breakthrough episodes of HE based on direct observation, while 40 patients were diagnosed to have such episodes by indirect means; thus, in the placebo group a higher proportion of the events, 42.9%, were diagnosed by direct observation.
- When the patients who were indirectly diagnosed were analyzed by admission to the hospital with a diagnosis of HE [Breakthrough HE Hospitalization], which would imply that diagnosis was made by observation of a clinician, who may not be the investigator, it is apparent that ca. 30% of patients in each group [33.3% in Rifaximin and 30% in Placebo] were diagnosed neither with clinician observation in a hospital visit nor an evaluation by an investigator during a site visit. The proportion of this event was slightly higher in the rifaximin arm.

The primary efficacy analysis was performed on the I-T-T- population[14]**.** Episodes of breakthrough overt HE occurred in 31/140 patients treated with rifaximin and 73/159 patients treated with placebo during the period from randomization until Month 6. The primary efficacy analysis indicated that the hazard ration for the risk of experiencing breakthrough episodes of overt HE was 0.421 (95% CI: 0.276 to 0.641; p-value < 0.0001) for the rifaximin group versus the placebo group, during the 6 month period of the trial. Various sensitivity analyses, carried out by Dr. B Vali, tended to support these results. Analyses based on the Cox proportional hazards model yielded at least nominally statistically significant results favoring rifaximin over placebo for two secondary efficacy parameters that were prospectively stipulated as being "key": the time to the first HE-related hospitalization and the time to any increase from baseline in Conn score. It is to be noted that, during deliberations by the participants at the AC meeting, there were concerns raised because of clinical efficacy data of use of the product as a sole agent without accompanying use of lactulose.

> Addressing the validity of the assessment tool for the primary endpoint in pivotal trial RFHE3001, Dr. J Mani, from CDER's Division of Neurology Products, raised questions about how and whether it was consistently used to perform assessments in the trial; he expressed concern regarding the interpretability of the observed clinical outcomes in light of these issues. Advisory Committee members expressed that it is difficult to define, describe, and assign a specific Conn score to a patient at any one specific time; mental status fluctuations are observed over the course of the day. Although the Conn Score is a simple and reasonable measure, the issue lies in that it may not be adequate to address the syndrome over time and to properly assess a patient[15].

Although there are some lingering concerns, in the main, the data in NDA 22-554 indicates that **rifaximin is safe**. In the randomized controlled trial the overall numbers of serious and common adverse events were similar in both the experimental treatment and placebo groups. The SAE of infection was higher in the Xifaxan® group, due mainly to increase incidence of pneumonia and colitis (Table 37 in Clinical Review), as were SAEs in the categories Gastrointestinal disorders and General Disorders (edema and pyrexia). Analysis of mortality by Child's class, showed some increase in mortality in the Child's C patients (a small subset of the total study population) in the Xifaxan® group, but the small number of observations does not permit conclusions. There were deaths in the Xifaxan® arm that the reviewer considered possibly related to Xifaxan®, and these are discussed in detail in the safety section of the clinical review.

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[14] This analysis involved a comparison of the two treatment groups on the primary efficacy parameter using the Cox proportional; hazards model with a two-sided test at a significance level of 0.05 under the proportional hazards assumption.

15 The Committee unanimously agreed that **a Conn Score of 1 is not remission**, based on the true definition of remission.

Regarding advice sought from the GIDAC, the principal efficacy issue confronting the Division in the evaluation of this application was whether the totality of the submitted data constitutes sufficient evidence that permits a conclusion that a clinically meaningful effect of Xifaxan in reduction of recurrence of HE events in a population of patients with a history of HE related to underlying liver disease has been established. A majority of GIDAC members [YES = 15; NO = 3] were of the opinion that the clinical data included in the rifaximin application provided substantial evidence of efficacy for an indication of maintenance of remission from HE and that the primary and secondary endpoints showed consistency of findings. Similarly, a majority of the Committee members [YES = 12; NO = 6] commented that the safety of rifaximin had been adequately addressed. For those that voted "NO", the concern raised was related to the expected long-term use of the drug, the effects of the drug on the gut flora, and the cardiovascular effects [QT effects] of the drug.

Lingering concerns about the safety of the drug – that are important issues in the risk/benefit assessment -- remain. The pre-clinical data are incomplete and difficult to interpret and in need of additional [post-marketing] studies. The sponsor has conducted a full battery of nonclinical studies, which included repeat-dose toxicology studies of up to 26-weeks in rats and 39-weeks in dogs. The PK data from a 26-week oral toxicity study in rats and a 39-week oral toxicity study in dogs show variability of results. Over the course of drug development, chronic oral toxicity studies in rats and dogs were performed in duplicate. There were discrepancies in toxicity, specifically in the histopathology results (primarily in the small intestine and liver), between duplicate studies in each of the species. The cause of these conflicting results was not established; however it was not due to dose levels. Although systemic exposure to rifaximin is low, one possible explanation for the discrepancies may be a variation in exposure levels between the different studies. The AUC values that occurred in the toxicity studies (42 to 127 ng·h/mL) were generally lower than those observed in cirrhotic patients (130 ± 78 ng·h/mL). There is also some concern regarding cardiac safety based on results of a study to test the effects of rifaximin on the hERG potassium channels expressed in human embryonic kidney cells.

The clinical data are also incomplete and in need of further [post-marketing] evaluations. In our presentations to the GIDAC, the Division summarized these issues as follows. Xifaxan is an antibiotic for which the proposed use is chronic. Its bioavailability after oral administration is low in healthy volunteers. However, PK studies in patients with hepatic impairment demonstrate that systemic absorption is higher in this population. The placebo-controlled safety data are limited to the 6 months of the randomized, controlled trial. The reviewers identified a possible increase in hepatic events in the patients treated with Xifaxan, but this finding was difficult to interpret in light of the small number of events and the relatively small size of the clinical trial. The hepatic events in the open label safety study cannot be interpreted because the natural history of the disease involves progression of hepatic dysfunction.

LIST of GIDAC Recommendations/Comments at February 23, 2010 meeting

EFFICACY	SAFETY	Additional Comments
-- Better capture uniform assessment of endpoints through the use of blinded, independent reviewers; -- Obtain mean cumulative frequency of episodes of HE as an endpoint to obtain assessment of effect over time; -- Obtain time to first hospitalization since this is a good and firm endpoint; -- Perform repeated measure analysis by measuring Conn score at specific points in time during treatment; -- Utilize neuro-imaging techniques; -- Utilize more sensitive neuro-psych testing in addition to the Conn score.	-- The conduct of additional studies during Phase IV post-marketing; -- Need to further evaluate patients with more serious liver disease, MELD score greater than 25; -- Long-term effects on gut flora and gut flora change with use; -- Development of drug resistant organisms with use; -- Surveillance occurrence and susceptibility of Clostridium Difficile; -- Further examination of QT effects.	-- A need to conduct Phase IV post-marketing studies; -- The conduct of further studies: on patients with MELD score of 25 or greater (the most ill patients) and for a longer duration; -- Labeling to reflect concomitant use with lactulose and suggested use only in patients with Childs Class A and B, MELD score less than 25; -- The clinical data supports the demonstration of significant improvement in patients with HE but does not support a finding of remission in patients with HE.

Source: Quick Minutes, K Khuc, FDA GIDAC, February 23, 2010

Table OES-1
NDA 22554

Review disciplines	Comments/ Conclusions/Recommendations for Regulatory Action
NOTE: As specified in the title of the right column, included are important Comments, Conclusions and Recommendations for Regulatory Action. However, for completeness, each item is discussed within the text of the CDTL review, highlighting the available granularity that it is believed necessary to best articulate or understand the issue at hand.	
3. CMC Dr. David Lewis	From the standpoint of CMC, this is a post-approval supplement. For regulatory purposes, this has been classified as a Type 6 NDA, and was assigned a new NDA number. **This application is recommended for approval.**
4. Nonclinical Pharmacol/Tox Dr. Niraj Mehta	The Review calls attention to the fact that there are inconsistent toxicity findings in animals, with liver and small intestine as the possible target organs; there are no pre-clinical data in hepatic failure animal models. Additional finding of concern**:** *in vitro* rifaximin concentrations of ≥ 30 µM had a statistically significant increase in inhibition of the hERG channel. The IC_{50} for the inhibitory effect of rifaximin on hERG K current was estimated to be 30 µM. Although the low systemic absorption of the drug is recognized preclinical data do not provide assurance of safety for the use of rifaximin in cirrhotic patients, where increased intestinal permeability is expected **The application is recommended for approval, with adequate wording in the label, including clarification on Pregnancy Category. Also recommended are PMRs to assess effects under adequate systemic exposures in animals.**
5. Clinical Pharm/Biopharm Dr. Insook Kim	The reviewer found several unaddressed questions for the safe use of rifaximin in target patient population. Those deficiencies are mainly due to the **greatly elevated systemic exposure to rifaximin in the target patient population who has hepatic impairment.** **Effect of rifaximin on the QT prolongation** A thorough QT study was not conducted for rifaximin. Although the systemic availability of oral rifaximin is limited, rifaximin is systemically available to an appreciable degree. The systemic exposure to rifaximin in the new patient population after 550 mg twice daily dosing is ca. 16 to 20 times higher than that in healthy subjects after 200 mg TID dosing, the approved dosing for the treatment of patients with traveler's diarrhea. As such, the current marketing experience with rifaximin cannot reasonably allay the cardiac safety issue in terms of QT prolongation potential of rifaximin in the proposed target population. This issue remains to be addressed. **Recommended Phase IV Commitments** -- That the effect of concomitant P-gp inhibitor(s) on rifaximin PKs be evaluated in vivo. The study may be conducted in healthy volunteers. -- That the applicant conduct in vitro studies to determine: • If rifaximin is a substrate of CYP enzymes • The inhibition constant ki of rifaximin -in inhibiting P-gp

	-- Evaluate in vitro CYP3A4 induction at lower rifaximin concentrations covering peak plasma concentrations of rifaximin in patients. **The CPB review recommendation for approval states that if the clinical division found the overall safety and efficacy of rifaximin in the target patient population acceptable, those deficiencies should be addressed through labeling and/or the post-marketing commitments proposed above.**
6. Clinical Microbiology Dr. Anne E Purfield	The review reiterates known facts about the experimental drug. Rifaximin, a structural analog of rifampin, acts by binding to the beta-subunit of bacterial DNA dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis. Rifaximin has a broad spectrum of antimicrobial activity both against gram negative and gram positive organisms, but certain strains of each of these **groups that colonize the gut lumen** are not sensitive to this antibiotic. In particular, many strains of ***Bacteroides fragilis***, anaerobic organisms that are major colonizers of the gut, are highly resistant to rifaximin. In addition, within a short time of rifaximin exposure many antimicrobial sensitive gram negative and gram positive luminal organisms develop **"significant resistance"** to the antibiotic; this issue needs to be further addressed. Rifaximin is approved for the treatment of traveler's diarrhea caused by noninvasive strains of *E. coli.* The approved dose and duration of treatment [200 mg TID for 3 days] is too short in comparison with the long-term use if the drug is approved for the indication sought by the applicant. The applicant is seeking approval for changes in the label that include: 1) PLR formatting; 2) revision of the label by adding information from 5 studies [3 pre-clinical; 2 clinical]. Two Consult reviews from Clinical Microbiology have been finalized. In the first, a microbiology assessment by the Division of Special pathogen and Transplant Products of publications describing results of in vitro studies and reports from two clinical trials for the short-term use in the treatment of traveler's diarrhea are addressed. It was found that results from these publications are inadequate to support sponsor's proposed labeling revisions. -- The in vitro data lacked information regarding specific methodology. -- Data from the two clinical trials were inadequate because these studies did not correlate changes in pathogen eradication with significant alteration of gut flora or describe a unique mechanism of action. In the second Consult review, comments on effects of long-term treatment on gut flora were included. For the He-related indication, the applicant is proposing a higher dose and duration [550 mg BID for about 6 months]; the reviewer that no microbiology information was collected in the 6 month RFHA-3001 study or reported in the literature publications submitted by the applicant. In the absence of any microbiology data, the L-T effects of rifaximin on the gut flora and any change in the *in vitro* susceptibility of gut flora to rifaximin and other antimicrobial drugs within the rifamycin class cannot be evaluated. Clinical Microbiology also has provided additional comments on the sponsor-proposed labeling revisions. These comments are separately addressed. **DSPTP/Micro recommends that if rifaximin is approved for an HE-related indication, Post-Marketing studies should be considered to evaluate the effect of L-T treatment with rifaximin on the gut flora and *in vitro* susceptibility to rifaximin and other rifamycin antimicrobial drugs. Depending on the outcome of such studies, consideration may need to be given to evaluating the**

	clinical significance of *in vitro* "resistance' on the efficacy of rifaximin.
7. Clinical/Statistical ---Efficacy Dr. Lara Dimick-Santos Dr. Behrang Vali Dr. Ranjit Mani	**Sponsor's Conclusions on Efficacy** • Rifaximin had a highly significant protective effect against breakthrough overt HE over a 6-month treatment period compared with placebo in patients in remission from overt HE. These results were also seen in covariate analyses, sensitivity analyses and in analyses of population subgroups. • Statistically significant results in favor of the rifaximin group were also seen for key secondary efficacy endpoints including protection against hepatic encephalopathy-related hospitalization and increases in Conn score. **CDTL's Conclusions on Efficacy** The CDTL formulates this conclusion on the basis of his consideration of the vigorous reviews by Drs, Dimick-Santos, Vali, and Mani. **Approval of NDA 22-554 is recommended.** Results from **RFHE3001**, a well designed and apparently well executed 6-month, 2-arm, randomized, double-blind, placebo-controlled, lactulose-based, stand-alone, pivotal study showed: a) a reduction of breakthrough overt HE in the rifaximin group [**p < 0.0001** for between-group difference in relative risk] in analyses of the **primary efficacy endpoint; and** b) a reduction in the risk of HE-related hospitalization in the rifaximin group [**p = 0.0129**] relative to placebo in analyses of a **clinically important key secondary endpoint of efficacy.** In addition, the CDTL concurs with Dr. Mani that, in view of the way the data were collected and analyzed and interpreted, a more adequate indication should read: **"Reduction in frequency of episodes of hepatic encephalopathy in patients 18 years of age and older", rather than maintenance of remission** (b) (4) **of hepatic encephalopathy.**
8. SAFETY Dr. Lara Dimick and other members of the Review Team	As noted by Dr. Dimick-Santos, the population under study is very ill and high incidence of AEs and variability of the course of HE confounds accurate assessment of safety. **However over-all rifaximin appears to be relatively safe**. Most common AEs are related to the gastrointestinal tract and include diarrhea, nausea and vomiting. Most of the other reported AEs are expected in this patient population. Immunogenicity-related AEs, such as arthralgia, pyrexia and pruritus/rash were higher in subjects receiving rifaximin [6%, 6%, and 21%, respectively] than in those receiving placebo [3%, 3%, and 15%, respectively]. The majority of complications were equally distributed between test rifaximin and the placebo control group. Nonetheless, a deficiency was noted: the sponsor failed to gather follow-up data from those patients who developed AEs; the subjects where dropped from the trial at the time they developed an AE that prompted withdrawal of the drug or if the subjects developed HE.

	Findings of concern include the occurrence of 5 events of *C. difficile* colitis: 2 in the RCT population and 3 in the long-term population. To these, 5 reported cases [1 death], that were reported post-marketing, are to be added. This information should be included in the labeling. After completion of Dr. Dimick-Santos clinical review, some lingering concerns remain. One is the possibility of DILI in a subset of patients administered rifaximin; in her opinion, this issue has not be adequately addressed and will require further clinical trials, with liver biopsy being preformed on patients with stable disease or low MELD scores who suddenly decompensate, to rule out the DILI possibility. **Dr. Dimick-Santos points out that the sponsor has failed to collect adequate data on Child's-Pugh Class C patients and patients with MELD scores above 25 as they were excluded from these studies. This group of patients would be at high risk for developing HE and thus use of rifaximin [off-label?]. Post-marketing studies in the most ill patient populations are being considered.**
9. SEALD Ms. Pavi Miskala Ms. Iris Massuci	No formal Consult review was issued by SEALD.
10.DNP Dr. Ranjit Mani Medical Officer, DNP	In his Consult Review, Dr. R Mani, our Neurology Consultant, included the conclusion that pivotal RCT RFHE3001 does **not** provide evidence for him to conclude that XIFAXZN® administered in a dose of 550 mg BID over 6 months has efficacy, in comparison with placebo, in reducing the risk of relapse of HE in patients with cirrhosis of the liver and/or portal hypertension. More specifically, Dr. Mani says, evidence is lacking in this submission that the main component of the primary efficacy parameter, breakthrough episodes of HE while on treatment with study drug, were accurately recorded. According to Dr. Mani, there is also insufficient evidence that the occurrence, or lack thereof, of episodes of HE in the months prior to study entry was accurately recorded, either; an accurate recording of the frequency and severity of such episodes was needed for one of the main inclusion criteria for this study to be fulfilled. Dr. Mani's review and evaluation has been very useful because, among other things, it has been a strong incentive for all kinds of reviewers/sponsor/DSI/AC members to consider/debate these possibilities in the most objective possible manner. Although the CDTL agrees with some of Dr. Mani's assertions, a number of clarifications are in order. HE in end-stage chronic liver insufficiency/failure is a very complex situation that has cognitive, psychiatric and motor components, high prevalence post-TIPS, and major impact on Health-related QoL. The spectrum of HE ranges from minimal HE to coma The differential diagnosis of HE is vast with several overlapping conditions that can co-exist in the same patients. MHE is an important public health issue because, among other things, it adversely impacts **driving ability**. Although overt HE can be diagnosed clinically, MHE requires specialized diagnostic testing **[by definition, MHE cannot be diagnosed through clinical means].** **There have been several clinical scales that have been used to gauge the severity of HE. But few of them have been able to completely evaluate the spectrum of these problems entirely. This is due to the lack of objective criteria for the clinical diagnosis of HE. But the most widely used is the West-Haven criteria [used in the current submission], in which the most reproducible stages are: stage 0 [i.e., no abnormality] and stages 3 and 4 [coma/decerebrate posture].**

	To quantify the severity, several questionnaires and blended psychometric and clinical scales have been used: HESA [Hepatic Encephalopathy Scoring Algorithm (used in pivotal study RFHE3001); CHESS [Clinical Hepatic Encephalopathy Scale]; and PSE-Index [Portal-Systemic Encephalopathy Index]. Thus, among the diagnostic tools for MHE are the PSE-syndrome test [consists of 5 subsets and has good sensitivity and specificity], the critical flicker frequency [CFF] and the inhibitory control test [ICT]. CFF and PSE-syndrome test have been validated outside the U.S. The ICT has been validated in a selected U.S. population and is freely downloadable at www.hecme.tv. RBANS is a test battery that has U.S. normative data but it has not been validated for the diagnosis of MHE in the U.S. This battery requires a psychologist for procurement, administration and interpretation. Although large-scale validation is on-going at this time, none of these scales has been validated in the U.S. For now, the West-Haven criteria [used in pivotal study RFHE3001] are still the standard in evaluating newer clinical scales. The neurologist consultant brings a series of interesting points, worth considering. These concerns were further considered at the Feb 23, 2010 Advisory Committee meeting. However, it is important to reiterate that that the HESA is only one of the approaches currently used to assign a Conn grade. HESA is yet to be validated [a validation attempt in a large number of patients is currently on-going]. None of the other approaches has been validated. On the other hand, it is worth keeping in mind that RFHE3001 was a randomized, placebo-controlled study that, **based on DSI inspection results**, was properly executed [neither protocol violations nor overt bias that might invalidate results were discovered by DSI]. The available HESA tool was applied, reasonable equally, in a double-blind/randomized fashion to the two experimental arms of the trial. **It is therefore concluded that, although it is recognized that the present state of affairs needs to be scientifically improved, results from RFHE3001 analyzing both the primary efficacy parameter as well as key secondary endpoints of efficacy, under double-blind, randomized conditions [adequate clinical trial approaches designed to minimize bias] seem to demonstrate a clear-cut different in efficacy between rifaximin and placebo.**
11.DSI Dr. Khairy Malek Medical Officer GCPB 2 DSI	The following is excerpted from the Overall Assessment of Findings and Recommendations included in their first memorandum: • Five sites were inspected in support of this NDA. These sites included: Fred Poordad, MD (Site 351, LA, CA); Muhammad Sheikh, MD (Site 799, Fresno, CA; Olga Alexeeva, MD (Site 938, Novgorod, Russia); Vladimir Gorbakov, MD (Moscow, Russia); and Vladimir Rafalsky, MD (Smolensk, Russia) • Although minor issues were noted at Dr. Poordad's and Dr. Gorbakov's sites, the findings are unlikely to impact data integrity. • The data from the 5 sites listed above are acceptable in support of the NDA. ***Note: Observations noted in the DSI report for Drs. Alexeeva, Gorbakov, and Rafalsky are based on the participation in the inspection by the DSI reviewer; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.*** Included in their second memorandum, was the following statement: RFHE3001 was a randomized, placebo-controlled study that, **based on DSI inspection results**, was properly executed [neither protocol violations nor overt bias that might invalidate results were discovered by DSI]. **The available HESA tool was applied, reasonable equally, in a double-blind/randomized fashion to the two experimental arms of the trial.**

12.OSE Ms Ann Corken Mackey, RPh, MPH Safety Evaluator, DPV I	As part of the evaluation of safety signals that may be associated with the use of Xifaxan®(rifaximin) for the indication of maintenance therapy for the remission of hepatic encephalopathy(DEPI), OSE provided total dispensed prescription, prescribing specialty, and diagnosis data for rifaximin from July 1, 2004 to June 30, 2009. (b) (4) data were used to determine the setting in which rifaximin tablets were sold. The examination of rifaximin utilization patterns focused on the outpatient setting. Proprietary drug use databases licensed by the Agency were used to conduct this analysis. The review included a detailed description of all data sources used (b) (4) The reviewers concluded that Total dispensed prescriptions for Xifaxan® (rifaximin) increased (b) (4) The top prescribing specialty for rifaximin was Gastroenterology. The most common diagnoses associated with the use of rifaximin were "GI System Symptoms NEC" (ICD-9 787.9), "Infectious diarrhea NOS" (ICD-9 009.2), and "Irritable colon" (ICD-9 564.1). The diagnosis code for "Hepatic Coma" (ICD-9 572.2) was mentioned approximately 1% of the time by physician survey for rifaximin. In an additional memorandum, DPV identified any safety signals associated with rifaximin (Xifaxan®) use. The sponsor, Salix Pharmaceuticals, is proposing an additional indication of "maintenance of remission of hepatic encephalopathy," an indication that may involve long-term use[16]. They reiterated that systemic absorption of oral rifaximin is 0.4%[17]. AERS was searched from May 2004 (approval of rifaximin to treat Traveler's diarrhea) to August 31, 2009 using the drug name rifaximin (Xifaxan). Three separate searches were performed as follows: 1. All AEs (involves all reasons for use), 2. AEs related to rifaximin use to treat or prevent HE using the search strategy specified above along with the reported indications of *hepatic encephalopathy* and *hepatic encephalopathy prophylaxis* using MedDRA Preferred Terms [PTs], and 3. All deaths (all adverse events with the outcome of death). ***All adverse events*** (all reported indications for use; n=173 [note raw data, duplicates could exist]): A PT printout was generated to identify adverse events reported for rifaximin. It appeared that most of these cases were confounded by the patients' underlying medical condition and/or concomitant medications. In addition, a line listing report found that uses for rifaximin, other than Traveler's diarrhea, included HE (not a labeled indication in the US), Crohn's disease, IBS, UC, and colitis. The majority of the 64 reports mentioned nonserious events (e.g., GI symptoms, rash); AEs such as pancytopenia, anaphylaxis, thrombocytopenia, and *Campylobacter* infection occurred in patients using rifaximin to treat HE and are described below within the body of the CDTL review. ***Adverse events associated with prevention/treatment of HE*** (n=21). All 21 cases are described in the OSE memorandum. Of the 21 cases, 2 cases provided little information to determine causality (reported as tongue discoloration and ataxia) and 1 case was reported as worsening HE (patient had additional adverse events, but all were related to worsening HE). Eleven cases reported labeled events. Of these 11 cases, 1 patient died (patient developed *C difficile*; see description in the body of the CDTL review) and 5 patients were hospitalized because of their adverse events (i.e., respiratory problems [1], anaphylaxis/angioedema [1], *C. difficile* [3]). Two cases reported bleeding disorders due to thrombocytopenia; one reporter stated that thrombocytopenia was secondary to cirrhosis (both patients were hospitalized). ***Under All death,*** the search identified two fatalities involving patients using rifaximin to prevent HE (n=1) or to treat small intestinal bacterial overgrowth (n = 1). The former patient (62-y-old male) used 1200 mg of rifaximin a day for 30 days (ceftriaxone listed as concomitant medication, but dates of administration were not reported); he developed *C. difficile* diarrhea and died 22 days later due to "complications of liver disease worsened by *C. difficile* diarrhea." The later patient (85-year-old female with end-stage renal failure) used 600 mg of rifaximin a day for 7 days; she hit her head and was found dead in the bathroom (exact cause of death not known[18]. • A review article summarizing studies in which rifaximin was used to treat HE found that only minor GI AEs were reported (ca. 180 patients in seven studies; exact number of patients who developed GI adverse events was not reported).[19] • Regarding drug use, there was an increase in the rifaximin market from 2004 to 2007; use has been the same from 2007 to 2009. Gastroenterologists were the primary

	prescribers for rifaximin. In their discussion, the reviewers indicate that overall, most of the AEs associated with rifaximin use identified in AERS are labeled or possibly related to the patients' underlying conditions. • Most of the adverse events that have been reported for patients receiving rifaximin to treat HE are labeled. • Antibiotics such as rifaximin are known to cause changes in gut flora possibly leading to infection. • No new safety signals were found in AERS or the literature in patients using rifaximin. There was one death described as possibly related to rifaximin use in a patient who developed *C. difficile* but rifaximin has been also been used to treat *C. difficile*; however, strains with decreased susceptibility have been identified.[20] • Given that the systemic absorption of rifaximin after oral administration is 0.4%, few systemic AEs would be expected. **OSE recommended that because of reports of *C. difficile* (including one fatality), DGP should consider including in the Adverse Events Postmarketing section of the label (in addition to the Warnings section) that cases of rifaximin-induced *C. difficile* colitis have been reported.** The following AEs, 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. **Postmarketing Experience** The following events: hypersensitivity reactions, including exfoliate dermatitis, rash, angioneurotic edema (swelling of face and tongue and difficulty swallowing), urticaria, flushing, and pruritus; have been identified during post-approval use of XIFAXAN® Tablets. These events occurred as early as within 15 min of drug administration.
13. DMEPA **OSE Carton and Container** Ms. Kallie Taylor Ms. Cathy A Miller Y Evaluator Division of Medication Error Prevention and Analysis	DMEPA evaluated the container labels, carton and insert labeling for Xifaxan® (rifaximin) tablets. Vulnerabilities that could lead to medication errors were identified. Specifically, DMEPA raise concern with the close proximity of the strength (550 mg) to the net quantity (6 tablets and 60 tablets) as presented on the principal display panel of container labels and carton labeling. DMEPA ask that the Applicant consider increasing the prominence of the 550 mg strength on the unit dose foil pack container to provide added differentiation from the 200 mg strength foil pack container. They believe **these vulnerabilities can be revised prior to approval. They** have provided recommendations in Section 5.2 *(Comments to the Applicant)* of their Consult Review that aim at reducing the risk of medication errors with regards to the proposed labels and labeling. **The CDTL agrees with these recommendations.** Lastly, DMEPA note that the container label for the currently marketed Xifaxan® 200 mg strength 100-count size is presented with a different color scheme (b) (4) than all other labels and labeling for the 200 mg strength, presented in (b) (4). DMEPA has concerns that the differentiation of the quantity of tablets between the 30-count and 100-count size is not necessary and may cause wrong strength selection errors once the 550 mg strength is available. In the belief that these vulnerabilities can be remedied through revisions to current labels and labeling submitted by the Applicant as a prior approval supplement to new drug application (NDA 21361) DMEPA have provided recommendations in Section 5.1 (*Comments to the Sponsor of their review)*. ***Comments to the Applicant:*** A. Container Labels and Carton Labeling and DMEPA comments related to other evaluations, are listed in the body of the CDTL review.
14.DDMAC Ms. Kathleen Klem	This discipline is yet to issue a Consult Review.

15. Advisory Committee Meeting of February 23, 2010

Acting Chair: Jean-Pierre Raufman, MD
Designated Federal official: Kristine Khuc, Pharm D
DGP Participants: Drs. D Griebel, J Korvick, R He, and L Dimick-Santos

Issue: The committee discussed the efficacy and safety of new drug application (NDA) 22-554 for XIFAXAN (rifaximin) Tablets 550 mg, manufactured by Salix Pharmaceuticals, for the indication (use) of maintenance of remission of hepatic encephalopathy, a condition in which severe liver disease contributes to an accumulation of toxic substances that impair brain function. This indication is for patients 18 years of age and older.

Questions to the Committee

1. …Two thirds of patients in the trial had a baseline Conn Score of 0 and 1/3 had a baseline Conn Score of 1. Ninety one percent of patients were taking lactulose. (Discussion)

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

Committee members expressed that it is difficult to define, describe, and assign a specific Conn Score to a patient at any one specific time; mental status fluctuations are observed over the course of a day or from day to day. Although, the Conn index is a simple and reasonably valid measure, the issue lies in that it may not be adequate to address the syndrome over time and to properly assess a patient. The committee unanimously agreed that a Conn Score of 1 is not remission, based on the true definition of remission. It is difficult to assess stability when patients may be fluctuating between scores on a given day.

(Please see official transcript for details)

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

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

Committee members commented that there is a need to:

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

(Please see official transcript for details)

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

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

- Which clinical data, if any, provide substantial evidence of efficacy?
- What, if any, are the deficiencies in the clinical data that make the evidence less than substantial?

Yes: 15 **No: 3*** **Abstain: 0**

The committee members who voted "Yes" expressed that the pivotal trial's primary and secondary endpoints showed consistency of findings. The consensus among the committee members was that the drug labeling needs to include information that rifaximin is to be used as an adjunct to lactulose. The committee voiced their opinion that clinical data deficiencies were related to the lack of use of MELD score measurement during the trial. They also expressed that they felt that patients with a MELD score greater than 25 should have been evaluated.

The committee members who voted "No" felt that the single study data was strong, but not compelling and that a second

confirmatory study should have been conducted. There were concerns raised because of lack of clinical efficacy data of use of the product as a sole agent, without accompanying use of lactulose. These members also opined that while the drug may have demonstrated improvement, it did not demonstrate remission. It was also suggested that the efficacy of the drug should be demonstrated in both concomitant and non-concomitant use of lactulose.

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

(Please see official transcript for details)

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

Yes: 12 **No: 6** **Abstain: 0**

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

The panel members recommended that the Agency consider:

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

(Please see official transcript for details)

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

Yes: 13 **No: 5 *** **Abstain: 0**

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

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

(Please see official transcript for details)

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

Yes: 14 **No: 4** **Abstain: 0**

The committee commented and recommended:

- *A need to conduct Phase IV post-marketing studies;*
- *The conduct of further studies: on patients with MELD score of 25 or greater (the most ill patients) and for a longer duration;*
- *Labeling to reflect concomitant use with lactulose and suggested use only in patients with Childs Class A and B, MELD score less than 25;*
- *The clinical data supports the demonstration of significant improvement in patients with HE but does not support a finding of remission in patients with HE.*

(Please see official transcript for details)

1. Introduction

General Introduction to the Subject of Hepatic Encephalopathy [HE]

Hepatic encephalopathy is a condition of disordered mentation and neuromuscular activity. HE is associated with deteriorating liver function and/or portal systemic shunting. HE emanates from a diminished capacity of the liver to metabolize substances generated in the intestinal lumen that are toxic to the brain, such as **ammonia, mercaptans [and manganese].**

HE is associated with a host of metabolic abnormalities. Included among these metabolic abnormalities are: a) increased circulatory levels of ammonia resulting in high levels of ammonia, glutamine and α-keto-glutaramate in the brain and CSF; b) increased short and medium chain fatty acids in the plasma; c) increased methionine, phenylalanine, tyrosine, tryptophan, aspartate and glutamate and decreased branched chain amino acids [leucine, isoleucine and valine] in the plasma and d) altered levels of neurotransmitters resulting in raised glutamine, asparagine and 5-HIAA levels in the brain[1].

The severity of HE, which occurs both in the settings of acute and chronic liver disease, depends upon the abruptness of onset and the degree of portal systemic shunting and/or hepatocellular damage. The following are listed among the precipitating factors that worsen encephalopathy include: nitrogenous overload in the lumen of the gut[2], sedatives, tranquilizers and narcotic analgesics; fluid and electrolyte abnormalities, including hyponatremia and hypokalemia; and infection particularly bacterial pneumonia, pyelonephritis, peritonitis, and septicemia.

Tests which detect early encephalopathic changes include: a) block design, digit symbol; b) speed of writing words or numbers; reaction time to light or sounds; and d) individual retention. Laboratory tests that may be helpful in the diagnosis of HE include:

-- **EEG**. While not pathognomonic, changes often occur early. These include the advent of random slow waves occurring at a frequency of 5 to 7 per second (theta waves). Theta waves are symmetrical beginning in the frontal areas and spreading backwards. These waves are followed by the appearance of triphasic waves which have a frequency of 4 to 5 per second. Triphasic waves are primarily detected in the frontal and central areas[3]. As coma deepens, random and arrhythmic waves with a frequency of 2 to 3 per second (delta waves) appear. No correlation between these EEG changes and blood or spinal fluid ammonia has been observed. **The EEG is not a substitute for careful clinical assessment nor for the clinical staging of HE.**

-- **Blood ammonia levels.** are frequently elevated in patients with hepatic encephalopathy. However, this measurement has little diagnostic value in patients with known liver disease, due to interpatient fluctuations[4].

-- Spinal fluid determinations of glutamine, α-ketoglutaramate also correlate with the severity of encephalopathy. **These measurements are not routinely used in clinical diagnosis because of the necessity of a spinal tap.**

The treatment of HE must take into account factors which precipitate its onset and duration as well as the underlying liver disease. Often, multiple therapeutic modalities are pursued. In the case of acute or subacute hepatic encephalopathy, the common measures of treatment include: (1) restriction of dietary protein, (2) application of retention enemas with 1% neomycin or 20% lactose to cleanse the entire colon of fecal matter, (3) oral administration of lactulose, (4) oral administration of neomycin or an absorbable antibiotic such as tetracycline or ampicillin[5]. Other treatments to treat acute encephalopathy which have not been fully substantiated include administration of arginine-glutamate, L-dopa and branched-chain aminoacids.

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[1]Additional abnormalities that may be associated with HE are: 1) respiratory and metabolic alkalosis; 2) electrolyte deficits (e.g. hypokalemia, hyponatremia); 3) hypoxemia and hypoxia; and 4) alterations of blood flow in the cerebrum

[2]This is associated with dietary protein or GI hemorrhage; azotemia due to the breakdown of gut luminal proteins, leading to the production of ammonia and other toxic products that are normally removed by the liver.

[3]As coma deepens, random and arrhythmic waves with a frequency of 2 to 3 per second [delta waves] appear.

[4]erial measurements of blood ammonia in patients with liver disease may be useful as correlative indices of severity of hepatic encephalopathy.

[5]These antibiotics effectively reduce colonic bacteria, which produce nitrogen breakdown products that cause encephalopathy after entering the circulation.

The management of chronic recurrent encephalopathy is similar to that of acute encephalopathy. In addition to the restriction of dietary protein, oral lactulose administration in a titrated dosage that is sufficient to keep the stool soft without inducing watery diarrhea is an effective treatment in many patients. Administration of Neomycin (1 gram administered orally) every 6 hours is a useful alternate form of treatment. The strategy to suppress colonic bacteria with orally administered antibiotics such as ampicillin and tetracycline is limited by the resistance to these agents that emerges in microbes over time.

2. Background

General Background

End-stage chronic liver disease [ESCLD] and portal hypertension [PH] result in exposure of vital organs such as brain to blood that has not been detoxified by the liver. Hepatic Encephalopathy (HE) is a common neuropsychiatric complication of end-stage chronic liver disease and is characterized by shortened attention span, sleep abnormalities and motor disturbances progressing through lethargy to stupor and coma. Clinical grading of HE in relation to these symptoms makes use of the West Haven criteria. HE comprises cognitive, psychiatric and motor symptomatology. Minimal HE (previously known as "subclinical HE") has a major impact on Health-related Quality of Life. HE occurs in up to 50% of patients post-TIPS. Ferenci et al[21] HE has recently been reclassified into three types. Type A, associated with acute liver failure; Type B, associated with portosystemic bypass with no intrinsic hepatocellular disease; and type C, associated with cirrhosis and portal hypertension. The comments below and those in **APPENDIX 1** focus primarily on Type C HE.

Ammonia toxicity is thought to be closely related to the pathogenesis of HE (Type C). Arterial blood ammonia concentrations are increased 2-3 fold in type C HE and PET studies using $^{13}NH_3$ as ligand in patients with mild HE show increased rates of ammonia delivery to the brain. Whether this increased blood-brain ammonia transfer results from increased arterial concentrations, increased flow or increased permeability of the blood-brain barrier to ammonia is the subject of ongoing debate. Ammonia removal by the brain involves synthesis of glutamine in the astrocyte and both biochemical and spectroscopic studies show that glutamine concentrations are increased in Type C HE and are better correlated with HE severity than are brain concentrations of ammonia.

A pathophysiologic link between ammonia toxicity and HE is further suggested by reports of Alzheimer Type II astrocytes in the brains of children with hyperammonemia due to congenital urea cycle disorders and by reports of similar changes in cultured cortical astrocytes exposed to ammonia in concentrations similar to those observed in Type C HE.

Hyperammonemia in Type C HE results from altered inter-organ trafficking of ammonia. The intestines express high levels of glutaminase, the enzyme responsible for the degradation of glutaminase, to glutamate and ammonia, and it is estimated that 505 of the ammonia produced in the portal-drained viscera is accounted for by this route, the remaining 50% being produced by the colon chiefly from urea. In ESCLD, the contribution of the intestine to hyperammonemia results primarily from reduced hepatic urea synthesis rather than increased intestinal ammonia production. Under normal physiological conditions, hepatic ammonia removal is compartmentalized involving two distinct but functionally-linked populations of hepatocytes. Periportal hepatocytes remove ammonia as urea – these cells express the component enzymes of the urea cycle. Perivenous hepatocytes express glutamine synthetase and have the capacity to remove ammonia in the form of glutamine. In end-stage chronic liver failure, both periportal and perivenous hepatocytes are lost leading to decreased production of both urea and glutamine.

In end-stage chronic liver failure, **skeletal muscle** adapts metabolically to become the major organ responsible for ammonia removal. This adaptation results from a rapid post-translational increase of glutamine synthetase gene expression in skeletal muscle. Brain glutamine synthetase expression is not induced in brain in chronic liver failure suggesting that increased brain glutamine is primarily the result of increased substrate (ammonia) supply and/or inhibition of glutaminase activity in brain.

Increased ammonia has deleterious effects on brain function due to multiple mechanisms including: i) direct effects of the ammonium ion (NH_4^+) on excitatory and inhibitory neurotransmission; ii) inhibition of the tricarboxylic acid cycle enzyme α-ketoglutarate dehydrogenase leading to brain lactate accumulation and impending cellular energy failure; iii) the toxic effects of ammonia may be enhanced by the presence of increased circulatory levels of

proinflammatory cytokines such as TNFα and the interleukins (IL-1β and IL-6) released into the circulation as a consequence of infection/sepsis or hepatocellular injury.

Practical issues in the evaluation and management of subclinical and chronic HE are further addressed in **APPENDIX 2.**

Spectrum of HE: From Minimal HE (MHE) to Coma

The spectrum of HE has expanded to include the subclinical or "minimal" aspect. Studies have defined this range using several criteria, but there is a growing body of literature that support MHE as a pre-clinical entity of clinical overt HE. Overt HE can be diagnosed clinically but MHE requires specialized diagnostic testing. MHE is found in 50-80% of patients tested for this indication and by definition cannot be diagnosed through clinical means. The classification of HE by the Working Party on HE is shown in Table 1.

Table 1
Current 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**
		Persistent HE	• Mild • Severe • Treatment • dependent
		Minimal	---

The encephalopathy associated with acute liver failure is clinically separate and the number of patients who have bypass without intrinsic liver disease are limited; therefore the clinical focus is on patients who have type C or cirrhosis-associated HE. It is clinically divided in to episodic or persistent HE depending on their chronicity and clinically undetectable in between HE episodes, persistent HE patients never become free of HE and patients with MHE remain below the clinical detection level.

Minimal Hepatic Encephalopathy

MHE is the pre-clinical stage of HE that affects 50-80% of patients tested. It was initially known as sub-clinical hepatic encephalopathy and as shown in Figure 1, is not diagnosable clinically. The characteristic profile of patients with MHE is attention deficits and problems with visuo-motor coordination. This is difficult to diagnose in the current practice situation. These can be diagnosed using specialized psychometric and neuro-physiological tools; most of which require trained personnel and equipment. The diagnostic tools for MHE are the PSE-syndrome test (consists of five subtests), which has good sensitivity and specificity. The other tools are the critical flicker frequency (CFF) and inhibitory control test (ICT). CFF and PSE-syndrome test have been validated outside the US. The ICT has been validated in a selected U.S. population and is freely downloadable at www.hecme.tv.RBANS is a test battery that has U.S. normative data but it has not been validated for the diagnosis of MHE in the U.S. This battery requires a psychologist for procurement, administration and interpretation.

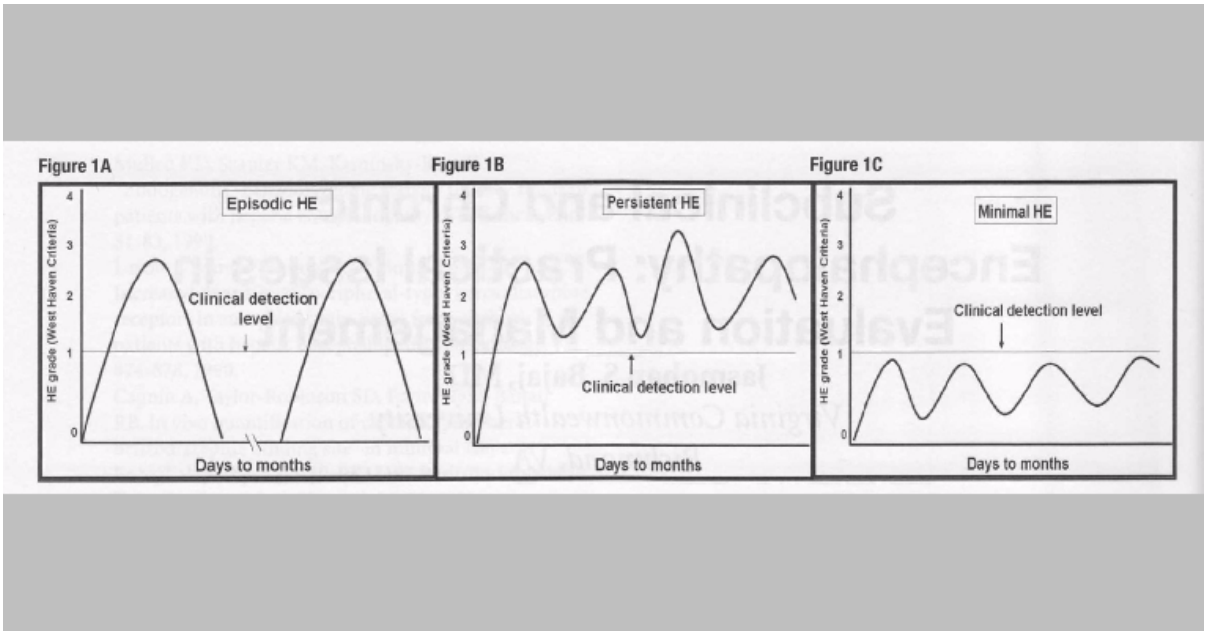


Fig. 1. - Temporal and clinical detection relationships of HE subtypes

Patients with MHE are predisposed to develop problems with their quality of life across several domains. This impairment in quality of life affects almost all aspects of daily living apart from communication skills. Apart from this there are differences in socio-economic status in MHE patients compared to those who are not MHE. MHE particularly affects "blue-collar" workers because of the inherent visuo-spatial and attention deficits, more than 'white collar" workers. This may increase the overall societal burden of MHE.

MHE, due to its effect on attention, working memory and response time affects driving skills. Driving assessments using driving simulation and on-road driving tests showed that patients with MHE were worse drivers i.e. required a higher intervention rate by the instructors and had several near-misses compared to those without MHE. The navigation skills and divided attention skills i.e. those that study answering a cell phone etc while driving, of patients with MHE were also impaired. MHE was also associated with a high rate of actual traffic accidents and violations compared to cirrhotics without MHE and healthy controls.

Patients with MHE have a significantly higher risk of developing overt HE. There are also isolated reports suggesting that MHE independently affects survival but this has not been corroborated as yet.

Therapeutic Strategies for MHE

There are several challenges that have prevented the ideal therapy of MHE to be established. Prominent among these is the lack of a uniform definition, the short-term duration of most currently published trials and the lack of hard outcomes such as overt HE development as the outcomes. Currently, lactulose has been shown to improve psychometric testing in MHE over two to three months duration. A recent trial also showed improvement in QOL as a result of lactulose therapy with >90% compliance. This compliance rate may not however be a reflection of actual clinical experience with lactulose even in overt HE. Trials with probiotics, including yogurt, have also demonstrated improvement over a short duration. However, there is no current standard of care for MHE therapy since none of the current treatment trials have been of sufficient duration and have not assessed clinical relevant outcomes.

Clinical Assessment of HE Severity

There have been several clinical scales that have been used to gauge the severity of HE. However, few of them have been able to completely evaluate the spectrum of these problems entirely. This is due to the lack of objective criteria for the clinical diagnosis of HE. The most widely used as the West-Haven criteria (Table 2), the most reproducible

stages are stages 0, i.e. no abnormality, and stage 3 and 4, which are coma. There is a large area of uncertainty in between (Figure 2).

Table 2
West Haven criteria for HE.

Stage	Consciousness	Intellect and Behavior	Neurologic Findings
0	Normal	Normal	Normal examination; if impaired psychomotor testing then MHE
1	Mild lack of awareness	Shortened attention span; impaired addition or subtraction	Mild asterixis or tremor
2	Lethargic	**Disoriented; Inappropriate behavior**	**Obvious asterixis; slurred speech**
3	Somnolent but arousable	**Gross disorientation; Bizarre behavior**	Muscular rigidity and clonus; Hyperreflexia
4	Coma	**Coma**	Decerebrate posturing

For now, the West-Haven criteria are still the standard in evaluating newer clinical scales.

With advancing stages of coma, the well-known Glasgow Coma Scale is useful to quantify the severity. Several questionnaires and blended psychometric and clinical scales have been used such as the Clinical Hepatic Encephalopathy Scale (CHESS), HESA and the PSE-index. However, large-scale validation is ongoing at this time. For now, the West-Haven criteria are still the standard in evaluating newer clinical scales.

A special mention must be made of **asterixis** or "flapping tremor" that is seen in West-Haven stages 2 and 3 of HE. Asterixis is caused by the disturbance in the oscillatory networks in the brain. It can be demonstrated in the tongue, and the upper and lower extremities. In patients who are too obtunded to raise their hands up "as they are stopping traffic," they should be instructed to grip the examiner's hands. The grip in patients with asterixis is never constant and oscillates between tight and loose. Care should be taken not to confuse asterixis with tremulousness associated with alcohol abuse or withdrawal.

Asterixis Grade

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

Treatment Directed towards HE

There are several therapies that have been used in research studies but lactulose and rifaximin form the bulk of the current therapeutic options in HE.

Lactulose

Lactulose has been used for several decades, with anecdotal and clinical trial experience. Since the use of lactulose pre-dated randomized controlled trails, the Cochrane review did not find any significant difference in outcomes in patients treated with and without lactulose. However, the large sample sizes needed to treat HE have not been achieved in prior lactulose trials, so it is not entirely accurate to dismiss the use of lactulose. The administration of lactulose while the patient is admitted with HE is associated with improvement in mental status, but since

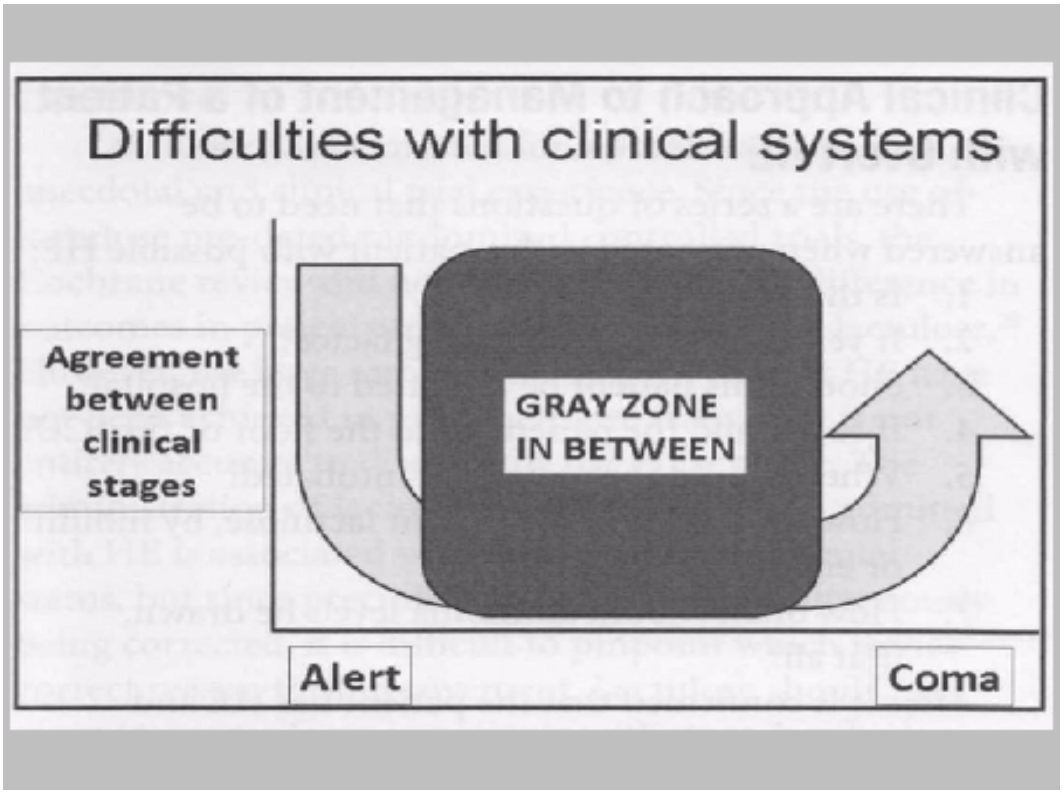


Fig. 2 - Difficulty in current clinical systems of HE gradation

precipitating factors are simultaneously being corrected; it is difficult t pinpoint which is the correct reason for improvement. Lactulose should be given in enema form in patients with stage 3 or higher HE. There has been a lack of scientific investigation into the mechanism of action of and the optimum dosage of lactulose, both in the inpatient and outpatient setting. In excess amounts, lactulose administration causes a number of adverse effects related to the osmotic character and bacterial fermentation in the colon. These include: flatulence, cramping, and osmotic diarrhea. When severe, lactulose-induced diarrhea induces hypokalemia, hypernatremia and hypovolemia. A Rating Scale: Symptoms of Intolerance to Lactulose, frequently used in clinical trials is given in **APPENDIX 3.**

Rifaximin

Rifaximin is a poorly absorbable antibiotic that has been used to treat HE in several European countries. It has a favorable impact and the Cochrane review recommended the use of non-absorbable antibiotics. It is currently available in 200mg form, which is given up to 1200mg/day. A recent trial presented in abstract form showed that rifaximin 550mg BID was significantly more effective than lactulose alone in the prevention of HE episodes in patients who had had two or more HE episodes in the past six months. The safety profile was good. Use of rifaximin is slowly becoming mainstream and it is well tolerated by patients compared to lactulose. The drug expense remains a concern but a recent study noted the reduced hospitalization rates after rifaximin therapy compared to lactulose.

Rifaximin [initial = under short-term use] Safety Experience

The most frequently reported adverse events have been flatulence, abdominal pain or cramps, weight loss, urticarial rash, nausea, vomiting and headache. Although the applicant has stated that rifaximin is not mutagenic, little information is presented about the genotoxic potential of this agent. In reproduction studies, there was a markedly increased incidence of associated skeletal anomalies and variants in the embryos of pregnant rabbits in all dose groups, compared with controls. In spite of this finding, the sponsor has concluded that: "Rifaximin appears to have no direct effects and few indirect effects on pregnancy, gestation or perinatal and postnatal development".

During the review of a number of INDs evaluating the effects of rifaximin, DGP recommended that because of the potential for the emergence of cross-resistance between rifaximin and rifampin, rifaximin should not be given to patients who have tuberculosis or other mycobacterial diseases.

Therefore, the phenomenon of high antimicrobial resistance rates of bacteria in the gut poses a significant conceptual problem in the proposed clinical application of this antibiotic. A comprehensive list of MICs for rifaximin against clinical isolates [*in vitro* antibacterial activity of the drug (mg/mL) is given in **APPENDIX 4.**

NOTE

There is no significant role of neomycin, flumazenil, metronidazole and zinc as stand-alone, therapies for HE. There are several other drugs in the pipeline for HE that are undergoing trials in the U.S. Other drugs that have been used outside the U.S. are LOLA (L-ornithine L-aspartate) infusion and oral forms, acetyl-carnitine and acarbose.

Morbidity Associated with Hepatic Encephalopathy

Owing to the deterioration of liver function, HE is associated with a host of metabolic abnormalities. Included among these metabolic abnormalities are: a) increased circulatory levels of ammonia resulting in high levels of ammonia, glutamine and α-keto-glutaramate in the brain and CSF; b) increased short and median chain fatty acids in the plasma; c) increased methionine, phenylalanine, tyrosine, tryptophan, aspartate and glutamate and decreased branched chain aminoacids (leucine, isoleucine and valine) in the plasma; d) altered levels of neurotransmitters resulting in raised glutamine, asparagine and 5-HIAA levels.

Expectations of early pharmacologic treatment

If, indeed, at the dose and regimen tested in RCT, rifaximin is safe and effective in maintaining remission from HE and remission is defined as a Conn score of 0, this means that no overt episodes of HE might be experienced by the subject. Morbidity manifestations of MHE, such as accidents due to impaired driving ability, can be prevented. This, of course, presupposes that the known precipitating factors that worsen HE[22] are carefully attended to.

HIGHLIGHTS OF INTERDISCIPLINARY REVIEWS

3. CMC

This application is recommended for APPROVAL from the standpoint of CMC.
The drug substance, rifaximin is manufactured and provided from two sources, (b) (4). The drug product is an oral immediate-release tablet formulated to provide 550 m of the drug substance, rifaximin. The drug product is intended for oral administration with recommended dose of 1,100 mg daily (one 550-mg tablet BID).

4. Non Clinical Pharmacology/Toxicology

This review found inconsistent toxicity findings in animals, with liver and small intestine as the possible target organs; there are no pre-clinical data in hepatic failure animal models. Summarized below is a finding of concern RE; Cardiac Safety. Although the low systemic absorption of the drug is recognized preclinical data do not provide assurance of safety for the use of rifaximin in cirrhotic patients, **where increased intestinal permeability is expected.**

Cardiac Safety

*In vitro r*ifaximin concentrations of ≥ 30 μM had a statistically significant increase in inhibition of the hERG channel. The IC_{50} for the inhibitory effect of rifaximin on hERG potassium current was estimated to be 30 μM.

The review and evaluation concluded that the toxicity studies in animals do not provide assurance of safety for the use of rifaximin in cirrhotic patients, where increased intestinal permeability is expected.

Human Carcinogenicity

There have been no studies on human carcinogenicity.

Human Reproduction and Pregnancy Data

Rifaximin at oral doses as high as 300 mg/kg/day had no adverse effects on general fertility of treated male and female rats. Similarly, oral doses as high as 300 mg/kg/day to pregnant rats had no adverse effects on postnatal development and reproductive performance of the offspring. Rifaximin was teratogenic during organogenesis in rats following doses of 150 to 300 mg/kg and in rabbits following doses of 62.5 to 1000 mg/kg. These effects included cleft palate, agnatha, jaw shortening, hemorrhage, eye partially open, small eyes, brachygnatia, increased incidence of incomplete ossification of cranial bones and pelvic bones and increased incidence of fetuses with an additional 13th rib or an additional vertebra in the thoracolumbar region in rat and rabbit fetuses.

(b) (4) re-examined the results of rat and rabbit reproductive toxicity studies at the request of Alfa Wassermann S.p.A. (Italy) and concluded that variations in the incidence of hemorrhages and the levels of ossification of cranial bones in rifaximin dose groups were "generally within the background control range."

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

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 rifaximin, 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.

Review by the preclinical team at the FDA recommended that rifaximin continue to be listed as a pregnancy Category C drug.

The application is recommended for approval, with adequate wording in the label, including clarification on Pregnancy Category and PMRs to assess effects under adequate systemic exposures in animals.

5. Clinical Pharmacology/Biopharmaceutics

Addressing her recommendations, Dr. Kim notices that the division of Clinical Pharmacology 3 has reviewed the efficacy supplement. The reviewer has found that there are several unaddressed questions for the safe use of rifaximin in target patient population. **Those deficiencies are mainly due to the greatly elevated systemic exposure to rifaximin in the target patient population who has hepatic impairment.** However, **if the clinical division found the overall safety and efficacy of rifaximin in the target patient population acceptable, those deficiencies should be addressed through labeling languages and/or the below listed post-marketing commitments.**

Comments to the Clinical Division

Effect of rifaximin on the QT prolongation

The CPB review notes that a thorough QT study was not conducted for rifaximin. Although the systemic availability of oral rifaximin is limited, rifaximin is systemically available to an appreciable degree. The systemic exposure to rifaximin in the new patient population after 550 mg twice daily dosing is ca. 16 to 20 times higher than that in healthy subjects after 200 mg TID dosing, the approved dosing for the treatment of patients with traveler's diarrhea. As such, the current marketing experience with rifaximin cannot reasonably allay the cardiac safety issue in terms of QT prolongation potential of rifaximin in the proposed target population. This issue remains to be addressed.

Phase IV Commitments

DCP recommends:

-- That the effect of concomitant P-gp inhibitor(s) on rifaximin PKs be evaluated in vivo. The study may be conducted in healthy volunteers.

-- That the applicant conducts in vitro studies to:

- Determine if rifaximin is a substrate of CYP enzymes
- Determine the inhibition constant ki of rifaximin -in inhibiting P-gp
- Evaluate in vitro CYP3A4 induction at lower rifaximin concentrations covering peak plasma concentrations of rifaximin in patients.

Highlights/Excerpts: Clinical Pharmacology and Biopharmaceutics Review

Mass balance study report was submitted to NDA 21-361 original submission. When radiolabeled rifaximin was orally administered, 97% of the administered dose was recovered in feces as the unchanged drug and a small amount (<1% dose) as the metabolite, 25-desacetyl rifaximin. Ca. 0.32% of the administered dose was recovered in urine, of which 0.03% of the administered dose was present as rifaximin. Rifaximin accounted for about 18% of radioactivity in plasma. **Biliary excretion** of rifaximin was suggested in a separate study. **Rifaximin was detected in bile after cholecystectomy in patients with intact GI mucosa.** In Caco-2 cell permeability study, the apparent apical to basolateral permeability of rifaximin was comparable to that of mannitol, a low permeability drug.

[24] **In cirrhotic patients, mean AUC: 130 ng.h/mL [Range = 28 to 359 ng.h/mL; in animal toxicity study, AUCs 42 to 127 ng.h/mL.**

Taken together, these results suggest that the oral absorption of rifaximin is limited yet once absorbed rifaximin may undergo extensive metabolism. Of note, the absolute bioavailability was not evaluated, and the relative contribution of biliary excretion and the enzymes responsible for the metabolism of rifaximin are unknown.

The proposed target population has a certain degree of hepatic impairment leading to reduced rifaximin metabolism. Therefore, the main clinical pharmacology question for this application has been if the submitted clinical pharmacology and biopharmaceutics information adequately supports safe and effective use of rifaximin in this new patient population.

Single dose and multiple dose PK

PKs following a single dose or multiple doses of 550 mg twice daily were characterized in healthy subjects (RFPK1007). After a single dose or after multiple doses, the median time to peak plasma concentration was 0.75 hours (Table 3). The mean Cmax was 4.04 ng/mL and 3.41 ng/mL after a single dose and multiple doses of rifaximin, respectively. After multiple doses for 7 days, the accumulation ratio based on AUC was 1.37. The mean half-life was 1.83 and 4.17 h after a single dose and multiple doses of rifaximin, respectively. The half-life at steady-state was comparable to that under fed conditions, while it was longer than that under fasting conditions. The shorter $t_{1/2}$ after a single-dose administration under fasting condition is likely due to the low plasma concentrations during the elimination phase.

Table 3
NDA 22-554
PK Parameters after a Single Dose and Multiple Doses of 550 mg Rifaximin in Healthy Subjects

	Single dose Under fasting condition (n=12)	Single dose Under fed condition (n=12)	Multiple doses 550 mg twice daily for 7 days (n=14)
Cmax (ng/mL)	4.04 ± 1.51 (37%)	4.76 ± 4.25 (89%)	3.41 ± 1.62 (47.5%)
Tmax[1]	0.75 (0.5-2.05)	1.50 (0.5-4.08)	0.76 (0.5-4.0)
AUCtau (ng·h/mL)	--	--	12.3 ± 4.76 (38.6%)
AUC_∞ (ng·h/mL)	11.1 ± 4.15 (37%)	22.5 ± 12.0 (53%)	--
CL/F (L/min)	959 ± 411 (42.8%)	--	863 ± 364 (42%)
$T_{1/2}$ (h)	1.83 ± 1.38	4.84 ± 1.34	4.17 ± 3.3

[1] Median (range)
This Table corresponds to Table 1 in Dr. Insook Kim's DCP review, with minor modifications.

Food effect:

A concomitant high fat meal delayed oral absorption of rifaximin and increased the mean AUC by 2 fold (Table 3).

The mean AUC was increased by 2-fold when rifaximin was administered within 30 min after a high fat meal. The median Tmax was delayed by 0.75 h with a high fat meal; the mean Cmax did not significantly change. The Cmax with a concomitant high fat meal was more variable than without a high fat meal.

Pharmacokinetics in patients

Systemic exposure to rifaximin was significantly higher in the target patient population (who had hepatic impairment) than in healthy subjects.

The PKs of rifaximin was evaluated in the target patient population during the open-label Phase 3 trial RFHE3002.

- PK blood samples were collected after dosing for 7 consecutive days in patients with Child-Pugh A or Child-Pugh B class hepatic impairment.. Because the PK study was done during any time of trial -3002, the total days of dosing for patients were $\geq$ 7 days.

- Overall, in patients with hepatic impairment the mean apparent oral clearance was reduced by 88% and the half-life was increased by 2 fold compared to healthy subjects. The mean Cmax and AUCtau were 6 fold- and 11 fold higher, respectively, than in healthy subjects (Table 4; Figure 3).
- When the PK parameters were analyzed by liver function, the mean Cmax and AUCtau in patients in moderate (Child-Pugh B) hepatic impairment were 28% and 36% higher than in patients with mild (Child-Pugh A) hepatic impairment (Table 4). The mean Cmax and AUCtau in patients increased as Model of End Stage Liver Diseases (MELD[23]) score increased (Figure 3).

Table 4
NDA 22-554
Pharmacokinetic Parameters by Liver Function After Multiple Doses of 550 mg Rifaximin Twice Daily

Liver function	Mild impairment Child-Pugh A (n=18)	Moderate impairment Child-Pugh B (n=7)	Overall (n=25)	Normal (n=14)[1]
Cmax (ng/ml)	19.5 ± 11.4 (58.5%)	25.1 ± 12.6 (50.2%)	21.1 ± 11.8 (56%)	3.41 ± 1.62 (47.5%)
Cmin (ng/ml)	5.13 ± 4.01 (78%)	7.90 ± 5.35 (67.7%)	5.91 ± 4.49 (76%)	0.275 ± 0.333 (121%)
Tmax (h)	1 (0.9-10)	1 (0.97-1)	1 (0.9-10)	0.76 (0.5-4)
AUCtau (ng·h/mL)	118 ± 67.8 (57%)	161 ± 101 (62.7%)	130 ± 77.6 (59.7%)	12.3 ± 4.76 (38.6%)
CL/F (L/min)	122 ± 101 (82.8%)	70.6 ± 29.2 (41.4%)	109 ± 90.1 (82.7%)	863 ± 364 (42%)
$T_{1/2}$ (h)	8.12 ± 3.58 (44.1%)	10.5 ± 1.5 (14.3%)	8.64 ± 3.63 (42%)	4.17 ± 3.3 (79%)

[1] RFPK1007 Cross-study comparison
This Table corresponds to Table 2 in Dr. Insook Kim's DCP review, with some modifications

The CPD reviewer commented that because both safety and efficacy were evaluated in patients with mild and moderate hepatic impairment receiving rifaximin at the proposed dosing regimen, no dosage adjustment is needed based on the systemic exposure. The CDTL agrees with this statement.

Protein Binding: hepatic encephalopathy patients vs. healthy subjects

Rifaximin is moderately protein bound and protein binding of rifaximin was slightly lower in patients with hepatic impairment.

Protein binding was evaluated in healthy subjects and patients with a history of HE.

- In healthy subjects, the average protein binding ratio was 67.5% [range: 62.5% to 72.8%].
- On the other hand, the average ratio of protein binding in patients with hepatic impairment after administration of the recommended dose and regimen [550 mg rifaximin twice daily] was 62% [range: 55.3 to 68.2%].
- The plasma concentration of rifaximin when the protein binding was measured ranged from 14 to 52 ng/mL in patients, which is higher than the < 10 ng/mL found in healthy subjects.

[25] MELD score was calculated as follows: MELD Score = 0.957 x Loge(creatinine mg/dL) + 0.378 x Loge(bilirubin mg/dL) + 1.120 x Loge(INR) + 0.6431

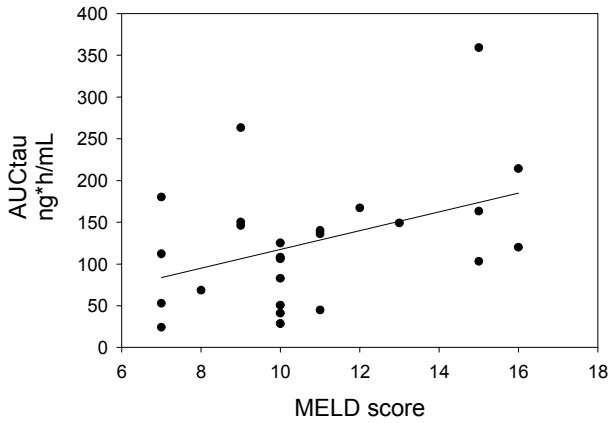


Figure 3. AUC increased with an increase in MELD score of patients

Dr. Kim noted that in an amendment dated 1/27/10, the sponsor submitted PK parameters for four patients with Child-Pugh Class C hepatic impairment. The mean ± S.D. AUCtau and Cmax were 245.9 ±119.6 ng·h/mL *and 35.5 ±12.5, respectively. The AUC and Cmax were 20- and 10-fold higher than those in healthy subjects and 2- and 1.8-fold higher than those in patients with Child-Pugh Class A hepatic impairment.*

Drug interaction

Effect of rifaximin on concomitant drugs which are substrates of CYP3A4:

- No clinically meaningful effect of rifaximin is expected on co-administered drugs which are metabolized by CYP3A4 in healthy subjects.
- However, **it is unknown if rifaximin in the target population, who have elevated rifaximin systemic exposure, would cause clinically meaningful drug interactions with other drugs which are metabolized by CYP3A4 enzyme.**

Rifaximin induces CYP3A4 enzyme activity in vitro. When Rifaximin 550 mg was administered three times daily for 7 days and 14 days, the AUC of midazolam, a probe substrate of CYP3A4 was 3.8% and 8.8% lower, respectively than when midazolam was administered alone, and Cmax of midazolam also decreased 4 to 5% when rifaximin was administered for 7 to 14 days prior to midazolam administration.

*The CPD reviewer commented that **this degree of drug interaction is not considered clinically meaningful**. Although the dosage regimen of rifaximin in this study i.e., three times a day, is different from the proposed dosage regime i.e. twice a day, the same conclusion is applicable to the proposed twice a day dosage regimen as this study was conducted under more stringent conditions and resulted in no significant effect.*

The induction of CYP3A4 by rifaximin may be dose- and treatment-duration dependent. Because the drug interaction was evaluated in healthy volunteers whose systemic exposure to rifaximin is much lower than in the target population, it is still unknown if rifaximin would induce CYP3A4 activity in target patient population with elevated systemic exposure to rifaximin (Table 5).

Table 5
NDA 22-554
Comparison of Mean Peak Plasma Concentrations

Study	Dosage regimen	Cmax (ng/mL)	Cmax (μM)	In vivo CYP3A4 induction
RFDI1002* [+]	7 days 200 mg TID	1.21	0.00154	None
RFDI1008[+]	7 days 550 mg TID	3.61	0.00459	< 25%

	14 days 550 mg TID	3.89	0.00495	< 25%
RFHE3002PK	7+ days 550 mg BID Child-Pugh A Child-Pugh B	 19.5 25.1	 0.0248 0.0319	Not evaluated

**submitted in NDA 21-361 original submission*
[+]in healthy volunteers
This Table corresponds to Table 3 in Dr. Insook Kim's CPD review, with some modifications.

In her review, Dr. Kim added the following comments. In the presence of 0.2 µM rifaximin, which is about 6 to 10 fold higher than the observed mean peak plasma concentration of rifaximin in patients, CYP3A4 enzyme activity was increased by 1.5 fold in vitro and the potency of induction was about 50% of rifampin, a strong CYP3A4 inducer. ***The CYP3A4 induction was not studied at lower rifaximin concentrations.***

Effect of P-glycoprotein inhibitors on rifaximin permeability in vitro

- In the presence of P-glycoprotein (P-gp) inhibitors, the efflux ratio (ER) of rifaximin decreased by 2 to 12 fold. Other transporters may be involved in efflux transport of rifaximin:
- The membrane permeability of rifaximin was evaluated in Caco-2 cell monolayer system. The apparent permeability of rifaximin from apical to basolateral direction was about $1*10^{-6}$ cm/sec; comparable to that of Mannitol.
- Rifaximin was greatly more permeable from basolateral to apical side. The efflux ratio of rifaximin at 5 µM was 45 to 135 while the efflux ratio of digoxin, a substrate of P-gp was 11 to 12. These results show that one or more transporters may be involved in the transport of rifaximin through Caco-2 monolayers.
- In the presence of P-gp inhibitors i.e. 60 µM verapamil and 0.5 µM GF120918, the efflux ratio of rifaximin decreased by 2 to 12 fold to 10 to 30.

Effect of rifaximin on the permeability of P-gp substrate (digoxin) in vitro

- In the presence of Rifaximin at 50 µM, the efflux ratio of digoxin decreased from 11 to 12 to 2 to 6. **However, the inhibition potential of rifaximin at the clinical use concentrations was not evaluated.**

The efflux ratio of digoxin decreased from 11 to 12 to 2 to 6 in presence of rifaximin at 50 µM. Known P-gp inhibitor, verapamil and GF120918 reduced the efflux ratio of digoxin to 1. **This result suggests that rifaximin at 50 µM has a potential to inhibit efflux transport of concomitant drugs which are P-gp substrates in vivo but its inhibitory potency is expected to be lower than that of verapamil.**

In her CPD review, Dr. Kim added the following comment. Nevertheless, this effect was studied only at one concentration which was much higher than the concentrations in the GI tract or the highest Cmax of 66 nM observed in a patient with moderate liver impairment. ***Additional study at lower concentrations of rifaximin will be helpful to determine if in vivo drug interaction study is warranted. The CDTL agrees with this suggestion.***

Exposure (Dose)-Response Relationship

Rifaximin for the proposed indication is presumably acting locally in the intestine. As such the systemic exposure may be more relevant to safety than efficacy. **Nevertheless, because only one dose level was studied in the target population for the proposed indication, there is insufficient information to draw a conclusion about the exposure-response relationship in terms of safety and efficacy.**

Question-Based Review

General Attributes of the drug

- **What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?**

Rifaximin (Xifaxan®) was approved in 2004 for the treatment of patients with traveler's diarrhea using a dosing regimen of 200 mg three times daily for 3 days (NDA 21-361). In this application, the sponsor is pursuing the use of rifaximin 550 mg BID for maintenance of remission of HE in patients ≥ 18 years of age. The 200 mg tablet approved under the parent NDA 21-361 and a new NDA number was granted to the current supplement due to systemic migration to DARRTS [Type 6 submission]

- **What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?**

Xifaxan 550 mg tablet is an immediate release tablet and compositional proportional to the approved 200 mg tablet. Rifaximin is practically insoluble in water. The solubility of rifaximin in 100mM sodium phosphate buffer at pH was (b) (4) mg/mL. **On the other hand, in presence of 0.25% sodium dodecyl sulfate [SDS], the solubility of rifaximin increased ca. 100-fold to (b) (4) mg/mL.**

Solubility of Rifaximin in Typical Dissolution Medium

Dissolution Medium	Solubility (mg/mL)
0.1 N Hydrochloric Acid	(b) (4)
22 mM Sodium Acetate, pH 4.5	
50 mM Potassium Phosphate, pH 6.8	
50 mM Potassium Phosphate, pH 7.4	
100 mM Sodium Phosphate, pH 7.4	

Reference: VALRPT-43, Revision 0

Solubility of Rifaximin in 100 mM Na Phosphate Buffer, pH 7.4 Containing Increasing Quantities of SDS

Dissolution Medium	Solubility (mg/mL)
100 mM Sodium Phosphate, pH 7.4, 0.25% SDS [a]	(b) (4)
100 mM Sodium Phosphate, pH 7.4, 0.5% SDS [a]	
100 mM Sodium Phosphate, pH 7.4, 0.8% SDS [a]	
100 mM Sodium Phosphate, pH 7.4, 1.0% SDS [a]	

Reference: VALRPT-43, Revision 0

a SDS = Sodium dodecyl sulfate

Solubility of rifaximin at different pH

Solvent system	Solubility (mg/l)
Purified water pH 4 buffer solution pH 7 buffer solution pH 10 buffer solution	(b) (4)

There was a dramatic increase in solubility to (b) (4) at pH 10 from (b) (4) at pH 7. There was no remarkable difference in solubility between at pH 4.5 and pH 7.4.

- **What are the proposed mechanism(s) of action and therapeutic indication(s)?**

The CP review noted:

-- The mechanism of action of rifaximin depends on the inhibition of DNA-dependent RNA polymerase of the target microorganisms, leading to the suppression of initiation of chain formation in RNA synthesis. Rifaximin binds to the beta-subunit of the bacterial DNA dependent RNA polymerase, resulting in inhibition of bacteria protein synthesis.

-- The etiology and pathogenesis of HE are not known. The main tenet for the pathogenesis of HE is that nitrogenous substances derived from endogenous bacterial metabolism in the GI tract adversely affect brain function.

-- Compounds gain access to the systemic circulation as a result of decreased hepatic function or porto-systemic shunts. Once in brain tissue, the compounds produce alterations of neurotransmission that affect consciousness and behavior.

-- Other gut derived neurotoxins have also been implicated. Some of these neurotoxins, which also accumulate and alter CNS function include: mercaptans, phenols, manganese, short chain fatty acids, bilirubin, and a variety of neuroactive medications

-- Rifaximin is proposed for the maintenance of remission of HE in patients aged 18 years or older.

- **What are the proposed dosage(s) and route(s) of administration?**

One orally administered 550 mg tablet; twice a daily.

Highlights of General Clinical Pharmacology Review

- **What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?**

-- For the proposed indication, target patient population has a varying degree of hepatic impairment, which could lead to increased systemic exposure of rifaximin.

-- In support of the proposed indication, the sponsor submitted three in vivo and two in vitro clinical pharmacology related studies. The three in vivo studies are:

(1) Study RFPK1007; to characterize single dose and multiple dose PKs and to evaluate food effect in healthy subjects

(2) Study RFPK1008; to assess drug interaction with midazolam in healthy volunteers,

(3) Study RFHE3002PK; to determine the effect of different degrees of hepatic impairment on the PKs of rifaximin.

The two in vitro studies were conducted to evaluate if rifaximin is a substrate and/or inhibitor of efflux transporter(s) and to evaluate protein binding in blood samples from PK studies. The sponsor also submitted the final study report of RFPK1002 titled *"A two-way crossover scintigraphic evaluation of the disintegration of two batches or rifaximin"* and used it to support twice daily dosing frequency. **The RFPK1002 is considered only supportive as it was a comparative study for 200 mg tablets.**

The clinical efficacy and safety of rifaximin for the proposed indication were evaluated in a pivotal phase 3 trial: (RFHE3001) and a long-term extension study: (RFHE3002).

- **What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical studies?**

The primary efficacy parameter for double-blind, placebo controlled study RFHE3001 was the occurrence of an episode of breakthrough overt HE during treatment. Breakthrough overt HE was defined as an increase of the Conn score to Grade ≥ 2 (i.e. 0 or 1 to ≥ 2) or an increase in Conn and asterixis score of 1 grade each for those subjects who entered the study with a Conn score of 0.

Efficacy endpoints were discussed at the AC meeting scheduled on February 23, 2010.

Venous ammonia

Elevation in blood ammonia, a key secondary endpoint in RFHE3001, is suggested to be associated with the CNS effects underlying overt HE. Comparison of changes from baseline to end of study in venous ammonia levels showed statistically significant, greater improvement over the course of the study in the rifaximin group when compared to placebo ($p = 0.0391$).

- **Are the active moieties in the plasma appropriately identified and measured to assess PK parameters?**

Rifaximin was measured in plasma using a validated HPLC-MS/MS method to assess PK parameters.

Exposure-Response Evaluation

- **What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?**

Rifaximin for the proposed indication is presumably acting locally in the intestine. As such the systemic exposure may be more relevant to safety than efficacy. Nevertheless, because only one dose level was studied in the target population for the proposed indication, there is insufficient information to draw a conclusion about the exposure-response relationship in terms of safety and efficacy.

Dose selection for the pivotal phase 3 trials

- ***Dose selection was based on results of a Phase 2 trial although the design of that trial was not optimal for the purpose.***

PSE-Index

The PSE-Index is a composite score of Mental State (Conn score), asterixis grade, Number Connection Test Score, Electroencephalography (EEG) score and venous ammonia levels.

While there was no statistically significant difference among three dose groups based on PSE-Index at the end of the treatment (Table 6), the change of PSE-Index from baseline after 7 days of rifaximin treatment tended to be greater for1200 mg and 2400 mg daily dose cohorts than for 600 mg dose cohort. The mean change of PSE Index from baseline to end of treatment was -6.4%, -10.3%, and -10.7% in 600 mg, 1200 mg, and 2400 mg rifaximin dose cohorts, respectively. The total daily dose of 1200 mg was further studied in supportive Phase 3 trials in active HE patients (RFHE9702, 9701).

Table 6
Study RFHE9702
Mean PSE-Index at baseline and after 7 days of treatment

Rifaximin daily dose		PSE Index (%)					Adjusted mean from analysis of covariance	
		N	Mean	St dev	Min	Max	Mean	95% CI
600 mg	Day 1	14	37.8	11.4	25.0	64.3		
	Day 7 or withdrawal	17	31.9	16.9	3.6	67.9	32.4	22.9, 42.7
1200 mg	Day 1	16	38.4	13.8	21.4	75.0		
	Day 7 or withdrawal	18	28.2	18.9	7.1	82.1	30.8	22.7, 39.2
2400 mg	Day 1	16	41.7	8.5	17.9	50.0		
	Day 7 or withdrawal	16	31.0	14.2	7.1	57.1	25.8	18.8, 34.4

NOTE: This Table corresponds to Table 10 in Dr. Insook Kim's CPD review.

Safety Analysis in Subgroup by Liver Function

- ***No apparent increase in the incidence of treatment-emergent adverse events (TEAE) under rifaximin treatment by decrease in liver function was observed. Nonetheless, it should be noted that the safety database for patients with severe hepatic impairment is relatively limited (See Clinical Review by Dr. Lara Dimick-Santos).***

Based on the increasing trend of systemic exposure to rifaximin with worsening the liver function, a subgroup analysis of AEs by liver function based on MELD score and Child-Pugh Class was conducted by the sponsor.

- Notably, a higher rate of death was reported in patients with severe hepatic impairment under rifaximin treatment in RFHE3001 compared to placebo group and groups with mild and moderate hepatic impairment. **It is not known if this could be attributed to other confounding factors or potentially higher systemic exposure to rifaximin.** The detailed review of safety signal by liver function is discussed in the clinical review.

- The incidence of treatment-emergent adverse events (TEAE) increased as the liver function decreased. Nonetheless, the incidence of TEAE increased in placebo groups as well and the TEAE rate was similar between rifaximin treatment group and placebo group among patients with the same Child-Pugh Class liver function. **Based on the current information, there is no obvious correlation between the degree of liver impairment and incidence of adverse event.**

In an additional comment, Dr Kim mentioned the following. It should be noted, however, that relatively limited safety data are available for patients with severe liver impairment. A similar trend in the incidence of TEAE and treatment-emergent serious adverse events (TESAE) was observed by hepatic function based on MELD score (Table 12 *in Dr. Dimick-Santos review).*

- **Does this drug prolong the QT or QTc interval?**

A thorough QT study was not conducted for rifaximin.

Pharmacokinetic Characteristics

- **What are the PK characteristics of rifaximin?**

The following is excerpted from Dr. Kim's CPD review.
-- Mass balance study report was submitted to NDA 21-361 original submission (please, see clinical pharmacology review by Dr. Kofi Kumi for more details).
-- When radiolabeled rifaximin was orally administered, 97% of the administered dose was recovered in feces as the unchanged drug and a small amount (<1% dose) as the metabolite, 25-desacetyl rifaximin (n=3-4; Table 7).
-- About 0.32% of the administered dose was recovered in urine, of which 0.03% of the administered dose was present as **unmodified** rifaximin.
-- Rifaximin accounted for about 18% of radioactivity in plasma.
-- Biliary excretion of rifaximin was suggested in a separate study. Rifaximin was detected in bile after cholecystectomy in patients with intact GI mucosa. After administration of 400 mg twice a day for 2 days, six out of 13 patients had measurable rifaximin in bile and the concentration of rifaximin in these patients was from 4.5 to 16.5 µg/mL. Seven patients had either non-detectable or trace amount of rifaximin in bile.
-- In Caco-2 cell permeability study, the apparent apical to basolateral permeability of rifaximin was comparable to that of mannitol, a low permeability drug.

Taken together, these results suggest that the oral absorption of rifaximin is limited yet once absorbed rifaximin may undergo extensive metabolism. *Of note, the absolute bioavailability was not evaluated, and the relative contribution of biliary excretion and the enzymes responsible for the metabolism of rifaximin are unknown.*

Table 7
Mass balance study
(NDA 21-361 original submission)

Parameter	Rifaximin	Parameter	Total Radioactivity[a]
C_{max} (ng/mL)	4.3 ± 2.8	C_{max} (ng equivalents/mL)	30.2 ± 7.4
T_{max} (h)	1.25[b]	T_{max} (h)	1.5[b]
AUC_{0-t} (ng•h/mL)	19.5 ± 16.5	AUC_{0-t} (ng equivalents•h/mL)	61.8 ± 20.0
% Dose Excreted in Urine	0.030 ± 0.020	% Dose Excreted in Urine	0.32 ± 0.05
		% Dose Excreted in Feces	96.62± 5.67

Source: RFPK9801 Tables 3, 4, and 5.
AUC_{0-t} = area under the concentration-time curve from time 0 (predose) to the last quantifiable concentration-time point; C_{max} = maximum concentration; SD = standard deviation; T_{max} = time to maximum concentration
a N=3 except for C_{max} and T_{max}
b Median values
NOTE: This Table corresponds to Table 13 in Dr. Kim's CPD review.

Protein binding: Rifaximin is moderately protein bound and in vivo protein binding of rifaximin was about 9% lower in patients with hepatic impairment.

- Rifaximin is moderately protein bound.
- In healthy subjects, the average protein binding ratio after administration of 550 mg rifaximin twice daily was 67.5% ranging from 62.5% to 72.8%.
- Rifampin, a structural analog of rifaximin is about 80% protein bound.
- On the other hand, the average ratio of protein binding in patients with hepatic impairment after administration of 550 mg rifaximin twice daily was 62.0 % ranging from 55.3 to 68.2%.

Dr. Kim added this clarification:

- *A blood sample for protein binding was collected 0.5 to 2 h post-dose in healthy volunteers and at 2 h post-dose in 9 out of 12 patients (75%).*
- *In 3 out of 12 patients, the samples were collected from 4 to 10 h post-dose. The plasma concentration of rifaximin when the protein binding was measured ranged from 14 to 52 ng/mL in patients and < 10 ng/mL in healthy subjects.*

The available information suggests that about 9% more free drug will be available in patients with hepatic impairment than in healthy subjects at given plasma concentrations. The lower protein binding in patients with hepatic impairment may be attributed to a lower plasma protein due to reduced liver function.

- **What are the single dose and multiple dose PK parameters?**

PKs following a single dose and after multiple doses of 550 mg twice daily were characterized in healthy subjects (RFPK1007). After a single dose and multiple doses, the median time to peak plasma concentration was 0.75 h (Table 3). The mean Cmax was 4.04 ng/ml and 3.41 ng/ml after a single dose and multiple doses of rifaximin, respectively. After multiple doses for 7 days, the accumulation ratio based on AUC was 1.37. The mean half-life was 1.83 and 4.17 hours after a single dose and multiple doses of rifaximin, respectively. The half-life at steady-state was comparable to that under fed conditions, while it was longer than that under fasting conditions. The shorter $t_{1/2}$ after a single-dose administration under fasting condition is likely due to the low plasma concentrations during the elimination phase.

It is worth noting that the dose-proportionality of rifaximin PK was not formally studied.

- **How does the PK of rifaximin in healthy volunteers compare to that in patients?**

Systemic exposure to rifaximin was significantly higher in the target patient population (who had hepatic impairment) than in healthy subjects.

- The PKs of rifaximin was evaluated in the target patient population during the open-label Phase 3 trial RFHE3002. PK blood samples were collected after dosing for 7 consecutive days in patients with Child-Pugh A and Child-Pugh B class hepatic impairment.
- As depicted in Table 4 and Figure 4, overall, in patients with hepatic impairment the mean apparent oral clearance was reduced 88% and the half-life was increased by 2 fold compared to healthy subjects. The mean Cmax and AUCtau were 6 fold- and 11 fold higher, respectively, than in healthy subjects.

When the PK parameters were analyzed by liver function, the mean Cmax and AUCtau in patients in moderate (Child-Pugh B) hepatic impairment were 28% and 36% higher than in patients with mild (Child-Pugh A) hepatic impairment (Table 4). The mean Cmax and AUCtau in patients increased as MELD (Model of End Stage Liver Diseases) score increased (Figure 4).

*The sponsor submitted PK information for patients with Child-Pugh C class hepatic impairment in an amendment dated 1/26/10. The mean AUCtau was 245. 9 (± 119.6) ng*h/mL and Cmax was 35.5 (± 12.5) ng/mL. The mean AUC and Cmax in patients with Child-Pugh C class hepatic impairment was 52% and 41% higher, respectively, than those in patients with Child-Pugh B Class hepatic impairment.*

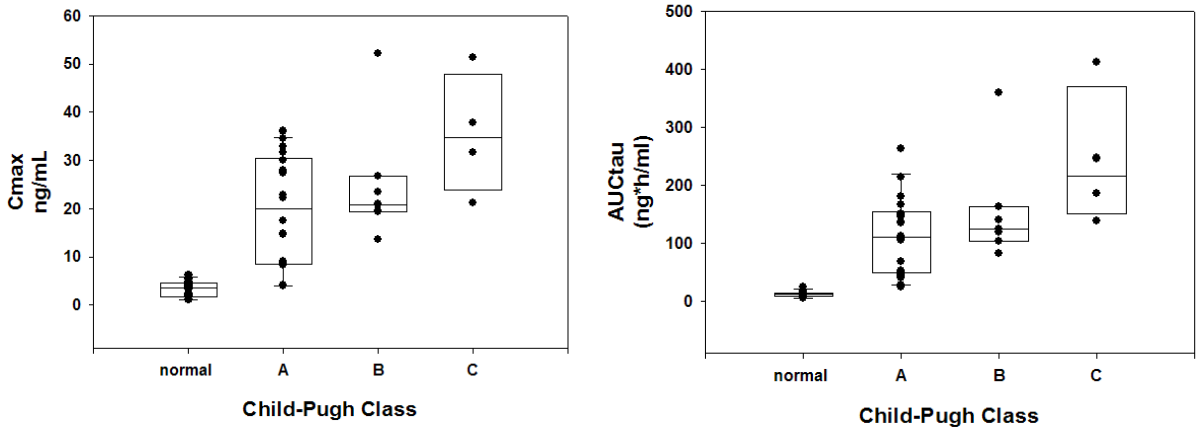


Figure 4. AUCtau and Cmax by Child-Pugh Class liver function

- **Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?**

The dose-proportionality was not formally studied for rifaximin.

- **How do the PK parameters change with time following chronic dosing?**

PK after multiple doses was predictable from PK after a single-dose administration of rifaximin. The accumulation factor after 7 days of 550 mg rifaximin BID dosing was 1.34.

- **What is the inter-subject variability of PK parameters in volunteers and patients?**

An inter-subject coefficient of variability (CV %) for AUCtau and Cmax ranging from approximately 50 to 63%. The variability observed in healthy subjects i.e. CV% of 45% to 60%.

Intrinsic Factors

- **What is the effect of gender and hepatic impairment on PK and what is the impact of any differences in exposure on safety responses?**

Gender effect:

The AUC and Cmax were slightly higher in healthy female subjects than in healthy male subjects. It may be due to a lower body weight of female subjects than male subjects.

	550 mg single dose[1]		**at steady-state 550 mg BID**	
	Cmax (ng/mL)	**AUCi (ng·h/mL)**	**Cmax (ng/mL)**	**AUCtau (ng·h/mL)**
Male (n=6)	3.12 ± 1.19	9.73 ± 4.27	2.95 ± 1.63	10.71 ± 4.13
Female (n=8)	4.70 ± 1.55	11.53 ± 4.32	3.67 ± 1.54	13.07 ± 5.33

[1]Male (n=5), Female (n=7)

In the RCT Study population, the pattern and frequencies of TEAEs were similar between the rifaximin and placebo groups for both male and female subjects.

- During the randomized placebo-controlled trial RFHE3001, the overall incidence of treatment-emergent adverse events (TEAE) was 82.2% (88/107) and 82.7% (62/72) in placebo-treated males and rifaximin-treated males, respectively.
- The overall incidence of TEAE in female subjects treated with placebo and rifaximin was 84.6% (44/52) and 78.5% (51/65), respectively.
- In general, the frequency of other TEAEs was comparable between gender subgroups.

Hepatic insufficiency

This subject matter is addressed above. As shown in Figure 5, when measured by the MELD score, **the systemic exposure increases as the liver function worsen.**

Extrinsic Factors

- **What is the effect of a high fat diet on PK of rifaximin and what is the impact of any differences in exposure on response?**

Food effect: ***A concomitant high fat meal delayed oral absorption of rifaximin and increased the mean AUC by 2 fold.***

The mean AUC was increased by 2 fold when rifaximin was administered within 30 min after a high fat meal. The median Tmax was delayed by 0.75 hours with a high fat meal and the mean Cmax was not significantly different. The Cmax with a concomitant high fat meal was more variable than without a high fat meal:

Parameter	Fasting	Fed
Cmax (ng/mL)	4.04 ± 1.51	4.76 ± 4.25
Tmax (h)	0.75 (0.5-2.05)	1.50 (0.5-4.08)
AUCi (ng*h/mL)	11.1 ± 4.15	22.5 ± 12.0
T1/2 (h)	1.83 ± 1.38	4.84 ± 1.34

Dr. Kim commented that during the Phase 3 trials, no specific instruction as to the meal intake was given so patients took rifaximin regardless of food intake. During the PK study in patients, a light meal was ingested immediately after the 1 hour post-dose blood sampling following overnight fasting.

Drug-Drug Interactions

- **Is the drug a substrate of CYP enzymes?**

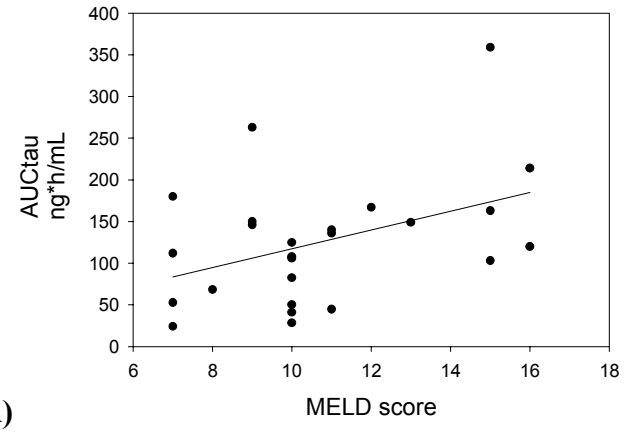
The enzymes responsible for metabolism of rifaximin were not studied.

- **Is the drug an inhibitor and/or an inducer of CYP enzymes?**

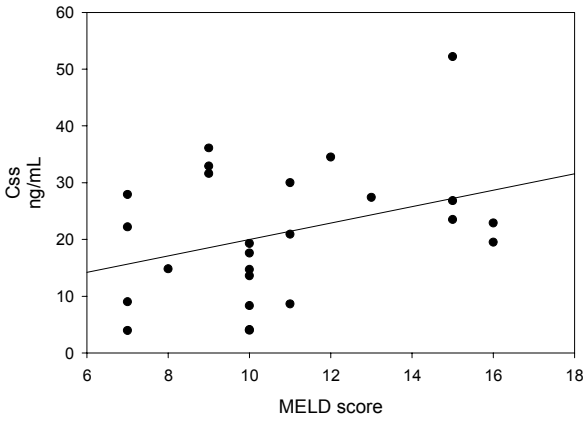
-- Effect of rifaximin on concomitant drugs which are substrates of CYP3A4:

No clinically meaningful effect of rifaximin is expected on co-administered drugs which are metabolized by CYP3A4 in healthy subjects.

However, it is unknown if rifaximin in the patients with a history of HE, who have elevated rifaximin systemic exposure, would cause clinically meaningful drug interaction with other drugs which are metabolized by CYP3A4 enzyme.



(A)



(B)

Figure 5. (A) AUC and (B) Cmax increased with an increase in MELD score of patients

Inhibition of CYP enzymes

CYP enzyme activity in vitro was not significantly inhibited in presence of rifaximin at 2-200 ng/mL concentrations and IC50 was estimated > 200 ng/mL (NDA 21-361 original submission. Please see Clinical pharmacology review by Dr. Kofi Kumi for more details). The mean Cmax in patients with Child-Pugh C class hepatic impairment was 35.5 (± 12.5).

Induction of CYP enzymes

Rifaximin, a structural analog of rifampin induced CYP3A4 in vitro (NDA 21-361 original submission. Please see Clinical pharmacology review by Dr. Kofi Kumi for more details). The potency of in vitro induction of CYP3A4 was about <50% of rifampin at given concentration (Table 8).

Table 8
NDA 22-554
In vitro CYP3A4 Induction (fold increase in CYP3A4 activity) Based On Rate of Testosterone-6β-hydroxylation (from Clinical Pharmacology review for NDA 21-361 original submission)

Conc. (μM)	Rifaximin	Rifampin
0.2	1.5	3
1.0	1.7	3.7
10	1.8	4
20	1.3	3
50	0.15#	3.2

appeared to alter the morphology of the hepatocytes as observed by light microscopy. Taken from original Clinical Pharmacology review for NDA 21-361.

The in vivo drug interaction via CYP3A4 induction by rifaximin was 3valuated in study RFPK1008 in healthy subjects. When Rifaximin 550 mg was administered three times daily for 7 days and 14 days, the AUC of midazolam, a probe substrate of CYP3A4 was 3.8% and 8.8% lower, respectively than when midazolam was administered alone, and Cmax of midazolam also decreased 4 to 5% when rifaximin was administered for 7 to 14 days prior to midazolam administration.

- **Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?**

-- Effect of P-glycoprotein inhibitors on rifaximin permeability in vitro:

In the presence of P-glycoprotein (P-gp) inhibitors, the efflux ratio (ER) of rifaximin decreased by 2 to 12 fold. Other transporters are likely involved in efflux transport of rifaximin:

The membrane permeability of rifaximin was evaluated in Caco-2 cell monolayer system. The apparent permeability of rifaximin from apical to basolateral direction was about $1*10^{-6}$ cm/sec and it was comparable to that of Mannitol. Rifaximin was greatly more permeable from basolateral to apical side. The efflux ratio of rifaximin at 5 □M was 45-135 while the efflux ratio of digoxin, a substrate of P-gp was 11-12. These results show that one or more transporters may be involved in the transport of rifaximin through Caco-2 monolayers.

In the presence of P-gp inhibitors i.e. 60 μM verapamil and 0.5 μM GF120918, the efflux ratio of rifaximin decreased by 2-12 fold (Table 9).

Table 9
NDA 22-554
Inhibition of Rifaximin transport by P-gp inhibitors

	ER	$ER_{Verapamil}$	$ER_{GF120918}$
Round 1	134.54 ± 0.1	10.89 ± 0.2	16.48 ± 0.17
Round 2	78.53 ± 0.32	11.56 ± 0.28	29.68 ± 0.11

Round: Independent experiment on different days
This Table corresponds to Table 19 in Dr. Kim's CPD review.

- ***Effect of rifaximin on the permeability of P-gp substrate (digoxin) in vitro:***
  In the presence of Rifaximin at 50 μM, the efflux ratio of digoxin decreased from 11-12 to 2-6. However, the inhibition potential of rifaximin at the therapeutic concentrations was not evaluated.

The efflux ratio of digoxin decreased from 11-12 to 2-6 in presence of rifaximin at 50 μM. Known P-gp inhibitors, verapamil and GF120918 reduced the efflux ratio of digoxin to 1 (Table 10). This result suggests that rifaximin at 50 μM has a potential to inhibit efflux transport of concomitant drugs which are P-gp substrates in vivo but its inhibitory potency is expected to be lower than that of verapamil.

Dr. Kim notes that nevertheless, this effect was studied only at one concentration which was much higher than the highest Cmax of 66 nM observed in a patient with moderate liver impairment. ***Additional study at lower concentrations of rifaximin will be helpful to determine if in vivo drug interaction study is warranted.*** *GF120918 also inhibits BCRP transporter. The CDTL agrees with this suggestion.*

- **Are there other transporter pathways that may be important?**

The P-gp inhibitor could not reduce the efflux ratio of rifaximin to unity suggesting potentially other efflux pumps may be involved in efflux of rifaximin. Interaction between rifaximin and other transporters was not studied.

Table 10
NDA 22-554
Inhibition of Digoxin Transport by Rifaximin

	ER	$ER_{Rifaximin}$
Round 1	11.35 ± 0.31	4.77 ± 0.27
Round 2	11.74 ± 0.32	1.99 ± 0.44
Round 3	12.32 ± 0.21	6.36 ± 0.28

- **What other co-medications are likely to be administered to the target patient population?**

Effect of Concomitant Lactulose Use

Lactulose is a standard of care for patients with HE and in the pivotal RFHE3001 trial, 91% patients based on patient's diary used lactulose concomitantly. ***Actually, there is the suspicion that rifaximin may not be effective as a stand-alone medication and that to benefit patients with HE, rifaximin need to be administered together with other anti-HE medications, such as lactulose.***

- 15 out of total 25 patients who participated in PK sub study were on concomitant lactulose therapy during the PK study.
- The mean systemic exposure in patients with concomitant lactulose use was higher than that in patients without concomitant lactulose regardless of liver function (Figure 6). The mean AUC in patients with concomitant lactulose was 142 ng*h/mL (61% CV) and that in patients without concomitant lactulose was 106 hg*h/mL (44% CV).
- Of note, 33% (5 out of 15) of patients who used lactulose concomitantly had moderate hepatic impairment and 20% (2 out of 10) of patients who did not use lactulose had moderate hepatic impairment. It is not known if the slightly higher systemic exposure observed is due to an interaction between rifaximin and lactulose.

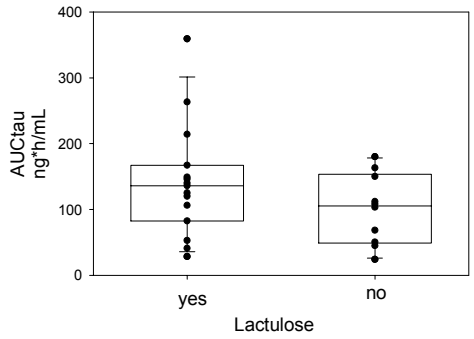


Figure 6. Mean AUC in patients with a history of HE by concomitant lactulose use

Dr. Kim feels that because of confounding factors such as hepatic insufficiency, a firm conclusion about effect of lactulose can not be drawn. The bacterial degradation of lactulose results in an acidic pH converting NH_3 to NH_4^+. It has been proposed that the conversion of NH_3 to NH_4^+ inhibits the diffusion of NH_3 into the blood. Since the solubility of rifaximin is not significantly different between pH 4.5 and pH 7.4, the increasing trend in AUC of rifaximin with concomitant lactulose is unlikely due to an increase in solubility. The CDTL agrees with this assessment.

- **Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?**

Induction of CYP3A4 in vivo by rifaximin in the target patient population

The induction of CYP3A4 by rifaximin may be dose- and treatment-duration dependent. The drug interaction study RFDI1008 which was conducted in healthy volunteers could not address the issue in the target population whose plasma concentration of rifaximin is $\geq$ 5 fold higher than in healthy subjects (Table 5).

Inhibition of P-gp transporter by rifaximin at therapeutic plasma concentrations

The effect of rifaximin on efflux ratio of P-gp substrate was studied only at one concentration which was much higher than the observed mean peak plasma concentration in patients. Therefore, it is unknown if rifaximin has P-gp inhibitory effect at therapeutic plasma concentrations. Additional study at lower concentrations of rifaximin will be helpful to determine if in vivo drug interaction study is warranted.

Effect of P-gp inhibitor(s) on rifaximin systemic exposure in vivo

The efflux ratio of rifaximin in vitro was significantly reduced in presence of P-gp inhibitors. The in vivo drug interaction between rifaximin and P-gp inhibitor(s) was not evaluated.

In her review, Dr. Kim explains how was rifaximin [properly] identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies and addresses the issue of the range of the standard curve, what are the lower limit of quantification (LLOQ) and what is the accuracy and precision at LLOQ.

In the remaining sections of her review, Dr. Kim provides detailed labeling recommendations, summaries of individual studies evaluated and Appendices mentioned in her review. Labeling issues and recommendations for post-marketing evaluations are addressed separately from the current CDTL review.

6. Clinical Microbiology

The Clinical Microbiology Consult review states that preclinical studies were previously reviewed (NDA #21-361 Microbiology Reviews by Mr. Peter Dionne and Dr. Avery Goodwin dated 3/14/02 and 4/13/04, respectively).
Rifaximin, a structural analog of rifampin, acts by binding to the beta-subunit of bacterial DNA dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis. Rifaximin has a broad spectrum of antimicrobial activity both against gram negative and gram positive organisms, but certain strains of each of these **groups that colonize the gut lumen** are not sensitive to this antibiotic. In particular, many strains of *Bacteroides fragilis,* **anaerobic organisms that are major colonizers of the gut**, are highly resistant to rifaximin. In addition, within a short time of rifaximin exposure many antimicrobial sensitive gram negative and gram positive luminal organisms develop **"significant resistance"** to the antibiotic. The CDTL agrees that this issue needs to be further addressed.

Rifaximin is approved for the treatment of traveler's diarrhea caused by noninvasive strains of E *coli.* The approved dose and duration of treatment [200 mg TID for 3 days] is too short in comparison with the long-term use if the drug is approved for the indication sought by the applicant. The applicant is seeking approval for changes in the label that include: 1) PLR formatting; 2) revision of the label by adding information from 5 studies [3 pre-clinical; 2 clinical]. Two Consult reviews from Clinical Microbiology have been finalized. In the first, a microbiology assessment by the Division of Special pathogen and Transplant Products of publications describing results of in vitro studies and reports from two clinical trials for the short-term use in the treatment of traveler's diarrhea are addressed. The applicant proposed to add the following to the existing label:

- *rifaximin has a unique mechanism of action which results in a lower rate of pathogen eradication and a lack of alteration of the gut flora in patients treated with rifaximin compared to fluoroquinolones and aminoglycosides.*
- *rifaximin may alter virulence factors of enteric bacterial pathogens without killing them, which has been seen with subtherapeutic levels of drugs and colonization fimbriae of enterotoxigenic E. coli.*
- morphological changes are observed when susceptible or resistant bacteria are exposed to low concentrations of rifaximin.
- rifaximin reduces the viability and virulence of resistant bacteria.

It was found that results from the 5 publications submitted in support of the changes, are inadequate to support sponsor's proposed revisions of the rifaximin labeling. Reasons:
-- The in vitro data lacked information regarding specific methodology.
-- Data from the two clinical trials were inadequate because these studies did not correlate (b) (4)

In the second Consult review, comments on effects of L-T treatment on gut flora were included. For the HE-related indication, the applicant is proposing a higher dose and duration [550 mg BID for about 6 months]; the reviewer commented that no microbiology information was collected in the 6 month RFHA-3001 study or reported in the literature publications submitted by the applicant. In the absence of any microbiology data, the (b) (4) to rifaximin and other antimicrobial drugs within the rifampin class cannot be evaluated.
Clinical Microbiology also has provided additional comments on al of the sponsor-proposed labeling revisions. These comments are separately addressed.

DSPTP/Micro recommends that if rifaximin is approved for an HE-related indication, PM studies should be considered to evaluate the effect of L-T treatment with rifaximin on the gut flora and *in vitro* susceptibility to rifaximin and other rifamycin antimicrobial drugs. Depending on the outcome of such studies, consideration may need to be given to evaluating the clinical significance of *in vitro* "resistance' on the efficacy of rifaximin.

Additional Labeling Comments from Clinical Microbiology

NOTE: FDA's version of the label: The label revisions are addressed separately.

7. Clinical/Statistical --- Efficacy

[Excerpts from reviews by Drs. Lara Dimick-Santos/Behrang Vali/Ranjit Mani]

List Of Common precipitating factors and concurrent causes of HE [APPENDIX 5]

Tables of Currently Available Treatments for Proposed Indications

Listed in Table 11 are important characteristics of drugs commonly used for the treatment/prevention of HE; included are indication, adverse event profile and proposed mechanism of action. Lactulose, a poorly absorbed disaccharide, is approved for the prevention and treatment of HE; although it has low toxicity, the use of lactulose is limited by the frequent side effect of diarrhea. Neomycin, an aminoglycoside antibiotic is approved for the treatment of hepatic coma, but can only be used short-term due to neuro, nephro- and ototoxicity. Although not specifically approved for this indication, the antibiotic metronidazole is frequently used to treat or prevent HE; however, it is not well tolerated long-term secondary to GI side effects. As previously noted other aminoglycoside antibiotics have been used in the past, but are currently not recommended because of increased toxicity seen in liver failure patients. There are also other therapies currently under investigation for the treatment of HE [APPENDIX 6].

Table 11

Drug Treatment for Hepatic Encephalopathy

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

This Table corresponds to Table 4 in Dr. Dimick-Santos' Clinical Review, with some modifications.

Important Safety Issues with Consideration to Related Drugs

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

rifabutin	rifametane	rifamide	rifapentine	rifaximin
rifalazil	rifamexil	rifampin[a]	rifaxidin	rifomycin

[a] rifampicin in Europe and Japan

Rifampin

The Warning Section of the label states:

(b) (4)

Under Precautions; General, the label states:

(b) (4)

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

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

The sponsor contends that rifaximin is poorly absorbed and therefore will not produce systemic toxicity. However, the clinical reviewer notes that the pre-clinical studies were all done on animals with normal GI tracts and normal liver and renal function. These animals would be expected to be poor absorbers and rapid metabolizers of rifaximin. Patients with hepatic dysfunction have been shown to have increased permeability of the GI tract and may be at higher risk for systemic- including liver- toxicity. This issue is further elaborated in Section 4.3. of Dr. Dimick-Santos Clinical review.

The Clinical reviewer also mentions examples of poorly absorbed drugs that cause significant systemic toxicity. For example, after its oral administration, Neomycin sulfate is 97% eliminated unchanged in the feces; the absorbed fraction is rapidly distributed throughout the tissues and is excreted by the kidney in keeping with the degree of

renal function. Yet neomycin is widely known for its adverse reaction of nephro- and neuro-toxicities which do occur with oral administration as per the black box warning on the label. The incidence of aminoglycoside-induced nephrotoxicity is substantially greater in patients with advanced liver disease than in patients without liver disease

Summary of Presubmission Regulatory Activity Related to Submission [Table 12]

Table 12
Highlights of Regulatory Activity History

Date	Activity	Purpose	Outcome
Feb. 10,1998	Granted orphan status	Response to request for Orphan Designation	(b) (4)
Oct 14,1999	IND submitted	Maintain remission HE	IND 59-133
Dec. 13, 2004	Type C meeting	Clinical Development plan	Primary end-point agreement
Pertinent Agreements Reached at End-of-Phase 2 Meeting (December 13, 2004) Based on the meeting minutes, the following appear to have been the key agreements pertaining to the pivotal Phase 3 efficacy study RFHE3001 – as then proposed- that were reached between the Division of Gastrointestinal and Coagulation Drug Products (as it was then known) and the sponsor at the End-of-Phase 2 Meeting held on December 13, 2004. ▪ A placebo-controlled superiority design would be acceptable for the key Phase 3 efficacy study. ▪ **The following text was acceptable for the primary efficacy endpoint for the proposed Phase III study: "*The primary endpoint is the proportion of treatment failures by treatment group at Day 56. Treatment failure is defined as an increase in the Conn score to Grade ≥ 2 (i.e., 0 or 1 to Grade ≥ 2) or a Conn and asterixis score increase of 1 grade each. Early study termination will be considered a treatment failure.*"** Note that a Xifaxan® dose of (b) (4) and a duration of (b) (4) of double-blind, placebo-controlled treatment was proposed for Study RFHE3001 at the time of the End-of-Phase 2meeting, whereas a Xifaxan® dose of 550 mg BID and a duration of 6 months (of double-blind, placebo-controlled treatment) was eventually used for this pivotal study.			
Nov. 14, 2007	Type C meeting	Design of PK studies	FDA recommends PK studies on all three Child's class of cirrhosis
Dec. 16, 2008	Type B meeting	Pre-NDA	Concern about end-point and protocol problems discussed

NOTE: This Table corresponds to Table 6 in Dr. Dimick-Santos Clinical Review, with major modifications.

Sources of Clinical Data

Tables of Studies/Clinical Trials

As summarized in Table 13 the sponsor submitted results from one placebo-controlled, confirmatory clinical trial, [RFHE3001] and another Phase 3, open-label, treatment extension trial [RFHE3002]. Emphasis is on the review and evaluation of the pivotal [RFHE3001] trial and its extension [RFHE3002].

NOTE: Additional clinical studies/trials for indications other than HE or other than clinical that were considered in Dr. Dimick-Santos review primarily for safety purposes are listed in **APPENDIX 7.**

Table 13
NDA 22-554
Studies/Clinical Trails

Study ID	Trial Type	Trial Design	Number Centers	Number subjects	Dosage	Duration
Primary integrated analysis - Rifaximin for the maintenance of remission of HE						
RFHE3001	**Efficacy Pivotal Phase 3**	Randomized, Placebo-controlled, Double-blind, Patients with HE	70	299 Rifaximin: 140, Placebo: 159	Rifaximin 550 mg BID or Placebo	6 months
RFHE3002	**Safety Phase 3**	Open-label, Treatment extension Patients with HE	70	267 From 3001: 152 New: 115	Rifaximin 550 mg BID	On-going; 2 years
Secondary Supportive Trials – Rifaximin for the Acute Treatment of overt HE						
RFHE9701	**Efficacy and Safety Phase 3**	Randomized, Active control		103 Rifaximin: 50 Lactilol: 53	Rifaximin 400 mg TID or lactilol	5 to 10 days
RFHE9702	**Efficacy and Safety Phase 2**	Randomized, Dose-finding Patients with HE		54 Rifaximin 200 mg TID [n = 18] Rifaximin 400 mg TID [n = 19] Rifaximin 800 mg TID [n = 17]	Rifaximin, either 200, 400, or 800 mg TID	7 days
RFHE9901	**Efficacy and Safety Phase 3**	Randomized, placebo patients with HE and intolerant to lactulose		93 Rifaximin: 48 Placebo: 45	Rifaximin 400 mg TID or Placebo	14 days

Discussion of Individual Studies/Clinical Trials

Pivotal Clinical Trial RFHE3001

The characteristics of the study population are depicted in Table 14.

Table 14
NDA 22-554
Study REHE3001
Characteristics of the Study Population

INCLUSION CRITERIA	REASONS for EXCLUSION
--Age ≥ 18 years --Male or female. If female, were to be of non-childbearing-potential or practicing adequate birth control --Conn score (see Table 2) of 0 or 1 at entry (ostensibly indicating that the patient was in remission from hepatic encephalopathy)	--Significant medical or psychiatric condition that, as per the investigator, precluded study participation --Expected to receive a liver transplant within 1 month of screening --History of lactulose intolerance and not willing to discontinue lactulose for the duration of the study --History of allergy to rifampin or rifaximin

--Two or more episodes of HE associated with cirrhosis or portal hypertension equivalent to a Conn score ≥ 2 within 6 months prior to screening. Note the following regarding this criterion: • An episode of HE was defined as the a Conn score rising from 0 or 1 to ≥ 2 and returning to a score of 0 or 1 • At least one episode of HE must be confirmed by reviewing medical records from a treating physician, clinic, or hospital. Other episodes may be documented from descriptions given by the subject's caregiver. --Model for End-Stage Liver Disease score ≤ 25 --If a patient has a history of a portal-systemic shunt, transjugular intrahepatic portosystemic shunt placement (TIPS) must have been > 3 months prior to screening --Family member or other individual who can provide oversight for and be available to the patient during the conduct of the trial. --Informed consent	--Participation in an investigational drug or device study within 30 days prior to screening --Pregnant or at risk of pregnancy; lactating --Consumption of an alcoholic beverage within 14 days of screening; evidence of drug dependence --Diagnosis of human immunodeficiency virus infection --History of tuberculosis. --Diagnosis of chronic renal and/or respiratory insufficiency, or of an intercurrent infection --Active spontaneous bacterial peritonitis or requiring daily prophylactic antibiotic treatment --Treatment with sedatives within 7 days prior to screening --Presence of intestinal obstruction; inflammatory bowel disease --Visual or neurological disorder that the investigator believed could have an effect on the patient's performance on neuropsychological testing --Active malignancy in the last 5 years, except basal cell carcinoma of the skin, or *in situ* cancer of that cervix that has been surgically excised --Any condition that the investigator believes would prevent study completion or proper analysis of the study results --Ongoing gastrointestinal bleeding or a history of gastrointestinal bleeding sufficient to require hospitalization and a transfusion of ≥ 2 units of blood within 3 months of screening --Serum creatinine > 2.0 mg/dL --Hemoglobin < 8 mg/dL --Significant hypovolemia --Any electrolyte abnormality that can affect mental function --Serum potassium < 2.5 mEq/L --Requires medications are on the list of prohibited medications for this study

Comments on the Study Population

Note that patients were to be considered to be in remission from HE at the time of randomization if they had a Conn score of 0 or 1 at screening, and no episodes of HE (based on the patient-recorded daily diary) during the observation period lasting a maximum of 6 days between screening and baseline, and, presumably, at baseline as well. ***Remission needs to be better defined and standardized. It does not seem appropriate to consider in remission those patients who had one episode of HE with a Conn score of 1 at the time of randomization. The CDTL reviewer believes that to be categorized as being in remission from HE, patients should have a Conn score of 0 at baseline, that is, prior to the start of test medication. A Stage 1 patient has mild lack of awareness [not entirely normal consciousness], shortened attention span, impaired addition or substations [alteration of the intellect/behavior] or mild asterixis or tremor [that is, neurological alterations]. This patient cannot be said to be in remission from HE.***

HE episodes primarily attributable to the following were to be excluded: gastrointestinal hemorrhage requiring ≥ 2 units of blood by transfusion; medications such as narcotics, tranquilizers, and sedatives; renal failure requiring dialysis; or a central nervous system insult such as a subdural hematoma.

Prohibited Concomitant Medications

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

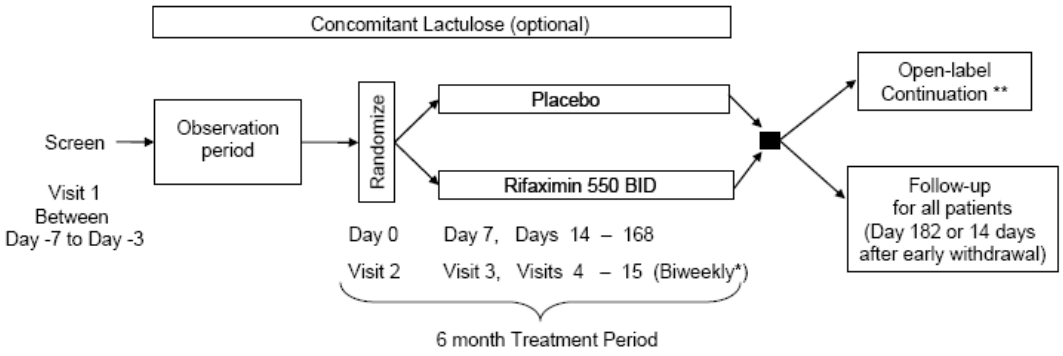
Comments on Prohibited Concomitant Medications

Not allowing the above-listed medications to be used concomitantly with the test medication, whether rifaximin

or placebo, is an adequate approach, as these medications may confound interpretation of results; imbalances between two experimental groups are not uncommon, even after using an adequate randomization procedure. It must be emphasized, however, that the majority of patients [91% in either arm of the trial] continued lactulose treatment. Therefore, RFHE3001 evaluated the effects of rifaximin when administered in conjunction with lactulose, in an add-on fashion.

- ***Concomitant medication and adverse event diaries were to be maintained during the treatment period.***

The following Figure gives details of trial design scheme. The schedule of assessments in Study rfhe3001 is given in **APPENDIX 8.**



* Visits 6, 8, 10, 12, & 14 on Days 42, 70, 98, 126, and 154 are OPTIONAL
**All Subjects may enroll into the open-label continuation study

Details of how were the efficacy data collected

The following is worth noting:

- During the observation period, lasting a maximum of 6 days, prior to baseline, patients were observed for episodes of breakthrough HE [BHE]. A symptom diary was maintained during that period. Patients who developed episodes of BHE during that period were not randomized.

- Concomitant medication and adverse event diaries were also maintained during the treatment period.

- Telephone contacts were made between the study site and patient in between study visits, according to the pre-specified schedule. At those contacts, the following were assessed: adverse events; concomitant medications; and changes in mental status. The date of the next study visit was also confirmed.

- The following is stated in the study protocol regarding the diary: "*A diary will be maintained by the subject during the observation period. An adverse event and concomitant medication diary will be used during the treatment period of the study. Subjects will be encouraged to complete the diary to the best of their ability and will be instructed on the importance of diary compliance".*

Given below is an example of an entry from the patient diary. It appears that such entries needed to be made daily during the treatment period of the trial.

DATE (Day/Month/Year)	# OF UNITS OF LACTULOSE (Total for Day) Dose 1 = 2 units Dose 2 = 3 units Total for day = 5 units	MENTAL STATUS (Check All Symptoms That Apply) Symptoms for Mental Status: 0=No Problems 1=Distracted 2=Sluggish (Lethargic) 3=Confused (Disoriented) 4=Change in Personality/ Inappropriate Behavior 5=Very Sluggish (Very Lethargic) 6=Very Confused (Very Disoriented) 7=Bizarre (Weird) Behavior 8=Not Responsive	ANY CHANGES IN YOUR HEALTH SINCE YESTERDAY?	ANY CHANGES IN YOUR MEDICATION USE SINCE YESTERDAY? (Other Than Lactulose)
1. 18 DEC 2005	05	0 [ ] 1 [X] 2 [ ] 3 [X] 4 [ ] 5 [ ] 6 [ ] 7 [ ] 8 [ ]	1 [ ] Yes 2 [X] No	1 [X] Yes 2 [ ] No

The evaluation tools [Conn Score and Asterixis Scale] have been referred to above. It is worth noting that the presence or absence of asterixis was not a criterion used to assign a Conn score in this study.

Description of the Hepatic Encephalopathy Scoring Algorithm [HESA]

In Final Study Protocol	In Study Report
-- This is a method that uses both clinical and neuropsychological assessments to evaluate mental status -- The algorithm has been validated previously and correlated with the Conn score -- The algorithm will be evaluated at screening and throughout the treatment period -- **The algorithm is to be used for exploratory purposes.**	-- The components of the HESA consisted of 2 sets of assessments: clinical and neuropsychological. --Each set of assessments was scored separately and an overall HESA derived from both assessments.

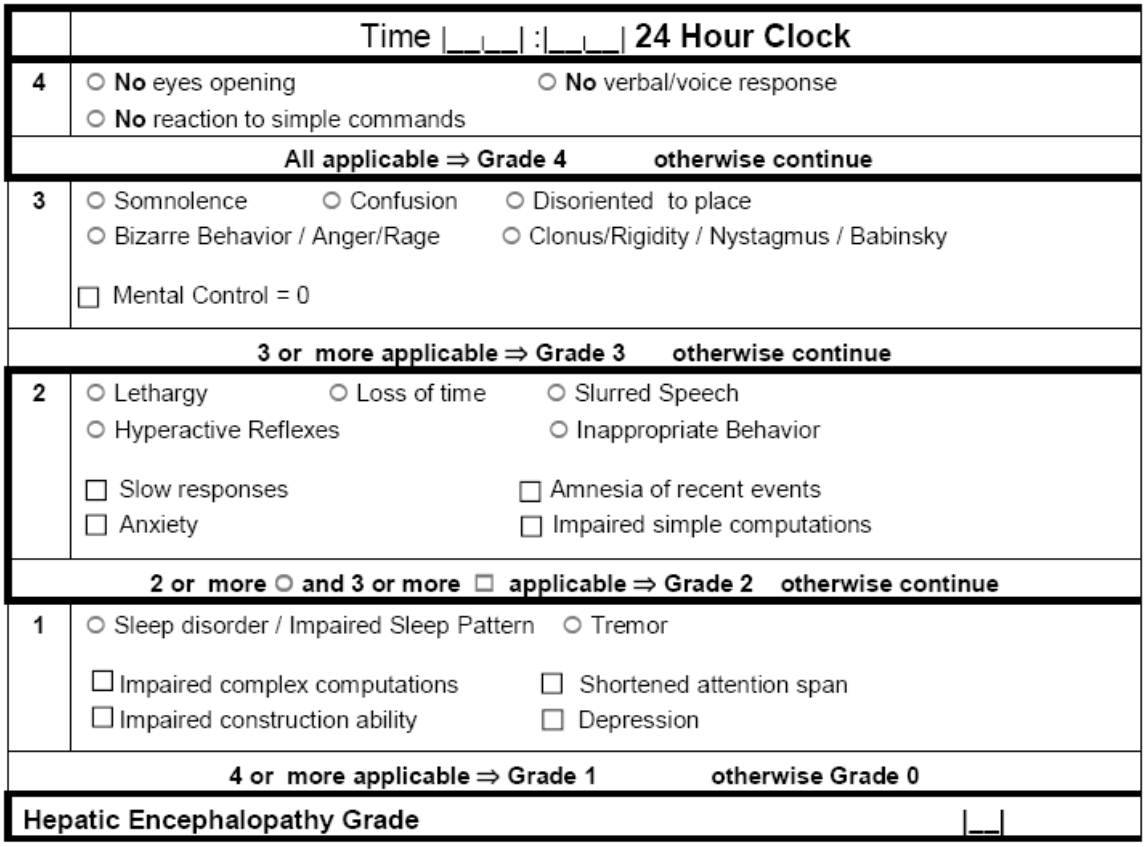
CDTL Reviewer's Comment: Note the inconsistencies between the versions in the Final Study Protocol and the Study Report, brought to our attention by Dr. Ranjit Mani, our DNP consultant. These inconsistencies are not expected to have a significant impact on trial results.

It is worth mentioning that several questionnaires and blended psychometric and clinical scales have been used to assess HE severity. These include HESA [the algorithm used in RFHE3001; for which large scale validation is on-going at this time]; the CHESS [Hepatic Encephalopathy Scale] and the PSE-index. None of these tools has been adequately validated.

The categories under which the Neuropsychological Assessments were performed are listed in **APPENDIX 9.**

Clinical Assessments as a function of HE Grade are listed in **APPENDIX 10.**

The overall HESA grading sheet was as follows:



NOTE: **Squares represent neuropsychological tests; circles represent clinical assessments; circles and/or squares were checked if impaired)**

The following was stated in the study report about the use of HESA measurement in this study:

> "Because HESA measurements are correlated with Conn score[24], the HESA worksheet and results of the HESA test were used as diagnostic tools to focus the clinical staff on HE clinical manifestations associated with the transitions from Conn scores of 0 through 4. Additionally, HESA worksheets were used in the evaluations of HE symptoms that were reported by caregivers and subjects."

Grades for the HESA were to be assigned based on assessments performed at study visits. However, these grades were not recorded in individual Case Report Forms, which also did not contain the Hepatic Encephalopathy Scoring Algorithm scoring sheets. It is worth clarifying that data from HESA assessments were considered to be part of source documents. These inconsistencies were discussed at the February 23, 2010 AC meeting. Based on the sponsor clarifications, it was concluded that there was no bias in the collection of the critical data.

Asterixis Grade

The presence of asterixis was to be evaluated by having the subject extend the upper arms and forearms, and dorsiflex the wrists while keeping the fingers open (spread) for ≥ 30 seconds. The severity of asterixis was to be measured on 5 grade levels, the criteria for each of which were listed on page 18 of the current review. The asterixis grade was to be assigned based on assessments performed at study visits.

[26] The following publication is cited in support of the sponsor's statement that HESA measurements are correlated with Conn Score: *Hassanein et al. introduction to the Hepatic Encephalopathy Scoring Algorithm. Dig Dis Sci 2008; 53: 529-538*

Critical Flicker Frequency Score

As noted in Dr. R Mani Consult review:

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

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

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

- A lower CFF score (in Hz) is considered to be indicative of greater impairment.

RFHE3001 also included measurements of **venous blood ammonia levels, chronic liver disease questionnaire (Health-Related Quality of Life Measure), Epworth sleepiness scale and The Short-Form 36 (SF-36).** However, results of efficacy based on these tools are not discussed further in the current CDTL review.

Summary of Efficacy Results of [pivotal] Study RFHE3001

This study was conducted at a total of 70 sites in the United States, Canada, and Russia, between December 2005 and August 2008. Changes in planned efficacy analysis, patient disposition, protocol deviations, study populations, demographic baseline characteristics are discussed in detail in the Clinical and Statistical reviews by Dr. Dimick-Santos and B Vali.

Demographic baseline characteristics were comparable between treatment groups. Selected Baseline Disease Characteristics, depicted in the Table below, were comparable. Also comparable were:

-- Time since the first diagnosis of HE

-- Past severity of HE (based on the Conn score during the episode of hepatic encephalopathy prior to the most recent one)

Duration of current remission-- Average critical flicker frequency

-- Average venous ammonia concentration

-- Daily dose of lactulose at baseline

-- Average daily stool count during the 2 days prior to screening.

Study RFHE3001

[Selected] Baseline Disease Characteristics

Characteristic	Placebo N = 159	Rifaximin N = 140
Conn Score At Baseline N/(%)		
0	107 (67.3)	93 (66.4)
1	52 (32.7)	47 (33.6)
Asterixis Grade At Baseline N/(%)		
0	108 (67.9)	96 (68.6)
1	45 (28.3)	41 (29.3)
2	5	2
3	1	1
Number Of HE Episodes During The Previous 6 Months N/(%)		
2	111 (69.8)	97 (69.3)
3	35 (22.0)	29 (20.7)
4	8	5
5	1	7
≥ 6	3	2
Missing	1	0
Model For End-Stage Liver Disease Score		
N	158	140
Mean (standard deviation)	12.7 (3.94)	13.1 (3. 64)
Median (minimum, maximum)	12.4 (6, 23)	13.1 (6, 24)
Model For End-Stage Liver Disease Score Category N/(%)		
≤ 10	48 (30.2)	34 (24.3)
11-18	96 (60.4)	94 (67.1)
19-24	14 (8.8)	12 (8.6)
≥ 25	0	0
Missing	1	0

NOTE: This Table corresponds to the Table on Baseline Disease Characteristics in Dr. Mani, Consult review, with substantial modifications.

- **lactulose use [nearly identical in both arms, at 91%]** (Table 15)

Table 15
Study RFHE3001
Lactulose Use

Characteristic	Placebo N = 159	Rifaximin N = 140
Prior Lactulose Use With Continuation During Study N/(%)		
Yes	145 **(91.2)**	128 **(91.4)**
No	14 (8.8)	12 (8.6)
Lactulose Use Newly Initiated During Study N/(%)		
Yes	2 (1.3)	1 (0.7)
No	157 **(98.7)**	139 **(99.3)**

Methods Used In Detecting and Documenting Episodes of Breakthrough Overt HE

Qualifications and Training of Study Personnel

These are described in detail in Dr. Mani's review.

Detection and Documentation of Episodes of Breakthrough HE

As detailed below this was conducted either "in person" or retrospectively

Study RFHE3001
Methods used to assess the detection and documentation of breakthrough episodes of HE

"In-Person" Assessment	Retrospective Assessment
This assessment was made in either one of the following circumstances: ▪ During a clinic visit by the patient ▪ During a stay in an emergency room or while a hospital inpatient. Detection and documentation (by the investigator or study personnel) of an episode of breakthrough hepatic encephalopathy during a clinic visit was based on: ▪ Assessment of the patient ▪ Information from the caregiver ▪ Patient diary ▪ Asterixis grade ▪ Hepatic Encephalopathy Scoring Algorithm grade. Detection and documentation of an episode of breakthrough hepatic encephalopathy during a stay in an emergency room or while a hospital inpatient was based on: ▪ Patient's medical record, including neurological signs and symptoms ▪ Discussion with a doctor who evaluated the patient ▪ Information from a caregiver or from another individual not involved in medical care	This assessment was made based on the following ▪ Caregiver description of signs and symptoms ▪ Patient diary ▪ Patient's medical record, including the description of neurological signs and symptoms ▪ Discussion with a clinician who may have evaluated the patient during the episode ▪ Information from an individual not involved in medical care.

The following were included among the materials provided to study sites to help in detecting and documenting episodes of HE:

- Study-specific source documents to record Conn scores, asterixis grade and HESA evaluation
- Pocket guidelines for the documentation of breakthrough episodes of HE
- HE breakthrough symptom checklist.

Reviewer's Comments

The CDTL agrees that none of these materials provides specific instructions as to how the Conn score was to be assigned. Dr. Mani seems to object to the obtaining of some data in a retrospective fashion, in some instances. It is worth noting that this type of study, where episodes of HE may occur when no one is supervising or monitoring the patient, does include a certain degree of retrospectivity, that cannot be avoided.

Dr. Vali provided the following summary of all patients who were counted in the datasets as a breakthrough HE episode for the primary efficacy analysis:

- Breakthrough HE primary reason for discontinuation: 28 rifaximin; 69 placebo
- One additional rifaximin subject (**764-0002**) completed the study although he/she experienced BHE during the study (a protocol deviation), therefore, 28 + 1 = 29.
- 2 additional subjects determined retrospectively to have BHE [30 rifaximin; 70 placebo]
    1. Rifaximin patient 478-0006 reason for discontinuation = other [cocaine abuse], with breakthrough experienced 36 days before discontinuation
    2. Placebo patient 761-0001 reason for discontinuation = subject request to withdraw, with breakthrough experienced 71 days before discontinuation
- 4 additional subjects experienced breakthrough HE after discontinuation [31 rifaximin; 73 placebo
    1. Rifaximin patient 893-0005 reason for discontinuation = occurrence of an AE, with breakthrough experienced 70 days after discontinuation but still within six months of first dose
    2. Placebo patient 106-0003 reason for discontinuation = subject request to withdraw, with breakthrough experienced 52 days after discontinuation but still within six months of first dose
    3. Placebo patient 891-0003 reason for discontinuation = subject request to withdraw, with breakthrough experienced 104 days after discontinuation but still within six months of first dose
    4. Placebo patient 893-0004 reason for discontinuation = subject request to withdraw, with breakthrough experienced 85 days after discontinuation but still within six months of first dose

In addition, Dr. Vali provided the following information and Table:

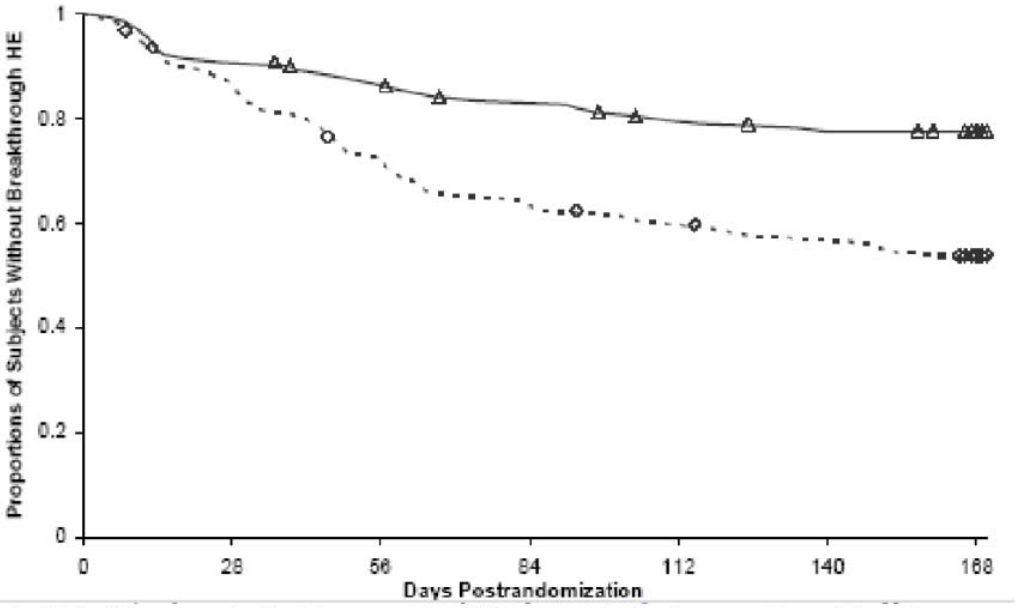
- In the rifaximin group, 8 patients were determined to have breakthrough episodes of HE based on direct observation by study site personnel, while 22 patients were diagnosed to have such episodes by indirect means; thus, only 27.7% of patients in the treatment group diagnosed with breakthrough episodes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

Study RFHE3001
Method of Diagnosing Breakthrough Hepatic Encephalopathy

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

Of patients with data available from CRF

Results of Primary Efficacy Analysis



Note: Dashed line represents rifaximin group and solid line represents placebo group. Open circles and open triangles represent censored subjects. Subjects who discontinued prior to a breakthrough overt HE episode and prior to completion of the 6-month treatment period (discontinuation reasons = death, withdrawal of consent [subject withdrawal], or withdrawal due to development of exclusion criteria) were censored at the time of discontinuation.

Figure 7. - Study RFHE3001. Kaplan-Meier estimates of the time [Days] to the first breakthrough episode of overt HE [ITT Population]

The Cox Proportional Hazards model, stratified by region, produced a hazard ratio(hazard of BHE in the rifaximin group + hazard of BHE in the placebo group) point estimate of **0.421** along with a corresponding **95% CI (0.276, 0.641).** The p-value corresponding to the test for treatment was **less than 0.0001.** Dr. Vali made the following observation: although there is a distinct separation between the two treatment groups at Month 6 [Figure 7 above], it appears that this separation was established between the beginning of Month 2 and the end of month 3. These two months are the major contributors to the overall six month results. During the last half of the study, the rate at which patients experience BHE events began to converge between the rifaximin and placebo groups. Dr. Vali notes that **this relative behavior of the survival curves representing both treatment groups is fairly consistent throughout all of the subsequent analyses pertaining to the key secondary endpoints as well.**

Additional Analyses on Primary Efficacy Parameter

These analyses included:

- A protocol-specified sensitivity analysis of the primary efficacy parameter was conducted after excluding those patients who had known precipitating factors for HE at the time of randomization; the population for this sensitivity analysis included 120 patients in the placebo group and 110 patients in the rifaximin group. A hazard ratio of 0.512 (95% confidence interval of 0.3137 to 0.839; p = 0.0068) for rifaximin versus placebo was seen in this population. A further analysis of the primary efficacy parameter using the excluded patients only (39 in the placebo group and 30 in the rifaximin group) yielded a hazard ratio of 0.248 (p = 0.0004) for rifaximin versus placebo. Both analyses otherwise used the same statistical method as that used for the primary efficacy analysis.

- A further sensitivity analysis of the primary efficacy parameter excluded 4 patients – all in the placebo group – who had used concomitant medication other than lactulose for the treatment of HE. This analysis, which was also otherwise similar to the primary efficacy analysis, yielded a hazard ratio of 0.419 (95% confidence interval: 0.275 to 0.640; p-value < 0.0001) for rifaximin versus placebo.

- An analysis of the primary efficacy parameter up to the time of last contact (for patients who did not experience an episode of HE during the 6-month period of the study – these patients were followed after the end of the study) revealed a hazard ratio of 0.461 (95% confidence interval of 0.307 to 0.693; p = 0.0001) for rifaximin versus placebo, using the same statistical model as for the primary efficacy analysis.

Table 16
Study RFHE3001
Rifaximin vs Placebo
Comparison of hazard ratio for the risk of experiencing breakthrough episodes of overt HE

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

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

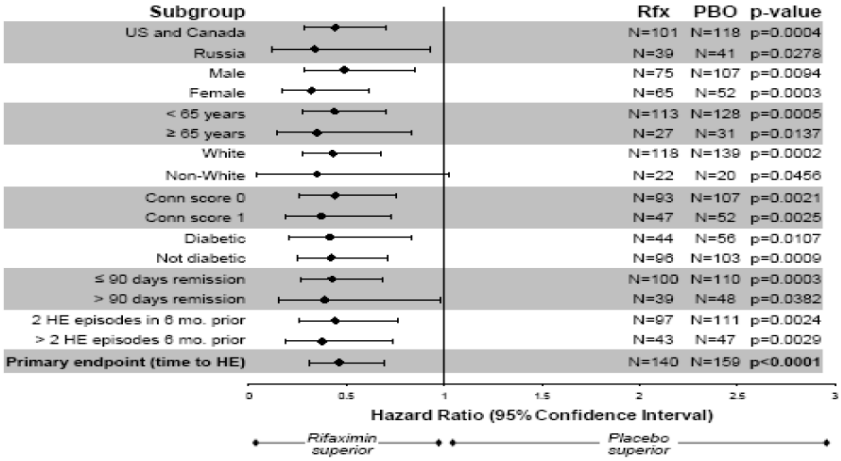
- Analyses examined the effects of the following covariates (potential prognostic factors) on the primary efficacy parameter, using the log rank test stratified for each covariate: sex; age; race; geographic region; Model for End-Stage Liver Disease (MELD) score at entry; Conn score at entry; diabetes mellitus at baseline; duration of remission at entry; and number of episodes of hepatic encephalopathy within 6 months prior to randomization. Covariates that were strong independent predictors of breakthrough episodes of hepatic encephalopathy included age, MELD score at entry, duration of remission at entry, and number of episodes of hepatic encephalopathy within 6 months prior to randomization. To control for the effects of these factors on the outcome of the primary efficacy analysis, a multivariate analysis was then performed on the primary efficacy parameter using the Cox proportional hazards model specified for the primary efficacy analysis and including age, MELD score at entry, duration of remission at entry, and number of episodes of hepatic encephalopathy within 6 months prior to randomization. The latter analysis revealed a hazard ratio of 0.403 (95% confidence interval of 0.264 to 0.617; p < 0.0001) for rifaximin versus placebo

Analyses of the time to the first breakthrough episode of overt hepatic encephalopathy through Day 170 in a number of **subgroups** in the intent-to-treat population, using the same statistical model as for the primary efficacy analysis yielded the results displayed in the sponsor's figure below.

Responder Analysis

- For all 'Time to Event' analyses, in general, a corresponding responder analysis can be determined by defining a responder (or a failure) as a patient who experiences the event of interest before, after or directly at a clinically relevant time point. During the course of the review cycle, the FDA requested that the applicant conduct a responder analysis by month. A responder was defined as a patient who had not experienced breakthrough HE by each month sequentially for six months. Two different presentations of this responder analysis are given in Dr. Vali's review. One presentation reconciles directly with the original primary efficacy analysis [Time to first Breakthrough HE episode (up to Month Six)]; the other presentation reconciles directly with the Missing Data Sensitivity Analysis II (Worst Case). As noted

previously, rifaximin's separation from placebo primarily occurs between the beginning of Month Two and the end of Month Three.



In the above figure: HE: Hepatic Encephalopathy RFX: Rifaximin PBO: Placebo

Principal Results for Sensitivity Analyses

Sensitivity Analysis	Placebo N =	550mg Rifaximin BID N =	Hazard Ratio Point Estimate	Hazard Ratio 95% CI	Treatment Effect p-value
Time to First Breakthrough HE (Exclusion of Six Patients)	159	140	0.419	(0.271, 0.647)	<0.0001
Time to First Breakthrough HE Episode up to Last Contact	159	140	0.461	(0.307, 0.693)	0.0001
Excluding Subjects who took Prohibited Medications	155	140	0.419	(0.275, 0.640)	<0.0001
Concomitant Comorbidity at Baseline					
Yes	39	30	0.248	(0.108, 0.571)	0.0004
No	120	110	0.512	(0.313, 0.839)	0.0068
Missing Data Strategy I	159	140	0.495	(0.342, 0.715)	0.0001

Missing Data Strategy II/Worst Case	159	140	0.533	(0.379, 0.749)	0.0002

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Analysis of Key Secondary Efficacy Parameters

Results of the sponsor's analysis of the first 3 key secondary parameters:

Key Secondary Efficacy Parameter	Hazard Ratio* (95% CI)	p-value
Time to first hepatic encephalopathy-related hospitalization	0.500 (0.287 to 0.873)	0.0129
Time to any increase from baseline in Conn score	0.463 (0.312 to 0.685)	< 0.0001
Time to any increase from baseline in asterixis grade	0.646 (0.414 to 1.008)	0.0523

In each instance, the results are based on a Cox proportional hazards model applied to the intent-to-treat population using data collected up to Day 170, and methods of censoring described in the protocol analysis plan. In the first 2 instances, a nominally statistically significant result favoring rifaximin was reported to have been seen. The changes in asterixis grade are borderline but seem to go in the same direction as those for the other two key secondary efficacy parameters

*Rifaximin relative to placebo CI: Confidence Interval

Subjects in the rifaximin group had a 50% reduction in the risk of hospitalization due to HE during the 6-month treatment period when compared with placebo.

The results of analysis of the remaining two secondary efficacy parameters and analysis of other secondary and tertiary efficacy parameters are addressed in Dr. Dimick-Santos Clinical review**.**

Changes from baseline in critical flicker frequency (CFF) at end of treatment [Table 17]

Increases in CFF results may represent improvement in neurological function in patients with HE. Subjects in the rifaximin group had significantly greater increases in CFF results from baseline to end of treatment when compared with placebo. Mean changes (±SD) in CFF results were 0.945 (±4.75) in the rifaximin group versus 0.355 (±4.70) in the placebo group (p = 0.0320 for between-group difference). *Dr Dimick-Santos stated that the CFF is experimental, though promising; it is not validated for evaluation of HE. The CDTL reviewer agrees with this statement.*

Changes from baseline in venous ammonia levels at end of treatment

In the current study, not surprisingly, venous ammonia levels were highly variable over the course of the study. However, as shown in Table 18, subjects in the rifaximin group had significantly greater reductions in venous ammonia levels when compared to placebo-treated subjects (p = 0.0391).

Table 17
Study RFHE3001
Changes from Baseline in CFF Test Results by Treatment Group (ITT Population)

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

Source: Summary Table 14.2.3.1, Section 14.2; corresponding Data Listing 16.2.6.8, Appendix 16.2.6.
Note: Baseline value was the last available value prior to first dose of study drug, and end of treatment value was the last available postbaseline value during the treatment period.
a P-value was calculated using analysis of covariance with effects for treatment and geographic analysis region, and baseline as a covariate.

Table 18
Study RFHE3001
Changes from Baseline in Venous Ammonia Level by Treatment Group (ITT Population)

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

Source: Summary Table 14.2.2.5, Section 14.2; corresponding Data Listing 16.2.6.6, Appendix 16.2.6.
Note: Baseline value was the last available value prior to first dose of study drug, and end of treatment value was the last available postbaseline value during the treatment period.
a P-value was calculated using analysis of covariance with effects for treatment and geographic analysis region, and baseline as a covariate.

Regarding the serum ammonia findings, Dr. Dimick-Santos offered the following comments. There is no direct correlation with and clinical chemistry levels or liver function tests and diagnosis of HE. Serum ammonia levels are commonly drawn in clinical practice; however, outside of very specific handling, serum ammonia does not correlate well with the clinical evaluation of the patient. In this study, there was not a defined protocol for handling of serum venous ammonia levels. Therefore, it is questionable if the results are reliable and clinically meaningful. The CDTL agrees with this statement.

Sponsor's Conclusions on Efficacy

- Rifaximin had a highly significant protective effect against breakthrough overt HE over a 6-month treatment period compared with placebo in patients in remission from overt HE. These results were also seen in covariate analyses, sensitivity analyses and in analyses of population subgroups.

- Statistically significant results in favor of the rifaximin group were also seen for key secondary efficacy endpoints including protection against hepatic encephalopathy-related hospitalization and increases in Conn score.

CDTL's Conclusions on Efficacy

Results from RFHE3001, a 6-month, 2-arm, randomized, double-blind, placebo-controlled, lactulose-based pivotal study showed: a) a reduction of breakthrough overt HE in the rifaximin group [$p < 0.0001$ for between-group difference in relative risk] in analyses of the primary efficacy endpoint; and b) a reduction in the risk of HE-related hospitalization in the rifaximin group [$p = 0.0129$] relative to placebo in analyses of a clinically important key secondary endpoint of efficacy. In addition, the CDTL concurs with Dr. Mani that, in view of the data collected and analyzed, a more adequate indication should read: **"reduction in frequency of episodes of hepatic encephalopathy in patients 18 years of age and older", rather than maintenance of remission** (b) (4) **of hepatic encephalopathy.**

8. Safety

Summary

As noted by Dr. Dimick-Santos, the population under study is very ill and high incidence of adverse events and variability of the course of hepatic encephalopathy confounds accurate assessment of safety. However over-all rifaximin appears to be relatively safe with most AEs related to the Gastrointestinal Tract, diarrhea, nausea and vomiting being common. Most of the other reported AEs are expected in this patient population. It is worth noting that the majority of complications were equally distributed between test rifaximin and the placebo control group.

Nonetheless, some deficiencies were noted. For example the sponsor failed to gather follow-up data from those patients who developed AEs; the subjects where dropped from the trial at the time they developed an AE that prompted withdrawal of the drug or if the subjects developed HE.

After completion of Dr. Dimick-Santos clinical review, some lingering concerns remain. One is the possibility of DILI in a subset of patients administered rifaximin; in her opinion, this issue has not be adequately addressed and will require further clinical trials, with liver biopsy being preformed on patients with stable disease or low MELD scores who suddenly decompensate, to rule out the DILI possibility. Dr. Dimick-Santos points out that the sponsor has failed to collect adequate data on Child's-Pugh Class C patients and patients with MELD scores above 25 as they were excluded from these studies. This group of patients would be at high risk for developing HE and thus use of rifaximin [off-label?]. Due to some absorbability of the drug, some systemic effects, yet to be properly characterized, need to be addressed. Adequate EKG data were not collected in the clinical trials; the issue of whether a thorough QT study is needed is open. Also open is the issue of effects of the drug in renally impaired liver disease patients: PK evaluations have not been performed in renally impaired patients. This seems to be an important omission, as renal insufficiency is common in the target population. Many of these liver insufficiency patients end-up with a serious hepato-renal syndrome.

Highlights of Safety Review

The Primary safety population originates from pivotal RCT RFHE3001 and its extension; RFHE3002-- At the time of the data cutoff for the original NDA submission, RFHE3002 was ongoing. Data from the ongoing RFHE3002 trial were available for all subjects up to 12 February 2009 (clinical cutoff date).

-- Safety data were summarized by group ('Continuing Rifaximin' and 'New Rifaximin') and overall ('All Rifaximin' subjects). The 'Continuing Rifaximin' group included safety data for subjects who received rifaximin in the double-blind trial RFHE3001 and the ongoing safety data for rifaximin-treated subjects in RFHE3001 who rolled over into trial RFHE3002. The 'New Rifaximin' group included those subjects who received placebo in RFHE3001 and rolled over into open-label RFHE3002 and new subjects who did not participate in RFHE3001, but who enrolled in RFHE3002 on the basis of a demonstrated history of overt HE. For the Long-Term Rifaximin Experience Tables in Dr. Dimick-Santos review, the treatment groups are presented as:

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

As noted in Dr. Dimick-Santos review, the sponsor's **Categorization of Adverse Events** was adequate. Details are found in Dr. Dimick-Santos clinical review.

Exposure

Detailed information is found in Table 28/19 of Dr. Dimick-Santos Clinical Review. Total number of subjects exposed to rifaximin at the indicated dose for 6 months or longer is 257.
-- Total number of subjects exposed to rifaximin at the indicated dose, for 12 months or longer is 114 subjects.
-- In addition, over 2000 subjects received rifaximin for the treatment of acute HE and other indications (generally for less than 14 days) in doses ranging from 550mg to 2400mg/day.
-- Combined data represent ca. 252 person years of exposure to rifaximin 550 mg tablets BID in the primary analysis studies.

In general, compliance was good in all studies. Specifically, in the Primary population (RFHE3001 & 3002), for All Rifaximin Subjects, compliance with dosing regimen was 80% in 94% of subjects.

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

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

The demographics [data displayed in Table 20 of the clinical review] were appropriate to the trial and comparable between groups.

Disease Baseline Characteristics

As already mentioned during the comments on efficacy results, the hepatic encephalopathy [and renal disease] baseline characteristics between groups were generally comparable between the treatment groups in the RCT Study population.
-- Mean (± SD) MELD score at baseline was 13.1 (3.64) in the rifaximin group and 12.7 (3.94) in the placebo group.
-- Most subjects in each group had MELD scores ranging from 11 to 18 (rifaximin: 67.1%; placebo: 60.4%).
-- The mean time since first diagnosis of advanced liver disease for the RCT Study population was > 50 months in both groups, but longer in the placebo group (60.5 months vs. 51.2.months).
-- The large majority of subjects in each group had serum creatinine levels at baseline < 1.5 times the upper limit of normal.

- Dr. Dimick-Santos noted and commented that the study population consisted of a low proportion of subjects with MELD scores above 18 (8-9%), making meaningful evaluation of subjects with severe

hepatic impairment very difficult. There were no subjects with MELD Scores above 25 enrolled in these trials.

Metabolic, Clearance, and Interaction Workup

The Sponsor has carried out few small PK trials on subjects with mild or moderate hepatic impairment. Results of these trials show that while <1% of rifaximin is absorbed in healthy individuals, in patients with Child's Class A and B cirrhosis the exposure values were 9.6 and 13.1 fold higher with significant inter-patient variability. No clinical trials have been done on patients with Child's class C or severe hepatic impairment.

Rifaximin's PK profile is addressed in Section 5. of the current review. This evaluation is based on a review by Dr. Insook Kim.

Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Rifaximin is a non-aminoglycoside semi-synthetic antibiotic (miscellaneous class), derived from rifamycin SV. The rifamycins are a group of structurally similar complex macrocyclic antibiotics originally isolated from *S. mediterranei.* One of these, rifampin, an antituberculosis drug that is structurally similar to rifaximin, has been shown to produce liver dysfunction; rechallenges have been observed; fatalities associated with jaundice have occurred in patients with liver disease and in patients taking rifampin with other hepatotoxic agents. Another example of a poorly absorbed drug that can cause significant systemic toxicity is neomycin, originally approved for the treatment of hepatic coma. After oral administration, the absorbed fraction of neomycin is rapidly distributed throughout the body and excreted by the kidney, in keeping with the degree of renal function. Yet orally administered neomycin is known to be associated with nephro- and neuro- toxicities. The incidence of aminoglycoside-induced nephrotoxicity is substantially greater in patients with advanced liver disease than in those who do not have liver disease.

Major Safety Results [Table 19]

-- During blinded treatment in the RCT Study population, the proportion of subjects with TEAEs was similar between subjects receiving rifaximin tablets 550 mg BID (80.0%) and placebo (79.9%).
-- No noteworthy differences were observed in the incidence of moderate (37.1%, 34.0%) or mild TEAEs (16.4%, 15.1%) in rifaximin and placebo subjects, respectively.
-- Severe TEAEs were recorded in a higher percentage of placebo-treated subjects (rifaximin: 26.4%; placebo: 30.8%), as were drug-related TEAEs (rifaximin: 19.3%; placebo: 21.4%) and SAEs (rifaximin: 36.4%; placebo: 39.6%).
-- The proportion of subjects with any TEAEs (87.2%), severe TEAEs (41.4%), or SAEs (49.1 %) was higher for All Rifaximin subjects in the Long-Term Rifaximin Experience population compared with the RCT Study groups. This difference was attributed to the increased time on the open-label study by the sponsor.
-- Overall event rates (per 100 person years) for subjects dyeing or experiencing TEAEs, SAEs, or TEAEs leading to trial discontinuation were lower in All Rifaximin subjects or comparable between All Rifaximin subjects and the RCT Study groups.
-- Additionally, a lower percentage of All Rifaximin subjects in the Long-Term Rifaximin Experience population experienced a drug related TEAE (13.7%) compared with the rifaximin (19.3%) and placebo (21.4%) groups in the RCT Study population.

Table 19
NDA 22-554
Summary of adverse events – excluding non-serious HE events

Category	RFHE3001 [pivotal RCT]			Long-Term Population		
	Placebo N = 159 N/(%)	Rifaximin N = 140 N/(%)	Total N = 299 N/(%)	New Rifaximin N = 196	Continuing rifaximin N = 140	Total N = 336 N/(%)
TEAEs	127 (79.9%)	112 (80.0%)	239 (79.9%)	172 (87.8%)	121 (86.4%)	293 (87.2%)

Serious TEAEs	63 (39.6%)	51 (36.4%)	114 (38.1%)	94 (48.0%)	71 (50.7%)	165 (49.1%)
TEAE drug related	34 (21.4%)	27 (19.3%)	61 (20.4%)	15 (7.7%)	31 (22.1%)	46 (13.7%)
TEAE by severity						
Severe	49 (30.8%)	37 (26.4%)	86 (28.8%)	80 (40.8%)	59 (42.1%)	139 (41.4%)
Moderate	54 (34.0%)	52 (37.1%)	106 (35.5%)	59 (30.1%)	44 (31.4%)	44 (31.4%)
Mild	106 (35.5%)	23 (16.4%)	47 (15.7%)	33 (16.8%)	18 (12.9%)	51 (15.2%)
TEAE w/ D/C drug	45 (28.3%)	30 (21.4%)	75 (25.1%)	30 (15.3%)	42 (30.0%)	72 (21.4%)
Deaths	11 (6.9%)	10 (7.1%)	21 (7.0%)	19 (9.7%)	17 (12.1%)	36 (10.7%)

This Table corresponds to Table 33 in Dr. Dimick-Santos Clinical Review, with modifications.[From sponsor tables 5.1.1b and 5.1.2]
If a subject experienced more than 1 AE, the subject is counted only once for the worst severity.
For subjects who experienced an AE leading to discontinuation, the investigator selected the reason for termination as either due to a) AE; b) breakthrough HE; or c) to liver transplant. The summary of Deaths While on Study Drug' includes subject deaths recorded during treatment, including through 5 days after the last dose. The summary of All Deaths' includes subject deaths during treatment or within 30 days after the last dose.

Deaths

In the primary safety pool mortality occurred at 7% in both the treatment and placebo groups. In summary,
double-blind RFHE3001-- The Clinical review also includes summaries of 4 additional subjects who died after completion of the protocol-defined interval for collection of SAEs (up to 30 days after last dose of study drug). According to Dr. Dimick-Santos, the deaths for these 4 subjects (rifaximin: 2; placebo: 2) were not collected on the SAE CRF page and are not summarized in the ISS for the RCT Study population. Instead, information regarding deaths for these 4 subjects were collected on the non-breakthrough HE early termination CRF page for subjects who withdrew early for reasons other than breakthrough HE. Dr. Dimick-Santos noted that none of the SAEs resulting in an outcome of death that occurred during the RCT Study or within 30 days after the last dose were considered by the investigators to be related to test medication.

Long-Term Rifaximin Experience population
A total of 36 subject deaths (10.7%) were recorded for All rifaximin subjects during the maintenance of remission of overt HE studies. The total number of deaths includes the 10 rifaximin –treated subjects who died during the RCT study. In addition, 23 subjects died during the -3002 study or within 30 days after the of the last dose; 3 additional subjects died in -3002 after completion of the planned interval for collection of SAEs (up to 30 days after the last dose of the study drug). According to the review by Dr. Dimick-Santos, the majority of deaths in both the placebo group and the rifaximin group appear to have been related to worsening of hepatic function and underlying disease progression (including variceal bleeding, hepatocellular carcinoma) or complications (sepsis, pneumonia, tuberculosis). Two patients treated with rifaximin, but none treated with placebo, developed *C. difficile* colitis.

- Death analysis by baseline hepatic function was requested of the sponsor using Child-Pugh Classification. The sponsor reported:

-- There were no notable differences reported between rifaximin and placebo groups in the proportion of subjects who died among Child-Pugh A, B, and C subjects.
-- According to the investigator, the SAEs resulting in death among subjects who were Child-Pugh C were congestive cardiac failure (subject 351-0001, rifaximin); esophageal varices hemorrhage (subject 456-0004,

placebo); multi-organ failure, portal vein thrombosis, and liver transplant rejection (subject 762-0001, rifaximin); and primary biliary cirrhosis (subject 902-0002, rifaximin). No event resulting in death was considered related to test medication by the investigator.
Additional analysis of deaths was requested by baseline Hepatic function.

Dr. Dimick-Santos, the Clinical reviewer, offered these additional Comments. While the sponsor reports no difference in death rates it is interesting to note in trial RFHE3001: Child C patients the 17.6% (#3) death rate in the rifaximin group vs. the 7.1% (#1) in the placebo group. Additionally in RFHE3002 there are 3 deaths (42.9%) in the placebo cross-over group. It is unknown if this could be attributed to other confounding factors or potentially higher systemic exposure to rifaximin. While the numbers are too small to permit any definite conclusion, the sponsor has failed to prove there is not an increase in mortality in this high risk group.

The Division requested additional analysis of time to death to last contact.

The analysis for overall survival up to time of last contact is presented in Dr. Dimick-Santos MOR.

- There was no significant difference between treatment groups in the risk of death in Study RFHE3001 [Note that in the original submission, 21 deaths were reported (11 placebo; 10 rifaximin)]
- The analysis shown in sponsor's Table 1.2 and Figure 1.2 includes 25 deaths (13 placebo; 12 rifaximin) because during post study acquisition of information for complete capture, i.e., complete follow-up for protocol specified primary outcome, 4 additional subjects who died were captured in the new analysis.

Lingering concerns about deaths

Table 20
NDA 22-554
List of deaths where the information is incomplete for adequate attribution

Pt. ID	Medical Officer's Rating of death	Succinct Narrative
706-0002	**Suspicious for DILI**	Death is labeled as due to hepatic failure and not changed; however the investigator reported this as not related to test medication. In the MO's opinion the death is suspicious for DILI because the patient had a MELD Score of 12 at screening with a Conn Score of 0 and asterixis grade 0. She died at home after developing rapid worsening of her condition, after 35 days (estimated) of exposure to test medication, and electing not to seek further treatment.
351-0012	**Suspicious for drug-related AE**	Diagnosis of worsening cirrhosis not changed. Baseline MELD is 11. Sudden onset gastroenteritis after < 2 months exposure to test medication (lactulose also stopped by patient?) and death after 67 days of exposure with positive cultures from lung biopsy, but autopsy reporting cirrhosis, pulmonary hypertension, and dilated cardiomegaly.
679-0005	**Suspicious; Cause of death unknown**	This is diagnosed as a cardiac death by the investigator but in reality the cause of death is known from the information given. The subject has a baseline MELD of just 7 and no listed complications of cirrhosis, yet died suddenly at home just after 29 days of exposure to test medication.
762-0001	**Questionable**	Death related to transplant complication ; it is not stated why the patient was placed on the transplant list; however she was on test medication for over 5 months (questions have been sent to the sponsor)
760-0001	**Not drug related**	Death reported as DIC; however, death was a result of transplant complications and cardiac disease; rated as unrelated to test medication by investigator.
893-0005	**Questionable**	Subject was stable with baseline MELD score of 17; then after 21 days on drug exposure developed worsening cirrhosis with edema and hydrothorax; no information is given for the subsequent 114 days. However, the patient expired from cirrhosis.

Possible hepatotoxicity induced by this drug was one of the subject matters discussed at the February 23, 2010 AC meeting.

Nonfatal Serious Adverse Events

The MOR notes that the rates of AEs were high in this population of very ill patients. In the primary analysis population there were 546 sever adverse event (SAE) incidents occurring in 63 (39.6%) of placebo subjects and in 165 (49.1%) of All Rifaximin Subjects. In Table 21, these are listed and analyzed by System Organ Class (SOC). The clinical review also presents these data by Preferred Term (PT) but, since there were little differences between rifaximin and placebo when comparing the Preferred Terms, this information is not presented in the CDTL review.

Table 21
NDA 22-554
Severe Adverse Events
RCT Study and Long-Term Rifaximin Experience Populations

MedDRA System Organ Class	RCT Study Population		Long Term Rifaximin Experience Population		
	Placebo (PEY = 46.0) (N = 159) n/(%)	**Rifaximin** (PEY = 50.0) (N = 140) n/(%)	**New Rifaximin** (N = 196) n/(%)	**Continuing Rifaximin** (PEY =109.7) (N = 140)	**All Rifaximin Subjects** (PEY = 251.9) (N = 336)
Any SAE	63 (39.6)	51 (36.4)	94 (48.0)	71 (50.7)	165 (49.1)
Blood and Lymphatic System Disorders	0	5 (3.6)	8 (4.1)	9 (6.4)	17 (5.1)
	5 (3.1)	5 (3.6)	5 (2.6)	5 (3.6)	10 (3.0)
Gastrointestinal Disorders	11 (6.9)	16 (11.4)	35 (17.9)	27 (19.3)	62 (18.5)
General Disorders and	4 (2.5)	6 (4.3)	12 (6.1)	7 (5.0)	19 (5.7)
	10 (6.3)	7 (5.0)	27 (13.8)	17 (12.1)	44 (13.1)
	0	1 (0.7)	2 (1.0)	2 (1.4)	4 (1.2)
	9 (5.7)	11 (7.9)	28 (14.3)	22 (15.7)	50 (14.9)
Metabolism and Connective Tissue	4 (2.5)	7 (5.0)	17 (8.7)	10 (7.1)	27 (8.0)
Neoplasms Benign,	3	3	4	6	10

Malignant and	(1.9)	(2.1)	(2.0)	(4.3)	(3.0)
	36 (22.6)	18 (12.9)	51 (26.0)	26 (18.6)	77 (22.9)
	6 (3.8)	2 (1.4)	14 (7.1)	4 (2.9)	18 (5.4)
Respiratory, Thoracic, and Mediastinal Disorders	4 (2.5)	4 (2.9)	11 (5.6)	5 (3.6)	16 (4.8)
	2 (1.3)	1 (0.7)	3 (1.5)	1 (0.7)	4 (1.2)

This Table corresponds to Table 37 in Dr. Dimick-Santos review, with some modifications.
NOTE: In this and other Tables, **Person-years of experience** is computed as the sum of exposure days for all subjects included in the analysis divided by 365.25.

Additional findings of interest:

- There were no remarkable between-group differences (rifaximin versus placebo) in the types and frequencies of SAEs in each Child-Pugh class.
- Similar results were observed in the analysis of SAEs by MELD score in that there was a trend toward increasing incidences of SAEs at higher MELD scores and there were no notable between-group differences in SAEs across MELD score categories.
- The most frequent SAEs (i.e., experienced by ≥ 5 subjects total) were hepatic cirrhosis (in 3 rifaximin, 6 placebo subjects), ascites (in 4 rifaximin, 3 placebo subjects), esophageal varices hemorrhage (in 4 rifaximin, 2 placebo subjects), acute renal failure (in 2 rifaximin, 4 placebo subjects), and pneumonia (in 4 rifaximin, 1 placebo subjects), excluding HE episodes that were SAEs due to hospitalization.

- Of the 43 subjects who experienced the most frequent SAEs, only 6 were Child-Pugh A; 37 were Child-Pugh B or C.

- The frequent SAEs occurred at comparable incidences between rifaximin and placebo groups, although rifaximin subjects had higher incidences of esophageal varices (3.1% rifaximin, versus 1.4% placebo); and pneumonia (3.1% rifaximin, versus 0.7% placebo) in RFHE3001.

- Dr. Dimick-Santos noted that pneumonia is common in cirrhotic patients in both the hospital and community settings. The incidence of community acquired pneumonia has been shown to range between 7% and 23% in cirrhotic patients.

- In study RFHE3001, pneumonia SAEs were experienced by 4 rifaximin treated subjects (3.1%) and 1 placebo-treated subject (1.4%). In review of SAE reports of pneumonia, the subjects had several predisposing risk factors for pneumonia; these factors included: chronic liver disease, alcoholism, hepatitis C, hepatic hydrothorax, chronic obstructive pulmonary disease, portal hypertension, diabetes mellitus, and smoking.

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

Dropouts and Discontinuations

There were only minor differences between rifaximin and placebo regardless of the groups being compared.

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

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

TEAEs resulting in study discontinuation in ≥ 1% of long-term rifaximin experiences [ISS] are displayed in Table 22.

Table 22
NDA 22-554
TEAEs Resulting in Study Discontinuation in ≥ 1% of Long-Term Rifaximin Experience ISS)
(From Sponsor submission, table 43, page 134)

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

Source: ISS Tables 5.5.1.1b and 5.5.2.1, Appendix C
Abbreviations: PEY = person-years of exposure; RCT = randomized controlled trials; BID = twice daily; and TEAE = treatment emergent adverse event.
a Person-years of exposure was computed as the sum of exposure days for all subjects included in the analysis divided by 365.25.
Note: TEAEs are summarized alphabetically by SOC and by descending order of frequency within each SOC using 'All Rifaximin Subjects.'

The disposition by Child-Pugh classification from study RFHE3001 is given in Table 23

Table 23
NDA 22-554
Disposition by Child-Pugh Classification (baseline) – RFHE3001

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

Source: Table 3.1; Abbreviations: BID = twice daily.
Notes: Twelve subjects in the rifaximin group and 17 in the placebo group had missing Child-Pugh classification. Child-Pugh subscores, total score (5-15), and classifications (A,B, or C) were obtained post study. Discontinuations due to breakthrough overt HE episode are not included in this table since subjects withdrew from the study at the time of first breakthrough overt HE episode (primary efficacy outcome), in accordance with the study protocol.

The disposition by Meld Score from study RFHE3001 is depicted in Table 24.

Table 24
NDA 22-554
Disposition by MELD Score (baseline) – RFHE3001

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

Source: Table 3.2; Abbreviations: MELD = Model End Stage Liver Disease; BID = twice daily.
Note: Discontinuations due to breakthrough overt HE episode are not included in this table since subjects withdrew from the study at the time of first breakthrough overt HE episode (primary efficacy outcome), in accordance with the study protocol.

The profile of AEs resulting in early study discontinuation across Child-Pugh class during long term rifaximin therapy was analyzed in subjects who entered RFHE3002 after participation in RFHE3001. Results were summarized in Table 39 of the MOR.

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

- **Dr. Dimick-Santos concluded that the increased frequency of hepatic failure during long-term treatment was likely due to the progression of liver disease during the increasing time on study in RFHE3002.**

- When adjusting for longer exposure in study RFHE3002, the event rates (i.e., events/PEYs) for AEs resulting in early study discontinuation were higher in rifaximin subjects in RFHE3001 than in placebo crossover subjects and rifaximin rollover subjects across Child-Pugh classes. The exception was

hepatic failure, which occurred at a lower event rate in RFHE3001 than in the RFHE3002 rifaximin groups.

Significant Adverse Events

Hepatic Failure - DILI

(From Page 122 in ISS) As noted earlier in Section 2.2.1.1, the incidence of serious TEAEs of hepatic failure was higher among all rifaximin subjects (5.1%) compared with the RCT rifaximin (0.7%) and RCT placebo (0.6%) treatment groups.

- Of the 17 subjects in the Long-Term Rifaximin Experience population with hepatic failure, 8 had liver transplants and 7 died due to the event.
- Investigators frequently attributed the preferred terms hepatic failure, hepatic cirrhosis, and alcohol cirrhosis for deaths associated with the progression of underlying liver disease. In addition to the 7 subjects who experienced an SAE of hepatic failure with an outcome of death in the primary studies.
- When the data from RFHE3001 were analyzed by change in MELD score during the study duration there was little change in the MELD score.

Submission Specific Primary Safety Concerns

Dr. Dimick-Santos pointed out that treatment-emergent AEs of special interest were determined on the basis of known, potential side effects of antibiotics as a drug class. These special interest AEs included respiratory infections, gastrointestinal-related infections, and symptoms of gastrointestinal or respiratory infections. The TEAEs of special interest were not summarized for secondary integrated and supportive safety analyses

In her review, Dr. Dimick-Santos calls attention to the following:

- As noted earlier, the incidence of serious TEAEs of hepatic failure was higher among all rifaximin subjects (5.1%) compared with the RCT rifaximin (0.7%) and RCT placebo (0.6%) treatment groups.
- Of the 17 subjects in the Long-Term Rifaximin Experience population with hepatic failure, 8 had liver transplants and 7 died due to the event.
- Investigators frequently attributed the preferred terms hepatic failure, hepatic cirrhosis, and alcohol cirrhosis for deaths associated with the progression of underlying liver disease.
- In addition to the 7 subjects who experienced an SAE of hepatic failure with an outcome of death in the primary studies, 3 additional subjects treated with rifaximin experienced events of hepatic cirrhosis or alcoholic cirrhosis with an outcome of death. Of these 10 subjects who died due to an event of hepatic failure, hepatic cirrhosis, or cirrhosis alcoholic, 9 had 1 or more conditions associated with hepatic decompensation at baseline, including esophageal varices, ascites, portal hypertension, jaundice, edema, and GI hemorrhage.
- Hepatic decompensation is associated with a far 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.
- None of the events of hepatic failure, hepatic cirrhosis, or alcoholic cirrhosis in rifaximin-treated subjects with an outcome of death were considered by the investigator to be related to study medication. Four (4) subjects (2.5%) in the placebo group in RFHE3001 had an SAE of hepatic cirrhosis with an outcome of death and each of these subjects had conditions associated with hepatic decompensation (in addition to HE) at baseline.
- Deaths for subjects experiencing SAEs of hepatic failure, hepatic cirrhosis, and cirrhosis alcoholic are described in more detail in Table 35 of the MOR.

Common Adverse Events

The following excerpts were taken Dr. Dimick-Santos MOR.

- Treatment-emergent AEs were most frequently reported in the GI disorders System Organ Class (SOC) (rifaximin: 51.4%; placebo: 42.1%) in the RCT Study population. Other SOCs [see list below] where TEAEs were reported in ≥ 25% of all RCT subjects (rifaximin vs. placebo):
    Nervous system disorders (37.9% vs. 40.3%)
    General disorders and administration site conditions (40% versus 32.7%)
    Infections and infestations (32.9% versus 30.8%)
    Respiratory, thoracic and Mediastinal disorders (25.7% versus 24.5%).

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

Subjects in the rifaximin group in the RCT study also had a higher incidence of TEAEs of anemia (7.9% vs. 3.8%) compared with the placebo group. Anemia is an event frequently associated with liver disease. ***The sponsor adequately examines and explains this difference; the anemia does not appear to be drug related.***

- The following were treatment-emergent AEs in the RCT Study population that occurred in 3% of rifaximin-treated subjects and at least twice as often (by proportion) in the rifaximin group as in placebo group:
    Anemia (7.9% vs. 3.8% placebo)
    Arthralgia (6.4% vs. 2.5%)
    Pyrexia (6.4% vs. 3.1%)
    Dehydration (3.6% vs. 1.3%)
    Hyperkalemia (3.6% vs. 1.3%).

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

- The overall proportion of all rifaximin subjects in the primary analysis studies who experienced TEAEs (87.2%) was slightly higher that the placebo (79.9%) and rifaximin (80.0%) groups in the RCT Study population. However, event rates for subjects experiencing TEAEs were comparable between the populations, indicating that the higher percentage in the Long-Term population were attributable to the increased time on the open-label study and increased duration under observation.

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

Analysis of SAEs by Child-Pugh Classification

As mentioned above, hepatic cirrhosis, ascites, esophageal varices hemorrhage, acute renal failure, and pneumonia were the most frequently occurring SAEs in RFHE3001. These SAEs are compared by Child- Pugh class in rifaximin-treated subjects in RFHE3001 and RFHE3002 in Table 11 of the MOR.

- Hepatic failure SAEs were experienced at a higher frequency during L-T rifaximin therapy (5 subjects in the placebo cross group and 4 in the rifaximin rollover group) compared with rifaximin therapy in RFHE3001 (0 subjects in the RFHE3001 rifaximin group). The increased frequency of hepatic failure during long-term treatment was likely due to the progression of liver disease during the increasing time on study in RFHE3002.

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

- The sponsor reported that while the overall incidence of TEAEs during the study was incrementally higher among subjects with more severely impaired hepatic function at baseline, **there were no remarkable between group differences (rifaximin versus placebo) in the types and frequencies of TEAEs in each Child-Pugh class.**

- Results of the analysis of TEAEs by MELD score were consistent with results of analysis by Child-Pugh class. The overall incidence of TEAEs during the study was incrementally higher among subjects with more severe hepatic disease, as measured by increased MELD score at baseline, and there were no remarkable between-group differences (rifaximin versus placebo) in the types and frequencies of TEAEs in each MELD score category.

Laboratory Findings

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

- In the RCT Study population, shifts from baseline were observed for subjects receiving rifaximin that were not also observed in the placebo group. These shifts were not very consistent since some shifts occurred with a higher incidence in the placebo than in the rifaximin group.

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

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

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

Serum Chemistry

- Mean AST (U/L) increased from 64.0 at Day 0 to 76.0 at EOT in the rifaximin group and decreased from 68.2 to 64.3 in the placebo group.

- Mean gamma GT (U/L) increased by 21.2 in the rifaximin group from baseline to EOT and decreased by -5.9 in the placebo group.

- Direct and total bilirubin (umol/L) increased by 6.7 and 10.2, respectively, from baseline to EOT in the placebo group and by only 0.3 and 2.4 in the rifaximin group.

- A higher incidence of shifts from normal to high at EOT were observed in the rifaximin group for creatinine (8.5% vs. 3.4%), lactate dehydrogenase (LDH) levels (17.2% vs. 6.9%), blood alkaline phosphatase (11.5% versus 5.5%), and gamma GT (7.7% vs. 2.1%).

- Among subjects in the placebo group, a higher incidence of shifts was observed from normal to high at EOT for urea (BUN) (8.9% vs. 4.6%) and from normal to low for calculated creatinine clearance (9.7% vs. 4.6%).

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

Urinalysis/Vital Signs/EKGs

- Changes from baseline to EOT in the RCT Study population in urinalysis parameters were minimal and there were no notable differences between rifaximin-treated subjects and placebo-treated subjects. Likewise, there were no clinically meaningful changes in urinalysis parameters from baseline to last value among All Rifaximin subjects in the Long-Term Rifaximin Experience population.

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

- The sponsor did not submit EKG data in the ISS. The sponsor did not perform EKGs on subjects in either trial.

A number of safety related items are addressed in Dr. Dimick-Santos MOR. These items include: Special Safety Studies/Clinical Trials [none reported], Immunogenicity [some anaphylactic reactions have been reported], Other Safety Explorations such as Dose Dependency for Adverse Events [Not examined by the sponsor], Time Dependency for Adverse Events [Overall, the types of AEs reported after the last dose of study drug were qualitatively similar to the AEs reported during the studies and were consistent with the population under study], Drug-Demographic Interactions, such as Common AE's by Sex [There were few notable differences in the safety profile of rifaximin between male and female subjects in the primary analysis studies. In the RCT Study population, the pattern and frequencies of TEAEs were similar between the rifaximin and placebo groups for both male and female subjects], Common AEs by Age Group [Overall, there were few notable differences observed in the safety profile of rifaximin when comparing subjects' $\geq$ 65 years and $<$ 65 years of age], Common AEs by Race [Few non-white subjects enrolled in the primary analysis studies (N=51) and there were no remarkable differences observed in the safety profile of rifaximin relative to placebo when comparing white and non-white subjects. In the Long-Term Rifaximin Experience population, the incidence of TEAEs was comparable for non-white subjects (91.9%) and white subjects (86.6%), and a similar pattern of TEAEs was observed in both groups], AE's by Geographic Location [Overall, subjects who participated at study sites in North America had a markedly higher incidence of TEAEs than subjects who participated in Russia in both the RCT Study (90.9% vs. 50.0%) and Long-Term Rifaximin Experience (94.5% vs. 56.3%) populations. While the overall incidence of TEAEs was higher in North America, the pattern and frequency of TEAEs was similar between rifaximin- and placebo-treated subjects regardless of analysis region in the RCT Study population]. The MOR comments that it appears that there was lower reporting of AEs overall in Russia. However, site inspection found no irregularities in documentation.

Drug-Disease Interactions

Common AEs by Hepatic Function

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

- For both the rifaximin and placebo treatment groups the incidence of TEAEs was highest among subjects with a baseline MELD score ≥ 19 (rifaximin: 91.7%; placebo: 100.0%); lower among subjects with a baseline MELD score between 11 and 18 (rifaximin: 85.1%; placebo: 87.5%) and lowest in those with a baseline MELD score ≤ 10 (rifaximin: 61.8%; placebo: 58.3%).

- While the overall incidence of TEAEs during the study was incrementally higher among subjects with more severely impaired hepatic function at baseline, there were no remarkable between-group differences (rifaximin vs. placebo) in the types and frequencies of TEAEs in each MELD score category.

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

Common AEs by Baseline Renal Function

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

Drug-Drug Interactions

This subject matter is addressed in detail by Dr. Insook Kim, in her Clinical Pharmacology review [Please see Section **5.** of the current review].

Pediatrics and Assessment of Effects on Growth

Not applicable

Overdose, Drug Abuse Potential, Withdrawal and Rebound

- No case of overdose has been reported during the clinical trials with rifaximin 550 mg tablets.

- No formal withdrawal or rebound study was performed. Data on TEAEs occurring after the last dose of study drug were analyzed for this discussion. All AEs following discontinuation of test medication underwent review at Salix and findings were not suggestive of an exaggerated or rebound pharmacological effect resulting in untoward clinical sequelae as a result of discontinuation of test medication.

- Greater than 5 days following the last dose was selected to allow for a sufficient washout period of rifaximin tablet treatment. Given that the RFHE3002 trial was ongoing, only subjects who had received rifaximin and subsequently concluded rifaximin treatment in the primary studies were included in a supplemental Table. There were a total of 16 (12.4%) post treatment AEs. There were 3 cases of worsening cirrhosis.

- With respect to episodes of HE, rifaximin has been evaluated in cyclic treatment regimens in 3 long-term studies from the published literature. Rifaximin was given in cycles of 2 weeks on drug followed by 2 weeks off drug for 3 or 6 months in comparison to neomycin, lactulose, and lactitol, respectively. According to the sponsor's update, in each of these literature studies, rifaximin was found to be as effective or superior to control treatments in reducing the neurological signs and symptoms of HE; and rifaximin treatment appeared to be efficacious throughout the long-term durations of the studies. There was no evidence of a rebound HE affect in any of these trials during time off of study drug.

Post market Experience

Distribution Data

In the US, rifaximin 200 mg tablets were approved for marketing in May 2004 for the treatment of travelers' diarrhea. Rifaximin has been marketed in Italy since 1987. Marketing authorizations have been granted to Alfa

Wasserman and others for rifaximin tablets (200 mg) and a cherry granulate for oral suspension in Italy and a number of other countries worldwide. Currently, one or both pharmaceutical forms of rifaximin are approved outside the US in 24 countries.

Globally, patients have received approximately (b) (4) days of rifaximin tablet treatment and approximately (b) (4) months of treatment during the post-marketing periods. Total worldwide distribution of rifaximin as oral suspension during the approximated 10 year postmarketing window was (b) (4) units (100mg/5mL). Globally, patients have received approximately (b) (4) days of rifaximin treatment as oral suspension and approximately (b) (4) months of treatment during the post marketing periods.

Drug Use Data – From Division of Epidemiology

Total dispensed prescriptions for Xifaxan® (rifaximin) increased (b) (4).
The top prescribing specialty for rifaximin is Gastroenterology. The most common diagnoses associated with the use of rifaximin were "GI System Symptoms NEC" (ICD- 9 787.9), "Infectious diarrhea NOS" (ICD-9 009.2), and "Irritable colon" (ICD-9 564.1). The diagnosis code for "Hepatic Coma" (ICD-9 572.2) was mentioned approximately 1% of the time by physician survey for rifaximin.

Postmarketing Clinical Data From Sponsor

A total of 38 subjects have reported 113 post-marketing SAEs. Most SAEs were reported spontaneously. Almost half of the serious events were Gastrointestinal Disorders, Skin and Subcutaneous Tissue Disorders, or General Disorders and Administrative Site Conditions. The most frequently reported SAEs (≥ 4 events) in descending order of frequency were abdominal pain, diarrhea, vomiting, and rash. There were no SAE terms reported in ≥ 5 subjects.
Other post-marketing SAEs reported at a frequency of ≥ 2 and < 4 events, in descending order of frequency, were: condition aggravated, musculoskeletal pain, headache, urticaria, vertigo, asthenia, drug ineffective, edema peripheral, clostridium difficile colitis, clostridium difficile toxin test positive, international normalized ratio increased, speech disorder, dyspnea, and pruritus.

Office of Surveillance and Epidemiology (OSE) Consult

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

Safety Evaluation - Division of Pharmacovigilance [Table 25]

Table 25
NDA 22-554
All Adverse Events in AERS N ≥ 5
* Labeled events for rifaximin

Diarrhea*	(n=30)		Pyrexia*	(n=7)
Abdominal pain*	(n=15)		**Asthenia**	(n=6)
Condition aggravated	(n=15)		Dyspnea*	(n=6)
Drug ineffective	(n=14)		Malaise*	(n=6)
Headache*	(n=12)		Rash*	(n=6)
Nausea*	(n=12)		Abdominal pain upper*	(n=5)
Flatulence*	(n=9)		**Anemia** (these cases are described below)	(n=5)
Abdominal distension*	(n=8)		Clostridium difficile colitis*	(n=5)

Myalgia*	(n=8)		Insomnia*	(n=5)
Vomiting*	(n=8)		**Edema peripheral**	(n=5)
Dehydration*	(n=7)			

SOURCE: OSE Consult Review. AERS was searched from May 2004 (approval of rifaximin to treat traveler's diarrhea) to August 31, 2009, using the drug name rifaximin (XIFAXAN®).

All adverse events (all reported indications for use; n=173 [note raw data, duplicates could exist]): A PT printout was generated to identify adverse events reported for rifaximin. The top 21 reported MedDRA Preferred Terms (n ≥ 5) are listed in Table 25.

Adverse events associated with prevention/treatment of HE (n=21 [deduplicated cases]): Since rifaximin is not approved domestically for this indication, at least 6 of these reports involved study patients and one case involved a foreign patient. The mean duration for patients using rifaximin to prevent or treat HE was 32 days; the range was 2 to 180 days (duration of use reported for 17 patients; 16 out of 17 patients used rifaximin > 3 days). All 21 cases are described below.

Of the 21 cases, 2 cases provided little information to determine causality, and 1 case was reported as worsening HE

Eleven cases reported labeled events:

- Chest pain/pruritus (1)
- Fatigue (1)
- Frequent bowel movements (1)
- Respiratory problems (1)
- Vomiting (1)
- Anaphylaxis/angioedema [hypersensitivity reactions, but not anaphylaxis, are labeled)
- *C. difficile/campylobacter* (5; the label states that antibacterial agents alter normal flora of the colon)

Of these 11 cases, 1 patient died (patient developed *C difficile*; see description below) and 5 patients were hospitalized because of their adverse events (i.e., respiratory problems [1], anaphylaxis/angioedema [1], *C. difficile* [3]).

Two cases reported bleeding disorders due to thrombocytopenia; one reporter stated that thrombocytopenia was secondary to cirrhosis (both patients were hospitalized).

The remaining 5 cases reported the following adverse events:

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

Of these 5 cases, 4 patients were hospitalized for their events (i.e., suicidal ideation, increased blood glucose, edema of lower extremities, pancytopenia).

All deaths (n=2 [deduplicated cases]): The search identified two fatalities involving patients using rifaximin to prevent HE (n=1) or to treat small intestinal bacterial overgrowth (1).

- The former patient (62-year-old male) used 1200 mg of rifaximin a day for 30 days (ceftriaxone listed as concomitant medication, but dates of administration were not reported); he developed *C. difficile* diarrhea and died 22 days later due to "complications of liver disease worsened by *C. difficile* diarrhea."

- The latter patient (85-year-old female with end-stage renal failure) used 600 mg of rifaximin a day for 7 days; she hit her head and was found dead in the bathroom (exact cause of death not known, the reporter did not feel that it was related to rifaximin).

Because of reports of *C. difficile* (including one fatality), it should included in the AE Postmarketing section of the label (in addition to the Warnings section) that cases of rifaximin-induced *C. difficile* colitis have been reported

Serious adverse events during postmarketing use of XIFAXAN ® by system organ class are listed in Table 26.

Table 26
NDA 22-554
Serious Adverse Events during Postmarketing Use of Xifaxan by System Organ Class

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

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

9. SEALD

SEALD did not issue a formal Consult Review.

10. DNP

Most of Dr. Mani review and evaluation in his Consult Review was incorporated in **Section 7. Efficacy** of the current review. Additional statements Dr. Mani incorporated in his Neurology review are listed below; this list is followed by the CDTL's comments on Dr. Mani's statements.

Dr. Mani's Discussion of Study (Efficacy) Results

"The materials below include Dr. Mani's discussion on the efficacy results from Study RFHE3001. He notes that despite the results of this study, as presented by the sponsor in the study report, ostensibly providing unequivocal evidence that rifaximin reduces the risk of developing relapses of more overt HE in patients with cirrhosis and/or portal hypertension, there are several serious concerns, further explained below, as to the validity of how such relapses (breakthrough episodes) were actually delineated during the study.

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

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

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

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

"The HESA has been proposed as a structured means of assigning Conn grades in an effort to make that assignment more precise, and on face, the algorithm, as described by Hassanein et al, would appear suitable for that purpose. However, as the same authors make clear, such information as is currently available regarding the validity of the HESA may be only preliminary.

"The HESA was to be applied to each patient in this study at each in-person visit during the treatment period and a score assigned, but the final score derived from the use of that algorithm was not recorded in the patient's CRF. Although the protocol and study report suggest that the HESA was to be utilized as a guide to help assign a Conn grade, the manner in, and extent to, which that was actually accomplished during the study are unclear. Thus it is unclear as to how structured – and therefore precise – the assignment of Conn grade was in this study, even by direct observation. A review of source documents, which are reported to include the HESA score sheets and final grades, in a sufficiently large sample of patients may be the only means of providing better clarification of how Conn grades were actually assigned during this study.

"More importantly, in an uncertain proportion of patients who were judged to have developed breakthrough episodes of hepatic encephalopathy during the study, that determination was based on Conn grades and asterixis scores derived not from direct observation, but indirectly – and sometimes retrospectively - from hospital medical records, treating physicians, caregivers, and other sources. The reliability of determining the occurrence of breakthrough episodes of HE by such indirect, and especially retrospective, means must be considered questionable at best. It is thus necessary for the sponsor to provide more compelling evidence that those patients who were indirectly diagnosed to have breakthrough episodes of HE in this study either did indeed have such episodes as defined by the criteria stipulated in the protocol or were otherwise not critical to the overall conclusions of the study.

"A related concern is whether a specific and key inclusion criterion for this study could have been accurately applied. Under that particular criterion, all patients enrolled in the study should have had two or more episodes of hepatic encephalopathy equivalent to a Conn score ≥ 2 within 6 months of screening. In fulfilling that criterion: an episode of hepatic encephalopathy was defined as a Conn score rising from 0 or 1 to ≥ 2 and returning to a score of 0 or 1; and at least one episode of HE should have been confirmed by reviewing medical records from a treating physician, clinic, or hospital, with other episodes being documented based on descriptions provided by a caregiver. Here again, the reliability of diagnosing episodes of HE, and especially those of a specific severity, by retrospective means is open to question, unless the sponsor can confirm to the Agency's satisfaction that the means used were, in fact, accurate.

"A further concern pertaining to the accuracy with which breakthrough episodes of (overt) HE were diagnosed is the extent to which such episodes may have been missed in between study visits and phone contacts with the patient, particularly since such episodes can be both frequent and short-lived, as well as associated with only a subtle change in mental state; that concern exists despite a study visit or phone contact with the patient occurring as frequently as every week throughout the study. While the study protocol indicates that patients were required to complete a structured daily diary, that included an assessment of mental status, those **with cognitive impairment, a *sine qua non* of having a Conn grade ≥ 1**, cannot be assumed to have been capable of reliably evaluating their own mental state (in fact, it is questionable, whether those who were even mildly cognitively impaired were capable of reliably completing other elements of the daily diary, either); at the same time, the degree to which patients were under observation by their caregivers (for example, were they required to spend a specified proportion of each day with the patient?), and the extent to which caregivers recorded their own daily observations of the

patient, were required to assist patients in completing the daily diary, and participated in phone contacts between the patient and study site is unclear and should be further clarified by the sponsor. Section 9.3.3 of the study report entitled Caregiver Responsibilities does not address those uncertainties adequately, and even indicates that caregivers were not required to attend all study visits".

Dr. Mani's Conclusion

The report of Study RFHE3001 does not provide enough evidence for this reviewer to conclude that Xifaxan® administered in a dose of 550 mg BID over 6 months has efficacy, in comparison with placebo, in reducing the risk of relapse of hepatic encephalopathy in patients with cirrhosis of the liver and/or portal hypertension. More specifically, evidence is lacking in this submission that the main component of the primary efficacy parameter, breakthrough episodes of hepatic encephalopathy while on treatment with study drug, were accurately recorded. There is also insufficient evidence that the occurrence, or lack thereof, of episodes of hepatic encephalopathy in the months prior to study entry was accurately recorded, either; an accurate recording of the frequency and severity of such episodes was needed for one of the main inclusion criteria for this study to be fulfilled.

CDTL Comments

The neurologist consultant brings a series of interesting points, worth considering. These concerns were further considered at the Feb 23, 2010 Advisory Committee meeting. However, it is important to reiterate that that the HESA is only one of the approaches currently used to assign a Conn grade. HESA is yet to be validated [a validation attempt in a large number of patients is currently on-going]. None of the other approaches has been validated. On the other hand, it is worth keeping in mind that RFHE3001 was a randomized, placebo-controlled study that, based on DSI inspection results, was properly executed [no protocol violations that might invalidate results]. The available HESA tool was applied, reasonable equally, in a double-blind/randomized fashion to the two experimental arms of the trial. Thus, although it is recognized that the present state of affairs needs to be scientifically improved, results from RFHE3001 analyzing both the primary efficacy parameter as well as key secondary endpoints of efficacy, under double-blind, randomized conditions [designed to minimize bias] seem to demonstrate a clear-cut different in efficacy between rifaximin and placebo.

11. DSI

Two memoranda were issued by DSI. The fist [11/02/09] detailed finding of the routine inspection of 5 participating sites. Although some minor issues were noted at Dr. F Poordad's [Site 351, LA, CA] and Dr. V Gorbakov's [Moscow, Russia], the DSI Inspector Dr. K Malek [MOR, Good Clinical Practice Branch 2] concluded that those findings were unlikely to impact data integrity. In a more recent memorandum, in response to the CDTL's request to further investigate for **bias or study execution that may impact data integrity**, Dr. Malek included explanations to some validation issues brought up by Dr. Mani in his Neurology Consult Review. Dr. Malek's reply is included below.

DSI REPLY: Some Validation Issues in Dr. Mani's Review

DSI sent A Clinical Inspection Summary early last December regarding the 5 sites chosen inspected in this NDA. These sites were: site 351, Dr. Poordad; site 799, Dr. Sheikh (both in the US) and 3 sites in Russia: site 938, Dr. Alexeeva; site 905, Dr. Gorbakov; and site 894, Dr. Rafalsky.

Although Dr. Malek reviewed the field investigator's inspection of the US sites, he did not participate personally in the inspection. At Dr. Poordad's site [#351] there were minor inaccurate records; at Dr. Sheikh site [#799] there were no violations.

Dr. Malek personally participated in the 3 Russian inspections and can report with confidence:

1. The study was well supervised and conducted in the 3 sites. There was one violation in Dr. Gorbakov site in that 8 subjects took a prohibited over-the-counter herb medication. In the other 2 sites there were no violations observed.

2. **The documentation of the 2 episodes of HE episodes during the preceding 6 months was accurately recorded through hospital or clinicians observations.**

3. **The Conn score for each subject was recorded clearly in the subjects' records.**

4. **Regarding the other validation issues detailed in the Neurology review, there were 2 groups in the study, one placebo and the other the active drug. Dr. Malek stated that he can assume that any inaccuracies were equally divided between the 2 groups.**

12. OSE

The Division of Pharmacovigilance I recommends adding **Anaphylaxis** to the **WARNING Section** of the label. In addition, cases of rifaximin-induced *C. difficile* have been reported (including one death) and should be included in the **Adverse Events Postmarketing Section** of the label (in addition to the Warnings Section).

Summary

AERS was searched from May 2004 (approval of rifaximin to treat Traveler's diarrhea) to August 31, 2009 using the drug name rifaximin (Xifaxan). Three separate searches were performed as follows:

- ***All AEs*** (involves all reasons for use); [n = 173]
- ***Adverse events associated with prevention/treatment of*** HE; [n = 21; deduplicated cases]
- ***All deaths*** (all adverse events with the outcome of death); [n = 2; deduplicated cases] .

NOTE:

-- Most of the AEs that have been reported for patients receiving rifaximin to treat HE are labeled

-- In addition, antibiotics such as rifaximin are known to cause changes in gut flora possibly leading to infection.

-- No new safety signals were found in AERS or the literature in patients using rifaximin.

-- The current domestic label recommends use of rifaximin for 3 days only to treat Traveler's diarrhea.

-- It appears that many patients in this case series used rifaximin beyond 3 days and for treatment of conditions other than Traveler's diarrhea (e.g., HE [not an approved indication in the US], Crohn's disease, irritable bowel syndrome, bacterial overgrowth). Based on AERS data in this case series, no conclusions can be made regarding safety for short-term (3 day) versus long-term use for most of the AEs identified; events such as bacterial overgrowth are known to occur with antibiotic use.

- **Most of the adverse events reported for patients receiving rifaximin to treat HE are labeled; there are no new safety signals associated with rifaximin use.**
- **Because of reports of *C. difficile* (including one fatality), DGP should consider including in the Adverse Events Postmarketing section of the label (in addition to the Warnings section) that cases of rifaximin-induced *C. difficile* colitis have been reported**

13. DMEPA; OSE CARTON AND CONTAINER

DMEPA evaluated the container labels, carton and insert labeling for Xifaxan® (rifaximin) tablets. Vulnerabilities that could lead to medication errors were identified. Specifically, DMEPA raise concern with the close proximity of the strength (550 mg) to the net quantity (6 tablets and 60 tablets) as presented on the principal display panel of container labels and carton labeling. DMEPA ask that the Applicant consider increasing the prominence of the 550 mg strength on the unit dose foil pack container to provide added differentiation from the 200 mg strength foil pack container. They believe **these vulnerabilities can be revised prior to approval. They** have provided recommendations in Section 5.2 *(Comments to the Applicant)* of their Consult Review that aim at reducing the risk of medication errors with regards to the proposed labels and labeling. The CDTL agrees with these recommendations.

Lastly, DMEPA note that the container label for the currently marketed Xifaxan® 200 mg strength 100-count size is presented with a different color scheme (b) (4) than all other labels and labeling for the 200 mg strength, presented in (b) (4) DMEPA has concerns that the differentiation of the quantity of tablets between the 30-count and 100-count size is not necessary and may cause wrong strength selection errors once the 550 mg

strength is available. In the belief that these vulnerabilities can be remedied through revisions to current labels and labeling submitted by the Applicant as a prior approval supplement to new drug application (NDA 21361) DMEPA have provided recommendations in Section 5.1 (*Comments to the Sponsor of their review)*.

Comments to the Applicant: A. Container Labels and Carton Labeling and DMEPA comments related to other evaluations, are listed in the body of the CDTL review.

DMEPA Comments to the Division

DMEPA limited their review to the proposed labels and labeling for Xifaxan 550 mg tablet and have provided our recommendations in Section 5.2. DMEPA notes, however, that while reviewing differentiating product characteristics between the proposed 550 mg strength and the currently marketed 200 mg strength, certain vulnerabilities were identified with container labels and carton labeling for the 200 mg strength product. They note that the strength on the currently marketed 200 mg strength container labels and carton labeling is not prominently displayed. With the introduction of a second Xifaxan strength, it will be even more important to provide strength differentiation for the 200 mg versus 550 mg products. Secondly, they note that the currently marketed Xifaxan 200 mg container labels have two different color schemes for the 30-count (b) (4) versus 100-count ((b) (4)) size container labels. Only the 100-count container label is presented in (b) (4) with all other container labels and carton labeling presented in (b) (4) They understand that this feature was likely implemented by the Applicant to differentiate the two size bottles (30-count versus 100-count), however, DMEPA is concerned that practitioners may misinterpret this as a 'strength' differentiating feature, especially with the introduction of the new 550 mg strength.

DMEPA asks that the Applicant submit a prior approval supplement to the application (NDA 21361) with the following revisions to labels and labeling:

1) **Increase the prominence of the strength presentation (200 mg) on the principal display panel of all container labels and carton labeling.**

2) **Revise the (b) (4) color scheme of the 100-count container label to align with the (b) (4) color scheme of all of the other Xifaxan 200 mg container labels and carton labeling.**

DMEPA Comments to the Applicant

1) Relocate the net quantity of tablets (6 tablets and 60 tablets) away from the strength. Currently, the strength and quantity are presented adjacent to one another inside a 'green arrow' on container labels and carton labeling. DMEPA understands that there is minimal chance that the strength '550 mg' will be confused or misinterpreted as the quantity '6 or 60', especially since the Xifaxan is not available in a 6 mg or 60 mg tablet. However, because the proposed new 550 mg strength and indication introduce a second Xifaxan product to the market, the presentation of this new strength while minimize any potential numeric confusion may help avert wrong strength medication errors.

2) Decrease the size of the graphic 'target' that appears adjacent to the strength '550 mg' on the principal display panel of container labels and carton labeling. While DMEPA agrees that this carton and container design differentiates the proposed 550 mg strength from the currently marketed 200 mg strength, the graphic 'target' appears larger than the proprietary name, the established name and the strength, which should be the most prominent information on the principal display panel of the label.

3) If space permits, consider increasing the size of the 550 mg strength presentation on the unit dose foil blister pack to help provide differentiation from the 200 mg unit dose foil pack label.

14. DDMAC: As of Sunday February 7, 2010, this discipline is yet to issue a formal Consult review.

15. AC MEETING of FEBRUARY 23, 2010

Information from the QUICK MINUTES of the Meeting, issued by Kristine Khuc, Designated federal Official, is incorporated at the end of Table OES-1.

APPENDICES

APPENDIX 1

Current Concepts in the Pathogenesis of Neuropsychiatric Dysfunction in Cirrhosis

Neuroanatomy, Neuropathology and Pathogenesis of Hepatic Encephalopathy

The following concepts pertain to the Neuroanatomy, Neuropathology, and Pathogenesis of HE (Type C). Modern imaging techniques demonstrate both global and region-selective changes in brain in HE. For example, positron Emission Tomography (PET) studies using fluorodeoxyglucose as ligand reveal early selective reductions of uptake in **anterior cingulated cortex**, a region of the brain that is implicated in the control of attention. Deficits in psychomotor test score (NCT-A,NCT-B for example) ratings were found to be significantly correlated with decreased signal in anterior cingulated cortex of patients graded as mild HE.

Magnetic Resonance Imaging (MRI) in cirrhotic patients with mild HE shows bilateral signal hyperintensities in **globus pallidus** and surrounding areas of the basal ganglia. The presence of pallidal signal hyperintensities in these patients has been attributed to the deposition of manganese in these patients.

The characteristic neuropathologic finding in Type C HE is known as "Alzheimer Type II astrocytosis" wherein brain **astrocytes** take on a particular phenotype consisting of a larger swollen nucleus, prominent nucleolus, margination of the chromatin pattern and glycogen accumulation. In addition, astrocytes in Type C HE manifest altered expression of several genes coding for key astrocyte proteins involved in cell structure and volume regulation and in the termination of neurotransmitter action. In 10-15% of cases associated particularly with multiple episodes of HE or prolonged coma, neuropathologic examination may reveal significant neuronal cell loss and the presence of neurodegenerative changes such as post-shunt myelopathy, cerebellar degeneration and acquired non-Wilsonian Hepatocerebral degeneration. The presence of such irreversible lesions may explain why liver transplantation does not completely reverse HE symptoms in some patients with end-stage chronic liver disease.

Arterial blood ammonia concentrations are increased 2-3 fold in type C HE and PET studies using $^{13}NH_3$ as ligand in patients with mild HE show increased rates of ammonia delivery to the brain. Whether this increased blood-brain ammonia transfer results from increased arterial concentrations, increased flow or increased permeability of the blood-brain barrier to ammonia is the subject of ongoing debate. Ammonia removal by the brain involves synthesis of glutamine in the astrocyte and both biochemical and spectroscopic studies show that glutamine concentrations are increased in Type C HE and are better correlated with HE severity than are brain concentrations of ammonia. The toxic effects of ammonia may be enhanced by the presence of increased circulatory levels of **proinflammatory cytokines** such as TNFα and the interleukins (IL-1β and IL-6) released into the circulation as a consequence of infection/sepsis or hepatocellular injury.

Pathogenesis of HE (Type C): Molecular Mechanisms

End-stage chronic liver failure and portal-systemic shunting result in altered expression of genes coding for key brain proteins. Using molecular techniques such as gene and protein microarrays, the following are examples of changes in gene/protein expression have been reported in the brains of HE patients or experimental animal models of type C HE: a) decreased expression of Glial Fibrillary Acidic Protein (GFAP), an astrocyte structural protein. Loss of GFAP expression results in impairment of cell volume regulation; b) increased expression of Monoamine Oxidase (MAO-A isoform). MAO-A degrades monoamine neurotransmitters such as serotonin and dopamine and polymorphisms of the human MAO-A gene are known to be associated with neuropsychiatric symptoms and c) increased expression of the mitochondrial (peripheral type) benzodiazepine

receptor (PTBR activation mediates the transport of cholesterol and is expressed principally by glial cells (astrocytes and microglia).

Pathogenesis of HE (Type C): Neurosteroids and GABA function

Neurophysiologic and pharmacologic studies in experimental animal models of end-stage chronic liver failure suggest that the γ-aminobutyric acid (GABA) system, the major neuroinhibitory system of mammalian brain, is upregulated. The concept of "**increased GABAergic tone**" was initially attributed to increased brain GABA concentrations or to increased concentrations of endogenous substances with action at benzodiazepine receptors that constitute neuromodulatory sites on the GABA-A-receptor. Studies in patient material failed to confirm these mechanisms. However, an alternative explanation for increased GABAergic tone in Type C HE has recently emerged.

Neurosteroids comprise a family of steroidal compounds that are synthesized in the brain, independent of their production in peripheral tissues (adrenals, kidney, gonads). Neurosteroids are synthesized in brain astrocytes following activation of the PTBR (see above, "Molecular Mechanisms"). PTBR sites are increased in brain in type CHE. Moreover, PTBR sites are increased following exposure of astrocytes to ammonia or manganese and endogenous ligands known to activate PTBRs in brain have been described in cerebrospinal fluid of patients with Type CHE. In addition to brain synthesis of neurosteroids, neurosteroids produced in peripheral tissues are able to cross the blood-brain barrier. Allopregnanolone is a highly potent inhibitory neurosteroid whose mechanism of action involves stimulation of the steroid modulatory site on the GABA-A receptor. Concentrations of allopregnanolone are increased up to 10-fold in autopsied brain tissue from cirrhotic patients who died in hepatic coma but are unchanged in the absence of HE. These findings strongly suggest that increased GABAergic tone in Type C HE results at least in part from increased brain concentrations of inhibitory neurosteroids such as allopregnanolone.

APPENDIX 2

Subclinical and Chronic Encephalopathy: Practical Issues in Evaluation and Management

Definition and Burden

Hepatic encephalopathy (HE) is defined as a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known brain disease. It effects up to 45% of patients with cirrhosis and is associated with an increased risk of hospitalization, morbidity and mortality. Mortality associated with HE has been influenced by its exclusion from the MELD score, despite recent evidence that it adds risk beyond simple MELD calculation. Recent trends have shown an increase in the number of hospital admissions and charges for HE, with conservative estimates of $932 million annually.

Effect of MHE on Daily Life and Long-term Outcomes

Patients with MHE are predisposed to develop problems with their quality of life across several domains. This impairment in quality of life affects almost all aspects of daily living apart from communication skills. Apart from this there are differences in socio-economic status in MHE patients compared to those who are not MHE. MHE particularly affects "blue-collar" workers because of the inherent visuo-spatial and attention deficits, more than 'white collar" workers. This may increase the overall societal burden of MHE.

MHE, due to its effect on attention, working memory and response time affects driving skills. Driving assessments using driving simulation and on-road driving tests showed that patients with MHE were worse drivers i.e. required a higher intervention rate by the instructors and had several near-misses compared to those without MHE. The navigation skills and divided attention skills i.e. those that study answering a cell phone etc while driving, of patients with MHE were also impaired. MHE was also associated with a high rate of actual traffic accidents and violations compared to cirrhotics without MHE and healthy controls. Patients with MHE

have a significantly higher risk of developing overt HE. There are also isolated reports suggesting that MHE independently affects survival but this has not been corroborated as yet.

Role of Ammonia levels in the Clinical Evaluation of HE

There is considerable controversy about the role of venous or arterial ammonia in the assessment of a patient with HE. Most studies have shown that neither venous nor arterial ammonia levels can be used to judge the severity of HE symptoms. Patients who have high venous ammonia levels without cognitive or mental status complaints are often treated as HE. Conversely, there are several instances of patients in coma due to HE with normal or only mildly elevated ammonia levels. Complicating these assessments are the methods for drawing the ammonia sample, which should ideally be performed without a tourniquet, should be tested within 30 minutes and should be kept on ice till testing. The specific situations where ammonia levels may help are in the rare patients with urea-cycle disorders or in the initial diagnosis of a patient with coma without any prior history of cirrhosis

Differential Diagnosis of HE and Search for Precipitating Factor

Although HE is the most likely cause of mental status changes in patients with cirrhosis, **there are several other important conditions that can either precipitate it or can mimic it.** In most cases, HE is not an excitatory disease; therefore seizures are not inherently part of HE (apart from patients with urea-cycle disorders). Additionally, new focal deficits are not part of HE. Therefore, a detailed history and physical exam should be undertaken in each patient with suspected HE. In addition to confirming cirrhosis and chronic liver disease, the mental status, including orientation, should be evaluated. Focal neurological deficits should trigger the search for alternative explanation, e.g. intracranial hematomas. Metabolic abnormalities, uremia, acidosis and drug intoxication can also be confused with HE. If in doubt, a head CT may be indicated along with basic blood work to evaluate for metabolic abnormalities. Once the diagnosis of HE is confirmed, an extensive search for **potential precipitating factors** should be instituted. The classic teaching is that almost all cases of HE would have a precipitating factor, but of late spontaneous HE cases have also been noted increasingly. Precipitants work by either increasing the underlying inflammatory milieu, increasing ammonia production, reducing the threshold for mental status decline or a combination of the above.

Clinical Approach to Management of a Patient with Overt HE

There are a series of questions that need to be answered when presented with a patient with possible HE.

1. Is this really HE?
2. If yes, is there a precipitating factor?
3. Should this patient be admitted to the hospital?
4. If so, should the patient go to the floor or the ICU?
5. When should the patient be intubated?
6. How should I give the patient lactulose, by mouth or enema/
7. How often should ammonia levels be drawn, if at all?

After it is confirmed that the patient has HE and while the search for a precipitating factor is going on, the patients should be assessed for consciousness, orientation and ability to protect the airway (Figure 3). Patients who have grade 3 or higher HE should be transferred to the intensive care or a step-down unit, since by definition they will have difficulty protecting their airways. Patients with stage 2, i.e. disorientation, should be admitted to the hospital in most cases to evaluate potential serious precipitating factors. There should be a low threshold for airway intubation in patients in the ICU, especially those with concurrent GI bleeding, to prevent aspiration. A complete infectious work-up including diagnostic paracentesis, pan-culturing of urine and blood, chest X ray and skin examination for possible cellulitis should be carried out. Patients with diarrhea could also benefit from stool toxin analysis for Clostridium difficile. Unless there is evidence of GI bleeding or sepsis, there is currently no role for prophylactic antibiotics in patients admitted with HE.

Metabolic abnormalities should be corrected as noticed and hydration should be gentle with care not to cause pulmonary congestion. Ammonia levels do not provide any additional information beyond the observation of change of mental status in HE and should not be performed with an aim to predict or correlate with actual clinical outcomes. An analysis of consciousness and orientation should be performed at least three to four times per day, especially in those patients who are admitted to the floor.

APPENDIX 3

Rating Scale: Symptoms of Intolerance to Lactulose
(to be used to assess the eligibility of patient for inclusion in the study)

Abdominal distension
0 = no symptom
1 = slight: causes discomfort not influencing daily activities
2 = mild: causes discomfort scarcely influencing daily activities
3 = moderate: causes discomfort significantly influencing daily activities
4 = severe: causes discomfort not allowing daily activities

Abdominal cramps
0 = no symptom
1 = slight: cause discomfort not influencing daily activities
2 = mild: cause discomfort scarcely influencing daily activities
3 = moderate: cause discomfort significantly influencing daily activities
4 = severe: *cause discomfort not allowing daily activities*

Meteorism
0 = no symptom
1 = slight: causes discomfort not influencing daily activities
2 = mild: *causes discomfort scarcely influencing daily activities*
3 = moderate: causes discomfort significantly influencing daily activities
4 = severe: causes pain not allowing daily activities

Flatulence
0 = no symptom
1 = slight: *causes discomfort not influencing daily activities*
2 = mild: causes discomfort scarcely influencing daily activities
3 = moderate: causes discomfort significantly affecting daily activities
4 = severe: causes discomfort not allowing daily activities

Nausea
0 = no symptom
1 = slight: causes discomfort not influencing daily activities
2 = mild: causes discomfort scarcely influencing daily activities (e.g.: decrease in appetite and motion activity, reduction in social relations)
3 = moderate: causes discomfort significantly influencing daily activities (e.g.: increasing loss of *appetite / reduction of motion activity, noticeable reduction in social relations)*
4 = severe: causes discomfort not allowing daily activities (e.g.: constant lack of appetite, abolition of motion activity, subject bedridden)

Diarrhoea
0 = no symptom
1 = slight: causes discomfort not influencing daily activities
2 = mild: causes discomfort influencing daily activities, but without pathological consequences
3 = moderate: significantly affects daily activities, and/or produces pathological consequences (e.g., dys-ionia, dyshydration)
4 = severe: *causes discomfort not allowing* daily activities and/or produces major pathological consequences (e.g., severe dys-ionia, heart rate/kidney function alterations, etc)

Vomiting
0 = no symptom
1 = slight: causes discomfort not influence daily activities
2 = mild: *causes discomfort that influences daily activities but without pathological consequences*
3 = moderate: significantly affects daily activities, and/or produces pathological consequence (e.g., dys-ionia, dyshydration)
4 = severe: causes discomfort not allowing daily activities and/or produces major pathological consequences (e.g., severe dys-ionia, heart rate/kidney function alterations, etc)

APPENDIX 4

NDA 22-554

Comprehensive list of MICs for rifaximin against clinical isolates

Table 1 ***In Vitro*** **Antibacterial Activity of Rifaximin (mg/L)**

Organism	MIC_{50}	MIC_{90}	Organism	MIC_{50}	MIC_{90}
Gram-positive			**Gram Negative**		
Staphylococci			Enterobacteriaceae		
S. aureus	0.015	0.015	*Citrobacter spp.*	>4	>8
S. aureus (OR)	0.015	>8	*Enterobacter spp.*	4	8
S epidermidis	0.015	0.015	*Escherichia coli*	3.12	>8
Streptococci/Enterococci			*Klebsiella spp.*	>8	>8
E. faecalis	2	8	*Proteus spp*	4	4
E. faecium	2	>8	*Salmonella spp*	2	>6.25
E. spp.	0.25	2	*Serratia spp.*	25	>50
Group A, B, C, F, G	0.12	0.25	*Shigella spp.*	4	8
			Yersinia enterocoliticia	3	>8
Clostridia			*Bacteroides fragilis*	0.1	12.5
C dijficile	0.2	0.8	*Bacteroides spp.*	0.1	50;4[a]
Clostridium spp	0.4	50	*Acinetobacter spp.*	2	4
Bacillus cereus	0.06		*Pseudomonas aeruginosa*	8	>8
Peptococcus spp	0.1	3.1	*Fusobacterium spp.*	0.4	50
Peptostreptococcus spp	0.2	25	*Helicobacter pylori*	8	16
			Campylobacterjejitni	6.25	>100

OR: oxacillin-resistant

[a]: *B. eggerethii, B. melaninogenicus, B. oralis, B. ruminicola, B. uniformis*

Source: adapted from Gillis and Brogden

APPENDIX 5

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Common Precipitating Factors and Concurrent Causes of Encephalopathy

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

APPENDIX 6

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Therapies under Investigation for the treatment of HE

Probiotics, Symbiotics
Acarbose
L-carnitine
Sodium benzoate, sodium phenylacetate
Liver-support devices
Ornithine aspartate
Bromocriptine
IND 103-579 - GT4P

APPENDIX 7

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Studies/Clinical Trials Indications Other Than HE or Data Other Than Clinical

Study ID	Trial Type	Trial Design	Number Centers	Number subjects	Dosage	Duration
Supportive integrated analysis–Rifaximin for the Treatment of Traveler's diarrhea						
RFID9601	Efficacy and safety Phase 3	Randomized, active control, parallel group, blinded, dose ranging	Multi – center Mexico	72 RFX 200mg: 18 RFX 400mg: 18 RFX 600mg: 19 TMP/SMX: 17	RFX 200mg, 400mg, or 600mg t.i.d TMP/SMX 160/800mg BID	5 days
RFID9701	Efficacy and safety Phase 3	Randomized, active control, parallel group, blinded	Multi-center Mexico and Jamaica	187 RFX: 93 Cipro: 94	RFX 400mg bid Cipro 500mg bid	3 days
RFID9801	Efficacy and safety Phase 3	Randomized, comparative, parallel group, blinded	Multi-center Mexico, Kenya, Guatemala	379 RFX 200mg: 124 RFX 400mg: 126 Placebo; 129	RFX 200mg or 400mg t.i.d or placebo	3 days
RFID3001	Efficacy and safety Phase 3	Randomized, placebo and active control, parallel group, blinded	Guatemala India Mexico Peru	399 RFX: 199 CIPRO: 100 Placebo: 100	RFX 200mg t.i.d Cipro 500mg bid Placebo	3 days
Supportive integrated analysis–Rifaximin for the Prevention of Traveler's diarrhea						
RFID2001	Efficacy and safety Phase 2	Randomized, placebo control, blinded, prophylactic use in subjects challenged with *shigella flexneri*	Single center US	25 RFX: 15 Placebo: 10	RFX 200mg t.i.d	3 days
RFID3003	Efficacy and safety	Randomized, placebo control,		210 RFX: 106	RFX 600mg daily or	14 days

	Phase 3	blinded, prophylactic use in healthy subjects traveling to Mexico		Placebo: 104	placebo	
RFID3004	Efficacy and safety Phase 3	Randomized, placebo control, blinded, prophylactic use in healthy subjects traveling outside the US	Multi-center	133 RFX: 107 Placebo: 26	RFX 600mg daily or placebo	14 days
RFID3005	Efficacy and safety Phase 3	Randomized, placebo control, blinded, prophylactic use in healthy subjects traveling from Thailand to Switzerland		231 RFX: 117 Placebo: 114	RFX 600mg daily or placebo	8 – 15 days
RFID3006	Safety Phase 3	Randomized, double blind in healthy volunteers		593 RFX 600mg qd: 234 RFX 600mg bid: 241 Placebo: 118	RFX 600mg daily RFX 600mg bid placebo	14 days
Additional Supportive Rifaximin Trials:						
Indication: IBS						
RFIB2001	Efficacy and safety Phase 2	Randomized, placebo control, blinded,	Multi-center US	674 RFX 275mg bid 14 days: 95 RFX 550mg bid 14 days: 190 RFX 550mg bid 28 days: 96 RFX 1100mg bid 14 days: 99 Placebo; 195	RFX 275mg bid RFX 550mg bid RFX 550mg bid RFX 1100mg bid placebo	14 – 28 days
Indication: Crohn's Disease						
RFCD2001	Efficacy Phase 2	Open label, subject's w/ active Crohn's disease	Single center	29 RFX: 29	RFX 200mg t.i.d	16 wks
Indication: Pouchitis						
RFPO2001	Efficacy Phase 2	2-phase (double-blind and open label) placebo control in subject's w/ pouchitis	Multi-center	20 RFX: 8 Placebo: 10 Control: 2	RFX 400mg t.i.d or placebo or control	28 – 56 days
Phase 1 Rifaximin Studies						
RFPK1007	Phase 1 PK, bio-availability	Open-label, randomized 2-part	Single center	28	Multiple differ doses	9 or 14 days
RFDI1008	Phase 1 PK drug interaction	Open-label, randomized	Single center	24	Interaction with midazolam	16 days

APPENDIX 8

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SCHEDULE OF ASSESSMENTS IN THE STUDY

	Screen	Treatment Period													
Procedure	Day 0	1	2	3[1]	4	5	6	7[1]	8	9	10[1]	11	12	13	14[1]
Inclusion/Excl. criteria	X														
Informed Consent	X														
Medical History	X														
Concomitant Meds	X	X		X				X			X				X
Physical Examination	X														X
Vital Signs	X			x				x			x				X
Blood Sample: benzodiaz.		X[2]													
Demographics	X														
EEG (optional)		X[2]													X
Mental State		X[2]		X				X			X				X
MMSE		X[2]		X				X			X				X
Asterixis		X[2]		X				X			X				X
NCT		X[2]		X				X			X				X
Blood ammonia (venous)		X[2]		X				X			X				X
PSE Index		X[2]		X				X			X				X
Haematology tests	X														X
Biochemistry tests	X														X
Urinalysis	X														X
Randomisation		X													
Collect Adverse Events		X		X				X			X				X
Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Scheduled visit to clinic for evaluations, **+/- 1 day**

[2] To be performed prior to randomisation and drug administration

APPENDIX 9

NDA 22-554

Study RFHE3001

Categories under which the Neuropsychological Assessments were performed

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

APPENDIX 10

Study RFHE-3001

Clinical Assessments as a Function of HE Grade

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

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

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/s/

HUGO E GALLO TORRES
03/08/2010