DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

Tuesday, February 23, 2010

8 o'clock a.m.

Hilton Washington DC/Silver Spring
Maryland Ballroom
8727 Colesville Road
Silver Spring, MD

PARTICIPANTS

Jean-Pierre Raufman, M.D., Acting Chair
Kristine Khuc, Pharm.D., Designated Federal Official

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

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

NON-VOTING INDUSTRY REPRESENTATIVE

Debra Silberg, M.D., Ph.D.

TEMPORARY VOTING MEMBERS

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

FDA (Non-Voting)

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

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Introduction of Committee

DR. RAUFMAN: I would like to call the Gastrointestinal Drugs Advisory Committee meeting to order.

My name is Jean-Pierre Raufman. I am head of the Division of Gastroenterology and Hepatology at the University of Maryland School of Medicine in Baltimore.

I will ask the other members of the Committee to please introduce themselves starting with Dr. Silberg.

DR. SILBERG: I am Debra Silberg. I am the Pharma representative. I am an Executive Director at AstraZeneca.

DR. KANE: Dr. Sunanda Kane. I am a gastroenterologist at the Mayo Clinic in Rochester, Minnesota.

DR. REHM: Susan Rehm. I am an infectious disease physician at Cleveland Clinic.

DR. KUMAR: Atul Kumar. I am a gastroenterologist and hepatologist at Stonybrook University, and I also work at the Veteran Affairs in Northport, Long Island.

DR. GITLIN: Norman Gitlin. I am a hepatologist at Atlanta in Georgia.

DR. MAXWELL: Celia Maxwell, Adult infectious

diseases, Howard University Hospital.

MS. CRYER: My name is Donna Cryer. I am the Patient Representative and a liver transplant recipient based in Washington, D.C.

DR. HERSCH: I am Steve Hersch, a neurologist at Mass General Hospital.

DR. DASARATHY: Srinivasan Dasarathy. I am a hepatologist at The Cleveland Clinic.

DR. HAUBRICH: Richard Haubrich, Professor of Medicine at the University of California in San Diego.

DR. SOLGA: I am Steven Solga. I have a part-time appointment at Johns Hopkins, but I am a solo private practitioner in gastroenterology and hepatology.

DR. KHUC: Kristine Khuc, Designated Federal Official of this committee.

DR. ANDERSON: Garnet Anderson, biostatistician, Fred Hutchinson Cancer Research Center in Seattle, Washington.

DR. LOCKWOOD: Alan Lockwood, Professor of Neurology at the University at Buffalo.

DR. COHEN: Jeffrey Cohen, neurologist, Dartmouth Medical School.

MS. SKLAR: Jill Sklar, Consumer Representative.

DR. HASLER: Bill Hasler, in Gastroenterology, University of Michigan.

DR. HE: Ruyi He. I am Acting Deputy Director and a medical team leader in the Division of Gastroenterology Products, FDA.

DR. GRIEBEL: I am Donna Griebel. I am the Division Director for the Division of Gastroenterology Products at FDA.

DR. RAUFMAN: For topics such as those being discussed at today's meeting, there are often a wide variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open

forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

I would like to remind everyone present to please silence your cell phones and any other electronic devices if you have not already done so.

The Committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

Thank you.

Conflict of Interest Statement

DR. KHUC: The Food and Drug Administration is convening today's meeting of the Gastrointestinal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the Committee are special Government employees or regular Federal employees from other Agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this

Committee's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this Committee are in compliance with the Federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Under Section 712 of the Federal Food and Cosmetic Act, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this Committee have been screened for potential financial conflicts of interest

of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting; expert witness testimony, contracts/grants/CRADAs; teaching/speaking/ writing; patents and royalties; and primary employment.

Today's agenda involves discussions of Xifaxan (rifaximin) tablets 550 mg, by Salix Pharmaceuticals, for the indication 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 is a particular-matters meeting during which particular matters related to Xifaxan will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Debra Silberg is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry.

Dr. Silberg's role at this meeting is to represent industry in general and not any particular company. Dr. Silberg is employed by AstraZeneca.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationship that they may have with the firm at issue.

Thank you.

DR. RAUFMAN: We will now proceed with the FDA opening remarks.

FDA Opening Remarks

DR. HE: Good morning.

[Slide.]

I am Ruyi He, Acting Deputy Director in the Division of Gastroenterology Products.

Today, we are talking about rifaximin, NDA 22-554 for hepatic encephalopathy. Hepatic encephalopathy is a serious and a progressive complication of advanced liver disease. There are few drugs available for this serious condition.

Published studies to support current utilization of treatments are limited in number, size and the design. Therefore, we are very glad to have this opportunity to discuss this application with you at this Advisory Committee meeting.

[Slide.]

The purpose of today's meeting is to discuss the efficacy and the safety of rifaximin for the proposed indication--that is, the maintenance of remission of hepatic encephalopathy in patients 18 years of age or older.

However, based on the design of the major clinical trial submitted to support product approval, it may be more appropriate to state the indication as decreasing the risk

for episodes of overt hepatic encephalopathy in patients 18 years of age or older.

[Slide.]

During the NDA review, the FDA identified the following major issues that we have put forward for your evaluation. We are looking forward to your discussion of those issues.

One issue is a single pivotal Phase III trial to provide substantial evidence of efficacy. As you may know, we generally have ask at least two adequate and well-controlled studies each convincing on its own to support evidence of efficacy.

Other issues are adequacy of the primary endpoint definition and assessment methodology to evaluate hepatic encephalopathy, and the safety of rifaximin at the proposed dose and duration in patients with hepatic impairment.

[Slide.]

I want to start the meeting today by setting a foundation for our discussion by going over the directory definition of substantial evidence.

This is the definition from the Food, Drug, and Cosmetic Act, and it is a long definition.

Basically, it states that evidence consists of adequate and well-controlled investigations, which it could fairly be concluded that the drug will have the effect under the conditions of use.

[Slide.]

The FDA Modernization Act of 1997 make it clear that it may consider data from one adequate and well-controlled investigation and confirmatory evidence to constitute substantial evidence. However, if there is a single adequate and well-controlled study, the submitted study is held to a higher standard.

[Slide.]

A single trial is generally limited to situations where an adequate and well-controlled trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome and a second adequate and well-controlled trial would be practically or ethically impossible.

[Slide.]

There are many limitations of reliance on a single trial for substantial evidence, such as any trial may be subject to unanticipated undetected systematic biases.

Any trial may have a positive finding due to chance alone, a false positive finding.

Independent results helps minimize a wrong conclusion that a drug is effective.

[Slide.]

During today's meeting, there will be several presentations from both sponsor and FDA. Please think about the following questions during the presentations and discussion. The questions are:

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

For future clinical trials, what clinically meaningful endpoints should be evaluated and how should they be measured for indication of decreasing the risk of episodes of overt hepatic encephalopathy or for the indication of treatment of overt hepatic encephalopathy?

Do the clinical data included in the rifaximin application provide substantial evidence of efficacy?

[Slide.]

Has the safety of rifaximin at the proposed dose and duration been adequately assessed?

Is the safety of rifaximin at the proposed dose and duration acceptable?

The last question is: Does the risk-benefit profile support approval of rifaximin for decreasing the risk for episodes of overt hepatic encephalopathy?

We will pose the questions again at the end of discussion. We look forward to a vigorous discussion.

Now, I turn the podium over to our chairman.

Thank you very much.

DR. RAUFMAN: Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants including the sponsor's non-employee presenters to advise the Committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor including equity interest and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the sponsor's presentations.

Sponsor Presentation

Introduction

MR. DOBROWSKI: Dr. Raufman, Dr. Griebel, members of the Advisory Committee, FDA staff, ladies and gentlemen, good morning.

[Slide.]

I am David Dobrowski, Director of Regulatory Affairs, with Salix Pharmaceuticals. Salix is a specialty pharmaceutical company dedicated to developing new therapies to prevent or treat gastrointestinal disorders.

I would like to begin with a brief history of rifaximin and then provide an introduction to the presentations you will hear today.

[Slide.]

Rifaximin is semisynthetic antibiotic of the rifamycin class. Its unique molecular structure leads to gut targeted action and minimal absorption. This minimal absorption provides therapeutic benefits which are noted here and will be discussed further this morning.

[Slide.]

Today's meeting is to discuss rifaximin treatment for the proposed indication of maintenance of remission of hepatic encephalopathy, or HE, in patients 18 years of age or older. The dosing regimen is one, 550 mg tablet taken twice daily.

Rifaximin was first marketed in 1987 and is now approved in 33 countries for numerous indications. It is approved in 22 countries for HE, hyperammonemia, or both.

In the U.S. rifaximin was approved in 2004 for traveler's diarrhea, and we now have five years of postmarketing experience.

In addition, our U.S. development programs include HE, IBS, and acute diarrhea in pediatric patients.

[Slide.]

FDA granted rifaximin orphan drug status in 1998 and we began U.S. clinical studies in 1999. Over many

years, we have worked with experts through numerous advisory panels to develop a comprehensive clinical program.

In December 2004, we met with FDA to discuss the status of the program, which included 19 acute studies and one meta-analysis. A potential maintenance of remission indication was proposed and through this meeting, FDA and Salix reached agreement on the Phase III study design and the primary efficacy endpoint. This included the Conn score and asterixis. The Conn score is the most widely used measure of mental status in HE patients. It is also endorsed by the World Congress of Gastroenterology.

Asterixis grade provides a sensitive measure of neuromuscular function. This became the basis of Study 3001. Based on the success of Study 3001, we submitted our NDA in 2009 and FDA granted us priority review.

As our presentations will demonstrate, the 3001 study data are significant, robust, and confirm a clinically meaningful benefit in accordance with FDA guidance.

[Slide.]

Currently, in the U.S., two therapies are approved to treat patients with HE. Both act to lower plasma levels of ammonia, and although lactulose and neomycin may be

effective, they are limited in their utility for long-term use by issues of tolerability, patient compliance, and toxicity.

Several other agents have been used, but are not FDA approved for HE. Thus, there remains an unmet medical need for a safe and effective long-term treatment for HE.

[Slide.]

There is a long history with rifaximin treatment of HE. There have been 28 published studies and two meta-analyses. The studies noted here investigated rifaximin in the acute treatment of patients with episodic HE.

Doses in these studies ranged from 800 to 2,400 mg per day. These data assisted us with the Phase III dose selection. The three published shown demonstrate the utility and safety of rifaximin treatment in HE over three to six months. The two meta-analyses support the use of rifaximin in patients with HE.

Our Phase III clinical studies included the confirmatory Study 3001 and Study 3002, which is an ongoing, open-label, extension study. The NDA includes data from these eight studies and two meta-analyses, all of which support the safe and effective use of rifaximin in HE

patients.

[Slide.]

Here are the key points that you will hear from our presenters today. Hepatic encephalopathy is a serious, debilitating condition with limited treatment options for which there remains an unmet medical need.

The primary endpoint agreed upon by FDA and Salix of breakthrough HE as determined by Conn and asterixis is clinically relevant. The Phase III study results are significant, robust, and confirm the efficacy and safety of treating HE with chronic administration of rifaximin.

Rifaximin treatment clearly reduced the risks of HE episodes, reduced the risks of HE-related hospitalizations, and the benefit correlates to multiple prognostic factors.

The data are supported by multiple clinical studies and the published literature. Finally, in the U.S., rifaximin represents the first new therapeutic advancement for HE in over 30 years.

Over the next hour, we will discuss these areas in greater detail. Specifically, we will provide an overview of rifaximin pharmacology, a summary of the current

treatment options for HE, reviews of our efficacy and safety data, and we will conclude with a discussion of rifaximin's benefit-risk profile.

In addition to our presenters, we have several experts here today to assist you with any questions.

I would now like to invite Dr. Golden to the podium to present an overview of rifaximin pharmacology.

Thank you.

Rifaximin Pharmacology

DR. GOLDEN: Good morning.

[Slide.]

I am Pam Golden, Director of Development at Salix Pharmaceuticals. Today, I will discuss our data characterizing the non-clinical and clinical pharmacology of rifaximin.

[Slide.]

Rifaximin is in the rifamycin class of antibiotics. The functional group, shown here in green, differentiates rifaximin from other rifamycins and leads to gut-specific activity.

Rifaximin is poorly soluble with low permeability and poor absorption, less than 0.4 percent. It is also the

substrate of P-glycoprotein, an efflux transporter. These properties result in very low exposure.

As a result, orally administered rifaximin is eliminated almost entirely as unchanged drug in the feces. The small fraction that is absorbed is cleared by multiple routes.

Rifaximin undergoes first-pass biliary excretion. There is one known metabolite, nearly undetectable in healthy subjects and at very low levels in HE subjects. And, in both healthy and liver disease subjects, rifaximin renal clearance is low, about 0.3 percent of the dose.

In non-clinical safety studies, at doses up to 125-fold higher than the dose in our Phase III study, no safety signals were observed.

In addressing QT prolongation risk, there were no signals in our clinical studies, and this is supported by the lack of findings in our non-clinical studies, as well as a 3,000-fold safety margin for hERG inhibition.

[Slide.]

Mechanistically, rifaximin binds to the beta-subunit of bacterial DNA dependent RNA polymerase, to inhibit RNA synthesis.

In vivo, rifaximin ameliorates bacterial diarrheal symptoms. The dose concentrates in the gut with approximately 8,000 micrograms per gram of stool. Efficacy in infectious diarrhea occurs independent of the drugs eradication of the infecting pathogen.

This very low systemic exposure minimizes the driving force for resistant bacteria to develop outside the intestine.

[Slide.]

In vitro, rifaximin has multiple effects at sub-inhibitory concentrations, some of which may relate to its activity in HE including curing host bacteria of plasmids, reducing plasmic transfer, and reducing virulence.

Effects observed in mammalian cells include upregulating gut detoxification mechanisms, and stabilizing epithelial cells against bacterial colonization and internalization. These effects may complement antibacterial mechanisms in HE.

Relevant to today's discussion, rifaximin reduces gut-derived neurotoxins, including ammonia, which lead to HE in liver-impaired patients.

[Slide.]

In work published by Ong, discrete venous ammonia concentrations in HE patients correlated with HE grade, supporting the hypothesis underlying antibiotic use in HE for the last 40 years, mainly that increases in gut-derived blood ammonia in liver-impaired patients are associated with worsening HE.

[Slide.]

Rifaximin treatment has resulted in ammonia reductions in several published studies. In this example, 50 subjects receiving rifaximin 1,200 mg/day showed significant ammonia reduction, and this reduction was accompanied by significant improvements in overall median HE grade and individual measures of HE.

Based on these and other similar studies, we measured serial ammonia concentrations in our Phase III Trial 3001. Dr. Forbes will describe those data in his presentation.

[Slide.]

Pharmacodynamics in two previous studies were used to select the dose for RFHE 3001. Study 9702 looked at total rifaximin doses of 600, 1,200, and 2,400 mg per day. Improvements in HE, as measured by PSE, were observed with

similar benefit between 1,200 and 2,400 mg per day.

Small intestinal bacterial overgrowth has been implicated in HE, and in the second study, 1,200 per day showed significant improvement compared to the lower doses.

We chose a twice-daily frequency based on intestinal transit time and the lowest number of doses to maximize patient compliance. A 550 mg tablet size resulted in the 550 mg BID regimen.

[Slide.]

Rifaximin exposure is quite low in all populations studied. In healthy volunteers, mean Cmax is less than 4 ng/ml. AUC and Cmax increase in liver-impaired subjects, however, the considerable overlap in the 95 percent confidence intervals across the Child-Pugh groups underscores that there is no significant difference among those groups, and even at their highest, exposures remain low.

Protein binding is not different among the populations, leaving shunted blood flow and reduced metabolic capability as more likely contributors.

We also looked at the contribution of renal clearance. Our analysis indicated that renal impairment did

not contribute meaningfully to the exposures seen, consistent with rifaximin's renal clearance in HE patients in a study published by Williams.

Overall, our data indicate that liver impairment is responsible for the increased exposure in HE subjects.

[Slide.]

To put this plasma exposure into further perspective, rifaximin exposures are shown here in comparison with other antibiotics. I would like to emphasize that the plasma concentrations on this graph are graphed on a log scale due to the wide differences in exposure among the antibiotics.

The highest plasma exposure of rifaximin are still more than 200-fold lower than those achieved with the systemic antibiotic like Rifampin, shown in yellow. It is also more than 10-fold lower than exposures observed with oral neomycin, shown in white which, per the product's label, is considered to be non-absorbed. The neomycin dose shown here is 4-fold lower than the dose used for HE.

Norfloxacin also is used commonly in this population. It's a systemic antibiotic with plasma exposures greater than 35-fold higher than rifaximin.

[Slide.]

In vitro, rifaximin does not inhibit any major p450 drug metabolizing enzyme, P-glycoprotein, or BSEP at physiologically relevant concentrations.

Regarding potential induction, we looked at rifaximin defect on midazolam, a classic CYP3A4 substrate in healthy volunteers. After 14 days of rifaximin 550 mg TID, a dose that is 50 percent higher than the dose used for HE, midazolam's AUC was reduced by 10 percent. In contrast, rifampin reduces midazolam AUC by 95 percent.

Our in-vivo study supports in-vitro data that rifaximin does not induce 3A4 to the degree that other rifamycins do. Based on our data, we do not anticipate clinically significant drug interactions.

[Slide.]

In summary, rifaximin has bacteriostatic and bacterial modifying characteristics. It lowers ammonia, the neurotoxin most commonly associated with HE. While liver disease leads to increased rifaximin systemic exposure, the highest exposures seen are substantially lower than what is observed with other oral antibiotics used in this population.

This low systemic exposure is associated with a minimal drug interaction risk, and that up to 125 times the proposed human dose, no non-clinical safety signals have been observed.

Rifaximin is distinguished from other rifamycins by its low absorption, low drug interaction potential, and gut-targeted therapeutic effects with limited systemic exposure.

Thank you.

Now, I would like to introduce Dr. Nathan Bass.

Overview of Hepatic Encephalopathy (HE)

and Current Management Practices

DR. BASS: Good morning.

[Slide.]

I am Dr. Nathan Bass, Associate Medical Director of Liver Transplantation, and Professor of Medicine at the University of California, San Francisco.

I would like to disclose that I have received consultation fees, an honoraria from Salix, as well as reimbursement of travel and accommodation expenses.

I was an investigator on the 3001 and 3002 clinical trials. Today, I will summarize the clinical

presentation and diagnosis of HE, its impact and current management. In considering the expertise of the Committee, I will focus on relevant highlights for today's meeting.

[Slide.]

Hepatic encephalopathy, or HE, is defined as a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known brain diseases. HE is a major complication of liver cirrhosis, the 12th leading cause of death by disease in the United States.

HE affects 30 to 45 percent of patients with cirrhosis. It affects cognitive, intellectual, and neuromuscular function, as well as personality, and it ranges in severity from minimal disturbance and cognition to coma.

[Slide.]

Ammonia plays a central role in the pathogenesis of HE. In the gut, bacteria act on nitrogen-containing substrates to generate ammonia, which is normally removed from the blood by the liver, converted to urea, and excreted by the kidneys.

In cirrhosis, vascular shunts and hepatic

dysfunction allow ammonia to bypass the liver, and the increased blood ammonia gains access to the brain where it causes deleterious effects on many aspects of brain function.

[Slide.]

The clinical presentation of HE proposed by the International Working Group on HE is shown in the scheme. HE associated with cirrhosis, the most common by far, is type C, and this is further subclassified into episodic, persistent, and minimal categories.

Episodic and minimal varieties are clinically apparent and hence, are denoted as overt. In contrast, minimal HE is not clinically apparent and requires specialized testing to detect it. Our focus today will be on episodic hepatic encephalopathy.

[Slide.]

Episodic HE presents with impairment in neurological functions that we have discussed and are listed here. There, of course, are periods between episodes when no distinctive symptoms are manifest. Episodes may be precipitated by factors, such as constipation, infection, dehydration, GI hemorrhage, or certain medications. If a

cause is not identified, the episode is referred to as spontaneous.

Episodes are usually reversible with treatment, but they often recur.

[Slide.]

The diagnosis of HE is made in patients with liver disease, as mentioned, after exclusion of unrelated neurologic and other metabolic abnormalities. The diagnosis and care of these patients typically falls to hepatologists and gastroenterologists, physicians who specialize in liver diseases and gastrointestinal disorders.

HE diagnosis is made and the severity graded by assessing mental status based upon clinical criteria using the West Haven or Conn score and the physical sign of asterixis.

Additionally, blood ammonia levels are often measured to support the diagnosis, while neurophysiologic tests, such as critical flicker frequency or EEG, while promising, are largely of investigational use in the United States.

[Slide.]

The Conn score ranges from 0, no impairment, to 4,

coma. Grades 1, 2, and 3 represent worsening impairment in consciousness, intellectual ability, and personality. Information provided by family or caregivers is helpful to gauge HE severity including for past episodes and, typically, patients present with a constellation of symptoms.

Successful management requires swift intervention to prevent further deterioration and hospitalization, so we encourage families to alert us to any worsening in mental status of their family.

If we intervene early, patients with Grade 1 can be managed at home. Escalation to Grade 2 or greater usually requires hospitalization.

[Slide.]

The HESA scoring algorithm is a new tool which has been used to train, reinforce, and assist investigators and their staff in accurate and consistent assignment of the Conn score within and across study centers.

HESA is based on the Conn score, but also includes neuromotor function and neuropsychological testing. This table shows how HESA criteria, shown in the white bars, map to the Conn score, which is shown in the green bars.

[Slide.]

For example, for Conn Grade 1, impaired attention span, computational ability, depression, and construction ability are measured in HESA using formal neuropsychological testing. Thus, by administering HESA, you gain additional objectivity and specificity that helps to establish an accurate Conn score.

[Slide.]

This is the grading system used for asterixis, which is a measure of neuromuscular dysfunction specific for metabolic encephalopathies. If an HE patient is asked to hold their hands hyperextended, thus, one can elicit a flapping or jerky tremor, and the number of beats can be counted and graded according to the simple scheme.

It is simple, but it requires a conscious and cooperative patient.

[Slide.]

Hepatic encephalopathy is a vicious cycle of dysfunction and disability that has a dramatic effect upon patients, families, and the health-care system. Early on, impairment at all levels of neuropsychiatric function affect the patient's family, family life and the patient's ability

to hold down a job.

As the condition worsens, it impacts the capacity for self-care and medication compliance. Lack of compliance further intensifies symptoms and the frequency of episodes of encephalopathy. As a result, the patient may ultimately require in-house assistance and may often land up in the emergency room or in a hospital bed.

In the last decade, HE-related hospital discharges have more than doubled.

[Slide.]

Because of its high recurrence rate and progressive nature of HE, the goals of therapy include resolving acute episodes and preventing recurrent episodes. Thus, there is a need for a safe and effective therapy that is well tolerated and tolerated well for long-term treatment.

[Slide.]

There are two approved therapies. Both target gut flora responsible for ammonia production. Lactulose results in frequent bowel movements. Its limitations include self-titration aiming for two to three loose bowel movements per day, and unfortunately, this goal is commonly exceeded with

a difficult impact upon the patient's quality of life.

Severe diarrhea from lactulose can cause dehydration and electrolyte abnormalities that may further aggravate hepatic encephalopathy, and these factors contribute to a varying efficacy for lactulose, poor adherence, and develop problematic use of this drug for the long term.

With the antibiotic neomycin, long-term use is severely limited by irreversible nephro- and oto-toxicity.

Given the limitations of both of these approved drugs, there is an unmet medical need for the treatment of HE.

Rifaximin has emerged in the setting as a promising option for long-term HE therapy. It has become widely used amongst physicians encouraged by the literature and by their own clinical experience.

[Slide.]

For example, the Cochrane Group published a meta-analysis on the use of non-absorbable disaccharides in the treatment of HE. As part of this analysis, they looked at the efficacy of antibiotics versus disaccharides including lactulose in treatment HE.

Aminoglycoside antibiotics shown in the top part of the analysis showed no significant difference in efficacy from disaccharides. In contrast, rifaximin, shown in the lower half of the graph, showed significant superiority to the disaccharides.

The overall superiority of this meta-analysis of antibiotics versus disaccharides is dominated by the treatment effect of rifaximin.

[Slide.]

Evidence from several small comparative studies of rifaximin in the literature have shown equivalence or superiority for rifaximin. These are three double-blind, controlled studies conducted in subjects with acute HE episodes showing that short-term treatment with rifaximin provides clinical improvement in acute HE with an optimum dose response at 1,200 mg/day as measured by HE improvement.

[Slide.]

Finally, there are additionally two retrospective pharmacoeconomic studies that have shown a reduction in mean hospitalizations and the average length of stay in patients taking rifaximin versus lactulose alone.

The meta-analysis data I have shown you and these

hospitalization studies are part of the reason rifaximin has emerged as a promising option for the long-term treatment of hepatic encephalopathy.

[Slide.]

To summarize, hepatic encephalopathy is a serious debilitating condition which disrupts the ability for self-care compliance and quality of life and results in frequent hospitalizations.

There are limited therapeutic options for HE and there remains an unmet medical need for a safe, effective, and well tolerated therapy for long-term treatment, and there has not been a new treatment for this debilitating disease for 30 years.

I believe the data to be presented today provide a very compelling case for adding this drug to the approved armamentarium for the long-term treatment of HE.

Thank you.

I would like to invite Dr. William Forbes to the podium.

Efficacy of Rifaximin for Treatment of Hepatic Encephalopathy

Dr. Forbes: Thank you, Dr. Bass.

[Slide.]

Good morning. I am Bill Forbes, Senior Vice President and Chief Development Office for Salix Pharmaceuticals.

[Slide.]

Since Dr. Bass has covered the supportive trials, I will focus on the confirmatory trial 3001 and specifically study design and results. I will also try to address the comments raised by the FDA in its briefing document.

[Slide.]

3001 was a randomized, placebo-controlled, double-blind trial. The objective was to assess the efficacy and safety of rifaximin for six months and maintaining remission in patients with documented episodic HE. For the purposes of this study, remission was defined as a Conn score of 0 or 1 at baseline.

299 patients were enrolled in a one-to-one randomization at 70 study centers in the U.S., Canada, and Russia.

[Slide.]

The trial design emphasized continuous surveillance of breakthrough to ensure completeness of

capture. Following screening, subjects entered a treatment period that included weekly visits and/or phone calls. In the event of early discontinuation, all attempts were made to follow subjects for the protocol specified for 168 days.

[Slide.]

Eligible patients generally were recruited within the site's clinical practice; thus, patients had a history with the physician and center staff. The study population can be described as having advanced liver disease, having at least two documented episodes of HE within six months of screen with a Conn severity greater than or equal to 2.

Patients had to be in remission, again, defined as a Conn score of 0 or 1 at baseline. They had to have a MELD score less than or equal to 25 and a caregiver. The protocol excluded patients if they had a condition or used medications or alcohol that could interfere with protocol assessments. Other key exclusion criteria are also listed here.

[Slide.]

The primary endpoint was defined as the time to breakthrough HE episode. This endpoint was met when

patients experienced a worsening in clinical status defined as reaching a Conn score of 2 or greater, or for patients with a Conn score of 0, breakthrough is also met if the Conn and asterixis grade worsened by one point each.

This composite endpoint was used to define a clinical deterioration from baseline in the patient's clinical status.

[Slide.]

The PI was the sole adjudicator of all breakthrough events. During visits, the HESA, Conn, and asterixis were assessed. Outside the clinic, PIs rely primarily on the Conn to establish breakthrough. Patients and caregivers were instructed to contact the site whenever the patient's behavior, clinical status or routine changed. When breakthrough was suspected between visits, PI's attempted to see the patient. When this was not possible the PI adjudicated events based on information obtained from ER and/or hospitalization records, as well as caregiver testimony.

[Slide.]

During visits, study coordinators performed HESA and the PI assessed Conn and asterixis. The PI and the

coordinator discussed all assessments prior to the final decision which, of course, was made by the PI. Visits were approximately 90 minutes in length with the HESA taking about half that time. Symptom-directed physicals, vitals, blood draws, critical flicker frequency, diarrhea review, and patient discussions also occurred.

[Slide.]

Identifying early changes in HE is a challenge for physicians. Conn is the most widely known, used, and taught method for grading HE. But, even with Conn, additional testing is needed to better distinguish these early changes. Our protocol added asterixis and HESA testing to assist with accurate classification.

For a Conn score of 2 or greater, obvious personality changes, inappropriate behavior, and disorientation are present. As we will discuss later, a Conn of 2 is considered an important clinical event that has been associated with mortality in the literature.

[Slide.]

3001 also used a five-point scale to assess the extent of asterixis, a selective neuromuscular symptom of metabolic encephalopathy as mentioned earlier by Dr. Bass.

[Slide.]

HESA provided a structured method for evaluating the patients. HESA gave the PI additional insight into the status of the patient both at baseline and during therapy. HESA, as shown on this slide, combines both clinical components as well as neuropsychological testing. Administration again took some time, but it was successful in adding standardization and accuracy to the Conn scoring.

[Slide.]

We enrolled a total of 299 patients at 70 study centers. 140 were randomized to rifaximin and 159 to placebo. Withdrawal was identical with 24 discontinuing in each group, and only two subjects in each group discontinued treatment without a follow-up through 168 days.

[Slide.]

In general, baseline demographics were representative of the population with advanced liver disease and were balanced between the two treatment groups. The majority of the patients were from the United States.

[Slide.]

Baseline liver disease and HE characteristics are presented here. For this trial, MELD, instead of Child-

Pugh, was used to assess baseline liver condition. On average, patients had a 4- to 5-year history of advanced liver disease, a MELD of 13, greater than or equal to 2 HE events over the preceding six months. Two-thirds had a Conn score of 0 at baseline, and values of ammonia and critical flicker frequency were consistent with the population being studied.

[Slide.]

Now, I am going to present the results of the confirmatory trial.

[Slide.]

For the primary endpoint, rifaximin demonstrated a 58 percent reduction in the risk of breakthrough HE with a high significant p-value. The benefit is striking in that 78 percent of the patients on rifaximin survived six months without an additional breakthrough.

In a sick population that suffers from frequent complications, restricted living, and a shortened life span, rifaximin prevents deterioration.

[Slide.]

Because lactulose was the most frequently used concomitant med, we looked carefully at the use at baseline

and during the study to ensure that rifaximin treatment effect was not modified. At baseline and during the trial, lactulose used between the groups was no different. Therefore, the results being presented are not influenced by the use of lactulose during the course of the trial.

[Slide.]

The primary endpoint is explained here, using a proportional analysis for the components. During the trial, there were 104 patients that experienced a breakthrough event. Eighty-two percent of the outcomes are assigned to a Conn score of greater than or equal to 2. Eighteen percent are assigned to a worsening of Conn and asterixis. Both groups possess a highly significant p-value.

104 events were followed and narratives written from source and medical records. It is from this follow-up that we determined that four of the 19 events in the second category subsequently worsened to meet the criterion of greater than or equal to 2 for Conn. These consisted of three placebo and one rifaximin.

[Slide.]

Consistency in response of subgroups is important in order to infer efficacy across the entire population.

Subgroups point estimates 95 percent confidence intervals and numbers of patients are presented here.

Hazard ratios less than 1 indicate that the outcome favors rifaximin. All subgroups consistently demonstrate the clinical benefit of rifaximin.

[Slide.]

Subgroup analyses by MELD and Child-Pugh also reflect that the effect is not limited by liver disease severity. Importantly, we also tested for a treatment by subgroup interaction to evaluate homogeneity in response across all of the subgroups that I have shown in the last two slides. There is no significant interaction.

In total, all analyses demonstrate a risk reduction in favor of rifaximin.

[Slide.]

This strength of consistency signal across subgroups comprising two geographic regions with 70 clinical center reinforces the reproducibility of efficacy for this valid primary endpoint.

[Slide.]

The FDA has identified a number of questions in its briefing document. I am going to try to address some of

those issues right now.

The first pertains to the validity of the Conn score. When the study was planned and still today, Conn score is the standard of assessment tool for evaluating HE through the clinically meaningful deterioration of mental state.

It is endorsed by the World Congress of Gastroenterology for use in trials and is routinely used in clinical practice, and its use in this trial was agreed upon with the FDA. Over the next few slides, we will address the FDA's questions regarding the accuracy of the Conn score.

[Slide.]

As noted, our protocol used HESA as a method of ensuring objectivity of Conn scores. At baseline, HESA assisted PIs in assigning less impaired HE patients to Conn 0, and more impaired to Conn 1, enabling them to differentiate between the two grades both within and among centers.

Precision is reflected in the significant difference between HESA results for each Conn category. For patients with Conn 1, there are more sleep disturbances, tremor and impaired neuropsych symptoms than for Conn 0.

No patients were enrolled with Conn 2, and, as expected, no patients were classified with HESA symptoms consistent with Conn 2, such as inappropriate behavior or disorientation. Thus, at baseline, patients were in remission defined as not having disorientation or inappropriate behavior. This accuracy at baseline using HESA and Conn score is also seen in post-baseline visits.

[Slide.]

Yet the FDA briefing document includes a table categorizing HE events. The basis of the data in the FDA table is from a data-collection form used in the trial. The form recorded the date of breakthrough and whether symptoms were assessed in person or by review of information provided by others.

The table suggests that approximately one-third were diagnosed in person and two-thirds were diagnosed through interaction with other physicians or caregivers. I have added the last row which includes four patients identified as having breakthrough through the post-treatment follow-up.

The issue raised by the Agency revolves around the source of the diagnosis and whether the events can be

considered equivalent when patients present to PI, hospital, or caregiver. Therefore, we reviewed the corresponding symptoms recorded for each breakthrough and compiled them according to the categorization used by the FDA in order to see if there were differences in the recording symptoms.

[Slide.]

For purposes of presentation, dominant symptoms were collapsed into lethargy and somnolence. Lethargy included disorientation, inappropriate behavior, slurred speech and increased tremor. Somnolence included confusion and personality changes.

As you can see, there are no meaningful differences in the reporting of the dominant symptom. For impaired computation, there are a few patients marked as indirect, however, this assessment can only be done in the office. Thus, we don't believe that this actually the most optimal way to present the data.

[Slide.]

When we reviewed the cases and categorized them by the actual intervention that occurred over the entire presentation of the event, even more events involved PI interaction prior to the event resolution.

Review of the totality of the events indicate that 41 percent were directly witnessed by the principal investigator at the clinic, ER, or hospital prior to event resolution.

Thirty-eight percent were adjudicated by the PI from ER or hospital physician notes, and 21 percent were adjudicated by the PI based on caregiver and patient interviews. Keep in mind, 100 percent of the events required intervention whether by caregiver, PI, or other health care professionals.

[Slide.]

A case review of the breakthroughs confirms that symptoms present across all groupings are comparable and we see strong corroboration between the groups for lethargy and somnolence. We conclude that the symptoms experienced by patients and adjudicated by the PI, whether seen directly, reported by other physicians, or reported from caregivers, are similar regardless of the origin of the information.

[Slide.]

To see if ammonia level and critical flicker frequency would truly correlate with breakthrough, we conducted analysis and divided our population into

breakthrough and non-breakthrough groups. This is regardless of therapy received.

For these analyses, we used a longitudinal approach referred to as weighted averaging. The power of this method is that it uses all available data. We have presented the data as a frequency distribution of the mean values obtained in patients with and without breakthrough, located on the top portion of the slide and, in tabular format, presented below.

Patients who maintained remission are in blue and patients who experienced breakthrough are in yellow. Ammonia, which was collected and analyzed using standardized and centralized laboratory procedures, supports the primary endpoint in that low ammonia neurotoxin levels is associated with no HE breakthrough, and high ammonia is associated with HE.

Similarly, critical flicker frequency, which was collected using standard protocol and equipment, also reflects responsiveness. Subjects with high CFF values reflecting normal optical recognition of light frequencies is associated with no HE breakthrough, and patients with low CFF values reflect altered recognition, is associated with

HE.

This certainly means that our primary endpoint is a reliable parameter measuring HE severity.

[Slide.]

Chronic liver disease questionnaire is a validated tool that has been correlated to HE severity in the literature, and so we also were able to correlate our primary endpoint breakthrough to the patient-reported outcomes using this tool.

Again, patients who maintain remission are in blue, and patients with breakthrough are in yellow. The vertical line depicts the minimum score across all domains at baseline.

Patients maintaining remission from breakthrough also maintain their well-being. In contrast, patients experiencing breakthrough do not. Again, this reflects the responsiveness of the primary endpoint used in the clinical trial.

[Slide.]

Dr. Dimick had made a note in the FDA briefing document which highlights an important HE mortality data published by Stewart, et al.

Stewart has published that patients with a Conn score of 2, who are hospitalized, had a 4-fold increase in risk of all-cause mortality. With motivation from the speaker that had presented in front of you, we wanted to see if the predicted ability of Conn score with regards to mortality were replicated in our data.

[Slide.]

3001 replicated Stewart's data. Subjects in 3001 experiencing a Conn score of 2 or more had a 4-fold greater risk of all-cause mortality when compared to subjects with a Conn of 0 or 1. Then, we turned our attention to see if this association was replicated in the longer term, open-label Study 3002.

[Slide.]

And it was, demonstrating a 2.6-fold increased risk of mortality for patients who achieved a Conn score of at least 2. Stewart's study concluded that HE is an important event in the natural history of cirrhosis predicting subsequent survival.

Analyses from our studies corroborate Stewart's finding and demonstrate that our primary endpoint is both responsive and specific.

[Slide.]

At this time I will return to the results of the secondary endpoints. The first of these is time to HE-related hospitalizations defined as hospitalizations directly resulting from HE, or He occurring during hospitalization.

[Slide.]

With rifaximin, we see a 50 percent reduction in risk with a significant p-value for time to HE-related hospitalization. In order to control for the probability of Type 1 error due to multiple comparison, the protocol outlines a hierarchical analysis of secondary endpoints.

HE-related hospitalizations was the first secondary endpoint in this hierarchy. Once the p-value exceeds 0.05 on a secondary endpoint, the remaining analysis becomes supportive.

[Slide.]

To understand how HE contributed to the key secondary endpoint, we performed some supplementary analysis in order to test the robustness of the findings seen with the key secondary endpoint.

Specifically, we analyzed time to HE-caused

hospitalization, which is defined as time to hospitalization as a direct result of HE and time to all-cause hospitalizations. Rifaximin reduced the risk of hospitalization by 56 and 30 percent respectively, adding to our understanding of how rifaximin reduced HE and all-cause hospital admissions.

[Slide.]

The remaining prespecified secondary endpoints are listed here.

[Slide.]

Time to first worsening and Conn reflects a 54 percent reduction in risk, strongly reflecting the results of the primary endpoint.

[Slide.]

Time to worsening of asterixis show that 35 percent reduction with a trend in p-value. Since the p-value did not meet the protocol-specified 0.05 value, subsequent analyses are considered supportive.

[Slide.]

Again, the CLDQ is a validated patient-reported outcome tool for assessing health perception in patients with liver disease. It uses the 7-point Likert scale with

greater values representing better quality of life.

All domains demonstrate significant differences in favor of rifaximin. This finding is important since patients with hepatic disease have poor quality of life.

[Slide.]

Ammonia and CFF are significantly different between the two treatment groups and reflect improvement in favor of rifaximin. These findings are in keeping with the literature and the understood biology associated with HE; namely, drugs that lower ammonia are effective in preventing and ameliorating the symptoms of HE and positively affect CFF.

[Slide.]

For 3002, we used this open label, long-term dosing to provide us information on long-term efficacy.

[Slide.]

Rifaximin patients who maintained remission throughout 3001 demonstrated continued benefit during 3002. Note that approximately 72 percent of these patients remained free of breakthrough after almost three years of treatment.

[Slide.]

Crossover of 82 placebo-treated patients from Study 3001 were followed in 3002. During 3001, 39 of the 82 had an event over 168 days while only 14 had an event over 168 days in 3002. This reflects an 80 percent reduction in risk.

[Slide.]

In conclusion, the meaningfulness of the results are reflected by a 58 percent reduction in the risk of breakthrough, 50 percent reduction in the risk of HE-related hospitalization, a 56 reduction in HE-caused hospitalization, and this benefit is seen across all subgroups and is well supported by the additional secondary endpoint.

The validity of the breakthrough HE endpoint has been established through correlation to changes in ammonia, critical flicker frequency, quality of life, as well as all-cause mortality.

Long-term therapy with rifaximin is durable and reproduces the findings seen in 3001. The data presented today, along with the literature that has accumulated over decades support the efficacy of rifaximin in treating this debilitating condition.

Rifaximin is effective in maintaining remission from HE breakthrough, the indication sought today.

I would now like to introduce Dr. Naga Chalasani, who will present the safety data for us.

Safety of Rifaximin for Treatment of Hepatic Encephalopathy

DR. CHALASANI: Thank you, Dr. Forbes.

[Slide.]

Good morning. I am a practicing hepatologist at Indiana University School of Medicine, and one of my research interests is in drug safety including hepatotoxicity.

For the sake of disclosure, I serve as a consultant to the sponsor and have received compensation for the time spent, related travel and accommodation.

[Slide.]

In the next 10 minutes, I will review the rifaximin safety database and focus on AEs of interest including C. diff. and hepatic events. We will also discuss mortality including deaths in low MELD categories.

[Slide.]

The rifaximin safety database includes 5,000

patients who participated in different clinical trials.

More than 4,000 patients were exposed to rifaximin including 572 who were in hepatic encephalopathy clinical trials, and there were an additional 3,500 patients who were in IBS and traveler's diarrhea clinical trials.

There were also more than 58,000 patient years of exposure in postmarketing since its approval in the United States for traveler's diarrhea.

[Slide.]

As was discussed by Dr. Forbes, both Studies 3001 and 3002 were well designed and patients were followed rigorously throughout the study. A question was raised in the Agency's briefing document regarding the follow-up of patients who were discontinued upon HE breakthrough.

When a patient had HE breakthrough, he or she was evaluated promptly by the investigator. In addition, all patients had a telephone follow-up at two weeks. Patients remained under the care of the investigator. Any SAEs identified within 30 days reported.

Approximately, 50 percent of the patients who were discontinued from Study 3001 due to HE breakthroughs were rolled over to Study 3002. I believe this assures the

patients who were discontinued because of HE breakthroughs had more than adequate follow-up.

[Slide.]

I will be referencing the data from Studies 3001 and 3002, which is a long-term extension. In 3001, the median exposure to rifaximin was 168 days versus 110 days in the placebo group. Similarly, the rifaximin group had higher total person years of exposure to rifaximin.

Shown in the right-hand column is the all-rifaximin group consisting of both Studies 3001 and 3002 who received at least one dose of rifaximin. This group consists of 348 patients with 347 total years of exposure. This is at least seven times longer than Study 3001.

[Slide.]

As you all well know, the cirrhotic patient population is very AE-prone, but the frequency of AEs, SAEs, AE's resulting in discontinuation were not statistically different between two groups in Study 3001.

Similarly, AEs resulting in deaths were similar between two groups. Again, in the far right column is the frequency of AEs, SAEs, deaths in the rifaximin group, all-rifaximin group from Studies 3001 and 3002. You see higher

numbers reflective off longer-term follow-up of these patients.

[Slide.]

AEs with incidence greater than 10 percent in Study 3001 are shown here. These AEs largely represent what is expected in a cirrhotic patient population. Peripheral edema, nausea, dizziness, fatigue, and ascites were reported more frequently in the rifaximin group whereas diarrhea and headache were reported at higher frequency in the placebo group.

[Slide.]

Shown here are SAEs with an incidence greater than 2 percent in Study 3001. Once again, SAEs were reflective of complications of underlying cirrhosis with no statistical difference between the groups. More episodes of anemia were reported in the rifaximin group. These patients had pre-existing anemia. In three out of four patients, SAE anemia was due to GI bleeding. It should be noted all four patients continued Study 3001, and three out of four were rolled over to 3002.

There were our episodes of pneumonia in the rifaximin group. There was one in the placebo. As was

noted in the Agency's briefing document, all patients with pneumonia had risk factors, such as COPD and chronic smoking, and all patients had relatively uneventful resolution of pneumonia upon treatment.

[Slide.]

There were no differences in hepatic and biliary SAEs in Study 3001 between placebo and the rifaximin group.

[Slide.]

Traditionally, AST/ALT and Hy's rule are used to monitor for drug hepatotoxicity in clinical trials. However, in a cirrhotic patient population, these methods are not valid, because there are baseline abnormalities in these liver tests and fluctuations expected in a liver disease patient population.

Nonetheless, we looked at fluctuations and liver tests, bilirubin, and occurrence of Hy's law in 3001, and we found no significant imbalances. There were some instances of jaundice in Study 3001 but, numerically, they were more so in the placebo group than in the rifaximin group.

[Slide.]

This slide shows AEs by baseline MELD score and by treatment group. The top two panels show AEs and SAEs, and

we see no significant differences between the groups. The bottom two panels show discontinuations and deaths stratified according to the treatment groups and MELD categories, and once again you see no differences between the groups.

[Slide.]

As the proposed indication calls for long-term use of rifaximin, we were interested in evaluating the frequency of infections, and the frequency of infection-related SAEs was not significantly different between two groups.

[Slide.]

Pneumonia and C. diff. are more frequently reported in rifaximin group, whereas sepsis and SBP had a higher frequency in the placebo group. Once again, these types of SAEs are common in this patient population.

In the far right column, you see data combined from 3001 and 3002. As you would expect, due to longer term follow-up, a higher number of patients with infections. But the type of infections is expected in this patient population when you follow them for a year or longer.

Although the incidence of C. diff. was low, we recognize the need to further examine the cases of C. diff.

reported in the studies 3001 and 3002.

[Slide.]

There were five instances of C. diff. infection in both studies together. There were two in 3001, both in rifaximin, and three patients in the open label, single arm study.

You all recognize the cirrhotic patient population often hospitalized, immunocompromised, received antibiotics, plus there is background risk of C. diff. infection. For example, patients prior to enrollment had a frequency of 1.4 percent reported in the past medical history of C. diff. infection, and five patients in the development program had C. diff. infection also giving rise to 1.4 percent.

All five patients had uneventful course. They were treated with usual vancomycin and metronidazole. It should be noted the current label for rifaximin informs prescribers about the risk of developing C. diff. infection in association with antibiotic therapy.

[Slide.]

Turning now to the review of deaths in 3001 and 3002, this slide shows all-cause mortality between the two groups in Study 3001 was not different. There were 11

deaths in the placebo, there were 9 in the rifaximin group. The overall hazard ratio is 0.81, the confidence interval shown there.

Although specific causes of death are not shown here, there were no surprises. In general, deaths were due to typical complications of cirrhosis, such as variceal bleeding, hepatorenal syndrome, and sepsis.

[Slide.]

For the analysis of mortality in all rifaximin patients, we used placebo from 3001 as the historical control, and we controlled for the duration of exposure. The event rate in all rifaximin was 0.1 with a hazard ratio of 0.58 and the confidence intervals are shown there.

These data I believe show that there is no excess mortality in the rifaximin group.

[Slide.]

The Agency noted three deaths in rifaximin patients with low MELD scores at baseline. I want to point out all deaths in 3001 were reviewed by the DSMB that was chaired by Dr. Schiff. In addition, all deaths were independently adjudicated by Dr. Bass and by myself, and none of the deaths were believed to be related to the study

medication.

The three cases outlined in the briefing document by the Agency are shown here. I apologize for the busy slide. The first patient is a 45-year-old patient with multiple medical problems who died and the postmortem showed pulmonary hypertension and dilated cardiomyopathy. The assessment of cause of death is pulmonary hypertension and heart failure.

The second patient is a 69-year-old patient who also had multiple comorbidities who. upon HE breakthrough. chose palliative care and died at home on morphine. We believe it is unrelated to the study medication.

The third patient is a gentleman with alcoholic cirrhosis who was taken off the study because of protocol violation. He admitted to taking Vicodin and tramadol on Day 29, and 10 days after discontinuation from the study, he was found dead at home.

Therefore, based on the review of the cases as well as independent adjudication of all cases, I believe that the deaths noted are unrelated to the study medication. It is also important to note, though, of 11 deaths in the placebo group, six patients had MELDs less than 14 in the

placebo group and, of these, there was one patient with a MELD score of 10, another patient with a MELD of 11. Therefore, low MELD deaths are not limited to one group. They were seen in both groups.

[Slide.]

To summarize, the AEs seen in this study are the ones you would expect from cirrhotic patient population rather than anything related to the compound.

Postmarketing experience also has not revealed any safety signals except for hypersensitivity, which is now addressed in the current label. Therefore, I believe rifaximin has more than acceptable safety in this patient population.

I want to thank you for your attention. Now, I invite Dr. Flamm to discuss risk/benefit ratio.

Clinical Perspective and Benefit/Risk

DR. FLAMM: Good morning.

[Slide.]

My name is Dr. Steve Flamm from the Northwestern Feinberg School of Medicine in Chicago.

For the sake of disclosures, I am a consultant for the sponsor, and I was also compensated for my time in

regards to this meeting.

[Slide.]

My task in the waning minutes is to discuss with you from the clinician's standpoint, the clinical perspective of caring for patients with chronic liver disease and hepatic encephalopathy.

I will discuss with you the impact of encephalopathy on patients, the impact on caregivers, and the impact on the medical care community including the physician who cares for the patient.

Within the context of my position as the Medical Director of Liver Transplantation at Northwestern for nearly 14 years, my practice is comprised mainly of patients with chronic liver disease, many of whom have been afflicted with hepatic encephalopathy.

We have hundreds of patients on the liver transplantation list, and we have performed more than 1,000 liver transplants during my tenure. Most of these patients had chronic liver disease and many of them were affected by hepatic encephalopathy.

It is important to recognize, however, that not only patients getting transplant evaluation have hepatic

encephalopathy. In fact, many patients with chronic liver disease are not eligible for liver transplantation, and still have encephalopathy. In fact, transplant patients represent only a fraction of the patients who have encephalopathy.

First of all, what is the impact of encephalopathy on patients? Dr. Bass discussed the background of hepatic encephalopathy earlier, and I want to expound upon this for a few minutes.

The clinical presentation in patients with encephalopathy is variable. The changes may be subtle, patients may have problems with sleep, overwhelming fatigue. They may have personality changes that are quite subtle. Short-term memory is a problem.

Patients who are normally laid back can become hostile, aggressive, and short tempered, and you can imagine the impact that this has on patients' families and on their coworkers.

Now, the symptoms can progress and patients can, as discussed this morning, develop bouts of overt confusion, which require medical evaluation and frequent hospitalization, and then you can have full-fledged coma.

Now, on top of this, the symptoms often present suddenly and without warning. Patients have normal mentation in between episodes frequently and then, without clear provocation, they can become seriously ill.

So, patients with encephalopathy present with a wide spectrum of problems, many of which can be devastating. So, what is the patient impact with this problem? There is great anxiety. Patients know they are not right even during periods of normal mentation. They often call the medical team and complain of--with the term they use--brain fog.

Their work performance is impacted, accountants can't compute, factory workers forget what they are doing at the factory, pilots can't fly, all this kind of thing, construction workers are afraid they are going to fall.

So, work is impacted. Patients often lose their jobs and then they lose medical insurance on top of it all, which is the critical lifeline for them to actually care for their illness.

Now, on top of this, patients with encephalopathy can't drive. Many states prohibit driving in patients with encephalopathy, and even in states that don't have official prohibition, we as physicians are counseled to instruct the

patients with encephalopathy that they shouldn't drive.

Now, you can imagine the loss of autonomy. These are people that are often very productive normally. They do have bouts or periods of normal mentation in between episodes, and now they can become essentially homebound. They can't even drive down the street a mile to get a gallon of milk.

So, how is the caregiver affected? We often don't focus on the caregiver because we are so focused on the patient. But, because of the episodic nature of this symptoms, the caregivers are also affected in an adverse way. There is great anxiety and fear for them.

Just a few weeks ago, I had a patient who was at home working on his computer. His wife left the room for a few minutes. She came back in the room, and he was slumped over the computer in a coma. He is better now. But now, of course, she is very concerned that every day she goes to work, even though he is normal when she leaves, that something bad is going to happen during the way.

So, she feels compelled to call the patient on an hour basis so that he answers the phone, so that she actually knows that he is well.

In other circumstances, other caregivers are sought, children may be enlisted, neighbors may be enlisted, and they are inconvenienced because they have to check up on the patient routinely.

Then, in other circumstances, caregivers can't be found, so normally productive people who have normal periods of mentation may be committed to a nursing home just because adequate caregivers are unavailable.

And what about the impact on the medical care community and the physician caring for the patient? Well, the financial burden in caring for patients with encephalopathy is clear. Patients are often hospitalized. They require frequent medical evaluation and this, of course, is costly. But even in a larger sense, in caring for patients with encephalopathy, I would submit to you that there is almost a feeling of despair. We don't have good treatment options for this problem.

Our job is to heal people, and we have difficulty doing it for these kinds of patients. So, if we can provide a medical advance, something that can help patients with these symptoms, this would be a significant improvement.

So, what are our options to treat right now? As

you have heard today, lactulose is the standard of care. I believe is you polled key experts in the field, they would tell you that, on an anecdotal basis, lactulose works.

It doesn't work on everybody. The data to support it is not robust, but I think people feel that it works. It doesn't work, though, as I said, in everybody. In Study 3001, this was illustrated well. A large group of patients with a history of encephalopathy who received placebo, 90 percent of whom were on lactulose, had a significant number of recurrent bouts of hepatic encephalopathy on the lactulose.

Now, even worse, lactulose is very tolerated. I believe truly that of all the oral medications that I administer for anything, lactulose is tolerated the worst. It was mentioned that we dose lactulose until patients essentially get diarrhea, two to three loose, watery bowel movements a day.

Of course, this is unpleasant, patients often can't even leave their house for a period of time, because they are worried that a bathroom isn't going to be readily available, and then on top of this, lactulose is an extremely distasteful product.

Now we have used antibiotics over the years in patients that can't tolerate lactulose or in people that have encephalopathy refractory to lactulose. The antibiotics that have been used mainly are neomycin and metronidazole.

They are also troubled by poor efficacy--I should say poor tolerability and side effects, and I believe if you polled key experts regarding antibiotic efficacy, I don't think you would get as favorable of a viewpoint as to the efficacy of these medications for encephalopathy.

So, what about rifaximin? What does rifaximin offer? You know, when we contemplate a medical intervention in medicine, we always have to assess the risk/benefit profile. So, what are the risks?

We have the good fortune in this case of evaluating a product that has already been on the market for many years for another indication, and we have the good fortune of evaluating a product that, in this study, in the appropriate patient population, has been evaluated for a six-month course.

There does not appear to be a safety signal for hepatotoxicity. There does not appear to be a safety signal

for nephrotoxicity which is also important in this patient population. And then what about clostridium difficile?

Dr. Chalasani discussed this topic earlier. This is, of course, a very important topic to consider when you contemplate using an antibiotic over the long term in a patient.

From my review of this data, I would submit to you that it is somewhat controversial whether there is an increased risk of clostridium difficile at all in this population, particularly attributed to rifaximin, and fortunately, even if it is, it seems to be very easily managed by appropriate medical therapy, and it seems to have a very low incidence.

What about the benefit, what potential benefit? Study 3001 had the main endpoints of recurrent encephalopathy and hospitalizations related to encephalopathy. Are these clinically significant endpoints, and is the Conn score an appropriate way to measure them?

Well, I would submit to you these are exactly the clinical endpoints that we need to examine in this patient population and this is exactly how we need to examine it. The Conn score is how we evaluate patients in the clinic.

It is how we determine when to use medications and whether they are effective or not.

Furthermore, the Conn score has been the main endpoint for clinical research trials in hepatic encephalopathy for more than 20 years. We don't really have anything else. In fact, it is unclear to me if we don't use the Conn score what we would use for evaluation for products that might advance this field.

So what did this study show? It showed a significant improvement in quality of life in a group of patients that have impaired quality of life. It also showed reduced recurrent hepatic encephalopathy of 58 percent and it showed reduced hospitalizations related to encephalopathy of 50 percent.

I believe there is an undeniable benefit in this patient population with rifaximin.

So, in summary, for the clinician, hepatic encephalopathy is a major problem. We are currently limited by our treatment options. Rifaximin for this unmet medical need offers a significant benefit and a minimal risk.

Consequently, I believe that rifaximin represents a significant advance in this field.

Thank you.

Conclusion

DR. FORBES: That actually concludes our presentation. I would like to turn it back over to the Chair.

Questions to the Sponsor

DR. RAUFMAN: We will now ask if the Committee has questions for the sponsor. Dr. Haubrich.

DR. HAUBRICH: I have a number of questions, but perhaps I will just start with the main issue at hand here, and that is the assessment of the endpoint.

You have a slide in here that details how the HESA clinical assessments were used to define the Conn score. Can you give me more details about the training that was done for the coordinators and investigators in performing these neuropsychologic evaluations, how they were recorded, and how the investigators then used this data to come up with the overall Conn score rating? I will stop there for my first of many questions.

DR. FORBES: I am going to ask Dr. Hassanein to address the HESA training that occurred during the course of the trial. I am going to put up for you the slide from the

core efficacy. Prior to getting into the HESA, regarding the Conn and also just in general, for training, there were investigator meetings that were held, that investigators and coordinators were required to attend, and if they didn't, it had to occur in person.

So, the training around the Conn and the conduct of the trial was done through investigator meeting, as well as web access that were conducted throughout the course of it, and obviously, the trial was monitored according to GCP criteria. So the Conn definitions and the asterixis definitions we used videos and cards and training. Also, some of them that you have already listened to this morning to make sure that everybody understood what the endpoints were for the Conn.

For HESA, we asked Dr. Hassanein's group to actually do this, I am going to ask him to address the HESA training.

DR. HASSANEIN: I am Tarek Hassanein. I am Professor of Medicine at University of California, San Diego. I am a hepatologist, gastroenterologist, and a transplant pathologist.

I am a consultant for Salix, and I was remunerated

for my effort, and occasionally, I give talks that is funded by their company.

The HESA, the Hepatic Encephalopathy Scoring Algorithm, was developed to give objectivity to the Conn score, so we took the Conn score and we adapted into what we call the HESA algorithm.

The whole idea was to turn the Conn score into a more objective tool to define the different grades of hepatic encephalopathy and different grades between these patients.

Over the last 10 years, there was a lot of effort. We developed a few years ago a training tool for the HESA and, for that specific study, we had our neuropsychologists and trainers train the study coordinators, the investigators in a structured training method on how to introduce the HESA, how to score the tests, how to fill the forms, and, accordingly, how to reach which grade of hepatic encephalopathy the patient is presenting in.

During that training course with the investigators and the coordinators, after the initial training, all of them went through testing, and as much as I remember, three cases, and they were evaluated and given certificates that

they completed the training.

So, from my experience with this, we give them an extensive training on how to score, how to fill the forms, and how to reach the final hepatic encephalopathy grade.

DR. FORBES: Does that answer your question?

DR. HAUBRICH: Yes. So, just to be clear, the scoring system had specific tasks that had to be done, and they used those to develop a Conn score, say, and each time a coordinator or an investigator went through. And it looked like there were some digit spans, Hopkins Verbal Learning, stuff like that, those were all filled out and then the Conn score was derived from those?

Is that something there is a chain of data that could be looked at? Somewhere in the briefing document, it said that that data wasn't available for review, but the case report forms just have the actual score, but it would be important to go through the trail to make sure everybody filled out all those forms, the HESA scoring the same, that then led to the determination of the endpoint.

DR. FORBES: Yes. Can I actually have the last slide back up again, please.

[Slide.]

I just want to point out that the HESA originally, when we implemented it and got all the sites going with it, which was very, very early in the study, really from almost the very first patient we had, the HESA was utilized.

When we got everybody to record these, we left them in the source documents, and the intent was always to do it, so they were recorded on standard forms, and they were conducted--as Dr. Hassanein mentioned, they were conducted in standard fashion. We were retrieving them for purposes of mining the data at a later time.

Obviously, with the issues that were raised in the FDA briefing document, we are presenting for you today the data that we have available to us right now, which correlates obviously with the Conn now.

I think the important thing about this diagram that we presented today is that you understand that the PI made the assignment of Conn, but they did it in collaboration with the study coordinator who performed the HESA training. So they were able to see whether or not there were minimal changes between Conn 0 or 1 or beyond with that kind of collaboration.

Ultimately, the decision on the Conn was the PI's

decision, but the coordinator conducted the HESA.

Does that help you?

DR. RAUFMAN: Dr. Lockwood.

DR. LOCKWOOD: In a somewhat related question, this is one of the unusual features of this study was the very large number of study sites and investigators who participated in this.

Do you have any data about inter-rater reliability on the Conn score and the HESA scoring?

DR. FORBES: Dr. Bortey, would you like to answer this question? Enoch Bortey is our head of Biostatistics Data Management and Programming.

DR. RAUFMAN: I would just like to point out that there is a microphone over there, so people don't have to walk all the way around.

DR. BORTEY: Enoch Bortey, Associate Vice President, Biostatistics, with Salix.

We have some data to share with you on this issue.

Could I have the slide?

[Slide.]

We didn't really conduct extensive analysis on this, but for all the methods of diagnosis, and across data

from all the centers, as you can see, it is very easy to deduce from the visual impression that the sites were consistently measuring the Conn accurately.

We haven't done, like I said, extensive analysis, but this data really addresses the fact that there is no variability within and among the study centers.

DR. LOCKWOOD: I am afraid I don't understand the response to the question. Could you be a little more specific as to how this shows the consistency?

DR. BORTEY: Well, this represents overall within all the centers, so what I am showing you here is the group data, and what I am saying is that based on the group data, we don't see any variability, because the data is coming from different sources, and from all the sources we don't see variability, because they are all giving similarities instead of variability.

From this we deduced that there are no really differences within the centers and across the study centers.

DR. FORBES: Can I have CE-22, please. I will try to answer this question, if I can. I think, Doctor, your question has to do with whether or not the Conn assignment to the HESA scoring is reliable; is that correct?

DR. LOCKWOOD: If multiple observers saw the same patient, would they all assign this patient to the same Conn score?

DR. FORBES: And you are right, with 299 patients coming from 70 centers, that is why we gave certificates to the coordinators, so they had to be trained on HESA in order to administer it. But we haven't done that formal analysis yet to make sure that we have.

DR. RAUFMAN: Dr. Gitlin.

DR. GITLIN: Thank you. Further to the lack of objectivity in some of the parameters--most of them are subjective--I just want to know why the number connection test or the alphabet connection test, which are reliable objective tests, were not performed, and likewise, why asterixis just had the very vague definitions of rare, occasional and frequent rather then a numerical number permanent.

Thank you.

DR. FORBES: Let me handle the asterixis question first. There was a video that actually was used to help the investigators and the coordinators, make sure that they understood exact definitions. With asterixis, the

investigator was actually told to do that. So there were definitions that were provided specific to the asterixis scoring.

Your question regarding the number of connection tests and some of the other tests that could be done at the time of breakthrough, that is my understanding.

DR. GITLIN: As an objective evaluation, yes, why you didn't do that number connection test, which is time stood and well documented, and the alphabet connection test, yes.

DR. FORBES: Of course, we did all of the tests that were associated with the HESA training that were included in the slide that I presented earlier, it was also discussed. I mean the breakthrough events could have occurred at home, they would have occurred at the hospital or the ER, and, of course, some of them occurred at the center when the patient was able to be transported to the center.

Of course, many of these patients started to break through in one location and ended in a different one. So we applied the HESA when we could, when the patient was available to the center. But, if they weren't, then, trying

to do those tests in assorted ERs and hospitals was something that we just didn't undertake. We had to rely on the symptoms associated with a Conn breakthrough.

That is why I mentioned earlier that really when the subject underwent a breakthrough outside of the clinic, the symptoms, the overt symptoms really became the driving force for the determination.

DR. RAUFMAN: Dr. Dasarathy.

DR. DASARATHY: I recognize many of the difficulties of assessing, but I think the reason why we are all focused on it is the whole study seems to be based on the improvement on these scores.

So, when you claimed to these coordinators, were they done once, or the study was done over an extended period of time, and if I do my math right, you had probably three patients per center. If you had only three subjects per center, you know, they are not seen there very often, were they called in again, and were they reassessed to see if they remembered what they were told on in the first instance?

The second question that I had was that we all recognize that assessing the mental status of patients with

encephalopathy varies over time. When I say "over time," there is diurnal variation, there is cyclical variation, and if I bring in somebody at Week 2, do I assess him at the same time of the day, has he had breakfast or not, was there a standardized way of assessing these people?

The last question I had was a follow-up on what Alan has said, which is were these coordinators all assessed in a centralized place to make sure that their inter-observer variability was minimized.

The earlier questions were focusing on intra-observer variability, you know, whether they remembered what they were trained, you know, 50 weeks ago or 80 weeks ago.

The second is, you know, you have people who don't speak English, and you are comparing them with people who speak English, and I am not sure whether you had a Russian training session or you had only an English training session. How were these adjusted for?

DR. FORBES: I am going to have to ask Dr. Hassanein to come up again, but I will just try to handle some of the questions that you have asked.

Again, I emphasized investigator meetings because that is where the first training occurred for the

coordinators. If coordinators were to assess a breakthrough with HESA, they were asked to do--they had to be trained in order to do that, so that training had to occur. So either somebody had to travel to the site to train them and provide the certificate of training, or they had to get it at the investigator meeting.

So, from that perspective, they were all initially trained. As the study went on, there were web access that were conducted with the study coordinators that reinforced the principals around how to do this and got them on the phone and on the web together in order to do that.

Of course, there were frequent visits by us and the monitoring company to make sure that we reinforced these things as we went.

Dr. Hassanein, I don't know if you can help me with a few of these questions, and then, I will try to pick up the ones that we don't cover.

DR. HASSANEIN: These are very relevant and very important questions we all face in our patients. The due diligence that was done in training the individuals, whether the PIs or the coordinators, study coordinators, at the different centers was done to standardize how the approach

or how they do the tests.

They were guided by special forms that they fill out as they to through the tests, and they were guided by protocol how to conduct the tests. Most of these tests can cross through different languages. They are enumerating numbers backwards, forwards, or letters.

Maybe one of these tests that might have an issue with translation, and that is a test that reflects the media. But, at any level, we didn't depend on one test to assign an individual the level of hepatic encephalopathy, to achieve at certain level. There is more than one test that has to show that the patient belongs to that level.

So, if there is a difference in one test, it might not make a big difference because you have to depend on other tests. It is a composite of tests.

So, I hope that could explain that. The inter-observer variability, to my knowledge, I don't know the data from the study, but it has been done and published before using the tests, and it is minimal.

DR. RAUFMAN: Dr. Hersch.

DR. HERSCH: My questions were similar and concerned inter-rater reliability.

So, my first question is were there unusual changes in either coordinator staff or investigator staff. Stability, in part, depends upon having the same investigator or coordinator doing the same rating in the same way.

Secondly, I know there were tests which I assumed were cases of HE that were scored by the investigator or the coordinator in their training. Was that done again after the study to look at whether there was stability in how the coordinators and investigators performed their ratings?

DR. FORBES: As far as investigator turnover, I am not aware of any off the top of my head. I don't think there was any PI turnover, so the end responsibility of adjudicating all the endpoints maintained stable throughout the course of the trial.

According to turnover, I believe it was fairly minimal. I am sure there were some cases where that occurred, but again, we sent people out to the center, the training center, to make sure the coordinator understood what he or she needed to do and made sure that they were trained on HESA prior to utilizing it.

From that perspective, we just tried to handle it

when it occurred.

DR. COHEN: Hi. Jeffrey Cohen.

DR. RAUFMAN: I would like to remind the members of the Committee to please wait to be recognized by the Chair.

DR. COHEN: I am sorry, I apologize.

DR. RAUFMAN: Dr. Cohen.

DR. COHEN: Thank you. Thank you.

Following up on one of the questions, as a clinician, when a patient has an encephalopathy, the course does change over time. I think the question was raised. So how is that factored in a patient's clinical status changing over time?

DR. FORBES: I think the "time to" factor on this study, if you will, since it's a time-to-event study, was recorded, and that is where a lot of the check boxes were completed as to where the source of information was obtained relative to when the breakthrough was believed to have occurred.

One of the reasons we went back and looked at whether or not the PI himself or herself actually saw the patient because these breakthroughs went on for a period of

time in many instances.

So, while the breakthrough could have occurred at home, with the patient having completely inappropriate behavior and disorientation, we end up with the investigator seeing them in the hospital and evaluating them there.

But what we did is we recorded the breakthrough, so the designation of greater than or equal to 2, or a change in 101 was done at the time the diagnosis was believed to have been made. That may have been done in person, in front of the PI, or just adjudicated at that point, but seen later by the patient, still while breaking through.

DR. RAUFMAN: Dr. Maxwell.

DR. MAXWELL: Yes, thank you. I have a question on a different aspect. I am looking at the reported data that the systemic absorption of rifamixin is fairly low in normal, healthy volunteers, and it is somewhat higher in patients that have hepatic dysfunction.

But I wanted to know if you had any additional data on patients that in addition to hepatic dysfunction, had any intestinal abnormalities, any chronic colonic illness or anything, what the absorption would be then. Do

you have any data on that?

DR. FORBES: No, I am afraid I do not have any data on that. There were very few patients enrolled in the study that had those types of conditions.

DR. RAUFMAN: Dr. Kumar.

DR. KUMAR: I have a question related to assessment of hepatic encephalopathy, as to why a more objective neuropsychiatric assessment wasn't utilized.

A question that was asked before, to which I didn't sort of really hear an adequate answer, and it was also sort of brought up in the briefing document, and those tests which are fairly reliable, just number connecting test or the trails-making test, why was that not used at baseline and at the intermediate points for assessment of encephalopathy, which would have introduced I suppose more objectivity with regards to assessment?

Thank you.

DR. FORBES: I am actually going to ask Dr. Butterworth if he could stand and be recognized, and answer this question. I believe Dr. Butterworth can answer this question, and we have a number of other experts that have been involved in the working party for the World Congress on

selection of Conn, as well.

DR. BUTTERWORTH: Yes. My name is Roger Butterworth. I am Professor of Medicine and head of Neuroscience at the University of Montreal.

I will attempt to answer the question from the standpoint of the number-connection test to start with. The number-connection tests is used nowadays as a way of quantifying subclinical of minimal hepatic encephalopathy. This was a group that was not enrolled or not identified in the study we are talking about

We did some additional studies. I think the reason for the asterixis grading was to bring in an element of specificity to this trial because metabolic encephalopathies, in particular, have a very high incidence of asterixis.

Also, what was included was the critical flicker frequency. We have a couple of slides on that if I could bring them up. CFS.

[Slide.]

Critical flicker frequency, which is increasing being used not so much in multicenter trials yet, but is being used in Europe to quantitate encephalopathy grades.

With critical flicker frequency, this is the ability to discriminate the flickering of a light beam, ability to discriminate flickering light as a function of light frequency.

Its basis is that there exists in this group of patients, and certainly in animal models of this condition, a retinal gliopathy where the Muller cells in the retina undergo morphologic changes, and this, associated with cerebrocortical dysfunction, is supposedly at the origin of this inability to discriminate flickering light. This critical flicker frequency has been used increasingly because of its objectivity and its sensitivity and its reproducibility.

[Slide.]

It is still a long way from being used in all clinical trials, and is not yet validated completely, but here I included this slide just to show you how it correlates with the Conn scores of HE0, HEI and HEII, as you can see on this graph here.

That is, as the encephalopathy grade particularly when these early grades worsens, we get a critical flicker frequency Hertz value that decreases continually in this

way, and there is a very good correlation between the Conn score and the HEI and HEII grading on the Conn score and the critical flicker frequency cutoffs.

I will just repeat again the SHE, which is nowadays called minimal hepatic encephalopathy, grade that was not a grade identified in this study, but it is a grade that would be identifiable with number-connection tests and neuropsychometric tests of this nature.

I am sorry, I forgot to point out I am a consultant for Salix and have received remuneration to come to this meeting today.

DR. FORBES: So, when the study was planned, the use of Conn was believed to give us something that was clinically meaningful and tied to things like the critical flicker and ammonia to be able to be shown to be predictive.

So the definition that we used in it, as I have gone through my presentation, showed that the ammonia and the critical flicker, as well as the quality of life, all validated tools of assessing different severities of HE, correlate with our breakthrough definition. And then, of course, the last piece was the mortality that I spoke to earlier, is that it is clinically meaningful because when

patients have a Conn score of 2, that is a bad sign of potential impending death. Stewart showed that, and our data also would suggest that that is the case.

DR. RAUFMAN: Ms. Cryer.

MS. CRYER: Thank you. I first have a corollary to sort of my colleague's questions and then an original line of inquiry.

First, since such a large proportion of the data was assessed from phone calls and based on caregiver assessments, what training was given to the caregivers, and then secondarily, since many of the underlying studies showed an optimal dosage at 1,200 mg daily, please help me with the decision-making to propose the dose for 1,100 mg daily.

DR. FORBES: Okay.

Do you have a slide on the caregiver training?

The protocol actually goes through the caregiver criteria that are used. Obviously, it had to be somebody that was close to the patient, that knows the patient, sees them frequently, doesn't live with them.

When we initiated the study, there were a number of things that we did to make sure that the caregivers were

provided ample information. We told them to basically monitor for changes in the subject's health and status.

Of course, they had to sign the consent form to be the caregiver, so that was the other thing. All the IRBs required, as the protocol did, that the caregivers also signed the consent. They had to assist with subjects attaining scheduled and unscheduled study visits.

Now, that doesn't mean that they had to come to every single visit. But oftentimes, because these patients can't drive, they did show up to visits; but keep in mind that the caregivers oftentimes are perhaps the spouse of the patient and they had to go to work, so occasionally, other people would bring them.

There were certain visits that were designated where the caregiver had to be present. The caregiver was given information, contact information and guidelines, as you see in this slide, to make sure that they were making sure that the patient was completing the diary, and completing it accurately, that they were making sure that the patient was taking the medication including lactulose, if they were on lactulose, and then, of course, they provided the information to contact the site at any time

were there a change in status or behavior of the patient.

That is how many of these patients were first found to have a breakthrough event. I think one of the unique things about this particular study in this field is the use of the caregiver to make sure that we have consented them along with the patient, and that really it required two people to participate in the study along with the study staff.

That may be typical in neurological fields, but it hasn't been the case in this field, to my knowledge.

MS. CRYER: The second question?

DR. FORBES: The second question was?

MS. CRYER: The second question was determination of the dose of 1,100 versus 1,200?

DR. FORBES: I am sorry, thank you.

Looking at the dose-response data that Williams et al. published, we looked closely at that. That was, of course, in a patient population that had an acute breakthrough. The doses that were used were 6-, 12-, and 2,400 mg per day in three divided doses.

In the acute setting, what we looked at, and found, is that really the 1,200 mg seemed to be the minimal

effective dose. There was no control group there. So, it was just 6-, 12-, and 2,400.

Also there is a lot of empiric evidence that 1,200 is a pretty good dose to use in this patient population, and also there has been a growing interest in small intestinal bacterial overgrowth in this patient population, and there have been some studies looking at small intestinal bacterial overgrowth that have looked at dose ranging and eradication of the bacteria in small intestinal overgrowth.

So, based upon those dose selections, we felt that somewhere in the range of 1,200 mg a day was the appropriate dose to try to use for prophylactic study long term and, from that, we tried to formulate a single tablet, and we wanted to get to BID dosing because we felt BID dosing in this patient population that has challenges with compliance was really key.

That got us to a 550 mg tablet given twice a day, and that is how we arrived at it. But we don't have, for a maintenance of remission study, a dose-response trial.

DR. RAUFMAN: Let me ask a question. Am I correct that in 3001, 90 percent of the patients were taking lactulose during the study?

DR. FORBES: That's correct, 91 percent.

DR. RAUFMAN: So, what is the evidence that rifaximin alone is beneficial for this indication?

DR. FORBES: If I could have the meta-analysis back up for just a minute.

[Slide.]

When Mr. Dobrowski was up here showing the studies that were included in the NDA, he mentioned a number of 3-month, and one six-month study that was conducted previously, back in the '90s.

DR. RAUFMAN: Let me stop you for a second in the interest of time. So, in 3001, what is the evidence of efficacy for rifaximin alone?

DR. FORBES: In the subgroup analysis, the point estimate goes in the same direction, the 95 percent confidence intervals overlap with one. For the patients that are not taking lactulose but receive just placebo or rifaximin--so the efficacy is based upon the fact that the point estimate moves in the same, actually, a little bit to the left of the lactulose/rifaximin group.

I will show this slide to you. It's about midway down the slide.

[Slide.]

Prior lactulose use and no prior lactulose use. A total of 26 patients that did not take lactulose during the course of the trial.

DR. RAUFMAN: I think we have time only for one or two more questions.

Let me ask Dr. Solga first since he hasn't asked any.

DR. SOLGA: Thank you, Dr. Raufman. I am very excited to shift gears and to ask this question of Dr. Bass. The slide you show on the second page, showing mechanisms. We all want biologic plausibility and, as you know, over the last century or so, there has been this silly circular logic in the literature that says ammonia matters for encephalopathy because lactulose, a treatment for encephalopathy, lowers ammonia, and then the other half of that circle is lactulose is a treatment because it lowers ammonia. But neither one of those are well supported.

As you know, as well, Ong's slide, which was shown previous to you by Dr. Golden, may be one of the only published slides, studies, that really show correlation between ammonia levels and encephalopathy grade.

So, we want to tell a story here, and I have shown that same slide in my own fashion to medical students and residents for years, saying gut-derived ammonia matters to encephalopathy, our goal is to reduce it. But I usually tell them this is a story of half-truths or even outright lies, because we just don't know.

I am afraid that we almost have a too simple path here, biological plausibility, that is sort of being spun out again. Over the last decade, most of the research in encephalopathy is running away from that. It has been looking at ammonia physiology and other matters, looking at glutamine in the small bowel, inappropriate deamination in the muscle tissues, and then inappropriate disposal by the kidney.

So, we have been moving away from the colon towards other tissue beds, and the other main line of research over the last decade has been looking at inflammation and cytokine signaling as triggers for encephalopathy.

So, peeling away, you are only getting away from rifaximin. In 2010, do you really believe that colon-derived ammonia matters for encephalopathy?

DR. BASS: Thank you. That is an exciting question, but it addresses I think the work that we have ahead of us for the future. Clearly, there may be other mechanisms other than the suppression of ammonia production by bacteria through antibacterial production.

As you point out, antibiotics may have other mechanisms including the prevention of production of other encephalopathogenic substances. Some are being raised, such as benzodiazepine-like agents, steroids, We don't know. What we do understand is that focusing in that area has been productive and shown on impact.

I believe the Ong data--which I am trying to bring up here for you--certainly shows that there is a correlation. But, of course, there are limitations to the usefulness in each individual patient.

There are other studies that I am aware of in which the correlation with ammonia has been shown. So, this is the best data that we have in terms of mechanisms, in terms of inflammatory process, in terms of location of the gastrointestinal tract.

More recent data has suggested that small intestinal bacterial overgrowth is increased in patients

with cirrhosis and that the prevalence of this correlates with the severity of cirrhosis and the prevalence of hepatic encephalopathy. So this is another area in which there may be an important impact.

Thank you.

DR. FORBES: I would also like to quickly add that the data that is shown there is just a single acquisition of ammonia. What we have tried to show is more serial.

DR. RAUFMAN: Dr. Rehm.

DR. REHM: After that profound question, this will seem quite trivial, but I wondered if you could go back to C5-13, the infection SAEs, and tell me what organisms cause the SAEs and whether there were any resistance patterns of significance.

DR. FORBES: I will ask Dr. Chalasani to address this. We didn't actually collect the organisms on these. But, of course, we do know from the hospital records some of the organisms responsible.

DR. CHALASANI: For the cases of pneumonia, I do not believe there is bacteriology, and the same thing with cellulitis. I can't on top of my head talk about the urinary-tract infection organisms, but we should be able to

get that for you after the break.

I think sepsis also, but we will be able to bring that to your attention.

DR. RAUFMAN: Dr. Haubrich.

DR. HAUBRICH: So, getting back to the considerations of the endpoint here, I think, fundamentally, what we have all alluded to is that there might be heterogeneity and imprecision of assessment of the endpoint.

So, one would consider--one would have to then say what would be the impact of that on the overall results of the study.

Consider that in the placebo group, the true endpoints without bias or without variability was 20, and in the treated group that was 10, so a 50 percent reduction.

Now, let's say we add on endpoints due to just heterogeneity or noise, and let's say we add to each group 30. That would then lead to 50 endpoints in the placebo group and 40 in the treated group.

So, if there is no bias in assessment of the endpoints, at least that should have a conservative bias rather than a non-conservative bias, and should tend to diminish the difference between the groups.

So, my question is, is there any evidence that anybody has seen in reviewing the data and reviewing the case report forms and monitoring, or in the FDA's review, that would suggest that there was bias in the assessments.

In other words, did our double-blind, placebo-controlled study remain true so that, even if there were noise in the assessment of the primary endpoint, that would happen on a non-biased basis?

DR. FORBES: Well, I am certainly not aware of any analysis that would suggest that bias is the reason for this. We have gone to great extent to try to show all the analyses that we possibly could in 20 minutes, and all of it goes in the same direction.

I will tell you from living with this data for the last year, I cannot see it.

DR. HERSCH: A quick question. Was there a blinding assessment done or have there been blinding assessments at this dose in the past?

DR. FORBES: Blinding assessments in what respect?

DR. HERSCH: Of whether subjects or investigators knew or had an idea of the identity of the study drug.

DR. FORBES: Monitoring through the course of this

trial, also doing IBS work with this drug. This drug is very well tolerated, so it doesn't have an adverse event that is rarely identifiable to patients or to caregivers.

DR. HERSCH: An assessment of that wasn't looked at specifically.

DR. FORBES: No, not a specific assessment.

DR. RAUFMAN: Dr. Anderson.

DR. ANDERSON: Yes, I have a question. Were there any deaths observed before a patient had a breakthrough episode, and if so, how were those deaths treated in the primary efficacy analyses?

A related question is, could you describe the censoring generally that was used in the analyses and how that is consistent with an intent-to-treat principle?

DR. FORBES: I am going to ask Dr. Bortey to come up and answer the statistical questions regarding how deaths were handled. The simple answer to your question on deaths is that there were nine deaths on drug or within 30 days for rifaximin and 11 for placebo.

Of course, through the entire follow-up, we collected it through 168 days if somebody terminated early.

DR. BORTEY: We have done a sensitivity analysis.

The primary analysis states it will count time to the event, so time to death, if you died before 168, you are censored.

However, if you discontinued the study prematurely, you are followed, you know, for the duration of the study, so we have complete capture on everybody.

For this sensitivity analysis, anybody who died during the study we assume they had breakthrough, and the outcome, as shown here, this really reflects the analysis. So here, if you have breakthrough or you died during the course of the study, we assume it is due to breakthrough, and the risk reduction is the same ballpark as the primary analysis.

So these dropouts or deaths really have no impacts on the final outcome of the study.

DR. FORBES: Thank you.

DR. ANDERSON: I am sorry, I am not quite sure I understood your answer. So, in your primary analysis that you showed earlier, deaths were not considered as an outcome?

DR. BORTEY: No, no, in the primary analysis, no, no. I mean, we know the cause of death. If the cause of death is attributed to HE, then, it is counted as HE, very

true. But, if not, you know, like the safety presentation illustrated, most of that due to underlying liver disease. So, that really does not reflect very true. So the primary analysis is produced not taking care of death as the truth.

DR. ANDERSON: So, if it was an HE-related death it was counted. The Conn score doesn't include a death in any of its categories, but it was counted as an event.

DR. BORTEY: Yes, yes.

DR. ANDERSON: And then censoring more generally, in the primary analysis you censored when individuals stopped their therapy, correct?

DR. BORTEY: The censoring really reflected four patients who were lost to follow-up, two in placebo, two in rifaximin group. Besides that, the censoring reflected those who died during the course of the study, six on rifaximin, three on placebo.

Anybody who exited the study prematurely was followed, so there was no bias at all in the assessment of breakthrough. So, everybody who dropped was followed, we have complete capture on everybody.

DR. RAUFMAN: To stay on time, I am going to ask Silberg to ask the last question. There will be another

opportunity for questions later on.

Dr. Silberg.

DR. SILBERG: Thank you.

We are asked as the Committee to look at the adequacy of the primary endpoint, the methodology. Could you please expand on what regulatory interactions you had with the FDA prior to starting the study that was the agreement on using this endpoint and the methodology for the protocol?

DR. FORBES: Okay. May I have the regulatory back up.

[Slide.]

In December of 2004, there was a meeting that was held between the GI Division and Salix. Some of this was actually presented in Mr. Dobrowski's presentation.

There was a back and forth around the use of Conn. Conn seemed to be always from the review of the back and forth that occurred. Conn seemed to be acceptable to both the Division--although I don't want to speak on their behalf --but it seemed to be, from our opinion leaders the information available to us in the World Congress, Working Party recommendations and guidelines of doing clinical

trials or assessing HE--Conn seemed to be the standard thing to start with.

The question of what constituted a breakthrough and a change that was meaningful in a patient's status, we proposed a greater than 2, and one of the things that the agency suggested is that we might want to add asterixis to it, and some of that was based on the data that had recently been presented at ASLD, Dr. Bass' previous study that was done in an acute setting.

So, we thought about this and in talking to our thought leaders that were going to be conducting the study, one of the concerns they had were patients that had started to progress, started to deteriorate. They wanted to intervene and get involved with the patient quicker, before there was a patient that went on to a Conn 2, 3, or possibly even a 4.

There were three patients that went on to a Conn status of 4, which is coma, and two were on placebo, and one was on rifaximin. So, the use of the 1 and 1 criteria was to catch those patients before they actually got to the point to where we felt they were going to need to be hospitalized.

As you know from the data, about 50 percent of the breakthroughs end up getting up getting hospitalized, so the back and forth that occurred with the Agency was around the specific endpoint and used for a trial to maintain remission and using these definitions for breakthrough.

Does that help you?

DR. SILBERG: Yes.

DR. RAUFMAN: We will now take a 15-minute break. We will reconvene again in this ballroom in 15 minutes at 10:30 a.m. sharp. Panel Members, please remember that there should be no discussion of the issue at hand during the break amongst yourselves or with any member of the audience.

Thank you.

[Break.]

DR. RAUFMAN: Before we start, could I ask, I think Dr. Brass, Dr. Dimick, Dr. Korvick to introduce themselves. They came in a couple of minutes after we started.

DR. KORVICK: I am Dr. Korvick. I am the Deputy Director for the GI Division for Safety.

DR. BRASS: My name is Steven Brass. I am Co-Director of Sleep Medicine at UC Davis in Sacramento,

California.

DR. DIMICK: Lara Dimick, Medical Officer for the FDA.

DR. RAUFMAN: Dr. Hilton also.

DR. HILTON: Joan Hilton, Division of Biostatistics, UC/SF.

DR. RAUFMAN: Thank you.

We will now proceed with the FDA Presentations.

FDA Presentations

Clinical Review of Safety and Efficacy

DR, DIMICK: Hello, I am Lara Dimick, Medical Officer with the Division of Gastroenterology Products.

[Slide.]

I will be presenting the main body of the FDA review today, and Dr. Mani, our neurologist from the Division, and Dr. Kim, our clinical pharmacologist, will also be presenting. Their talks will be interspersed within mine.

The applicant has already shown you the data, so we are not going to review all the data results again, but we are just going to go over some issues that were raised during our team's review.

[Slide.]

You have already heard the proposed indication. I will start with a quick review of the risk factors and then discuss currently available treatments and the history of the approval of drugs for similar treatments.

[Slide.]

This is a partial list of some of the risk factors and we bring it up just to point out a couple of things. Hypernatremia and dehydration and constipation are significant risk factors for development of episodes.

Although protein restriction is no longer recommended, a high protein diet is a risk factor.

The applicant did address these issues with patient education to the patients who had noted these in the first six months prior to admission. There was a slight imbalance of correctable causes favoring the treatment group.

[Slide.]

You have kind of seen this before, but these again are the currently available treatments and only lactulose and neomycin have FDA approvals for hepatic encephalopathy. Lactulose is approved for both decreasing blood ammonia

concentrations and for prevention and treatment.

Neomycin, originally approved just for hepatic coma, was subsequently given an indication for decreasing ammonia levels.

Neomycin is really not used much as was mentioned prior, because of the significant oto and neurotoxicity despite the fact that it is also a poorly absorbed drug that is 97 percent excreted in the feces.

The remainder of the drugs on this slide are antibiotics, and again they have been utilized in an effort to reduce intestinal ammonia production, but there is limited data regarding efficacy.

Metronidazole has not been approved although it is frequently used, and the other antibiotics here are used off label, as well as rifaximin.

[Slide.]

The non-absorbable disaccharides include lactulose and Lactulol, and their intended role in treatment is to reduce intestinal production and absorption of ammonia, which is achieved both by the laxative effect and interference with uptake of glutamine by the intestinal mucosa and its subsequent metabolism into ammonia.

We retrieved the archived documents for lactulose NDA, which was approved in 1974 originally. It was supported by multiple small studies. The trial results were mixed. Most of the trials evaluated lactulose in the treatment setting, some compared lactulose to neomycin, and some compared to placebo, and the efficacy results were mixed.

[Slide.]

The neomycin NDA, originally approved back in 1965--I noticed your slide had a different date. I think it was subsequently re-approved in the early 1970s, and given the indication for reducing ammonia at that time.

But most of the original studies were conducted back in 1957. they were small trials, they had various indications like chronic, acute treatment, and coma. There was little data provided in the label, but the endpoints were mental state, recovery from coma, EEG, and arterial ammonia.

[Slide.]

We then looked to the literature and we also looked at the Cochrane Review, and we were looking for more contemporary evidence of efficacy.

The Cochrane Review, initially published in 2004, and captured studies up to 2003, although it was entitled "Non-absorbable disaccharides for Hepatic Encephalopathy," it actually did go quite a bit into antibiotic use, and we will go over that in the next slide.

The methodology used for that is summarized here, only randomized, controlled trials, included patients who had a range of HE including acute, chronic, and minimal. They were treatment trials. The trials were designed high quality. There was adequate blinding, and if the trial had adequate concealment of allocation.

[Slide.]

The reviewers published their findings in the British Medical Journal. They made the following observations. Although lactulose has been considered the standard of treatment, it achieved its place in standard therapy based primarily on conclusions from limited study data that lactulose is, quote, "equally effective to neomycin," despite the fact that evidence from placebo-controlled trials demonstrated no benefit.

The authors point out the conclusion that lactulose is effective because it is efficacious as neomycin

is flawed as little evidence seems to exist that neomycin itself is effective, and the trials were not designed to demonstrate non-inferiority.

They stated that a lack of significance in outcomes does not equate to comparable efficacy in the context of a trial that is not designed to demonstrate non-inferiority.

[Slide.]

Because most of the trials that were identified compared lactulose to antibiotics, the authors then went into the evidence for antibiotics and their observations were that none of the trials were designed as non-inferiority trials, and all were under powered.

Again, they stated lack of statistical significance observed in the trial that is not appropriately designed does not allow for a valid conclusion that the two interventions are equivalent in efficacy.

They stated, "It seems that the research was continually building up on both insufficient evidence and inadequate methods."

[Slide.]

Placebo-controlled trials of antibiotics also did

not establish efficacy, but the meta-analysis did indicate that antibiotics were superior to non-absorbable disaccharides, And they asked does statistically significant difference really equate with a clinically important difference.

Their conclusion was that they really had insufficient evidence to support antibiotic use.

[Slide.]

Now, the Cochrane Review that looked at lactulose versus placebo; there were 10 randomized, controlled trials comparing lactulose to placebo or no treatment, but only two were considered high-quality trials. These two trials enrolled a total of 44 patients, were published in 1970 and 1973.

A significant beneficial effect was observed in the analysis of these low quality trials, but the event rate in the placebo control arm was much higher.

[Slide.]

There were 12 randomized trials comparing lactulose to antibiotics including neomycin, vancomycin, and rifaximin, but only 5 were considered high quality trials. Those 5 enrolled a total of 413 patients, and were published

in 1977 and '81 for three neomycin studies, and in 1993 and 2003, for the rifaximin trials.

The low quality trials, 5 compared lactulose to rifaximin, and the authors reported that for the overall analysis, patients who took lactulose had a higher risk of having no improvement in their HE symptoms than if they took an antibiotic. They did not break that analysis out by-high quality versus low-quality trials, but they did kind of state that there was no significant difference when the trials were stratified by quality.

[Slide.]

And relevant to our discussion today, as you had previously gone over, there were rifaximin studies identified in the Cochrane Review, two of which identified as-high quality studies, where rifaximin was compared to lactulose.

[Slide.]

Mas, A, et. al, a Spanish study published in 2003, enrolled 103 patients with Grades I to III, acute HE, and evaluated changes in the portosystemic index, which has the 5 weighted components that you notice here.

The trial was designed to show superiority of

rifaximin on basis of the assumptions of success that the authors had established.

[Slide.]

Their conclusions were there was no discussion of adjustment for multiplicity. For the overall PSE index, there was significant improvement with rifaximin as compared to lactulose. However, for the global assessment of efficacy, both groups showed similar clinical efficacy.

They also concluded that rifaximin is as effective as lactulose, and there was greater reduction in ammonia levels, improvement in EEG, which led to a better PSE index.

But for the second study, they really couldn't-- the authors felt they couldn't estimate the treatment effect.

[Slide.]

Now, we are going to proceed with the FDA's review of the NDA application. We will focus just on the issues that we raised during the review process, and the main points are going to include the population definition, the issues surrounding the Conn 4 assignment for the efficacy evaluation and safety issues that will include infection, hypersensitivity, and discussions about a possible concern

with hepatotoxicity in the cirrhotic population.

Dr. Kim will also present pharmacokinetic data showing increased exposures in this population.

[Slide.]

As you are aware, the current submission included just one, Phase III controlled trial. There was no trial conducted to verify the outcomes observed.

There was one treatment extension trial, open label, two years in length, and that is helpful for providing safety data, and trials from studies in treatment of HE and other trials for other indications, such as traveler's diarrhea and irritable bowel, also provide additional safety data, however, all these other trials with short durations, three to 14 days.

[Slide.]

The major focus of our talk today will be on the results of RFHE3001.

[Slide.]

Again, patients who entered the study were required to have a Conn score of 2 with two or more episodes within the last six months. One of these episodes needed to have medical documentation--i.e., medical records, hospital

discharge summaries, et cetera.

As you know, it can often be difficult to obtain accurate medical histories from patients especially if they have impairment in their mental function. In addition, since the patients could have a Conn score of 0 or 1 at entry, we have questioned whether this trial actually studied maintenance of remission.

We agree that patients with a Conn score of 0 definitely are in remission, but we are not sure about the patients with a Conn score of 1.

[Slide.]

Also, just note that the episodes that they had in the two months prior excluded such things as GI hemorrhage, episodes that were from medications, renal failure, or CNS insults did not qualify, and we also questioned the patient's ability to recall if they had had precipitating causes for their HE events. These were not excluded when patients had breakthrough HE events on the trial.

[Slide.]

Two-thirds of the patients had a Conn score of 0, one-third had a Conn score of 1 at entry, and again patients with a Conn score of 1 in remission.

[Slide.]

We believe this impacts the appropriateness of the remission indication as proposed by the application. As Dr. He mentioned earlier, in light of the population entered in the study, we believe that an indication of decreasing the risk of developing episodes of overt HE might be a more accurate description of the trial results.

[Slide.]

Another thing to note about the population at entry is that they were a relatively healthier set of cirrhotic patients.

The protocol excluded patients with a MELD score of over 25, and only 8.6 percent of the patients in the treatment arm had a Child Class C--I mean 12.1 percent had a Child Class C--and if you scored it by MELD score, 8.6 had a MELD score in between 19 and 25.

Now, Dr. Mani from our Division of Neurology Products is going to discuss his evaluation of the trial's inclusion criteria and primary endpoint assessment.

Neurological Evaluation of Inclusion Criteria and Primary Endpoint Assessment

DR. MANI: I am Ranjit Mani.

[Slide.]

I am a medical reviewer in the Division of Neurology Products and a neurologist.

[Slide.]

My presentation is directed at highlighting several concerns about how the inclusion criteria for the key efficacy study would apply and about the manner in which the primary efficacy assessment was performed for that study.

Despite the partial discussion earlier today, these concerns warrant reiteration.

[Slide.]

As you have heard, the Conn scoring or grading system had a key role in the application of the inclusion criteria for this study, and in determining the primary efficacy outcome.

As you have also heard, the Conn scoring system is the most widely used means of grading the severity of hepatic encephalopathy. As depicted in this table, this categorical scale has five possible scores ranging from 0 to 4 with a high numerical score indicating a greater severity of hepatic encephalopathy.

[Slide.]

Despite its wise usage, the Conn grading system for hepatic encephalopathy is also well known to be imprecise, dependent on clinician judgment and insensitive in differentiating milder degrees of severity of hepatic encephalopathy.

[Slide.]

I will first address the inclusion criteria for the main efficacy study.

[Slide.]

The inclusion criteria for that study, as you have already seen, required that each patient be in remission from hepatic encephalopathy based on a Conn score of 0 or 1 when initially selected.

The inclusion criteria also required that each patient have had a minimum of two episodes or hepatic encephalopathy within the six-month period prior to the study. That determination was made retrospectively with an episode being defined as a Conn score that rose from 0 or 1 to 2 or greater, and then returned to 0 or 1.

Further, while at least 1 episode should have been confirmed from the patient's medical records, confirmation

of other episodes could have been based on a description provided by a caregiver.

[Slide.]

As I have already pointed out, the Conn grading system has significant limitations even when applied during a face-to-face assessment of a patient.

In selecting patients for the study, however, the diagnosis of prior episodes of hepatic encephalopathy required that Conn scores be assigned retrospectively and sometimes based on information provided by the caregiver.

Thus, a key question is whether prior episodes of hepatic encephalopathy were reliably identified and scored for severity as required for inclusion in the study.

[Slide.]

I will now discuss the assessment of the primary endpoint for this study.

[Slide.]

The primary efficacy parameter for this study was the time to the first breakthrough overt episode of hepatic encephalopathy.

A breakthrough episode of hepatic encephalopathy was defined as an increase in Conn score to at least Grade 2

or an increase in Conn score by 1 and an increase in asterixis score by 1 in those with a baseline Conn score of 0.

Thus, the assigned Conn score was also important in determining whether a breakthrough episode of hepatic encephalopathy had occurred.

[Slide.]

Both Conn scores and asterixis grade were determined either by direct assessment at study visits or indirect means, such as medical records, descriptions provided by hospital or emergency room physicians, and the accounts of caregivers, as well as other sources.

[Slide.]

Given the limitations of the Conn scoring system that I have already mentioned, the hepatic encephalopathy scoring algorithm, or HESA, has been proposed as a structured means of assigning Conn scores.

While published experience with the HESA is limited, and the validity of that measure may still be uncertain, the HESA instrument appears on its face to be a more precise and reproducible means of assigning Conn scores than the more arbitrary judgment of a clinician.

In the main efficacy study in this application, the HESA was to be used as a guide to assigning Conn scores during direct assessment and study visits. However, the HESA was not recorded in the case report forms for the main efficacy study and, therefore, how and to what extent the HESA was actually used to assign Conn scores in individual instances after direct patient assessment at study visits is not entirely clear.

[Slide.]

The manner in which Conn scores was assigned based on indirect patient assessment during the study is even less clear. Intuitively, it does seem that the assignment of Conn scores based on indirect assessment may be even more problematical than assigning scores based on a direct face-to-face evaluation.

[Slide.]

The next two slides indicate that a majority of patients diagnosed as having overt episodes of breakthrough hepatic encephalopathy was so diagnosed by indirect means.

The first slide displays the results of an FDA analysis based on statistical data sets that were derived from case-report forms included in the original application.

[Slide.]

The second slide displays the results of a corresponding analysis performed by the applicant, which has been provided to us by very recently. As you will notice, the second table indicates that a larger number of patients had episodes of breakthrough hepatic encephalopathy than was indicated in the first table.

In explaining the differences between the two tables, the applicant has stated that the data provided in the case report forms and statistical data sets derived from those forms did not fully capture either the total number of patients with such episodes or the specific situations in which they were determined to have the primary efficacy endpoint.

Regardless of the differences between the two tables, however, both lead to the same conclusion, namely, that the majority of patients diagnosed as having overt episodes of breakthrough hepatic encephalopathy had that diagnosis made by indirect means.

[Slide.]

Thus, a key question is how reliably breakthrough episodes of overt hepatic encephalopathy were diagnosed

during the study.

Dr. Dimick will now continue her presentation.

Concurrent Lactulose

DR. DIMICK: Thank you, Dr. Mani.

[Slide.]

One more issue we want to go over about efficacy is the concurrent use of lactulose. We have talked about it a little bit already.

[Slide.]

Ninety-one percent of patients in both arms used lactulose throughout the study. Lactulose use was higher in North America than in Russia, and there was such a small number of patients, 26, who did not use lactulose, that conclusions cannot be made about efficacy in that small group.

[Slide.]

So, technically, this was an add-on study of rifaximin versus lactulose.

[Slide.]

As presented earlier, several times now, the primary endpoint was the time to first breakthrough overt HE event.

[Slide.]

The trial results demonstrated a significant risk reduction in experience HE event in between placebo and rifaximin, with a very robust p-value, and there was a 58 percent risk reduction in an experience in an HE event.

[Slide.]

You have seen these Kaplan-Meier curves, actually better pictures of them, and one thing we noted was that in the first month, the curves parallel, In months 2 through 4, you see quite a bit of divergence in the slope of the curve and then, at month 4 through 6, the slopes seem to be equal, fairly parallel again.

[Slide.]

We will now go over the secondary endpoint results.

[Slide.]

These are the key secondary endpoints as prespecified in the hierarchy by the applicant, and note that the endpoint time to first HE-related hospitalization includes two categories of patients, those who were admitted to the hospital with a diagnosis of HE and those who were admitted for other causes but then developed encephalopathy

after they were in the hospital.

Also, note that there were four patient who were admitted with the diagnosis of HE but later the site investigator assessed and thought that the patient did not meet breakthrough HE criteria and those patients were not counted as an event. An investigator could make this change through retrospective review of the records.

It should also be noted that 0.2 increase in baseline Conn score and 0.3 increase in baseline of asterixis grade are components of the primary endpoint.

[Slide.]

The applicant designated these secondary endpoints as most clinical important, and the applicant pre-specified the order of their analysis.

[Slide.]

Remember that the gate-keeping strategy utilized for these efficacy endpoints means that when an endpoint in the hierarchy fails, then all subsequent analysis are exploratory only and cannot be used as the basis for efficacy claims.

[Slide.]

As you can see from this slide, the first key

endpoint in the hierarchy is statistically significant, again, with a robust p-value. However, note that there are no protocol-specified criteria for admission and, therefore, there could have been significant variability in thresholds for admission to the hospital.

Comorbid conditions and other issues could have influenced decisions regarding hospitalization. The site investigator was not necessarily the admitting physician, and designation of whether a hospitalization were HE related could be retrospectively determined with Conn scores assigned based on review of the medical records.

Breakthrough events could have been triggered by other conditions that led to hospitalization.

[Slide.]

Conn score and asterixis grade are components of the primary endpoint, and the primary endpoint results were really driven by the Conn score as is illustrated by the fact that time to increase in Conn score is statistically significant, while time to increase in asterixis grade failed to meet significance. Therefore, all the following secondary endpoint values cannot be used for efficacy claims, including those p-values reported on the venous

ammonia and critical flicker frequency.

[Slide.]

Now, we will move on to safety results. The most common adverse events again are GI related with nausea, vomiting, and diarrhea. The other common adverse events seen in the cirrhotic population, hyperkalemia, hypernatremia, anemia, edema. The majority of these adverse events really were found to be secondary to the patient's underlying disease when we closely examined them.

[Slide.]

Because rifaximin is an antibiotic, we wanted to look closely at the incidence of infections, and we did note this slightly higher incidence in the treatment group. You have seen this slide already, although my numbers are slightly different because this one is from the original application and your numbers were from the 120-day safety update. But they say essentially the same thing.

I gave you more columns to explain this a little better. In the original randomized, controlled trial, you have the placebo and the rifaximin. But the long-term safety data, you take all of the rifaximin patients, the 70 of them that continued on to the second study and the 70 who

didn't, and you put them here. And that is to capture--I mean they did that for a good reason, to capture all the patients in the safety data but. when you look at the slide, it can be a little confusing where patients came from.

Then, 82 of the placebo patients moved on to become new rifaximin patients, and then the rest of these patients were newly recruited patients.

So, when you look at this C. diff. two cases here and two cases here, these are the same two cases, and these are three new cases, for the total of five that was presented earlier.

The pneumonias, you see one in the placebo group. Well, that patient didn't move, so these are seven new cases, and you can only tease that out by going and looking at each patient individual, which I didn't do for this all infection, so I am not sure how many of these jump to here.

But of this, these four, only one of these is new, so you get a total of 12. Then, all these lobar pneumonias are new. I would put this total just so that you could see the total, it looked like about 15 percent, which would not be significantly unusual in this population.

[Slide.]

Also, note in C. diff. colitis, we have seen 5 postmarketing events with one death.

[Slide.]

Hypersensitivity reactions are known to occur in this drug class. There appears to be an increased incidence of hypersensitivity type reactions in the treatment group. As you can see by all these subcategories, there were no cases of anaphylaxis in the Phase III trials, but there have been postmarketing cases of anaphylaxis.

[Slide.]

One other thing we noted when we went to look at the cardiovascular data from the study, it does show the hERG is a very weak study in in vitro inhibition, and the sponsor elected not to do a thorough QT study for that, but then they performed no EKGs in any Phase III trials.

There were EKGs done in one small Phase I GI transit study in healthy volunteers, but they did not perform those at Tmax, so they are not really useful for analysis.

[Slide.]

They presented the deaths data, but I wanted to present it by Child class. This, of course, is very

difficult to interpret, because you would expect patients in Child Class C to have a much higher mortality than patients in Child Class A so you can't just definitely look at the numbers. And these numbers are really too small to make a lot of decisions off of, but you do notice that there is this higher incidence in the rifaximin group in the Child Class C and, when you look at the 3002 data, and rifaximin rollover and placebo rollover, again, in the Child C, we are seeing a high incidence.

[Slide.]

One other thing we noted when we were going through the case report forms, there was frequently no lab data on the patients when they discontinued. We looked at this in various ways, from seven days before to 30 days after, two days before to forever after. But, basically, we came up with about a 44 percent lack of LFT data on the patients when they discontinued.

[Slide.]

Then, I went to the rifampin drug class to look at the kind of reactions you would see, and hypersensitivity, anaphylactic reactions, acute renal failure, and hepatitis are most commonly reported and, while drug-induced liver

injury is common when rifampin is used in combination with tuberculous drugs, drug-induced liver injury is actually very rare in this class when it is used in the non-cirrhotic patient population.

But there were two small case report studies of hepatotoxicity in the cirrhotic population with primary biliary cirrhosis who were taking low doses of rifampin to prevent pruritus, and they were taking, not the 600 mg dose of rifampin that was seen on the PK slide that was shown by the sponsor, but they were taking 150 mg a day, the majority of patients. But these are small case reports.

[Slide.]

So, therefore, we are left with this question, is rifampin hepatotoxic. The drug class raises some potential. Animal toxicity studies don't really address this issue, and I am going to show that in a minute.

We know that there is increased systemic exposure with increasing Child-Pugh class, and Dr. Kim is going to show you that data, and this lack of LFT data on the discontinued subjects leaves us with a question and the possible increased death rate in Child-Pugh class is there for us to see.

[Slide.]

Then, about the preclinical data; there are inconsistent toxicity findings. They don't really address this. The chronic toxicity studies did show a subset of studies that did show liver toxicity and small-intestine toxicity, but we didn't have any data in preclinical hepatic failure models to look at.

These animal studies, there was very low absorption, and you can see that AUCs in the animal studies that were obtained were 42 to 127 nanograms. This was because the absorption is so low in a fairly healthy animal where. in the cirrhotic population, we have a mean of 130 with a range of 28 to 359. And this is just in the Child Class A and B patient because we got the Child Class C data very late, but Dr. Kim is going to go over that.

Clinical Pharmacology Review

DR. KIM: Good morning.

[Slide.]

My name is Insook Kim and I am a clinical pharmacology reviewer for this application.

[Slide.]

The most important difference between this

proposed target patient population and the patient population for the approved indication, which is traveler's diarrhea, is liver function. By definition, this target patient population has varying degrees of hepatic impairment whereas hepatic impairment to this degree is unlikely in patients with traveler's diarrhea.

The pharmacokinetics of rifaximin in this patient population was evaluated during the open-label, Phase III trial 3002. The PK data was compared with that obtained in healthy subjects and so it was analyzed by the degree of hepatic impairment.

What was found was the systemic exposure to rifaximin was greatly elevated in this patient population and, and the greater the degree of hepatic impairment, the greater the systemic exposure to rifaximin.

[Slide.]

This table presents the PK parameters from patients and healthy subjects and, when you see this AUC value which is systemic exposure, systemic exposure in this patient population who has history of hepatic encephalopathy was about 10 to 24 higher than AUC observed in healthy subjects.

Among patients, depending on the degree of hepatic impairment, systemic exposure was even higher. You see these two values, mean AUC and Child-Pugh Class C patients, it was about two-fold higher than in the patients who has Child-Pugh A Class hepatic impairment.

Also, it was noted that four patients in this Child-Pugh C Class got hepatic impairment, the AUC values are all above them, higher than the high AUC value observed in non-clinical studies.

Another clarification, this Child-Pugh C Class data was not available by the time when we submitted the AC briefing document, so it was not included in FDA's AC briefing document.

[Slide.]

Also, the same trend of increasing the systemic exposure to rifaximin was observed when the MELD score increases.

[Slide.]

In addition to this intrinsic factor which is liver function, there are potential factors, extrinsic factors, which may further increase the systemic exposure to rifaximin.

For example, food; the AUC value was increased by two-fold when a high-fat meal was given 30 minutes prior to dosing of rifaximin.

Also, potentially, there are other concomitant medications for which the potential was not fully explored during this development program. For example, in vitro studies show that rifaximin is a substrate of P-gp efflux transporters and, in the presence of P-gp inhibitors such as verapamil, the efflux ratio of the rifaximin was reduced by greater than 50 percent. Yet, the potential interaction in vivo was not evaluated.

[Slide.]

In summary, what we found is systemic exposure; rifaximin is systemically available and the degree of the hepatic impairment has a significant impact on the level of systemic exposure of rifaximin.

Also, there are other factors which may further increase systemic exposure to rifaximin, and then this may have some implications to systemic toxicity, known/unknown, of rifaximin.

Now, Dr. Dimick will continue to present clinical summary.

Conclusion

[Slide.]

DR. DIMICK: The FDA recognizes the great difficulty in designing clinical trials in hepatic encephalopathy. These trials are limited by the real world in which we work and the fact that there are no established standards and no validated outcome measures.

While it is our job to look at the data very critically, we commend the applicant's efforts to develop and establish the efficacy of an effective treatment for this debilitating disease.

[Slide.]

I would like to summarize some of the major review issues now.

The level of evidence. There is only one controlled study, and thus, we are unable to verify the observed results. The entry criteria appears to involve two populations, those with remissions and patients with a Conn score of 1 that might be defined as minimal HE.

We question the reproducibility of the assignment of Conn scores both for defining the patient population who entered the study and for defining the endpoint of

breakthrough HE episodes, and the effectiveness of this drug as a stand-alone treatment without lactulose was not established in this trial.

[Slide.]

On the safety review, there remain unanswered questions about the possibility of increased infections and clostridial colitis. There does appear to be anaphylaxis associated with this drug, and we would like to add this to the labeling, and we still have unanswered questions about the possibility of hepatotoxicity.

The drug class history, the lack of preclinical data, and the increased systemic exposure and cirrhosis leaves this unanswered.

[Slide.]

I would like to thank the team that participated in our review. It was a large project, came in over 100 file boxes. I would especially like to thank Sheila Lianos, our project manager, who kept us all together, and Brent Vali, our statistician. There people and many others were invaluable in helping us.

Thank you very much.

DR. RAUFMAN: We will now ask if the Committee has

questions for the FDA. Dr. Dasarathy.

Questions for the FDA

DR. DASARATHY: I am not necessarily sure, either the sponsor or the FDA really addressed what you had raised. This is an application for use of rifaximin as a single agent whereas everything that has been done seems to be in addition to lactulose. I am not sure what the debate is going to be, whether it is going to be approved for single use for prevention of remission or in combination with lactulose.

DR. RAUFMAN: Who is responding to that?

DR. GRIEBEL: I can start and the team could correct me if I am wrong. I think we are here to get your input on that. I mean most of the patients, the vast majority of the patients, in the study were on lactulose and, as Dr. Dimick pointed out, technically, that's an add-on study.

We would like to hear your thoughts on that and then we will incorporate that in our decision-making, and it would impact labeling.

DR. RAUFMAN: Dr. Kane.

DR. KANE: We have heard about the variability of

the outcome assessments using Conn scores. FDA has approved lactulose and neomycin. What sort of outcome assessments were used for those trials to get FDA approval?

DR. GRIEBEL: Those are ancient approvals as we tried to point out, so those, based on dates, I believe pre-dated Conn scores because they were studies done in the '60s, '70s. We were able to get the archival records for lactulose and we are going based on the label for neomycin, and it appears that there are things like mental state and how that was assessed. I don't know if the team knows the details on mental state.

DR. DIMICK: No. The labeling and the trial data that I could get from our files really were very vague.

DR. RAUFMAN: I would like to follow up on a question that Dr. Silberg asked at the end of the last question session, having to do with the lactulose and discussions between the sponsor and FDA.

Was there consideration for stopping lactulose and treating only with rifaximin? How was that aspect of the study handled?

DR. DIMICK: I actually appreciate the sponsor's dilemma and that it would be difficult to withdraw lactulose

from patients because if they then develop increasing episodes or failed, this could be considered somewhat as withholding treatment.

DR. GRIEBEL: In terms of the record of the discussions, the meeting discussions, I don't think anyone at the table can answer what the actual meeting discussions were at the time that the trials were designed.

Dr. He, are you aware of--

DR. HE: No.

DR. GRIEBEL: I don't know if the applicant recalls either.

DR. RAUFMAN: It's just puzzling to me that this dilemma that we are faced now with, the treatment with both drugs, wasn't considered at the beginning as a potential problem.

Does the sponsor want to address that question?

DR. FORBES: Yes, if it's okay. There was an awful lot of discussion in December of 2004 and through the early part of 2005, not necessarily all of it with the FDA, but this was a very contentious issue for the investigators and the thought leaders that were helping us with this, because withdrawing lactulose, as was mentioned by the FDA,

was seen as something that just was a non-starter.

It wasn't going to be accepted by the IRBs. It wasn't going to be accepted by the clinicians participating. So that is what led us down the road of bringing patients in and the decision being made at baseline whether or not they were on or off of lactulose.

DR. RAUFMAN: Dr. Gitlin.

DR. KORVICK: Can I respond to that from the FDA? Sorry. Yes, all the things that have been said are true. Many times when we set up experiments, and we have this kind of uncertainty, it is a little bit tricky how you think about the study.

So, the majority of the patients had lactulose. It may or may not be effective but they had that. So the major comparison really is the combination of lactulose and rifaximin to placebo and lactulose.

So, the study doesn't exactly prove, answer your question. You could look at it as the difference in the two would be the add-on benefit if you believe lactulose is effective, or you could believe that if nothing, if all things were the same, then, that complete activity that you are seeing in this study for the primary endpoint is related

to rifampicin.

So, we don't necessarily have to totally prove that unless the Advisory Committee thinks we need to. However, it would be coming up in the label as to whether or not we think that, based on the clinical trial design, you would have to use concomitant lactulose therapy because that's how the study was conducted.

So, I think maybe that would help.

DR. FORBES: Just to kind of follow on with Dr. Korvick's comments, again, I think, to emphasize, this was really designed as a real-world study. It was using Conn criteria that assessed breakthrough, which is used in the clinic. It allowed for patients to maintain their therapy and brought them in and added on rifaximin or placebo and looked for a difference.

The point estimate on or off of lactulose would suggest that the efficacy is the same. But I understand that there are 91 percent of the patients that are on lactulose and 9 percent that weren't. But again this was designed as a real-world study to see if adding rifaximin to whatever the patients were doing, since they had already had at least two breakthroughs in the prior six months, could

actually result if reduction of that.

DR. RAUFMAN: I am a little troubled by the notion of adding the new drug to lactulose after several of the sponsor's experts have told us how terrible the drug lactulose is and patients can't tolerate it, et cetera.

Dr. Gitlin.

DR. GITLIN: Thank you, Mr. Chairman.

One of the beneficial effects, if there is, with lactulose is it acts as an osmotic laxative. So, I would be interested to know whether the sponsors, when the patients were on combination therapy, did a stool count on a daily basis to see whether, in fact, there was an osmotic laxative effect from lactulose. If there wasn't, then, clearly, most of the beneficial effects would be from their drug.

DR. FORBES: There was a diary card that recorded them or of stools per day, and that was one of the ways that we kept track of how many the patient had.

DR. GITLIN: What were the results of the diary counts?

DR. FORBES: I am afraid I don't have those right now. I will have to get back to you on that.

DR. DIMICK: I can tell you that the stool counts

were lower in Russia where the lactulose used averaged about two-and-a-quarter cups a day, and they were higher in the United States where the lactulose used averaged a little over four cups a day.

DR. RAUFMAN: Other questions? Yes.

DR. HAUBRICH: A couple of questions related to the microbiology here. Obviously, one of the considerations for giving a continuous antibiotic is the development of resistant organisms.

The C. diffs that were diagnosed, were they cultured or were they just toxin and, if they were cultured, what was the susceptibility to rifaximin, as well as to vancomycin and metronidazole?

Similarly, were there any studies that were done just to do surveillance of the GI tract to look for development of multi-resistant pathogens or just multi-resistant gram-negative rods in the stool as a result of chronic antibiotic use?

DR. FORBES: I am going to ask Dr. DuPont if he could step forward and answer this question on behalf of the sponsor.

DR. DuPONT: Herbert DuPont from the University of

Texas, Houston, and Baylor College of Medicine. I have received funding from the sponsor for travel, for speaking, honoraria. I have no other business relationship with the sponsor, and have no benefit related to the outcome of this meeting.

Looking at rifaximin and resistance, and then C. diff., I will make some comments. There are good studies in both artificial media, Lowenstein-Jensen media, with rifaximin or rifampin incorporated into the medium, showing that rifaximin does not induce Mycobacterium tuberculosis-resistant mutants.

Experimental studies with infected guinea pigs given rifaximin, and does not lead to resistance of Mycobacterium tuberculosis.

In our traveler's diarrhea studies, we have administered three days of therapy and looked for coliform resistance and enterococcus resistance and then, in our prophylaxis trials, we gave 7 days and 14 days of rifaximin, and looked for enterococcus and coliform changes in MICs.

The counts essentially remained the same pre-treatment and post-treatment, and the MICs were essentially identical.

There have been two Italian studies. The drug has been available in Italy for a couple of decades. There have been two Italian studies looking at resistance of gut flora after administration of rifaximin.

One of them was just all-drug usage and another was in ulcerative colitis patients that received 30 days of rifaximin treatment. Both of those studies showed that there were a very small number of strains of bacteria in the gut that became resistant to the study drug. The majority of the organisms remained susceptible. Once the drugs were discontinued, the resistant mutant strains disappeared.

[Slide.]

The next slide deals with the issue of C. diff. All antibiotics predisposed to C. diff. I mean I think we have to say that and understand that to begin with.

There are three points about the pathogenesis of C. diff. One is alteration of colonic flora by antibiotics. The second is comorbidity of patients. And third is exposure to spores generally in a hospital environment.

Hepatic encephalopathy patients are comorbidly significantly ill and are very susceptible to C. diff. Rifaximin preserves the colonic flora, which we believe is

an important defense against C. diff. development.

We have looked at MICs of almost 600 isolates of C. diff. over three years at our university hospital in Houston. The median MIC is 0.01, and only 3 percent of strains of C. diff. that we have seen over three years are resistant to rifaximin, and we use a lot of rifaximin in our hospital.

I will point out that rifaximin has been used successfully to treat C. diff., diarrhea and colitis, and to treat recurrences of C. diff., and we have published our studies on this within the last two years.

Getting back to the questions at hand, the organisms isolated from these infections, and the C. diff., these five C. diff. infections that were identified in 3001 and 3002, were not cultured for C. diff. and MICs were not performed.

I will point out that all five of these patients received expanded-spectrum penicillins, cephalosporins and fluoroquinolones, before they develop their C. diff., which are drugs which are well known to predispose to this infection.

DR. KORVICK: From the FDA side, to directly

answer your question regarding the study that was done, during our review, and our colleagues from the Anti-infective Special Pathogens Division looked at this, there were no microbiologic sensitivity type information collected during the six-month HE study or in the reported literature.

So, the absence of any microbiologic data and the long-term effects on the gut flora and any change in the in-vitro susceptibility of that flora to rifaximin and other antimicrobial drugs treated with rifaximin class can't be evaluated.

I think that some of what you heard is somewhat reassuring, but, you know, we would be interested in actual follow-up where patients are receiving this for long term.

We do acknowledge, as Dr. Dimick said in her slides, that these patients were perhaps receiving a lot of other antibiotics that could lend you to get C. difficile, but we feel that perhaps longer-term data should be collected and, if this were recommended for approval, that those definitely should be done, those studies, either pre- or post-approval.

DR. RAUFMAN: Dr. Hersch.

DR. HERSCH: I had two questions related to

toxicity. First, does the Division see the need for QT study to be related to the systemic exposure, and the increasing systemic exposure, does that reach a level of that requirement?

My second question, the issue about having an hepatic animal model for animal-toxicity studies. Are there accepted models, and is there a precedent for doing toxicity studies in hepatic animal models?

DR. BINA: I am Niraj Bina, a pharmacologist for the FDA. There are two models. There is a bile-duct ligation model that is used in rats and specific rodents, and a pentobarbital and carbon tetrachloride model, as well, so given subsequently to animals to actually mimic liver cirrhosis.

DR. KORVICK: Su-Chi-Li is our biopharm team leader, and she might want to make a comment on a QT study.

DR. LI: This issue is still under discussion internally. However, I can make one comment, and that is, normally, thorough QT study is conducted in healthy subjects. In this case, though, because the systemic exposure is much lower in healthy volunteers compared to the patient population, so if we conduct a study, we will find a

way to reach to reach that kind of concentration.

In certain cases, you may see drug interaction will be one way to reach a higher concentration, however, we don't have any information that a specific type of drug interaction will give us that kind of concentration.

DR. RAUFMAN: Dr. Hilton.

DR. HILTON: I have three questions. The first is for Dr. Dimick. I wonder if you think that the patients or the caregivers would be able to detect which treatment arm the patient was on based on the features of the experience.

DR. DIMICK: I am unaware that there was any unblinding, and I know the sponsor was asked this question earlier. We actually did do some analysis to look for evidence of unblinding and we did not find any.

DR. HILTON: My second question is, related to the age of the patients, the median age is about the mid-fifties, and the episodic nature of the disease, and trying to imagine what the treatment management strategy would be for this treatment.

Since the data only focused on the first episode, I wonder what the plan would be for the patients after the six months. They still have the disease, they are still at

risk of another episode, and I am wondering, in the rollover from 001 to 002, if the patients on the original rifaximin arm rolled over, any of those rolled over, to the second trial.

I couldn't tell from the briefing document.

DR. FORBES: Let me see if I can address your questions. I think the treatment options for the patients is something that I would have to ask Dr. Mullen to step forward and answer for us because he is more qualified to answer how these patients would be handled given that they have another breakthrough. But keep in mind the patients that were brought in, as you are well aware, had at least two breakthroughs within six months prior to.

So, what would happen to them afterwards, I will ask Dr. Mullen to answer. But the patients that came in to the open-label study remained in there as long as they wanted to, so that once they came in, there were patients that had multiple breakthroughs in the open-label study and they maintained rifaximin treatment through those.

What you would expect to find is what we found, which is that they tended to have fewer events than what they had reported at baseline during their follow-up in the

open label. So, all of the data from the open label, as we presented earlier, continues to reaffirm that patients that received rifaximin have a lower risk of having a recurrent event.

Dr. Mullen.

DR. MULLEN: My name is Kevin Mullen and I am a Professor of Medicine and hepatologist at Case Western Reserve University. I have received consulting fees and travel costs to come to this meeting.

I think your question is what would be the treatment regime applied to patients in real life after this trial is presumably approved for therapy. I would imagine that the patients that have been slated out in the study are people at great risk for recurrence almost be definition, so they would be specifically targeted for therapy to prevent multiple relapses, or merely because, at each relapse, there is such a deterioration in the overall status of the patients, you are trying to prevent these admissions to the hospital and these bouts of encephalopathy.

Does that answer your question, or did you have something more specific?

DR. HILTON: Well, as I understand it, when a

breakthrough event happened, the patient went off treatment, it was a treatment failure. So, then, when would they then be put back on treatment, when would it make sense to put them back on?

DR. MULLEN: Well, of course, we have the same dilemma with lactulose. That is the only drug we have now, and when people fail, and break through, we scratch our heads, we try and correct them as best we can, but we don't have very many options at all. At least in this circumstance, we could potentially switch over to rifaximin if a patient fails on lactulose, which basically, all of these patients were failed lactulose patients.

DR. FORBES: So, when they failed the double-blind trial, they were allowed to roll in to the open-label study, and that's where we continued therapy with them typically.

DR. HILTON: Okay. So, stratifying those results by their 001 experience will be really interesting.

DR. FORBES: We will have to get back to you on that one.

DR. HILTON: Yes, of course. My third question, my last question, is I realize that one of the good reasons for using Conn scores is that, because the patients and

caregivers themselves can assess it, very frequently, over time, you can get a very fine assessment for, say, time to first episode of breakthrough.

I wonder if MELD scores are also an outcome that can be assessed relatively easily and accurately by patients, and if that might be a candidate for an outcome variable for trials like this.

DR. FORBES: Well, let me clarify that. First of all, if the caregiver witnessed a breakthrough, then, there was a discussion between the caregiver and the principal investigator. The principal investigator had to adjudicate all the outcomes.

So, the symptoms that were reported from the caregiver and from the patient, who had also, they would as best we could, try to talk to them as well, but the symptoms were obviously something that were related to the principal investigator, who is skilled in the art of taking histories. So I just want to make sure that everybody on the panel is clear that the PI ultimately had to be satisfied that the symptoms were there prior to calling it a breakthrough.

The MELD, as you know, is the model for end-stage liver disease, so that is actually done by analytical

methods and stages, liver, and also renal severity of these patients and the importance of that has to do with transplant listing and prioritization of patients.

We obviously looked at the data, at different MELD scores to see how the patients functioned as far as prevention of relapse, but I don't know that we could anything else with MELD.

DR. HILTON: Did you have any follow-up MELD scores?

DR. FORBES: Yes, we were able to calculate the follow-up MELD scores as often we received labs on these patients, and we were actually able to do some analysis on change of MELD score over time.

DR. RAUFMAN: I would like to ask the sponsor, in Study 3002, what percentage of the patients were co-treated with lactulose?

DR. FORBES: Approximately, I believe the number is in about the 70, 75 percent range were treated concomitantly with lactulose. Once they came into the open-label study, we did notice that there were fewer patients that continued on in their lactulose.

DR. RAUFMAN: Dr. Solga.

DR. SOLGA: I would like to follow up to some important comments that Dr. Dimick made in her talk and also in her writing, and I apologize, this will probably come across as more of a comment than a question.

I have already thrown a few rocks at the crazy old story about colon-derived ammonia, but I am going to throw that story a bone for the moment. She articulated a, quote "concern" on her slide on page 22, that it seemed to take four weeks or so for the lines to diverge between placebo and rifaximin.

In this indication, this instance, what we are talking about is not trying to treat a pathogen, but rather completely redirect the colon metabolic milieu. There are, grossly speaking, two kinds of colon bacteria, mucosal derived and lumen derived, and I don't consider myself an expert on gut bacteriology, there are only a handful of true experts in the country, but I have had the privilege of knowing a few.

I have had the privilege of musing with them, if you were going to completely redirect the colon milieu, is this going to take two weeks, four weeks, six weeks, or eight weeks, I don't know, but our guess is we are in the

range of four to six weeks, and it certainly wouldn't be overnight.

One thing that Lara Dimick put in her most excellent clinical review, on page 25 of 148, is that she reviewed the three trials for acute treatment of hepatic encephalopathy submitted by rifaximin, which ranged in days from five to seven days, to 10 to 14 days, and these did not seem to work.

I am not surprised by that, and so I am actually not concerned, but actually rather heartened that all four studies seemed to say the same thing, namely, if rifaximin is going to work for this purpose, it ought to take at least four weeks before it is judged to be efficacious or fail to be efficacious.

So, I guess after this long-winded comment, my question to Dr. Dimick, could she redirect her concern on page 22 to more of an I am encouraged by this reality.

DR. DIMICK: I think I actually didn't say I was concerned, I just pointed it out, because I couldn't actually come up with an explanation.

DR. RAUFMAN: Dr. Anderson.

DR. ANDERSON: Yes, I have a couple of questions.

Were you able to do an intention-to-treat analyses of the data that were provided to you? If so, how did they correspond to the primary analysis that the sponsor provided?

DR. VALI: Brent Vali, the statistical reviewer on this application. If by intent-to-treat analysis you mean handling censored patients appropriately, correct? The way you handle censored patients appropriately in an ITT setup in survival analysis is that when they drop out, on their study drug discontinuation, they are censored at that time point.

We did conduct that analysis and the results were consistent with the results that the sponsor provided.

Does that answer your question?

DR. ANDERSON: So, you also censored them at the time that they stopped their therapy?

DR. VALI: That's correct.

DR. ANDERSON: That's not my understanding of an intention-to-treat analysis.

DR. VALI: Well, all patients that were treated were rifaximin were analyzed that way, if you are randomized, okay. We took all randomized patients and we

analyzed time to breakthrough, censoring them in the way I just described.

DR. ANDERSON: Okay. So, if they stopped therapy on Day 47 and. Day 48, they had a breakthrough event, that would not be attributed to whatever arm they were on?

DR. VALI: That's right, they would be discontinued at Day 47.

DR. ANDERSON: I think some of us would not consider that an appropriate way to analyze these data.

DR. VALI: How would you suggest?

DR. ANDERSON: I would consider all events during the follow-up period to be attributed to the arm to which they were randomized.

DR. VALI: Well, and they did that, and they also did that, as well. I mean that is how they actually conducted it. So, when a patient drops out, they have a non-breakthrough termination follow-up where patients were followed up to six months after post-initial dose and, if they broke through, they would be categorized as breakthrough at that point.

So, yes, I am sorry, I just got a little confused. That is what the sponsor did provide. Actually that was the

way they approached their analysis; that's right.

DR. ANDERSON: That wasn't so clear to me. Okay.

Then, another question, maybe not as directly related. So, in our understanding of how this might play out if we approve this for this indication, what would be the expected exposure time for a patient, for maintenance of remission? And then, how many patients have we seen, in these combined 3001 and 3002, who have experienced something close to that level of exposure duration?

DR. GRIEBEL: I will defer to the applicant, but for maintenance of remission, I would say it would be for as long as they had hepatic-impairment cirrhosis, which is until transplant if they were lucky enough to be on transplant lists.

Then, median duration of that by Child Class, I would have to defer to the experts.

DR. FORBES: The information that we have right now in the open-label extension is that we have data out as long as three years and the mean data that is in the submission right now is about 347 patients exposed for 348 patient exposure years, so on average, the patients that we have, have a mean follow-up of one year.

I wanted to go back for a moment just to--I feel like we are not answering your questions around some of the sensitivities in the handling of the dropouts of the patients, whether that be death or by adverse event, and we do have a series of slides that have addressed this.

We have worked with the Division on this, and they have asked for some very detailed analyses around this, and I think we can, when the time is appropriate, and the Chair agrees, we can try to present these to you if you so wish, so that we can clear this up.

DR. RAUFMAN: Dr. Gitlin.

DR. GITLIN: I would just like to remind my late Dame Sheila Sherlock that the role of the colon was very effectively shown about 30 years ago when I was working on the late Dame Sheila Sherlock, in which patients with intractable encephalopathy, they either had colonic exclusion or colectomy with very, very good results, unfortunately, a radical operation in very ill patients, but that pointed the finger to the colon rather decisively.

Thank you.

DR. DASARATHY: I keep going back to the lactulose with the rifaximin. In the 3001 study, I understand they

say that 91 percent were on lactulose. Were they on lactulose all the time, was the dose of lactulose changed, how many of them discontinued the lactulose for what periods of time, was it estimated that in the total of 168 days, how many days patients are off the lactulose in the rifaximin group versus the placebo group?

That could help us re-interpret this data to see if the rifaximin would work alone.

DR. FORBES: Let me try to answer one of your questions regarding the daily use of lactulose.

[Slide.]

This actually a graph again. This information is coming from the diary data that the patients completed with caregiver assistance, and was reviewed by the coordinators and the study staff as it came in, and this is just the raw data that is in there, and you can see that, really, the use of lactulose during the course of the trial by treatment group is superimposable, so it really didn't change during the course of therapy.

We took a look at whether or not patients, once they started to have a breakthrough, started to change their lactulose dose.

One of the problems that we have is obviously, when you have varying cognition in a patient, that then they start to forget doses, and, of course, that did get picked up. So there is some variability in lactulose use in some of the patients that have breakthrough around that time, both increasing their lactulose and trying to avert it, well as maybe not taking their doses, because now they have become non-compliant.

Again, that was why we had caregivers to pick up the phone and call the study center as soon as there was a change in lactulose dose, the study centers were alerted, because that was a sign of an impending bad event.

DR. RAUFMAN: These are data for 3001?

DR. FORBES: Correct.

DR. RAUFMAN: Do you have similar data for 3002?

DR. FORBES: No; we don't

DR. RAUFMAN: Dr. Hasler.

DR. HASLER: My question relates to the data relating to Clostridium difficile infections. Do you think that you have accurate numbers as to the number of patients who actually had C. diff.? The reason I ask that is that about 90 percent of patients in both groups were on

lactulose, so essentially, all your patients had diarrhea. Were there specific criteria you used to test for C. diff., or was this center dependent?

DR. FORBES: I am going to ask Dr. DuPont again to answer this question, because I think the difference between the diarrhea that you see with lactulose and what you would see with the C. diff. infection is better left to Dr. DuPont.

DR. DuPONT: This has not been analyzed, to my knowledge, but looking at the data, the diarrhea is different with C. diff. The leukemoid reaction, leukocytosis, increased severity of the diarrhea, maybe some fever, it looked clinically different, and that is why the physicians sought a diagnosis of C. diff.

DR. HASLER: Was specific surveillance for C. diff. done on a routine basis in any of these patients who perhaps had a little bit of an increase in diarrhea?

DR. DuPONT: Not to my knowledge.

DR. FORBES: I think if there was a symptom of an increased diarrhea, though, it was followed up. I mean obviously, as I said, these patients were either called or seen in the clinic every week.

DR. RAUFMAN: Ms. Cryer.

MS. CRYER: Thank you. To follow up on the question of lactulose, this has been described as a real-world study. The FDA referred to some country differences in the underlying dosage amounts of lactulose.

Could those differences between, say, Russian sites versus U.S. sites have made a difference in the response, and was that analysis done, and is that available?

DR. FORBES: As I mentioned in my presentation, all the subgroups were tested for an interaction, and that was not found to be significant. So, that testing procedure, as I understand it, takes into account the things that you are worried about, which is whether or not there were discrepant results seen between geographic regions in the case of Russia versus U.S. and Canada, or lactulose use, and so all of the subgroups that I presented earlier do not show positive for a treatment interaction.

DR. RAUFMAN: Are there any additional questions?

Dr. Hilton.

DR. HILTON: Just a follow-up on my earlier questions. Would it be possible to see the change in MELD scores by arm, as well as the repeated episodes by arm?

DR. FORBES: Yes; it would be. It might take a minute to get it up. I am actually looking for the change in MELD score by treatment group, over time. Since this might take a minute for us to bring up, I don't know if we wanted to move on to another question.

DR. RAUFMAN: Is there one more? Ms. Sklar.

MS. SKLAR: When patients were admitted, how were their previous hepatic encephalopic events assessed? I know there are some medical records, but could you speak to that a little bit?

DR. FORBES: Certainly. As I mentioned in my talk, many of these patients were known already to the clinical centers, so what was required of them was that they had to either have within their clinic charts themselves or they needed to retrieve from hospitals or emergency rooms discharge or admit summaries that reflected symptoms consistent with having an overt breakthrough event.

So, one of those had to be documented, and the other one could be verifiable through the caregiver. So, that was the requirement coming in. So, when we went to monitor it, of course, we made sure that those events were documented and the records were available. So, that is how

we made sure.

Of course, there are a number of other things that had to be in place. Obviously, they had to have advanced liver disease and other things that made sure that we were dealing with a population of HE patients.

So, in totality, the inclusion/exclusion criteria and the documentation tells us that we have a very defined population of hepatic encephalopics.

DR. RAUFMAN: We can address the answer to the MELD question after lunch. It will give you time to find the data.

DR. FORBES: There is recurrent also, there is a recurrent HEF in 3002.

DR. RAUFMAN: Let's do that after lunch, so you can get that together.

We will now take a one-hour lunch break. We will reconvene again in this ballroom in 60 minutes from now, at 1:00 p.m. Panel members, please remember that there should be no discussion of the issue at hand during lunch amongst yourselves or with any member of the audience.

Thank you.

[Luncheon recess taken at 12:00 p.m. to 1:00 p.m.]

AFTERNOON PROCEEDINGS

[1:00 p.m.]

Open Public Hearing

DR. RAUFMAN: We will now proceed with the Open Public Hearing.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have

any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the Agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, speak only when recognized by the Chair.

Thank you for your cooperation.

We have I believe one speaker, Ms. Dorman, if you could please identify yourself.

MS. DORMAN: Yes. My name is Diane Dorman. I am Vice President for Public Policy for the National Organization for Rare Disorders. Because I am the only speaker, I promise not to take a full hour, just a few moments of your time.

I have no personal financial relationship with Salix, nor does NORD have a financial relationship with the company. I am here today, not on behalf of Salix or the therapy under consideration by this Advisory Committee today. Rather, I am here on behalf of the millions of men, women, and children in the United States affected by one of the 7,000 known rare diseases that, in the aggregate, affect approximately 30 million people.

Since 1983, NORD has been dedicated to helping people with rare or orphan diseases and assisting the organizations that serve them. A rare disease, as defined by the Orphan Drug Act, as you probably well know, affects fewer than 200,000 people in the United States.

We serve as the primary nongovernmental clearinghouse for information on rare diseases, and we are committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.

Today, there are nearly 350 orphan drugs and biologics that treat about 200 rare diseases and chronic conditions. Given that there are thousands more rare diseases without any specific treatment, it is easy to

understand there are millions of people who can only hope that one day someone will take on the significant financial risk to develop a therapy for their condition.

As you deliberate today, I ask only that you keep in mind that patients affected by rare diseases are willing to take on a far greater degree of risk than those affected by more widely understood diseases affecting larger populations.

Thank you.

DR. RAUFMAN: Thank you.

Are there any other public comments?

[No response.]

DR. RAUFMAN: The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the Committee, as well as the public comments.

Before we continue with the panel deliberations, we will conclude the questions and answers this morning.

Further Responses from the Sponsor

DR. RAUFMAN: Does the sponsor wish to address the

issues raised about the MELD?

DR. FORBES: Yes, thank you. I know that there were a number of issues that we said we would come back to. I am going to begin with multiple breakthroughs in 3002, if that is okay with the Chair. I will try to move through these quickly.

The slide that you have in front of you lists the subjects with at least one breakthrough in the 3002. You can see that there are a total of 280 patients that were put into this open-label study either from the double-blind trial or presented new.

As you can see, there are about 33 percent of them that have at least one breakthrough through their extensive follow-up.

Keep in mind that these patients had multiple breakthrough within the first of the six months preceding their participation into the double-blind trial, if that is where they came from.

So, the fact that we were able to follow these patients for so long and only have 33 percent of them when all, or 100 percent, of them had breakthrough and experienced multiple breakthroughs prior to coming in, I

think speaks volumes to the efficacy that they see with rifaximin. To be able to keep that many patients symptom-free from breakthrough is really quite remarkable.

The next thing I am going to move to is the MELD over time change, and I am going to ask that Dr. Kim step forward quickly and help me with this. We have actually transferred our data set to the Mayo, and Dr. Kim has been working with us on some other things that we won't get into today, but I wanted him to address the MELD changes since he is an expert in this area.

DR. KIM: My name is Ray Kim. I am a practicing hepatologist at Mayo Clinic in Rochester. I am also compensated to prepare for this meeting and to be here today. I have no other financial relationship with the sponsor.

[Slide.]

I had a chance to look at this data between placebo patients and study-agent patients. The slide shows baseline MELD score and end-of-treatment MELD score, so at baseline, placebo patients at 12.7, rifaximin 13.08. At end of treatment, the MELD score did not change substantially, 12.8 as far as the mean for the placebo patients, 13.06 in

the rifaximin group. If you look at the delta, that is essentially zero--if I can go to the next slide--

[Slide.]

DR. KIM: --because the follow-up duration might be slightly different between the rifaximin and placebo patients, we also did a linear regression model to get at the slope of change given the unit of time, The placebo group that will be the mean value is 0.0046, and the rifaximin group 0.0055, so essentially the MELD score did not change. The delta is zero over time, and the p-value is highly nonsignificant.

So, I don't see any change in the MELD score in either group.

DR. FORBES: Thank you. The next issue that we deferred had to do with the organisms present during infections. I am going to ask for Dr. Naga Chalasani to quickly come up and talk to us about this.

DR. CHALASANI: Thank you. During lunch break, we were able to look at the database to capture or come back with some of the bacteriology data. These are the infection SAEs in 3001. I will go entity by entity.

In case of pneumonia, the bacteriology was not

recorded, but all patients were treated with usual antibacterials and patients continued through the study.

In terms of C. diff., I think it was already discussed. As far as sepsis was concerned, there were two instances of sepsis, but both were in the placebo group. One was due to reportedly gram-negative rods. The other one was reported as Torulopsis glabrata.

As far as the urosepsis as SAEs, there were three instances, two in rifaximin, and one in the placebo group. Patient 1 in the rifaximin group initially had an E. coli UTI reported as resistant to ciprofloxacin but sensitive to cefazolin and trimethoprim/sulfamethoxazole, treated with cefazolin.

Patient A a month later had Proteus UTI, treated with papercillin/tazobactam, was discharged home on oral cephalosporin.

The second patient in the rifaximin group with the UTI had due to Klebsiella, poorly sensitive to levafloxacin, was successfully treated with levafloxacin.

There were sixinstances of SBP, four in the placebo, two in the rifaximin. The database that we have does not consist of the bacteriology, but oftentimes SBPs

are neutrocytic, non-culture negative.

Thank you.

DR. FORBES: There was one other question on inter-rater analysis, but I am not sure if that is actually ready yet. No. Okay. We can actually touch on this since this was a question from earlier in the morning that we weren't able to answer.

[Slide.]

DR. BORTEY: This analysis deals with the inter-site differences in the accurate assessment of Conn. The dominant features for Conn 2, that is lethargy, and the dominant features for Conn 3, that is somnolence.

So, to be able to have a meaningful data presentation here, we have to pool the centers. We have 70 centers participating in this study. So, we used a cutoff of 30 per site, to pool to have a meaningful presentation of the data.

The analysis reflects that we don't have inter-site differences, you know, with respect to the assessment of Conn 2 and Conn 3 post-baseline.

DR. FORBES: I believe that concludes all the outstanding issues that we were asked to address.

Committee Discussion and Questions

DR. RAUFMAN: We will now begin the panel discussion portion of the meeting. Although this portion is open to public observers, public attendees may not participate except at the specific request of the panel.

The first question we have is a discussion question, not a voting question. I will read it. I know it's up there.

Question No. 1. Study RFHE3001 enrolled a patient population with hepatic encephalopathy. To be eligible, patients had to have a history within the past six months prior to screening of equal to or greater than two episodes of overt hepatic encephalopathy defined as Conn Score greater than or equal to 2.

At enrollment, the patients were required to have Conn scores of 0 or 1. At least one of the prior episodes must have been verifiable from medical records. Hepatic encephalopathy episodes primarily attributed to GI hemorrhage requiring greater than or equal to two units of blood, medications--for example, narcotics. Renal failure requiring dialysis, or CNS insult were not counted as a prior qualifying episode of hepatic encephalopathy.

Two-thirds of patients in the trial had a baseline Conn score of 0 and one-third had a baseline Conn score of 1. Ninety one percent of patients were taking lactulose.

The first two discussion questions: How should remission be defined in overt episodic hepatic encephalopathy? Should patients with a Conn score of 1 be considered to be in remission?

I will open it up to the Committee. Dr. Lockwood.

DR. LOCKWOOD: It seems inconceivable to me that one could say that an individual had symptomatology referable to malfunction of the central nervous system and consider that person to be, quote, "in remission," unless there is some strange new definition of remission, that, to me, remission would mean that that person had returned to a completely normal state.

If you moved from, say, for example, Conn score 2 to 1, that would be an improvement given the caveats that we have heard about this morning about the Conn scoring system, but I don't see how a Conn score of 1 should be considered to be a remission.

DR. RAUFMAN: Additional comments? Dr. Brass.

DR. BRASS: I agree about the Conn score of 1.

There is some evidence in the literature to suggest that the Conn score of 1 may still be associated with problems with daily functioning both at work, as well as with driving abilities at the level of Conn score 1, so I wouldn't consider a Conn score of 1 to be evidence of remission.

DR. RAUFMAN: Dr. Dasarathy.

DR. DASARATHY: I agree that we probably, in the usual sense of the word, would not consider Stage 1 as in remission. But we do have people who are in a basal state of about 1 or 0 to 1 that fluctuates during the day.

It would be very difficult for us to maintain them constantly in a state of 0 without putting them through the degree of treatment or interventions which are probably going to be more difficult to handle than a Stage 1 itself, and, if people who are waiting for a transplant where we expect the outcome is going to be complete recovery, in that state, going from a 3 or a 2 to get basal state of 1 could be considered to be in a state of remission for that specific patient.

We have all faced these situations. We have people in our practices who remain in a state of 0 to 1, and it also depends how accurate you are in trying to define 1.

As I said earlier, the status changes during the day. Somebody might be in a state of 0 in the morning, by afternoon they are in status 1. How do you classify them, I mean how do you define them? Do you want to call them in remission? This is what the usual status is.

You ask the family members. They say, yes, this is what he is. Ask the guy. He says, yes, this is how I usually am, I am back to my usual self. So, I am not necessarily sure it is very easy to define saying that somebody is in remission or not bases on Status 1, based on an observation at one time point.

So, we need to be very careful about defining or excluding Status 1. That is why I was pursuing in the morning as to when was this assessment done, was it done at one point, was it standardized, how do we define it.

DR. RAUFMAN: Additional comments on this discussion question?

DR. COHEN: Yes, I would agree. In clinical practice, it is very hard to ascribe a specific number to a patient particularly when you see them at multiple times over that 24-hour period and, from day to day, the fluctuation does occur.

DR. RAUFMAN: Dr. Brass.

DR. BRASS: In essence, it is not an issue about remission. The issue is about the rating scale being used. It may not be sufficient to adequately address what is a syndrome then. If it changed from 0 to 1 in a matter of a day, then, maybe it is not totally reflective of what we need in order to totally evaluate the patients.

DR. RAUFMAN: Why don't you respond.

DR. DASARATHY: This has been an issue for, at least to the best of my knowledge, at least the last two decades when urologists and hepatologists will never, ever agree on this, because for a neurologist to say that the malfunction is fine, they have to be in a perfect condition.

For us, as long as they are in a reasonable state of functionality, at their basal state, we are willing to accept it. So, it's a question of philosophic differences. So, if you ask any hepatologist, we are facing imminent death.

You know, somebody is alive, he's talking, he's giving out his name, and they say, well, to communicate, we think he is functioning reasonably well, and this is what his usual status is, short of being in permanent treatment.

Either you block their tips, or you transplant them, we accept Status 1, and that is probably--so, I can understand how the design was done, that 0 to 1 would be considered as remission depending on what the patient is.

So, if you ask a neurologist--and I have met neurologists with special interests in hepatic encephalopathy, and they are eternally confused as to how do you define, with clarity, encephalopathy. And we are the first to recognize that the Conn index is not the best. But it is simple, it has stood the test of time, and it is reasonably valid.

DR. RAUFMAN: Dr. Rehm.

DR. REHM: As a non-gastroenterologist, I am not burdened with excessive knowledge about the Conn scale, but it seems to me that the difference between 1 and 2 is much greater than the difference between 0 and 1. In a clinical trial like this, I think that is really important.

The second part of my comment or question is it seems--I am getting the idea that it is possible for a patient perhaps to go from 0 to 1, and back to 0, over a period of time without changes in therapy whereas, to go from 1 to 2, it sounds as if it's less likely for them to go

back down to 1 without changes in therapy.

Is that a valid assumption?

DR. RAUFMAN: Generally.

DR. DASARATHY: I completely agree with that, because, you know, when we looked at--and one of my colleagues looked at differences in the reproducibility of the grading, if you were to differentiate between 3 and 4, from 0 to 1, it was very clear.

So, from 0 to 1, it is a lot harder than to differentiate from between 2 and 3, and to say that yes, somebody is in 0 to 1, it is easy to say. If you say somebody is in 2, you can be reasonably certain even if there are different observers.

But between 1 and 2, I think you can be pretty certain. I don't know of any studies which have specifically looked at Kappa statistics on inter- and intra-observer variability, which is what I would have liked, but we don't have the data. Short of that data, we have to live with the soft data that exists, that the differentiation of 0 to 1 is hard but, after that, it becomes a lot easier.

DR. RAUFMAN: Those data I believe Dr. Anderson was asking for earlier this morning, and we don't have them.

Dr. Hersch.

DR. HERSCH: Actually, I think my comments have been covered.

DR. RAUFMAN: Dr. Hilton.

DR. HILTON: Following up on changing treatment between 1 and 2, or 2 and 3, I am still not clear on what that would be. I think we are calling, in this study, a 2, a treatment failure, and the patient is being taken off treatment.

But, in fact, maybe the treatment is keeping that patient from going from a 1 to a 3, so it still is perhaps showing effectiveness. I don't know that there is a treatment strategy envisaged for a patient who moves from 1 to 2, what treatment strategy would be implemented in that case. Maybe the best strategy is maintaining them on the treatment.

DR. RAUFMAN: Dr. Lockwood.

DR. LOCKWOOD: It is typical of metabolic encephalopathies, particularly HE, for patient to fluctuate even from hour to hour and day to day in terms of how severely they are affected.

I think the question is whether the person is in

complete remission and free of all symptoms, which would seem to me to be the most logical definition, or improved. There are some patients for whom you cannot achieve a remission. But you can make them better, and that may be the case with the drug under consideration,

But I think it's a mistake to consider someone who is in Conn score 1 status to be in remission. They might be substantially better than they were before, able to function more independently and have a better quality of life, and all of the things that that implies.

But to say that they are in complete remission I think defies what the definition of remission ought to be.

DR. RAUFMAN: I am hearing a consensus on that point. I don't think that there is argument about that point. I think the argument is more about how stable these patients stay at 0 at that they fluctuate frequently between 0 and 1, and for purposes of a study like this, it may be difficult to get all the patients at 0 at the time of entry.

Are there other comments? Ms. Cryer.

MS. CRYER: In my 15 years of working with patients with advanced liver disease, in addition to my own experience, I find it surprising that we could find anyone

going through the stress of this condition who rates a 0 on a score.

The condition itself almost necessarily gives you a shortened attention span and some of the other things listed as a Conn score 1, so I just underscore the difficulty of distinguishing for any patient suffering from this condition between a 0 and a 1.

DR. RAUFMAN: Dr. Gitlin.

DR. GITLIN: Just to illustrate the complexity, that the changes in the staging of clinical encephalopathy can be dietary, and we always tell our patients, for example, to avoid Jello. Jello is the stable food at all hospitals. So every time I used to do a ward round at nighttime, regardless of what illness my patients had, they had Jello because it is the most cost effective and it is easy to prepare.

So I think that just illustrates with the gelatine products how you can get fluctuation in the clinical scenario without any--if I can use the word--endogenous reason. It is just an exogenous dietary factor.

I know that neurologists and hepatologists are poles apart, and they are always going to stay poles apart,

but it is a different concept.

DR. RAUFMAN: Any additional comments? Again, I think we have a consensus. I don't think we are going to get any closer to a uniform answer to the question.

So, again, just to rephrase that, I think we are agreed that a Conn score of 1 is not remission. However, it is difficult in some cases to, as we just heard, to tell the difference between 0 and 1, or for a patient to maintain stability at 0 without flip-flopping between 0 and 1.

One more comment? Dr. Hersch.

DR. HERSCH: The issue is not--I mean the definition of remission is one thing, and the issue of whether there is a material benefit is separate, so it's a semantic issue around remission that certainly can be reconsidered as a word use.

DR. RAUFMAN: Should we move on to the next question?

Question No. 2 is also a discussion question, not a voting question. This one may be a little more challenging.

For future clinical trials, what clinically meaningful endpoints should be evaluated (as primary and key

secondary endpoints), and how should they be measured for decreasing the risk of episodes of overt hepatic encephalopathy, and treatment of overt hepatic encephalopathy?

Again, I will open the floor.

DR. HAUBRICH: I again being an ID person don't have to worry about how good the Conn score is or isn't, but I do have a few things to suggest in terms of clinical-trial issues from 20 years of experience doing HIV clinical trials.

In the early days, our studies used clinical endpoints of progression of age or death, and although that seems easy to do, it is pretty easy to tell if someone is dead or not, defining whether someone has a new age-defining condition, since there are 13 some-odd conditions, can be quite complicated.

So, one thing that could be used here, assuming the Conn score is a reasonable thing to do, would be to be very specific in the capture of the data for the HESA, if that is the way that it seems that's a good way to capture the Conn score.

Instead of having the final adjudication of the

endpoint at the level of the investigator, which can have a lot of variation, have those endpoints looked at in a blinded or a masked fashion centrally by preferably two or three reviewers who are independent of the study and don't care what the outcomes of the study are.

So, there would at least be a uniform assessment of the endpoints so that we wouldn't be having the discussions like we had today whether the endpoints are good or not.

Another thing that could be added to that, and it actually goes along nicely with what people said here and actually get back to points of, well, people go off the study, would be to look at something like a mean cumulative frequency as an endpoint of the study, so that people that have recurrent and multiple episodes of increase in their score could be counted multiple times, and you could get an assessment of the effect over time.

So, in other words, yes, we prevent the first one but, if they all go back to the same rate after the first episode, you know, in the long term, you haven't really achieved things. So, other sorts to clinical trial type of things that are well known from other fields could be

brought to bear here to make the assessment of this endpoint, if it's considered to be the right endpoint, and that would work well whether it's decreasing the risk of episodic disease or for treatment of an overt encephalopathy.

DR. DASARATHY: Unfortunately, despite our what I would say pretty extensive reading of how to do clinical trials and endpoints, there are some diseases in hepatology where the endpoints are much clearer.

Portal hypertension is one where we have clear endpoints, we know what to look for. Encephalopathy, unfortunately, is a field which is hard to capture because the endpoints vary. So, this is why it's very difficult and I think the only other good randomized trial that I am aware of in encephalopathy in the last 10 years is one which was done by Andy Blei and Juan Cordoba on protein restriction.

It is so difficult because the reviewers have the same critiques that we are having right now, I mean how to define it, when to do this, what would be a perfect way to do this, have them all on a 7-day GCRC standardized diet, have them constantly monitored, connected to electrodes everywhere, and how do you do this.

So, this is the best that we can do, that we recognize the big differences we can make, we know when somebody is really sick. The guy is now back to baseline, so I am not sure whether we will be able to identify perfect endpoints. So, in the absence of perfect endpoints, we have to learn to accept imperfect endpoints.

DR. RAUFMAN: Dr. Maxwell.

DR. MAXWELL: I just wanted to underscore that point, because there are several factors outside of the drug, the treatment, that impacts on a person's improvement or not. So, just talking about Jello, you know, the drug could be quite effective, but if there is a dietary mishap even in the most controlled of conditions, then, it is going to be impossible to come up with a defined primary and secondary endpoint, so you might have to go to the next best thing, which is probably improvement.

DR. RAUFMAN: Other comments? Right now it sounds like we are saying that we can't do better than was done. Is that actually the case? Dr. Solga.

DR. SOLGA: I really like the time-to-first-hospitalization as a firm endpoint, something that is very easy to look at. Is Jack in the hospital or is he at home?

I find that key secondary endpoint very compelling with this data. I think that was very wise. In retrospect, I wish it was the primary endpoint.

DR. RAUFMAN: Dr. Hilton.

DR. HILTON: I like that last proposal. In general, I like the idea of repeated measures analyses, and I think that if we are analyzing the Conn score repeatedly, we don't need to dichotomize it. Why not allow the whole spectrum 0 through 4? We would get a lot more information.

DR. RAUFMAN: Dr. Kumar.

DR. KUMAR: My comment was about a measurement of an imprecise point and, if that were the case, maybe we ought to look at it from various dimensions to make sure that a measurement or the way it goes from one dimension, indeed, is very friable from another, the point being that we might have to use several scores or a composite of different scores.

Coming back to the point that was made about, you know, trail-making tests or number-counting tests, you know, to use minimal MMSE, the Mini-Mental Status Exam, which has been used, a score of 24 or under being sort of evidence of overt hepatic encephalopathy, to confirm that indeed there

is only minimum hepatic encephalopathy given that the Mini-Mental Status Exam score is 24 or greater, to use a number-connecting test, trail-making test, and so on, and so forth, ought to be sort of, you know, used as additional data that then verifies or provides further support for the Conn evaluation.

DR. RAUFMAN: That might help to tell, distinguish between a 0 and a 1.

Dr. Lockwood.

DR. LOCKWOOD: There are a couple of other avenues I think that could be explored. One would be to make better use of our colleagues in neuropsychology to get better input about how they can use their expertise and their way of testing the central nervous system to make the kinds of judgments that are faced in clinical trials like this.

Another avenue that might be explored would be to support additional studies using neuroimaging techniques, particularly those of functional magnetic resonance imaging, to look at some of the nervous system functions, such as attention, that are impaired in metabolic encephalopathies.

DR. RAUFMAN: I think one issue with those is I am not sure that they have been adequately validated for this

particular purpose.

DR. LOCKWOOD: Perhaps not for this purpose, but I think we are looking at a question here that is going to be facing this field for some time, and encouraging support of those kinds of studies on the part of appropriate agencies would be appropriate.

DR. RAUFMAN: Dr. Solga.

DR. SOLGA: I was just going to chime in. The EEGs and MR spec studies are really challenging. They have their up side. The MR spectroscopy I think is fairly mature, looking at glutamine-choline ratios in the brain, but it takes a considerable radiology expertise to pull that off consistently.

The EEG, I remember taking the Working Party paper from 2004 that was supposed to settle this issue to the Chief of Neurology and saying, look, it says here I am supposed to do an EEG with P300 auditory oddball paradigm, and he said I have no idea what you just said.

This has been a real challenge, you know, it just seems that about a 20- or 30-year effort, but the batteries and the panels haven't settled the issue, which is I agree more research is needed. But we are where we are, which is

why I really like the hospitalization endpoint.

DR. RAUFMAN: Dr. Cohen.

DR. COHEN: Steve could probably do a better job, but a couple of observations apropos the HIV literature. One can do more and more sensitive neuropsych testing. I think the point here is we have to have a way of evaluating patients that is relatively simple and easy to train people with.

There are some subsets of neuropsych testing that could be done, particularly tablet tests that the patient has that can be scored. The other thing is the EEG. You know, we have done frequency analysis and all this, and it is just too cumbersome. It is interesting for research as is functional MRI.

I like Dr. Gitlin's idea about actually counting asterixis, you know, and listening to this on how to judge asterixis, that seems difficult to me. There ought to be a way that you could just film and count the number of beats of asterixis and actually get a finite number, but best I think the hospitalization is a very simple endpoint to use.

DR. RAUFMAN: Dr. Kane.

DR. KANE: I just wanted to say that, you know,

functional MRIs and EEG studies are all very well and good for research purposes, but when you are talking about trying to do a trial with 70 centers, those in Canada and Russia and the United States, that is not going to be technically or fiscally possible.

So, I think that we are using what we have, that is somewhat reproducible, you can train people to do this, and you are not looking at extra millions and millions of dollars.

DR. RAUFMAN: But I would point out that this is a research purpose.

Dr. Gitlin.

DR. GITLIN: This is more of a question than an answer. What happened to the five-point star that we used to have to do? When I trained under Professor Sherlock, you weren't allowed to lift up the pin, the patient wasn't, and, as a control, the doctor did his next turn, and we had to identify which was the doctor and which was the patient.

[Laughter.]

DR. DASARATHY: I have two comments now. One is in response to what Kane said, and I agree. When we want standardized equipment, then, you want to make sure the

everyone is using the same company's equipment, everybody is doing it the same way. Even for research when it is multi-departmental, I am not talking about multi-center or multi-country, multi-departmental, it becomes a challenge.

The second comment that I had was that this attempt to have a standardized endpoint has eluded us and the appropriate funding agency.

The National Institutes of Health, to the best of my knowledge, has not funded a single clinical encephalopathy study in the last 10 years. All the studies that are getting funded are cell studies. They are studies on genes.

So who is going to fund these things? You know, it is easy to say that this should be done, but who is going to pay for these?

So, we just have to--you know, that's why the Working Committee for the Encephalopathy was held twice, and I think that the recommendations of that committee are pretty acceptable for most clinical practitioners.

I believe with what Dr. Cohen said, that it has to be clinically simple to apply, otherwise nobody is going to use them.

DR. RAUFMAN: I would argue that when those bodies make recommendations for clinicians to use in clinical practice, the approach we would take for a clinical study of this kind could be more rigorous. I mean there is a difference between what you expect somebody in the field to be doing compared to what we might expect in a study evaluating the efficacy of a particular drug.

DR. DASARATHY: It is interesting, but in response to that, the considerations that were made in many of those meetings are under ideal, utopic conditions, with no restriction of money, no restriction of capabilities. Even then it is difficult to define what would be a perfect endpoint, which keeps changing all the time, and it changes depending on who is measuring it.

DR. RAUFMAN: Dr. Hersch.

DR. HERSCH: As a neurologist with a lot of experience with using neuropsychological measures and neuroimaging measures, and outcomes in multi-center trials, I would tell you one of the biggest problems with them is that the clinical significance of those measures can be really hard to know or make use of.

I think measures like hospitalization where there

is a real world significance to that measure are far superior for things like --

DR. RAUFMAN: But even with hospitalization, there may be some variability in the observer, the clinician's threshold for admitting a patient. Financial reasons, you can think of a host of reasons that have nothing to do with the actual stage of encephalopathy.

DR. HERSCH: Oh, absolutely, but you can anticipate some of those and study some of those, and you can use some. I am not disparaging all these measures, I think they are useful for doing things like determining if a 0 is a 0 on a Conn scale, for example.

But I actually like scales like the Conn scale in part because they sort of capture more globally the process and direction of the disorder, and a lot of the more technological or fine-tuned measures capture such a small fraction of what is going on that interpreting their meaning gets harder and harder.

DR. RAUFMAN: Dr. Anderson.

DR. ANDERSON: I wanted to speak in favor of the hospitalization endpoint, because it's hard. It's not perfect, There is a chance for variability, as you just

described. But the randomization, if there is adequate blinding, should take care of any potential bias in that, and give you a very hard endpoint that you can go to the bank on.

I also think it should be supplemented with a repeated measures analysis of the Conn score to detect somewhat more subtle differences, and there I would do it at defined points in time, not generated by something that is happening in the patient, but at specific points in time in the treatment process.

I would like to see it decreasing the risk of episodes over time, so it is not time to the first necessarily, because I think in the clinical setting, you are going to treat the patient when they have an episode and bring them back and want to continue on this kind of therapy.

DR. HAUBRICH: So, I think we are all enamored with things that nobody disputes, like being hospitalized. But, although that is a great endpoint, when you look at the data from this trial, even hospitalization that is ascribed to hepatic encephalopathy, the first thing you see is that the number of events is smaller, and that means the power of

the trial is less, which could mean that a future trial would have to have a bigger sample size to be able to detect an effect, which, of course, it then means it is harder to do the study, and it sounds like this study was hard enough to get this many patients in.

DR. RAUFMAN: That is an excellent point.

Dr. Hilton.

DR. HILTON: It could be that a different eligible patient population might be used in the trial to better target that outcome.

DR. HE: If we are going to use hospitalization as a primary endpoint, we will like to prespecify the standard for hospitalization. Could you give some comment how we can specialize, you know, standardize the standard for hospitalization?

DR. RAUFMAN: So, what criteria would one use to hospitalize a patient with hepatic encephalopathy? Comments?

DR. DASARATHY: You know, the question is whether we hospitalize for the precipitating event or do we hospitalize for encephalopathy. They are going to be grossly overwhelmed by the number of hospitalizations for

the precipitating event, GI bleed, sepsis, renal failure. So it is going to be very challenging to even find patients who are getting hospitalized only for the encephalopathy.

Now, I have something else interesting to note in the data that they had, that about the half the patients did not have a precipitating event for the worsening of encephalopathy, which itself is a little unusual because most patients who are stable usually remain in a stable state unless they have severe liver disease.

But the patients who did not have very severe liver disease, most of their patients are Child's Class A and B, they had a low MELD score. So they are able to at least identify patients who have these spontaneous episodes of worsening without contamination by precipitating factors.

So, I thought that they had a pretty good population of patients.

DR. RAUFMAN: Dr. Solga.

DR. SOLGA: No, it was more of a thought. I guess I wouldn't over-think the hospitalization thing. It is hard to get into hospitals these days. You know, the insurance companies have all sorts of barriers.

It is for sick people, you know, and when they are

done being sick, they go home. Again, I think it's a real strength of the study that this was blinded and placebo controlled, and that was something that was very important. You know, as Leslie Nielsen said in Airplane, "This passenger needs to go to the hospital," and the stewardess says, "A hospital! What is it?" "It's a big building with beds, and it is for sick people."

So, I think to me, that works out really well.

DR. RAUFMAN: I don't know if we have answered this question. I think, if I were to summarize, that the Committee favors hard endpoints like hospitalization. But then you get into the question of what are the criteria for hospitalization, are there going to be enough people who meet those criteria in a study of this kind to achieve a sufficient N to make comparisons between groups.

I am hearing also that it would have been I think preferable to have some additional, relatively easy, tests as part of the evaluation of the patients, trail tests, number-connection tests, some things that would give some numeric data in addition to a more subjective evaluation of the Conn score.

Is that a fair summary of what people have said?

Dr. Hilton.

DR. HILTON: And not focusing on the initial recurrent event. To focus on repeated recurrences over time, I think would be very valuable.

DR. RAUFMAN: More of a longitudinal approach.

DR. DIMICK: I would like to ask the panel another question, which is do you think the length of hospitalization or the severity of the episode is data that you would collect or be interested in?

DR. RAUFMAN: I would think not. I think again there are so many variables that would determine the length of hospitalization that I think that that would muddy the question and make it less hard of an endpoint, but again any comments on that?

DR. HAUBRICH: Number of hospital days is an easy metric and can sometimes provide more granularity than just the bivariate outcome. I completely agree there is a gazillion things that contribute to long stays, but if you just barely make it in because you are doing okay, and you are not quite so encephalopic, maybe you will have shorter stay.

DR. RAUFMAN: Dr. Hersch.

DR. HERSCH: I am not sure you couldn't make those details primary or secondary outcome measures, but I think as supportive data, there would be a lot of really invaluable information around secondary diagnoses and length of stay, and there will be all kinds of laboratory data that might answer questions related to infectious disease or other things that come up.

DR. RAUFMAN: Additional comments on that? Dr. Kumar.

DR. KUMAR: With regard to using hospitalization or length of stay, I think the variables that go into hospitalization and the length of stay are really several and they include whether the patient is arriving in the day or at night, patient preferences, physician preferences. And the length of the stay is often a function of also variables that really are not reflective of the condition itself.

So, I think to use both of those would be fraught with problems and would be an imperfect yardstick.

DR. RAUFMAN: Other comments on that? I think can move on to the four voting questions. We will be using the electronic voting system for this meeting. Each of you have

three voting buttons on your microphone labeled Yes, No, and Abstain.

Once we begin the vote, please press the button that corresponds to your vote. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. I will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state their name and vote into the record, as well as the reason why they voted as they did.

If we could have the first voting question, and I will read the question.

This is Question 3, again a voting question.

Do the clinical data included in the rifaximin application provide substantial evidence of efficacy for an indication of maintenance of remission from hepatic encephalopathy--that is, decreasing the risk for episodes of overt hepatic encephalopathy?

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?

Please push the appropriate button.

There is a question?

DR. DASARATHY: I am back to my same question. Are we talking about efficacy as a stand-alone drug, or are we asking for its efficacy in combination with lactulose?

This is a question that I have been asking repeatedly, and we still don't have an answer to that.

DR. RAUFMAN: The indication as I read it, did not include lactulose.

DR. GRIEBEL: The study as designed was an add-on study, and its design isolates the effect of rifaximin. So the study design has the capability of demonstrating whether rifaximin is effective for reducing the risk of episodes of overt HE.

You can give in your answer how you vote and your reasons for voting, how you would see the indication reading. But we can certainly write in the indication how it was studied. It was studied in patients who were taking lactulose at the same time, and lactulose carries the indication I believe of prevention of HE.

So, it is not out of line to do that.

DR. RAUFMAN: If there is no additional discussion, you can vote Yes, No, or Abstain on the microphone.

[Electronic voting.]

DR. RAUFMAN: Please press one more time.

The voting result. We have 16 Yes votes, two No votes, and no Abstentions.

We will start with Dr. Kane and I guess move around in that direction, so if you would identify yourself, tell us how you voted, and the reason for that.

DR. KANE: Sunanda Kane, Mayo Clinic.

I voted Yes and I said that, on the thinking that this was an add-on product in patients who are already on lactulose, experiencing repeated episodes of hepatic encephalopathy, that I was happy with the robust outcome of time to--or decreasing the risk of episodes to overt HE with the statistic that they provided, the narrow confidence intervals, and also the timing of the changes seen as we discussed the two- to four-month window where maybe there is colon eradication of certain bacteria that we just haven't identified yet short of taking their colons out.

I am feeling very confident that this is an efficacious agent. I guess my deficiencies are that we just have one trial. But I am supported by all of the other data that have been supplied in the treatment of acute treatment, as well as other smaller trials that were not controlled.

DR. REHM: Susan Rehm, Cleveland Clinic.

I voted Yes for similar reasons. This is a single trial and I think that the data potentially would be more compelling if there had been an additional trial, and we have talked about some of the methodologic issues. But I believe that the data as presented do support the efficacy.

I would like to see in the labeling, to be sure that it is clear that this was an add-on to lactulose as a primary therapy.

DR. KUMAR: Atul Kumar. I voted Yes. There is biological plausibility for the effect of this drug. Despite the methodological problems, imperfect yardstick, and issues about data collection, as were pointed out, it seems that the drug was fairly effective in line with the biological plausibility.

I think additional data supportive of this would, of course, be very helpful but, to the extent that we have

data, this appears to be effective.

DR. GITLIN: Norman Gitlin. I voted Yes. I believe that, although it is a single study, this is a very difficult field to study and I think they did it outstandingly under the circumstances, and the results were extremely compelling. Like the previous colleagues, I do believe that the final ruling will have to be that it is given in conjunction with lactulose.

DR. MAXWELL: Celia Maxwell. I voted No only because I didn't think that there was clearly demonstrated maintenance of remission. I thought that there was improvement. It was a single trial.

I feel that it has to be considered an add-on with lactulose. I thought that it's difficult to do this kind of trial in that in the data that was submitted, patients did respond well, but I did not think that is showed maintenance of remission. It showed significant improvement.

MS. CRYER: My name is Donna Cryer. I voted Yes. I found the clinical evidence persuasive, if not dispositive in this case, there being one trial. I would like to see further development of data, and I phrase it that way, whether it be by surveillance or a study at this particular

dosage.

As far as the labeling, I concur with my colleagues that I would like to see the label reflect the add-on position of the drug, and I want to express a preference for the language of decreasing the risk for further episodes rather than the maintenance of remission language. Thank you.

DR. HERSCH: I am Steve Hersch. I voted Yes. My reasons really echo the ones that we have heard. I agree with the suggested change in the indication as more reflecting what was actually shown.

I would also like to see data in the future with respect to repeated episodes as others have mentioned before. I think that would be important to know and worth figuring out how to study in advance.

DR. DASARATHY: I am Dasarathy. I voted Yes because I think that despite the concerns raised that it is a single trial, sometimes we can only afford one trial, and if it is done well, and if we are convinced that the trial data are in keeping with what the expectations are, that one trial should be enough as long as it is monitored carefully, and I am convinced that the investigators have done their

best to be as objective as is possible in this field.

The only caveat would be that it should be stated as in combination with lactulose, because we don't know if it works as a single agent.

DR. HAUBRICH: Richard Haubrich. I voted Yes. I am strongly impressed by the magnitude of the primary endpoint and the primary analysis. I feel that the secondary analyses of related endpoints are completely consistent both in magnitude and in odds ratios and support the primary endpoint.

The one caveat that we have discussed a lot is the accuracy of assessment of the endpoint. However, I have found and heard no evidence that there was bias in assessment, so lack of accuracy in this endpoint would actually serve to introduce, be a conservative bias in the case here, which would actually suggest that the benefit might even be more than we see.

As with the other colleagues I agree with the changes to the wording of the label and the use of lactulose.

DR. SOLGA: I voted Yes for all the reasons already articulated. My major concern with the deficiency

in the efficacy is that Salix chose to look at the middle sick here. There is nobody with a MELD greater than 25, and if it ultimately comes to approval, it will surely be used by clinicians everywhere, in patients who are much, much sicker.

Folks, when they get to be a MELD 25, 30, 35, 40, they are really different than they used to be at 5, 10, 15, and I think that is going to be a significant concern moving forward.

DR. RAUFMAN: Jean-Pierre Raufman. Despite what it says on the board, I voted No. I hope it's a glitch in the machine, and not encephalopathy, but I am pretty sure I pushed the No button. My reasoning for this had to do with the word "substantial" in the efficacy question.

I am concerned about the fact that the drug, we don't have information from the pivotal trial regarding the efficacy of the drug by itself, that we have heard a lot of negative things about lactulose, and now we are going to propose an indication to use this new agent with lactulose doesn't sound good economically either.

So, based on those concerns, I voted No.

DR. ANDERSON: I am Garnet Anderson. I voted No.

I think I also had trouble with the word "substantial." I do believe there is a lot of strong data. It is just not compelling to me.

It was a single study. The endpoint is a bit soft, and it was not a verified, a centrally adjudicated kind of outcome. I didn't feel like we had ever been given the true intent-to-treat analysis, which I consider as the anchor. All the other analyses are fine to do, but I need to start with an intention-to-treat analysis.

I think we would like to see efficacy in a different framework, both with and without lactulose, and also in a continuing setting, where you don't withdraw the patient from treatment after the first overt episode.

DR. LOCKWOOD: I am Alan Lockwood. I voted Yes.

I found the hospitalization data to be compelling. I think all of the vagaries of the Conn score that we spent a good deal of the morning debating supported that. It's a difficult study, and I think the investigators probably did about as well as one could expect given the circumstances.

I, too, would support additional trials in the future that move beyond sort of the middle sick as was discussed by one of my colleagues to the right here,

particularly the people who are less sick than these, the people at the minimal encephalopathy.

DR. COHEN: I am Jeffrey Cohen. I voted Yes. I won't repeat what everyone else said. I thought it was a very spirited discussion. It points out the difficulties that we all have in clinical practice with this, and I think as we discussed it more, I realized the vagaries of this.

I think we need to have better assessment scales of this condition, and the way I envision this drug to be used is the patient who is on lactulose, who still has episodes of hepatic encephalopathy or who is very ill, that this drug would be used in that context.

MS. SKLAR: I am Jill Sklar. I voted Yes. I felt that the data was compelling. Was it perfect? No. But I think it was important to have this for the patients. Would I like to see other things in the future? Yes, I would like to see a larger study. I don't know how feasible that would be. It is probably difficult to get all of these patients in the first place, and I would only imagine that it would be more difficult to have a larger study for that.

Also, clear guidelines in prescribing this, essentially, that we also include lactulose on the label. I

could see a lot of physicians using this just on its own, and I don't think that that is enough data to support something like that. So, for the safety of the patients, I would want to include that.

DR. HASLER: Bill Hasler. I voted Yes with the caveat that it is co-administered with lactulose. I found the data compelling. I was very impressed with the study design, that 70 centers across international borders were recruited and almost 300 patients were recruited, and that there was no one dominant center that had positive findings.

So, it really crossed national and international borders. I also did not have significant trouble with the primary endpoint. I know there were discussions about the Conn score, but I think the sample size significantly takes care of that.

The other comment I will make about the Conn score comes from actually comments made by Dr. Rehm and that as a non-hepatologist, I have come away impressed with the Conn score as being somewhat nonlinear, that the scores of 0 to 1 are relatively tight, and that everybody with a score of 2 and above is sick, but that there is a big difference between 1 and 2, so I thought that their primary endpoint

was reasonable.

DR. HILTON: I am Joan Hilton. I voted Yes because I was impressed by the strength of the overall analysis as well as the consistency across subgroups defined by baseline characteristics and the consistency of the findings across primary and secondary endpoints.

I agree with the earlier speaker who mentioned that this will probably be used in patients with higher MELD scores, and there was very little evidence in the MELD score category 19 to 24, but some evidence of efficacy. So I would encourage expansion to include more patients in those groups.

DR. BRASS: My name is Steven Brass. I voted Yes based on the findings of the primary and secondary endpoints in the study, despite the limitations that we discussed.

In terms of the labeling, I agree with my colleagues about that they should be labeled as an adjunct to lactulose.

DR. RAUFMAN: Great. We will move to the next voting question.

Question No. 4. Has the safety of rifaximin at the proposed dose and duration been adequately assessed? In

answering this question, please discuss whether additional analyses or trials are needed.

Is there any discussion on this question?

DR. DASARATHY: The only concern I have is that it is going to be used predominantly in Child's Class C, MELD over 25, because these are the patients who are going to be encephalopathic.

So, once you have encephalopathy, your Child score is an automatic 7. You can't be lower than a 7. So, you are automatically B. Now, if somebody is going to be using it in Child C, and there is some minimal evidence that the absorption of rifaximin is greater in Child's Class C, I don't know whether giving a blanket approval for its safety without considering the Child's Class would be safe. It would probably be a good idea to say very clearly that it is approved for Child's A and B and, if somebody is using it in Child C, they are using it outside of FDA approval.

If you want to do it, you can do it should be made very clear, because that is really concerning me because the numbers are very small for me to be confident. But it seems like as the Child's Class gets higher, the plasma concentrations near the end of the curve keep increasing, so

we don't know what the toxicity of this is going to be. as you increase the area under the curve, how long it is going to last.

Now, once you say it is approved, what is going to happen is people who have got renal failure also are going to get it. The example that was given by I think Dr. Dimick was that neomycin was approved. They said that it is minimally absorbed, but it was then found that people who were getting renal failure, it was compounded by the addition of neomycin. So we don't know what this is going to do in people who already have renal failure in a disease which is potentially progressive.

So, I am just a little concerned about the wording of this question that is this safe or not. It is like a blanket safety approval which is not true. But. at the same time have they assessed safety, you know, it could be answered depending on what viewpoint you are taking.

DR. RAUFMAN: I don't read the question as is it safe or not. It is simply asking whether the safety at this dose and duration has been adequately assessed, and your response would be that not in patients with worse stages of liver disease.

DR. DASARATHY: So, the question is yes or no. I don't have any way to say that yes, given this, or no, given this, it is yes or no.

DR. DIMICK: I think that the next question addresses your concerns.

DR. RAUFMAN: Dr. Cohen.

DR. COHEN: Yes, a clarification question. So, in the study, the patients who received the drug, the longest duration was how long, how many months?

DR. RAUFMAN: I think we heard about a year, something like that.

DR. COHEN: About a year. And as a non-gastroenterologist, the treatment of patients would be ad infinitum? Okay.

DR. RAUFMAN: Yes, until transplant or death.

DR. COHEN: Got it.

DR. RAUFMAN: Dr. Maxwell.

DR. MAXWELL: Just a question for the GI team. I think in reviewing, I saw data that suggested that the absorption in patients that had liver disease, or the systemic absorption was higher than expected and higher than you would see in normal volunteers. So I just wanted to

make sure, is that correct? Okay.

DR. RAUFMAN: As I recall the data, the area under the curve was as much as 20-fold higher in patients with advanced liver disease.

DR. LI: We have data that says systemic exposure in hepatic-impairment patients will be higher, and the more severe it is, the higher it is. But we don't know if it's due to absorption. It may be due to elimination, and not absorption, but we don't have hard data.

DR. RAUFMAN: Do you have a comment?

DR. FORBES: Yes, just a couple of points of clarification. First of all, as I mentioned earlier, we have an ongoing study that has been open for years now, so our patients have been on it for up to three years. We have also looked at hepatotoxicity, looking at different severities based on MELD as well as Child-Pugh and, long term, it looks very good from an hepatotoxicity point of view. So I just want to emphasize those data. They are in a briefing document.

The other thing, too, of course, the rifaximin PK and liver impairment, it does show elevations. But I will remind you that, in fact, the amount that is absorbed is far

less than other antibiotics that these patients are routinely being given, and we talked about that in the clin-pharm presentation that we had earlier.

DR. RAUFMAN: Thank you.

Yes.

DR. DASARATHY: I would have substantial concern about that concept because saying that it is absorbed less than other antibiotics is good, but the other antibiotics are not going to be planned for six months or one year. They are given for one week, two weeks, or three weeks. We are talking about something that is going to be there for a long time, so we don't know what the consequences of such an extended period of administration are.

Secondly, the safety profile looks very good, sounds good, but I don't see evidence to convince me that this has been addressed and it is okay because the numbers are so small that we are looking at.

DR. RAUFMAN: Question? Yes.

DR. GRIEBEL: I just wanted to echo that as well. We don't make decisions about the safety of drugs based on comparisons to the levels of other drugs, because that would make drug development very easy. You would just say oh, if

you don't go above this level in the blood, then, it's safe. So I just want to be sure that is clear.

DR. RAUFMAN: Dr. Hilton.

DR. HILTON: I just want to make sure that I answer the question correctly when I vote. I don't know if the duration recommended is up to six months or if that is just for the first episode. I am actually really confused about the treatment management.

DR. RAUFMAN: Is there a duration in the indication?

DR. KORVICK: No.

DR. RAUFMAN: So, maybe it shouldn't be in this question.

DR. GRIEBEL: We are actually asking how, if it has been studied long enough, in light of the fact that a product such as this, as we have heard, you will be on it until you get a transplant or die, is the safety data adequate to support that kind of chronic use.

DR. RAUFMAN: Additional comments? Yes.

DR. HAUBRICH: Just a comment about the levels of the drug. There are three things that we want to think about in terms of having systemic exposure to

antimicrobials. Number one is toxicity, That is assessed by the clinical trial that we have seen. So, if there was systemic exposure leading to hepatic toxicity or whatever toxicity you want to have, that is based on levels that we have already seen.

Number two is system toxicity leading to antimicrobial pressure in the body, which can lead to development of resistant organisms or other problems like that. There, I think it is valid to say that the levels that are seen in Class C are in the order of nanograms per ml, systemic exposure to most antibiotics are micrograms per ml or 1,000 times more than that.

So, again, the issues that we would want to see are production of infections with resistant bacteria due to chronic exposure to the antibiotic. I think I had three points, but I can only think of two.

DR. RAUFMAN: Dr. Rehm.

DR. REHM: I think I will tag onto that by saying that yes, the systemic levels are a whole order of magnitude less than we would see with other antibiotics, which doesn't negate the fact that it is there.

But the point about resistance, I think is one

that is potentially more subtle, and that is, that by long-term antimicrobial use, the gut flora would be altered, the colonizing flora would be altered, and the longer term, there at least is a theoretical concern about infection with multi-resistant organisms, which there hasn't been enough experience with this drug to be able to determine whether that is actually going to be an issue.

DR. RAUFMAN: Dr. Cohen.

DR. COHEN: That was my question, because it sounds as if the patients will be on this drug until, as you said, death or transplant. So, it seems to me that the gut flora would be radically--not maybe radically--but certainly changed over time with the possibility of resistance.

DR. RAUFMAN: Dr. Anderson.

DR. ANDERSON: My question was really to know what the time frame was if someone could answer that for seeing whether you develop the resistant bacteria. So we know what it is, is a year--we heard the average exposure time that we have observed is a year in 300-and-some patients.

Is that enough exposure time to see this happen in the gut?

DR. HAUBRICH: Just a couple of other points.

There are plenty of diseases where we give people systemic antimicrobials for an extended period of time. In the HIV arena, we give trimethoprim sulfa at systemic doses for years before we could get them on antiretroviral therapy, and yeah, they can get some resistant organisms, and they can get infections that are resistant to the things that they are already taking, but there are plenty of other disease models where chronic antibiotics are given.

So, what you have to do is look for consequences of that which is emergence of infections resistant. How fast this agent changes the gut flora, I don't honestly know. That is going to be one of my recommendations of what ought to be done. Since most of the concentration of this agent is not systemically, I am not really worried about that, to be honest, I am worried about how it will change the gut flora.

The only thing I could consider happening is then they might, instead of having their regular E. coli, which is sensitive to everything, so when they get their spontaneous peritonitis, it is with a sensitive E. coli. They get a spontaneous peritonitis, that is with a resistant E. coli.

But again if it's resistant to this agent, who cares as long as it's sensitive to all of the rest of the agents we have to use for bacterial infections if they become ill.

DR. RAUFMAN: Dr. Solga.

DR. SOLGA: Of course, we do see folks who are on SBP prophylaxis with norfloxacin and cipro, and end up with more gram-positive and fungal peritonitis than they might otherwise. But that is easy to recognize and easy to handle, and there was no increase in peritonitis in this study for six months.

DR. RAUFMAN: Dr. Dasarathy.

DR. DASARATHY: I am all right. I think we already addressed it, because my question was I am not worried about the antimicrobial pressure based on systemic values.

I am more worried about systemic toxicity in the long term, what are its effects going to be, does it have any mutagenic effects, does it have any effect on DNA expression, on expression of different genes in other tissues, do we really know what it does to other organs. I don't know the answer to that, and I am not sure that it

will be easy to answer that question.

I just have these concerns. It doesn't mean that they cannot necessarily be addressed, but they do exist. We just need to say that we recognize that, in the future, we may find problems, but the concern is do we need to treat these people right now. The answer is yes.

Are we going to become therapeutic nihilists saying that, you know, something may come up after 10 years, do we not treat now? No, I don't think so, but at least we should be aware that this may happen.

DR. RAUFMAN: FDA raised questions about lack of EKGs and QT interval. Does anybody have any concerns about that? Nobody said anything about that. I will take that as a no.

DR. DASARATHY: I was actually puzzled. Is there a reason why the QT interval was focused on--is this class of drugs known to prolong QT or produce torsades? I mean is there a reason why QT was looked at because, if you look at the literature in cirrhosis, people who have decompensated cirrhosis have EKG abnormalities. They have cirrhotic cardiomyopathy. So that is why I was puzzled and I couldn't find out, but I saw this QT, so I said maybe there is

something that I am not aware of.

DR. GRIEBEL: It is part of our standard battery of looking at products when we are reviewing NDAs and making sure that we have done everything that we should be, picking up every rock and examining what we need.

DR. DASARATHY: The trouble would be because cirrhotic patients have the potential to develop this condition cirrhotic cardiomyopathy. You may find EKG changes. You may find a co-cardiographic changes. That doesn't mean it is related to the drug. It may just be progression of disease.

The fact that there is a placebo group and they are pretty much matched would probably have answered if it is a drug-related effect or a disease-related effect.

DR. RAUFMAN: Dr. Gitlin.

DR. GITLIN: I think we may have lost our way slightly. We have got to bear in mind as clinicians, those of us who are clinicians, that these patients' life expectancy with and without this medication is very limited. So people who are worried about mutagenic effects and other effects, these cause the patients to live that long and I think we are offering them an improved quality of life and

perhaps an improved quantity of life mostly short term as a bridge to a potential transplant.

They need 5,000 transplants a year in the United States, and we heard how many people have got encephalopathy. We don't cure these patients, we control them.

DR. RAUFMAN: Dr. Hersch, did you have a comment?

DR. HERSCH: I was just going to raise a concern about the QT study just in regards to--the question is unanswered whether the systemic exposure with more severe patients--it is just unanswered at this point.

DR. RAUFMAN: Any additional comments before we go to a vote?

DR. HE: Just one comment about thorough QT. Typically, we do thorough QT in house volunteers, and we typically don't do in patient population.

DR. RAUFMAN: If there is no further discussion on this question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote.

[Electronic voting.]

DR. RAUFMAN: The voting result, we had 12 Yes, 6

No, and no Abstentions.

Again, we will start with Dr. Kane. Please identify yourself, your vote, and why you voted as you did.

DR. KANE: Sunanda Kane. I voted Yes, because I specifically looked at the question reading adequately assessed for safety at the proposed dose and duration, and I thought that the investigators did a very appropriate job in following all patients whether they were in treatment or placebo groups.

This is a very sick population, and we did not see any new signals for important SAEs, and I was satisfied with my concerns about the deaths in the study. I think that the numbers are too small in the Child's Class C to draw any conclusions, so I think that assessment of safety is appropriate.

DR. REHM: Susan Rehm. I voted yes, as well, although I went back and forth many times. I hinged my answer on adequately, and I believe the assessment has been done adequately although there are many other questions that we have talked about here and that would be of interest.

The question is are they the types of things that would impact patients if they were given access to this drug

tomorrow and I would have to say that we have adequate information now and that further studies will be interesting. I think we will talk about that later.

DR. KUMAR: Atul Kumar. I sort of vacillated also between Yes and No, and I did vote Yes based on whether it has been completely addressed, no; adequately, yes, and potentially, it can never be completely addressed in a study of this size and magnitude, and that data will probably continue to have to be collected as with future use of this drug, which would potentially provide that answer.

DR. GITLIN: Norman Gitlin. I voted Yes. The second part was in answering the question, please discuss whether additional analysis or trials are needed, I think we would like to have either a Phase IV postmarketing surveillance in people with high MELD scores or people who have very long-term duration, work that in somehow into the wording.

Thank you.

DR. MAXWELL: Celia Maxwell. While I voted Yes, I have some concerns about the long-term use of the drug over the time that has been detailed in the study. I do agree with the fact that Phase IV studies might be good

information to obtain on this.

MS. CRYER: Donna Cryer. My vote is Yes. With a literal reading of the question, like my colleagues, surrounding the word "adequate," I believe that given the benefits or the proposed benefits of the drug, the needs of the population, the robust body of long-term use of this agent across varying patient populations, and the existence of ongoing studies, I do believe that there has been an adequate assessment.

An optimal assessment? Perhaps not particularly with those for MELD scores over or equal to 25, and I look forward to additional generation of data for those patients.

DR. HERSCH: I am Steven Hersch, and I voted No because of concern about longer-term use and also about use in more severely affected patients.

On the other hand, I also vacillated a lot, and I think that a lot of those concerns can be assessed in postmarketing studies or in further studies. So, I think I voted No for the same reasons a lot of people also voted Yes.

DR. DASARATHY: Dasarathy. I voted Yes because I compared it to other long-term medications that are

generally approved, anti-hypertensives, anti-HIV agents. We don't have any drug which we can say I have 100 years of experience other than aspirin, so I said okay. But the only reservation I have, which I would like to be stated on the pamphlet, would be that it has been studied only--the safety has been established in the vast majority of patients who have Child's A and B, so its use in Child's Class C or MELD over 25 should be tempered by clinical judgment.

I think if that statement is included, I think it should be okay.

DR. HAUBRICH: Richard Haubrich. I voted Yes. I think for the duration, an indication clearly the potential benefits outweigh the risks. I have three recommendations in terms of things that should be looked at.

One would be to look at the occurrence of C. diff. Obviously, since there is no control group now, the reason would be to look for susceptibility of isolates from those patients and, in the same way. do a study to look at changes in bowel flora, and you would have to find someone smarter than me to know exactly how to do that.

Finally, because of the concerns raised in patients that have Class C disease, who have higher levels,

it might be interesting to do a study to look at systemic absorption and those with Class C who are given an inhibitor of PGP that might be expected to decrease the excretion of the drug. So, at least that way, you would have the opportunity to look at the highest possible concentrations just to give you an idea of what those might be.

The drug that comes to mind that is a good PGP inhibitor is ritonavir. You don't have to give it for more than a few days since the onset of inhibition is quite rapid, and you could do a PK study relatively rapidly with that.

DR. SOLGA: I voted Yes for reasons already articulated. I do think it would be very interesting to know how this affects the gut flora long term, but it is awfully hard to do those studies. The science isn't quite there.

This would not be the only medicine which could have potential impact on gut flora. Whole other classes of medicines--for example, the proton pump inhibitors, which were originally approved for eight weeks only, you know, are often taken for months to years to decades, have unknown effects on the gut flora and they are still unknown.

So, I would hope that perhaps we can get smarter in the future, but I see no compelling safety reason to hold up this drug at this time.

DR. RAUFMAN: Jean-Pierre Raufman. I voted No for some of the concerns that already mentioned, that the drug has not been adequately studied in patients with more severe liver disease, that there are concerns about drug effects on arrhythmia, QT interval, and it would be rather I think straightforward to measure those things in these patients even recognizing that there may be some underlying cardiac pathology related to liver disease itself.

Regarding changes in the gut flora, methods of analysis, molecular methods to identify changes in species, and so on, could be used to determine the effects of this agent.

DR. ANDERSON: Garnet Anderson. I voted No. The reason is I am concerned about some of longer-term exposure issues particularly in some of the subgroups that were identified previously.

My concern is based mostly on the fact that I think the randomized trial provides the best evidence of the impact of this agent. The longer-term study, the

continuation study is more difficult to interpret with the crossover. It is not clear to me what the correct historical control is, if there is one, and so I just have some concerns that we don't understand the longer-term effects.

DR. LOCKWOOD: I am Alan Lockwood. I voted No.

It is almost certain that--well, one of the surprises that came to me in reading the documents was that this drug was being applied for under orphan drug status.

We heard earlier this morning, I believe it was, that cirrhosis of the liver is the 12th ranked cause of death in the United States. The number of patients with cirrhosis is thought to be on the increase because of the number of people who have hepatitis C and may go on to develop cirrhosis.

Almost surely as night turns to day, the inclusion criterion of two or more episodes of overt HE, as soon as somebody has at least the initial episode of HE, they are going to be started on this drug. So I think the number of people who are going to be taking the medication for the rest of their lives, and some of them even after transplantation, may be in need of drugs to maintain a HE-

free status.

I just think that the number of people that have been studied for the length of time and with the severity of disease is not adequate to determine that it is completely safe. And I think I would urge the Agency to undertake postmarketing surveillance of this drug.

DR. COHEN: Jeffrey Cohen. Obviously, by my questions, I had a great deal of trepidation about the duration of treatment. But I think Dr. Gitlin's point is well taken that these are not patients that are typical patients that would be in great health.

These are people that are in serious medical straits, and this treatment, albeit that there are probably risks associated with it, that we will only, unfortunately, know as time goes on with treatment is probably worth it.

MS. SKLAR: Jill Sklar. I voted Yes. I felt that the data between the placebo group and the treatment group showed very favorable data for safety.

My concern would be in the future, to look at C. diff., the effect on Class C patients, and the effect on people with MELD scores equal to or greater than 25 in longer term studies.

DR. HASLER: Bill Hasler. I voted Yes. I agree with most of the things that have been said. I think that there has been an adequate assessment. With specifics, I know we heard that you can't predict toxicity based on plasma levels. But, if you compare absorption of this drug even in severe liver disease, it is still 200-fold less than what we see with related drugs, such as rifampin, so it is remarkable poorly absorbed.

With respect to additional trials, I agree we should follow people with more serious liver disease and also do surveillance for C. diff. With respect to following bowel flora, that is being extensively studied now using molecular techniques after administration of probiotics. We do see substantial differences in bowel flora.

The problem with all those studies is we don't know how to interpret them. So, I don't know that that--it will be interesting, but I don't know what the fruitfulness of that pursuit would be.

DR. HILTON: Joan Hilton. I voted No because I think that in the rollover to the 3002 study, there were data on prior study patients with a failure rate comparable to patients who were new to rifaximin. They were comparable

whether they had longer term exposure or shorter term exposure, but we have no data on a comparable no-treatment group for that duration.

Also, the dose maybe is appropriate for induction and maybe there should be a lower maintenance dose. I thought that both the dose and duration questions were still open.

DR. BRASS: My name is Steven Brass. I voted No. The reason why I voted No is essentially, we are not sure of the long-term effect of this on patients. If this is a drug that is going to be given until liver transplantation or death, we are not sure of information based on the trial.

Secondly, we don't know the effect in a sicker group of patients, so those are the two reasons why I voted No.

DR. RAUFMAN: We will move on to Question 5.

Is the safety of rifaximin at the proposed dose and duration acceptable?

I will open that to discussion although we may have beat it to death already, but if anybody wants to say anything pertaining to this question?

[No response.]

DR. RAUFMAN: Okay.

If there is no discussion, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote.

[Electronic voting.]

DR. RAUFMAN: The voting results. We have 14 Yes, 4 No, and 0 Abstentions.

We will start again with Dr. Kane, please, your name, your vote, and why you voted as you did.

DR. KANE: Sunanda Kane. I actually voted No, because of all the issues that we just raised with Question No. 4, for which I answered Yes.

[Laughter.]

DR. KANE: And not so much the long term effects because as Dr. Gitlin has already pointed out, these patients are not living 10 years. That would be lovely if they did. So, I am not so worried about the long term, but I do agree also with what was said about this drug is going to be used in those patients with MELD scores greater than 25 and Child Class C, and that we don't have a lot of safety data on, and it just makes me a little bit concerned.

Now, is this something that would be something

that would keep me from voting favorably on other questions? Not necessarily. I think that if we agree that there need to just be some postmarketing Phase IV trials, that this is information that we will be able to get.

DR. REHM: Susan Rehm, and I voted Yes for many of the same reasons that you voted No. I actually do think that there is a lot of room for Phase IV trials. I wonder whether one can manage the concerns about use of this drug in populations that have not been studied in the pivotal trial by package wording.

It may be I think useful to describe the patient population where it was tried, and state that the trials in patients with more severe liver disease and combined liver and hepatic dysfunction, for example, have not been done yet.

But assuming that caveat, I would feel comfortable going ahead. And I should have listed some of my wish list for Phase IV trials or ongoing monitoring. It would be in the MELD 25 and higher, the combined renal and hepatic dysfunction, and then surveillance for emergence of clinical infections due to organisms that are multi-resistant.

DR. KUMAR: Atul Kumar. I voted Yes again for the

reasons that we have been discussing in the context of the last question. So, if the safety of the drug at the dose and duration had been adequately addressed and if the outcome was a favorable one, then, it potentially is acceptable.

Of course, I think postmarketing data collection might change that, and that still needs to be determined. Hopefully, it will be marketed as safe for duration of six months, which is what we have data for.

Thank you.

DR. GITLIN: Norman Gitlin. I voted Yes, and to avoid reiteration, I just would like to see either Phase IV study or some long-term observations in patients with very high MELD scores or longer duration.

Thank you.

DR. MAXWELL: Celia Maxwell. As several of my colleagues, I voted Yes, but with caveats that Phase IV studies be conducted.

MS. CRYER: Donna Cryer. I voted Yes. Acceptable is a term of art representing a risk/benefit analysis for a specific patient population. Just for the record, some of us do live past 10 years.

Thank you.

DR. HERSCH: Steven Hersch. While I voted No for adequately addressed, I voted Yes for the current questions, because I think the benefits outweigh the risks, and I won't repeat all the considerations and request for Phase IV studies that I agree with.

DR. DASARATHY: Dasarathy. I voted Yes and actually, the 3002 trial dose have data for one year follow-up at six months, and I think as long as it is explicitly stated that these data are for Child's B and C and MELD less than 25, outside of FDA would be what the other classes would be, I voted Yes.

DR. HAUBRICH: Richard Haubrich. I voted Yes. I agree again with the comments about needs for ongoing data, and I thought it was interesting that we spent a lot of time discussing the changes and inaccuracy in Conn score. I guess that could also be consistent with panel voting as well.

DR. SOLGA: I voted Yes for reasons already articulated. I won't keep going with it.

DR. RAUFMAN: Jean-Pierre Raufman. I voted No because of risk/benefit ratio. If I voted No on the benefit

question, then, the risk is not acceptable.

DR. ANDERSON: Garnet Anderson. I voted No. I took it the previous question asked, whether safety had been adequately assessed, and voting No, then, I didn't feel like I could actually say that I found it acceptable when I didn't think it had been adequately assessed.

DR. LOCKWOOD: Alan Lockwood. I voted Yes. These are sick people. If we had adequate treatments for this disorder, we wouldn't be here today.

DR. COHEN: Jeffrey Cohen. I voted Yes, because of the clinical issues that were just articulated, as well as the word "acceptable."

MS. SKLAR: I voted Yes for the same reasons that I had stated before.

DR. HASLER: I voted Yes also for the same reasons, and would reiterate the need to follow these people in the postmarketing arena.

DR. HILTON: Joan Hilton. I voted No to be consistent with my previous vote, but I have high hopes for this drug.

DR. BRASS: Steven Brass. I voted No to be consistent with my previous answer.

DR. RAUFMAN: We will move on to the last question, Question 6.

In light of the safety and efficacy data presented in this application, does the risk/benefit profile support approval of rifaximin for an indication of maintenance of remission from hepatic encephalopathy--that is, decreasing the risk for episodes of overt hepatic encephalopathy?

Discussion? Again, we may have beaten this to death. Any comments? Any discussions before we vote?

[No response.]

DR. RAUFMAN: If there is no further discussion on this question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote.

[Electronic voting.]

DR. RAUFMAN: The voting results on Question 6, 14 Yes, 4 No, no Abstentions.

Again, we will start with Dr. Kane. Please identify yourself, how you voted, and why you voted.

DR. KANE: Sunanda Kane. I voted Yes. I think that with the indication being in patients who have MELD scores less than 25 or Child's A, B cirrhosis, that this

provides more benefit than risk.

DR. REHM: Susan Rehm. I voted Yes, and I would like to see the labeling reflect the study conditions--that is, the concomitant use of lactulose and the clinical situation of the patients who were studied.

DR. KUMAR: Atul Kumar. I voted Yes and would reiterate what was voiced by Dr. Rehm; that is, it should carry specific labeling indications with regards to its use in patients with MELD scores of under 25.

DR. GITLIN: Norman Gitlin. I voted Yes and I would just like to say I have already indicated what I would like to be added to my vote of the Phase IV and long-term follow-up.

Thank you.

DR. MAXWELL: Celia Maxwell. I also voted Yes, but I would like specific labeling indications and perhaps the removal of the word "maintenance" of remission, because I think what it shows is significant improvement.

MS. CRYER: Donna Cryer. I voted Yes with the use of the language "decreasing the risk for future episodes" rather than the remission language.

DR. HERSCH: Steven Hersch. I voted Yes, and I

agree with previously mentioned rephrasing of the indication, as well the caveats for the labeling.

DR. DASARATHY: Dasarathy. I voted Yes with the same caveats in addition to lactulose and in Child's A, B, MELD less than 25.

DR. HAUBRICH: Richard Haubrich. I voted Yes. I agree with all the label changes that folks have recommended. I think the hard part now is trying to prioritize both what is feasible, reasonable, and just plain old affordable to do to collect data.

It seems likely that the patients that need this treatment the most are the ones that were the least studied, because people with worse disease probably will have more episodes and, since all of the patients in the study were already on lactulose, meaning those patients are going to need something that they can't already get under approved therapies.

So, I think sorting out which of the priorities to do in post-commitment is really going to be the difficult task, and I think the Committee has provided a lot of insight to help guide those decisions.

DR. SOLGA: I voted Yes. I think this will be a

real step forward in our options for caring for patients with cirrhosis.

DR. RAUFMAN: Jean-Pierre Raufman. I voted No to be consistent with my previous votes, and I am still concerned that the studies have not met the bar of substantial evidence of efficacy.

DR. ANDERSON: Garnet Anderson. I voted No very much in line with the previous speaker although I feel like if another study could be done, another trial that supported these results, I would be ecstatic with the data.

DR. LOCKWOOD: I am Alan Lockwood. I voted Yes. I believe that the risk/benefit ratio supports approval and voted accordingly.

DR. COHEN: Jeffrey Cohen. With again the caveats of it being an add-on, about the issue of remission, and also the category of patients, when this--if this does get approved, the patients that will most likely be the first ones treated will be, as it was stated, the most ill patients, and those patients really weren't studied as well in this study.

MS. SKLAR: Jill Sklar. I voted Yes. I feel that it should, however, include some language on the label

regarding lactulose and the Child's Class A and B patients being studied, and not enough data for the Child's Class C.

DR. HASLER: Bill Hasler. I think the benefits significantly outweigh the risks, so I voted Yes. I agree with the labeling of co-administering the drug with lactulose.

DR. HILTON: Joan Hilton: I voted No, but I am strongly ambivalent and maybe should have abstained.

Just to criticize my vote a little bit, I have been trying to scan one more time to find the subpopulation analyses based on history of baseline repeated measures, to think about whether we have shown reduction in risk just based on two prior, as well as based on three prior, as well as based on four prior--do we really mean this in the global sense that the question is stated.

That is where I got hung up is had we really looked at just an episode, or did this represent risk of recurrent episodes.

I am looking for repeated measures data on repeated episodes.

Thanks.

DR. BRASS: Steven Brass. I voted No. When I

looked into the benefit/risk ratio, I was concerned that this drug will be used for the sickest patient population and because I don't feel the data is adequate for this group of patients. So when I took that into account, I felt, first, do no harm, so I voted No.

DR. RAUFMAN: Are there any additional comments or issues? With that, this brings this meeting to a close and I want to thank--Dr. Lockwood.

DR. LOCKWOOD: Sorry. One of the disadvantages of sitting on the end here. I have some concerns that the sentiments expressed by the panel are going to institutionalize and mandate continued treatment with lactulose as a prerequisite for utilizing this drug.

If we look at Slide 11 on page 6 of the FDA handout, the summary of the Cochrane Review of lactulose versus placebo, there were two, high-quality studies, and the conclusion was that there was no significant effect there.

I have some concerns that insurance companies and other providers will refuse to pay for this drug unless you give them concomitant lactulose. I think that if lactulose were coming before this panel for approval by the FDA, it

might not meet the standard.

I would be very cautious about requiring or putting on the label that this drug may only be used concurrently with lactulose because lactulose, itself, I think there are some questions as to its efficacy.

I think it is an indication of the desperation of clinicians who care for these patients that lactulose continues to be used on occasion, non-absorbable antibiotics like neomycin. I don't want to see an institutionalization of another therapy that may not meet the standard.

DR. RAUFMAN: Dr. Maxwell.

DR. MAXWELL: Just to make a comment on the previous comment is the only way that I certainly could make a determination on this is because it was used concomitantly with lactulose. So, it would hard for me to separate them out. I mean the studies, most of the patients were on lactulose also. So, I think that that is an important consideration.

DR. RAUFMAN: I voted No on issues specifically for that same reason. Again, we are going over territory we have already covered.

Any additional comments?

DR. GRIEBEL: I think those comments are important for us to hear, because we can finesse how we write the indication. We can describe how the study was done, and not necessarily say it must be given with, and people can make their own decisions.

Is there an interest in the group? Conceivably, you could answer this question by entering patients who are on lactulose or require lactulose, start rifaximin and then see if you stop the lactulose. Do you think that is a worthwhile study that is needed?

DR. RAUFMAN: I would have hoped that the previous, the 3001 had been done that way.

DR. DASARATHY: Maybe it will be answered in Phase IV studies where patients are going to spontaneously stop taking lactulose whether we tell them to or not, because they are going to have so much diarrhea. They are going to say--they are not going to wait for us to give advice. They are going to try it themselves and see, and such data, if it is collected, would probably help to say that, yes, even if lactulose is stopped, it works.

DR. RAUFMAN: Additional comments?

[No response.]

DR. RAUFMAN: I would like to thank all participants for very thoughtful comments, very thoughtful discussion. Have a safe trip home.

[Meeting adjourned at 3:00 p.m.]