FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

WEDNESDAY, NOVEMBER 16, 2011

8:00 a.m. to 4:15 p.m.

Holiday Inn Washington DC/College Park

10000 Baltimore Avenue

College Park, Maryland

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P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. RAUFMAN: Good morning. I'd like to call this meeting to order. This is the Food and Drug Administration Gastrointestinal Drugs Advisory Committee meeting, and we'll start with introductions. My name is Jean-Pierre Raufman. I'm head of the Division of Gastroenterology and Hepatology at the University of Maryland School of Medicine in Baltimore.

DR. KHUC: Kristine Khuc, designated federal officer of the GIDAC.

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

DR. MCDONALD: Cliff McDonald. I'm a senior advisor for science and integrity in the Division of Healthcare Quality Promotion at the Centers for Disease Control and Prevention in Atlanta.

DR. SPIEGEL: I'm Brennan Spiegel. I'm a gastroenterologist at the West Los Angeles VA Medical Center and the UCLA Schools of Medicine and Public Health.

DR. SOOD: I'm Gagan Sood. I'm a gastroenterologist and hepatologist at Baylor College of Medicine at Houston.

DR. HASLER: William Hasler, professor, Division of Gastroenterology, University of Michigan Health System.

DR. LIAS: I'm Courtney Lias. I'm the director of the Division of Chemistry and Toxicology Devices at the Food and Drug Administration.

DR. KIM: I'm Insook Kim, clinical pharmacology reviewer, Office of Clinical Pharmacology at FDA.

DR. MULBERG: Good morning. I'm Andrew Mulberg, division deputy director, Division of Gastroenterology and Inborn Errors Products, FDA.

DR. HE: I'm Ruyi He. I'm a medical team leader in the Division of GI, FDA.

DR. DIMICK: Lara Dimick, medical officer, GI Division, FDA.

DR. SOLGA: Steve Solga, private practice, gastroenterology, in Pennsylvania.

MR. MATSON: Tracy Matson, patient advisor, Little Rock, Arkansas.

DR. PASRICHA: I'm Jay Pasricha, a professor of medicine and a gastroenterologist from Stanford University School of Medicine.

DR. FLEMING: Thomas Fleming, Department of Biostatistics, University of Washington.

DR. SEPTIMUS: Ed Septimus, infectious disease professor at Texas A&M Health Science Center in Houston and medical director of infection prevention and epidemiology at HCA.

DR. ROSEN: I'm Rachel Rosen, a pediatric gastroenterologist at Children's Hospital, Boston.

DR. RAUFMAN: Thank you.

For topics such as those being discussed at today's meeting, there are often a 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 this 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 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 during lunch. Thank you.

We'll now have the conflict of interest statement.

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 the committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug & 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 federal ethics and conflict of interest laws. Under 18 USC 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 services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Federal Food, Drug & 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 USC 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.

The agenda for today's meeting involves discussions of the design of clinical trials to evaluate the safety, efficacy, and durability of response with repeat treatment cycles of Xifaxan, rifaximin, by Salix Pharmaceuticals, Inc., for irritable bowel syndrome with diarrhea. This is a particular matters meeting, during which specific matters related to Salix's Xifaxan will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee's 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 may have concerning the issues being discussed today.

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 participants need 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 relationships that they may have with the firm at issue.

Thank you.

DR. SPIEGEL: There's one additional potential conflict that the FDA is aware of that wasn't in the formal briefing documents prior. I have been consulted by a third party financial firm, Summer Street Research Partners, to receive my views about irritable bowel syndrome in general, including information that has been publicly available in my written materials. So I just wanted to disclose that as well.

DR. RAUFMAN: Thank you, Dr. Spiegel.

We will proceed with the FDA opening remarks. Dr. Mulberg?

Opening Remarks

DR. MULBERG: Well, good morning, Dr. Raufman, GI Advisory Committee members, Salix Pharmaceuticals, fellow FDA attendees, and the general public. We are discussing today the design of clinical trials to evaluate the safety, efficacy, and durability of response with repeat treatment cycles of Xifaxan, rifaximin, for irritable bowel syndrome with diarrhea. Xifaxan is an non-aminoglycoside, semisynthetic antibiotic derived from rifamycin that has broad spectrum antimicrobial activity against Gram-positive, Gram-negative, aerobic, and anaerobic enteric bacteria similar to rifampin. It is a poorly absorbed antibiotic with low systemic exposures that have been recorded.

The proposed indication is non-constipation irritable bowel syndrome, IBS, and IBS with bloating in patients greater than 18 years of age. For this regulatory history, this initial NDA

1 was approved for traveler's diarrhea in May 2004
2 at a dose of 200 milligrams three times a day for
3 three days. Also, it was approved for a treatment
4 of hepatic encephalopathy in March 2010 at a dose
5 of 550 milligrams twice daily. The NDA submitted
6 for IBS was in June 2010; the proposed dose was
7 550 milligrams three times a day for 14 days.
8 The basis for the complete response letter
9 to Salix Pharmaceuticals was issued on March 7,
10 2011. The details of that are pictured on the next
11 2 slides. Importantly, the lack of durability of
12 response of rifaximin was noted. Please note for
13 the GI advisory committee members that we have
14 detailed package information, both from Salix
15 Pharmaceuticals and the FDA with regards to this
16 issue, which was an issue of much discussion during
17 the deliberations.
18 Other issues included the lack of
19 demonstration of efficacy for retreatment, an issue
20 that is a major focus for today's discussion; the
21 lack of definition of the effect of frequency for
22 retreatment or prevention thereof of recurrence;

lack of adequate definition of the patient population who would benefit from rifaximin; the concern with bacterial resistance, particularly to Clostridium difficile and the potential for serious enteric infections, resulting in insufficient proof for product labeling and a chronic disease such as irritable bowel syndrome characterized by recurrence.

Additional comments in the complete response letter included that the trials included only patients with IBS-D, and the general indication extended to non-C IBS was not appropriate. The patient population in the clinical trials also excluded patients with severe IBS-related symptoms.

As a point of background, it's important to note that the EMA has developed its own points to consider in the evaluation of products for the management of irritable bowel syndrome. Importantly, as delineated here, they have recommended and require short- and long-term continuous treatment programs; and as quoted here,

1 "The demonstration of efficacy with repeated use
2 would be required for a short-term indication, and
3 a minimum of two cycles would be needed, as the use
4 of the medication would be used chronically."
5 This is a slide resembling the multiple
6 evolving concepts of irritable bowel syndrome
7 borrowed from Dr. William Chey and others. The
8 multifunctional aspects of IBS-related symptoms are
9 an interplay of many different factors leading to
10 the understanding of what really is resulting in
11 the signs and symptoms of IBS. There are many
12 pathobiological factors, including the role of
13 food, central nervous system interplay, an issue of
14 the microflora and microbiota, which will be an
15 issue of much discussion in this morning's session,
16 and the role of genetics. How these all interact,
17 resulting in patients who have resulting symptoms
18 of IBS, will be the functional discussion for
19 today's meeting.
20 It's important that this literature is
21 evolving, and I've just pictured three recent
22 manuscripts, published papers on the issues of the

CNS-gut interactions. One interesting paper is the role of probiotics, specifically lactobacillus, in the regulation of behavior and neurotransmitter function in animals, as well as two recent gastroenterology papers that have published specific microbiota signatures in both children and adults with irritable bowel syndrome. These are areas that are continuously now evolving.

As much of a concern is the potential use and overuse of antibiotics for many indications, this work has recently been presented by Martin Blaser in Nature this past year, particularly focusing on the use and frequent use of antibiotics in children. As demonstrated here, depending on the number of courses of antibiotics, there seems to be a rising increase of risk of various diseases. And the concern about use of antibiotics will be the focus of today's discussion for this particular NDA.

So what is the role of the microbiome in pathogenic bacteria? It's clear that one of the important roles of an intact microsystem is to

resist intrusion by pathogenic bacteria. It's very clear that changes, as referred to by Martin Blaser in his manuscript and others -- that we must and should be concerned about the role of antibiotic use in the dissemination and the transmission of deadly organisms, importantly, including C. difficile.

So what are the next steps in the development program for rifaximin in irritable bowel syndrome? We agree that two single-cycle rifaximin trials provide evidence of efficacy but not durability. It's important for the GI Advisory Committee to ask several important questions, some of which are reflected here.

What trial designs are adequately defining the ongoing treatment regimen that will involve rifaximin? I will later in the morning discuss some of these potential trial designs for you to consider. It's important to note that reasonable information suggests that bacteria do play a role in irritable bowel syndrome signs and symptoms, at least in a subset of patients. But how can we

1 better identify that subset? And if we should, how
2 can we? These are topics of today's discussion.
3 So what are the points to consider in this
4 future development program? I think it's important
5 for the GI Advisory Committee members to ask what
6 is the major goal of rifaximin treatment in the
7 management of IBS-D patients? How does our lack of
8 understanding the natural history, if so, impact
9 trial design for rifaximin? Importantly, what is
10 the goal of management of rifaximin of the general
11 population? Should it be focused on short-term
12 treatment of exacerbations in patients?
13 As you will hear from Dr. Paterson later
14 in the morning, this is the proposed current trial
15 design. Or should a trial design focus on
16 prevention of recurrent symptoms, or the induction
17 of cure, or the long-term remission? Importantly,
18 as you'll hear repeatedly this morning and during
19 today's discussion, are there subpopulations of
20 IBS-D that require a different approach?
21 As you will hear shortly from Salix
22 Pharmaceuticals, this is the proposed

1 treatment -- excuse me -- repeat treatment design
2 that will be the focus at least of part of today's
3 discussion. My goal is not to walk through this
4 now, but to set the stage for what will be, indeed,
5 hopefully a very interesting discussion. Thank
6 you.
7 DR. RAUFMAN: Thank you, Dr. Mulberg.
8 Both the Food and Drug Administration,
9 FDA, and the public believe in a transparent
10 process for information gathering and decision
11 making. To ensure such transparency at the
12 advisory committee meetings, FDA believes that it
13 is important to understand the context of an
14 individual's presentation.
15 For this reason, FDA encourages all
16 participants, including the sponsor's non-employee
17 presenters, to advise the committee of any
18 financial relationships that they may have with the
19 firm at issue, such as consulting fees, travel
20 expenses, honoraria, and interests in the sponsor,
21 including equity interests and those based upon the
22 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. Dr. Forbes?

Sponsor Presentation - William Forbes

DR. FORBES: Dr. Raufman, Dr. Griebel, Dr. Mulberg, members of the advisory committee, the FDA, ladies and gentlemen, good morning. I am Bill Forbes, executive vice president of medical and R&D at Salix Pharmaceuticals. I would like to thank the FDA for inviting us to participate in this important meeting.

Salix is a specialty pharmaceutical company committed to developing innovative products to treat gastrointestinal disorders for the improvement of patients' health. We have been working closely with the FDA and other experts in

the field to identify the most appropriate design of a repeat treatment clinical trial for the use of rifaximin in IBS-D. This is the focus of our meeting today.

As Dr. Mulberg mentioned, rifaximin is a semisynthetic antibiotic of the rifamycin class. Rifaximin is unique because it has gut-targeted action with only minimal systemic absorption. In vitro, rifaximin binds to the beta subunit of the bacterial DNA-dependent RNA polymerase to inhibit bacterial RNA synthesis, resulting in its classification as a broad spectrum antibiotic. However, in vivo, rifaximin does not appear to affect the numbers or diversity of the endogenous enteric bacteria at all therapeutic doses that we've tested.

The FDA has raised a number of questions regarding the use of this antibiotic in a patient population without clear identification of patients most likely to respond by surrogates, clinical presentation, biomarker, or pathogen.

While we are here today to discuss

1 rifaximin's role in IBS-D, specifically, in a
2 larger sense, these questions are not new to
3 rifaximin. In fact, we have had many of these same
4 questions in some of the other development programs
5 that we have progressed for rifaximin.
6 Rifaximin experience is extensive. It has
7 been available since 1987 following initial
8 approval in Italy. Today rifaximin is approved and
9 in use in 36 countries for a number of GI
10 indications. Rifaximin possesses an outstanding
11 safety track record. There's not been a market
12 withdrawal or challenge for safety-related reasons
13 worldwide. Adverse events are well-characterized,
14 generally mild, and similar to placebo.
15 Collectively, there are greater than 700
16 publications in the scientific literature,
17 including 90 preclinical and approximately 180
18 clinical study reports. Specific to our experience
19 in the United States, rifaximin has been
20 extensively studied with approximately 5,000
21 subjects enrolled in clinical trials. We also have
22 more than seven years of postmarketing surveillance

data, which contributes to our understanding of safety in the United States.

IBS is the third major development program for rifaximin, following treatment of traveler's diarrhea and the prevention of overt hepatic encephalopathy recurrence, two approved indications in the United States.

Additionally, we are in various stages of development in other areas. For Crohn's disease, we are hoping to initiate a study in the U.S. in the next year following some positive results out of Europe from phase 2. There is also prophylaxis of traveler's diarrhea, and one study in Clostridium difficile infection. I will touch briefly on each of these programs in order to provide you with some important applicable highlights for your discussions today and for your consideration today for some of the issues related to IBS-D and some of the issues raised by the FDA.

The first approval for rifaximin in the U.S. occurred in 2004. At that time, Salix worked with the Special Pathogens Group at the FDA. The

result of this program is presented from the current label and has been a source of presentations at other ad comm meetings.

Rifaximin does not behave like a typical broad spectrum antibiotic. Its potential modes of actions appear to be unique. In infectious diarrhea, rifaximin is clinically efficacious without evidence of eradication of the offending pathogen.

The table on the top highlights the clinical efficacy. On the bottom, you can see that there is little difference in microbial eradication rates with therapy. The text in the middle, which is also excerpted from the label, emphasizes that patients should be managed based on clinical instead of microbiologic response.

Recurrence of overt hepatic encephalopathy was a source of discussion at this very same committee last year. Data used to secure approval for hepatic encephalopathy demonstrated reduced systemic bacterial-derived neurotoxins, namely ammonia, following rifaximin treatment.

Presumably, this ammonia reduction was through either the reduction of bacterial generation of ammonia, host permeability, or both.

The correlation of reduction in overt HE events seen in rifaximin versus placebo-treated patients, which is pictured here, to the reduction in serum ammonia was something that was statistically significant and continued through the course of the trial. While there were no specific pathogens identified and eradicated in this program, the reduction in ammonia and the reduction in risk appear to stay constant. The clinical relevance of this effect is also noted in the label, namely, the 50 percent reduction in hospital-related events due to HE.

We've also run a number of trials for prophylaxis in traveler's diarrhea. The offending pathogen is, more times than not, pathogenic E. coli. Important lessons from this program include the lack of effect on the number or biodiversity of the microbiome while significantly preventing the occurrence of diarrhea.

To both prevent and treat a pathogen with an antibiotic that does not seem to have in vivo microbiological activity, or has microbiological activity similar to placebo, makes for a strong case for an alternate mechanism or mechanisms to be coming into play.

One of these alternate mechanisms may be in play in another serious and debilitating GI condition. In Crohn's disease, a recent study conducted by our partner, Alfa Wassermann out of Italy -- and this study was conducted in Europe -- reported the efficacy of rifaximin versus placebo. The role of inflammation, PXR activation, and the role of rifaximin is also a focus of ongoing research. Rifaximin may up-regulate gut detoxification mechanisms and stabilize epithelial cells against bacterial colonization and internalization.

In C. diff, we have run one trial that enrolled 232 of a planned 300 patients. The trial compared a 10-day course of rifaximin to vancomycin. The primary endpoint was defined as

1 the number of patients achieving clinical success.
2 Clinical success was defined as the absence of
3 severe abdominal pain, fever, and diarrhea at test
4 of cure.
5 As you can see from this, the primary
6 endpoint was not met in this study that only
7 enrolled 232 of the 300 patients. However, the
8 point estimates appear to be slightly in favor of
9 vancomycin, but rifaximin appears to be somewhere
10 in the range of minus 6.2 as a point estimate on
11 clinical success. I will point out, just for your
12 interest as far as diarrhea, it has a point
13 estimate of minus 1.5. And, of course, this has
14 not been powered or completely enrolled, so this is
15 not considered a completed trial.
16 All of these data bring us to what brings
17 us today to this meeting on rifaximin in IBS.
18 Dr. Mulberg pointed out a few of these things.
19 Salix submitted a supplemental NDA for the
20 indication of irritable bowel syndrome last year
21 for rifaximin that was subsequently granted a
22 priority review. This NDA included a phase 2 and

two phase 3 multi-center randomized controlled clinical trials.

After the GI Division completed their review, a complete response letter was issued in March. We have held an end-of-review meeting, as well as several other meetings with the GI Division and recommendations to address the outstanding issues of the complete response letter were discussed, including demonstration of efficacy following repeat treatment with rifaximin in IBS. Of course, at that time it was also determined that a GI advisory committee would be convened to discuss the optimal design for a clinical study to gather repeat treatment and efficacy data for rifaximin, which is why we are here today.

It is estimated that IBS affects 10 to 15 percent of the population. However, approximately one-third have IBS-D, and only 25 percent of these patients seek medical care. IBS is characterized by chronic recurring GI symptoms of abdominal pain, bloating, and altered bowel habits that lower quality of life by disrupting

work, lifestyle, and well-being.

Most current treatments require chronic daily dosing for adequate control of IBS symptoms. There has only been one approved therapy for IBS-D, Lotronex, or alosetron, 11 years ago. This product was subsequently withdrawn from the market and then relaunched with an important restriction to women with severe IBS-D.

We have the DESI agents, which are older agents marketed before 1962 that are available for use without the requirements of registration trials, and we also have OTC products. All of these vary in efficacy and cost and are not subject to the same rigors of clinical development.

Given the seriousness of IBS-D and the significant need for safe and effective therapies, the FDA decided to grant rifaximin a priority review for this indication.

In 2009, the American College of Gastroenterology Task Force on IBS published the evidence-based position statement on the management of irritable bowel syndrome. This publication

reported the efficacy of treatments for IBS.

Receiving a 1B grading, and I quote, "a short-term course of a nonabsorbable antibiotic is more effective than placebo for global improvement of IBS and for bloating." This is a strong recommendation that applies to most patients in most situations where the benefits clearly outweigh risks and burdens.

The task force recommendation was supported by the literature specific to rifaximin at that time. But it is also important to note that the pivotal trials that you will see in just a few minutes, the TARGET 1 and TARGET 2, were still ongoing at the time this publication was made available.

The two pivotal phase 3 trials in patients for the treatment of IBS-D and IBS-related bloating, TARGET 1 and TARGET 2, met their primary endpoint. Both studies demonstrated rapid onset of symptom relief and a persistence of efficacy. Both met their key secondary endpoints. There were no unexpected adverse events, and the safety profile

for rifaximin was similar to placebo in both trials.

I will close with a few important points that I will ask that you keep in mind for the balance of today. Rifaximin is safe and effective in the initial management of IBS-D. We look forward to sharing the results of our clinical development program, expressing our commitment, and collaborating with this committee and the agency in determining the most important and most appropriate path forward.

We are here today to discuss how, in a population of IBS patients that initially responds to rifaximin, we can better understand how and when to retreat upon the recurrence of IBS symptoms, thereby demonstrating the efficacy of rifaximin upon repeat treatment. And Salix is also committed to securing appropriate labeling that will provide physicians the information needed to prescribe this agent to patients for the relief of their symptoms of IBS.

At this time I will review our

presentation agenda. In just a moment, Dr. Anthony Lembo from Harvard University will present an overview of IBS and describe the clinical background and role of biomarkers. Dr. Stephen Collins from McMaster University will discuss IBS and the role of the microbiome. From Salix, Dr. Pamela Golden will present the clinical pharmacology of rifaximin and our current understanding of how this agent may be influencing the host-microbiome relationship.

Also from Salix, Dr. Craig Paterson will describe the rifaximin clinical development program that has demonstrated the efficacy and safety of rifaximin IBS-D. This will demonstrate the paradigm shift of using an agent for a short-term course to produce a positive impact in IBS symptoms and IBS-related bloating. Then later we will review the proposed repeat therapy study design, which appears in both the Salix and the FDA briefing documents. This will set the stage for your discussions and the goal of this meeting.

During the day, you may have some

1 questions for us. In addition to myself and the
2 presenters I just reviewed, there are several other
3 experts available to the advisory committee. Drs.
4 Carroll, Chalasani, DuPont, Koch, Pimentel, and
5 Schoenfeld are all participating in the meeting to
6 ensure that you as a committee get the answers that
7 you need from Salix.
8 At this time, I will ask Dr. Anthony Lembo
9 to come forward. Dr. Lembo is a gastroenterologist
10 who divides his time between clinical medicine and
11 research at Beth Israel Deaconess Hospital in
12 Boston. He serves as the director of the Motility
13 Center and Gastroenterology Department, and as a
14 clinical instructor in academic medicine at Harvard
15 Medical School. And he has offered numerous
16 original research articles in IBS, and in fact has
17 co-authored or primary-authored two in the New
18 England Journal in the last year, one for rifaximin
19 and one for another drug in IBS-C. Dr. Lembo.
20 **Sponsor Presentation - Anthony Lembo**
21 DR. LEMBO: Good morning, Dr. Raufman and
22 members of the committee, the FDA, and the public.

1 My name is Tony Lembo, and as Bill has indicated,
2 I'm a clinical gastroenterologist at the Beth
3 Israel Deaconess Medical Center. By way of
4 disclosure, Salix Pharmaceuticals is providing
5 compensation for the time and travel expenses, but
6 I have no other financial gain for the outcome of
7 this meeting.
8 So my objective over the next few minutes
9 is to give you a brief overview of the irritable
10 bowel syndrome in terms of its definition, its
11 prevalence, diagnosis, and burden of illness. I'll
12 also briefly discuss evidence about the
13 recommendations for the current treatment for
14 patients with IBS, particularly with IBS with
15 diarrhea.
16 As shown in this slide, IBS is a common
17 condition that's characterized by recurrent
18 abdominal pain associated with alteration of bowel
19 habits. It's also associated with the negative
20 impact on quality of life. And, unfortunately,
21 there are no clinically useful biomarkers currently
22 available for IBS in clinical trials. It is

1 multifactorial in ideology, and the diagnosis is
2 symptom-based, and there's an unmet need for safe
3 and effective therapies in IBS.
4 Now, IBS is a heterogeneous disorder
5 that's associated with recurrent symptoms that
6 include abdominal pain and discomfort, bloating,
7 and altered bowel habits, either diarrhea,
8 constipation, or oftentimes both. The diagnosis is
9 based on symptoms, and the most common criteria
10 that's used for the diagnosis of IBS is the Rome
11 criteria, which is a consensus definition that has
12 been revised on several occasions.
13 Now, this slide shows you the Rome II
14 criteria, which was used in the two phase 3
15 clinical trials with rifaximin. Now, in order to
16 meet the Rome II criteria for IBS, individuals must
17 report at least 12 weeks, which need not be
18 consecutive, in the preceding 12 months with
19 abdominal pain or discomfort that has two out of
20 the three features; either it's relieved with
21 defecation, the onset is associated with a change
22 in the frequency of stool, or the onset is

1 associated with a change in the appearance or form
2 of stool.
3 Now, the Rome III criteria was
4 subsequently published in 2006, and is the most
5 recent criteria for IBS. And it's made some minor
6 modifications to the Rome II criteria that's shown
7 on this slide schematically. And most notably, the
8 changes include -- the most notable change is with
9 regard to the frequency and duration of IBS
10 symptoms. In addition, patients are required to
11 have symptoms for at least six months.
12 While these changes have resulted in some
13 differences in the overall prevalence of IBS in the
14 community, it's important to note that for the
15 purposes of clinical trials, where most patients
16 will have frequent and more severe symptoms, the
17 vast majority of patients who meet the Rome II
18 criteria also will meet the Rome III criteria.
19 Now, IBS can be divided into subtypes that
20 are based on stool consistency. There are three
21 major subtypes: IBS with constipation, shown on
22 the far left, or known as IBS-C; IBS with diarrhea,

or IBS-D, which is shown on the bottom right; and IBS mixed, or IBS-M.

The prevalence of each of these subtypes varies from studies, as shown in this slide with the percentages that are listed, but it's approximately a third for each subtype. An IBS patient is considered to have IBS-C if they report hard or lumpy stools, as shown in the description with this Bristol stool scale, with at least 25 percent of their bowel movements, and with no more than 25 percent of their bowel movements being associated with loose or mushy stools.

On the other extreme is IBS-D. A patient is considered to be IBS-D if they report loose or mushy stools, as shown by the Bristol stool scale here, for at least 25 percent of their bowel movements, with no more than 25 percent being associated with hard or lumpy stools. The remainder of patients generally fall into the IBS-M subgroup.

Now, it's important to note that many patients will change subgroups over time, and

1 patients are more likely to transition to IBS-C
2 than to IBS-D.
3 Now, 10 to 15 percent of the general
4 population in western countries report IBS
5 symptoms. However, only about 25 percent of these
6 people will ever seek medical care for their IBS.
7 Numerous studies have looked at the burden of
8 illness in IBS, and I'll quote the ACG task force
9 that recently reviewed this that summarized it very
10 nicely. And they said that patients with IBS
11 "visit the doctor more frequently, use more
12 diagnostic tests, consume more medications, miss
13 more workdays, have lower work productivity, are
14 hospitalized more frequently, and consume more
15 overall direct costs than patients without IBS."
16 From my own experience for caring for
17 these patients for over 15 years, I can tell you
18 that although IBS is a non-life-threatening
19 disease, it can significantly impact their overall
20 quality of life as well as the quality of life of
21 those that are near and dear them, including their
22 friends and family.

This is a study that looked at the quality of life. This is a study that was done at UCLA and looked at the quality of life using the SF-36 scale, which is shown here. And this is the seven different subdomains for it, and you can see that patients at UCLA that had IBS had a lower quality of life for all seven subdomains than did the general U.S. population.

Our understanding of the pathophysiology of IBS continues to evolve. You've heard a little bit about this from Dr. Mulberg, and we'll hear more later. Depicted on this slide are some of the more prominent theories over the past four to five decades. And most recently, a great deal of attention and research has been directed at the role of genetics and the microbiome and the neuroimmune function, and you'll be hearing more about this from Dr. Collins shortly.

Now, even with these multiple pathophysiological theories, there are currently no reliable biomarkers for the diagnosis and management of IBS in clinical practice or in

clinical trials. Specific criteria for a potential biomarker are listed on this slide, and it would include one that objectively defines a disorder and defines a patient subgroup within a disorder, that demonstrates a low inter-subject variability that predicts treatment response, that meets criteria for reproducibility, correlates with symptoms and/or severity, and is practical with regard to cost, availability, and ease of use. And as indicated, none currently exist.

So the lack of a proven biomarker in IBS is only one of several challenges to the design of IBS clinical trials. There's heterogeneity. Fluctuation and subjectivity of symptoms is another. The multiple potential pathophysiological mechanisms, which exist, is an important one. Study of methodology issues, including the maintenance of blinding and study duration, contamination by other parallel interventions, and a high placebo response rate are other significant challenges.

Now, this slide depicts the differences

1 between a drug arm and a placebo arm in a well-
2 conducted, randomized clinical trial on IBS. In
3 this case, it's a study of those done with
4 alosetron in women with IBS-D. Now, the blue line
5 represents the percent of patients receiving
6 placebo who report adequate relief, while the
7 yellow line shows the percent of patients receiving
8 the drug who reported adequate relief for each week
9 of this 12-week trial.
10 The shaded area therefore represents the
11 therapeutic gain over placebo. What constitutes
12 the placebo response is incompletely understood.
13 Now, we believe that contributors to the placebo
14 response include the natural history of the
15 disease, which includes spontaneous remission and
16 regression to the mean; and what is known as the
17 placebo effect, which includes a number of
18 different factors, including other co-
19 interventions, report bias, measurement artifacts,
20 the Hawthorne effect, and, importantly, the
21 patient-doctor interaction.
22 One of the fundamental questions in

placebo research is whether or not deception is necessary in order to harness this placebo effect. We attempted to answer this question in a recent trial, where we randomized 80 IBS patients to either two tablets twice daily of an open label placebo, i.e. placebo without deception, or usual care.

Now, importantly, in order to maximize the placebo effect, we emphasized to all patients four important points: one, that the placebo is a powerful medication, and that the body automatically responds to taking placebo pills, that a positive attitude helps but isn't necessary, and taking pills faithfully is critical.

So all patients got that, and then they were randomized to one of these two groups, and the result at 3 weeks -- after 3 weeks of treatment or usual care shown in these two graphs. But on the left is for adequate relief at 3 weeks, and the right is for the change in IBS quality of life score.

As you can see, a greater percentage of

1 patients who received open label placebo reported
2 adequate relief, as shown in the graph to the left,
3 than patients receiving no treatment or usual care.
4 And likewise, patients receiving open label placebo
5 also reported a greater change in their IBS-QOL
6 compared to those who received no treatment.
7 Now, this study does suggest that placebo
8 effect can be harnessed in the proper clinical
9 setting. However, the duration of response and
10 effects on individual bowel symptoms remains
11 unknown.
12 Our current clinical approach to patients
13 with IBS is shown in this slide. The largest group
14 of patients who seek medical care have relatively
15 mild symptoms, and many of these patients can be
16 managed with diet alteration, lifestyle advice, a
17 positive and confident diagnosis of IBS,
18 explanation of their symptoms, and reassurance.
19 A smaller subset have moderate symptoms
20 which may impact their quality of life and daily
21 function, and for some of these patients,
22 pharmacotherapy may be needed, and if necessary,

stress management may be also given.

The smallest subset of patients have severe symptoms. Some of these patients will require the addition of psychological treatments and possibly a multidisciplinary approach with other specialists.

This slide depicts the medications included and available in the ACG IBS task force evidence-based systemic review on the management of IBS. Currently, there are limited pharmacological treatment options for patients suffering from IBS, and only alosetron and lubiprostone are currently available and approved by the FDA for the treatment of IBS.

For the sake of time, I'll be focusing in the next few slides on the treatment options for IBS with diarrhea, with the exception of the nonabsorbable antibiotics, which will be covered in more detail by Dr. Paterson.

Now, loperamide is a peripheral opioid agonist that decreases intestinal motility. There's only been two randomized controlled trials

that have been conducted in patients with IBS and diarrhea, and both of these trials showed improvement in stool consistency and frequency but not in overall global improvement of symptoms or in abdominal pain. The ACG task force has given this a grade 2C rating, which is based on the low quality of evidence.

Probiotics are commonly used for IBS. However, there are relatively few randomized trials with probiotics in IBS, particularly IBS with diarrhea. A systemic review published by Dr. Schoenfeld and colleagues in 2009 at the University of Michigan found 16 randomized controlled trials at that time that included extractable data for analysis, and concluded that only Bifidobacterium infantis demonstrated efficacy in two appropriately large, well-conducted, randomized controlled trials.

Now, similarly the ACG -- which is shown on the right, task force, their recommendations are shown on the right -- also concluded that Bifidobacterium infantis and certain probiotic

combinations demonstrate efficacy for the treatment of IBS, but their recommendation was a grade 2C, which is a weak recommendation based on the low quality of evidence. Nevertheless, these results, particularly with B. infantis, support the potential importance of the microbiome in IBS, but clearly further studies with individual strains and combinations of probiotics are needed.

This study reviews the results of a recent meta-analysis of alosetron, or a 5HT3 antagonist, in IBS. There have been eight well-conducted, large, randomized, double-blind, placebo-controlled trials in IBS with diarrhea, and they found, in this meta-analysis, that there was a significant improvement in global IBS symptoms in pain, with the overall number needed to treat being equal to 8. And the ACG task force has given alosetron a grade 2A, which is a weak recommendation, despite the high quality of evidence, which is due to potential safety concerns.

While there's evidence for its clinical response of alosetron, its use in clinical practice

1 has been limited by the risks of rare but serious
2 adverse events, particularly that of ischemic
3 colitis, and currently, alosetron is regulated by a
4 prescribing program designed with the FDA.
5 Now, finally, tricyclic antidepressants in
6 IBS have been shown to reduce pain and improve
7 global symptoms in patients with IBS and has
8 received a 1B recommendation by the ACG task force.
9 A TCA may be more effective in patients with IBS
10 with diarrhea than with IBS with constipation due
11 to their anticholinergic properties. The largest
12 and best-designed clinical trial was that with
13 desipramine, which gave doses between 50 and 150
14 milligrams in patients with IBS and other
15 functional disorders. And at these doses, though,
16 it's important to note that TCAs were generally
17 poorly tolerated, with significant side effects,
18 and the discontinuation in that trial was over 28
19 percent.
20 So to summarize, IBS is characterized by
21 recurrent abdominal pain that's associated with
22 alteration in bowel habits. IBS can have a

significant negative impact on quality of life and creates a substantial economic burden for patients and society. IBS symptoms reflect a multifactorial etiology. No clinically useful biomarkers have been established, and IBS diagnosis is symptom-based. There is an unmet need for safe and effective therapies for patients suffering from IBS.

Thank you.

DR. FORBES: Thank you, Tony.

I'm going to ask Dr. Collins to step forward at this point. Dr. Collins is the professor of medicine, associate dean of research, and chair of gastroenterology at McMaster University. His field of research has been focused on the microbiome-gut-brain interaction, and he's a worldwide recognized expert in this area.

Dr. Collins?

Sponsor Presentation - Stephen Collins

DR. COLLINS: Good morning, Mr. Chairman and members of the Food and Drug Administration Advisory Committee, and ladies and gentlemen,

1 guests. First of all, by way of a disclosure,
2 Salix Pharmaceuticals is providing me compensation
3 for time and travel expenses. I have no financial
4 gain from the outcome of this meeting.
5 My job is to provide you with a framework
6 to consider the role of the microbiota in the
7 irritable bowel syndrome. And as the previous
8 speaker, Dr. Lembo, had told you, there are a
9 number of shortcomings in the treatment and the
10 diagnosis of this condition that, in my opinion,
11 reflect the lack of a generally acceptable
12 conceptual framework for this condition upon which
13 we could base rational therapies and potentially
14 develop biomarkers.
15 In this slide, I'm going to discuss the
16 current conceptual models for irritable bowel
17 syndrome. And one model, or the central model,
18 really emphasizes the role of behavioral factors;
19 up to 60 percent or more in some cases of patients
20 with this condition have psychiatric comorbidity
21 and display attention-seeking behavior. And this
22 behavioral component is largely responsible for the

reporting of symptoms by IBS patients.

How behavioral factors can produce chronic rather than acute gut dysfunction remains to be determined, and this may contribute in some way to symptom generation. But this is really quite an unsatisfactory explanation as to why the gut should be dysfunctional in this chronic condition. And this gave rise to the notion that there could be a peripheral model that has its origins in the environment that could somehow trigger events such that the gut became dysfunctional.

The breakthrough for this came with the proof that acute gastroenteritis, acute enteric infection by bacteria, parasites, or viruses, could result in a chronic condition that bore strong similarity to irritable bowel syndrome and has become known as post-infectious irritable bowel syndrome.

While this has been suspected, on the basis of just pure clinical observation and some retrospective studies, it was really never put together until the '90s and later, when cohort

1 studies were performed. In outbreaks of large
2 contaminations of food and water, patients
3 suffering from this exposure were followed
4 longitudinally and were found to develop a
5 condition that was very similar to irritable bowel
6 syndrome. It's been calculated that acute
7 gastroenteritis has the largest risk factor known
8 for the development of IBS; it's over 10.
9 This relationship between transient and
10 acute infection of the GI tract and the subsequent
11 development of persistent gut dysfunction has been
12 proven in animal models, therefore providing proof
13 of concept of this relationship between infection
14 and chronic dysfunction; and it's therefore
15 prompted the acceptance of this peripheral model of
16 irritable bowel syndrome.
17 In studying these patients, there's been
18 evidence of gut dysfunction, particularly increased
19 intestinal permeability, the lining of the gut
20 being more permeable to luminal content, and to the
21 presence of low-grade, non-damaging inflammation.
22 Now, there are several lines of evidence

to support the existence of low-grade inflammation in at least a subset of irritable bowel syndrome patients. These lines of evidence are as follows.

First of all, using semi-quantitative analyses, increased numbers of inflammatory cells have been found in the lamina propria of IBS patients. Focus has been on mast cells in most cases, lymphocytes in others, and other inflammatory cell types in the minority of cases.

Second, several studies have now shown that IBS patients have a genetic susceptibility to the production of pro-inflammatory cytokines -- interleukin-1, interleukin-6, TNF-alpha, for example -- compared to the secretion of counter-inflammatory cytokines such as IL-10 and TGF-beta.

This prediction, based on these genetic abnormalities, has been borne out in some functional studies measuring the release of these cytokines in, for example, peripheral blood monocytes taken from patients with irritable bowel syndrome.

These findings are not by any means restricted to those patients who declare a history of previous infection and may apply to a broader segment of the IBS population.

So if there is low-grade inflammation in IBS patients, what is the trigger? What are the factors that maintain this? And this has, in turn, focused attention on the intestinal microbiota.

There are several lines of evidence that I'll describe for you implicating the intestinal microbiota in the pathophysiology of irritable bowel syndrome, and these are illustrated on this slide. First of all, factors that have been described to trigger either the onset or relapses of IBS are also known to influence or destabilize the microbial composition of the gut. These include acute enteric infections and the use, or the extensive use, of broad spectrum antibiotics, at least in the pediatric patient population.

Second, symptomatic improvement has been seen in IBS patients -- this has been alluded to before by previous speakers -- following therapies

that modulate intestinal microbial composition or activity. And these include probiotics, prebiotics, and antibiotics, not the broad spectrum ones, of course.

Then finally, there are, as the first speaker this morning alluded to, some recent findings that there are alterations in the microbial composition or the activity of bacteria in IBS patients.

So this slide summarizes a rapidly emerging but nevertheless small field addressing the nature of changes in the microbiota in IBS patients. These studies are limited in terms of their size, in terms of the patients that were studied, and in terms of the approaches that were used to profile the microbiota in these studies.

I think it can be safely said that despite a couple of claims, that there is no microbiotal signature that will identify all IBS patients from the rest. There are no uniform alterations in composition of the microbiota seen in IBS patients compared to healthy controls when one takes these

data as a whole.

Another important finding, and relevant to this morning's proceedings, is that subgroup analyses indicate that diarrhea-predominant IBS patients exhibit the greatest deviation from healthy controls in terms of their microbial composition.

Important with respect to what we know of the natural history of IBS -- its chronicity and also its fluctuation in the quality and severity of symptoms -- is the fact that there is, clearly, greater instability of the intestinal microbiome over time in IBS patients compared to healthy controls. Unfortunately, these fluctuations have not been compared to the symptomatic fluctuations that occur in IBS patients.

Then finally, there's recent evidence that in chronic functional diarrhea that's very similar to IBS diarrhea, changes in the biofilm that separate the microbiota from the host have been found; and one of the findings in that study was restriction of certain potentially beneficial

1 bacteria to access the epithelium, where they exert
2 anti-inflammatory effects, and in particular, to
3 faecalibacterium prausnitzii, which has been shown
4 to be reduced in abundancy in inflammatory bowel
5 disease patients. And if its access is restricted
6 in IBS, it may contribute to the low-grade
7 inflammation seen in those patients.
8 So we've discussed changes in the
9 bacterial composition. Let's address changes in
10 microbial activity. Through the work of
11 Dr. Pimentel, it's been known that abnormal
12 excretion profiles of hydrogen and methane have
13 been documented in IBS patients. And certainly the
14 excessive production of methane has been linked to
15 the constipation-predominant irritable bowel
16 syndrome. So these findings suggest that there are
17 altered fermentation profiles in IBS patients.
18 Another study examined organic acid levels
19 in the stool of IBS patients and found some of
20 these to be increased, particularly acetic acid and
21 propionic acid, but not butyrate, in patients with
22 IBS. And they found a correlation between total

1 organic acid production and the presence and
2 severity of abdominal bloating and abdominal pain,
3 as well as global well-being. Unfortunately,
4 state-of-the-art assessments of activity in terms
5 of metabolomics have not really been applied to the
6 field of irritable bowel syndrome at this time.
7 So there are changes, then, in the
8 composition and in the activity, the metabolic
9 activity, of the intestinal microbiota, and
10 evidence of instability over time in these
11 patients. And so it generates the question, does
12 perturbation of the microbiota in an otherwise
13 healthy, stable organism induce some of the
14 features that we find in IBS, such as low-grade
15 inflammation and alterations in gut function?
16 This slide here -- I apologize; it's a
17 mouse study. This slide here demonstrates, in my
18 opinion, proof of concept of this. And in this
19 study we took mice, healthy, adult mice with a
20 stable microbiota, and exposed them to a cocktail
21 of broad spectrum antibiotics as well as an
22 antifungal agent. And in the gel, as you can see

below, we were able to cause a shift -- we didn't eliminate, we caused a shift -- in the microbial composition of the gut, just using denaturing gel electrophoresis to document that. This resulted in an increment in what we call controlled or physiological inflammation, much like we see in IBS patients. This is without tissue destruction; it's not IBD. And we found that there was an increase in abdominal pain, using fairly widespread techniques to measure that.

So perturbation of the microbiota can produce some of the changes that we have now associated with IBS from this animal study.

But, as most of you know, the perturbation of the microbiota -- for example, by infection, acute infection, and so forth, and even antibiotics, broad spectrum antibiotics -- is very short-lived, and it doesn't really explain the chronicity of irritable bowel syndrome, and so we have to come up with a model that tries to reconcile that.

So this is my attempt at that. On the

left panel, you can see that if you have a stable microbiota, we know from longstanding work that the microbiota educates and informs many functions in the gastrointestinal tract. It educates the mucosal immune system, and it instructs intestinal physiology. This leads to a normal gut physiology, hopefully a normal brain-gut interaction, and a stable environment for those bacteria to live in.

However, in a condition such as IBS, where a trigger like an acute infection produces a temporary disruption in the microbiota, as you can see here on the right of the slide, this results, as you'll recall from the mouse study, in a small increment, in the inflammatory presence in the gastrointestinal tract.

We know from a wide body of literature that if you slightly increase mucosal immune or inflammatory activity, you cause widespread and extensive changes in neuromuscular function in the gastrointestinal tract, which is thought to be the driver of symptoms, of gastrointestinal symptoms, in IBS. And this in turn may have influences on

the gut-brain axis. Stress and other behavioral factors remain important, and can feed into this system.

As a result, one gets an unstable gastrointestinal tract in terms of its physiology, its motility, its secretory process, its mucous introduction, and this creates an abnormal and unstable habitat. And as a result, we get a vicious cycle in which what starts off as a transient destabilization of the microbiota becomes a vicious cycle, and this is maintained over time.

So to come to a microbe-centric model of irritable bowel syndrome, we believe that behavioral factors are important in the clinical expression of irritable bowel syndrome, in the behavior of these patients, and particularly in terms of symptom reporting and healthcare seeking. It may, under acute circumstances of acute stress, have an impact on gut function.

But I'd like to emphasize the role of environmental factors, particularly acute infection and possibly others, such as the usage of broad

spectrum antibiotics, to destabilize the microbiota to produce low-grade inflammation and to produce chronic gut dysfunction; and that this chronic gut dysfunction, this change in the physiology of the gastrointestinal tract, feeds back in that vicious cycle that I just showed you in the previous slide to account for chronic gut dysfunction and then to symptom generation over a long period of time in IBS.

So, in conclusion, ladies and gentlemen, I believe that changes in the microbiota do exist in IBS patients, and this is definitely a work in progress; that alterations in the microbiota may drive low-grade inflammation and gut dysfunction in IBS; and that therapies directed at the microbiota constitute a novel and rational approach to the treatment of IBS.

Thank you very much for your attention.

Sponsor Presentation - Pamela Golden

DR. GOLDEN: Dr. Raufman, advisory committee members, FDA members, ladies and gentlemen, good morning. I'm Pam Golden. I'm

executive director of nonclinical and clinical physiology at Salix Pharmaceuticals. Today I'll discuss our data characterizing the pharmacology of rifaximin.

Rifaximin is a member of the rifamycin class of antibiotics. In a normal drug discovery program, this compound might never have been developed. It's physicochemical properties predict poor oral absorption. The fact that it undergoes P-glycoprotein-mediated efflux in the gut, and the small fraction absorbed is almost completely cleared by first pass elimination, leaves more than 99 percent of an oral dose exactly where it's dosed and where it acts, in the GI tract.

The use of rifaximin in such diverse therapeutic areas a hepatic encephalopathy from chronic liver disease, infectious diarrhea, inflammatory bowel disease, and, of course, irritable bowel syndrome has contributed to the diverse mechanistic research that's been conducted on the drug.

While rifaximin is known as an

antimicrobial agent, it doesn't have potent antibiotic activity in vivo, nor does it wipe out the gut microbiome like other antibiotics. We are focused on characterizing rifaximin's subinhibitory effects on bacteria, as well as its host effects. Our data don't indicate that affecting GI disorders by these two mechanisms shows tachyphylaxis or resistance to rifaximin's efficacy. I'll emphasize that, based on our data, these effects are also specific, targeted to the GI tract, and don't occur systemically.

To illustrate the uniqueness of rifaximin from a systemic exposure point of view, I have a concentration-time profile on a log scale shown here. Rifaximin's systemic exposure is low in IBS patients as well as in healthy volunteers, and compared to antibiotics that are commonly used in patients with known intestinal as well as systemic infections, you can see exposure differences of about three orders of magnitude.

Combined with the low systemic exposure of rifaximin is a high local GI exposure. Despite

1 this high exposure, we see minimal impact of
2 rifaximin on overall colonic flora counts. Again,
3 this behavior is in stark contrast to that seen
4 with other antibiotics.
5 On the left are gut flora data,
6 specifically coliforms, with and without treatment
7 with the quinolone antibiotic norfloxacin. On the
8 Y axis are mean coliform counts per gram of stool
9 on the log scale, and on the X axis, we're looking
10 at a comparison of norfloxacin versus placebo-
11 treated subjects on days 7 and 14 of a 14-day
12 course of norfloxacin.
13 In the graph on the right are rifaximin
14 data in ulcerative colitis patients. Again we're
15 looking at changes in stool flora counts, this time
16 in terms of multiple specific subpopulations over
17 repeated courses of rifaximin treatment in
18 ulcerative colitis patients.
19 Over repeated rifaximin treatment cycles
20 of 600 milligrams three times per day for 10 days,
21 followed by 25-day off-treatment intervals in these
22 patients, there were no pronounced changes in these

gut flora counts, and any modest reductions returned to baseline after completion of therapy. I'll point out that this was at a dose higher than the one that was tested for IBS by Salix. Similar results have been observed for rifaximin treatment in healthy subjects.

In total, these data suggest that rifaximin could be acting not like a conventional antibiotic, killing bacteria and wiping out conventional gut flora -- excuse me -- beneficial gut flora along the way, but instead by nonconventional mechanisms that likely include altering metabolic activities of gut microbial communities.

Rifaximin has multiple modes of action that have been characterized in the literature. Its pharmacology in the GI tract can be viewed under three classifications. Some of these may be linked or may be independent. They include effects on gut bacteria, both the direct antimicrobial effects and effects occurring at subinhibitory concentrations, including reduced production of

virulence factors and altered bacterial metabolism;

Effects specific to the host, including up-regulation of enzymes and transporters, like CYP3A4 and MBR1 or P-glycoprotein, that may improve the host intestinal epithelium's response to bacterial dysbiosis, and reduced inflammatory cytokine release, again addressing a possible response to dysbiosis; and

Effects on the bacteria-intestine interface, including reduced bacterial adherence to and internalization into the epithelium.

Research specifically looking at the impact of high-dose rifaximin on the gut microbiome has resulted in some interesting data from in vivo and ex vivo studies in inflammatory bowel disease patients. Both studies were performed with rifaximin doses at or approximating an 800-milligram-per-day dose.

In a clinical study in ulcerative colitis patients, this rifaximin dose did not significantly modify overall colonic microbiota in terms of gut flora counts. Eight years later, the investigators

used an ex vivo model to further characterize rifaximin's effects in a human gut model with feces obtained from Crohn's patients. Overall, microbiome results mirrored those of the in vivo study and indicated that both bacterial counts and bacterial diversity remain stable.

There was a notable exception of significant increases in beneficial species noted here, including F. prausnitzii, mentioned earlier by Dr. Collins. Additionally, genotoxic and cytotoxic effects of the bacterial supernatants from this model were decreased in rifaximin's presence, suggesting a protective effect. Short chain fatty acids increased, as did their corresponding derivatives, and ethanol, methanol, and glutamate decreased.

In vitro, rifaximin inhibits a number of bacterial activities. With respect to bacterial communication, rifaximin has been shown to both cure bacteria of plasmids and to reduce their transfer. Reduced virulence has also been demonstrated.

In relation to the effects on the bacteria-host interface, rifaximin inhibits adherence and internalization of bacteria into epithelial cells. These effects were not observed with rifampin, gentamicin, or doxycycline, setting rifaximin apart.

Moving to effects on bacterial metabolism, last year we presented data to this committee on alteration of bacterial metabolism in our pivotal phase 3 study for hepatic encephalopathy. Ammonia, a byproduct of gut bacteria metabolism, was reduced significantly by rifaximin in comparison with placebo.

So these data continue to underscore the role of rifaximin in altering bacterial metabolic processes. Some of these alterations may be of benefit in treating IBS.

We know that rifaximin activates the nuclear receptor PXR and up-regulates target genes. We also know, from a growing body of literature, that the underexpression of genes linked to PXR is associated with inflammatory bowel disease and that

PXR activation and up-regulation of these genes may help IBD patients.

PXR activation up-regulates enzymes that increase metabolism of luminal bacterial products and bile acids. Importantly, data from mouse models as well as our clinical data indicate that rifaximin-mediated up-regulation of PXR occurs specifically in the gut.

While this link to polymorphic PXR expression has not been established for IBS, given the hypothesis that Dr. Collins put forth regarding the role of inflammation in response to dysbiosis in IBS, rifaximin may modulate intestinal lumen response to dysbiosis in certain IBS patients.

Now I'll walk you through our rationale for dose selection for our IBS phase 3 studies.

The dose and dosing regimen and dosing duration used in TARGET 1 and 2 were based on multiple data sets, including clinical response from phase 2 and GI transit data as well as efficacy data in patients suspected of small intestinal overgrowth. Given the potential for

1 dysbiosis and resulting host response to occur in
2 the small intestine, the colon, or both, we wanted
3 to cover both areas with the appropriate rifaximin
4 regimen.
5 Analysis of results from our phase 2 study
6 showed greater efficacy in the 550-milligram BID
7 dose group versus placebo. This regimen had a 14-
8 day duration. The study also contained a lower
9 dose, a higher dose, and continuous dosing for 4
10 weeks. The results indicated that none of the
11 alternate regimens suggested better overall
12 efficacy than 1100 milligrams per day for 2 weeks
13 for adequate relief of IBS symptoms, with the
14 exception that only the 2200-milligram-per-day dose
15 significantly improved abdominal pain. In another
16 published study, patients were treated successfully
17 with a 2400-milligram-per-day regimen.
18 In terms of dosing frequency in a phase 1
19 trial, scintigraphy data on intestinal transit time
20 of rifaximin suggested that a TID regimen would
21 maintain rifaximin exposure of the intestine over
22 the majority of the day, which could be needed for

1 significant effects on gut flora, metabolism, and
2 host epithelial response. As I indicated earlier,
3 we're aiming for continuous coverage in both small
4 and large bowel.
5 Additionally, we looked at the results of
6 two studies that performed breath testing in
7 patients suspected of small intestine bacterial
8 overgrowth. Following baseline testing, patients
9 were given rifaximin and assessed for symptoms, and
10 tested to see if the hydrogen breath test
11 normalized.
12 Breath hydrogen testing is performed by
13 administering a carbohydrate dose. When the dose
14 reaches intestinal bacteria, hydrogen is produced,
15 absorbed, and excreted via the lungs. Early peaks
16 in hydrogen from the lungs may reflect bacteria in
17 the small intestine. The investigators were
18 determining whether rifaximin treatment in these
19 patients resulted in both symptom relief and
20 normalization of the breath test.
21 There are many questions around the
22 sensitivity and specificity of breath testing.

Even with those issues, what we felt was compelling about these results were the use of glucose, which may avoid the motility questions associated with other substrates and the dose-dependent findings. Extrapolating beyond this relationship, we also have seen abdominal pain relief at 2200 milligrams per day.

In total, the results demonstrate both improved symptoms and breath test normalization at progressively higher rifaximin doses using TID administration, providing further support for both a higher daily dose and three-times-daily treatment.

I've reviewed data that indicate that rifaximin differs from traditional antibiotics in a number of important aspects. It has high concentrations in the gut lumen after oral administration and negligible systemic exposure. Its high local exposure along with its modes of action contribute to its efficacy in a range of conditions associated with GI dysbiosis. These modes of action include PXR activation that appears

to be limited to GI epithelium, and bacterial effects that don't appear to include the effects on gut flora that would be attributed to traditional antibiotics, but instead result in beneficial alteration of bacterial metabolic activities and shifting of subpopulations. One or more of these actions may play a role in rifaximin's efficacy in IBS.

Since rifaximin is classified as an antibiotic, we monitor our data closely for any trends that indicate antibiotic resistance. I'll review those data for you now.

I've discussed the potential for a common etiology for GI disorders that are responsive to rifaximin, that being bacterial dysbiosis in the lumen. If resistance to rifaximin's bacterial or nonbacterial mechanisms were common, we would anticipate a loss of efficacy over time, but we haven't seen that to date.

In hepatic encephalopathy, we have patients who are followed for a median of 19 months and up to 4 years without diminished efficacy. In

1 Crohn's disease, new phase 2 data show significant
2 efficacy during 12 weeks' treatment and for 12
3 weeks of follow-up. And in IBS, while we don't yet
4 have prospective data, there are several published
5 retrospective studies showing successful treatment
6 with rifaximin for up to six cycles. So the data
7 we have to date don't suggest diminished efficacy
8 with chronic or repeated treatment.
9 As Dr. Paterson will describe, we'll be
10 examining efficacy with repeated treatment cycles
11 in our upcoming IBS retreatment study.
12 In terms of clinical data that would
13 suggest resistance to antibiotics, we've monitored
14 our safety data for hepatic encephalopathy patients
15 who receive rifaximin as chronic daily therapy.
16 Here we've looked at these rates in both our
17 randomized controlled trial and then the long-term
18 rifaximin study.
19 I'll call your attention to the rates
20 indicating incidence per person-exposure year.
21 Infection rates in this immunocompromised
22 population who received rifaximin for a total of

510 person-years are similar to those reported in the literature for chronic liver disease patients and don't suggest development of microbiologic resistance resulting in infection.

In addition, two studies were reported at last week's AASLD meeting that examined infection rates in liver disease patients taking rifaximin. In the first study, C. difficile infection incidence was examined retrospectively. Patients taking rifaximin had a significantly lower incidence of C. difficile-associated diarrhea than those taking lactulose.

In the second retrospective study also reported last week, rates of antibiotic-resistant infection in hospitalized cirrhotic patients were studied. Compared with an odds ratio of 1 for patients with no antibiotic exposure in the prior 30 days, patients receiving systemic antibiotics had an odds ratio of 4.8 compared with patients receiving a non-systemic antibiotic, primarily rifaximin, who had an odds ratio of .48.

The data from both studies provide

additional indication that rifaximin treatment is not associated with increased risk of antibiotic resistance and, in fact, may reduce this risk.

In terms of monitoring potential development of resistance going forward, we have agreements with the FDA, outlined here, to monitor development of antibiotic resistance in our postmarketing trials for hepatic encephalopathy. We look forward to discussions with the panel today regarding the monitoring and biomarker assays that might be used in an IBS retreatment trial.

Thank you for your attention. Now I'd like to introduce Dr. Craig Paterson, who will be reviewing the clinical development program for rifaximin.

Sponsor Presentation - Craig Paterson

DR. PATERSON: Dr. Raufman, members of the advisory committee, and FDA, good morning. I'm Craig Paterson, vice president, medical and clinical development at Salix Pharmaceuticals. As Dr. Forbes stated, my presentation will focus on the clinical development program for rifaximin in

IBS with diarrhea.

Rifaximin's development program in IBS is the culmination of input from three areas of available knowledge: other programs in IBS, consultation and input gathered from the FDA, as well as dozens of key opinion leaders. The endpoints used in the rifaximin trials are based on approximately 20 years of experience in IBS and other drugs, including ranitidine and famotidine, all of which used binary adequate relief or global symptom improvement constructs as primary efficacy endpoints.

The Rome working group recently evaluated the binary endpoint of adequate relief in analysis of pooled data from 12 IBS drug trials involving over 10,000 patients. The binary endpoint was equivalent to the 50 percent improvement endpoint in their psychometric properties. There was no impact of baseline disease severity, and both were optimized for the IBS-D population.

The classical treatment paradigm in IBS therapy is shown here with this example of

alosetron, which also used adequate relief and met with regulatory success. Therapy was given daily over the course of 12 weeks and measures of efficacy over the 3 months were designed to ensure no loss of response with chronic dosing. Adequate relief was achieved and sustained as long as daily dosing was continued. Conversely, the loss of efficacy occurred almost immediately upon withdrawal of therapy.

In contrast to therapies such as alosetron, it was evident that rifaximin required only a short course of therapy to provide effects that lasted well beyond the completion of treatment, a unique paradigm in IBS therapies. With the potential mechanisms of action of rifaximin, it might be predicted that onset of effect would be relatively rapid, followed by an eventual and gradual loss of efficacy over time in some patients. It is important to consider the implications of this different dosing and effect paradigm on the assessments of efficacy and durability which are based on the more traditional

chronic dosing model.

Summarized here are several studies which helped to shape the clinical development program for rifaximin. The potential utility of rifaximin in the treatment of IBS was recognized by its positive effects in the treatment of bloating, abdominal pain, and diarrhea. In some of these studies, reduction in intestinal gas production correlated with improvement in symptoms that were also characteristic of IBS.

The development of rifaximin as a treatment for IBS was initiated in the fall of 2005 with a meeting between Salix and the FDA. The results achieved in the literature were replicated in our phase 2 program and subsequently confirmed in two pivotal trials conducted primarily in the United States.

The phase 2 study evaluated the efficacy of rifaximin, 550 milligrams BID, versus placebo and evaluated the relative efficacy and safety of four rifaximin dosing regimens in patients with IBS. Co-primary endpoints were assessed using

1 weekly subject global assessment questions similar
2 to those subsequently used in the TARGET studies.
3 The primary analysis compared a 2-week
4 course of rifaximin, 550 milligrams BID, versus
5 placebo. In the intent-to-treat population,
6 52 percent of patients in the rifaximin group
7 experienced adequate relief of IBS symptoms versus
8 44 percent of patients in the placebo group, a
9 statistically significant difference. Similarly,
10 46 percent of patients in the rifaximin group
11 experienced adequate relief of IBS bloating
12 compared to 40 percent of patients in the placebo
13 group, which was also significant.
14 The efficacy and safety of rifaximin in
15 the treatment of IBS-D is supported by the totality
16 of evidence from clinical studies in phase 2 and 3
17 as well as several published reports, which I have
18 mentioned. Specifically, the primary clinical
19 efficacy data comes from two pivotal, identically-
20 designed, double-blind, placebo-controlled phase 3
21 studies, TARGET 1 and TARGET 2. Full results of
22 the TARGET studies have been disclosed in a peer-

reviewed scientific journal.

IBS is a debilitating condition that impacts patients, families, and challenges the overall well-being of those suffering. While IBS is life-altering, it is not perceived as life-threatening. So while therapies need to be effective, there is little tolerance for life-altering safety issues.

Listed here are the approved and, with the exception of tegaserod, currently marketed therapies for IBS, as well as the numbers needed to treat to derive benefit. Below alosetron are the therapies that have been used for IBS with constipation.

I will now discuss our pivotal phase 3 studies.

The phase 3 confirmatory TARGET trials were randomized, double-blind, and placebo-controlled studies that were identical in design. Salix conducted the TARGET studies following recommendations of the agency and with the support of key thought leaders in the IBS community.

The primary endpoint chosen at the time of study inception was consistent with that used for other IBS products that were approved. Recognizing the potential for recall bias on the weekly questions comparing symptoms to baseline, daily assessments were also included.

TARGET 1 and TARGET 2 were powered to demonstrate benefit over placebo during the primary evaluation period, or PEP. All enrolled subjects suffered from IBS, as defined by Rome II criteria, and had symptoms of bloating.

Beginning in the screening phase and continuing through the end of the study, patients are required to record both daily and weekly IBS symptoms with an interactive voice response system. Following screening, eligible patients were randomized one to one to receive either rifaximin or placebo for 2 weeks, and then followed post-treatment for an additional 10 weeks, as shown here.

Endpoints were based on the responses to weekly questions regarding global IBS symptoms and

IBS-related bloating. Efficacy was assessed using the number of weekly responders over a 4-week period, as per the FDA draft guidance document. Efficacy endpoints were also assessed for daily responses to symptom-specific measures of overall IBS symptoms, IBS-related bloating, IBS abdominal pain, as well as stool consistency, frequency, and urgency.

It is important to define what constituted the primary analysis time point, referred to as the primary evaluation period or PEP. Both the primary and secondary endpoints were measured at the PEP, which is defined as weeks 3 through 6 following completion of the 2 weeks of treatment.

In order to establish whether or not a patient was a responder in a given week, answers to both the weekly and daily questions were assessed. For the primary efficacy analysis, a responder is defined by an answer of yes to the weekly question of adequate relief of global IBS symptoms over the past 7 days, as compared to how they felt before treatment.

The key secondary efficacy analysis was likewise based on a weekly question of adequate release of IBS-related bloating in the past 7 days, again compared to how they felt before treatment. Efficacy criteria were considered met for a defined 4-week period if a patient had adequate relief; that is, they answered yes for at least 2 of the 4 weeks.

Prespecified additional secondary endpoints were also assessed based on daily questions addressing how bothersome patients' IBS symptoms were on a day-to-day basis. Their criteria listed indicate what was considered to be a positive weekly response. In a requested exploratory analysis, we likewise evaluated responders based on the FDA draft guidance criteria.

Efficacy endpoints based on the weekly questions are presented here. The primary endpoint was the proportion of subjects that indicated adequate relief of global IBS symptoms during the PEP. The key secondary endpoint was adequate

1 relief of IBS-related bloating, which was also
2 assessed during the PEP. Agreement on these
3 endpoints was reached with the FDA at the end of
4 phase 2 meeting in December of 2007.
5 Disposition of the patients in the TARGET
6 trials is presented on this slide. Of the total
7 1,260 patients randomized, the completion rate was
8 greater than 90 percent in each study and for each
9 group. In the TARGET studies, similar proportions
10 of rifaximin and placebo patients discontinued
11 early, and there were no notable differences
12 between groups or in the reasons for early
13 discontinuation. In contrast, several other IBS
14 drugs have had much higher discontinuation rates,
15 in some cases because of constipation.
16 Demographic characteristics for the
17 intent-to-treat population of the TARGET studies
18 were similar between groups as well as the two
19 studies. Mean age was 46 years, with most patients
20 being white and female. Overall, these findings
21 are consistent with the demographic characteristics
22 of IBS patients in the United States.

Evaluation of the baseline IBS characteristics revealed no remarkable differences between studies or treatment groups. Each treatment group and study had comparable IBS histories and similar average daily symptom scores at baseline. In each study, approximately 70 percent of the patients were categorized as non-severe based on scores from the IBS quality of life instrument.

Shown here are the primary results of TARGET 1 and TARGET 2 in a side-by-side comparison. For the primary endpoint, during the PEP, rifaximin demonstrated a statistically significant benefit in symptom relief versus placebo. TARGET 1 and TARGET 2 each met the prespecified primary endpoint. Significantly more rifaximin patients had adequate relief of global IBS symptoms over the one-month PEP following treatment based on the weekly subject global assessment question.

In TARGET 1, the respective rates of meeting the primary endpoint were 41 percent and 31 percent for rifaximin versus placebo, a p-value

of 0.0125. Similarly, in the TARGET 2, rifaximin met the primary endpoint in 41 percent of patients versus 32 percent in placebo. This p-value was also statistically significant at 0.0263. The comparative clinical relevance of these findings will be shown later in this presentation.

Here are the results for the key secondary endpoint, IBS-related bloating, from the TARGET trials. Significantly more rifaximin patients had adequate relief of their IBS-related bloating over the month following treatment when compared to placebo. TARGET 1 produced a 40 percent versus 29 percent response in favor of rifaximin, and TARGET 2 a 41 percent versus 32 percent response, again favoring rifaximin. Both were statistically significant.

Looking at this forest plot, point estimates to the right of the line of no effect represented outcome favoring rifaximin therapy. Both the primary and key secondary efficacy point estimates with 95 percent confidence intervals, which are based on the weekly questions, are

completely to the right of the line of no effect.

The efficacy endpoints labeled as "other secondary" demonstrated the outcomes when the daily bothersome symptom measures were used. These endpoints tracked similarly to the weekly measures and support the positive effects of rifaximin.

Finally, additional exploratory analyses requested by the GI Division, based on draft FDA guidance, were also consistent in favoring rifaximin. These findings were all statistically significant and demonstrate the consistency of efficacy of rifaximin for both global and individual symptom-based endpoints in IBS-D subjects.

Dr. Mulberg has addressed the issues with durability, and I will not repeat that.

I discussed earlier that treatments for IBS needed to be effective and have an excellent safety profile. To understand the treatment effect seen in the TARGET studies, the relative effect size of several therapies for IBS are shown here.

When compared to rifaximin, it is evident

that the effect size of other products that have met with regulatory approval is similar. The numbers needed to treat for rifaximin was confirmed in a recently published meta-analysis by Chey and colleagues. The balance of drug benefit in relation to treatment-related side effects is also an important consideration in deciding which therapy should be used in a given patient.

The relative safety of rifaximin in IBS is supported by data from the TARGET studies. Most adverse events reported in these studies were mild or moderate in intensity, and there were few serious adverse events or adverse events resulting in study discontinuation. There were also no differences in the types of adverse events resulting in study discontinuation.

In addition, there was no indication of clinically significant bacterial resistance that occurred during the studies or subsequent study follow-up. The safety findings of the TARGET studies, with event rates comparable to those observed with placebo, did not add to or result in

any changes to the current Xifaxan label.

We welcome your feedback and look forward to a fruitful discussion on the repeat treatment trial. Thank you.

Clarifying Questions to the Presenters

DR. RAUFMAN: Thank you.

We will now ask if the committee has questions for the sponsor. I remind you to please wait to be acknowledged by the chair before asking a question.

Dr. Pasricha?

DR. PASRICHA: So I just want to clarify from the sponsor that, according to the presentation that we heard today, the mechanism of action of rifaximin in IBS is unknown; is that correct?

DR. FORBES: That's correct. We have a number of theories around how rifaximin may be acting in IBS to provide, following a short-term course, prolonged benefit. And as you can imagine, from the presentations, those involve microbiota in the small intestine, large intestine, the interface

with the host, and how the host is actually receiving that.

Slide up, please.

DR. PASRICHA: But that's all circumferential. There is no link that we know of between its apparent or putative effect on dysbiosis and what's happening in IBS. And I was wondering if you had any preclinical data that is exploring that link or have any evidence to suggest that, in fact, that link exists, because otherwise we're talking about a black box in terms of mechanism of action.

DR. FORBES: Let me ask Dr. Collins if he has any further thoughts on this beyond what he's actually already elaborated on. But I don't know that --

DR. PASRICHA: I'm talking about your drug specifically.

DR. FORBES: Okay. Dr. Pimentel, would you like to step to the microphone and give us your thoughts on mechanism? Dr. Pimentel's thoughts and research, as you know, revolve around small

intestinal bacterial overgrowth.

DR. PIMENTEL: Thank you. Mark Pimentel from Cedars Sinai Medical Center. My disclosure is that Cedars Sinai Medical Center does have technology and technology relationships with Salix. But I will not be speaking about rifaximin at this moment, I'll be speaking about the discussion about bacterial overgrowth and gut flora.

There are some who still believe that colon cancer screening doesn't work or taking polyps out doesn't work. There are some who will never believe that bacterial overgrowth is a cause of IBS. But the whole purpose is to continue the scientific exploration to determine if this is real or not.

Ten years ago, we embarked on some breath testing studies that suggested that IBS patients had more positive breath tests than healthy controls. We couldn't keep publishing breath tests studies because some would say, well, it's only a Cedars Sinai phenomenon. So we had to wait 10 years.

1 We recently did a meta-analysis of the
2 10 years of data, and the 10 years of data suggest
3 that the odds ratio -- when you use the age- and
4 sex-matched studies only, the odds ratio is 10. So
5 breath testing does detect a signal in IBS. The
6 question is, is it bacterial overgrowth?
7 The second is culture studies. So there
8 are now two culture studies, the Posserud
9 study -- the Posserud study is a Swedish study that
10 looked at 165 IBS patients and 26 healthy controls,
11 and while they didn't see or detect a difference of
12 greater than 10 to 5th, which is an old standard
13 for bacterial overgrowth, greater than 10 to 5th is
14 not a good standard for bacterial overgrowth
15 because it was only verified or validated in
16 Billroth II patients or post-surgical patients.
17 When you look at smaller numbers of
18 coliforms, you actually see a significant
19 difference in the Posserud study. A more recent
20 study from Athens that we're collaborating with,
21 they demonstrate that 60 percent of diarrhea-
22 predominant IBS -- this was presented at DDW; 60

1 percent of diarrhea-predominant IBS patients have
2 bacterial overgrowth by the definition of using a
3 healthy control of what is normal. As we move
4 forward, we're now doing PCR studies to suggest the
5 same kind of phenomenon, and these will be
6 presented at DDW.
7 So as the data continue to accumulate, I
8 think the evidence weighs in favor of the fact that
9 there is excessive coliform bacteria in the small
10 intestine of IBS patients. If you don't want to
11 call it overgrowth because you want to be a strict
12 purist and use greater than 10 to 5th, you can call
13 it dysbiosis. But there's definitely an excess of
14 coliforms, as evidenced by the literature.
15 DR. RAUFMAN: One follow-up?
16 DR. PASRICHA: I want to clarify that I'm
17 not doubting that there is fairly reasonable
18 evidence linking alterations in microflora within
19 the small bowel or colon to IBS. I'm questioning
20 what is the link between rifaximin and that
21 phenomenon, and is there any evidence to suggest in
22 fact that alteration of the microflora is what's

responsible for the improvement in symptoms?

DR. RAUFMAN: I'll ask for a very focused answer to that question.

DR. FORBES: Okay. Can I have slide up, please? I'm going to try to stay as focused as I can here. And I think the direct answer to your question is we don't know yet. We're still looking at a lot of things, and we're looking for input from this committee on what else we should look at as well, so in the next study we obviously have plans and thoughts around what we need to do.

But when you look at rifaximin as a molecule, what we do know of it is it's highly insoluble in the stomach. It is highly soluble in the small intestine. So one could speculate it's such a high solubility that perhaps the antimicrobial activity is in play in the small intestine.

As the drug moves down into the colon, we believe it actually precipitates, if you will, and is not as soluble in the colon where some of the subinhibitory effects may come into play; PXR,

along the way, obviously, a lot of that in the small intestine but some in the large intestine.

So we have some thoughts from a physicochemical property of where the drug is available to provide action at higher or lower concentrations. Exactly how or where it's working in IBS we can't tell you today.

DR. RAUFMAN: Thank you.

Dr. Solga, you had a question?

DR. SOLGA: Yes. I guess I'm -- and I think we're going to be hitting on the same themes. I have a lot of questions, actually, about the gut flora. And it came up over and over again that SBIO [sic] and IBS were related, or the glucose testing were related, but it's unclear that they are.

The Italian studies that were used for dose-finding were actually looking not for SIBO; they were looking for irritable bowel patients. And those patients then had abnormal blood glucose testing, and then we said, okay, look at this dose-response curve. But then later on we said,

we're not sure that we actually believe glucose breath testing, then it falls away.

I guess my question actually is, where is the in-between? When I look at your 187 references in this guidance document that you provided the FDA, there is some data about rifaximin in molecules, the PXR story. There's data looking at questionnaire studies. But where's in-between when we're looking at continuous flow culture data, where we're looking at stool studies aggressively, as this gastro did in November of 2011 using Agilent 16S or ribosomal assay microarray.

Dr. Collins suggested peripheral blood monocyte studies for signaling. Of your 187 studies, one of them I found to be very useful, and that's reference 54, where they actually used a continuous flow culture model and said, okay; let's do something that is physiologic. We're going to look at using protein MMR and using GC and mass spec. We're going to ask, where is the short-chain fatty acids? Where is the propanol? Where is the ethanol? Where is the methanol?

Why can't you do those studies in humans? Why aren't those being done?

DR. FORBES: Dr. Golden, would you like to answer this question?

I'll answer it briefly. Obviously, as I said before, we have plans to initiate many of those types of studies, and we understand the interest in getting that kind of information and being more aggressive about that. But I'll have Dr. Golden talk about where we are and where we're going.

DR. GOLDEN: Briefly, I absolutely agree with you. I'm very interested in the findings of that study in the human gut model, and I showed some of those data earlier.

We absolutely share your interest in linking those results to what we see in our next trial. We don't have those data, including the sequencing or the metabolic products from our TARGET 1 and 2 studies. But we're interested in discussing with this committee sequencing data, metabolic profiling data in vitro or in vivo, that

may help us solidify that link.

DR. FORBES: The other thing I'd like to mention is that, obviously, in working with the GI Division for hepatic encephalopathy, there are two clinical trials that are just getting ready to start right now. And we hope to be able to utilize information from HE patients. But in IBS going forward, we're also very interested in being aggressive on this and doing the right studies to get the right information.

DR. SOLGA: I don't want to monopolize, but multiple times during Salix's information provided to the FDA, it says there are no major perturbations to beneficial gut flora. And there are references that I looked up that really don't say that. What they say is there were no major alterations to coliforms in old studies looking at traveler's diarrhea.

So there are a number of almost half-truths in sort of some of that. And yet we say, okay, look at the impact on glucose hydrogen testing. It seems to be inconsistent to say there

are no major alterations, but, gosh, we can use glucose breath testing when it's helpful and then forget about it when it doesn't seem to be helpful; and then say, okay, we're not going to do the physiologic or haven't done the physiologic studies somewhere in between.

DR. RAUFMAN: I'd like to move on, and we'll take that as a statement, not as a question.

Dr. Spiegel?

DR. SPIEGEL: Thank you. Following up, I think, on some of the themes I've been hearing about, in particular, the breath test, the original observation that the lactulose hydrogen breath test, that Mark Pimentel demonstrated, is abnormal in IBS, really started this discussion and was a fruitful line of inquiry.

We've since learned that the lactulose hydrogen breath test is almost assuredly a measure of intestinal transit time, not necessarily a measure of SIBO, as opposed to the glucose hydrogen breath test which you've shown us there's some dose-response data with rifaximin.

1 So to me that brings up two questions.
2 One is our understanding that lactulose hydrogen
3 breath tests are abnormal in IBS, is that really an
4 indicator that dysmotility is a major driver of the
5 illness experience in IBS? And maybe dysmotility
6 itself secondarily leads to dysbiosis. And if we
7 were to alter motility, that might be one mechanism
8 to change the microbiota just as we could in, say,
9 scleroderma, where no one would argue that SIBO is
10 causing scleroderma, scleroderma causes SIBO.
11 So is that possibly the case here? Could
12 that be contributing?
13 The second line of inquiry from me is,
14 knowing that there is a dose-response relationship
15 between rifaximin exposure and dosing and glucose
16 hydrogen breath test results, why not measure
17 glucose hydrogen breath tests initially in the
18 TARGET study or even moving forward into your
19 additional planned studies?
20 Would that be a biomarker that's as good
21 as any right now that could be used, and also could
22 be used clinically to help guide decision making

for clinicians about whether and when to use this therapy?

DR. FORBES: Sure. Dr. Schoenfeld, could you step to the microphone for us? I think -- and, actually, if you could put slide up for just a minute -- the data I believe Dr. Spiegel is referring to is on this slide. It came from you, et al. And it actually is talking about orocecal scintigraphy and using that to actually measure transit time, and what happens with the lactulose breath test.

I mean, in short, the glucose breath test is more specific but less sensitive. So glucose obviously gets absorbed in the small intestine. If you have bacteria and it metabolizes in the small intestine from bacterial overgrowth, then the glucose breath test would be a good test, perhaps, to use. But you might miss some of the bacteria that's in the distal part of the small intestine.

But I'll ask Dr. Schoenfeld to describe what his thoughts are on this.

DR. SCHOENFELD: Slide up. This is a

1 fascinating discussion, but I think there are
2 probably about four points that are going to be
3 very important to make.
4 The first is that per the Rome committee,
5 IBS is a symptom-driven diagnosis; not a diagnosis
6 of exclusion based on having a bunch of negative
7 tests, but a symptom-driven diagnosis where there
8 isn't a clear biomarker to identify IBS patients,
9 nor has there ever been a clear biomarker to then
10 identify a treatment to use specifically in IBS
11 patients.
12 So that's the Rome committee of IBS
13 experts. That opinion's endorsed in the ACG's
14 evidence-based position statement about the
15 treatment of IBS.
16 So, having said that, moving on then to
17 breath testing. The problem with breath testing,
18 as illustrated very well in this recent meta-
19 analysis from Ford and colleagues, is the results
20 are quite heterogeneous. Now, part of that does
21 depend on the substrate used, the protocol that you
22 used, things that Dr. Spiegel pointed out. Part of

it's also because how you maintain your equipment can lead to highly variable results.

That leads to the kind of statement you see here from that meta-analysis, all kinds of conflicting evidence about the yield of tests for SIBO in individuals who meet the diagnostic criteria for IBS compared to healthy individuals in the general population. Prevalence varies according to the criteria used to define a positive test.

Now, again, maybe at a center of excellence, where you have very precise technology, you might be able to reproduce things; doesn't seem to be the case when you see results like this. And that's why the conclusion of those experts -- many of which are on the ACG's evidence-based position statement -- said, role of testing for SIBO in individuals with suspected IBS remains unclear. ACG evidence-based position statement says you should not routinely check for SIBO by doing breath testing.

So why is that the case, beyond the fact

1 that breath testing equipment tends to produce
2 highly variable results? I think the other
3 reason -- again, to go back to what Dr. Collins
4 said, if we say breath testing is going to identify
5 people with IBS, to some extent it's implying that
6 breath testing is identifying SIBO, and that's the
7 reason people get IBS that responds to rifaximin.
8 I'd really venture to say that many IBS
9 experts now really think that, although a subset of
10 people with IBS who respond to rifaximin may have
11 SIBO, many more have colonic dysbiosis that is not
12 going to have -- I mean, may have a positive breath
13 test just because of your protocol, but you're not
14 identifying SIBO in those IBS patients who respond
15 to rifaximin because the cause is colonic
16 dysbiosis.
17 So, again, I really endorse Dr. Pasricha's
18 statement. I mean, this is a black box, but it's
19 probably -- when you think about these statements
20 and the data, it's not a black box that's going to
21 be corrected by doing breath testing. I mean, as
22 an exploratory analysis, maybe in a subgroup of

people, in further studies it could be helpful. It's not the answer right now.

DR. RAUFMAN: In the interest of keeping on time, I ask everyone to please focus their questions and their answers. I know we have a few people who want to ask questions.

Dr. Septimus?

DR. SEPTIMUS: Just one quick question. The influence of PPIs on gut flora; and, secondly, you talked about clinical resistance. Have you actually looked at resistance at the microflora that's not clinically related?

DR. SCHOENFELD: I'll go ahead and take the PPI question.

Could you repeat it? Because I want to make sure I answer precisely and in a focused way for Dr. Raufman.

DR. SEPTIMUS: Have you looked at the influence of PPIs on the gut microflora in this syndrome?

DR. SCHOENFELD: No.

DR. FORBES: No, we have not explored that

specific question. We looked at the efficacy of patients taking PPI versus the patients that did not, and we didn't see a significant difference between the two groups when it came to rifaximin response. But we haven't looked at the microbiome as it relates to PPI or not PPI in IBS.

DR. SCHOENFELD: And just to provide a very brief addition to that, it has been looked at in TARGET 1 and TARGET 2, whether non-PPI users were less likely to have a response to rifaximin compared to PPI users because of the hypothesis that PPI use might lead to colonization in the proximal small intestine, and that's what's actually being treated.

When you stratify the results in TARGET 1 and 2 for non-PPI users versus PPI users, actually non-PPI users are more likely to respond with a similar delta versus placebo patients, and that, again, the delta for non-PPI users versus PPI users is the same across global IBS symptoms, weekly bloating, daily bloating.

So it's an interesting hypothesis to

explore further, but at least in terms of results to TARGET 1 and 2, there is not a difference in responder, in the delta for responder rates between non-PPI users and PPI users.

DR. RAUFMAN: Dr. Rosen, you had a question?

DR. ROSEN: So when deciding who should get antibiotics and shouldn't get antibiotics, can you give us some more information about the nonresponders in TARGET 1 and 2, specifically related to their IBS symptoms but any other medication-related differences or anything that you can think might be relevant?

DR. FORBES: We've actually looked at the data very closely to try to pick out those patients that either may have a tendency to respond to rifaximin or not respond, and I think that those analyses really didn't come to bear.

If I could see the multivariate-univariate analyses of response; maybe we could put a slide up for you.

Slide up, please.

There were a few things on a univariate approach that came out statistically significant. Gender, while significant, both of them went in the same direction; the race was something that even the FDA pointed out in their briefing document, the whites versus the nonwhite, the African American versus others. We did see that as well.

But for the most part, when we went to adjust everything for all of these multivariates, we weren't able to see, really, a significant difference. So the multivariate didn't seem to really collaborate or corroborate the univariate very much.

DR. RAUFMAN: A quick follow-up.

DR. ROSEN: You just mentioned PPI data that we hadn't seen. So are there any other medication-related things that we should know about, or other -- you know, stool consistency, things like that, that we need to know?

DR. FORBES: No. I mean, all of our probing around other common meds and everything else didn't really give us a clear signal that

there was one particular variable that either helped patients to respond better or not.

DR. RAUFMAN: Dr. Hasler?

DR. HASLER: My question follows up and has actually partially been answered by the response to Dr. Rosen. Again, a clarification of who you consider to be the patient population you want to aim this drug at.

In the briefing documents, we were all informed that this drug is designed for people with mild to moderate non-constipated IBS. And I was going to ask a question about severe versus non-severe patients, and your slide there shows a .3 p value in terms of the multivariate comparison.

Why aren't you proposing this for more severe cases in that instance?

DR. FORBES: So if I could have the baseline characteristic response slide. I think, when we look at severity, one of the things that we did is we looked at the IBS quality of life that was given to the patients at baseline, and then post-baseline at weeks 4, 8, and 12. What we found

on that is that, really, about 25 to 30 percent of the patients actually scored on the quality of life in the severe range.

So I understand that the GI Division believes that we did not include severe patients. The baseline criteria or the inclusion criteria that we use, abdominal pain and bloating, with cutoffs on the high mark on the Likert scales that we were using, on the bothersome scales, I think precluded the very severe patients from coming in. But when we look at IBS quality of life and we break it down by their score at baseline, about 25 or 30 percent of these patients score severe on that.

Slide up, please.

So this is the intent-to-treat data based on baseline characteristics. And you can see here the 26, 29, 28, and 28 percent on the IBS severity being severe. And the response in that group is actually fairly good. I think going forward what we're interested in is what should the inclusion criteria be to also include the more severe

patients.

Also, on abdominal pain, from phase 2, we know that the patients with the most severe abdominal pain did very well from phase 2, and we also believe that's the case here as well.

DR. HASLER: Can I just ask one brief follow-up to that? Did you see a similar, say, 10 percent difference between active drug versus placebo in the severe group?

DR. FORBES: Yes. It was about that.

DR. RAUFMAN: Dr. Fleming for the penultimate question.

DR. FLEMING: Well, actually, there are several things; the rigor to address the lack of efficacy loss long-term in HE, and the claims of statistical significance in phase 2 when four of the six pairwise comparisons went in the wrong direction by dose and by endpoints. But if I'm allowed one question, the focus of that would be to follow up on what was just said.

The FDA noted the exclusion of patients with severe symptoms. We just heard that some got

in; I don't know if we got an adequate representation, though. And only those patients with IBS-D were in, we understand from the FDA.

DR. FORBES: Correct.

DR. FLEMING: Yet I understand that your indication is to be inclusive. Is that correct, or will you exclude severe patients in your indication? Your label seems to be non-C IBS, not IBS-D. So there seems to be a disconnect between the eligibility in 3007 and 3008 and what your label is.

DR. FORBES: The TARGET trials enrolled patients that were in a diarrhea state and were not constipated. What we ended up with was IBS-D. So we understand that, essentially, TARGET 1 and 2 is 100 percent IBS-D, and we don't have any argument on that. We did have some mixed IBS in phase 2, and, unfortunately, we didn't get to the point of negotiating the label. But I think we're both in agreement, Salix and the FDA, that we have an IBS-D population in TARGET 1 and 2.

DR. FLEMING: And then in the label.

DR. FORBES: And in the label. And the severe patients is something that we also didn't get to discuss in a way that I would have liked. But with the severe patients, going forward, we'd like to hear your thoughts around how to include more severe patients in the next trial.

DR. RAUFMAN: I'll take the privilege of asking the last question. And we'll have more time and there'll be other question-and-answer sessions as we proceed, but I do want to keep us on schedule.

I'll address this to either Dr. Lembo or Dr. Collins. I found it curious that there was no discussion of bile acid malabsorption in IBS-D. There are European data over the last couple of years suggesting that as many as a third of the patients who are diagnosed with IBS-D have primary bile acid malabsorption, and there are biomarkers -- fibroblast growth factor 19 or C-4 from Mike Camilleri's lab at the Mayo Clinic -- that have been proposed to identify or help identify those patients.

I'd just like your comments on that and whether this is something that should be considered in prescreening patients for other trials.

DR. LEMBO: Thank you. I do recognize that data. A lot of the European studies haven't really diagnosed IBS when they've looked at the effects of bile acid sequestrants. There's a good study with functional diarrhea, but, again, whether or not those patients had IBS or not is unclear.

There are limited studies in IBS, in IBS-D, and in fact no really good studies to quote with bile acid sequestrants that are available. My own personal experience is that we do try cholestyramine, which is clinically available here, with limited success in IBS. We may be able to reduce frequency of stools, but have very little effect on abdominal pain.

So while it's an area of interest going forward, it's not one that I think is playing a major role in IBS.

DR. COLLINS: Yes. I would concur with that. And just taking it one step further, it's

highly likely that if one does have bile acid malabsorption, that it will influence the microbiota, but that has not been fully characterized yet.

DR. RAUFMAN: Thank you.

At this point we'll take a 10-minute break. We will reconvene again in this ballroom in 10 minutes from now, let's say at 10:15 a.m.

Panel members, please remember that there should be no discussion of the issue at hand during the break amongst yourselves or with any members of the audience. Thank you.

(Whereupon, a brief recess was taken.)

DR. RAUFMAN: We will now proceed with the FDA presentations. Dr. Dimick?

FDA Presentation - Lara Dimick

DR. DIMICK: Hello. I'm Lara Dimick, and I'm the primary medical reviewer for this application. I wanted to refocus the committee on the questions the review team was asking as we were discussing this application, and introduce the next speakers.

While the dose level and the length of treatment selected by the applicant was considered to be reasonable, and it was not the reason the application was given a complete response, still, the dose justification did generate a lot of discussion within our division, and that led to a discussion about the overall goal of treatment.

We thought the goal could be prevention of recurrent symptoms, treatment of symptom recurrence, or possible cure or remission, with a different dosing regime. And Dr. Kim, our clinical pharmacologist, is going to review our analysis of the phase 2 trials and the dose selection.

Other issues that obviously arise when reviewing an antibiotic application is the possibility of development of resistant bacteria and the long-term impact on the GI flora of repeat uses. The Division of Anti-Infective Products was consulted, and Dr. Purfield will discuss their analysis.

Given the large population of IBS patients and the concern about the possible long-term

consequences on public health, we considered the advantages of attempting to narrow the population. And while we recognize the significant limits to hydrogen breath testing as it now stands, as we begin discussing the design of the retreatment trials, we thought that possibly further research and development might yield a predictive biomarker that could be used to narrow the population, and we consulted the Division of Chemistry and Toxicology Devices.

One thing that was clarified in our discussion with them is that we really weren't talking about the development of a biomarker to diagnose SIBO. What we're talking about is the development of a predictive biomarker that would really just be narrowly predictive of the response to rifaximin itself, and Dr. Lias is going to discuss that all in detail with you.

I also wanted to thank all the many people that were involved in the review of this application. There were over 26 MDs, PhDs, and other professionals who helped in just the initial

review, and then more who have been involved as we prepared the retreatment trial data.

Thank you. Dr. Kim?

FDA Presentation - Insook Kim

DR. KIM: Good morning. My name is Insook Kim. I'm the clinical pharmacology reviewer for rifaximin.

So that was a very good presentation by the sponsor and covered many of my aspects in my talk. However, my presentation will focus on the dose-response relationship observed in phase 2 trial and also how the dose was selected for phase 3 trials, ultimately the proposed dose for IBS-D population.

So before that, I'll just briefly go over and remind you about the characteristics of rifaximin. Rifaximin is considered a locally-acting antibiotic because of its limited oral bioavailability. Rifaximin is practically insoluble in water, but the solubility can increase in presence of surfactants such as bile salt. Limited oral bioavailability, after oral

administration, less than 1 percent of the oral dose is absorbed. Once absorbed, rifaximin undergoes extensive metabolism, mainly by CYP3A4 enzyme.

PK in IBS patients was generally similar to that in healthy subjects. Mean plasma concentration, peak plasma concentration was about 4 nanogram per mL after multiple doses of 550 milligrams TID dosing in IBS patients. Peak plasma concentration can be increased in patients with hepatic impairment. So the highest peak plasma concentration observed up until now is about 50 nanogram per mL, which is about tenfold higher than that observed in healthy subjects or in IBS patients.

Just give you a relative sense, the mean Cmax of rifampin, which is a structural analog of rifaximin, is about 7 microgram per mL after a single dose of 600 milligrams, which is about two to three orders magnitude higher than that of rifaximin at a similar dose level. Current labeling does not recommend rifaximin for systemic

bacteria infections.

So I'm going to talk a little bit in more detail about the phase 2 program. Dose-response relationship was explored in phase 2 trial, which was multi-center, randomized, double-blind, placebo controlled trial in patient IBS-D by Rome II criteria.

Treatment effect of rifaximin was evaluated after 2-week treatment at three different dose levels, 275 milligrams, 550 milligrams, and 1100 milligrams, given twice daily. And active treatment, 2-week active treatment was followed by additional 2-week treatment with placebo to make a total of 4-week of treatment period. In addition to 2-week treatment period, there was another treatment duration, which is 4-week treatment, studied at the one dose level, which was 550 milligrams.

Similarly, in phase 3 trial, the efficacy of the rifaximin treatment was evaluated by two co-primary endpoints. At the end of the 4-week treatment phase, patients were weekly asked whether

she or he feels adequate relief of global IBS symptoms or adequate relief of IBS-related bloating. If the patient says yes in 2 weeks out of final 3 weeks during this 4-week treatment phase, then patients were defined as a responder. Of note, about 600 patients were renewed in phase 2 trial, and the trial was primarily powered for 550-milligrams BID dosing regimen.

So in result, in this graph what you're seeing is the proportion of responder -- excuse me -- proportion of the responder was shown by dose group. Not surprisingly, there was very high placebo effect for both endpoints here, and then 550-milligrams twice-daily dosing for 2 weeks resulted in higher proportion of responders than placebo and the other dose levels studied.

However, there was no apparent obvious dose-response across dose levels, as you can see; and also especially the highest dose studied, which was 1100 milligrams BID, which is 2200 milligrams total daily dose, did not really show any treatment effect compared to the placebo group.

On the other hand, this is the effect of treatment duration. So treatment duration was compared at 2-week treatment and 4-week treatment. Again, 4-week treatment did not result in any additional benefit over 2-week treatment, and apparently there was no treatment effect compared to the placebo. Again, this study was not really well-balanced in terms of the number of subjects.

So findings from this phase 2 trial, what we learned was there was high placebo response for both endpoint, which is not that surprising. And 550 milligrams BID dosing for 2 weeks resulted in higher proportion of responders than placebo and the other two dose levels.

There was no apparent dose-response relationship among 255 milligrams, 550 milligrams, and 1100 milligrams given twice daily for 2 weeks. And apparently there was no treatment effect with the highest dose studied, which is 1100 milligrams BID. And there was no observed benefit with the longer-term treatment, which was 4 weeks, at dose 550 milligrams.

1 So the phase 3 trial employed dose regimen
2 550 milligrams TID for 2 weeks. Total daily dose
3 is 1650 milligrams. So as Dr. Golden mentioned
4 earlier this morning, more frequent dosing was
5 rationalized to maintain higher intestinal
6 concentration of rifaximin, and it was based on the
7 initial small intestinal transit time determined in
8 healthy subjects. On the other hand, higher daily
9 dose of 1650 milligrams was rationalized based on
10 some published study result. Especially this one
11 study shows that significantly higher rate
12 for -- normalization rate of breath test was shown
13 in 1600 milligrams daily dose group than in 1200
14 milligrams daily dose. Of note, this dose was
15 given in three divided dose, and the treatment
16 duration was 7 days.
17 So to summarize, rifaximin dosage regimen
18 for IBS-D patients, which is 550 milligrams TID for
19 2 weeks, it's still unknown if this proposed dosage
20 regimen is optimal. And that's because there's
21 only one dose level studied with proposed dosing
22 frequency, which is three times daily, in phase 3

trial. And different dosing frequency was studied in phase 2 trial, which was BID. And treatment duration shorter than 2 weeks was not explored.

While we cannot verify any published literature data at this point, there are several data published literature showing some positive effects of rifaximin in either SIBO or IBS with shorter-term treatment, which is about 7 to 10 day of treatment duration. So we are not sure. We are wondering whether that will be a viable treatment duration option for this IBS-D patient.

Last but not least, effect of rifaximin of different doses or different treatment durations on the gut flora was not assessed during this development program.

Thank you. And Dr. Purfield will continue on microbiology assessment.

FDA Presentation - Anne Purfield

DR. PURFIELD: Good morning. My name is Anne Purfield. I'm the clinical microbiology reviewer for this product. Today I'm going to share with you the clinical microbiology

1 perspective of this application, and provide
2 background for the committee concerning questions
3 for discussion later this afternoon. The
4 information I discuss today is based on rifaximin
5 labeling and a summary of an independent literature
6 search.
7 Before I get started, I would just like to
8 wish everybody a happy Get Smart About Antibiotics
9 week. Get Smart week is a one-week observance
10 period sponsored by the CDC to bring awareness to
11 antibiotic resistance and the importance of
12 appropriate use of antibiotics. Small victories
13 for microbiologists.
14 Rifaximin is in a class of rifamycin
15 antibiotics. The mechanism of action is believed
16 to be inhibition of protein synthesis by targeting
17 the DNA, independent RNA polymerase activity in
18 bacteria, as other rifaximin products have been
19 shown to do.
20 Rifaximin was approved for the treatment
21 of traveler's diarrhea caused by E. coli in 2004.
22 The approved dose is 200 milligrams three times a

day for three days. For IBS, the applicant has proposed a rifaximin regimen of 550 milligrams three times a day for 14 days. In clinical practice, it is possible that repeat intermittent rifaximin therapy will be prescribed, and I will discuss the potential for the development of rifaximin resistance with such exposure.

There are several in vitro studies that have been conducted to assess the potential bacterial resistance to develop against rifaximin. One method is to culture bacteria under selective drug pressure and measure the frequency that mutant bacteria arise with decreased susceptibility.

To give you perspective, the normal mutation rate based on estimated polymerase errors is one mutant bacterium for every 10 to the 10th bacteria. For bacteria exposed to rifaximin in vitro, the frequency of spontaneously resistant mutants was approximately 1 times 10 to the minus 8, or one bacteria for every 10 to the 8th bacterium for many enteric pathogens, which is higher than the rate observed with

fluoroquinolones. For rifaximin, the resulting mutant bacteria were resistant due to a single-step chromosomal mutation, and were stable through multiple passages without the drug pressure.

The mechanism of bacterial resistance to rifaximin is not known at this time. However, studies have shown that bacteria less susceptible to rifaximin harbor polymorphisms in a conserved region of the target protein RNA polymerase subunit B, or rpoB. Likewise, bacterial resistance to other rifamycin drugs, such as rifampin, which is approved for the treatment of mycobacterium tuberculosis, are also associated with mutations in this conserved region of rpoB.

Susceptibility of clinical isolates to antimicrobial products is determined by break points that are specific to pathogen and drug products. Break points are established based on the correlation between clinical outcome and in vitro susceptibility. Once break points are established, resistance to a drug may be interpreted based on the minimum inhibitory

concentration, or MIC, that is measured in a clinical laboratory using a standard method to measure in vitro susceptibility.

At this time, the interpretive criteria for rifaximin break points have not been evaluated for any pathogen. Therefore, there is no interpretive criteria to determine resistance by MIC, and at this time, interpretation of MIC values are all relative.

Although we are not able to assess MIC values to determine whether or not the isolates are resistant or susceptible to rifaximin, we have evaluated MIC for different enteric pathogens measured using standard methods since the approval of rifaximin for traveler's diarrhea in 2004.

Increasing MIC values over time is an indicator of the development of resistance. At this time, there is no evidence the rifaximin MIC for different enteric pathogens has increased over the past seven years.

C. difficile is a clinically relevant pathogen for patients receiving antibiotic therapy.

Based on surveillance studies, a subset of C. difficile, clinical isolates have higher relative rifaximin MIC values. In general, the vast majority of MIC values for C. difficile are far below 16 micrograms per mL, regardless of prior exposure to rifaximin. However, surveillance of rifaximin susceptibility in clinical isolates often shows MIC values, and a portion of the isolates are higher than 1,024 micrograms per mL, or the upper limit of detection in the standard assay.

In general, higher MIC values for bacterial pathogens are associated with decreased susceptibilities to drug and clinical outcome. At this time, rifaximin is not approved for the treatment of C. difficile, and the correlation between in vitro susceptibility and clinical outcome is not known.

The prevalence of C. difficile isolates with higher relative MIC values varies by study design and geographic location. Based on my review of the literature, it appears that a larger proportion of C. difficile isolates have higher MIC

values in countries were rifaximin is used in the population more frequently.

We acknowledge that the limited clinical data does not show an effect on the quantity or diversity of fecal flora or on in vitro susceptibility to rifaximin. These trials are limited by the dose of rifaximin studied, the short duration of treatment, or the population studied. These effects haven't been studied in an IBS population, which may have abnormal fecal flora diversity or quantity.

The effect of the proposed dose of rifaximin on microbial flora and susceptibility needs to be assessed with intermittent repeated use in an IBS population. We are particularly concerned about the effect on the drug on hetero-resistance, changes in gut flora, and susceptibility to Gram-negative pathogenic bacteria or C. difficile.

Hetero-resistance refers to bacterial populations with mixed susceptibility. Intermittent repeated use may select for minor

populations of bacteria that are less susceptible to rifaximin. With more repeated use, it's possible that a minor population may gain a foothold and eventually become nonsusceptible to rifaximin.

IBS patients may harbor abnormal diversity of commensal bacteria in the gut. Changes in the diversity of gut flora may alleviate symptoms of IBS, but there may be other unforeseen consequences on patient health.

In addition, individuals may be asymptomatic carriers of Gram-negative pathogens such as E. coli or salmonella. C. difficile is a clinically relevant pathogen for any patient who receives multiple treatments with broad spectrum antibiotics. In addition to breakthrough resistant infections on a patient level, there is a public health concern for the spread of potentially resistant Gram-negative enteric pathogens or C. difficile in healthcare institutions.

In general, the selective pressure applied to microorganisms by the use of antimicrobial

agents results in the development of resistance over time. The rate at which this occurs varies by organism and antimicrobial agent. In the case of rifaximin, we don't have data at this time to predict how the proposed use of rifaximin in the IBS population will affect the emergence of rifaximin resistance. However, the development of some resistance is probable and likely.

For future trials using antimicrobial agents to treat chronic disease, including IBS, with intermittent repeated treatments, we expect investigators to determine whether subject diarrhea may be caused by enteric pathogens or is related to the nonbacterial indication such as IBS.

If diarrhea occurs in study subjects, stool specimens should be collected for identification of pathogens by culture or other validated molecular techniques. Patients should be tested for the presence of C. difficile toxin at screening. Any patient with a C. difficile toxin-positive result should be excluded from participation in the study. All C. difficile

isolates recovered from study subjects should be evaluated for susceptibility in vitro.

I'd like to acknowledge all my colleagues at FDA who helped me with this presentation. And Dr. Courtney Lias will now speak about the use of biomarkers in future clinical trials.

FDA Presentation - Courtney Lias

DR. LIAS: Hello. My name is Courtney Lias, and I work in FDA's Office of In Vitro Diagnostics. Our office regulates diagnostic laboratory tests. Today I'm going to talk to you about the development of biomarkers, with a particular focus on the study of new biomarkers that may be able to identify specific subgroups of patients that would be likely to respond to therapy.

So what is a biomarker? A biomarker is a characteristic that is an objective indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention.

Biomarkers have been touted as being useful for many different purposes within drug

development. They may be used in the discovery phase to help identify new drug targets, in the preclinical testing to better the evaluate safety profile of a new compound, and in the clinical phase for a variety of purposes.

Today I will focus most on considerations for assessing biomarkers that may identify a group of patients that may respond, or potentially not respond, to therapy. I refer to these as predictive biomarkers.

I would like to first make an important distinction. Though many use these words interchangeably, "biomarker" does not equal "test." A biomarker is simply a characteristic. For example, hydrogen production may be a biomarker of bacterial overgrowth. A biomarker test is the method of measuring the characteristic, and the test may or may not correlate well with the biomarker. That correlation is the function of the test design and the test performance.

For example, a breath test may be developed to try to assess bacterial overgrowth by

measuring hydrogen production. Neither of these address how effective the measurement is for a particular purpose. For example, can a breath test be used to predict who will respond to rifaximin? It is important to evaluate any biomarker test for its effectiveness in achieving its intended purpose.

It is worthwhile to consider how biomarkers can be helpful for particular purposes. A biomarker test may be intended for many things, including diagnosis of a disease or a subclass of disease, estimating future risk of disease, or estimating the prognosis of a patient already diagnosed with a disease.

Each use requires a specific study design to demonstrate that the test measures what you think it measures, which we call analytical validity, and that the test means what we think it means, which we call clinical validity.

Most of the time, a test's effectiveness for a particular intended purpose is expressed as sensitivity and specificity or as predictive value.

Sensitivity tells how likely the test will be positive in someone who has the disease, and specificity tells you how likely the test will be negative in someone without the disease. Sensitivity and specificity must be evaluated together, as they are dependent on one another.

Similarly, we consider positive and negative predictive values together. A positive predictive value tells you how likely someone is to have the disease if they have a positive test result. A negative predictive value tells you how likely someone is not to have the disease if they have a negative test result.

Positive and negative predictive value are often preferred because the information is more reflective of the decision the clinician must make when they receive a laboratory report. Predictive values depend highly on the prevalence of disease in the population, so it's critical that a study intended to evaluate the performance of the test is designed correctly.

To that end, the effectiveness of a

biomarker test should be evaluated in the population in which the test will be used. For example, if you studied a test intended to diagnose a particular disease only in people who clearly have the disease or who are clearly very healthy, the test may appear to work quite well.

However, because many diseases manifest as a spectrum of symptoms, by this study design, test performance and people with unclear symptoms is not known and is often not as clear-cut. Ironically, this is often the population of patients in which the test is most needed. Therefore, it is critical to assess test performance in the intended use population to avoid biased estimates of performance.

To assess test performance, the test result is compared to some sort of truth standard. Often, for new biomarker tests, the truth standard is clinical diagnosis. In the case of predictive biomarkers, the truth standard is the clinical endpoint or endpoints used in the drug trial.

I will now begin to specifically discuss

the evaluation of predictive biomarkers. There are a variety of study designs that may be used. I have illustrated two common designs here. On the top example, all subjects are tested when enrolled in the trial, but the test results are not used to stratify them. In this case, the predictive value of the biomarker is often analyzed at the end of the trial. This design is most useful when the biomarker identifies a relatively common subpopulation because you are more likely to get enough biomarker-positive patients in each arm to do a valid analysis.

The bottom example illustrates a design that best evaluates the use of the biomarker test. In this design, all subjects are tested on entry in stratified biomarker status; then both biomarker-positive and biomarker-negative patients are stratified into either therapy or standard of care arms.

There are four potential outcomes of a study like this. The drug may be effective only in the biomarker-positive arm and not in the

biomarker-negative arm. This would indicate that the therapy is effective in a targeted population identified by the biomarker test.

Conversely, the therapy may be effective in the biomarker-negative arm and not in the biomarker-positive arm. This also indicates that the biomarker test identifies a population in which the drug works, in this case the negative population.

If the drug is effective in both the biomarker-positive and biomarker-negative population, the drug works but the biomarker test is not a useful predictive marker. And finally, the drug may not be effective in either arm.

Please note that using this type of study design, one can only conclude that the biomarker can identify a test-defined population in which the drug is effective. This study design gives no other information about the test and its use.

For example, we could not conclude from this design that a breath test is diagnostic of a subset of IBS-D with bacterial overgrowth. We can

only conclude that the test identifies patients who will respond to therapy. Please note also that a predictive biomarker is not the same as a surrogate biomarker.

So why is it necessary to study the biomarker test in the whole population? If the test-negative population is not included, you cannot determine how the test works. You cannot calculate sensitivity or specificity, and you cannot determine the negative predictive value of the test.

The time and study needed to understand many novel biomarkers' significance have not often been achieved before a drug trial starts. Therefore, care is needed in applying biomarker tests for patient management. Incomplete understanding of what the biomarker means can lead to misperceptions about the best population for use of the drug.

An example is in the selection of patients for drug clinical trials. A trial designed under the expectation that effectiveness of the drug

depends on the presence of a biomarker, such as a breath test, might establish a benefit for the studied subpopulation, that is, the biomarker-positive group. However, such a trial does nothing to establish the biomarker's meaning. This presupposition that biomarker-positive patients are enriched for responders remains a presupposition.

By itself, such a trial is incomplete since we only obtain half of an answer to the question of optimal drug use if we lack evidence establishing that biomarker-negative patients will not significantly benefit from the drug. We really want to know whether the biomarker distinguishes patients who will benefit from patients who will not benefit from the drug.

For illustrative purposes by a series of sketches, let us presume that a new targeted drug has beneficial effect compared to a standard therapy for some population. Perhaps the beneficial effect can be detected even in an unselected population, as illustrated in this first panel. What follows are illustrations of three of

the many ways in which predictive and prognostic effects may occur.

In the first example, a biomarker is predictive for benefit in that marker-positive patients benefit from the targeted drug while biomarker-negative patients do not. As another illustration, it is also feasible that a biomarker is simply prognostic, with no predictive value. It is prognostic in that marker-positive patients do better than marker-negative patients. However, the drug effect does not differ between the marker-positive and marker-negative patients. Therefore, the biomarker has no predictive effect and may be ineffective in assessing who should or should not receive the therapy.

It is also feasible that a marker is neither predictive nor prognostic if the benefit from the targeted drug does not vary between marker-positive and marker-negative patients, and there is no difference in outcome between marker-positive and marker-negative treatments within the group.

This all can be a very complex question to resolve, partly because there are two ways in which the biomarker's expression might have medical significance. In one way, the biomarker predicts which patients will benefit from the drug; for example, patients who express the biomarker will benefit, and patients who do not express the biomarker will not benefit. But it is also feasible that the biomarker's expression simply denotes the aggressiveness of disease, without regard to how the disease is treated.

So in summary of that, assuming a biomarker is predictive can be misleading. Complete data is necessary to distinguish a prognostic effect from a predictive effect. The most useful study design to demonstrate this is a study that includes both test-positive and test-negative patients. It's important to note that any test required for the safe and effective use of the drug must be cleared and approved along with that drug.

I hope that this introduction will help

the panel as they discuss the question of whether there is value in exploring biomarker testing to enrich a potential responder population. In closing, the identification of novel biomarkers to target drug therapy promises to enable better medical decision making. It is critical that any approach includes the use of a biomarker test. Consider that proper validation must be done to understand the value of the novel biomarker and the performance of the test that measures it.

Thank you very much. I'll now turn this back over to the chair, Dr. Raufman.

Clarifying Questions to the Presenters

DR. RAUFMAN: Thank you.

We will now ask if the committee has questions for the FDA. And, again, please wait to be called. Dr. Rosen?

DR. ROSEN: This is for the microbiology colleagues, or I suppose the pharmacologist. Is there any data to show that twice-a-day versus three-times-a-day antibiotic dosing changes the development of resistance? So not with this drug,

1 but with other drugs. And I'm most worried about
2 those patients who are going to get rifaximin as a
3 one-time course and how that's going to impact
4 resistance long-term.
5 DR. PURFIELD: We have no evidence. There
6 are no microbiology endpoints in the TARGET 1 and
7 TARGET 2 studies to look at any changes in flora or
8 susceptibility. So we don't know what a 2-week
9 course -- at this treatment and this population.
10 DR. ROSEN: What about with other
11 antibiotics, like amoxicillin or Cipro or other
12 antibiotics, where they've tried twice a day versus
13 three times a day, or once a day versus twice a
14 day?
15 DR. PURFIELD: I'm not aware of that data.
16 DR. KIM: Just one more to add. It will
17 be also important to notice the dose level. If
18 you're giving the same dose twice daily versus
19 three times daily, your total daily dose will be
20 increased. So that may have some impact, but I
21 don't know.
22 DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: I keep coming back to this. I guess, as a cliche, if you start with a hammer, everything looks like a nail. The assumption here is that we are starting with an antibiotic, and then we're groping for mechanisms to explain its effects in terms of the construct we have in our minds that this is an antibiotic. But the evidence that's been presented earlier this morning and now in this session, for me -- and I'm not a microbiologist, but for me, the evidence is that this drug is not an antibiotic in vivo, regardless of its in vitro profile.

Is that an accurate interpretation of the data, or is there actually evidence that it works as an antibiotic in vivo? And if it doesn't, it has implications for how we're going to approach study design, because if you don't know how it acts, we don't really know what the rational basis of dosing is, what the frequency is, whether we should be targeting the small bowel or the large bowel.

There's a lot of data here that we need to

reinterpret if you stop thinking about this as an antibiotic. And so I'd like to hear comments on that.

DR. PURFIELD: We do not have evidence that there is grand changes in the microbial flora. Most of the studies have been conducted with 3- to 7-day treatments. There is the study with repeated use in Crohn's disease patients -- ulcerative colitis patients, and they did not find an effect. Partly what they look at is the effect on the quantity of bacteria. I don't expect to see a change in quantity of bacteria. What we're more interested in is a change in diversity of bacteria.

But, yes, we do not have evidence that it has antibacterial activity in vivo.

DR. RAUFMAN: Could I ask a follow-up to that question? Absence of evidence is not necessarily evidence of absence. Is that a function of how the measurements were done? How secure are you in that conclusion?

DR. PURFIELD: Not secure at all. The gut biome is extremely complicated, as we've been

discussing this morning, and isolating pathogens is a difficult process in itself. Quantifying pathogens or quantifying bacteria is very difficult. And you're looking at an extreme diverse biome; so we do not know.

DR. PASRICHA: I just want to clarify that. So there are lots of drugs that can alter the enteric microflora without being antibiotics. Right? You don't have to -- you can increase gut transit, for instance, and you can alter microflora, and that doesn't mean it's an antibiotic.

So I think it's really important for us to understand whether, in the classical sense, this drug is an antibiotic in vivo, and I think you agree that it isn't.

DR. PURFIELD: We don't know.

DR. PASRICHA: Well, the evidence you have so far is that there is no alteration. You don't kill bacteria. You don't reduce the bacterial count. You don't substantially alter diversity. That's what an antibiotic does, especially one

which has the in vitro profile that this drug has, which is very broad spectrum.

I think that's a fair statement. I think it's really important for us to have a reasonable construct about what the MOA of this drug is or isn't before we go forward to study design. It's really critical for this committee, I think, to understand that.

DR. RAUFMAN: Dr. Mulberg?

DR. MULBERG: Yes. I wanted just to comment that one of the objectives for today is to understand answering your question because we have our a priori conclusions from a short-term exposure, yet we don't have the answers to the chronic long-term exposure that's potentially expected in this population.

That's part of the objective, for us to address or for you to address what is the effect of retreatment on the microbial ecology of the gut, and does that have an impact, at least from a theoretical perspective?

From a mechanism of action, I think you've

heard from both Salix Pharmaceuticals and Dr. Kim about presumed mechanism. But for approvability of a drug, mechanism of action is not a required construct. It's often very helpful for us, but not a requirement.

DR. RAUFMAN: So far we have a gastroenterologist on the panel asking questions about bacteriology. If somebody from ID, Dr. McDonald, could comment?

DR. MCDONALD: Not comment. I'll try to ask a question. I know this is a question period.

Is it not true that there's estimated 24- to 26,000, or 30- to 40,000, different species in the lower intestinal microbiota? I think that's the most recent estimates that I'm aware of.

I guess the question is, how well has the microbiome been studied using nonculturable techniques? I'm talking about modern metagenomics. Dr. Solga mentioned 16S ribosomal tag sequencing, the pyrosequencing. I've actually seen that there's a little bit coming out, but can you say something about that and how thoroughly that's been

explored?

DR. PURFIELD: I would say that this is very new technology. There's a fairly wide confidence interval when you have any microarray data. A paper recently came out, just several months ago, by Stojanovic; sorry if I mispronounce the name. But what they did was they looked at bacterial or fecal stool samples from patients with IBS and without IBS. They amplified using PCR 16S ribosomal RNA, which is specific to the bacteria, and then they used a microarray to look at diversity of flora, and they found that there were changes.

A lot of the changes were around 1 and a half-fold, which in microarray, it's still -- I interpret that information with caution. I think in the next 5 to 10 years, we are going to see amazing leaps in the technology, in the ability. We'll have to put confidence in this data. But it's still very new right now.

DR. MCDONALD: More specific, to hone this a little bit more, I was asking specifically about

rifaximin and the study of rifaximin, because the statement was just made that this does not act like an antibiotic in vivo. And I guess I'm challenging that with the fact that over half these organisms in the lower intestinal floor have never been successfully cultured in vitro.

So that's what I'm really getting at, is rifaximin, looking at its profile, impacting the human microbiota. Has that been really explored using these modern techniques, in your sense?

DR. PURFIELD: No.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: Leading to a question for Dr. Purfield, we're talking about here the potential for widespread use in a chronic indication, which I would think would provide real risk for resistance. And I think, in your words, you said development of some resistance is probable and likely. I would think it might take some time to see. I think with VRE it took decades.

You also mentioned cross-resistance with rifamycins is likely. Rifampin is critical for TB.

Is it logical to say we could be putting that at risk?

DR. PURFIELD: Usually, from an infectious disease physician's perspective, I would say that you're most concerned when the patient population is overlapping. And I'm not a physician. I can't tell you the patient overlap between those with mycobacterium tuberculosis infection as well as IBS. I assume there's not that much overlap in the United States.

However, you also get MAC, and you get enteric mycobacterium infections. And it's possible. It's probably going to be a very, very small population of having that overlap and having that exposure of mycobacterium to rifaximin, but it's an unknown.

DR. RAUFMAN: I may be misunderstanding this, but the concern isn't necessarily overlap in a particular patient, but releasing drug-resistant organisms into the environment.

Dr. Spiegel, you had a question?

DR. SPIEGEL: Thank you. My question has

1 to do with a similar topic. And, again, I'm not a
2 trained microbiologist at all, but I did review
3 this study by Valentin, which is in your
4 references. And it came to my attention when I was
5 reviewing the letter to the editor of the New
6 England Journal in response to the TARGET study,
7 and when I looked at that paper, I saw that they
8 took some normal, healthy controls who didn't have
9 any rifampin resistant staph species, and then the
10 majority of them did have it after roughly a 10-day
11 course, I think. And what was alarming to me was
12 they were able to recover the species, I think, up
13 to 9 weeks out.
14 So this brings up the issue about not just
15 TB, but infectious endocarditis and foreign body
16 infections, that patients with IBS should not have
17 that, necessarily. But they could walk around with
18 it on their torso and arms, according to this
19 Valentin study.
20 Even for hepatic encephalopathy, which is
21 in the hospital, where they're sharing a ward with
22 somebody with an infection -- which isn't the topic

of today -- but we're seeding the population, tens of thousands of young people, with an antibiotic that could lead to resistant strains on their body.

That's a small study to make such a huge conclusion. So I'm just curious, from somebody who knows more than I do, should we trust that study? What should we take from that study?

DR. PURFIELD: Well, in that study -- if I may . In that study they took swabs, skin samples, from the perianal region, from the arms, and the hands of subjects, and they looked at staphylococcus. And there were several different species of staphylococcus. There were seven -- I'm sorry my numbers might be slightly off, but it was a small proportion of the isolates that were resistant, but they were resistant for a long time. There were 2 staph aureus isolates, I believe, out of, I think, a total of 11 isolates out of 710 susceptible, completely susceptible isolates.

So they were looking at rifampin resistance, and they also looked at cross-resistance with rifaximin. But those were skin

isolates persisting for many weeks on the hands.

DR. RAUFMAN: Dr. Septimus?

DR. SEPTIMUS: I was going to make that comment. The other thing about the microflora is that if you just look at gross colony counts, it was well shown in the original Condit and Nichols studies looking at bowel preps for colon surgery that if you continued therapy too long, there was a regrowth of other organisms.

So if you're just looking at colony counts, that doesn't really answer the question. I think that Dr. McDonald's comment about looking at 16S is a better way to get at that.

Also, in terms of development of resistance and how frequently you give the antibiotic, it depends upon the mechanism of action. If you're talking about beta-lactams, it's time above the MIC that seems to be critical. If you're looking at, let's say, aminoglycosides, you're looking at concentration-dependent because it has a long post-antibiotic effect.

So those are the kinds of things you'd

have to look for in this particular drug. And again, I would caution that if this were to get the indication for this -- and, again, we have to study this, that this is going to be used on a widespread basis for long periods of time, and that's very different from how the drug has been used now.

So I think it is critical for us to look at this prospectively in a controlled manner.

DR. RAUFMAN: Mr. Matson?

MR. MATSON: In regard to the widespread use of antibiotics on this IBS population, what is the incidence of IBS in the American public?

DR. DIMICK: So most of the literature reports 10 to 15 percent. I got an epidemiology consult within the FDA, and they actually said they thought it was more like 7 percent. But the literature throughout says 10 to 15 percent. Approximately a third of those patients would be IBS-D. So you'd be talking somewhere in between 2 to 5 percent of the population.

DR. RAUFMAN: Dr. McDonald?

DR. MCDONALD: Just one question about

rifampin resistance since this is a rifamycin. My understanding is that all the rifampin resistance is point mutations in the rpoB. Is that correct that there's no plasmid-borne or transferable resistance between species? Is that your --

DR. PURFIELD: Yes. I don't want to back myself in a corner and say no, there's no plasmid. But most of the biomarkers or the markers for resistance are polymorphisms in rpoB, single nucleotide polymorphisms in rpoB. Some of those overlap between rifampin and rifamycin.

They're usually in a very conserved, 270-base-pair region of rpoB. So those are the ones that are most studied and most correlated, then, with clinical treatment failure.

DR. MCDONALD: Of course, with rifampin, we've always had problems with resistance developing on therapy. And I think that C. diff, the recurrent C. diff treatment where they've had some of these C. diff patients they've treated, they've actually found some rifampin or rifaximin-resistant C. diff strains. I don't know if those

developed on therapy, though. Did they?

DR. PURFIELD: There is that subset of C. difficile isolates that have been identified in surveillance studies. Whether or not they've actually --

DR. MCDONALD: They're just out there?

DR. PURFIELD: They're out there. And they have MICs that are higher than the limit of detection for the assay.

DR. MCDONALD: Yes. Right.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: A question for Dr. Lias. I don't want to ignore that great presentation. I thought it was really interesting.

So I kind of brought this point up earlier about biomarkers, and the response I heard was that there's so many issues with the test itself currently in terms of the glucose hydrogen breath test. And you didn't really address Bayes' revision, but there's sort of a Bayes problem here.

So there's a pretest likelihood for SIBO. Then a test is employed with operating

characteristics and a likelihood ratio. And then you calculate a post-test likelihood. And the expectation is that the test is performing at a high enough level that we can assume that the post-test results are sufficiently accurate to then use it to do the survival curves that you were showing us. But I think the argument I'm hearing is that we can't really talk about those survival curves because we can't trust the operating characteristics of the test.

My question, I guess, is if you can just sort of discuss that aspect of this, and also, are there standards for how good a test needs to be? And in this case, to make it even more complex, we don't really have a truth standard. So that's, I think, a circular problem. It's almost like an Escher print, where a circular perpetuity is going around and around. So I'm not sure where we start this argument.

DR. LIAS: Okay. There are several questions in there. I'll start with how good does a test need to be.

It varies on the purpose. So if you're talking about how well does the test work, how reliable is the instrument you're using, and I know that came up a little bit earlier, it depends on the level of distinction you're trying to make. So if you're trying to detect a small effect, then it has to be really precise; if you're trying to detect a large effect, a very big difference, then you can accept more variability in the test measurement.

So I can't really comment whether or not any of these particular breath tests, or some other biomarker that might be developed, would be suitable for this purpose. I think, potentially, you'd have to have some feasibility data to go into determining whether or not you should make that hypothesis. What's important is that before you do that, you do understand how well the test works and whether it meets your needs, and that's true.

The truth standard question is a tricky one we deal with all the time. Certainly, we get applications in-house for diagnosis of various

diseases, often for unmet needs. They're often unmet because it's difficult to diagnose something. We have to deal with what we can deal with.

So the truth standard ends up usually being some sort of composite of how you all diagnose something clinically. It's not a perfect situation. You can't, in that instance, determine that the test is actually more effective than the truth standard you're using. But over time, sometimes you can gather that type of evidence.

I'm not sure if I got all of your questions.

DR. SPIEGEL: There were probably some comments hidden in there, so I apologize for that.

DR. RAUFMAN: We will take one more question, if there is one, and move on. Jay?

DR. PASRICHA: Actually, this is for Dr. Lias, too. So you mentioned that when you do a biomarker, you need to have the biomarker-negative population as well in order to get a complete picture of the performance of the test as well as the outcome of the disease.

So I think we'll get to this later. But in the proposed design here, in lieu of a biomarker, they're taking response to drug that's sort of a surrogate, I guess, in some way. And should it not be including the nonresponders, then, to complete the analogy with the biomarker or the placebo responders?

DR. LIAS: I think you may be mixing up two different things. A predictive biomarker is very different than a surrogate biomarker. So if you were to use a test to determine some sort of an efficacy of the drug or monitoring the drug's effect over the study period, that's different than what I was talking about, which is simply an enrollment criteria to determine who may, at the end of the day, have clinical benefit using the clinical study endpoints.

Does that clarify that a little?

DR. PASRICHA: Well, that's exactly what I'm saying. So their entry criteria was previous drug responder. So they're enriching the population of the previous drug responder. But I

1 think that for the study to have probably broader
2 meaning, they should include the nonresponders as
3 well, but we can have that discussion later.
4 DR. LIAS: That's possible, yes.
5 DR. RAUFMAN: Okay. Let's move on now.
6 We will proceed with the sponsor's presentation.
7 Dr. Paterson?
8 **Sponsor Presentation - Craig Paterson**
9 DR. PATERSON: Reports in the literature
10 have described clinical experience with repeat
11 courses of rifaximin therapy in the IBS population,
12 with several summarized here. It would appear that
13 patients do not develop tolerance even after
14 several courses of rifaximin. Further, the
15 duration of response, although variable, may exceed
16 one year in some patients.
17 Although these studies have the limitation
18 of being observational, they reflect real world
19 experience in a clinical setting. Combined with
20 our underlying scientific observations, these
21 findings form the basis of the predication that
22 repeat treatment of IBS patients with rifaximin

will be successful.

The study design proposed here today and outlined in the briefing documents has been developed in collaboration with the GI Division as well as a number of thought leaders in the areas of IBS, study design, and statistics. In developing this study, a number of potential design options were jointly considered, including several discussed in the FDA briefing document.

An approach similar to one used in the development program for a drug used in cystic fibrosis patients was discussed. However, it was felt that such a study design would not address repeat treatment efficacy and likely result in over-treatment.

During our interactions with the FDA, it was agreed that the first repeat treatment period would be sufficient for purposes of demonstrating efficacy. However, a second repeat treatment period will also be included. The issues of repeat treatment efficacy and durability of effect raised in the complete response letter will be addressed

with a single robust study.

It was agreed that a replication of TARGET 1 and TARGET 2 studies would not be necessary. Inclusion of a placebo arm in the initial treatment phase would result in responders to placebo being followed for recurrence and subsequently retreated with placebo. A reason for inclusion of these patients would be unclear as they would not be counted in the analysis and would add no other value to the study.

Consequently, we have considered study designs that select the responders and allow an early escape for those that fail to respond to initial treatment, best reflecting actual clinical practice.

There is considerable support for studying only patients that initially respond to treatment, as they would be considered candidates for repeat treatment. The feasibility of this study and overall chance for success are improved with a study population of treatment responders.

As stated earlier, rifaximin represents a

1 different treatment paradigm for IBS-D. Alosetron
2 can be dosed daily in response to return of
3 symptoms. Rifaximin, with the different potential
4 mechanisms of action, will require patients to meet
5 a more clear definition of sustained recurrence
6 prior to repeat treatment so that unneeded repeat
7 treatment does not occur prematurely.
8 For the purposes of encouraging discussion
9 with the committee, I will walk you through the
10 essential features of the design, then follow with
11 more detailed explanations.
12 Potential patients will be required to
13 undergo screening assessments, including
14 colonoscopy, if necessary, and complete the diary
15 eligibility period. Screening will last no longer
16 than 30 days.
17 The initial treatment phase will be used
18 for responder identification. All eligible
19 patients will receive a course of rifaximin, 550
20 milligrams, three times daily for 2 weeks, followed
21 by 2 weeks of follow-up. At the end of this phase,
22 patients will be assessed for response. Only

identified responders will enter the treatment-free maintenance phase, whereas nonresponders will be withdrawn from the study.

The duration of the first maintenance phase will be variable and depend upon whether or not there is a recurrence of IBS symptoms based on the regular assessments. As shown, only patients who meet criteria for recurrence will enter the double-blind, first repeat treatment phase.

Not depicted on this diagram is that patients who do not meet recurrence criteria by the end of the first maintenance phase may be allowed to continue up to an additional 12 weeks, if necessary, to meet recurrence criteria. Patients meeting recurrence criteria during this time will enter the randomization phase, whereas patients who still have not met criteria for recurrence at the end of the additional 12 weeks will be discontinued.

The primary efficacy analysis will be performed at the end of the first repeat treatment phase once the predetermined numbers of patients

have completed the 4-week period. Only responders in the first repeat treatment phase will be eligible for the second maintenance phase, and will continue with an additional treatment-free follow-up period of up to 8 weeks. Patients who do not meet recurrence criteria by the end of the 8-week maintenance phase will be withdrawn from the study.

Finally, patients who meet criteria for recurrence in the second maintenance phase will be eligible to enter the second repeat treatment phase and will receive a second repeat treatment of rifaximin or placebo. The treatment assignment from the first repeat treatment phase will be maintained in this phase. All patients will undergo end-of-study assessments.

The primary objective of this study is to evaluate the efficacy of repeat treatment with rifaximin in patients with IBS-D who responded to an initial course of rifaximin treatment and subsequently experienced recurrence. A secondary objective is to evaluate the safety of rifaximin in patients with IBS-D.

1 Key inclusion criteria are similar to
2 those used in the TARGET 1 and TARGET 2 studies,
3 with a few notable exceptions. Criteria for a
4 diagnosis of IBS will now be based on Rome III
5 criteria, and scales for abdominal pain and stool
6 consistency have been expanded in line with current
7 draft guidance. The baseline enrollment criteria
8 are listed.
9 The key exclusion criteria remain
10 essentially the same as those used in the TARGET
11 studies, and are designed to exclude patients with
12 current constipation as well as those with a
13 possible anatomic or metabolic cause for the
14 diarrhea.
15 The primary endpoint is the proportion of
16 patients who are responders to repeat treatment in
17 both IBS-related abdominal pain and stool
18 consistency during the first repeat treatment
19 phase. Weekly response for the primary endpoint is
20 based on the daily IBS symptom-related questions.
21 Weekly treatment success in IBS-related
22 abdominal pain is defined as a 30 percent of

1 greater improvement from baseline in the weekly
2 average abdominal pain score. Weekly treatment
3 success in stool consistency is achieved when a
4 patient has at least at 50 percent reduction in the
5 number of days per week with at least one stool
6 which has a consistency of greater than or equal to
7 Type 6 on the Bristol Stool Scale. This is based
8 on the patient's description of their bowel form in
9 the past 24 hours.
10 Secondary endpoints for the study assessed
11 during the first repeat treatment phase are listed
12 here. Durability will be discussed shortly.
13 While there are no readily available or
14 validated biomarkers for IBS with diarrhea, we are
15 committed to helping advance the science as well as
16 identify the patient characteristics that best
17 predict response to treatment. As in TARGET 1 and
18 TARGET 2, we'll perform a rigorous review of all
19 data collected in this study with a view to
20 identify demographic and/or symptom characteristics
21 that might better predict future recurrence and
22 potential response to therapy.

We are proposing to collect stool samples at various time points in order to evaluate for possible antibiotic resistance. These assessments will also be performed in our hepatic encephalopathy studies with rifaximin, which will provide for a larger database. Additionally, we would consider exploring the use of other biomarkers.

While bloating is a common symptom in patients with IBS-D, the role of breath testing in small intestinal bacterial overgrowth remain controversial, as we have discussed earlier. The lactulose hydrogen breath test was originally described as a measurement of orocecal transit time. There have been several changes over the years to the definition of a positive test, and a noninvasive gold standard reference test is lacking. Glucose hydrogen breath testing appears to have greater predictive value for proximal small bowel overgrowth, but lacks sensitivity for the distal small bowel.

There has been some investigation into

combined lactulose hydrogen breath testing in scintigraphy. In a recent publication in which the combined technique was utilized, the current 90-minute cutoff for the rise in breath hydrogen, indicating a positive test, was brought into question. In many cases, the lactulose has reached the cecum well prior to the 90-minute mark, and an interpretation of small bowel bacterial overgrowth would likely be a false positive result.

A study referenced in the FDA briefing document illustrates the potential difficulties resulting from the interpretation of lactulose breath testing results. This study evaluated the effects of rifaximin in children with a heterogeneous group of functional disorders, including functional dyspepsia, IBS that was not further defined, and functional abdominal pain.

Interpretation of the breath test data in this mixed population was based on that 90-minute cutoff time for the rise in breath hydrogen. When the issues with orocecal transit time are considered, this study may have reported many false

positive results, and no benefit would be observed with treatment regardless of whether or not there was one.

The combined use of lactulose hydrogen breath testing with scintigraphy does not appear to be feasible on a widespread basis. In addition, there still remain questions with interpretation, even on the combined study results.

Another approach to the interpretation of lactulose hydrogen breath testing is to consider the total gas production from all sources. An increase, as compared to normal controls, would there reflect an overproduction from hydrogen-producing bacteria. We are continuing to evaluate the role of breath testing in this study.

As noted, the current FDA draft guidance defines a responder, and we will use this definition in the proposed study. That is, a subject will be considered a responder in a given month if they have a positive response during at least 2 out of 4 weeks based on daily questions for the weekly responses for both abdominal pain and

stool consistency. There is currently no proposed definition of recurrence in the draft guidance. We propose that a subject will be considered to have recurrence when criteria for response is absent for at least 3 weeks during a 4-week period.

The durability assessment conducted at the end of the study will consist of rates of responding patients without recurrence among all randomized patients, with exposure time on study taken into account. The assessment period will be 12 weeks in duration and consist of the 4-week first repeat treatment phase and the subsequent 8-week second maintenance phase.

Thank you.

DR. RAUFMAN: Thank you.

We'll now proceed with the FDA presentation. Dr. Mulberg?

FDA Presentation - Andrew Mulberg

DR. MULBERG: I hope everyone is as exhilarated from the morning's discussion as I am. I want to thank all the previous presenters from both sides for very nice presentations. I'm going

1 to attempt to just provide some comments on study
2 design, and then the charge to the committee
3 members.
4 Dr. Paterson has presented the proposed
5 trial design for at least part of the initial
6 discussions. The next few slides are culled from a
7 reference cited at the bottom, from stakeholders
8 who were involved in development of drugs for
9 irritable bowel syndrome, and I do hope that these
10 provide some footing for you in your deliberations
11 this afternoon.
12 This trial design is referred to as
13 intermittent treatment design, which reflects that
14 there is initial randomization to either active or
15 placebo, carried out through multiple cycles
16 through 24-week observation, through, in this case,
17 four periods with treatment-free intervals of 2 to
18 12 weeks, during which time there will be different
19 recrudescence of signs and symptoms for individual
20 patients.
21 This re-randomization design has some
22 components of -- a withdrawal component after the

1 initial randomization, as demonstrated here. The
2 active arm is then re-randomized either to active
3 or placebo, whereas the placebo arm is re-
4 randomized to active. One will note that the
5 treatment-free intervals for this phase studies are
6 the same as pictured in the first design.
7 This last design, the randomization of
8 partial responders with withdrawal design, is
9 similar to the design presented by Dr. Paterson.
10 We'll be discussing this in a few moments, at least
11 our perspectives on strengths and weaknesses. But
12 I first wanted to cover, as per the authors of this
13 reference, the advantages and disadvantages in
14 short order. The designs here are broken down
15 either by, first, treatment design A versus the two
16 subsequent designs, B and C, which were inverted on
17 the previous two slides.
18 I think what's important to point out is
19 that there are distinct advantages of an
20 intermittent treatment design, particularly with
21 low sample size, but there are a number of
22 disadvantages that might lead to interpretation,

interpretability problems.

In contrast, the two other designs, at least both are favored by our EMA colleagues, but do have problems with regards to large sample size particularly, and the randomization to retreatment may not necessarily reflect clinical practice.

The purpose of bringing these presentations to you is for the GI advisors, in your deliberations, to please consider the different iterations of potential trial designs because that's what's really important for us in order to know how to advise and to guide potential development programs.

As you've seen from Dr. Paterson's presentation and the deliberations we've had this morning, several questions have come up about the role, potentially, of breath testing as a predictive biomarker. Is there a role potentially of a no-treatment arm, potentially, and is there enough information gathered about the natural history of IBS-D? Should the treatment-free intervals be necessarily lengthened as part of a

1 putative trial design?
2 These are issues that we expect and do
3 hope and encourage all of the committee members to
4 please deliberate and discuss openly in this
5 presentation.
6 The strengths of the proposed trial are
7 those pictured here. We do feel that durability of
8 response to rifaximin is addressed, at least to a
9 maximum of 20 weeks in phase 1 and to a maximum of
10 8 weeks in phase 2. We feel that the trial design
11 does address the effect of retreatment paradigms
12 after the recurrence of symptoms, and this would be
13 done to maximum of three cycles.
14 The time to retreatment, as we discussed
15 and Dr. Paterson has discussed, is individualized
16 for individual patients. The question again must
17 be asked, is the treatment-free interval long
18 enough for us to understand when symptoms may recur
19 in these patients. Importantly, also, the impact
20 of retreatment on intestinal flora will be
21 discussed as part of that initial trial design.
22 But the weaknesses of the proposed trial

1 design are that it does not address prevention of
2 symptom recurrence, if the GI committee members do
3 feel that's important to address. It does not
4 address the targeting of cure or more durable
5 remission in individualized patients with a
6 different dosing strategy. And as you've heard,
7 there's only one dose being examined and assessed
8 in this clinical trial proposal.
9 Is it possible that different cycles,
10 moving forward from the initial treatment, would
11 require a different dose? And again, as stated,
12 the phase 2 8-week treatment-free period may not
13 necessarily be long enough for having symptom
14 recurrence.
15 Lastly, is the population adequately
16 defined? Are clinical criteria sufficient to
17 identify the population of IBS patients for whom an
18 antibiotic is appropriate, sufficient? We've had
19 lots of discussion this morning from around the
20 table around that subject.
21 Is there a better way to define the
22 population than an initial course of treatment with

1 rifaximin? This was again referring to Dr. Lias'
2 presentation on the potential role of a predictive
3 biomarker. And importantly, as Dr. Spiegel has
4 discussed, is there a truth standard for us to rely
5 upon? Again, the operational constraints on the
6 proposed trial design are significant, and those
7 also should be discussed.
8 I'm not going to read the questions for
9 the committee, but leave that to Dr. Raufman for
10 the afternoon session, but just try to summarize
11 the objectives for today's advisory committee.
12 It's important for the committee members
13 to discuss the goals of treatment of rifaximin as
14 you deliberate what trial designs are important.
15 That is going to become very important, whether one
16 refers to short-term treatment of recurrence,
17 prevention, or induction of long-term remission.
18 The design that has been presented, is that
19 acceptable to address the short-term retreatment
20 paradigm for rifaximin? And if it's not, we expect
21 and hope that you will discuss that.
22 If you believe that a different treatment

1 paradigm is important for the development program
2 for rifaximin, we hope that the trial designs that
3 we have offered will serve as a potential
4 introduction to those discussions.
5 Again, referring to our concerns and
6 issues raised about dose, should other regimens be
7 explored? What other regimens should be explored
8 for the retreatment paradigms or for the trial
9 designs being discussed?
10 For the labeling of this product, is it
11 acceptable to define the population, again, based
12 upon one course of rifaximin treatment? Again
13 referring to the role of other types of biomarkers
14 to necessarily enrich the population. And again,
15 if you feel that targeting a population is
16 important, do you believe that there is a role for
17 breath hydrogen testing as a predictive biomarker?
18 And if so, we're hoping you discuss your
19 perspectives.
20 As has also been deliberated this morning,
21 in short -- I'm sure more to come -- is the role of
22 your concerns and deliberations about antibiotic

resistance and how should that concern affect the clinical development program for rifaximin in this population.

Lastly, if you are concerned about the chronic use of rifaximin in changing the gut microbiology and the ecology, is that a concern about specific adverse events and health in the population? How would you address that in the clinical development program?

Thank you.

Clarifying Questions to the Presenters

DR. RAUFMAN: Thank you, Dr. Mulberg.

We'll now ask if the committee has questions for the FDA or the sponsor. Dr. Hasler?

DR. HASLER: Yes. One number I haven't heard from this morning is, of the people who initially responded to active drug therapy, what was the percentage of people who relapsed after 12 weeks? And as a follow-up question to that, how are you using that number to design your sample size for the next trial, and what do you think that sample size will be?

DR. FORBES: Let me try to answer your first question simply. There was a 10 percent therapeutic gain, approximately 42 percent to 32 percent, over placebo. What I believe is the case is after week 6 -- so there was 2 weeks of treatment, 4 weeks. At that point, we had a 10 percent therapeutic gain. Within about the next month, we lose about a third of that 10 percent therapeutic gain. The remainder of that, somewhere in the 5, 6, 7 percent range, depending on how you look at the questions and use the data to determine success, you end up with patients that last about three months.

Slide up, please.

Now, to answer your question specifically as it relates to going forward, we've modeled some numbers here for you so that you could take a look at this. If you use abdominal pain and stool consistency -- I'm sorry, abdominal pain or stool consistency, this means that if a patient is a responder on both and then they lose response on one or the other, then by the time 12 weeks has

elapsed, approximately 37 percent will have -- you get total recurrence in month 1 responders, 37.1 percent. So that gives you an idea of how this would be going forward.

The real question we have as a company is how do you define relapse? So if you have to have two conditions met to be successful at that point, if you lose one of those conditions, are you now considered relapsed? And as you think about this, I think the important thing is that now they have not gone all the way back to baseline. If you wait for these patients to go all the way back to baseline -- and this is not specific just to TARGET 1 and 2 or to the rifaximin IBS program; we believe this is across the board.

Patients appear to rate their symptoms the worst at screening. And trying to get them to a point to where they return all the way to the severity that they were at screening would result in very few patients actually being retreated. So this is a very important question for us as we go forward.

DR. HASLER: To clarify; so the people you're going to retreat at 12 weeks out are going to be people who have shown some measure of relapse? And if that's the case, I presume that's going to be a relatively small number. Aren't you going to need a pretty big sample?

DR. FORBES: So the data that I just showed you would be over 12 weeks. As was mentioned earlier, we'd go out a little bit further. The retrospective chart reviews and also the natural history data that we've culled from looking at just the use of the product would suggest that about four months is the median retreatment. That doesn't mean that every patient is included in that. Some patients never get retreated. But of the patients that get retreated, it's about four months.

So as we look at our data, we have about 37 percent at 12 weeks. We would imagine, as we move out another one or two months, that we would get to the point to where we are actually capturing a lot of these patients.

DR. RAUFMAN: I have a couple of questions for Dr. Paterson regarding the protocol.

It was stated that at entry, the patients -- or the subjects, I should say -- would have colonoscopy, as necessary. If you could define what you mean by "as necessary"?

DR. PATERSON: The screening criteria for the TARGET 1 and TARGET 2 studies was similar to this. We had asked that patients have a colonoscopy within two years, and that same criteria will apply to the study being proposed. That is, we want to make sure there's no anatomic reason, a large polyp, any other reason why they might be having diarrhea and abdominal pain. It's a safety issue.

DR. RAUFMAN: Thank you. And the other question, again regarding the protocol, is how do you propose to evaluate or measure changes in stool flora during the course of the study?

DR. GOLDEN: Again, that's an issue we'll have to discuss with this committee today. Primarily, we'll be tracking, as we are in our

hepatic encephalopathy studies, any antibiotic resistance as well as we're very -- we think it's a terrific opportunity to take advantage, as Dr. Purfield indicated, of the new technology that's available for sequencing so that we can more finally identify subpopulations that may be changing in the presence or absence of rifaximin.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: Could we put up the slide that shows the design? I'd like to target a three-part question to either Dr. Paterson or Dr. Mulberg; either the FDA slide of it or the sponsor slide.

Okay, this is great. Thanks.

So we'll come back to the discussion later about the nonresponders. But, basically, you're randomizing here, leaving out people that wouldn't respond the first time -- I'm glad you made this 20 weeks -- also leaving out the people who respond extremely well and haven't had recurrence of symptoms by 20 weeks. Then you're randomizing.

So the first part of my three-part

1 question is, nonresponders are withdrawn. I surely
2 hope you mean that you're going to follow everybody
3 so you can do a true ITT analysis. I think that
4 was indicated as at least one of the analyses.
5 The second part of the question: You're
6 suggesting here, though, by nonresponders
7 withdrawn, that these folks won't get getting the
8 second retreatment if they don't succeed here. And
9 I would argue you should do whatever you would do
10 in the real world.
11 These are people who did, in fact, have in
12 their first course a response. They may have come
13 very close to a response here. They may have had a
14 really good response in pain relief, and they may
15 have just missed in the second of the 4 weeks in
16 stool consistency hitting it.
17 Are you telling me, in the real world, you
18 wouldn't then retreat those people because they
19 just missed on one of the cycles? I would think
20 you would. And because I'd want to see an ITT
21 analysis, I would hope that you would in fact allow
22 those people to be retreated.

The third question is, why is this at 8 weeks? Let's do this in the real world. This second retreatment should occur when you've had recurrence of symptoms past the first retreatment.

DR. FORBES: Dr. Koch, would you like to help me by addressing a few of these on responders/nonresponders? You've asked a number of probing questions which actually are things that we've struggled quite a bit with, as you can imagine.

DR. KOCH: Gary Koch, Biostatistics Department, University of North Carolina at Chapel Hill. My activity with Salix is through a cooperative agreement with my university, which has a structure for partial salary support and travel reimbursement.

So part of the concept of the design is related to avoiding over-treatment. So one avoids over-treatment by only treating the patients who do respond. That's the rationale of the initial treatment period. The patients who do not respond in the initial treatment period could be re-

randomized, but if they didn't respond in the initial treatment period, they're probably less likely to respond if you were to treat them again, or the treatment difference may even be smaller than what it would have been in the initial treatment period, and you are exposing them. So that's one of the reasons why they would be set aside.

DR. FLEMING: Time is short, Gary. That's not my question.

DR. KOCH: In terms of your question about the first repeat treatment phase, my understanding is that currently the primary endpoint would be whether they would respond within the first 4 weeks. And so everybody who was followed for ascertainment of response would indeed contribute to that intent-to-treat analysis. And if one did a time-to-treatment failure analysis by looking at consecutive 4-week periods, for whether they achieved response and maintained it for successive 4-week periods through 12 weeks, all patients would contribute to that analysis from an intent-to-treat

point of view.

You are correct. The nonresponders would not contribute to the second retreatment period. And that's a clinical judgment. I don't know whether clinicians -- if a patient responded the first time and then did not respond a second time, whether they would consider that patient a reasonable candidate for another retreatment. If they did, then yes, I would agree it would be okay to continue those patients and retreat as indicated.

Now, a further practicality is that the number of patients that may be in the initial treatment period could be somewhere between 2500 and 3,000. Based upon the slide that you showed a little bit earlier, based on the TARGET studies, 1 in 6 patients qualify for retreatment.

Now, in the new study, it will probably be a little bit more. But we need probably somewhere in the vicinity of 3,000 patients to get 500 patients to this primary retreatment period. So then, of those patients, how many will end up being

a responder who has a recurrence? Well, maybe it'll be 1 in 4, but, again, it will be a relatively small number.

So, again, this slide could be put up. So although I certainly agree that the second retreatment period is very valuable and will be very informative, the number of patients that actually get to that second treatment period among people who respond in the first retreatment period could be relatively small, even if the follow-up is extended out to 20 weeks, again, to identify who would be a second or another recurrence qualifying for the additional retreatment.

Certainly these are important questions. I think the sponsor is flexible in doing whatever the committee would consider to be generally sensible, and I've just tried to clarify. Intent to treat will be addressed for the first retreatment period.

DR. RAUFMAN: Dr. Spiegel, I think you had a question?

DR. SPIEGEL: Yes, I did. I feel like I

need a laser pointer, though.

My question is a question and a comment. The comment is, as I'm thinking about this study, what we're doing is -- however the final design looks, taking an enriched group of people who are confirmed responders. They've responded to the drug. And we're going to retreat them again. I would expect that they're going to respond again. I mean, if we believe TARGET, which why wouldn't we, this is going to be an even larger response, I would think.

So I'm wondering, just even as I'm sitting here, what's the purpose of that? Is the purpose of the study to look at safety, or is it to confirm in an enriched population that the drug works again?

I'm just thinking in my mind, why wouldn't it? Why wouldn't it? To me, I need to know about safety in this study. If it doesn't work in an enriched population, then that really calls into question everything we know about it to date.

So we can talk about the study design, the

ITT, and the secondary analyses that FDA has conducted. Actually, I need to understand more because there's a concern that may not have even been significant in TARGET. But along those lines, I'm just curious what people think about that.

But are there going to be swabs performed based upon Valentin and the concern we talked about earlier?

DR. FORBES: Yes. Again, I think all of those areas, we're interested in hearing your thoughts on them. And so we are planning at this point on moving forward with some testing, and as you say, something along the lines of Valentin and doing some swabbing and trying to understand the ramifications of that one. I mean, we have a lot of questions. There was no control group in that one, and so we have some questions as well.

Dr. Mulberg, I don't know if you have any thoughts on this because, obviously, the FDA has their own theory.

DR. MULBERG: Well, I think our perspective is that this retreatment -- or the

1 proposed study design does address retreatment, and
2 does in some ways address more information on
3 natural history because of the variable treatment-
4 free interval that extends to 20 weeks. We'd like
5 your discussion of those two topics.
6 So the objectives -- as I put up my
7 strengths, I'd love to call up my slide, just
8 because that seems to be the -- slide up; or
9 Captain Picard said, "Make it so."
10 [Laughter.]
11 DR. MULBERG: I've always wanted to say
12 that in an open meeting.
13 The fact is that the strengths of this
14 trial -- again, our iteration is that is addresses
15 durability of response and retreatment paradigm.
16 Safety is an important part. That's part of this
17 committee's charge, to address how best to address
18 safety.
19 Does that answer your question?
20 DR. SPIEGEL: That does. I think the
21 bigger issue that we'll talk about is whether we're
22 trying to treat recurrence or prophylax against

recurrence. To me, that's a bigger --

DR. MULBERG: That's question 1.

DR. SPIEGEL: Right. We'll talk about that.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: So in response to Dr. Spiegel's comment, if I understand rightly, the screening part of this study is all patients come and get treated. That's correct? Open label?

DR. FORBES: Correct.

DR. PASRICHA: Oh, yes. It's an open label study. So that's going to include a substantial portion of placebo responders.

DR. FORBES: Yes.

DR. PASRICHA: It's not open label? That's what I want to clarify?

DR. FORBES: Well, I think we can have this discussion about whether it's a single-blind or an open label study. But, clearly, everybody's going to get rifaximin in the first --

DR. PASRICHA: Yes. But regardless, there's going to be a significant proportion of

placebo responders in that. So at your first retreatment phase, you're going to be able to figure out some of that.

So I'm not concerned about -- but if your first retreatment phase does not show a difference between active and placebo, is there any point in continuing with the second retreatment phase?

DR. FORBES: Well, I think because the study's going to be ongoing, the analysis will obviously cut the data when it's available, and that would be submitted as part of a complete response. The study will go on in order to allow patients to complete the trial. So by the time that all occurs, in reality, as you well know, the study will be probably almost finished.

DR. PASRICHA: But theoretically, if your first retreatment phase does not show any efficacy, the study basically has not proved the hypothesis.

DR. FORBES: Correct.

DR. RAUFMAN: Dr. Septimus?

DR. SEPTIMUS: This is a hypothetical and gets to the placebo effect. So let's assume that

1 this treatment regimen has proven some efficacy
2 with repeated use, and we address, hopefully, some
3 of the safety issues, although I'd like to see a
4 lot more detail about how you're going to look at
5 the microflora over time.
6 Since there's such a large placebo effect,
7 when this is now used clinically, we're going to
8 have a large number of patients that are going to
9 be receiving this drug that have a placebo effect.
10 And so the development of some biomarker as part of
11 the study I think is critical for the most
12 appropriate and effective way to use this drug, if
13 in fact the study design shows effectiveness over
14 time.
15 DR. RAUFMAN: Dr. Anderson?
16 DR. ANDERSON: Yes. I want to follow up
17 along that, the placebo effect. If we believe the
18 TARGET studies, which we have no reason not to,
19 75 percent of the responders are really placebo
20 responders.
21 So I was wondering, in your discussions
22 about possible designs, whether you considered a

placebo run-in, where individuals who responded to placebo would be dropped from further study.

DR. FORBES: Yes. I think we've considered, over time, just about every possible deviation to this design. And we're certainly open to discussing whether or not placebo lead-in would help in some of this.

I want to point out that one of the strengths from the TARGET studies is how few patients actually dropped. If you go back and take a look at the other development programs in IBS, you'll find that the discontinuation rate is actually somewhere around 20 percent of the population. We had about half of that in TARGET 1 and 2. We did not lose that much data over time.

So in our conversations with the GI Division -- and I think it was Dr. He that pointed this out, which is it's difficult sometimes to do studies beyond 12 weeks. We're asking a lot of these patients to stay in a study a long period of time.

I'm just a little sensitive about loss of

patients. And when we get into analyses and the areas that you and Dr. Fleming are going to be interested in after the fact, how did we account for patients that left and we lost to follow-up, et cetera, I think that we obviously want to build a study that gives us what we need. But at the same time, we've toyed with other designs that would be better, we believe, in some respects, but might take longer. And so we're trying to balance duration with what the information is that we need.

DR. RAUFMAN: Dr. Solga?

DR. SOLGA: Can I please have from Salix the slide that shows rifaximin in hepatic encephalopathy and the difference in the primary endpoint at day 28? And I'm going to ask for that slide to ask a really simple question because I just need to know.

Last year, we learned from Salix that rifaximin does not work for acute encephalopathy. These were different studies than the one we're fishing for here. And in this study, we saw that rifaximin does not work until day 28, at least; the

lines diverge. And so it earned a maintenance of an indication, maintenance of remission of hepatic encephalopathy. It does not work for acute encephalopathy. It does not work to induce encephalopathy.

The study design we're talking about for irritable bowel syndrome is exactly the opposite. Rather than talking about chronic dosing, we're talking about acute induction and then repeat dosing. Of course, these are different entities, but irritable bowel and hepatic encephalopathy share the features that they are both chronic relapsing disorders affected by millions of patients. And, frankly, the biological mechanisms of rifaximin are somewhat mysterious.

Why not just do that study?

DR. FORBES: Well, let me back up. Let me talk first about the HE data because you mentioned that it didn't work in acute. Actually, it did work in acute. And, in fact, some of the dose-ranging data that we talked about last year came from Williams' group over in the U.K., and it

1 looked at different doses in patients that were
2 hospitalized for acute hepatic encephalopathy. So
3 that was part of what we used to justify the dose
4 of the 550 BID.
5 At one month, this is actually a
6 borderline p-value. So it actually -- I mean, I
7 know a lot of people interpret this as it doesn't
8 work for one month; in fact, we actually believe it
9 is working in the first month. And we know from
10 experience that when patients just stop rifaximin,
11 they end up in some trouble not too long after. So
12 I think, from that perspective, we've learned some
13 lessons from HE.
14 If I jump over to Crohn's, which I know
15 I'm jumping now therapeutic areas, this is an area
16 where they have an exacerbation of their Crohn's.
17 It is dosed acutely, or I should say for three
18 months. That effect maintains for an additional
19 three months. So those patients were followed for
20 six months.
21 So we have -- I mean, and not only in IBS
22 with multiple studies in the literature as well as

the phase 2 and phase 3 where we've dosed acutely in symptomatic IBS patient, shown that they have prolonged benefit as it relates to symptom relief, we see it in other disease states as well.

I realize that as we jump from therapeutic area to therapeutic area, that can be very dangerous to try to draw lessons on. We give that information to you, and I touch on this, just so that we can remind you of some of the things that you're bringing up now, is that we do have lessons learned from other areas. We're not real clear on the mechanism today. We are continuing to do research and try to focus that research to get a better idea of how this drug is working in various therapeutic areas.

What we struggle with is that we're not really clear if there is a mechanism in common in all these different therapeutic areas that is coming into play, or if it is different mechanisms.

DR. SOLGA: Thank you. Can I just ask, in follow-up?

Have you looked at irritable bowel

1 rifaximin for 4 weeks, 6 weeks, 8 weeks, 12 weeks,
2 continuously versus placebo, rather than 2 weeks?
3 We've talked about different dosing intervals, but
4 not so much about length of therapy.
5 DR. FORBES: So earlier Dr. Fleming
6 pointed out some of the weaknesses of our phase 2
7 study, and many statisticians have pointed that
8 out to me. We had a 2 to 2 to a 1 to 1 to 1
9 randomization, which meant that at the dose of
10 550 BID in phase 2 for 28 days, what we saw was
11 really no added benefit of taking it continuously
12 relative to the 550 BID for 14 days. However,
13 there were twice as many patients in that, and also
14 twice as many in the placebo group. That was the 2
15 to 2.
16 So the preliminary information that we
17 have is that continuous use wouldn't suggest a huge
18 benefit to patients. So that got us to the 14 days
19 and the 550 dose, and then, of course, you've heard
20 the discussion around the glucose breath testing
21 that told us that maybe a slightly higher dose
22 might also beneficial for abdominal pain and for

1 helping in those patients that might have dysbiosis
2 of the small intestines.
3 DR. RAUFMAN: Dr. Spiegel?
4 DR. SPIEGEL: Thank you. Just a brief
5 question/comment about the placebo run-in phase. I
6 wanted to just add one other piece of information
7 about this.
8 I think I share the same concern about
9 treating with an antibiotic for somebody who's
10 responding to placebo. It's hard to know who those
11 people are, of course. I think there are some
12 advantages of a placebo run-in. We've heard from
13 Dr. Lembo that placebo without deception is perhaps
14 the single most effective treatment we have in IBS;
15 not even being facetious, number needed to treat
16 is 4, according to his excellent randomized control
17 trial. So we know placebo without deception works.
18 That doesn't mean active pharmacotherapy doesn't
19 work at all; it just means placebo does work.
20 If there's a run-in phase and people are
21 still not responding, and then bring
22 in -- actually, Mark Pimentel has described what he

calls pre-SIBO, which I think is a fascinating concept. And I could speak for Mark, or maybe he wants to say something about it. And that is, if a patient with IBS knows that they're going to be getting an antibiotic, it's almost like they've been prepared. Their standards are much higher. Right? This better work really well because I'm about to get an antibiotic for this.

So if somebody responds after a placebo run-in and then they respond to rifaximin, to me that's a real responder. That's somebody that didn't respond to placebo without deception, and despite the pre-SIBO effect, rifaximin still prevailed.

Now you've tried, I think, the best we can to find people that are truly responding as best as we can to the antibiotic and not to some kind of a placebo effect. And that would strengthen, moving forward, the group with some assurance that they seem to be responding to the rifaximin as they enter the second phase. So I think there are some things to think about there.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: I just want to go back on the comment that you made about the phase 2 trial because I was meaning to bring it up. There hadn't been a lot of discussion on that.

So if I understand the data correctly, neither 4 weeks or 550 BID, nor the higher dose -- I think 2200 -- actually showed any significant difference over placebo. It's not that it didn't add any benefit to your current regimen. It actually did not show any effect at all.

Are there concerns about that? Again, this goes back to the mechanism of action, which seems like just an amazingly narrow window of efficacy, or is a bell-shaped curve. But we're now entering a study where we're going to give this drug for longer and longer periods of time. And I'm just not sure how to interpret the phase 2 data unless you tell me that it's just statistically not really that robust.

DR. FORBES: Well, maybe I can take -- we did a lot of probing of the phase 2, as you can

imagine. We actually held an awful lot of webcasts and advisory boards with consultants over the phase 2.

Part of the problem that we have is, on the patient-reporting outcomes, these measurements aren't the most sensitive and specific. They have a lot of variability in them, and it's difficult, I think, sometimes to see differences.

We get a 10 percent difference when we have good numbers. When we had half the population in the other treatment groups, it was difficult. However, when we looked at refining the population and probing it, we did actually get the treatment groups to go the right direction. But those are all post hoc analysis.

Put the slide up, please.

One of the areas that we noticed on the higher dose group is this is actually abdominal pain by week. And I know there are a lot of lines on here, but what you'll notice is that the 1100 milligrams for 2 weeks, and BID is 2200 milligrams, actually did very well on

abdominal pain. And this was actually one of the analyses that we spent a lot of time on because we knew how important abdominal pain was. We wanted to make sure that we not only handled bloating and stool consistency and a number of other -- obviously, global IBS is hugely important as well -- but we also wanted to impact on this one. And this is where 1100 milligrams twice a day hit, where the other ones just didn't seem to be able to perform that much differently.

So in trying to impact all of the symptoms that are important to an IBS patient, this is one of the things that led us to considering a higher dose and actually a greater frequency of the three times a day versus twice a day.

So I really that phase 2 data being what it is, we use it to try to cull for the signals that will make us successful in phase 3 to bring a proposed treatment forward. So I understand that there's some discomfort with 550 TID. But the splitting of the doses to go to a three-times-a-day regimen had been done in many clinical studies in

different centers, and we felt that it would be more successful here to go to 1650 for various reasons we've discussed before.

In the end, TARGET 1 and 2 set out to do what they do, which is show benefit over placebo.

DR. RAUFMAN: On that last slide, if I could comment again, it speaks to the high efficacy of the placebo. And I don't see any statistical analysis to really indicate that that higher dose is better than the other lines.

DR. FORBES: Enoch, you want to address the statistics on this? Enoch Bortey is the head of biostatistics at Salix.

DR. BORTEY: Yes. So we did a repeated measures analysis looking at all the lines displayed in the figure, and 1100 is found to be superior to placebo using the repeated measures analysis.

DR. RAUFMAN: Other questions? Dr. Fleming?

DR. FLEMING: Just a comment. It's treacherous to throw up curves and point out the

curve that looks the best. Okay, 1100 looked good on that curve. 550 times 2 didn't, and that's what was actually on the primary endpoint, the more favorable result.

The reality is that the totality of the data there showed very modest effects, much of which was due to placebo. The attention really probably is more on the TARGET 1 and 2 trials that are confirmatory, although of only one dose and schedule.

DR. RAUFMAN: We have time for one question, or we can break for lunch.

[No response.]

DR. RAUFMAN: So moved.

We'll now take an hour lunch break. We'll reconvene again in this ballroom one hour from now at 1:00 p.m. For panel members, lunch will be served at the Moose Creek Steakhouse located near the lobby. Again, for 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.

(Whereupon, at 12:01 a.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:44 p.m.)

DR. RAUFMAN: We will now resume the meeting. We will now proceed with the open public hearing session. We do not have any registered open public speakers for this open session meeting.

Are there any requests to speak at this time?

[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.

Questions to the GIDAC and GIDAC Discussion

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.

1 There are discussion questions and voting
2 questions. And before we start, I had requested,
3 and I think Dr. Forbes agreed, that we would look
4 one more time at the proposed study design.
5 DR. PATERSON: Good afternoon. I'm just
6 going to recap the features of the proposed repeat
7 study design, just for the purposes of
8 clarification and to familiarize the committee with
9 what we had put together.
10 As I mentioned, the screening phase will
11 last no longer than 30 days, and during the
12 screening phase, if they have not had a colonoscopy
13 within the past two years, we would require that
14 they have one. During this eligibility phase, they
15 will also fill out a diary, and those responses
16 will enable us to determine who should be or should
17 not be included in the study.
18 Following this, the eligible subjects will
19 be placed into the initial treatment phase, which
20 is 2 weeks of rifaximin, 550 milligrams TID,
21 followed by 2 weeks of non-treatment or
22 observation.

At the end of the initial treatment phase, nonresponders are withdrawn from the study. Those that respond will go into a first maintenance phase. And shown here, it's up to 8 weeks in that first maintenance phase. But as we discussed earlier, recognizing that some people may not meet recurrence criteria within that 8 weeks, we are allowing an additional 12 weeks, which I haven't depicted, to allow for recurrence to capture as many patient recurrence episodes as possible. Those that meet the definition of recurrence will then go on to a 1 to 1 randomization with rifaximin, again 550 milligrams TID, versus placebo.

The primary efficacy analysis is conducted at the end of this first repeat treatment phase. Following this, we had discussed this morning that only those who are responders would continue in maintenance phase 2, but there was a comment that perhaps, at the judgment of the clinician, even those that did not respond could potentially be included. But as we had discussed and designed

this morning, we had it that nonresponders would withdraw the study at this time point.

This is a period of up to 8 weeks, again to allow for recurrence. Once they meet the definition of recurrence, they're brought in for a second repeat treatment phase, and the treatment they receive during the first repeat treatment phase will be continued in this phase. After the end of the 4 weeks, all end-of-study assessments will be completed.

DR. RAUFMAN: Are there any additional questions about this before we start?

Dr. Pasricha?

DR. PASRICHA: I just want to clarify that. So in the first repeat treatment phase, if a patient gets the active drug, and if they recur, the symptoms recur, they're going to get the active drug again.

Is that correct? So there's no randomization, basically, at the second repeat treatment phase?

DR. PATERSON: Correct. So whatever

treatment they received in the first repeat treatment phase they will receive in the second repeat treatment phase.

DR. PASRICHA: And the logic for that is?

DR. PATERSON: I'm going to ask Dr. Koch to address that.

DR. KOCH: Gary Koch. The logic for that is that one would be simply trying to identify whether they could replicate their response to the first retreatment phase. So they had a recurrence. They got the first retreatment. They responded. They had another recurrence. Does that response replicate?

It more or less is attempting to simulate what might happen in clinical practice, where a patient responds, actually, to the original initial treatment, recurs, is randomized to rifaximin in the first retreatment phase, gets rifaximin, responds, then they recur again, and then they have a third treatment with rifaximin.

So one gets to understand whether or not their response to rifaximin gets replicated. One

will also get information on the time intervals between treatment. So the time to the first retreatment could be anywhere from 6 weeks to 20 weeks, and the time for the second retreatment could be anywhere from 6 weeks up to 12 weeks, with all of that being potentially flexible. But the concept was, simply, could they replicate their response to the first retreatment phase.

DR. PASRICHA: I understand the concept for repeating the rifaximin in those who got rifaximin. I was more curious about the patients who got placebo and then got another placebo.

Is that an opportunity to do something different for those patients? What value do we get from repeating the placebo at the second retreatment phase?

DR. KOCH: Well, these are patients who have responded to placebo, so the rationale for giving rifaximin to someone who's responded to placebo is uncertain, according to my understanding. But certainly they could be re-randomized. But if they were a placebo responder,

they're benefitting on placebo, so there would seem to be less need to expose them to rifaximin, my understanding. But others could comment on that as well.

DR. RAUFMAN: Are there any other questions regarding -- Dr. Fleming, did you have --

DR. FLEMING: Just from you, what the right time is if we want to provide some more perspective on this design. Would you rather wait for later in the discussion?

DR. RAUFMAN: Yes. Let's do it now as part of the questions. If there are any other questions that would help clarify this proposed design.

Dr. McDonald?

DR. MCDONALD: Just a question about sample sizes and the placebo effect. From the first treatment, they're going to be all responders, and 75 percent of that response is ostensibly placebo. So you end up, out of that with a -- you have 25 percent of whoever comes out

of that first 2-week treatment appears responding. Only 25 percent of that is probably due to the drug. Your sample size calculations consider all that, right?

Then only 25 percent are truly -- remember that in this maintenance phase 1, of who have responded, who are staying in the study, only 25 percent of those did that because of rifaximin. And so that's fine if the sample size is big enough now to go on. I'm just worried about this being futile if that hasn't been considered.

DR. FORBES: Well, it certain has crossed our minds as to how difficult this could be. But Dr. Bortey, would you like to comment on some of the assumptions that are in here?

DR. BORTEY: Yes. We haven't really decided on the sample size, per se, because this is definition-dependent. It is based on the relapse or the recurrence. So right now we've proposed recurrence, and we're looking to the committee. Maybe if, for instance, you modify the definition, for instance, we're going to have different

numbers. But as far as the design is concerned, we're going to run it in event-driven style. We know that for the first repeat treatment phase, for TARGET 1, TARGET 2, if we have like 600 subjects, we were able to see differences.

So we're going to keep subjects into the study, like the first maintenance phase is a variable. So we're going to keep getting subjects into the first repeat treatment to attain this minimum number of subjects, at least 600. But everything is definition-dependent.

DR. MCDONALD: And I agree. You look at those bifurcation points, and you say in both of those arms, you want 600 because that's where you were able to show a response before. I'm just concerned that the population going into that may be different. But maybe I don't know enough to figure that one out. That's why I'm worried.

DR. BORTEY: Yes. We want to agree to the design and the definitions. And then we're going to look at the estimates, confidence limits, lower/upper, and the company will make a very

informed decision based on the sample size.

DR. FORBES: I think the hardest part of trying to design a retreatment study, at least from my perspective on the clinical, is how do the statisticians decide what to analyze.

So when we talk about patients receiving active, then patients receiving active or placebo, and then downstream maybe receiving something else again, crossing over, that was difficult for us to understand how to handle them in an analysis. And so we obviously have patients that are leaving the study as we go forward because they are nonresponders, and, really, it's an enriched study.

I guess, in the end, we looked at the primary efficacy endpoint and said if the question is as simple as if you respond and you get a treatment of rifaximin, will you respond on the second treatment? Then this design we felt answered that question.

DR. MCDONALD: Yes. Except that it's enriched now for placebo responders to the tune of 3 to 1. And so I guess one question I have is, do

1 we know about placebo responders to IBS? Do they
2 tend to respond repeatedly?
3 Someone said that there's data already for
4 IBS, and the response to placebo is -- someone
5 quoted that; very robust. What was it? A relative
6 risk of -- the number needed to treat was 4, with
7 placebo. I'm wondering if there's any data on
8 repeat treatment placebo response.
9 DR. FORBES: I'm not aware of retreatment
10 on placebo response data in IBS itself. Obviously,
11 placebo response is an issue in whatever
12 therapeutic area you're in.
13 Dr. Koch, I don't know if you have any
14 comments in general about placebo response
15 repeaters.
16 DR. KOCH: Well, my only understanding on
17 this is that one would expect that those who
18 respond to placebo, they probably respond to
19 rifaximin as well. I'm not sure there would be a
20 patient who would necessarily be a rifaximin
21 nonresponder and then be a placebo responder.
22 So the main issue is whether or not

1 rifaximin can convert enough placebo nonresponders
2 into a rifaximin responder so that you get a
3 treatment difference. Now, in TARGET 1 and
4 TARGET 2, you did get treatment differences.
5 Now, in this study, you're going to have
6 patients who respond, and then a certain amount of
7 time will go by and they'll get re-randomized.
8 Certainly, among those who respond, some of them
9 would have responded to placebo; but the ones you
10 see are the ones that are responding to rifaximin.
11 When you re-randomize those that have a
12 recurrence, those who would have responded to
13 placebo, like what they did the first time, they'll
14 have a placebo response rate during the retreatment
15 phase. And those who respond to rifaximin but
16 would not have responded to placebo will, in the
17 rifaximin arm, show a response rate, and one would
18 be looking for whether the difference in response
19 rates was either about the same as in the TARGET
20 study or, ideally, a bit bigger.
21 DR. FORBES: I think the other issue that
22 we have on the placebo response -- keep in mind,

TARGET 1 and 2 only dosed patients for 2 weeks. So for 10 weeks, they weren't taking anything other than filling out questionnaires.

I think one of the hardest things for us to understand, as I mentioned earlier in the morning, these patients, when they come in, they score more severe than we see them scoring subsequent to that. So I think this issue of placebo response, we're not sure if it's a waxing and waning in their condition, and that they come into the studies when they're sickest and then after that they get better, and that's the 30 percent that we see in TARGET 1 and 2 subsequent to the completion of the dosing.

So I think it's going to be a tough thing for us to sort through how to get the placebo response completely out of these patients.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: We seem to be talking about the design, so I can't resist, but just to try to point out a couple of features.

I think this design does answer some

important questions. It, however, does so in a certain conditional context. The conditional context is to assume that if you don't respond the first time, or if you respond so well that it takes you more than 20 weeks to develop recurrent symptoms, then we're not addressing you. We're taking out the nonresponders and those that have a great response.

I'm not sure whether that's right or not. But if we accept that that's the right thing to do, then we're randomizing. And one of the strengths of this design is it's going to tell us, after you've already had a previous cycle over this 4 weeks, do you in fact respond better than placebo? And that's a strength.

Coming, though, to what I was arguing before, and the sponsor's already said there are some complexities in how to interpret, my sense here of what we're trying to do at this randomization is answer the question -- I think it's the sponsor's intention, too -- is an acute short-term treatment of symptomatic recurrence a

good strategy? So you're taking that strategy.

So if that's the strategy we're taking, we should be randomizing here to that strategy versus not that strategy. And that's why the control arm continues to get placebo, whereas the intervention arm should continue to get intervention. Because what we're saying is, conditionally given that you did have a previous response, now we're times zero randomizing you here and asking whether or not a strategy of treating and retreating of symptoms beats a strategy of not using it, which means three things that I was trying to get earlier.

One is, you don't leave these people out. They remain. You don't not treat these people if in the real world the strategy would retreat them, if they already had a nice response here and then somewhat miss it here. Do whatever you would do in the real world if you believed in the therapy. And you don't restrict this to 8 weeks; you retreat when you have symptomatic response because that's the strategy we're testing.

So fundamentally it seems that there are

good elements of this design as long as we're willing to look at durability in a group of people who did have one response and didn't have it so well that they at least recurred within 20 weeks, and this could be a primary endpoint; that's fine, but that's only looking at durability over 4 weeks. It's interesting to know what happens to you when you're between symptom responses but not within 2 weeks of treatment.

So, therefore, we want to preserve this randomization against this one with ITT following everybody forward, retreating if you would do so in clinical practice, even if you didn't recur here, even if you didn't respond here. And this interval is not 8 weeks. It's whatever the time is to the subsequent recurrence. And then you're just documenting at every week along here, what is the difference between the strategy here and this strategy for differences in response.

So much of the design is fine, with those refinements.

DR. RAUFMAN: I'd like to move on. So

we'll take two more.

Dr. Spiegel, I think you had -- no. Dr. McDonald, we'll make yours the -- okay.

I would ask the sponsor, if you would, to have this slide accessible because I suspect it's going to come up again. And at this point, we'll move on to the questions. There are both discussion questions and voting questions.

For the voting questions, we'll be using the electronic voting system, which is on your microphones. Each of you have three voting buttons on your microphones, 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.

So if we could have the -- and I'll read

the questions as we go along.

So the first question is a voting question. Which of the following goals for rifaximin treatment of IBS should be pursued in its development to support product labeling; A, prevention of recurrence symptoms; for example, starting treatment before symptoms occur and/or continuing rifaximin on a chronic basis as a maintenance regimen; B, acute short-term treatment of symptomatic recurrence; C, induction of cure or long-term remission?

I'll open the floor to discussion. Dr. McDonald?

DR. MCDONALD: These are not mutually exclusive, I assume. Right? That they can -

DR. RAUFMAN: Correct.

DR. SEPTIMUS: I'm confused. Are we voting on A, B, and C?

DR. RAUFMAN: Separately, voting on these separately. So my interpretation is there'll be three votes, for each A, B, and C.

DR. SEPTIMUS: So you'll tell us when it's

time to vote for each one of them?

DR. RAUFMAN: I will do that.

DR. SEPTIMUS: Thank you.

[Laughter.]

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: Thank you. Just looking at this to begin with, to require any therapy for irritable bowel syndrome to induce a cure or a long-term remission to me is a very high bar, and not something that I think is fair to ask, in my opinion. Whether it's antibiotic treatment or any other treatment, we don't talk about IBS as -- we don't induce cures.

Now, there's certainly individuals who respond very well to antibiotics and perhaps are truly cured. But I think those individuals are relatively uncommon compared to the folks that will have recurrent symptoms and will benefit from repeated therapy.

So just to start with the low-hanging fruit, to me that's a very high bar to ask of any drug for irritable bowel syndrome, and would be, to

me, unfair to require of rifaximin. So I'd just start with that one.

That said, I also have concerns about using long-term therapy as sort of prophylaxis against recurrence. To me, when using an antibiotic, whatever its mechanism -- for a condition that remits, relapses, and is very unpredictable, to me, whether it's an antibiotic or any other medication, the way I manage these patients is to treat them when they're having symptoms. And, frankly, that's how patients take their therapies. They don't usually take daily PRN therapies when they're feeling well. And that's the case with many chronic disease, but especially irritable bowel syndrome.

So those are just some general clinical thoughts.

DR. RAUFMAN: So what I'm hearing, just to summarize, and I'll keep summarizing as we go along, is that, again, we may be voting on these individually but you favor B as a rational strategy for this question.

Dr. Pasricha?

DR. PASRICHA: I want to actually pick up on that a little bit. Induction of cure, I agree, is obviously ideal, but, probably at this point in our understanding of IBS, not really achievable. However, long-term remission is potentially a desirable goal. And by that, of course, we have to define what we mean by long-term remission. But maybe six months, four months, six months, would be long-term enough. Twice a year, if you have to give --

So this question is tied in a little bit to what is meant by short-term and what is meant by long-term. So we have to really parse that out in our discussion.

Prophylaxis, there is a precedent for that. We do that. For instance, when patients recur on SIBOs, we do put them on prophylaxis rather than wait for them to get really morbidly symptomatic and get their -- we'd like to prevent that. So there is a basis for thinking we want to avoid symptoms from developing in these patients,

and I think there could be a role for prophylaxis also.

So I think all these points are up for discussion, but we probably need to parse them out a little more finely.

DR. RAUFMAN: As a follow-up, would you propose a definition of short-term and long-term in this disorder?

DR. PASRICHA: I think that's something we should discuss, what would we mean by that.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: Just briefly. So I really agree with the spirit of those comments. I think what I'm struggling with is, is this an infectious disease? It's not. I think the sponsors themselves have written that dysbiosis is different from septic arthritis, where there is a pathogen. We expect a cure. We don't expect to treat pneumonia and just hope it doesn't come back next month unless there's some underlying explanation. We expect it's gone.

Is that the same expectation of this? Is

this an infectious disease? It can't be, as far as I'm concerned. And I like the idea of a dysbiosis because it distinguishes it in my mind from an infectious disease. If we use that paradigm, then we should expect a cure, for the most part, unless there's some underlying predisposition.

So I don't know that that's fair, but I do think it's reasonable to expect some long-term improvement because if we're going to be using this in tens if not hundreds of thousands of young people, it's not like scleroderma. Okay? That's a rare condition where people have recurrent SIBO, and we have to keep them on recurrent doses, month after month, because they're going to have a recurrence; whether it's that or something else. I think we should expect some fairly robust cessation of symptoms. The exact amount of time we could debate.

DR. PASRICHA: If I may respond, I agree with you, Brennan. So if this trial is successful, potentially the label could apply to patients who get symptomatic every 3 or 4 weeks after their last

course, and they could be eligible for recurrent.

Is that kind of what we want to see happen, or would we like to specify that this should be successful in suppressing symptoms for at least three months, maybe six months? I don't know, that's up for discussion.

I'm not sure I'd like to see it being used every 2 weeks or every 3 weeks. It may not happen in the real world. But that's a potential for happening.

DR. RAUFMAN: I'd just comment that for those of us who are older, we couldn't conceive of peptic ulcer disease being an infectious disease, either. So I would be cautious about making that conclusion.

Dr. Sood?

DR. SOOD: Yes. My only comment is, because we are talking about prevention of recurrent symptoms, there is so much subjectivity of the symptoms there, we don't have any objective biomarker to put for -- like if we are putting a corollary for hepatic encephalopathy where we use

1 continuously, I think we have some objectivity in
2 the symptoms. I don't know.
3 DR. RAUFMAN: Dr. Rosen?
4 DR. ROSEN: So I think when you're
5 thinking about changes in flora, there are some
6 studies looking at 16S sequencing in things, the
7 effect of antibiotics over time, and changes in the
8 flora.
9 One of the things that's striking about
10 all of these studies is this is very individual-
11 dependent, and that their return to baseline of
12 flora after giving antibiotics using 16S sequencing
13 is very variable, and we don't know what those
14 variables are.
15 So setting a fixed window like
16 three months I don't think really applies in this
17 case because there are lots of things that affect
18 the flora. Your diet affects your flora, your age;
19 what other people you're around affects your flora.
20 So I think saying that there's a treatment
21 failure if you don't make it to the 3-month mark
22 worries me a little bit because there's multiple

things that change your flora, and you may need that antibiotic sooner because of whatever else you're exposed to in your environment.

So I'm not sure that it's so cut and dry, especially looking at the 16S data, that you treat, and the flora changes, and you should be cured. I don't think it's as simple as that.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: So again, this dysbiosis stuff is great. I do research in this area, as do many people here. But I want to just remind the committee, this is all speculation. So for us to start again thinking about how we're going to approve a design or a label for this drug based on complete speculation about its mechanism of action is probably not the most accurate way to go about it.

Secondly, I'm not saying it's going to be a treatment failure, necessarily, if the recurrence occurs in less than three months, but it's a practical issue. What should we set the standard for as to how long the remission should really

last? Because we could be getting into where these patients are almost continuously on this drug, and do we want to allow that to happen? And that's a question up for debate.

DR. RAUFMAN: Well, I think we should focus the discussion on this question as it's currently worded here. And getting back to the issue you raised earlier of short-term, and what is short-term, what is long-term, I would take that within the context of the proposed study design.

In the study design that we just reviewed a few minutes ago, are the weeks of follow-up and treatment and so on consistent with your impression, or the committee's impression, of short-term and long-term? And if not, how would members of the committee advise revising the study design to address those concerns?

Dr. Fleming?

DR. FLEMING: I don't know if I'm going to revise your study design, but I'd like to just step back and look at the options again. And what influences my thinking about these options is that

we have a very prevalent clinical condition here that is being proposed to be treated on a chronic basis.

If we went option 1, which would be prevention, my worry is that if we're going to give high exposure or continued long-term treatment, we're going to increase risk for resistance. And I worry about that greatly in the benefit to risk. So my biggest concern with option 1 is what is this going to do in terms of enhancing our risk of inducing resistance?

Option 2 is what I understand the essence of that design is, that the sponsor and the FDA are putting forward, and it does make logical sense to me subject to being able to understand adequately, in a true ITT fashion, what is the nature of the durability of effect.

In option C, I wasn't thinking that that was the only way to go, but I do think of that as, if someone in fact believed we could achieve, if not cure, long-term remission, to me, that would be a very strong positive scenario, where we're

getting very important clinical benefit with less frequent dosing, less risk of resistance. So if someone believed we could achieve C, to me that would give me the greatest sense of positive benefit to risk.

DR. RAUFMAN: Dr. McDonald?

DR. MCDONALD: I just wanted to say I never saw B and C as mutually exclusive, and I think that this is the idea; that, also, try to think -- we have here a therapy that is out ahead of our understanding of the disease itself, and that will hopefully fill in, in the coming years.

I think maybe one thing is to say a study design that shows this true ability of the agent, but also its limitations, that are clearly demarcated so that if other agents come later that can do more, that they get clear market advantage to do more with less risk. I agree also with the concerns about option A at this time. The risks right now are really unknown, but have a very good scientific basis.

The generation of resistance -- also, I'll

bring up, and I'll bring it back again later -- the concern about just altering the microbiome, microbiota enough that you decrease colonization resistance. It's not just the generation of resistance to rifaximin and the rifamycins, but reducing the colonization resistance to other multi-drug-resistant organisms, especially the Gram-negatives that are now becoming highly resistance across the world. And that sets a whole nother thing to be concerned about, and I think especially with A.

DR. RAUFMAN: Dr. Hasler?

DR. HASLER: Yes. I just kind of want to echo what Dr. Pasricha said in terms of ramping up the use of antibiotics in this condition and just say that, as I'm sure you're all aware, we already see this. This drug is being used off-label to treat this condition. And I have seen several patients who are on every-month or every-six-week treatments.

The other scenario which has been troubling to me to observe is that a person will go

through two or three or four courses of Xifaxan, and it will stop working. And the patient has the mindset that they do have an infectious process going on, and then they get switched over to another antibiotic, which is systemically absorbed, which does induce resistance. And I think there's a little bit of a slippery slope here we have to be concerned about.

DR. RAUFMAN: Dr. Anderson?

DR. ANDERSON: Yes. I just want to support the idea -- Tom's recommendation for looking at duration of response. And both the retreatment interval or the maintenance phases really supports this long-term remission goal, and I think that's a really good one.

In terms of defining short-term versus long-term, if we make the duration of response pretty short, 8 weeks, 12 weeks, something like that, then I think we want to think about making the trial have additional retreatment phases, so when patients recur pretty rapidly, that they go through even yet another episode of treatment so

that we can see what happens for the fourth treatment episode, if we're going to allow such a short-term response.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: I think that -- I mean, I agree with you. I'm concerned if there are no limits on how frequently we can treat it, we're going to get into all kinds of issues. Remember, in practice, nobody's giving questionnaires to patients and determining whether they meet the criteria for recurrence or not. Typically, these are 15-minute interviews -- I mean, patient visits: "I'm feeling bad and my bloating is back." "Okay. All right. Here's another scrip," if that's what this drug is approved for. And that's how it's going to be practiced.

So nobody's going to meet a 50 percent criteria cutoff or anything like that. It's just symptoms come back and there's -- going back to Dr. Sood's point, since there's no real biomarker, it's all extremely subjective. And if you don't have limits on how often this can be prescribed,

then you could be giving this every month.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: I've been listening to this conversation and thinking just clinically. We all see three types of patients with regards to antibiotics. There's the group that does not respond, has no response. There's the group that does respond, but recurs relatively quickly, and there's the group that responds and is cured. And those people exist. That is achievable. I mean, I've seen it. And we've all seen patients who are better, robust better. They're unusual, but they get better.

So the question I'm thinking here, should we group that second and third patient in the same bundle? There's major implications in how we manage those two different patients, the issue of antibiotic resistance, recurrent treatments, the implications of what it means to have the illness. All of that is baggage that the second patient has to carry. The third patient doesn't carry any of that baggage.

The question is, isn't it the ultimate proof of principle to require that? It may be unusual, but as long as it's more usual than placebo, that's a major achievement, in my view, to have demonstrated a robust cure with this antibiotic, and actually identify that group of patients and show that it's better than placebo. Even if it's a 12 percent response versus a 2 percent response, that's still a pretty good number needed to treat for a cure. Those people do exist, and I think they're very different.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: I agree, and I may be kind of jumping ahead here. But the concept is, we could benefit patients in at least a couple of different ways. We could benefit them in the spirit of what you're saying, which is, if not a cure, long-term remission.

So long terms between treatments, and then when you do treat them, they also respond, which is why -- coming back to the figure here, which is why I think you randomize and you follow everybody.

1 You follow everybody. You follow the controls.
2 You follow the treated patients. If, in fact, the
3 treatment strategy is stretching out the times
4 between retreatment, then you see that. Then you
5 document that. If it doesn't but you're still, on
6 average, reducing symptoms, then you see that.
7 So as long as you design your trial and
8 follow ITT for sufficient duration, if you're
9 providing benefit in either of those two ways, it
10 will show up, and you reward the treatment by
11 virtue of the fact that it's reducing symptoms
12 mediated through much longer times between
13 recurrence or at least effective reduction of
14 symptoms at the time of recurrence.
15 DR. RAUFMAN: So if part of our role here
16 is to advise the sponsor on the study design -- and
17 I'll maybe start with Dr. Fleming since you brought
18 this up; you know, a study has to end at some
19 point, obviously -- how would you change the design
20 we just saw in terms of the follow-up period? What
21 would you propose?
22 DR. FLEMING: So I like a lot of aspects

of it because, in fact, in my view it can incorporate both the second and third aspects of what we could do with an effective therapy. And so there's no single right answer. I'm not going to try to micromanage this.

But do we truly want to restrict to people that did respond the first time, and do we really want to rule out the people that responded so well that we're not going to randomize? That's a separate issue. That's what we're doing.

Once you've randomized, though, as long as you're following people sufficiently long, the sponsor proposes to look at 4 weeks as a primary. That's okay. I mean, that's a relevant, interpretable outcome. But much richer than that is what happens with this therapeutic strategy set up to retreat at the time of symptoms over time. How are you stretching out the symptoms? How are you affecting the symptoms at the time that you're treating?

All of that's extremely interpretable by just following a randomization to a strategy of

1 continued retreatment versus not. This is also a
2 staggered-entry clinical trial, and so not
3 everybody has to be followed from week 12 to week
4 28. The people that are coming in earlier can be
5 extended to a longer period of time without costing
6 the sponsor any additional time in the overall
7 length of how long it takes to conduct the trial.
8 So there are ways of tweaking this design
9 to greatly enhance the sensitivity to treatment
10 effects, if it's real, or to detect that they're
11 not long-term if it's not.
12 DR. RAUFMAN: Dr. Pasricha?
13 DR. PASRICHA: I agree with that. But if
14 you're going to address the issue about induction
15 of long-term remission as being the primary goal,
16 then you're going to have to change your primary
17 endpoint and tailor the design accordingly.
18 DR. FLEMING: So my comments weren't doing
19 that, although one could. One could randomize from
20 time zero and follow ahead and look at time to
21 symptoms or time to recurrence, and that would be
22 sensitive to that.

I was thinking more of what I think Dr. Spiegel was saying, which is a design that would incorporate both elements of how you might be affecting patients, and being sensitive to whichever are the ones that are relevant.

DR. RAUFMAN: Mr. Matson?

MR. MATSON: Dr. Spiegel spoke of seeing cures from antibiotic treatment. How rare is that, and was it one course? Was it a chronically-taken antibiotic? How long? Et cetera.

DR. SPIEGEL: I probably have less experience than others in this room in terms of the sample size that I've personally worked with. But even though I've been publicly, or even in my writings, questioning the hypothesis, I've certainly seen patients who have been cured.

Now, that's sort of -- they stick in my mind, so I can't tell you really how many. It's, in my experience, relatively uncommon; maybe 10 to 15 at most, 20 percent of responders, will remain with a robust, durable response a year later, let's say. But that's my own experience. I think we

have -- I'm sure that Mark Pimentel and others have better data than I could provide from my own personal experience.

DR. RAUFMAN: Dr. Septimus?

DR. SEPTIMUS: Well, we talked before lunch about having a placebo run-in phase. Is that sort of off the books now? And, secondly, if someone responds to either a placebo or the drug and has a long-term remission, okay, how do we know it's either one of those since we don't have a biomarker to guide us?

So that's not to say that your experience is invalid. It's just that it could be the natural history of what we're treating.

DR. RAUFMAN: I think we can address that in the next question, question 2. Were there -- Dr. Pasricha?

DR. PASRICHA: Exactly. I think -- when you say cured, that you've seen patients who were cured, what you mean is you've seen patients who have remained asymptomatic for the time that you have chosen to follow them, which is a long time,

1 and not necessarily their lifetime.
2 So that's my point, I think. When we talk
3 about this, in practical terms we have to think
4 about what do we mean by that in terms of the
5 actual duration? Do we mean six months? A year?
6 Three months? Whatever it is, we need to have that
7 time constant factored into this trial design.
8 DR. RAUFMAN: Is there additional
9 discussion of this question?
10 [No response.]
11 DR. RAUFMAN: So to summarize and before I
12 reread the question prior to the vote, although
13 there was some question initially of whether a cure
14 was a reasonable objective, I guess there is still
15 question about that because the issue is, is one
16 year or two years a cure or is that a long-term
17 remission? But in either event, I think there's
18 some agreement that that would be a worthwhile
19 goal.
20 Likewise, it seemed that there was
21 reasonable enthusiasm for acute short-term
22 treatment of symptomatic recurrences, and, overall,

unless I'm misreading everybody, there's much less enthusiasm based on current knowledge for the use of rifaximin for prevention of recurrent symptoms.

Is there any additional discussion? Is my paraphrasing missing anybody's opinion?

[No response.]

DR. RAUFMAN: So, with that, let me reread the question, and then I guess for each of the lettered questions, I'll stop, we'll vote, and then move on to the next one.

So for question number 1 overall, which of the following goals for rifaximin treatment of IBS should be pursued in its development to support product labeling?

The first voting question is, A, prevention of recurrence symptoms, e.g., starting treatment before symptoms occur and/or continuing rifaximin on a chronic basis as a maintenance regimen?

Again, please use the three voting buttons on your microphone to vote either yes, no, or abstain.

If everybody could please press your buttons one more time.

[Vote taken.]

DR. RAUFMAN: The voting results are 1 vote for yes, 11 votes for no, and no abstentions, and everyone voted.

So we'll go around the room, I guess starting with Dr. Anderson.

DR. ANDERSON: Yes. I voted no because I believe that we don't know enough about the long-term effects on resistance to launch into a prevention paradigm.

DR. RAUFMAN: Dr. McDonald?

DR. MCDONALD: I voted no, for the same reasons.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: I voted no, for the same reasons.

DR. RAUFMAN: Dr. Sood?

DR. SOOD: I voted no, for the same reasons.

DR. RAUFMAN: Dr. Hasler?

DR. HASLER: I voted no, again, out of concerns about potential resistance. And also the sponsor showed some, albeit weak, data suggesting that long-term treatment may be less efficacious than short-term treatment.

DR. RAUFMAN: Dr. Solga?

DR. SOLGA: No. Nothing to add.

DR. RAUFMAN: Mr. Matson?

MR. MATSON: No. Nothing to add as well.

DR. PASRICHA: No. Same reasons.

DR. FLEMING: Fleming. No. Same reasons.

DR. SEPTIMUS: Septimus. Same reasons.

DR. ROSEN: I have different reasons. I actually voted yes, and I think that you are far better at managing IBS than, clearly, I am because I think that when these patients flare, it's much harder to get them under control than if you can keep them in maintenance.

So, ideally, I think finding a maintenance drug for a subpopulation of patients who respond and an appropriate maintenance interval would be far better than waiting till crisis phase.

DR. RAUFMAN: And I voted no, again for most of the reasons articulated. I don't think it's really know whether it's true that retreating is less likely to be efficacious than keeping somebody on maintenance treatment for this disorder.

Okay. So we'll now vote, again yes, no, or abstain for part B of this question, acute short-term treatment of symptomatic recurrence?

[Vote taken.]

DR. RAUFMAN: So here there were 11 yes votes, no no votes, and one abstention, and everyone voted. And let's go around the room the other way this time. Dr. Rosen?

DR. ROSEN: So I support this. I think it's always good to have something else in your armamentarium of drugs.

DR. RAUFMAN: Dr. Septimus?

DR. SEPTIMUS: Yes. I think this is an important question to answer, and I think we ought to -- I think this is the way we ought to go, is look at acute short-term treatment for symptomatic

occurrence.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: I voted yes, subject, of course, to being able to have sufficient evidence of favorable benefit to risk, where risk factors in risk of resistance.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: I abstained because I'm concerned about not having any limits as to how often we want to treat these patients. I think that's not within our current comfortable levels about how much we know about this drug and its safety. If we had that, I would vote for a yes.

DR. RAUFMAN: Mr. Matson?

MR. MATSON: I voted yes. I felt like it had effectiveness in the short run and should be used.

DR. RAUFMAN: Dr. Solga?

DR. SOLGA: I voted yes. I share Dr. Pasricha's concern and Dr. Hasler's concern that this becomes a slippery slope and treated over and over again, and patients end up on

inappropriate antibiotics.

In the end, though, I think that we have to understand that there has to be thoughtful restraint on behalf of prescribing physicians in the community. And I don't know that there's a way around that. I know at times it's been disappointing, in the cases of drugs like cisapride or the over-prescription of PPIs, that we don't always see that. But even in the context of a 15-minute office visit, the goal for somebody with IBS is to say, okay, is this patient flaring? Is there danger here? Am I missing an actual dangerous diagnosis other than IBS? And if it's just IBS, then how do I provide comfort?

In four out of five offices, it should be about apple juice versus fructose -- apple juice versus orange juice and fructose or stress or something else. But, periodically, you're going to want to reach for Xifaxan if it works. And to that end, I don't think we can expect that we're going to be able to control the number of times this ends up getting prescribed.

In the real world, I think the brakes are going to be put on by the payers, who are going to say, okey-doke; we're not going to pay for Xifaxan more than three times a year or something, the way that CVS and Walgreens light up my fax machine daily about whether or not I should be prescribing the PPI to the patient.

DR. RAUFMAN: Dr. Hasler?

DR. HASLER: I voted yes. I think the data from TARGET 1 and TARGET 2 are very convincing and show response rates comparable to receptor-based therapies approved previously.

DR. RAUFMAN: Dr. Sood?

DR. SOOD: I voted yes, but I really share the concern of Dr. Pasricha and other members that how long -- how many recurrences it will treat. I think that's the question.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: I voted yes. This reflects how clinical practice is -- the process of clinical practice. But I really endorse everything I just heard from Dr. Solga, virtually every word of it.

I agree with that. That's not inconsistent with this decision, but I do think those are important considerations.

DR. RAUFMAN: Dr. McDonald?

DR. MCDONALD: I voted yes, with a lot of the other caveats that have been mentioned. I think that this is the beginning; we're going to see more and more agents like this. And as we get to understand, really, how these agents impact the microbiota, I think that there might be some more reason for restraint. But there's always going to be risk-benefit analysis that you're going to do, even in those 5-minute office visits.

DR. RAUFMAN: And Dr. Anderson?

DR. ANDERSON: Yes. I voted yes with some trepidation, knowing that the risk-benefit issues haven't been fully identified yet.

DR. RAUFMAN: And I voted yes, and I have nothing to add to the other comments that were made.

So now we'll vote on the last remaining part of this question, C, induction of cure or

long-term remission? Use your buttons.

[Vote taken.]

DR. RAUFMAN: And here we have an even split. We have 6 members of the committee voting yes, 6 members voting no, no abstentions, and everyone voted. Let's start again with Dr. Anderson.

DR. ANDERSON: Yes. I voted yes because I really like the idea of doing a trial that would look at long-term remission rates. I think that would be a very compelling endpoint.

DR. RAUFMAN: Dr. McDonald?

DR. MCDONALD: Yes, for the same reasons.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: I voted yes, but I need to qualify this because it's inconsistent with how I started. I still don't think cure is an acceptable benchmark under any standards. Even a one-year cure is unacceptable, really, to require that, in my opinion, at this point.

But I've been persuaded by this argument, and keeping in mind these are not mutually

exclusive, to collect information on longer-term remission, let's call it, I think is very, very valuable to distinguish those cured, so to speak, or long-term remission patients from the recurrent patients. So if it were possible, I would support that.

DR. RAUFMAN: Dr. Sood?

DR. SOOD: I voted no. Still I don't know what's really the long-term remission, what the duration is. I don't think that's feasible with our present understanding.

DR. RAUFMAN: Dr. Hasler?

DR. HASLER: I voted no. I'm a bit more pessimistic than Dr. Spiegel. I have a busy practice, and I have yet to see a person respond completely and permanently to antibiotics. And I think when people get better, they get better on their own as opposed to with any medications.

DR. RAUFMAN: Dr. Solga?

DR. SOLGA: I actually agree with Dr. Spiegel. I just happened to vote the other way. I do think long-term remission is often

there. I just don't know that we have enough of them to make it an appropriate goal.

DR. RAUFMAN: Mr. Matson?

MR. MATSON: I think the word "cure" is an awfully high bar to set. And I've been to Mayo Clinic several times. I'm in a 4-year remission from Crohn's disease, and I'm assured I'm not cured. So I don't know exactly where the long-term remission equals the cure.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: I voted yes. I think it's not so important as to what we mean by long-term, whether it's a year or a few months. But I think the expectation that we should have some kind of a sustained response from a drug that is potentially capable of making some profound changes in the enteric microflora, or dysbiosis, as has been pointed out -- although I'm not sure I believe that. But it's important for us to have some expectations of the durability of the response. Otherwise, this is like taking Levsin or hyoscyamine, putting it under your tongue every

time you have a symptom. What's the difference between that and this drug?

So, conceptually, I think there's a higher bar for a drug like this because of all the potential for adverse effects, both to the community as well as to the individual patient. So some expectation of sustained response should be there.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: I voted yes, not because it's the only goal, but because it's one of the important goals. If we could achieve long-term remission, that's a very important clinical benefit. Everything's benefit to risk, and the stronger the signal is for benefit, the more confident or comfortable we're going to be with risks that are there, resistance and otherwise.

So while it's not the only goal, if we could achieve this goal, it gives me a much greater sense of confidence that an agent that does so would have favorable benefit to risk.

DR. RAUFMAN: Dr. Septimus?

DR. SEPTIMUS: I voted no, not because it's not a desirable goal, but because I am still unclear whether, A, it's achievable, B, what the definition would be. And so until I can get a definition that is objective and has some biomarker or some other thing that we can follow, I think it's a very difficult definition to achieve.

DR. RAUFMAN: Dr. Rosen?

DR. ROSEN: I agree with everything that Dr. Hasler had said.

DR. RAUFMAN: And I voted yes on this, focusing on long-term remission, not on cure. For these patients, a year or two, I think, would be beneficial if they were asymptomatic.

So if we could bring up the second question, which is also a voting question.

The study design presented in this meeting addresses acute short-term treatment of symptomatic recurrence. Is the proposed study design acceptable to address this issue? If not, please explain.

Maybe, Dr. Septimus, if you'd like to

bring up, or Dr. Anderson, the issue of the placebo run-in.

DR. SEPTIMUS: I think that would enhance the study design if we had a placebo run-in prior to randomization.

DR. ANDERSON: Yes. I think somewhere I read in the sponsor's document that this was a trial in responders. And I really feel like we should -- that the trial would benefit by being in responders to this very treatment, not just placebo. I think it would be a much stronger trial.

DR. RAUFMAN: Dr. Pasricha, did you have -- no.

Dr. Spiegel?

DR. SPIEGEL: So as I'm thinking about this now, I can see a few different groups. We kind of parsed this earlier, and Dr. Koch mentioned a few permutations: the patient who responds to treatment but not to placebo; the person who responds to treatment and placebo, you don't know which; the patient that responds to neither.

But there is a possibility, despite what I heard, to respond to placebo but not treatment. And that would be depending upon what placebo we're talking about. If it's Tony Lembo's placebo, which is placebo without deception, they may very well respond, but not respond to rifaximin. So it even gets a little more complicated. What placebo are we talking about here? And then there's the whole pre-SIBO effect.

But all that said, to the degree that we can carve out some group that is responding to placebo and not other things, to the degree we could figure that out, I think it helps refine the ultimate population that moves into the second phase. And if that's one of our goals, that would achieve it. But it is fairly onerous to require such a run-in period.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: I worry in this disease setting about whether there is such a group or if we could find such a group. And to my way of thinking, there are at least three fundamental

reasons why people are responding to placebo.

First, it's a disease where there's an ebb and a flow. And I might respond to a placebo at some point just by the timing of where that ebb and flow hits. It's not meaning that I'll respond to the placebo the next cycle, but it's a function of the ebb and flow.

Secondly, there's a psychological effect. If I'm on a true placebo, that means I'm randomized with the understanding that I might be getting active or placebo. That brings the psychological effect forward.

Third, we're using outcome measures that are inherently very noisy, and so we're setting arbitrary success thresholds. This isn't a setting where it's crystal clear somebody is a success or a failure. It's a continuum. And we're setting an arbitrary threshold and pretending like everybody above that's the same and everybody below that's the same. And we're setting the threshold low enough that it can be achieved by no treatment.

So if you have an OARA patient, you're

looking at an AACR measure, use AACR-20, you get lots of placebo responses. Use AACR-50, you don't get so many. It's not because placebo changed. It's because the threshold of what we define to be a success is specific to what is happening in the ebb and flow of the disease.

So all of those things are contributing here, and I'm not sure that we can get rid of them. I suppose we could, over time, refine the outcome measure and not just economize it in such an arbitrary fashion; and probably like we're doing the AACR-20, where so many people on control will, in fact, achieve this just by random noise. But it's all of those things contributing, and I'm not sure that we can get rid of it.

DR. RAUFMAN: So given some suggestions for improving the design, let's go back to the question. And the question is, is the proposed design acceptable? Comments on that? Dr. Fleming?

DR. FLEMING: To me, this is a very difficult question to vote yes and no on, and I will tip my hand. I think, before FDA advisory

committees were called advisory and not decision making, the most important thing we do is provide advice.

So I'm going to abstain, I can tell you that right now, because I like a lot of features of this design, but I think there are some fundamental improvements that would be integral to its interpretability. I've already mentioned them. I won't re-mention them again unless the discussion persists, and it would be useful.

DR. RAUFMAN: But having said that, what keeps you from voting no?

DR. FLEMING: Because I like certain features of the design. I voted yes to 1B. I think it does make sense in this setting to look at a strategy that is assessing acute short-term treatment of symptomatic recurrence, and this is a very nice design for that, as long as we maintain intervention and control groups over a sufficiently long period of time, post at randomization at week 12, that we really get an adequately informative sense about not just an effect, but durability of

the effect. And then I'm going to say later -- and I want two things postmarketing that will be very important to understand durability of effect and off-target effects on E. coli -- on C. difficile.

DR. RAUFMAN: Other comments?

[No response.]

DR. RAUFMAN: Okay. Before we call the question -- Dr. Anderson, I'm sorry?

DR. ANDERSON: I was just going to say I still think that some kind of placebo run-in is beneficial in trying to keep the treatment targeted towards people that are at greater -- where the risk-benefit ratio is likely to be greater, and this is one way to do that. And it's not perfect because of the problems and measurement error, as well as other things.

But the placebo trial data that we were shown earlier I found very compelling. And then the fact that so many of these patients don't get back to baseline also suggests to me that this run-in period would be very effective in narrowing down the patient population. So we wouldn't be

1 treating -- have this 3 to 1 ratio of placebo
2 responders to true treatment responders. We may
3 narrow that. And I think that would be very
4 helpful.
5 DR. RAUFMAN: If I could ask you to follow
6 up on that. So, again, based on the way the
7 question is framed, would you then propose voting
8 no if there's not a placebo run-in to the study?
9 DR. ANDERSON: Yes, that's where I'm going
10 to be. And I also think the suggestions that
11 Dr. Fleming has made are important enhancements to
12 this. So between all of those, I would prefer a
13 different design.
14 DR. RAUFMAN: Dr. Mulberg?
15 DR. MULBERG: Yes. I just wanted to
16 follow up, if I may. If we do have a placebo run-
17 in, could Dr. Fleming or Dr. Anderson just please
18 then walk through the design on what you're
19 suggesting for the next phase? Because I guess I'd
20 like to ask the question, if the placebo
21 nonresponders will be then put on rifaximin, is
22 that going to be -- how do we discern between the

placebo effect of being now on a new active that may have its own inherent effect?

So I don't believe that without changing the next phase of what we have up there -- I need to understand what that's going to look like. It's not sufficient, I think, if I'm interpreting your comments, to just move to rifaximin with those nonresponders. Right?

DR. ANDERSON: I guess I don't understand the confusion. So I was just thinking of putting an additional box between the screen phase and what's now the initial treatment, which would look like the initial treatment, only with a placebo period, 2 weeks of treatment and 2 weeks of --

DR. MULBERG: I understand that it's placebo. So your next phase would stay the same as rifaximin?

DR. ANDERSON: Yes.

DR. MULBERG: I would think that that would have inherent problems with the fact of how do we discern between the nonresponders to placebo, who would then be, obviously, on active drug. How

do we discern what the true effect of that drug is to the whole issue of dysbiosis and/or to only relying on signs and symptoms? Is there not a placebo effect similar to what's been described by being on another active drug?

The psychological benefit of being put on -- so I'm asking you to walk through the design for how is a patient going to be approached from a consent perspective?

DR. ANDERSON: Yes. I haven't actually worked all of that out. It's true, if you are open to an open label placebo, that kind of simplifies it because you just do that. But I was going to say that the consent would be for the entire period that you would -- in this study, you may be on placebo or active at different points in the study, and there's a randomization involved at some point.

DR. MULBERG: Thank you.

DR. ANDERSON: It would have to be kind of vague in those respects.

DR. RAUFMAN: Any additional comments, questions, before we vote? Dr. Spiegel?

DR. SPIEGEL: Maybe I'm just trying to clarify. I guess I can see -- the idea is if they haven't responded to placebo, we think we've carved out those nonresponders. But, of course, the second round with the activation still may carry a placebo opportunity for sure.

Really, I don't think there's much written about that, whether that's going to be smaller and there's like a diminishing returns curve. That's the idea. We think there's diminishing returns on placebo, and now we're trying to really focus in on the active ingredient. But there might have been -- expectations can go either way.

Maybe they say, oh, my God, I didn't respond to the first round, and I don't know if it was placebo or not. I'm not responding to the second round because I've got the worst disease there is. Or they might say, oh, I bet you that was the fake one and now I'm getting the real one, so I'm pretty amped up. Or they might say, well, actually, this is an antibiotic, and I have really big expectations for this, getting to Mark's data.

So it's really hard to anticipate. The placebo run-in may not solve any of this, but at least it helps us try to experiment, manipulate at least one variable that's within our influence.

DR. RAUFMAN: Dr. Dimick?

DR. DIMICK: I just wanted to bring up the point that as you lengthen the trial, you increase the problem with the placebo effect. We saw in some of the other IBS drugs that we approved that they would lose their delta as the trial went on because you have an increasing placebo effect towards the end of the trial, probably mostly because of the waxing and waning of the disease. So there is some disadvantages as you make it longer and longer.

DR. RAUFMAN: Dr. McDonald?

DR. MCDONALD: Just from my understanding of this trial design, I'm not so concerned about the placebo effect on, needing this placebo run-in, necessarily. It seems to me that coming in with a population to that first bifurcation, that recurrent randomization, is just that you do have

an enriched population with 3 to 1 or three-quarters that have responded to placebo. But to me that's just a problem with your sample size. It just means you're going to need a bigger and bigger sample size. The good thing about this is, of course, this is not a noninferiority study. This is superiority.

So I think that if you were going to buy something, I think some of the things that Dr. Fleming is talking about, lengthening the study, where you can in several different parts, and treating -- and trying to simulate how this is going to be used. This is going to be used in a population of patients who initially present with IBS. And probably if they don't respond the first time, they're not going to try it again. So that makes sense.

But then after they've responded once, as has been pointed out, just because they don't respond the second time, the way clinicians practice is they say, oh, I remember that they once responded; by golly, I'm going to try it again.

And you're only going to do it when they do recur. You're not going to do these artificial things at X number of weeks.

Now, of course, you need to keep the study in a finite time frame. But I think extending out the period, treating them with recurrence, and then this intention to treat analysis over the whole ball of wax, those are the key things to really get at because you really want to say, are we going to make patients better as a population with this, and how much better?

It's not in individual treatments. It's in the whole shebang of treating them over six months to eight months -- I mean, right now they're talking about a 6-month, 7-month, 8-month study design. Why not just go out to the year and say, over a year, randomizing people to recurrent treatment with this versus this, how much time do you buy off therapy, extension between bouts, all those kinds of things, survival analysis. And there's a lot of granularity in those kinds of analysis, too, that can bring power to the whole

thing.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: I was going to wait and make this comment later, but it actually fits in at this point. I'd like to congratulate the FDA, and also the sponsor, for thinking about the endpoints here. And I know we haven't talked about it today, but it's in the briefing document that you've done a lot of thinking about, as the FDA's very important PRO guidance was developed in 2009, how can that guidance help us to better improve how we get valid, well-defined, and reliable endpoints with sensitivity that are clinically relevant, and that takes time.

So my understanding of your approach here is to say, we're going to bridge. So at this period of time, because the PRO development will take some time, we're going to use this measure based on pain intensity and stool consistency.

What I like about it is while it's not fully validated as well-defined and reliable with content and construct validity, it has a lot of

important positive features to it. It's a bit reminiscent to me of what the FDA has done in calling up the foundation of NIH to work together to develop measures for community-acquired pneumonia and SSSI, where they're doing the same thing. They're bridging with measures now while future research is going forward to develop PROs, which I would just wonder, how are you going to get that to be done in this setting? FDA took a very proactive stance with FNIH to develop a process where those PRO developments will occur in a timely way.

It won't answer everything, but it will somewhat contribute to our concerns here, because one of the three features that I think creates this placebo effect is measures that have a lot of noise to them and that can create a substantial impression of success, even in the control arm.

So I really endorse what you're thinking. I hope that you have a process in place to do this in a timely way because it will contribute to helping solve -- it won't totally solve, but it

will help contribute to solving this high placebo rate problem in the control.

DR. RAUFMAN: Dr. He?

DR. HE: Yes. You are right. PRO instrument currently is on the way. It is under development. Under C-Path Institute, we create a working group that includes academic, industry, and as well as government. So that instrument, working group is under -- develop that instrument, yes.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: I am a member of that working group. There's a question in this. So we are in the midst, under the C-Path framework, of developing this instrument, with the assistance of the CRO. Probably it will be delivered, if it remains on schedule, a year and a half from now, I would say. It's been kind of a moving target.

I do wonder if there's reason to wait. Probably there's lots of strategical reasons one way or the other. I'm sure the sponsor would want to move forward as quickly as possible, but then, again, the existing instruments may not have enough

resolution to actually identify differences, especially when we start talking about this unique population that we don't know exactly how they're going to behave versus placebo.

So there could be an argument made -- and we're not voting on this, but there could be an argument made to wait until the best instrument that's available comes off the assembly line and we use it because as far as we know, it's going to be hopefully better than the existing, as you say, unvalidated, insofar as we don't really have construct validity or any of these kind of criterion validity for it.

So I just wanted to give that brief update.

DR. RAUFMAN: I'd like to move ahead. So if I could just summarize what I've heard before I read the question for a vote.

Several suggestions were made to improve the study design. The two prominent ones were to have a placebo run-in to the study whereby those who were then treated with rifaximin would be

subjects who did not respond to placebo. And the other suggestion was to lengthen the course of the trial, to have a longer period of follow-up, and then other comments were made as well.

In reading again the question, when you vote, the question is whether the design we're shown is acceptable given that, certainly, any study design could be improved, but is the study design acceptable?

So, again, to read this, the study design presented in this meeting addresses acute short-term treatment of symptomatic recurrence. Is the proposed study design acceptable to address this issue? And that's what you need to vote on, yes, no, or abstain.

[Vote taken.]

DR. RAUFMAN: And the results were 9 yeses, 1 no, 2 abstentions, and everyone voted. And I guess I'll start this time.

I voted yes. I agree with all of the comments regarding means of improving the study design. But a drug is needed, or new therapies are

needed, for this disorder, and I felt that the study design, as detailed, was acceptable for its intended purpose.

Dr. Rosen?

DR. ROSEN: I voted yes. I actually like the study design because I think it's realistic about what happens in the world. The patients are going to get this drug, and then you need to decide, do they get it again? So I think this is a reasonable approximation for what's going to be happening. I voted yes.

DR. RAUFMAN: Dr. Septimus?

DR. SEPTIMUS: I voted yes. Except for some tweaking that Dr. Fleming has mentioned, I would agree with Dr. Rosen. This is how the drug will be prescribed. And I think, with some tweaking, I think this is a reasonable study design.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: I abstained. This is a very large indication on obtaining reliable insights about efficacy, safety, and resistance. It's of

broad public health importance.

I think the design offers us an opportunity for obtaining very significant insights. As I have mentioned, my most fundamental change in how I would hope the design would be carried out is that once we randomize, roughly that 12- to 16-week period, we do follow real-world. We do follow a real-world strategy of implementing the antibiotic at the times when symptom recurrence occurs; and we follow the controls, and we don't lose them. We continue to follow everybody so that there would be an assessment, as the sponsor proposes, as 4 weeks, but there's also long-term aligned assessments that will, in fact, much enhance our sensitivity to understanding longer-term benefits and risks. And, if, in fact, we are inducing prolongation of time between symptom recurrence, the treatment's going to be rewarded because that's going to show up as a positive.

But I say longer-term, so there are two other things that I would request to at least think about. And, again, this is based on the high level

1 of importance of this clinical scenario, but also
2 the high level of importance that resistance could
3 play.
4 The first is that I'd like to see a
5 postmarketing randomized trial proposed using
6 Dr. Mulberg's randomized discontinuation design.
7 And effectively what we'd be saying is after this
8 intervention is in place, we're going to get people
9 that have been on it for a long time. And after
10 they've been on four cycles or more, for
11 example -- I'm not going to expect we're going to
12 wait that long before approving it if the results
13 look favorable in this trial -- would be to
14 randomize a group of people where there's equipoise
15 as to whether you're still getting benefit,
16 randomize them if they've been on for a long time
17 to getting another cycle versus not, and finding
18 out whether, at discontinuation, you're still
19 carrying benefit after that long period of time.
20 The second fundamental issue is
21 pharmacovigilance. I would really like to see a
22 meticulated, validated document of C. difficile so

that we are following prospectively -- I'm not going to ask for a randomized comparative controlled trial, which is the best evidence, but to be able to look at, in an active surveillance scenario, pharmacovigilance following a large cohort forward in time where there is validated documentation of C. difficile occurring on this regimen against a proper control that would be a truly comparable but non-randomized control to get a sense of whether or not we're going to be increasing the rate.

This is not going to be sensitive to odds ratios of 2. That's the down side. It's going to have to be an odds ratio of 5 for this to be sensitive. But at least, over an extended period of time, are we creating opportunistic infection risk that you can actually pick up?

These are two steps that could be done postmarketing that would greatly enhance our understanding about durability of effect and off-target effects induced through opportunistic infection risks with C. difficile.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: I voted yes because I interpreted the question very strictly. We're not talking about changing the goals. We're talking within the context of addressing acute short-term treatment. This is an appropriate design.

DR. RAUFMAN: Mr. Matson?

MR. MATSON: I voted yes. I have nothing to add.

DR. RAUFMAN: Dr. Solga?

DR. SOLGA: I voted yes. I'm learning so much from Dr. Fleming, this has really been something. Thank you for all those comments.

I'm not sure I have much to add except I think that the sponsor's taking a big chance this may not work. If it does work and shows a signal, it would, I think, be the best IBS trial to date, to my knowledge, anywhere, and certainly knock the socks off of the thousands of probiotic studies that are even published in high impact journals that many colleagues use as rationale to treat IBS. So I think this is very thoughtful.

DR. RAUFMAN: Dr. Hasler?

DR. HASLER: I voted yes. I agree with Dr. Rosen that this replicates a real-world environment, and I think it's a nice compromise between what could be done in a really elegant sense, like Dr. Fleming describes, and what practically can be conducted in a formal trial setting.

DR. RAUFMAN: Dr. Sood?

DR. SOOD: I voted yes. I believe it's a reasonable strategy to answer this question of acute short-term treatment of recurrences. And I think the sponsors have already agreed to increase the treatment re-interval or the maintenance phase, which was 8 weeks. I probably will be likely to pick up all the recurrences this interval, maybe, for the probably prolonged. That may be better.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: I voted yes. I have no additional comments.

DR. RAUFMAN: Dr. McDonald?

DR. MCDONALD: I abstained, for a lot of

the same reasons Dr. Fleming mentioned. I've learned also a lot from Dr. Fleming today.

I would say also I'm just a little concerned. Even though it sounds like what he's proposing is much more expensive, when you think about something getting larger or longer -- and that's true -- but I'm also very worried about this study design, what they have, and the enrichment -- those who have been talking about the enrichment -- of patients who respond to placebo and what that does to sample sizes, and actually shooting yourself in the foot, being unable to show a difference in that recurrence, in treating the recurrence. Because you really had a small group of patients that were in that who were really ready to demonstrate that.

DR. RAUFMAN: Dr. Anderson?

DR. ANDERSON: Yes. I voted no. And the reason was I think, first, the changes Dr. Fleming described with regard to following nonresponders and retreatment, I think those are really important. And I don't think, even for this short-

term treatment of symptomatic recurrence, we should let this opportunity get by and not address those issues.

I also think the placebo response in the initial period is a valuable perspective to look at. I was looking forward to seeing the kinds of data that we would get from that. And also, I think the sponsor might have a better chance in the retreatment phase by looking at those who truly responded to therapy.

DR. RAUFMAN: Thank you.

The next question is for discussion. It's not a voting question. And we've discussed a lot of this, but I'll open it up.

If you believe that a different treatment paradigm than acute treatment of symptomatic recurrence is relevant for rifaximin treatment of IBS-D, please discuss the clinical trial designs that will best meet those objectives.

Dr. Fleming?

DR. FLEMING: Just a very brief comment. And actually, I'm happy with the previous design

with those refinements. I'm not saying we would have to change to this.

But if your view was that you believed you had an agent that really could stretch out the time period between remissions, then randomizing and following for those long-term remission rates, a strategy of treatment and retreatment when necessary against control, looking at things like time to recurrence, would be also an acceptable approach, although I'm not advocating for that instead of what we talked about in question 2.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: What I like about that idea is that it is giving us a glimpse of natural history now a bit more, of the disease and of the treatment. That gets to this earlier discussion, what really is the purpose of this additional study? Is it to show that it works again, or is it to give us additional information on safety and/or natural history that we didn't already know?

I think some of these refinements you've been talking about, we've been talking about as a

group, start to get us more in that direction of distinguishing this trial from the previous one.

I'll just say it again, seeing it work again doesn't help me better understand that it worked the first time. What's the difference now? And time to event, these kinds of analyses, give out very different kind of information that is interpretable and useful to the clinician, and in speaking with patients, quite frankly.

DR. RAUFMAN: Are there any other comments before we move on to the next question?

[No response.]

DR. RAUFMAN: So everybody heard that. But just to summarize briefly, a study design that took longer, a longer period of time, to measure time to recurrence is thought to be beneficial.

Dr. Spiegel?

DR. SPIEGEL: Just one last thought. There was an earlier comment made about how in previous studies, including approved therapies, there's a convergence. We always ask the question, what if the study went one week longer? Would it

be not significant any more?

So that's a reason to keep studies short. On the other hand, here we were talking about lengthening it. And you might think, is that fair to the sponsor? There's recent data on new agents that don't demonstrate -- as far as my review of the data, don't demonstrate that convergence.

So you could say, well, if the treatment's really working, you shouldn't see convergence and it should be able to make it through longer periods of time. But then the counter-argument might be, but that's just not fair. No one else has been asked to do this. Why should this agent be given that bar? But the counter-argument to that is, this is a different agent with a completely different paradigm and a different treatment structure. So maybe it is reasonable to require or ask for a longer term.

I'm not saying there are answers. I'm just trying to spell out some of the conversations that I hear around this.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: I think the second part of your statement answered the question. Yes, you're arguing with yourself, but thank you. You're arguing for all of us, too.

DR. RAUFMAN: Any additional comments before we move on to the next question?

[No response.]

DR. RAUFMAN: Okay. So question 4, and this is a voting question. The applicant is proposing to study rifaximin at a dose of 550 milligrams three times a day for 2 weeks, repeated as needed based on symptom recurrence. Should other dose levels and regimens be explored in future clinical trials? If so, describe what other regimens should be explored.

Dr. Rosen?

DR. ROSEN: Yes. I'm having a hard time with this question because the only reason I can see to change the dosing interval is if it affects resistance, unless somebody else can give me another reason to.

But I don't think we have any data on

whether twice a day or three times a day changes your development of resistance because that's really the only thing that matters as far as changing the dosing interval; I mean, efficacy, of course, but you have efficacious studies in twice a day and you have them with the three times.

So I guess I just open up, is there anything else that we should be thinking of other than the development of resistance that I may not understand?

DR. RAUFMAN: Well, if I could make a comment because I don't -- I guess the question is, is there any benefit to using lower doses? Because I wasn't convinced from the data that Dr. Kim showed of true benefit at the higher doses. So is there a benefit to using this agent or studying this agent at lower doses? And I don't know what the answer is. I'm just asking that.

Dr. Spiegel?

DR. SPIEGEL: Well, I guess I'll make the obvious comment, since I teach health economics in the School of Public Health. We haven't talked

about cost, and it's not our purview to discuss cost. It is an expensive drug, and there's probably a difference between paying for three times a day and two times a day.

I do think, practically, there would be more penetration of this drug if it worked and was successful at a BID dose because maybe more people would pay for it, and maybe more people would use it. So I do prescribe it from time to time, and I frequently have people that simply cannot afford it, won't get it, are never going to get it. And maybe there would be a different barrier. But I say that knowing that we're really not here to discuss cost.

DR. RAUFMAN: But there are two questions in that comment. One is dosing interval versus total daily dose. Is there a compelling reason to dose this three times a day? It's not just the cost. Adherence to BID dosing is better than adherence to TID dosing.

Dr. Hasler?

DR. HASLER: Yes. The briefing documents

actually gave insight into that specific question. They went to TID dosing based on studies of small bowel transit, that it would sort of keep the small bowel almost continuously bathed. And I don't think that's necessarily relevant since I'm not sure how many of these cases are related to small intestine bacterial overgrowth. So BID dosing with the same total dose might be comparable.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: I have a couple of comments. I think I am concerned about -- well, I guess dosing regimens are not always rationally constructed, but I am concerned about how we seem to have figured out this almost magical TID, 550 milligrams, because anything over that doesn't work, anything less than that doesn't work, and there doesn't seem to be really any logical issue about it. So I am a little concerned about that.

The other issue, which Dr. Hasler has raised, I think is also important, is what is the site of action? And we're talking about what I'd like to see in the future in terms of clinical

trials, and maybe this is asking for too much. But what I'd really like to see the sponsor come up with is a colonic delivery only, to try and separate out whether there's a small bowel effect or a colon effect, because that is really going to the heart of the matter as to how this drug really works.

Is it the small bowel? Is it enteric microflora? If you believe the dysbiosis thing, then you should see an effect with something that's targeting only the colon and bypassing the small bowel. I'd love to see that kind of design. I'd like to see some more science going to the mechanism of action of this drug.

I mean, this is 2011. I know we don't know much about IBS, but we're basically throwing stuff at -- we're treating a disease which we know nothing or very little about with a drug that we know little or nothing about. And that's not quite right for the way we should be with our approach to treatment.

DR. RAUFMAN: Dr. Fleming, did you --

DR. FLEMING: Yes. The cup is partly full. The sponsor has done, in phase 2, some direct evidence-based assessments that provide us some insight, and then, as Dr. Hasler said, using some hypothesis-generating evidence, shifted from the 550 BID that showed forward in a U-shaped dose-response curve to the TARGET 1 and 2, to 550 TID but without ever obtaining direct evidence-based justification about how those two relate. So that's at least one question that's out there.

Another one is, do we know it's 14 days? Do we know whether a shorter time period would be sufficient? How strong is our current evidence to say 14 days is the right duration? So those are two issues.

Again, I come back to, sadly, from a public health perspective, there are a huge number of patients that suffer from this condition. The one silver lining is it gives us an opportunity to do trials that are actually more powered, that have the ability to answer, yes, a three-arm trial could be done without radically changing the duration and

cost of the trial, subject to, though, how strong the evidence is that benefit to risk could be fundamentally different with TID from BID or with less than 14 days versus 14 days.

DR. RAUFMAN: So in terms of answering the question, it would seem from the discussion I'm hearing that almost everybody would vote yes on this, that other dose levels and regimens should be explored in future clinical trials.

So does anybody want to propose dose-ranging trials or looking at BID versus TID dosing, or any thoughts on that?

[No response.]

DR. RAUFMAN: Okay.

DR. MCDONALD: How would you do those, I guess is the question. I mean, this U-shaped dose-response curve makes me really personally wonder whether this is all in the colon. And this is just achieving certain MICs and then going on and getting other MICs.

I really think, and I was going to save this for later, that some studies, or part of this

1 study, needs to include some state-of-the-art
2 metagenomic study of the microbiota. I mean, you
3 could even ask for that even before this study, if
4 you're going to sink all this money into this big
5 study, is to see -- here's an intermediate study,
6 is to see signals from the microbiota using
7 metagenomics and how they change with different
8 dosage regimens in healthy volunteers.
9 You see all this literature of this drug
10 doesn't affect the microbiota, and then at the same
11 time you're saying, oh, but this changes the
12 equilibrium of the microbiota. Obviously, this
13 does change the microbiota; it's just that we need
14 to use some standardized methods for assessing the
15 microbiota population.
16 I was going to bring this up. I do think
17 that FDA, in a larger sense with the anti-
18 infectives program, we need to start talking maybe
19 across agencies -- CDC, NIH, and FDA -- about
20 coming up with some standard measurements of the
21 intestinal microbiota and assessing anti-infectives
22 in general and what they're doing to disrupt the

microbiota because this is going to be very important.

I'll say this again, but I do think the biggest risk here is not rifaximin resistance, but it's altering the microbiota in a way to make people more susceptible to colonization with multi-drug-resistant Gram-negatives that are carbapenem-resistant, and all these other things out there.

DR. RAUFMAN: We'll be discussing that a little bit at greater length for question 8.

DR. MCDONALD: Just to summarize, the dosing where you try to look at the dose and see how it affects the intestinal microbiota might be a way to get into this. Because there's no reason why you should have a U-shaped curve if it's just affecting the small bowel. You just wipe out those bacteria and that's the end of the story, until you're wiping out something else.

DR. RAUFMAN: In terms of dose, I would suspect that there wouldn't be great enthusiasm for testing the higher doses, that most people would be

curious to see if lower doses of the drug would be as beneficial as the proposed dose.

Dr. Septimus?

DR. SEPTIMUS: You already said it.

DR. RAUFMAN: Any other comments?

[No response.]

DR. RAUFMAN: So to summarize here, it seems like there's a general consensus that, yes, it would be of value to explore other dose levels and regimens in future clinical trials, with an understanding that that is a difficult undertaking. And the question of what doses and regimens to explore would be of interest, and also to tie that into potential effects on the gut microbiome, and whether lower doses and less frequent dosing might be as beneficial with a lesser effect on changing that microbiome.

Does that pretty much capture?

So let me read the question and we'll vote on this. The applicant is proposing to study rifaximin at a dose of 550 milligrams three times a day for 2 weeks, repeated as needed based on

symptom recurrence. Should other dose levels and regimens be explored in future clinical trials? If so, describe what other regimens should be explored. Yes, no, or abstain.

[Vote taken.]

DR. RAUFMAN: So the voting result was 11 yes, 1 no, no abstentions, and everyone voted.

I can't remember which way we started the last time. Let's start with Dr. Anderson.

DR. ANDERSON: I voted yes. I'd be interested in studies that looked at BID dosing and also shorter duration of therapy.

DR. RAUFMAN: Dr. McDonald?

DR. MCDONALD: I voted yes. Nothing further.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: I voted yes. I agree with that.

DR. RAUFMAN: Dr. Sood?

DR. SOOD: I voted yes, for the similar reasons.

DR. RAUFMAN: Dr. Hasler?

DR. HASLER: I voted yes, again aiming to investigate either lower dosages or shorter duration treatments. I will add the caveat that if Salix has X number of dollars and they have it to devote to their various studies, I would prefer to have them concentrate on the first study, looking at recurrences, than this.

DR. RAUFMAN: Dr. Solga?

DR. SOLGA: Yes. I actually voted no, for more or less the same reasons. I just don't know how we'd ask for different dosing regimens. And surely TID dosing is much more onerous on the patient than BID dosing. But, frankly, that's probably a good thing in this instance. It's only a 2-week trial, after all. And if you forget the middle-of-the-day dose, I guess your IBS didn't really matter to you that much after all.

DR. RAUFMAN: Mr. Matson?

MR. MATSON: I voted yes. It's such an individualized disease that I think more studies and more regimens could be warranted.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: I voted yes. Nothing else to add.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: I voted yes, for reasons our chair already articulated.

DR. RAUFMAN: Dr. Septimus?

DR. SEPTIMUS: I voted yes, for the same reasons.

DR. RAUFMAN: And Dr. Rosen?

DR. ROSEN: I voted yes, for the same reasons.

DR. RAUFMAN: And I voted yes, for the same reasons.

Question 5 is another voting question. For product labeling for a chronically administered antibiotic, is it acceptable to define the target population of IBS-D patients for long-term treatment based on whether they respond to therapy in the first cycle of treatment? If not, how do you suggest defining the appropriate population?

Dr. McDonald?

DR. MCDONALD: One idea would be that

maybe if they respond once, then, yes, they can be treated a second time. And then if they don't respond the second time, then could be tried a third time, but then after that, two strikes, you're out; two strikes without a response, and you're out, so that -- but even then, there's going to be a lot of problems with this, is that people -- endpoints and whatnot.

But to just say that long-term treatment is acceptable in anyone who has responded in the first cycle without any other caveats, no, that's not sufficient.

DR. RAUFMAN: Dr. Anderson?

DR. ANDERSON: Yes. So can I ask, this is the first time we've seen "for long-term treatment." I was kind of curious to know what that really meant in this setting.

DR. RAUFMAN: Dr. Dimick?

DR. DIMICK: Yes. I think we were just talking about recurrent courses of treatment over a long period.

DR. RAUFMAN: Any other discussion?

Dr. Septimus?

DR. SEPTIMUS: Again, if it's only after one cycle, and since there's so much noise related to placebo effect, I think one cycle would not be sufficient to give an indication for long-term recurrent management.

DR. RAUFMAN: I guess I'm confused because I thought that that was the study design that was being proposed, was to look to see if people who responded the first time responded on subsequent treatments, in which case it would seem that this would be acceptable.

Dr. McDonald?

DR. MCDONALD: I was just thinking if we did have time to recurrence, boy, wouldn't that be interesting to also see if -- they recur right away, you do an end-of-year analysis, and people that recurred within X number of weeks didn't get overall long-term benefit versus people who went a certain amount of time. I mean, it just comes back to this issue of designing this next study with more sensitive outcomes to help us inform how to

manage these people.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: I think we had this discussion on the first question, basically, goes to heart of the problem, is what is the goal? And one of the reasons I abstained from this was because there are no limits. Once you've said this patient is a responder, that's it. There are no limits on how many times that patient is going to be treated, how frequently that patient is going to be treated. And that's where we're going to end up with this label.

DR. RAUFMAN: Although I would suspect that in the real world, if it doesn't work at some point, the patient's going to say, look, I already tried that. It doesn't work. Is there anything else we can do? So I would think that it would only be used repetitively if it was working every time that it was employed.

DR. PASRICHA: Yes. And I think the question is, what's the comfort level of saying, this patient can have unlimited cycles of

treatment, seven or eight times a year or whatever it takes, for the next 10 or 15 years? We're trying to see whether that's something that can somehow be factored into this study design or to the label in some way.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: My concern here is that I think we're partly led down this pathway by the nature of the design that we have put forward in question number 2. And I understand the logic to that design; it's really trying to get at durability of effect. So we start off with people that are responders for one cycle, and we go from there. And I also believe that the label should correspond to what you scientifically did, although the TARGET trials weren't that restrictive or exclusive.

What worries me is in the real world, are we saying that if somebody -- again, if somebody had profoundly convincing evidence they weren't responding to treatment, don't retreat them. But we're defining response not irrationally but still

1 somewhat arbitrarily based on whether or not there
2 were not more than 2 of 4 weeks in which you had
3 both the pain intensity and stool consistency drop
4 by 30 percent on pain intensity and no more than
5 50 percent stools, et cetera, et cetera.
6 Okay. Somebody could come close to that
7 and not hit it. And so we're going to say, you're
8 not going to be treated again? And if somebody
9 actually had a baseline that was actually qualified
10 to get into the trial, but not very significant as
11 much as what, in ebb and flow, they might have in
12 other settings, they may not hit this target. And
13 we're not going to treat them again?
14 So I understand a bit how this evolved,
15 but I'm not sure it really matches what clinical
16 judgment would be. If you had an intervention
17 that, based on all these data we're going to get,
18 shows -- if it's positive, if it shows durability
19 of effect in a population and if, as data evolve,
20 C. difficile doesn't seem to be an emerging problem
21 and there is durability, would you really say I'm
22 not going to give another person an opportunity

because they didn't hit these arbitrary standards for response?

So if it's compelling evidence of no response, sure; I would believe that I wouldn't retreat them. But if it's marginal, I probably would.

DR. PASRICHA: So if I may respond to that, I think in the real world we don't have strict criteria that we have the patients fill out forms or questionnaires. If a patient tells you they're better, we say they're better.

So, actually, it's the other way around. We may be letting people in or labeling them as responders when they're not necessarily responders by most objective measures. So, in fact, we land on the other side, in my opinion.

DR. FLEMING: And that's true. But that then just points out the tenuousness of how well we can really understand your true benefit in a chronic setting just from what happened the first cycle.

But, by the way, if you do this, then

please remember that we have to factor in -- for the people that you're not including in this label, they're still being exposed for one cycle to find out whether they are included, and the safety profile in those people have to be factored into your assessment of benefit to risk because you had to expose them in order to find out if they're responders.

So you take on an added burden of, okay, they're not going to be benefitted, but you're going to have to carry their risk; and that has to be factored into your assessment of benefit to risk.

DR. RAUFMAN: I take this question as I think Dr. Pasricha does, not from the study design we were showed and not the criteria for improvement in that study design, but simply if somebody was treated before and they responded, which means they felt better, then that would be justification for a repeat cycle of treatment if their symptoms -- if they relapsed.

DR. FLEMING: Yes. But this isn't

1 challenging that. This is saying, what if you
2 didn't respond? Because as I read this, is it
3 acceptable to define the target population based on
4 whether they respond to the first cycle? Which I
5 interpret to say, if you don't, you're not in the
6 target population.
7 DR. RAUFMAN: Yes. But what I'm saying is
8 that for nonresponse, I also -- the way this is
9 worded, I wouldn't use the sponsor's study criteria
10 for nonresponse. Nonresponse to me would be the
11 patient comes in and says, look. I tried this
12 before; it didn't work. And I wouldn't try it
13 again.
14 DR. FLEMING: I'm more comfortable with
15 that. That's part of what I'm trying to get at.
16 What do we mean by -- how persuasive do you mean
17 nonresponse to be in order to say those people
18 aren't included? I agree with you.
19 DR. RAUFMAN: Dr. Sood?
20 DR. SOOD: Can we answer this question
21 right now? Because long-term treatment has to be
22 based on efficacy and safety. We are talking of

1 only efficacy. We have not come to the safety
2 issue of resistance and other things. If we say
3 yes, we have to put some caveat for that here.
4 DR. RAUFMAN: Other comments?
5 Dr. Septimus?
6 DR. SEPTIMUS: Maybe I'm easily confused,
7 although most of the postprandial slumber has worn
8 off.
9 We don't even know how to define who's
10 likely to respond. So if I'm looking at this
11 question correctly, and I may not be, if 75 percent
12 have a placebo effect, then everyone's okay with
13 saying we should give them repeated courses, I'm
14 not okay with that. I think that's an excessive
15 use of the drug, and possible ecological and
16 microflora problems.
17 I think, again, I'll come back to what I
18 said before. I think we need to come up with a
19 marker that defines that subpopulation of patients
20 that, when they do respond, we know it's due to the
21 drug. But if you're just going to talk about first
22 response and that's an indication they should

receive it long-term for occurrences, I have a hard time answering yes to that question.

DR. PASRICHA: But that's the study design, right?

DR. RAUFMAN: Right.

DR. PASRICHA: So you're saying that the study shouldn't be done?

DR. SEPTIMUS: No, no. I'm saying the study should be done.

DR. PASRICHA: But intrinsic to the study is that if you're a responder, then you are -- what the study is trying to prove is if you're a responder and the study shows that second and third treatments -- or the second treatment, which is the primary endpoint, is effective, then you are a candidate for indefinite therapy.

DR. SEPTIMUS: But you said second and third treatments. This says first. Maybe that's why I'm reading the question -- that's why I'm having a problem with what --

DR. PASRICHA: But the study is using the first response as the criteria for entry into the

randomization phase. That's why I'm saying that. So, by definition, the study has already -- if we approve the study, then we are approving this concept, let me put it this way.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: If the study to be done is the only source of information, I'd be more in agreement because I believe the label should match your scientific trials. But my understanding is this study is following on TARGET 1 and 2 that weren't restrictive, and that the sponsor, at least, is interpreting as establishing effect in that first cycle.

Now, building on that, if you assume effect in the first cycle, now we're looking at the new study as to whether or not you have persistence of effect. So if you put all of that together, I'm not sure that it leads us to being restricted to only labeling it in people that respond in the first cycle because you also have TARGET 1 and 2.

DR. PASRICHA: I don't follow that. I'm sorry.

DR. FLEMING: TARGET 1 and 2 is looking at pristine patients, and randomizing them to treatment versus control, and following them for a cycle, and showing a difference in response rates. But it doesn't tell us whether there's persistence in that effect.

DR. PASRICHA: That's true.

DR. FLEMING: So then after having said there is an effect taking naive patients, there is an effect by one cycle versus not getting it, now we're going to build on that and see if it's persistent effect. So then we treat everybody for that cycle and then randomize them to see if there's persistent effect.

If that new study is the only thing that existed, then I can see why you would restrict the label, but you also have TARGET 1 and 2. So unless I'm missing something, it would seem that --

DR. PASRICHA: We're talking about the long-term treatment.

DR. FLEMING: Yes.

DR. PASRICHA: We're not talking about the

first time short-term treatment.

DR. FLEMING: Yes, which is why I hope the new study is more long-term because I'm taking TARGET 1 and 2 together with the new study to get the entire picture.

DR. PASRICHA: So I guess the question is, what do we mean by long-term? It goes back to what do -- are we confusing recurrent, intermittent treatment with long-term treatment? And my assumption is that we are, that what you mean by recurrent treatment is that over the long term, these patients will get recurrent interventions in terms of treatment.

So I guess we need to clarify that.

DR. RAUFMAN: Let me ask Dr. Mulberg, then. For clarification of the question, "long-term treatment" doesn't mean maintenance therapy with the drug; it means recurrent treatment for episodes of disease?

DR. MULBERG: Correct. That was the context of the question.

DR. PASRICHA: Without specifying how many

cycles, how frequent, or how many years?

DR. MULBERG: Correct.

DR. RAUFMAN: Dr. McDonald?

DR. MCDONALD: I think I'm hearing a lot of uncomfortableness with this alone as labeling indication for the long-term recurrent -- long-term treatment of recurrences, that this is not enough for a labeling claim. It's fine for putting it into the study as the study was being designed originally. We're talking about different designs.

I think we're sort of saying that, boy, if this is going to give license to people using this over a number of years, there needs to be some additional criteria along with it, in part because three-quarters of the initial respondents were explained by placebo alone, and then there are other unknown long-term consequences or risks.

I think that that all goes back to tying this into a larger study we've been talking about that could assess some of those long-term risks, but could also give some greater granularity of predictors for people with a durable response as

well. And I'm thinking that maybe one would be how quickly they relapse -- or recur might be one -- that sort of predicts long-term benefits. There might be some other markers we need to get out.

But I think I'm hearing some discomfort with this alone being the indication gate for people to get years of this drug. That's what I said also may be a criteria; two bouts in sequence where they didn't get response puts them out of the game. And one reason why this could happen if this is an effect on the microbiome, that there's now resistant members of that microbiome that have this role that rifaximin was previously knocking down, and now they can't do it any more.

DR. RAUFMAN: Taking the other side of that argument, though, we've got a disease which afflicts many people in this country, to some degree of severity for many of those people, and we've heard that there really aren't any currently efficacious treatments.

Is it reasonable to withhold a treatment

that could be given? Somebody responds. They do fine for several months. They have a relapse. They get treated. They respond again for several months. And to go on like that, in the absence of -- we have theoretical concerns about the risk to the gut microbiome, et cetera, but nothing that was presented that suggests any real concern at this time.

DR. MCDONALD: It's interesting. Basically, C. difficile has been brought up by Dr. Fleming several times. Basically, C. difficile has been associated with every antibiotic and every antimicrobial out there that's ever been used except maybe aminoglycosides.

So for this not to increase risk for C. difficile, I would be very, very surprised. And all it's going to take is some rifaximin-resistant strains to get into the population, and I think you'll start to see that. You won't see it until you get the rifaximin-resistant strains of C. difficile into the population. But they're there already, and they will enrich, and you'll get

more of them.

I mean, I don't think this is totally theoretical. I mean, the theoretical risk of antibiotics for C. difficile is not theoretical at all, and it's universal across all the antibiotics except maybe aminoglycosides. So that's not quite so theoretical.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: I think this discussion goes to case selection, which we haven't too much about, exactly who should be receiving this drug, right? I mean, it is unsavory, if not unethical, to hold off from giving somebody a medication in whom it works. But the question is, what else have they tried?

So in my own personal practice, I do use antibiotics, but rarely. I use it in my own practice after I've tried many different things, working with a dietician and FODMAP diets, and standard available therapies. Even charcoal, believe it or not, I use from time to time; there's some data about that. Probiotics.

All right. If that stuff doesn't work, I'm happy to use antibiotics, and I do. But that's a group of people that has announced themselves as resistant or severe or persistent. And we're not here to legislate exactly what sequence of events should occur before somebody gets into a trial. But I think the theme is we're worried about putting some limits on who this get used in. And I think the biomarker discussion will help refine that a little bit in a useful way. Because I've been holding off on talking about that because, to me, that's the issue for question 6, is -- or question 5, is case selection.

I think we're saying that response to the first round of therapy is, I guess, as good as any clinical definition, but do we have some way to really tie this down and refine it, short of legislating that these six things have to happen before you are even given antibiotics.

So this is a little flight of ideas, but it just got me thinking in terms of, yes, we shouldn't hold off on giving a therapy to somebody

who needs it, but who is that person exactly?

DR. RAUFMAN: Well, getting back to something that Dr. Pasricha brought up at the very beginning, it would be very nice to know how this drug works because if the actions of the agents are not based on antimicrobial properties, and one could develop a drug that did whatever the beneficial actions of the drug are without killing necessary flora, that would be terrific.

Dr. Pasricha?

DR. PASRICHA: I'd like to ask the FDA a question. So, theoretically, if this trial goes forward as it's designed and the primary endpoint is met, so the first retreatment criteria are fulfilled, but the second are not -- so, by inference, it loses its efficacy after your second treatment -- will this drug still qualify for approval with the caveat that it's only known to work with one repeat treatment?

DR. MULBERG: I was just getting some senior counsel --

[Laughter.]

DR. MULBERG: -- that I think we would be coming back to you, pending the data, for that answer.

DR. PASRICHA: So currently you have lots of precedents where you say this drug is not approved for beyond a certain duration of treatment or a certain -- I guess I'm not sure whether we have precedent for the number of times a drug can be used, but certainly have for duration.

Take the example of metoclopramide, for instance, not being approved beyond 12 weeks. And that's clearly stated in the label, and now there's a black box on that.

DR. MULBERG: I would answer by saying since we're a data-driven organization, we'd wait for the data to make a decision.

DR. PASRICHA: So I guess the relevance of this question is that if you can factor that into the trial, two, three, or whatever times we feel is comfortable, we can put that into the trial design because that may be an outcome that we could see going into the label.

DR. RAUFMAN: Any other comment before I try to summarize the discussion?

[No response.]

DR. RAUFMAN: Okay. So what I'm hearing is pretty significant concern about long-term repetitive use of this agent and its potential effects on altering normal and abnormal, or potentially pathogenic, flora, and specific with regards to C. difficile in colitis; and that knowing more about the long-term safety profile of the drug, I think, would be reassuring to most people.

Also the issue, again, which we've brought up several times, is how many of the folks who've responded the first time to this drug are responding to a placebo effect and not really responding to rifaximin?

So it seems like that there is a consensus that putting some endpoint on the number of recurrent uses of rifaximin, even if it's beneficial, might be warranted until more information is obtained.

Does that seem reasonable? Any comments?

[No response.]

DR. RAUFMAN: So let's go to a vote here. So question 5, for product labeling for a chronically administered antibiotic, is it acceptable to define the target population of IBS-D patients for long-term treatment -- and, again, that's not maintenance treatment, it's recurrent treatment for symptomatic episodes -- based on whether they respond to therapy in the first cycle of treatment? If not, how do you suggest defining the appropriate population? Yes, no, or abstain.

[Vote taken.]

DR. RAUFMAN: So here we have 2 yes votes, 8 no votes, 2 abstentions, and again, everyone voted.

Since I'm in the minority here, I'll go first. I voted yes, again, for the reasons I said before, that this is a disorder which, in many people, is incapacitating or nearly incapacitating, for which there is limited therapy. And at present, I'm not convinced -- although I understand

the arguments, I'm not convinced that there is an obvious risk to repetitive treatment.

Dr. Rosen?

DR. ROSEN: So I voted no. And I have issues with the fact that you have to respond to the first treatment to get additional treatments because I do think there are some patients that may not respond initially who may benefit. And I fear that by coming down like this, you may, from an insurance perspective, exclude patients who may need that medication at a later point but now have been shut out from it.

DR. RAUFMAN: Dr. Septimus?

DR. SEPTIMUS: I voted no. I have problems with trying -- I think we need a better way to look at case selection, and I would feel better if I knew about the long-term safety profile.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: Well, I, too, share the concerns. I'm evidence-based as well, and what is long-term, and let's get the data and come back and

revisit that aspect when we get the data, assuming that the trial is well-done and does give us more insights about long-term.

I'm also unclear how reliable the response at the end of that first cycle will be. It will give us a clue, but I don't know how reliable that clue will be, as to whether that person should be part of the target; although, as our chair defined, if it's clear-cut, then that makes it a little bit easier.

Should there be such a definition, though, as I mentioned before, safety needs to factor in, the safety profile of those people also that you had to challenge to find out they weren't responsive, because there may be down sides to having done that to those folks.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: I said no. I think the question is open-ended in terms of what long-term treatment is. But the trial that we are looking at is not open-ended; it has one or two retreatment points only.

So I think this question should be framed in the context of the trial that's going to be done rather than have an open-ended approval for a label that is not really going to be proven by this trial design.

DR. RAUFMAN: Mr. Matson?

MR. MATSON: I was not comfortable with the wording of the question, and rather than make an uneducated vote, I decided to abstain.

DR. RAUFMAN: Dr. Solga?

DR. SOLGA: I'm not sure I have much to add. I agree with your points on this. Sometimes, practically speaking, you prescribe a therapy for irritable bowel, FODMAP diet or whatever else, and if patients respond, they don't come back to you for two years, and there have been many life events, and they may or may not remember, oftentimes. Other times they respond in exactly the opposite.

It's going to be hard to follow. I don't see people 2 weeks after I prescribe them a therapy for irritable bowel; usually I see them back in

three or four months.

DR. RAUFMAN: Dr. Hasler?

DR. HASLER: I voted no. I agree with the comments of Dr. Pasricha.

DR. RAUFMAN: Dr. Sood?

DR. SOOD: I voted no. I was not comfortable with the phrasing of the statement for the long-term treatment. I think we have to define. I agree with other members.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: I abstained because I weaseled out of this one because I've been ruminating about the answer. I really agree with a lot of what's been said, the concerns. And I also recognize that it's a pragmatic definition. And I think clinically it's quite reasonable, and I'm having trouble replacing it at this time. But I had enough concerns that I didn't feel comfortable voting one way or the other.

DR. RAUFMAN: Dr. McDonald?

DR. MCDONALD: I voted no. This is a drug that was originally developed as an antimicrobial.

And everything to me says its mechanism of action here is antimicrobial, and, therefore, resistance is likely to develop; therefore, there will be an attenuation, probably, of response while there will not be an attenuation of risk. In fact, the risk will go up as the response goes down. That's the nature of antibiotic resistance.

DR. RAUFMAN: Dr. Anderson?

DR. ANDERSON: I voted no, for the reasons others have mentioned.

DR. RAUFMAN: So if we could go on to the next voting question, number 6.

Identifying a more targeted patient population of rifaximin responders for treatment of IBS-D would limit exposure of this drug more conservatively than the larger at-risk population with IBS-D. Do you believe that there is a potential role of a predictive biomarker, i.e. breath hydrogen testing, to achieve this goal? If so, please describe your perspectives.

So we've been talking a little bit about biomarkers before, and this question is general and

also specific to the use of hydrogen breath testing.

Comments? Dr. Hasler?

DR. HASLER: Can I get a clarification of the question? Is it basically a theoretical question like, if there is such a biomarker, would we use it, or should we specifically address the role of breath hydrogen testing?

DR. RAUFMAN: I suspect it's both. I think that the general question is, would identifying a biomarker be of help in patient selection, and are there data or what's anybody's comfort level in suggesting that breath hydrogen testing meets that objective.

Dr. Fleming?

DR. FLEMING: This is such an important question and very strongly motivated as we try to take an intervention that seems to have an effect, but it's not a strong effect, and there are risks. And we could enhance benefit to risk if we could really find the patients.

Can we do an EGFR inhibitor in colorectal

cancer and find that all the effect is in the KRAS wild type, not in the mutant patients? And then you double the benefit to risk, and you reduce by a factor of four sample sizes, and you reduce the resistance exposure by half for the benefit.

So, great motivation and really hard. And Dr. Lias' presentation was spectacular. It's so nice to have that so clearly laid out. So many people confuse the distinct purposes of biomarkers. The low-lying fruit, relatively easy, is to find biomarkers that you can use to diagnose disease or to assess prognosis as prognostic factors. The high fruit, the really difficult ones, are to show that they could be used as replacement surrogate endpoints, or as in this case, for enrichment, where you have to have a much clearer understanding of the causal pathways of the disease process and how this intervention is affecting those causal pathways in some patients and not in others.

My sense about this is it's on target to ask the question. Most disease settings, it's really hard. It's a very data-intensive approach.

Typically, the best approach, as was laid out in the FDA presentation, is a randomized block design where you find out the characteristics at baseline.

So we might assess in everybody what the H2 breath testing result is, and then use that to categorize, exactly as you said, the groups that are in one category versus the other, and find out if the relative risk for treatment differs.

There are no shortcuts. It takes that. And if we don't have a good theory in advance, it's highly data-intensive to use the data to, in essence, explore and develop the hypothesis and then confirm it as well. It sounds great, another one of the adaptive approaches where what you're being sold is sounding great, but the reality of the operating characteristics just doesn't deliver.

So this is exactly -- your presentation is on target for what the challenge is, and I don't want to discourage people from pursuing this, but the reality check is, this is really hard. The better the biology we can bring into this for what should be an effect modifier greatly enhances

statistics because statistics can't do this alone. It's too data-intensive. We need good theoretical bases for generating some hypotheses and then trying to validate them.

As you also pointed out, if there truly is a biological characterization that means you benefit and you don't, but our biomarker is fuzzy and doesn't correctly characterize who you are, you've just further diminished the power of that biomarker to distinguish who the people are that are sensitive versus not sensitive.

So right on target to want to do this, and it's really hard.

DR. RAUFMAN: So with that preamble, which I mean in the best way, does hydrogen breath testing meet that threshold? Is there any sentiment around this table supporting the use of, as it specifically says here, breath hydrogen testing for that purpose?

Dr. Spiegel?

DR. SPIEGEL: I do think so, but I want to really add a few caveats to this. I made this

comment earlier, and I appreciated Dr. Schoenfeld's response and some of the practical concerns.

But a theme of this afternoon has been that the stakes are high. Okay? I don't need a biomarker to determine whether to use an antispasmodic. I don't need one. I just use it.

I would really like a biomarker to case-select patients who are going to respond -- a predictive biomarker for treatment, not necessarily to discriminate IBS from other, not to distinguish disease from non-disease. We have other criteria for that. This is to predict treatment response. That is absolutely vital here, as far as I'm concerned.

So does the glucose hydrogen breath test achieve that? Well, the breath test, to begin with, was the test used to promulgate this hypothesis. It led to 10 years of investigation. It's the test that's being used in the sponsor's presentation to demonstrate dose-response effects. It's the best biomarker we have that's available to us at this time.

Now, that doesn't mean that it needs to be used in everyday practice. But for a clinical trial, it seems to me if we're going to know which of those four survival curves we're dealing with, we have to at least measure some biomarker. And I think that's as close as we've got right now. I think the onus is on somebody to come up with a better biomarker in the meantime.

So I'm thinking about those four survival curves. I'll let you speak because maybe I'm misinterpreting. But without the biomarkers, we don't know which one of those we're going down. And I think the accuracy of the test, it's reasonable to at least hypothesize that it might make a difference. I don't know yet.

DR. LIAS: I can't comment on whether or not it's reasonable to try the breath test, but I do want to clarify one thing.

The information presented on whether or not the breath test changed as a result of therapy isn't necessarily indicative of whether it would choose the right population. Those are two

1 different things.
2 So I wouldn't necessarily say you could
3 conclude that from those studies. But it certainly
4 is a biomarker that is used in this area. But I
5 think the statements that Dr. Fleming made about
6 how you would normally want to have some sort of a
7 reasonable expectation that you know that it might
8 work before you try because --
9 DR. SPIEGEL: It's the biomarker that
10 started this area.
11 DR. PASRICHA: May I?
12 DR. RAUFMAN: Okay, and then Dr. Hasler
13 after.
14 DR. PASRICHA: Okay.
15 DR. HASLER: Well, I guess I disagree with
16 most of what you said. I think the breath test is
17 a bad biomarker. It's insensitive, and
18 specifically with lactulose, it's highly
19 nonspecific.
20 If you look at the glucose hydrogen breath
21 test, that was not designed as a test of D-IBS. It
22 was designed as a test of small intestinal

bacterial overgrowth, and it probably misses about a third of cases. So you're going to be excluding cases right off the top.

If you look at lactulose, there's a huge number of false positives, most likely due to rapid transit and perhaps bacterial composition in the colon. This trial would not be a trial of IBS. This trial would be a trial of small intestinal bacterial overgrowth.

You addressed one issue. Say we were to do this trial with a biomarker like a glucose hydrogen breath test. How would the FDA approve the drug in that setting? Would they approve it only after a positive glucose hydrogen breath test? Which would really change the way irritable bowel is managed by physicians around the country.

First of all, it would take it completely out of the primary care realm since very few primary care physicians have hydrogen breath machines. And, in fact, it would almost certainly shift the burden of care for most D-IBS patients to academic gastroenterologists, and we already see

enough of them.

I think there are enough problems with it. I don't think it defines the disease. I don't think it's appropriate for this point, which is why I asked Dr. Raufman my first question, is this a theoretical question or should we address breath hydrogen testing? Because I would answer those two questions differently.

DR. RAUFMAN: Again, in interpreting the question, I think there's a big difference between i.e. and e.g. So here, it says predictive biomarker that is breath hydrogen testing, not, for example, breath hydrogen testing. So it is specifically asking about that, although clearly there's a consensus around the table that a predictive biomarker, a good biomarker, would be helpful.

Dr. Pasricha, I cut you off.

DR. PASRICHA: Thank you.

Dr. Hasler, I don't want to repeat your statements because I agree with them. But in practice, actually, it's the other way around. We

actually use a drug like rifaximin to test for whether they have -- as a therapeutic trial, that's more accurate than actually using a breath test. So I think the breath test, for all the reasons, is a flawed biomarker. And a flawed biomarker is worse than having no biomarker, in my opinion. So I would not use it.

Maybe you would allow me to do that, or you can do that. I would actually like Dr. Collins' opinion on whether, either now or in the very near future, there can be a microbial signature that we could use for IBS patients, and if so, could that be a potential biomarker.

We talk about this a lot, and I just wanted to hear from an expert about whether this is really a pipe dream or is it feasible, and if that's the direction that we need to be going.

DR. COLLINS: Can you hear me? I think it's feasible in the longer term, about three to five years, depending on the availability of the technology, and the cost of the technology, and the depth of resolution that you go into to

characterize the microbiota under any given circumstances. I think there is a chance that one could develop -- that there could be a microbial signature that would identify IBS, and possibly IBS subtypes, from the rest.

At the moment, faecalibacterium prausnitzii keeps coming up in the studies that have been done and are emerging. A reduction in that, particularly in those patients who have low-grade inflammation, that might be one. The other is activity. And there is a recent study that you well know, Jay, where they measured organic acid production as a measure of fermentation activity in the stool using HPL. Yes, I think it was mass spec. And that again could be a marker for something abnormal in terms of the activity of the microbiome in an easily accessible specimen. Again, that's based on one study and needs to be confirmed. But that could be a biomarker for this usage.

DR. PASRICHA: Thank you. So the patterns are emerging that we can identify group

differences, perhaps, amongst IBS and controls, or within IBS, or for that matter, other conditions such as obesity, just looking at some broad changes in diversity.

But do you think this can be brought down to an absolute personalized individual level, which is what we're talking about in terms of a biomarker? Can I profile a patient's stool and say, yes, you have IBS, and therefore this is a potential biomarker for a drug that theoretically alters that profile?

DR. COLLINS: Well, I don't think you'd need the profile to make the diagnosis. The patient's in front of you. He's got IBS by clinical criteria. The question is, is he going to be an IBS patient? IBS is heterogeneous.

So is he that subgroup in which the microbiome plays an important role? And either an analysis of fermentation on the stool or an analysis of the microbiome itself would help you determine, given the patient's already got IBS clinically, whether or not you'd use a drug like

this. So it would come down to a personalized thing. You wouldn't need it to make a diagnosis or to --

DR. PASRICHA: You're right.

DR. RAUFMAN: Let's move on.

Dr. Spiegel?

DR. SPIEGEL: So we're not three years out yet. We're here. And this is fascinating, and I think we're all looking forward to that.

But I just wanted to just push back just a little bit on Dr. Hasler's comments. I recognize that the lactulose hydrogen breath test will provide too many false positives. It's maybe a measure of intestinal transit time, and probably we all agree that's not a good biomarker. And I also recognize that the glucose breath test may rule out people that have the disease.

But is that a problem? Isn't the working hypothesis as of right now -- at least, it has been in the literature -- that SIBO is what we're treating? And it's a positive glucose hydrogen breath test a measure of SIBO? If not, what is a

positive breath test a measure of?

I realize it may miss people with important SIBO. But as a proof of principle, isn't that okay as long as we're enriching our sample with people who we think do have SIBO?

DR. RAUFMAN: Before I let you -- let me ask -- the question here, though, is whether using the breath test would better target rifaximin responders, and are there data speaking to that question?

DR. SPIEGEL: We saw some data earlier, I thought, that there's a dose-response relationship, at least in terms of breath test positivity, in rifaximin dosage, didn't we?

DR. RAUFMAN: Yes. But the question is how strong those data were.

Dr. McDonald? Or, actually, I cut off Dr. Hasler, so let him --

DR. HASLER: I don't have too much to say to Dr. Spiegel. I think what he says is certainly valid. And he's absolutely right; that's how this whole field came about 12 or so years ago, is to

examine small intestinal bacterial overgrowth. But that wasn't done for the TARGET trials, and I suspect that if they had done that and they unblinded their results, they might see very little association to breath test results.

I know that the working hypothesis when this whole field started was small intestinal bacterial overgrowth, but I don't personally believe that. I think it's much more likely that these are colonic bacteria. In fact, I think that a lot of the positive lactulose breath tests that have been found over the years in these patients have little or nothing to do with small bowel bacterial overgrowth. They're colonic bacterial populations which are generating hydrogen gas when the lactulose zips on through.

One of the things that hasn't come up in today's discussion is the actual dynamics of the lactulose breath test. I mean, lactulose itself is a stimulant of small bowel transit. So in a subpopulation that, at its very basis, has somewhat rapid small bowel transit, and if you make it more

rapid with lactulose, you're going to enrich your population with positive breath tests through nothing going on in the small bowel.

DR. RAUFMAN: Dr. McDonald?

DR. MCDONALD: Maybe this is for clarification from FDA. I mean, it would be fine to say -- I guess maybe the question is, should we be recommending to the sponsor to put this test in, in the population, not to select patients for study, but to have there so that they can correlate response to the findings on the, quote, "biomarker tests" or the putative one? And to me it seems like that's an open question still; we don't know how well they correlate.

But I think everyone keeps jumping to the saying that if it did correlate with response, you wouldn't want to lock out -- you wouldn't want to then come up with a clinical criteria for only treating those patients. But it would be possibly informative, just in terms of pathogenesis and understanding the disease.

I guess this sort of gets back to where is

FDA's mission and asking the sponsor to do certain things. I think your goal would be to have a biomarker if -- you're sort of asking us, is the biomarker ready for prime time enough that it could select a subset that would be more likely to respond? I think the answer is no. But this is an opportunity for that study to show whether it could enrich for such a population. And yet it won't be able to ever be used, from what people are saying here, as an absolute criteria.

So I don't know. How does that help at the end of the day? I don't know. It probably just tells you something about pathogenesis and maybe toward the development of future biomarkers.

DR. LIAS: I think one of the challenging things here is the nature of this test. A lot of times, these types of predictive biomarkers are discovered within the development phase, potentially by looking at the differences between responders and nonresponders retrospectively. And you can't do that with a breath test.

So, potentially, part of this is that if

you believe that it's a hypothesis that's reasonable to test, you almost have to set up a trial to test it prospectively. So that's one thing. Certainly you would want to believe that, potentially, it has a chance of working to do that.

But I don't think that FDA is asking the question -- and please correct me if I'm wrong -- about whether or not the breath test correlates with effectiveness. Really, the question is, can any type of biomarker, whether it be a breath test of some type or another biomarker, be used to target the population so that that population can be better defined, and the people who get the drug actually respond?

DR. RAUFMAN: I think we can go on, unless there's a comment that's going to be radically different than anything we've heard. And I suspect that the vote itself is not going to be that helpful to FDA. I think it's the discussion here that's helpful. I'm not even sure this should have been a voting question, frankly.

Having said that, let me summarize what I

understand as the opinion here. And there is no consensus on this one; we've heard some voices speaking for the legitimacy of the hydrogen breath test in this regard, others against it, and a general consensus, I think, that better biomarkers are necessary.

We've heard some discussion of using the microbiome signature as a potential biomarker in this regard, not for diagnosis but perhaps to identify subjects who might be more likely to respond to rifaximin therapy.

Does that pretty much summarize it? Any additional comments?

[No response.]

DR. RAUFMAN: So I'll read the question and we'll vote. Identifying a more targeted patient population of rifaximin responders for treatment of IBS-D would limit exposure of this drug more conservatively than the larger at-risk population with IBS-D.

Do you believe that there is a potential role of a predictive biomarker, i.e. breath

hydrogen testing, to achieve this goal? If so, please describe your perspectives. Yes, no, or abstain.

DR. FLEMING: A quick clarification on this? And it's the same point you raised. Is the question i.e. or e.g.?

DR. DIMICK: E.g.

DR. FLEMING: It is e.g.

DR. RAUFMAN: Is that the uniform FDA decision, that it's e.g. and not i.e.?

DR. DIMICK: I think it would be easier for you to ask the question if we leave it as is because if we change it to e.g., then it becomes two questions. But, in general, I think we were interested in any kind of biomarker that would be helpful to narrow the population.

DR. PASRICHA: So just another clarification. Any kind of existing biomarker that's currently in use. Right? Not any kind of future biomarker? Obviously, because that's --

DR. RAUFMAN: So yes, no, or abstain.

[Vote taken.]

DR. RAUFMAN: So we've got a spectrum of response here, 3 yeses, 6 nos, 3 abstentions. Again, everyone voted.

We'll start with Dr. Anderson.

DR. ANDERSON: Yes. I abstained. I support the goal, but I'm not that familiar with the breath test. And I think the operating characteristics don't sound that promising at this point.

DR. MCDONALD: I voted no. I certainly support the goal. There isn't such a test at this time.

DR. SPIEGEL: I voted yes. I can't disagree with that. I guess what I'm voting yes for is I would like to see the data. And really, that's what I'm thinking about. How it's used in the future, whether that means that every gastroenterologist needs to have a glucose breath test machine in their office, that's not what we're deciding. I'm just trying to figure out what are the actual data going to show. And right now I'm just looking for any handle I can get on how to

case-select. And as far as I can tell, sitting here, that's what we've got.

Maybe it's not good enough, and that's certainly debatable. But, to me, a glucose hydrogen breath test is pretty close to the best we've got right now, as flawed as it is. And adding it into a study to me isn't unreasonable.

DR. RAUFMAN: Dr. Sood?

DR. SOOD: I said yes because I agree with the first part of the question about the biomarker. Probably I don't have much clarity about this breath hydrogen test. I thought it is any biomarker, not particularly breath hydrogen test. So I said yes.

DR. RAUFMAN: Dr. Hasler?

DR. HASLER: I said no. I interpreted this as i.e. instead of e.g. And I think the best in 2011 is nowhere near good enough, and I don't think it's ready for use in such a setting.

DR. RAUFMAN: Dr. Solga?

DR. SOLGA: Yes. I agree with Dr. Hasler. We're just not there yet. I believe Dr. Pimentel's

work over the last decade has been extremely valuable. I've got his most recent review article here in front of me, which I printed out for this meeting. But it didn't start 10 or 12 years ago. QuinTron's been making this machine for over 30 years, and people have been linking lactose intolerance, fructose intolerance, fructose malabsorption, so on and so forth, for all through the '80s and into the '90s, and looking at gut flora in different ways. The last time I did a PubMed search on hydrogen breath testing, there were over 300 different citations. If this were further along at this point, we would know.

What I alluded to earlier in the morning about the dose-finding study is that there were two studies that were done in Italy that were cited in the sponsor's materials where they said, okay, there's SIBO, and we gave him some glucose breath test and then we gave him some rifaximin and looked at the dose-response curve. But they had no -- the methods paper, the methods sections in those papers, had no risk factors for SIBO. These were

not patients with scleroderma or blind loops. These are people who approach with irritable bowel.

So there's this long history of confusing and intertwining those terms that has helped to some degree, but I think it's over. We simply need better biomarkers, and tooling around with biomarkers that have limited utility at this point is confusing more than it is helpful.

DR. RAUFMAN: Mr. Matson?

MR. MATSON: I voted yes. I would hope that the test could eventually identify a subset of patients that would be beneficial in treatment.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: I voted no. I don't think there is a biomarker today that comes anywhere near fulfilling a role for a predictor. I also think that the data on the dose-response of rifaximin and the results of the glucose breath test are irrelevant. They have nothing to do with predicting responsiveness to treatment.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: I abstained. I surely

1 believe this is an important issue and we need to
2 finding effect modifiers. But if it's an i.e., I
3 don't have a sense, a good sense, about whether the
4 hydrogen testing is ready. I've heard enlightening
5 perspectives that make me unsure.
6 We can -- without altering the trial
7 design, size, et cetera, in a fundamental way, we
8 can still do a randomized block design, finding out
9 what the baseline values are and then analyzing in,
10 I would call it, a supportive analysis. I wouldn't
11 call it an alpha spending analysis, but in a
12 supportive analysis whether there is evidence.
13 But I'm not pushing for that just because
14 a large fraction of prognostic factors aren't
15 effect modifiers. So there's a considerable
16 likelihood that when we would do it, we wouldn't be
17 impressed with an enormous level of interaction
18 that would show up. But it is, in fact, something
19 that we could do for those that believe that this
20 really could be an effect modifier. It wouldn't
21 significantly alter the design. But I would be
22 inclined to think of it as a supportive analysis,

based on what I'm hearing.

DR. RAUFMAN: Dr. Septimus?

DR. SEPTIMUS: I abstained. I strongly support the goal, but I'm not sure that the hydrogen breath test is that test. So I'm really torn, and that's why I abstained.

DR. RAUFMAN: Dr. Rosen?

DR. ROSEN: I voted no. I'm not a big believer in the breath testing, but I do think there is a role for doing bacterial screening using some of the new technology, which I do think will be a biomarker. And so hopefully we'll talk about that next.

DR. RAUFMAN: And I voted no, for the same reasons that the others who voted no already stated.

We've been lobbied to take a break here. So we will take a -- let's make it a 10-minute break. We'll reconvene in this ballroom in 10 minutes, at approximately 3:50. Please remember that there should be no discussion of the issue at hand during the break.

(Whereupon, a recess was taken.)

DR. RAUFMAN: If I could get everybody together, please. We have two more questions.

So the next question, question 7, is not a voting question. Please discuss your concerns regarding the potential for future development of antibiotic resistance due to chronic use of rifaximin. How can your concerns be addressed in the clinical development program for rifaximin in the IBS-D population? So, obviously, we've touched on this issue a few times.

Dr. McDonald, do you want to start the discussion?

DR. MCDONALD: Yes. I do think that it would be very useful to have in this next study, or in some study, some profiling of the microbial signature, the microbiome, using metagenomics, and that maybe there has to be some ongoing commitment to doing that.

Of course, technology is changing. I think we heard from Dr. Collins that in three to five years, we may have really the profile, the

signature of IBS. But, boy, you look at the technology and how quickly it's moving, it's anybody's guess, just in terms of the ability to sequence the entire genomes of these organisms.

The microbiome -- by the way, we've been throwing that term around, and if you talk to the people who are really in the field, they'll tell you that that's actually the collective genome of all the bacteria and all the microbes in the intestinal microbiota. And then the microbiota is really what we're usually talking about, is distribution of species.

So, yes, I think understanding so that we don't just throw around the statement that has been thrown around that, oh, rifaximin does not affect the microbiota, well, that seems awfully strange, as we've already alluded to, when also one of the mechanisms of action is exactly this dysbiosis theory.

So really getting a better profile of how it perturbs in seemingly a healthful way, how it perturbs the microbiota would be useful using

metagenomic methods, either 16S or otherwise, and comparing that to some other methods as well. Of course, it is an evolving technology, and whether -- I don't know that we're at the point necessarily for that to predict risk. I think some other parts of the studies that should be done would include actually looking for the RPO point mutations in some of the bacteria, so people who've been on for a long period of time, screening for some of the nucleotide polymorphisms -- we think they're probably single-nucleotide polymorphisms -- screening for those with genetic probes and looking for those in the microbial flora would be useful also, especially when you're talking about a year of treatment. And that might actually be very important to do as part of this long-term study, where you see these people with their flora assaulted over and over again with the drug -- sorry, not assaulted, perturbed; appropriately rearranged.

[Laughter.]

DR. MCDONALD: Yes, appropriately

rearranged. That's what we hope.

DR. RAUFMAN: And Dr. Fleming, I think you earlier proposed long-term postmarketing surveillance for C. difficile infection and potentially other associated disorders?

DR. FLEMING: Yes. And let me just give a little bit more background since it's asking us for our concerns. I don't know that all of this is happening, but these are my concerns, and I think they actually reflect some other insights we've heard from Dr. McDonald and others.

My sense about this, my concerns about this, is I think it's likely there's an effect. I don't know the magnitude and durability of that effect. And, therefore, the bar for risk is more tenuous or concerning, and I consider resistance one of the risks.

My sense, from what I know here, is that these risks aren't just hypothetical; they're real. And there are risks within the person and then there are risks across the population. And when we look within the person, I don't know if tobramycin

in CF is a good example, but I see there emerging resistance over time and attenuation of effects.

It could come from a lot of different factors. It comes from the fact that there are billions of bacteria, and they are very heterogeneous, and the effect of the antibiotics may not be uniform. The distribution may not be uniform. There may be some bugs that are innately resistant, and we're changing the flora. And it seemingly creates, at least, the potential for opportunities for resistant organisms and opportunistic infections.

Then systemically, while we're told it's poorly absorbed, it's not completely unabsorbed. And my understanding is minimal absorption could be worse; subtherapeutic concentrations can actually create a greater enhanced opportunity for resistance.

So these are concerns. I don't know how they're going to play out. But the way they could play out is reducing efficacy over time, increasing the risk within individuals for opportunistic

infections such as C. difficile, and also transmission of resistant disease is another potential. And I worry about rifampin class since it has such a critical role in TB. Well, I'm reassured that TB in the U.S. isn't a rampant problem, but worldwide, it's one of the number one killers. So are we creating potential down side or unfavorable risks with the benefits that we're getting?

So how do we address it? And that comes back to the question you're asking. I would hope that our efficacy is as strong as possible. I hope that we get some sense about durability of efficacy. And I hope that we can get the best kind of evidence possible about the off-target effects and using active pharmacovigilance to try to assess whether or not there's emerging evidence about C. difficile. But some of these off-target effects, if they're real, are going to be very difficult to formally document.

DR. RAUFMAN: Dr. Septimus?

DR. SEPTIMUS: Real quick, first of all,

I agree with everything that Dr. McDonald said. Just one thing about tuberculosis; as someone who resides in a border state, TB is still alive and well in many places in the United States. And we're a very global society, so I think we have to think about it in those terms, not just about our world but in terms of the larger community.

DR. RAUFMAN: Dr. McDonald?

DR. MCDONALD: I had jumped right into studies to do, and I should just come back to the number one concerns. So my major concerns is in resistance, affecting this agent and affecting public health. Affecting the agent, that you'd see an attenuation of response, and we've discussed this, that this may actually be having its effect through changing populations.

If some of those populations become resistant, you'll have an attenuation of that effect. But that wouldn't harm the patient, presumably; it's just they would no longer see an effect from it. But they would go on with this other risk.

My major concern of possible risk, is co-resistance. There is this concern of the rifamycin class being knocked out by this use. That would affect just the TB population. Well, that's not "just," that's a major thing. But there's a small overlap, probably, in general of TB patients who are also getting this drug.

I'm more concerned about co-resistance, which I think is the problem with C. diff. In general, as long as the C. diff in the population that you're dealing with are susceptible to this drug, you will not see this increase the risk of C. difficile very much at all. It's when you get a highly resistant strain in the population being passed around that you start to see this.

This was seen historically with clindamycin. Before we even knew about C. difficile being etiologic for pseudomembranous colitis, we called it clindamycin colitis. Now, in retrospect, it was probably because there were highly clindamycin-resistant strains of C. difficile circulating, and they're not uniformly so

highly resistant.

This happened most recently with fluoroquinolones. The fluoroquinolones, of course, were approved back in the early '80s with ciprofloxacin. The first respiratory fluoroquinolone was approved in the late 1990s, some of the most successful drug launches out there. Now they've started being used widely in older populations.

It was then three or four years after that that we first started to see highly fluoroquinolone-resistant C. difficile strains. It happened to be this epidemic strain that we're dealing with now. It suddenly got a tremendous selective advantage because these fluoroquinolones were being used so commonly.

So these things can happen. I don't think that we can totally predict them, but they can happen. And my concern is for C. diff, but also for some Gram-negative bacteria. And the multi-drug-resistant Gram-negative bacteria, these are mostly these -- they're coming out of Asia,

especially, but also homegrown here. They're carbapenem-resistant, enterobacteriacae-resistant, to basically all the beta-lactam drugs.

If one of them also developed an RPO mutation so it's resistant to the rifamycins, there's at least conceivably that, again, people on this agent could be more likely colonized with those, and it could potentially spread colonization in those patients.

So I think that that is probably the major concern. I think, then, the actual resistance to the rifamycins and that overlapping in the tuberculosis is probably a lesser concern.

So a loss of attenuation, cross-resistance to other multi-drug-resistant pathogens, because you're just treating this large population with antibiotics, and then, finally, the rifamycin class itself.

DR. RAUFMAN: Any other comments regarding that? Dr. Pasricha?

DR. PASRICHA: Thank you for those comments. I think that's very helpful, a little

alarming, but very helpful.

So the statement that you made that this may not cause any harm to IBS patients, in other words, development of resistance, apart from the C. diff, isn't there a possibility that the very same bacteria that we are implicating as a cause of their symptoms are now resistant to this treatment? And if they get another course of the same drug, their proliferation may be favored. And so you could actually potentially worsen IBS symptoms if that theory is correct.

DR. MCDONALD: That's a good point. I stand corrected. At least theoretically, that would be a concern. I said it would be an attenuation first, but then it could actually lead to an exacerbation.

DR. PASRICHA: The data that Dr. Collins presented showed that, in general, antibiotics --

DR. MCDONALD: Right.

DR. PASRICHA: -- broad spectrum antibiotics, could produce an IBS-like condition and low-grade inflammation.

DR. MCDONALD: Right. I mean, that raises the specter that the efficacy of this drug could be short-lived for this condition, and that it could actually become a drug that actually brings on this condition. That's a potential out there, depending upon the pathogenesis, the pathophysiology of how this drug acts and everything else. But if it's all through altering the microbiome with resistance, you could actually see, eventually, this drug actually acting like other antibiotics, potentially.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: I'm still caught up on that Valentin study, the one that demonstrated rifampin-resistant staph species perirectally and throughout the body 9 weeks later.

So I guess the question is, is it reasonable to do swabs as part of a clinical trial? I don't know much at all about the accuracy of these tests. And how tenable is it that people would have these species, these resistant species, all over their body after a 10-day course of

treatment weeks and weeks out?

To me, that's the most alarming thing that I've heard, and I don't know much about this. So maybe you can help elucidate that.

DR. MCDONALD: I don't know in -- well, I think it is of concern, and these are -- we think right now the main mechanism of resistance would be point mutations, you know, where these -- but the retention of those continue to be colonized with them after a period of time is not unheard of. I'm not surprised, necessarily, by that.

In terms of testing for that, I don't know. I think there are molecular methods, possibly, for actually amplifying for these genes and sequencing those amplicons, and doing that as another nonculture method. The swab is fine for the skin, but you can't use culture methods, really, to find these resistances so easily in the complex microbiota of the lower intestine.

So I think we have to think a little bit more about methods. And maybe the most sensitive methods might be, actually, amplification of

specific sequences and looking for the point mutations.

Now, I don't even know if those have been characterized for this drug. And I think we've talked a little bit about this. It's not -- or we haven't talked about it, but I asked you a question earlier, that you're not familiar with the point mutations, actually, that have been described for this particular rifamycin.

DR. PURFIELD: There are multiple point mutations. There's a -- I think it's a 270 base pair region that's conserved. There are some point mutations that overlap with rifamycin or rifampin resistance. And there's no clear, direct correlation between these particular point mutations as biomarkers for resistance to both drugs, but there's indication that isolates that have these point mutations may or may not be resistant to both rifampin and rifaximin. And that's also explained in the Valentin paper.

So at this point in time, it's kind of a sensitive area. And whenever you see point

mutations popping up in this sensitive area that's actually the target for the drug, then it seems like you're likely to get reduced susceptibility.

DR. MCDONALD: And of course, these are happening all the time. These are random, chance events that we're selecting for.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: So I noted with interest your comment earlier in the day that there doesn't appear to be an overlap between the IBS population and mycobacteria. And that is correct, but there was another indication that the sponsor is looking at, which is Crohn's disease, and there is a theory that it's actually caused by mycobacteria.

So just kind of throw that out there, for whatever it's worth.

DR. RAUFMAN: Are there any other comments before we move on to the next question?

[No response.]

DR. RAUFMAN: Just, again, to summarize -- and this actually deals with the next question as well -- that there are concerns not

only about the development of antibiotic resistance, possibly development of C. difficile that are resistant to antibiotic treatment; that changes in the microflora of the gut not only might attenuate the response of IBS patients to rifaximin, but actually cause a worsening of disease down the road; and just general concerns about changes in microflora and resistant organisms that may be let loose, I guess, in the environment.

So if we could go on to the next voting question -- and I don't know that we need much additional discussion here because I think it would be repetitive of things that have already been said.

Does anybody have anything to add to this discussion relevant to this voting question?

[No response.]

DR. RAUFMAN: So let me read the question.

Are you concerned that chronic use of rifaximin could cause changes in the GI microbiome that would result in an adverse effect on patient health? If so, what are your concerns and how

should they be addressed in the clinical development program?

So, again, regarding, I think -- I'll be surprised -- well, you can always surprise me. I think there'll be a lot of yes votes on this. And it's already been addressed that incorporated in the proposed studies there should be state-of-the-art methods to evaluate changes in the microbial flora of the gut; and that it was thought -- I think somebody said to look at skin swabs and so on might be a little bit too much at this point, but certainly something to keep on the radar for future studies.

Any other comments before we vote?

[No response.]

DR. RAUFMAN: Okay. So it's yes, no, or abstain on this.

[Vote taken.]

DR. RAUFMAN: So obviously a unanimous opinion that there is concern here, and everyone voted. And I'll start. I'm not going to add anything. I think everybody heard the concerns

that were voiced regarding this.

Dr. Anderson?

DR. ANDERSON: I voted yes. And my only addition would be that the question, as it's worded, it's talking about patient health, and I think we should also incorporate public health in that statement.

DR. RAUFMAN: Dr. McDonald?

DR. MCDONALD: Yes; nothing to add.

DR. RAUFMAN: Dr. Spiegel?

DR. SPIEGEL: Yes; nothing to add.

DR. RAUFMAN: Dr. Sood?

DR. SOOD: Yes. My other question is how we are going to address this. Did we say that? Are we going to stick to the new molecular signatures, or we are going to do the routine stool cultures also?

Because if I am correct that -- when they used the ciprofloxacin and norfloxacin for a long time, there were kind of a colonization of the gut with a Gram-negative bacteria, and these were all picked up by the standard stool culture or the

culture of the gut secretions or something like that.

DR. MCDONALD: I mean, there was -- there's been some work done on this with previous indications for rifaximin using culture methods. And that's where the statement has been promulgated from, is that this doesn't affect the microbial flora.

Stool cultures are one way to do it. It's not the state of the art now, though, really. And the fact that so many of these microbes are not even culturable, and you can't get them apart from each other, and everything else, it really seems like we should be moving towards metagenomics. Maybe some culture of specific organisms, there's still a role for that, too.

DR. RAUFMAN: Dr. Hasler?

DR. HASLER: I voted yes, for reasons which have already been stated.

DR. RAUFMAN: Dr. Solga?

DR. SOLGA: I voted yes. But I think there is a potential for undue burden or unfairness

in some respects to the sponsor here for this indication because, again, if this comes to fruition and this gets the indication, I'm probably going to prescribe this occasionally and with restraint. It's not going to be an all-the-time thing. There will be some doctors that prescribe it sloppily, but of course we're all concerned.

But it's potentially unfair to Salix in two ways. Number one, we don't have a surveillance program or a method set out. And we talked earlier briefly about the reality that perhaps the FDA needs to get together with the NIH, not just for this indication but for so many different kinds of medicines that affect the gut flora, and say, okay, from here moving forward, what are we going to expect? Where is the bar? And get it done, not just for this, but for all other antibiotics and PPIs, and so many different things can affect the bowel flora.

Then, number two, I think they've already done more than most other approval processes for antibiotics than have been done. And I don't want

us to be over-scared about this issue. And I may be naive, but I'm the sort of person that watches documentaries like Food, Inc., and think that we're missing the ball talking about this issue at all anyway.

DR. RAUFMAN: Mr. Matson?

MR. MATSON: Yes, for reasons that have been stated.

DR. RAUFMAN: Dr. Pasricha?

DR. PASRICHA: Yes, for the reasons that have been stated.

DR. RAUFMAN: Dr. Fleming?

DR. FLEMING: Yes, for reasons I've already stated. Also, though, very much with the insights from Dr. McDonald. And also, as the FDA quoted, the Martin Blaser article just published in Nature entitled, Stop Killing the Beneficial Bacteria.

DR. RAUFMAN: Dr. Septimus?

DR. SEPTIMUS: Yes, for the reasons stated.

DR. RAUFMAN: And Dr. Rosen?

DR. ROSEN: Yes. And I just wanted to add that I do think that stool is cheap and easy to store. And so it seems to me that if you're going to go through all of this trouble, it doesn't hurt to collect some stool pre and then post. And even in a subgroup of patients, in both the placebo arms and the treatment arms, in a very small number, if you will, you could even collect it daily, just so you understand what you're doing.

Again, you don't know the interval to dose it, as we've talked about, is 14 days too long? The only way you're going to know that is if you look at the flora. I'm not saying the flora is causing the disease, but at least you'll know what the drug is doing to the flora.

So I do think that it would be remiss not to collect it if you're going through the trouble because maybe in three years or five years you will be able to understand what it's doing.

DR. RAUFMAN: Great. Are there any additional comments before we adjourn?

[No response.]

Adjournment

DR. RAUFMAN: I'd like to thank the members of the FDA, the representatives from the sponsor, all the members of the committee, for an outstanding and enlightening session.

We are adjourned. Thank you.

(Whereupon, at 4:15 p.m., the meeting was adjourned.)