DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

NDA 21-200, Zelmac (tegaserod)

Novartis Pharmaceuticals Corporation

Monday, June 26, 2000

8:30 a.m.

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service; the Food and Drug Administration makes no representation as to its accuracy.

Marriott Washington Center
9751 Washington Boulevard
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
735 8th Street, S.E.
Washington, D.C. 20003-2802
(202) 546-6666

PARTICIPANTS

Stephen Hanauer, M.D., Chairperson
Thomas H. Perez, M.P.H., Executive Secretary

MEMBERS

Loren Laine, M.D.
George D. Ferry, M.D.
Christina M. Surawicz, M.D.
Joanne A.P. Wison, M.D.
Joel Richter, M.D.
M. Michael Wolfe, M.D.

INVITED CONSULTANTS AND GUEST EXPERTS

Richard Buyalos, M.D.
Richard J. Hammes, R.Ph.
Samuel Smith, M.D.

FDA

Lilia Talarico, M.D.
Sonia Castillo, Ph.D.
Hugo Gallo-Torres, M.D., Ph.D.
Florence Houn, M.D.
Raymond Joseph, M.D.
Robert O'Neill, Ph.D.

C O N T E N T S

	Page
Call to Order, Introduction: Stephen Hanauer, M.D.	4
Meeting Statement: Thomas H. Perez, M.P.H.	4
Opening Comments: Lilia Talarico	5
Novartis Pharmaceuticals Corporation Presentation	
Introduction: Mathias Hukkelhoven, Ph.D.	6
Irritable Bowel Syndrome: Arnold Wald, M.D.	11
5-HT_4 Receptor Activation: Michael Camilleri, M.D.	18
Efficacy of Tegaserod: Martin Lefkowitz, M.D.	27
Preclinical Findings: Philip Bentley, Ph.D.	95
Review of Data on Ovarian Cysts: Bruce Carr, M.D.	101
Safety of Tegaserod: Martin Lefkowitz, M.D.	109
Closing Remarks: Sidney Cohen, M.D.	118
FDA Presentation	
Statistical Reviewer: Sonia Castillo, Ph.D.	130
Medical Reviewer: Raymond Joseph, M.D., FACP,	142
Open Public Hearing: Ms. Nancy Norton	167
Responses from Novartis	176
Discussion and Questions	214

P R O C E E D I N G S

Call to Order, Introduction

DR. HANAUER: I would like to call this meeting to order. I am Steve Hanauer, Chair of the FDA GI Advisory Panel.

To begin this meeting, Thomas Perez is going to give some opening remarks.

Meeting Statement

MR. PEREZ: Good morning. The following announcement addresses the issues of conflict of interest with regard to this meeting and is made part of the record to preclude even the appearance of such at this meeting.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the Agency has determined that all reported interest in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208(b), full waivers has been granted to Dr. Michael Wolfe and Dr. George Ferry.

Copies of these waiver statements may be obtained

by submitting a written request to the FDA's Freedom of Information Office located in Room 12A-30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvements with any firm whose products they may wish to comment upon.

In addition, I have been informed by Novartis, they have asked us to bring to your attention that their handout was inadvertently printed with a stamp of "Confidential" on it. They wish to make it clear that it is a public document and completely releasable.

DR. HANAUER: Thank you.

To begin the meeting, I believe Dr. Lilia Talarico wishes to provide some opening comments.

Opening Comments

DR. TALARICO: Good morning. My name is Lilia Talarico. I am the director of the Division of GI and Coagulation Drug products. I wanted to welcome you all to

this advisory committee and before we open the meeting, I would like to make a couple of comments.

Two members of the GI Advisory Committee, Dr. Laine and Dr. Hanauer, will leave us because they have completed their tenure as members of the committee, and we wanted to take this opportunity to express our gratitude and thanks for the help that they have provided.

Our thanks go particularly to Dr. Hanauer on whom we have called on several occasions without problem, and he has always been very helpful with his immense scientific knowledge and clinical expertise.

In way of our appreciation and for their contribution, and with our thanks, we want to provide them with a little token.

[Presentation of awards to Dr. Laine and Dr. Hanauer.]

DR. TALARICO: Thank you very much from all of us.

[Applause.]

DR. HANAUER: We are going to go right ahead into the presentation by Novartis. Dr. Mathias Hukkelhoven will introduce the group.

Novartis Pharmaceuticals Corporation Presentation

Introduction

Mathias Hukkelhoven, Ph.D.

DR. HUKKELHOVEN: Thank you.

Dr. Hanauer, Dr. Houn, Dr. Talarico, members of the FDA Advisory Committee, FDA, and guests: Good morning.

My name is Matt Hukkelhoven. I am vice president of Regulatory Affairs for Novartis Pharmaceuticals Corporation. On behalf of Novartis, I would like to thank you for the opportunity this morning to present and review tegaserod, also known by its trade name Zelmac.

[Slide.]

Zelmac has been developed to treat multiple symptoms of irritable bowel syndrome. Specifically, we are seeking FDA approval of Zelmac for the following indication.

[Slide.]

Zelmac, or tegaserod, is indicated for the treatment of irritable bowel syndrome (IBS) in patients who identify abdominal pain or discomfort and constipation as their predominant symptoms.

[Slide.]

Before discussing tegaserod, I would like to review briefly some aspects of irritable bowel disease. IBS is a common functional gastrointestinal disorder characterized by chronic or recurrent abdominal pain or discomfort, bloating, and altered bowel habits in terms of both frequency of bowel movements and stool consistency.

The disorder has a broad range of severity ranging from mild symptoms to severe and intractable symptoms.

Although the pathophysiology of IBS is not fully understood, symptoms appear to be due to disturbances in GI motility and enhanced visceral sensitivity.

IBS is highly prevalent in the general population and associated with significant disability and health care costs. Prevalence estimates indicate that IBS affects 14 to 24 percent of women and 5 to 19 percent of men.

[Slide.]

The most common subdivision of IBS is based on altered bowel habits with classification into diarrhea-predominant IBS, alternating IBS, and constipation-predominant IBS.

The arrows indicate that this is really a spectrum of symptoms rather than three very separate distinctions.

In our clinical studies, we enrolled patients who identified abdominal pain or discomfort and constipation as their predominant symptoms. It is important to note that Zelmac is the first drug developed for constipation-predominant IBS.

[Slide.]

Tegaserod is a new chemical entity which has the following pharmacologic profile. Tegaserod is a potent and selective 5-HT_4 receptor partial agonist. It modulates normal and impaired motility throughout the gastrointestinal tract.

It modulates intestinal chloride/water secretion, it inhibits visceral sensation upon colorectal distension, and tegaserod lacks cardiovascular, renal, respiratory, central nervous system, and endocrine effects.

[Slide.]

With regard to the clinical development of this drug, it is important to realize that at the time of the design of the Phase III program, there were no established clinical guidelines and no medical consensus in the field regarding appropriate outcome measures in IBS.

Because of this lack of reference guidelines, Novartis conferred with medical experts and had several interactions with FDA regarding the most appropriate outcome measures for the three tegaserod phase III studies.

In addition, we had a specific consultation with FDA's GI Division on the outcome measures following the analysis of the first phase III study. That is study B351. The results of this consultation, i.e., modified outcome measures were subsequently applied to the other two Phase III studies, studies B301 and B307, in a fully prospective way and prior to unblinding of these studies.

[Slide.]

The totality of the data both in terms of primary outcome measures and secondary endpoints drawn from over 4,000 subjects of whom more than 3,000 IBS patients were

enrolled in tegaserod clinical studies support the following clinical profile for tegaserod.

Tegaserod given as 12 mg/day (6 mg BID) is effective in relieving abdominal pain or discomfort, bloating, and constipation in patients who identify abdominal pain or discomfort and constipation as their predominant symptoms.

The cumulative safety experience further indicates that tegaserod is safe and well tolerated.

[Slide.]

This morning we would like to present to you detailed data on the role of tegaserod in constipation-predominant IBS.

First, Dr. Arnold Wald, Professor of Medicine at the University of Pittsburgh Medical Center, will present an overview of the disorder IBS.

Then, Dr. Michael Camilleri will discuss the 5-HT_4 receptor physiology and the pharmacodynamic effects of tegaserod. Dr. Camilleri is Professor of Medicine and Physiology at the Mayo Clinic.

Subsequently, Dr. Martin Lefkowitz, who has been involved in the clinical development of tegaserod at Novartis, will review the efficacy and safety data of tegaserod.

Dr. Philip Bentley, from Novartis Preclinical

Safety Department, will then discuss preclinical findings with tegaserod.

Subsequently, Dr. Bruce Carr will review the data on ovarian cysts. Dr. Carr is Professor and Director of the Division of Reproductive Endocrinology of the Department of Obstetrics and Gynecology at the University of Texas in Dallas.

Finally, Dr. Sidney Cohen, Chairman of the Department of Medicine of Temple University in Philadelphia, will present the conclusions of these presentations to the members of this advisory committee.

I would now like to turn the podium over to Dr. Arnold Wald for an overview of the disorder irritable bowel syndrome.

DR. HANAUER: Just before Dr. Wald starts, I would mention that the sponsor has asked that we hold questions until the end of their complete presentation. So, we will try, unless there is something burning, to hold it until the end, which is going to take just about an hour and a half total.

Irritable Bowel Syndrome

Arnold Wald, M.D.

[Slide.]

DR. WALD: Dr. Hanauer, members of the Advisory Committee, ladies and gentlemen: as Dr. Hukkelhoven has

mentioned, irritable bowel syndrome is a chronic functional disorder which is characterized primarily by altered bowel habits and is associated with lower abdominal pain and discomfort and bloating.

Like all the other functional bowel disorders, it is characterized by having no biologic disease marker. Of course, the hallmark of the syndrome is that the symptoms, which are generally nonspecific, are not explained by structural or biochemical abnormalities.

[Slide.]

From a clinical standpoint, there are a variety of subgroups which are based primarily upon bowel habits. We think of these as constipation-predominant, as diarrhea-predominant, and those patients who have alternating constipation and diarrhea.

I would emphasize the word "predominant" in that these symptoms are not exclusive, but they do provide the major bowel habit which characterizes each of the subgroups.

[Slide.]

The subgroup that we wish to focus on today is that of the constipation-predominant patients with irritable bowel syndrome. Now, this is a disorder which has often been diagnosed by nonspecific terms and by excluding organic diseases and therefore the imprecision has characterized both its clinical activity, as well as the clinical research

which has been done on it.

In an effort to be more precise, a number of criteria have been advocated to define irritable bowel syndrome, particularly for clinical research and epidemiological purposes.

[Slide.]

One of these criteria which is now in widespread use is the so-called Rome criteria, and I have listed the Rome II criteria which were published in 1999 and in book form this year.

According to these criteria, patients with irritable bowel syndrome should have at least 12 weeks or more, which need not be consecutive during the preceding 12 months, of abdominal discomfort or pain that has at least two out of the following three features:

There should be relief of that discomfort or pain by defecation. The onset of discomfort should be associated with a change in the frequency of stool or with a change in the form or the appearance of stool.

Rome II differs significantly from Rome I criteria, the original criteria, and that Rome II requires that two of these features be present whereas Rome I criteria required that only one of the three be present.

The study that you will hear today uses the Rome I criteria in the patients who were entered into it, of those

patients, 90 percent would fulfill the criteria of both Rome I and Rome II.

[Slide.]

Now, from an epidemiologic standpoint, irritable bowel syndrome is quite common in the U.S. population. Population surveys have estimated that between 15 and 20 percent of the population will exhibit symptoms which are consistent with this disorder.

Fortunately perhaps only 20 percent of such patients seek medical attention. The vast majority of these patients are seen by primary care physicians. Perhaps 20 to 25 percent will be seen by specialists, mainly gastroenterologists, because of severe disease and other related concerns.

On the other hand, 25 to 50 percent of all outpatient referrals to gastroenterologists are patients who have IBS or related disorders. Importantly, 70 percent or more of these patients, whether non-consulters or patients who are seeing physicians, are women, and these are reflected in most studies and are reflected in the studies that will be presented today.

[Slide.]

Now, the prevalence of these disorders, IBS compares with other disorders, such as GI disorders and non-GI disorders, shown here. Dyspepsia is defined as greater

than one episode per week, 8 percent of the population will exhibit this. Seven percent of the adult population will experience GE reflux symptoms on a daily basis. Four percent have asthma. Three percent have diabetes.

So, IBS is quite prevalent and is a potentially significant disorder in our adult population.

[Slide.]

Now, it is important to emphasize that the concept of irritable bowel syndrome is not one which causes increased mortality or shortens life span, but it has a significant effect on patient well-being, and well-being really is affected by the two most prominent symptoms which characterize this disorder. On the one hand, abdominal pain, on the other hand, altered bowel habits.

This will vary from patient to patient, but it is important to emphasize that it's the totality of the symptoms which are important in defining clinical success, that one cannot look at one or the other in isolation, but one should look at both in a given patient, and we hope to convince you of this today.

[Slide.]

Now, the medical costs associated with irritable bowel syndrome are considerable. In 1992 dollars, it was estimated that $8 billion were spent annually on irritable bowel syndrome patients in terms of direct medical costs.

It has been shown that there are increased physician visits by IBS patients for both GI and non-GI complaints, and that IBS patients incur 74 percent more health care costs than do non-IBS sufferers. This is a significant medical issue.

[Slide.]

But in addition, what is not shown by such data is the impact of IBS on work and other economic factors. In a study recently published, it was found that 30 percent of patients with IBS had missed work during the previous 30 days that they were asked, and this averaged 1.7 days per patient for IBS symptoms.

Forty-six percent of the survey population reported that they reduced the days that they worked, and the average for this was three days because of IBS symptoms. Sixteen percent of those queried said that sometime during their careers that they had turned down promotions or advancement because of their IBS symptoms, 9 percent indicated that they had changed jobs for their health reasons, and 8 percent had changed their work schedules to accommodate their disabilities, a significant economic impact for patients with a disorder which does not decrease mortality or shorten life span.

[Slide.]

The pathophysiology of irritable bowel syndrome is

rather complex, and it has been labeled a biopsychosocial disorder because there are both biologic and psychosocial factors that are at work.

From a biologic standpoint, there is good supporting data that suggest that altered GI motor activity and altered visceral sensations or visceral hyperalgesia play important roles in the pathogenesis of symptoms.

Psychosocial issues do not produce the symptoms, but behavioral, cognitive, and emotional factors may influence the perception of the patient of their symptoms and their health-seeking behavior. Both need to be incorporated into the holistic management of these individuals.

[Slide.]

It is not surprising that in such a disorder, that multiple medications have traditionally been used to treat IBS. I have listed some of the more prominent ones - anticholinergic agents, tricyclic antidepressants, selective serotonin re-uptake inhibitors, antidiarrheals, bulking agents, laxatives, and finally alosetron.

I would emphasize for the first six that there is no supporting data that suggest efficacy for any one or a combination of these agents for the treatment of IBS or the diarrhea-predominant or constipation-predominant.

As this committee knows, the committee recommended

the approval of alosetron for women only who had diarrhea-predominant irritable bowel syndrome earlier this year based on the data at hand.

We are not dealing with diarrhea-predominant IBS. The subgroup that we are looking at today are those who have constipation-predominant IBS.

[Slide.]

What we propose perhaps is a new treatment paradigm for constipation-predominant irritable bowel syndrome shown here. Looking at brain gut interactions, we see that there are altered motility and altered sensation.

Dr. Michael Camilleri will present the physiologic and pharmacologic data that suggests that 5-HT_4 agonists alter both GI motility and also alter visceral sensations.

We believe that based upon the benefits of the drug shown, and the safety profile, that this drug that we are presenting today fulfills the paradigm and is indicated for the treatment of patients with constipation-predominant irritable bowel syndrome.

Thank you for your attention, and I would like to introduce Dr. Michael Camilleri, who will make the next presentation.

5-HT_4 Receptor Activation

Michael Camilleri, M.D.

DR. CAMILLERI: Thank you, Dr. Wald. Good

morning, Dr. Hanauer, members, and guests.

[Slide.]

It is my pleasure today to review with you some of the aspects of the 5-HT_4 receptor physiology and pharmacodynamic effects of tegaserod. My talk will consist of two parts. I will review first the physiological role of serotonin and its type-4 receptors in GI functions, and secondly, review the effects of this partial 5-HT_4 receptor agonist, its pharmacodynamic effects on the GI tract.

[Slide.]

As we all know, serotonin is a biogenic amine which is located predominantly in the gastrointestinal tract. In fact, 90 percent of this serotonin in the gastrointestinal tract is in the lining of the intestine, in the enterochromaffin cells, and 10 percent is located in neurons.

[Slide.]

There are four main 5-HT receptor subtypes which have been identified in the human gastrointestinal tract. There are designated 5-HT_1 to 5-HT_4. Indeed, the diverse effects of serotonin are due to the different receptor subtypes that are activated in the mucosa, serosa, or the muscular layers, or indeed in the afferent functions.

5-HT_3 and 5-HT_4 receptors are involved in multiple GI functions including motor, sensory, and secretory

functions. These receptors are located on neurons, enterochromaffin cells, enterocytes, and smooth muscle cells.

[Slide.]

In this cartoon, we have depicted the potential role of serotonin in intrinsic signaling pathways in the gastrointestinal tract. Note here at the bottom the mucosal aspect and the top the serosa of the intestine.

Note also that in response to local stimulation either by chemical or mechanical stimuli, the enterochromaffin cells act as transducers, releasing 5-HT to activate receptors on the intrinsic primary afferent neuron.

Data which we will present later indicate that the 5-HT_4 receptor is located on this intrinsic primary afferent neuron, and this is essential for the establishing of the peristaltic reflex which involves an excitation above, and an inhibition below, the area of local activation of the mucosa.

There are also 5-HT_4 receptors located strategically on intrinsic cholinergic neurons and excited motor neurons, as well as cholinergic neurons that activate the inhibitory responses. These receptors located in the myenteric plexus are accessed also via the circulation, such that circulating 5-HT or a circulating systemically administered 5-HT_4 agonist would be anticipated also to have

an effect on these important receptors in the myenteric plexus.

[Slide.]

5-HT is also involved in extrinsic signaling pathways. The most important for today's discussion pertains to the role of 5-HT receptors in afferent, visceral afferent functioning. Visceral afferents arise in the mucosa or in response to stretch of tension receptors in the circular muscle there and activate these visceral afferent fibers that send a message of sensation to the brain.

We will show you evidence that this 5-HT_4 agonist, tegaserod, inhibits these visceral afferent pathways to reduce activation and sensation perception in the brain.

[Slide.]

I now want to review for you the pharmacodynamic effects of tegaserod on motility. Tegaserod is a representative of a new chemical class of compounds, the aminoguanidine indoles, which are designed to act specifically at 5-HT_4 receptors in the gastrointestinal tract.

[Slide.]

Its pharmacological profile is as follows. It is a partial agonist, which displays high affinity for human 5-HT_4 receptors with the affinity constant in the nanomolar range. It mimics the action of 5-HT and potently

stimulating that intrinsic primary afferent neuron that is so important for the activation of the peristaltic reflex.

Tegaserod has negligible affinity for 5-HT_3 receptors, and therefore is devoid of relevant 5-HT_3 antagonism.

[Slide.]

This is a model of the peristaltic reflex, and as mentioned previously, tegaserod mimics the effects of endogenously released 5-HT to activate this 5-HT_4 receptor on the intrinsic primary afferent neuron. This then results in an ascending excitation, which results in contraction and descending inhibition, which results in relaxation, facilitating the passage of the bolus down in an aborad direction.

In response to the activation of this intrinsic primary afferent neuron, data which you will see on the next slide indicates that the excited retransmitter, substance P, is released, and the inhibitory transmitter VIP is released. Therefore, it has been demonstrated that the mechanisms for this peristaltic reflex that are classically described have been activated in response to 5-HT agonist tegaserod.

[Slide.]

This slide also demonstrates the effect is selectively inhibited by a 5-HT_4 antagonist. Note here that in several species, there is activation of the excited

retransmitter substance P, as well as the inhibitory transmitter VIP. These are crucially involved in that peristaltic reflex and that are inhibited only and selectively by the 5-HT_4 antagonist, not a 5-HT_3 antagonist.

[Slide.]

Tegaserod induces propulsion in the guinea pig colon, and it does this in a dose-dependent manner.

[Slide.]

Tegaserod has also been demonstrated in vivo to activate important peristaltic functions in the intestine. Propulsive activity has been demonstrated in this in vivo canine study, and the propulsive activity is shown in the jejunum, the ileum, as well as these prolonged contractions in the colon that are involved in aborad transits of content through the colon.

[Slide.]

Simultaneous studies were performed using a radio tracer instilled into the colon of the dog, as shown in this cartoon here. In response to tegaserod in a dose-dependent manner, there is increased aborad movement of the content into the more distal regions of the colon following the intravenous injection of tegaserod.

[Slide.]

In human studies, it has been demonstrated that tegaserod accelerates gastric emptying. This is achieved

both with intravenous tegaserod, as well as with oral tegaserod, suggesting that there may be a local effect from the absorption of the tegaserod, but also probably a systemic effect, which we believe likely activates those 5-HT_4 receptors on the cholinergic neurons in the myenteric plexus.

Similarly, tegaserod also accelerates small bowel transit. Shown here is a reduction in small bowel transit time relative to control.

[Slide.]

In patients with constipation-predominant irritable bowel syndrome, it has been demonstrated that tegaserod accelerates oral-cecal transit. This is measured radioscintigraphically, and is quantitated as the colonic filling at six hours, a validated endpoint that has been previously demonstrated to correlate very significantly with the oral-cecal transit time.

Notice that tegaserod accelerates or increases the proportion of isotope reaching the colon at six hours, whereas, placebo does not do so.

[Slide.]

In the same studies, it was also demonstrated that tegaserod accelerates colonic transit in the patients who received the tegaserod. You can see the increase in the geometric center, the location of isotope in the colon is

further onward toward the stool following treatment versus baseline.

[Slide.]

In summary, tegaserod mimics the physiological response to serotonin released from the enterochromaffin cells, triggering the peristaltic reflex, and it also promotes motility throughout the gastrointestinal tract in animals and humans.

[Slide.]

Next, I would like to discuss the data on visceral sensitivity effects of tegaserod.

There are several models in small animals to assess visceral sensitivity effects of medications. The two models which are used in the current portfolio are the single afferent fiber recordings following distension of the colon in the experimental animal and a pseudo-affective measurement, which is a robust endpoint, the development of abdominal contractions in response to colorectal distension.

[Slide.]

Let me remind you of the methodology here. Distension apparatus is placed into the colorectum or the lower bowel of the cat, and a single afferent fiber in the dorsal root of S_2, the appropriate dermatome for the segment of the colon, is then assessed.

The firing frequency increases with the increased

pressure of distension of the balloon within the colorectum of the cat. Notice here, it has about 50 mm of mercury, here is a submaximal increase in the firing rate in these visceral afferents. Therefore, this distension stimulus is used as a means to assess the dose-related effects of tegaserod in the subsequent slide.

[Slide.]

Here, you can see that in response to this standardized stimulus of 50 mm of mercury distension, the firing rate in that S_2 afferent is then measured relative to the vehicle control. As you increase the dose of tegaserod, you will see a reduction dose relatedly in the firing rate of those visceral afferents in response to rectal distension.

Importantly, it has been demonstrated that this effect is inhibited by a 5-HT_4 antagonist, suggesting that 5-HT_4 receptors are indeed important in the visceral afferent sensitivity of the lower bowel of the cat.

[Slide.]

In a separate series of experiments looking at a pseudo-affective endpoint, which is demonstrated by the abdominal contractions developed in awake rats following colorectal distension, it has been demonstrated that tegaserod reduces the number of abdominal contractions for five minutes in response to that rectal distension.

[Slide.]

To summarize the sensory effects of tegaserod during colorectal distension, tegaserod reduces visceral afferent firing in cats via stimulation of 5-HT_4 receptors. Tegaserod also inhibits visceral discomfort and pain in rats, as demonstrated by the experiment looking at abdominal contractions, a validated pseudo-affective endpoint for pain.

[Slide.]

In summary, Dr. Hanauer, ladies and gentlemen, serotonin and its 5-HT_4 receptors are involved in motor, secretory, and sensory processes in the gastrointestinal tract.

Tegaserod, a partial 5-HT_4 receptor agonist, stimulates GI motor functions, and inhibits visceral sensitivity.

These data suggest to us that tegaserod may influence the sensory motor dysfunctions and symptoms of constipation-predominant irritable bowel syndrome.

To discuss the safety and efficacy of tegaserod in constipation-predominant irritable bowel syndrome, I would like now to introduce Dr. Martin Lefkowitz for the core presentation.

Efficacy of Tegaserod

Martin P. Lefkowitz, M.D.

DR. LEFKOWITZ: Good morning, members of the Advisory Committee, members of the Reviewing Division, Dr. Hanauer, ladies and gentlemen. Thank you for the opportunity to review with you today the efficacy and safety of tegaserod in irritable bowel syndrome.

I will begin the presentation with a review of the efficacy data followed by a presentation of the safety profile.

[Slide.]

The results that I will present today on efficacy and safety support the following: the totality of the data provides convincing evidence of efficacy for tegaserod at a dose of 12 mg/day on a global relief measure and multiple secondary parameters of efficacy. The drug is safe and well tolerated, and has a favorable benefit-to-risk profile in constipation-predominant irritable bowel syndrome, a disorder with no proven therapeutic options.

[Slide.]

The principal studies that form the core of our clinical program, and which I will review today, are shown here. A large Phase II dose-ranging study, Study 251, was conducted, which evaluated doses of tegaserod ranging from 1 to 24 mg/day of tegaserod in 547 patients drawn from the United States, Europe, and Canada.

The Phase III program consisted of three large

well-controlled, placebo-controlled studies. Study B351 and Study B301 used identical study designs. Patients received placebo 4 mg/day, or 12 mg/day of tegaserod. Study B351 was conducted primarily in the United States, and Study B301 predominantly in Europe.

The third Phase III study, Study B307, used a dose titration design in which patients received either placebo 4 mg/day, or a dose titration regimen of 4 to 12 mg/day. This study enrolled patients, about two-thirds from the United States and one-third from Europe.

In addition, we performed a long-term 12-month safety study, Study 209, which also utilized a dose titration regimen of 4 to 12 mg/day of tegaserod, in 579 patients from Europe, the United States, and Canada.

Throughout the tegaserod clinical program, the drug was dosed twice a day.

[Slide.]

The efficacy presentation will proceed as follows. In the interests of time, I will briefly review the Phase II data and present in more detail the Phase III design and endpoints, Phase III results, and then summarize the data.

[Slide.]

The study design of our Phase II dose-ranging study is shown here. Patients underwent a four-week baseline treatment period during which they received no

placebo medication, and recorded their symptoms in a patient diary.

Those patients eligible for randomization were randomized to placebo or 1 to 24 mg of tegaserod with approximately 100 patients per treatment arm, and received medication for 12 weeks.

[Slide.]

The results for the primacy efficacy variable in Study 251 was the subject global assessment of overall GI symptoms. The results, response rate shown here for placebo in blue, followed by increasing doses of tegaserod.

The placebo response rates were 31 percent with 1 mg/day showing no evidence of efficacy. The 4 to 24 mg/day doses all had higher response rates compared to placebo. In our Phase III program, we chose to study both the 4 and 12 mg/day doses, as the 24 mg/day dose offered no additional efficacy benefit.

[Slide.]

An important consideration for our Phase III program was the choice of the primary outcome measure. At the time that the Phase III studies were initiated, and indeed the case today, there was no consensus in the primary outcome measure in trials of IBS.

This relates both to the assessment variable to be used, that is, the symptom or symptoms to be measured, as

well as the measurement scale. Both an overall measure that integrates the IBS symptoms, as well as a specific symptom measure, particularly abdominal discomfort and pain, have been advocated as primary outcome measures.

Recently, the Rome II Consensus Committee on Treatment Trials has recommended that the primary outcome measure in treatment trials of IBS should be an overall integrative measure. In our Phase III program, we elected to utilize two primary outcome measures - a global relief measure, the Subject Global Assessment of Relief, and a subject global assessment of abdominal discomfort and pain.

Both ordinal and visual analog scales have been used to measure symptoms. Recently, some concerns have been expressed regarding the difficulty of defining a responder on visual analog scales.

[Slide.]

There is agreement on a number of issues regarding designs of trials in IBS, in particular that the primary efficacy variable should be based on a responder approach, that is, a positive response definition should be defined and then responders compared across treatment groups.

In addition, frequency of the primary outcome measures should be done at least once a week due to potential recall problems, and the scales should be self-administered by the patient.

In our Phase III program, our primary outcome measures were measured once a week, and they were performed by the patient in their diary.

[Slide.]

Shown here is the design of the first of our Phase III studies, Study B351. Again, there was a four-week baseline. Patients recorded their symptoms in their paper diary and received on placebo medication.

Those patients eligible for randomization after the four-week baseline were randomized in a 1 to 1 to 1 fashion to 4 mg/day, 12 mg/day, or placebo for 12 weeks during which they continued to record their symptoms in their diaries.

Study B301 had an identical design.

Study B307 used the dose titration regimen in which patients received 4 mg/day placebo or dose titration regimen where at one month non-responders were dose escalated to 12 mg, and responders remained on 4 mg/day.

As was mentioned earlier, once the results of B351 became known, and while B301 and B307 remained blinded, and in agreement with FDA, we modified the primary efficacy variables for Study 301 and 307. The rationale for this modification will be discussed shortly.

[Slide.]

Inclusion criteria were similar for the three

studies. Males and females greater than 18 years of age were included. The lower age limit in Study 351 was 12 years, but very few adolescents were enrolled.

There was a requirement for an evaluation of the colon within the last five years, was dependent on age, consisted of either a colonoscopy, sigmoidoscopy, or barium enema.

As Dr. Wald mentioned, at the time of the Phase III program, the Rome I criteria was used, and as he mentioned, 90 percent of these patients did also fulfill Rome II. Rome I criteria, shown here, patients were required to have continuous or recurrent discomfort or pain in the lower abdomen in the last three months.

In addition, they had to fulfill one of the three, of having the discomfort either relieved by a bowel movement, associated with the change in frequency of the bowel movements, or associated with a change of consistency of the stools.

In addition, to make a diagnosis of constipation-predominant IBS, the patient needed to fulfill two of the following three constipation symptoms at least 25 percent of the time. That is, less than three bowel movements a week, hard or lumpy stools, or straining.

Thus, the diagnosis of IBS and eligibility for the study mirrored clinical practice in that it was based on the

patient history following exclusion of other causes of the symptoms.

[Slide.]

The major exclusion criteria are shown here. Patients who had diarrhea associated with their IBS at least 25 percent of the time were excluded. Patients with other relevant GI conditions, such as inflammatory bowel disease, were excluded.

Concurrent use of narcotics and motility agents were prohibited. Laxative was not allowed except as required as rescue medication, which was defined as at least four days with no bowel movements and associated with abdominal discomfort.

In addition, for patients who are on bulking agents for at least one month prior to the study, they were to continue their bulking agents throughout the 16 weeks of the study.

[Slide.]

Following the four weeks of baseline, for randomizations, patients were required to have had at least a score of 35 mm on a 100-mm visual analog scale. This requirement was to ensure a diagnosis of irritable bowel syndrome. However, there was no upper limit required cutoff for pain severity, such that patients with more severe degrees of pain were allowed to be enrolled.

There was no specific stool consistency mean score required for enrollment, so that again, eligibility for randomization was also largely based on the clinical history of abdominal discomfort and pain and constipation.

An attempt was made to enroll a wide spectrum of patients into the study that would likely receive the drug in clinical practice.

[Slide.]

One of the two primary efficacy variables used in Study B351 was a global relief measure, the Subject Global Assessment of Relief. Patients answered the following questions or responded to the following questions in their paper diary once a week.

Please consider how you felt this past week in regard to your IBS, in particularly your overall well-being, and symptoms of abdominal discomfort, pain, and altered bowel habit.

Compared to the way you usually felt before entering the study, how would you rate your relief symptoms during the past week: completely, considerably, somewhat relieved, unchanged, or worse.

A positive response was defined as at least 50 percent of the week, complete or considerable relief at study endpoint.

[Slide.]

The second primary efficacy variable was the Subject Global Assessment of abdominal discomfort and pain. This utilized a visual analog scale, a 100 mm visual analog scale with variable descriptors.

Patients were instructed to place a vertical line on the scale in response to the question, how much of a problem was your abdominal discomfort or pain over the last week. A positive response here was defined as greater than a 40 percent reduction and at least a 20 mm absolute reduction from baseline at study endpoint.

The stool definition of response was utilized, such that patients who came here into the study at the lower end would still have a significant reduction of their abdominal discomfort of at least 20 mm.

[Slide.]

Statistical methodology for the primary efficacy variables are shown here, study endpoint being defined as the last four available weekly scores. In the great majority of the patients in this study, this corresponded to their last four weekly scores.

Treatment comparisons were by the Mantel-Haenszel test stratified by center, and a multiple comparison procedure was used to ensure that the overall two-sides type 1 error rate was less than an alpha of 0.05.

[Slide.]

In addition, for the primary analysis at study endpoint, specific adjustment criteria were applied. Specifically, if a patient had no post-randomization subject global assessments, they were considered a non-responder. This applied mainly to patients who dropped out of the study very early, within the first week.

In addition, however, patients with less than 28 days of treatment were also considered non-responders for the primary analysis. At the request of FDA to account for the potential confounding influence of laxative intake, use of laxatives was also included as one of the adjustment rules, such that if a patient used laxatives more than five days overall in the study or any use in the last four weeks, that is, at study endpoint, they were also considered a non-responder regardless of how they may have answered their subject global assessments.

[Slide.]

The secondary efficacy assessments are shown here. In addition to the two weekly assessments, the SGA of relief and SGA of abdominal discomfort, the third weekly assessment was a subject global assessment of bowel habits, which used the same visual analog scale and definition of response that you saw earlier.

In addition, four questions are asked of the patients on a daily basis - the intensity of abdominal

discomfort and pain, and the intensity of bloating was rated on a six-point scale from zero being none to 5 being very severe. Days of significant abdominal was defined as days with mild or more pain. In addition, patients recorded the number of bowel movements on a daily basis, and rated their stool consistency on a seven-point scale, from 1 being water to 7 being very hard.

Endpoint for the daily diary measures were the last 28 days in the study. Thus, the bowel habits were evaluated both by the weekly subject global assessment and recording of bowel movements and stool consistency, and abdominal pain was evaluated with the weekly subject global assessment of abdominal pain the daily recording of the intensity of abdominal pain in the diary.

[Slide.]

Patient disposition across the three studies are shown here with approximately 1,100 to 1,160 patients enrolled across the three studies with a discontinuation rate during baseline of 21 to 27 percent. The most common reason for discontinuation during baseline was an inability or unwillingness to fill out the patient diary.

Please note the discontinuation rate of 21 to 27 percent was less than the reported greater than 50 percent discontinuation rates in recent trials of IBS during the baseline.

Study B351 randomized 799 patients; 301, 881 patients; and 307, 845 patients. Seventy-nine to 85 percent of patients completed the study with a corresponding discontinuation rate during the double blind of 15 to 21 percent. The discontinuation rate in the placebo group and the 12 mg/day groups were similar, and approximately 5 percent higher in the 4 mg/day group.

[Slide.]

Patient demographics are shown here for the three studies with a mean age across the studies of 43 to 46. The study was predominantly female with approximately 85 percent of women in the studies. It was largely Caucasian. Importantly, patients had a fairly long duration of IBS of 13 to 14 years. Use of bulking agents ranged from 11 to 18 percent, and patients recorded their fiber intake as being approximately 10 grams a day.

Thus, the three studies generally had similar demographics with the exception of a high Caucasian population here in Study 301, and less use of bulking agents here in 301. In addition, the treatment groups within the individual study were well balanced.

[Slide.]

Baseline demographics for the three studies showed that the visual analog scale and the discomfort/pain and the bowel habit ranged from 60 to 64, corresponding to greater

than moderate pain on the scale.

Days with significant discomfort and pain, and days with significant bloating, again, days with mild or more pain was approximately 85 percent. The number of bowel movements ranged from 5.4 to 6.2 per week. Days without bowel movements were 41 to 46 percent; with hard stools, approximately 30 percent.

The stool consistency score was 4.7, generally corresponding to somewhat hard on the scale. Again, the treatment groups were well balanced within the studies for these baseline characteristics.

[Slide.]

I will now proceed to review the efficacy results as follows. The efficacy results of 351 will be shown, followed by the modification of the primary efficacy variable and the rationale for the modifications in Study 301 and 307, and the results of 301, 307, and a summarization of those results.

[Slide.]

For clarity of presentation, shown here schematically, is how the subject global assessment will be presented. Endpoint, which was the primary analysis, is shown here for patients who complete the study, the last four available SGA scores. Patients who drop out would have their endpoint their last four weeks in the study.

As was mentioned, adjustment rules as shown here, patients without any SGAs, less than 28 days of treatment, or laxative use as defined earlier, would be defined as a non-responder for the endpoint analysis.

However, given that irritable bowel syndrome is a disorder of varying severity that waxes and wanes, it is also important to present the longitudinal time course effect of the drug, so we will present results at month 1, month 2, month 3, as well as the actual weekly responses that patients recorded in their daily diary.

[Slide.]

Shown on this slide are the results for the primary efficacy variables for study 31, the SGA or relief on the left, and the SGA of abdominal discomfort here on the right, placebo in blue, 4 mg in red, and the yellow being 12 mg/day. As you can see, response rates were higher in the tegaserod groups than placebo, but these results were not statistically significant.

We did not, however, that response rates overall, and particularly in the placebo groups of 19 and 22 percent, were lower than what we had seen in Phase II, which were about 30 percent, lower than what has been reported recently in the literature, 40 percent or more, suggesting that the definitions used in 351 established a high hurdle for response and potentially may have made detection of a drug

effect, or was not sensitive to detect a significant drug effect.

[Slide.]

Shown here are the weekly results with the SGA of relief for patients who responded complete or considerable relief on a weekly basis in their daily diary. As you can see, for the 12 mg/day group here in yellow, the percentage of people responding complete or considerable relief was higher than placebo throughout the study with the 4 mg/day group having a more variable response.

[Slide.]

The results for the weekly subject global assessment of abdominal discomfort and pain are shown here, again with the 12 mg group tending to have higher response rates throughout the study, with the more variable response seen for the 4 mg/day group.

[Slide.]

The results for the third weekly subject global assessment, the subject global assessment of bowel habit are shown here, again with similarly higher response rates in the tegaserod group, but not statistically significant, again with a low placebo response rate.

When one looks at the weekly scores, again, there is a tendency for the tegaserod 12 mg/day group to have higher response rates.

[Slide.]

Now, in contrast to the results for the weekly subject global assessments, when one looks at the daily dairy variables in Study 351, one consistently shows a favorable significant effect for the tegaserod groups compared to placebo.

Shown here on the left, this is for abdominal discomfort and pain as recorded in the daily diary. Shown here on the left is the reduction in days of significant pain in the daily diary or reduction in days with at least mild pain at study endpoint, the last 28 days in the study. Thus, patients on tegaserod, the 4 and 12 mg groups, had significant reductions compared to placebo at study endpoint.

Shown on the right are the actual pain scores from which this data is derived and which patients recorded in their diary. As you can see, during the four-week baseline period, patients recorded a score of approximately 3, corresponding to moderate pain.

During the course of the study, beginning at week 1, for the 12 mg/day group, pain scores were significantly lower throughout the course of the study, again with an intermediate result for the 4 mg/day group.

[Slide.]

Results on abdominal bloating are shown here in a

corresponding fashion, again showing an improvement or a reduction in the days of significant bloating shown here for the tegaserod groups compared to placebo, which was significant for the 12 mg/day group.

One looks at the weekly score. Again, the rating of approximately moderate during baseline for the 12 mg group showing an effect here a month 1, and then again towards the end of the study, during month 3.

[Slide.]

The last two questions in the daily diary are related to the recording of bowel movements and stool consistency, bowel movements shown on the left, stool consistency on the right, and one can see an early dose-dependent increase in the number of bowel movements, that then for the two groups were similar and stayed generally different from placebo for the remainder of the study.

The results for stool consistency mirrored these effects with an early dose-dependent decrease, and then similar effects for the two studies, and a persistent effect throughout the remainder of the study.

Of note, this early dose-dependent increase in bowel movements and stool consistency translates into an early transient diarrhea that is seen with the drug and which I will review during the safety profile.

[Slide.]

To summarize Study 351, although response rates were higher for tegaserod compared to placebo, these results were not statistically significant for the primary efficacy variables. Noted, however, with the low placebo response rates suggesting a high hurdle for response.

In contrast, for the daily diary variables, significant treatment differences with tegaserod were seen. Thus, a consistent pattern of improvement for tegaserod across the primary and secondary variables were evident.

It was this combination of findings with higher or trends towards the higher rates for the weekly subject global assessment with significant differences in the daily diary variables that suggested that the response definition used in this study may have been too stringent to allow for the detection of a treatment effect.

Accordingly, we consulted with medical experts in the field, as well as with FDA, and considered an alternative definition of response.

[Slide.]

Compared to the response definition here, used in Study B351, a component was added to the response definition to include patients with a persistent positive relief as defined as patients who had at least somewhat relief as complete considerable or somewhat relief for 100 percent of the time at study endpoint.

It was felt clinically meaningful to include patients who had a persistent positive response, such that the response definition now captured those patients who had a significant magnitude of response from the 50 percent complete or considerable part of the definition, as well as those who had a persistent positive response from the 100 percent at least somewhat part of the definition.

[Slide.]

Further, we performed associations, as shown at this slide, which supported the clinical relevance of this modified definition.

Now, importantly, I need to be very clear here. We are not looking at differences between tegaserod and placebo, but rather what you are looking at is on patients who rated their response as a positive response, how they recorded their other symptoms of irritable bowel syndrome compared to patients who were non-responders to this modified definition of response.

Thus, if one looks at abdominal pain in various ways, these are using the VAS score, visual analog score, days with significant pain, daily pain score, different ways of looking at bloating or different ways of looking at bowel habit, one can see that patients with a positive response had a clinically meaningful and statistically significant response of approximately 35 to 45 percent improvement

compared to patients with non-responders, thus indicating that this modified definition of response appeared to be a clinically relevant definition of response.

Further, since somewhat relief was now incorporated into the response definition, we also evaluated how patients perceived their specific response on the SGA scale.

[Slide.]

Shown here are the responses for the last study week for patients who reported complete, considerable, somewhat, unchanged, or worse. As expected, patients who recorded complete relief had very substantial reductions in their symptoms of approximately 70 percent.

Patients who recorded unchanged or worse had either small decreases or improvements in their symptoms or actual worsening of their symptoms. Patients who recorded somewhat relief perceived somewhat as a positive response with improvement in all their symptoms and compared to the unchanged and worse of approximately 15 to 25 percent improvements on most of these secondary efficacy variables, thus justifying the use of somewhat relief, especially when used as a persistent response as part of the modified response definition.

[Slide.]

Accordingly, for Study 301 and 307, this modified

response definition was adopted as the primary efficacy variable, again 50 percent complete or considerable relief, 100 percent somewhat relief. The subject global assessment of abdominal discomfort or pain was retained as a secondary efficacy variable, thus, in 301 and 307, the SGA of relief was a single primary efficacy variable.

[Slide.]

We then retrospectively analyzed the data in SGA of relief according to this new, modified definition of response, and as expected, all response rates increased, now with the 33 percent placebo response, now also showing a dose response for the tegaserod groups with a 12 percent difference in response rates between tegaserod 12 mg/day and placebo.

[Slide.]

I will now go on to present the results of 301. As a reminder, the study design of 351 and 301 was identical, 351 being conducted primarily in the United States and 301 in Europe.

[Slide.]

Shown here are the results for the primary efficacy variable, the SGA of relief at study endpoint. The results of the tegaserod group showed statistically higher response rates compared to placebo of approximately 9 percent and 8 percent.

[Slide.]

Now, as mentioned previously, laxative use was used as one of the adjustment factors for the primary analysis. This was done to try to control for the confounding influence that laxative may have for the primary analysis.

The criteria used was patients with greater than five days of laxatives or any day within the last 28 days were considered as non-responders. Approximately one-third of the patients in the trials used laxative for one day, one-third for two to four days, and one day for greater than five days.

Laxative use was generally well balanced within the groups. In Study 301 in particular, 27 to 28 percent of patients in the different treatment groups used laxatives. As expected, response rates when laxative adjustment was not applied were all greater than when it was applied here in the primary analysis.

Now, as you can see, response rates in the placebo and 4 mg/day groups were decreased by approximately 4 percent, however, were decreased by 7 percent in the 12 mg/day group. Thus, when not applying the laxative adjustment, the laxative non-adjusted response rate showed a difference for the 4 mg/day group of 10 percent compared to 12 percent in the 12 mg/day group.

For comparative purpose on this slide and the next several slides are presented the results for 351. Again, in 351, laxative use was generally well balanced between the group, actually slightly higher in the placebo group. The laxative adjustment in this study affected all groups to a similar extent.

Note that the difference in the 12 mg/day and the placebo group in Study 351 was 12 percent, the exact difference as seen for the 301 study.

[Slide.]

Shown here are the monthly results in Study 301 of the subject global assessment of relief. At month 1, month 2, and month 3, the results of the 12 mg/day group showed higher response rate that was significantly different from placebo. For the 4 mg/day group, the response rates were significantly different at month 1 and at month 3.

When looking at 351, these higher response rates that were significant in the 12 mg/day group at month 1 and month 3 with higher response rate at all months. The results for Study 301 and 351 were therefore quite consistent.

[Slide.]

Shown on this slide are the weekly responses of the patient on the subject global assessment of relief. These are patients who responded complete, considerable, or

somewhat relief.

Here, at week 1, both groups had higher response rate compared to placebo, that then persisted for the remainder of the study.

Results for 351, shown here, again showed an early response at week 1, that for the 12 mg/day group again persisted throughout the study, with more variable results in the 4 mg/day group.

[Slide.]

I will now go on to present the secondary efficacy variables in Study 301, the subject global assessment of abdominal discomfort and pain shown here at study endpoint and shown here for the weekly results.

At study endpoint, response rates were higher in the tegaserod group and significantly higher for the 12 mg/day group. The weekly results showed that the 12 mg/day group again had consistently higher response rates compared to placebo, the 4 mg/day group again with intermediate results.

[Slide.]

The results for the SGA of bowel habits showed higher response rate in tegaserod groups, but these were not significant. One looks at the weekly values, one again sees higher response rates throughout the study with the tegaserod groups.

[Slide.]

Now, for the daily diary variables, the days of significant pain for tegaserod was reduced compared to placebo although this reduction was not statistically significant. When one looks the pain score, one can see for both groups significant reductions in pain score and lower pain scores throughout the study.

[Slide.]

Significant days of bloating were also reduced at endpoint, but these were not significant with bloating scores also tending to be lower with tegaserod patients compared to placebo.

[Slide.]

The number of bowel movements and stool consistency was similar to what you saw in 351, with an early dose-dependent increase and then a persistence of effect for both groups throughout the study, similar results on stool consistency.

[Slide.]

Thus, in Study 301, there was clear evidence of efficacy, with a significant difference for the primary efficacy variable, the subject global assessment of relief, and consistent positive findings on the secondary efficacy variables.

[Slide.]

Study 307, as mentioned before, used a dose titration regimen. Patients were randomized to 4 mg/day, placebo or dose titration regimen, following one month, patients who were non-responders were dose titrated to 12 mg/day, patients who were responders remained on 4 mg/day. Approximately two-thirds of the patient were dose titrated and one-third remained on 4 mg/day.

For the 4 mg/day group and the placebo groups, patients underwent mock titration. Patient received two tablets twice a day throughout the study.

[Slide.]

Shown here are the results for the subject global assessment of relief, both the adjusted and values not adjusted for laxative, this being the primary analysis, and although the response rates at endpoint were higher for the dose titration groups, here in green, compared to placebo, these results were not significant.

Shown here are the monthly results at month 1, month 2, and month 3. The tegaserod groups at month 1 and month 2, the dose titration groups had higher response rates that were significant from placebo, but at endpoint, the response rates were similar.

To point out a discrepancy in the results here, at month 1, remember that the dose titration group at month 1 were also receiving 4 mg/day. The reason for the

discrepancy in results is not clear.

[Slide.]

Shown on this slide are the weekly results for patients on the SGA of relief, the dose titration group, again, early higher response rates in the dose titration group. If one looks at the placebo group, one can see a significant increase in placebo response rates here at week 4. It then persisted for the remainder of the study with no significant differences seen at study endpoint.

The reason for this increase in placebo response, which occurred at the time of dose titration here at week 4, may have been related to heightened expectation, may have been due to random variability.

[Slide.]

The results for the subject global assessment of abdominal discomfort and pain are shown here, with response rates at study endpoint being lower in the tegaserod groups compare to placebo.

If one looks at the weekly results, one again sees an early effect of the drug here on abdominal pain for the dose titration group. Interesting, at week 4, all response rates were similar, and this time, following dose titration, there was a significant increase in the response rates in the dose titration group with no differences here seen at study endpoint.

[Slide.]

The results of the subject global assessment of bowel habit were similar. At endpoint, response rates were similar with no differences, again, with an early effect seen in the dose titration group that did not persist at study endpoint.

[Slide.]

Shown here are the results for the bowel movements and stool consistency, this time again showing early effect that more tended to persist for the remainder of the study for bowel movements and here for stool consistency.

[Slide.]

In summary, then, for Study 301, favorable effects for tegaserod at months 1 and 2 with mixed results seen at endpoint. The results were not statistically significant for the primary efficacy variable endpoint. These results may have been related to the trial design.

[Slide.]

Now, to put this data across the three studies in perspective, on the next several slides I will present the results in a slide-by-slide presentation.

[Slide.]

Shown here are the results you have seen earlier on an individual study basis for at least somewhat relief, this time showing the results for the 12 mg/day group in 351

and 301, and the dose titration group in 307 compared to placebo.

For 351 and 301, for both studies, despite differences in placebo rates, the difference from placebo for both these groups were similar in the two studies, again showing the consistency of results between the two studies, and as you just saw for the 307 study, these early results did not persist at study endpoint.

[Slide.]

Shown here are the results for complete/considerable relief on the SGA of relief. Again, 351 and 301, consistent results with higher response rates seen in 351 and 301, that interestingly in 307, persisted out to about week 9 and 10, but then not at study endpoint.

[Slide.]

Now, this is a rather busy slide where we show the efficacy variables, both primary and secondary efficacy variables across the studies at study endpoint.

Now, at the SGA of relief in Study 351 is the one efficacy variable shown here, which was a retrospective analysis. All these other efficacy variables were defined prospectively and administered similarly in the two studies.

P-values are shown that were less than 0.05. These pluses indicated that there was a favorable effect for tegaserod, but the results were not less than 0.05, these

negative results indicating that there was a negative effect with tegaserod, again with the results being not significant.

If you first focus on 351 and 301, one can see the consistency of the finding with either statistically significant effects in favor of tegaserod or favorable effects that did not reach statistical significance.

In 351, for the 12 mg/day group, the diary variables achieved significance, whereas, the subject global assessments had trends in favor of tegaserod, which is mentioned for 301, a combination of favorable findings.

In Study 307, although some of the bowel habit criteria had significant results, in general, the results at endpoint presented a mixed picture.

[Slide.]

To gain more insight into the strength of the evidence across the three studies, we performed several additional post-hoc analyses.

[Slide.]

To examine the data for a positive drug effect across the three studies, we performed a pooled analysis. This pooled analysis was done applying the prespecified primary efficacy variables.

Despite differences in study design between Study 307 and Studies 351 and 301, we believe that this pooling of

studies is justified when using the prespecified efficacy variables and in an effort to evaluate whether a drug effect is present looking across the three studies.

Thus, in this analysis in 351, both the original SGA of relief and the SGA of abdominal discomfort was used, and in 301 and 307, the SGA of relief was used. The 4 mg/day groups were pooled across the studies, and the high-dose groups, the 12 mg/day and dose titration groups, pooled across the study.

The analyses were performed at study endpoint, that is, the last four available SGAs, as well as in a longitudinal analysis, using response rates at month 1, month 2, and month 3.

As you can see for the high-dose groups, using either the endpoint analysis or in the longitudinal analyses, strongly significant results in favor of tegaserod were seen, suggesting strongly that a drug effect is seen when integrating the results across the three studies.

[Slide.]

In an analysis that was presented to this advisory committee in November for the approval of another drug in IBS, alosetron, the primary analysis that was used there, using the approach, we looked at the number of months with a positive relief throughout the study.

Thus, patients who had three months of a positive

relief were given a score of 3; two months, a score of 2; one month, a score of 1, and no relief, a score of zero, and then these scores were compared.

Shown here are when this analysis was applied to the tegaserod data. For 351, for the original SGA of relief, the results were not statistically significant due to the multiple testing, however, this is consistent with the high hurdle of the response.

However, when look at 301 and 307, for the high-dose groups, when looking across the three months of the study, one sees a significant effect in favor of tegaserod.

[Slide.]

Now, further, we then simply did not use a responder approach here. We simply compared the percent of weeks in the three studies that patients had at least somewhat relief, were 351, 301, and 307.

As you can see for the high-dose groups in each study, the results had higher rates and were significantly different in favor of tegaserod. Similar significant results are seen for complete considerable relief, although the differences from placebo were less.

[Slide.]

We then also finally looked at the impact of gender on the results, as shown here. As you will recall, 85 percent of the patients enrolled into the study were

women. We did look at baseline differences, and male patients tended to have less constipation than the women in the study.

Shown here are the results at month 1 and then at endpoint, and as expected for the women being the predominant population, the results were consistent with the overall results, showing significant results here at month 1, as well as at endpoint in a dose-dependent fashion.

For the males in the study, at month 1, higher response rates were seen, whereas, at endpoint, the response rates were similar when looking across the three studies.

Given the small number of men in the study, it is difficult to draw any reliable conclusion concerning the evidence of efficacy in men. It should be noted that there was variability, as you see here, over time, as well as between studies in the male population.

[Slide.]

Shown on this slide are the results at study endpoint specifically using the placebo-subtracted approach where we subtract the placebo response rates from the tegaserod response rates, and looked at the therapeutic gain for 351, 301, and 307.

For the male patients in 301, the results were in a negative direction as it was in 301, and in a positive direction here on 307.

For the women in the study, in 351 and 301, the treatment difference for the tegaserod groups were 14.2 and 11.4 percent. Again, given the small numbers of males in the study, and the variability seen over the course of the study, no reliable conclusions can be drawn, but certainly no evidence efficacy here at study endpoint.

[Slide.]

In conclusion then, or in summary, for Study 301, we showed clear evidence of efficacy with significant treatment differences for the SGA of relief, consistent positive findings on the secondary efficacy variables.

For Study 351, although not statistically significant on the prespecified primary efficacy endpoints, the overall results are strongly supportive of efficacy, with daily diary variables showing statistically significant results in favor of tegaserod and positive trends for all SGA assessments.

[Slide.]

When looking at the results across 301 and 351, the B351 results were largely replicated in Study 301, with results being highly consistent between the two studies.

In addition, consistent results were seen between the weekly SGA assessments and the daily diary variables. Tegaserod at a dose of 12 mg had the most consistent effect across the efficacy variables and over time.

In Study 301, favorable effects were seen at month 1 and month 2, with mixed results at endpoint, and no statistically significant results for the primary efficacy variable.

[Slide.]

In addition, the additional analyses including the pooled analysis, number of months with positive relief, or percent weeks with relief, or reinforce the findings of a positive treatment effect.

The overall positive treatment effect was primarily due to the efficacy of women, for men, no evidence of efficacy was seen, possibly due to the small numbers.

Overall, the totality of the data across the multiple efficacy variables, including the global relief measure and secondary symptom variables, provides convincing evidence that tegaserod is effective in the treatment of constipation-predominant IBS.

DR. HANAUER: Thank you, Dr. Lefkowitz.

I am taking a chairman's prerogative and change my mind. Rather than going through the entire presentation by the sponsor, what I would like to do is stop at this point and allow the panel to discuss any questions that they might for Dr. Wald or for Dr. Camilleri or Dr. Lefkowitz, since obviously, a series of studies have had complicated changes in their design and analysis and methods.

Dr. Laine.

DR. LAINE: I just had a couple or three maybe statistical questions.

First of all, can you share with us what, when you first designed these studies, were your baseline assumptions? You know, usually, you say we expect our primary endpoint to be positive and X percent in control and Y percent, and this is the difference that we are looking for.

Can you tell us what those were when you designed your endpoint and perhaps when you changed your endpoint?

DR. LEFKOWITZ: The sizing of the study was sized on 15 percent treatment difference with the placebo response rate being 30 percent. When we changed our endpoint, the studies were all fully enrolled and it really didn't come into consideration, the changing in the endpoint were more related to the --

DR. LAINE: The 15 percent was your?

DR. LEFKOWITZ: The 15 percent was what the studies were sized on, yes.

DR. LAINE: And also in your analysis when you are showing the daily --

DR. HANAUER: Was that 15 or 50?

DR. LEFKOWITZ: 15.

DR. HANAUER: 15.

DR. LAINE: An absolute difference was 15 percent?

DR. LEFKOWITZ: Right, assuming a placebo response rate to 30 percent is what the sizing was based on, yes.

DR. LAINE: Up to 45 basically.

DR. LEFKOWITZ: Correct.

DR. LAINE: Also, when you are presenting the daily diary weekly scores, are you presenting each day, in other words, what I am looking for is how many data points are there, is it like seven days? We have lots of data points there.

DR. LEFKOWITZ: Right, each weekly is based on the mean of the seven days of that week, yes.

DR. LAINE: So there are seven data points for each patient per week?

DR. LEFKOWITZ: Correct.

DR. LAINE: So, we have a lot more data points than, for instance, the overall end of thing.

Finally, the pooled analysis, was that just kind of combining all the numbers together, or was there actually a weighted statistical, you know, quote "meta-analysis" to combine them, or you just kind of add all the numbers together?

DR. LEFKOWITZ: I think it would probably best if perhaps Dr. Fisher would respond to how the pooling was done. He could probably give you a more definitive answer.

DR. FISHER: I am Lloyd Fisher, biostatistician, from the University of Washington, and a paid consultant for Novartis on this project.

I am glad you asked this question because it will come up again in the FDA presentation, and I think it is quite important in this context.

I will first answer the direct question, and then if I might add a few other comments. The studies were adjusted for the comparison basically within study. All the data was not thrown in without regard to doing it within study, which is more in the meta-analytic tradition.

Your task, of course, as well as the Agency and the sponsor's, is to assess whether or not there is substantial evidence of efficacy according to the regulations, and the assessment must integrate in some way, either formally or informally, the entire development program.

I would like to think we have advanced a little beyond the primitive tribe that can only count to two, and I would suggest that pooling in one sense is always done. Let me give you an example to illustrate it in the opposite direction.

If you saw a development program that had six clinical trials, two of which were statistically significantly positive, and the other four went in the other

direction with fairly strong trends, let's say, p-values between 0.05 and 0.10, any rational reviewer would assess the totality of the data, and assuming the trials all had the same size, and so on and so forth, would put it together and you would end up saying no, this is not adequate for approval.

So, I would submit that one way or another, pooling is done formally or informally, and now certainly if we had had three studies, all of which were statistically significantly positive on the primary endpoint, the pooling wouldn't have been presented, but part of the reason it is not presented is because everybody knows what it would show, I mean so there was no need for it.

But that doesn't mean to me it isn't there in the back of your mind. The pooling as done here has statistically correct properties. You will notice that your document on page 66, and the slide that Dr. Lefkowitz presented, used the prespecified primary endpoints for each of the studies, in other words, the p-values you saw did not use the new retrospective endpoint which undoubtedly is biased in a favorable direction, because, after all, they looked at their database to see what went wrong and come up with a good endpoint.

But the numbers you saw were not biased, they used the endpoint. Clearly, if you are going to do a pooling or

meta-analytic type approach, you should use all the data, you shouldn't just select positive studies or negative studies, but in general, that is compelling reasons to exclude things, you want to use all the data.

In the data you saw, the p-value was 0.0028, and if you used a longitudinal approach, which of course has more statistical power, but was not used by the sponsor, the p-values were, as you can see for the high dose, 0.0001. I personally find this fairly compelling evidence, you may not, and we will hear your discussions shortly.

You are also, of course, perfectly free, and it may be that you personally, when you try to integrate a clinical development program, don't like to go to an analytic approach, but like to do it informally, but one way or another, it always has to be done.

The Agency presents a number of possible criticisms on pages 10 to 12 of their review. I think there are good responses to each point. I know that Dr. Castillo is going to speak about some of these, and so, although I would be happy to talk to anybody on the panel about any of this right now, it might be better to wait until the FDA has had their say.

DR. HANAUER: I agree, but did that answer your question?

DR. LAINE: Kind of. Did you test for statistical

heterogeneity? In three studies it looked similar, but in combining them?

DR. FISHER: The p-value for an interaction or heterogeneity was 0.58, so there is really no evidence.

DR. LAINE: So, the answer was there was a formal analysis, and not just adding up the numbers together.

DR. FISHER: Correct.

DR. HANAUER: Dr. Wolfe.

DR. WOLFE: You have properly broken down the data into responses with males and females. There is also large differences between Americans and non-Americans.

Have you broken those data down to look at response, have you broken down the analysis to look at response at Americans versus those in Europe and other countries?

DR. FISHER: I am not the best person to speak to that.

DR. LEFKOWITZ: We looked at several things, first, whether, as far as we can determine, whether the disorder seemed to be different between Europe and the U.S., and we did that based on looking at the demographics and the baseline variables, which I can show you in Slide QA65 to begin with.

[Slide.]

As you can see here, we looked at 351, which was

97 percent U.S., 100 percent North America, and then we broke out the European patients in 301. As you can see demographically, with a high Caucasian rate and a low use of bulking agents, but other than that, very similar demographics.

[Slide.]

On the next slide, QA66, when we looked at the baseline variables, again, very similar across the studies. We did break out the results in 301, and we looked at response rates specifically on QA75 in this study by region.

Shown here are the results overall. Shown here are the results in Europe. Again, U.S. did not contribute a whole lot to the study, also, in the study, specifically with Turkey and South Africa.

As you can see, response rates in Europe obviously were similar overall. Response rates in U.S. also showed effects in favor of tegaserod. Actually, in Turkey, we really had this very high placebo response rate. Demographics and baseline characteristics, in fact, Turkey were different than what I just showed you in Europe and the U.S. in several things, and in South Africa, sort of mixed results. Again, very small numbers here in South Africa.

So, as best we can determine -- what we also did, for example, the associations that I showed you earlier, the patients, the scale difference, how they responded to the

scale, the associations in 351 and 301, in Europe versus the U.S., was also very similar, so they seemed to understand the scale similarly, as well.

DR. HANAUER: Go ahead.

DR. HOUN: I am wondering if Dr. O'Neill could comment on the meta-analytic tradition at FDA and looking at the total database versus pooled analysis.

DR. O'NEILL: Well, before that, I have a couple questions just in terms of -- just replay for me how these trials were powered, sample size-wise, originally, because as I understand it, a couple things happened. One, the size were up-sized, and the trials were up-sized dramatically. The endpoint was restated.

Was the up-sizing done on the basis of the original or the restated endpoint? And how were these trials monitored? I would suspect that monitoring multinational, multi-regional studies might be kind of difficult. How was that done?

DR. LEFKOWITZ: Let me try to remember the first point being the general sizing, increase in sample size. If you go to Slide 012, the original size was originally based on one primary efficacy variable. An amendment was made to the protocol, which added the second primary efficacy variable, the subject global assessment of relief.

At the time that these studies were initiated,

there was a lack of consensus both in the medical community, as well as at the Agency, whether the primary variable should be pain or should be an overall relief measure.

Accordingly, we then added the second primary efficacy variable, and because of the multiple testing, the sample size was then increased accordingly to maintain the same power of the study.

DR. O'NEILL: That was added prior to or during the trial?

DR. LEFKOWITZ: Prior to the beginning of the study, prior to the start of the study, yes.

What then happened here, these were the actual enrollment into the study. Please note, however, that Study 301 and 307 were fully enrolled, before 351 were completed. So, there was no -- the over-enrollment was clearly not due to looking for any -- driven by anything other than the fact that we had over-enrollment into the baseline phase, and we allowed all patients who signed informed consent to be randomized.

So, this is how the enrollment went to the study.

DR. O'NEILL: So, there was over-enrollment.

DR. LEFKOWITZ: There was over-enrollment, yes, and again the point being the enrollment in both 301 and 307, they were fully enrolled before 351 ever completed.

DR. O'NEILL: And originally, you said this was

powered for an absolute 15 percent difference in response rates or something along those lines?

DR. LEFKOWITZ: That was the size that we powered the studies for, yes.

DR. O'NEILL: In absolute difference in response rates based upon the original?

DR. LEFKOWITZ: Correct, based on an assumption of the 30 percent placebo response we saw --

DR. O'NEILL: Okay. I am just curious. What was the effect size in the meta-analysis?

DR. LEFKOWITZ: The effect size in the meta-analysis across the three studies was 6 to 7 percent.

DR. O'NEILL: What?

DR. LEFKOWITZ: Six to 7 percent.

DR. O'NEILL: Six to 7 percent?

DR. LEFKOWITZ: Right.

DR. O'NEILL: About half of what you anticipated. I mean these are big studies, 800, 900 subjects for a trial, that's big-time studies.

DR. LEFKOWITZ: Yes. I think, however, what we were doing in the pooled analysis was trying to integrate the results of the three studies.

DR. O'NEILL: I understand.

DR. LEFKOWITZ: Including Study 307, which clearly had a different result from the other two studies at study

endpoint, so we wanted to see, even taking that study into account, whether we would see a treatment effect.

Certainly if the issue is magnitude of effect, I understand that certainly an important issue in the benefit-risk profile of the study. I would submit, however, that the intent to treat analysis that was used generally, and used in the study, is necessarily a conservative analysis that is there to look for evidence of efficacy.

I think if you are really wanting to look at magnitude effect, I think the real question to answer is what is the magnitude of effect that patients can be expected to get the drug in clinical practice, that is, patients who will remain on the drug, patients who may or may not use laxatives, and if you look in Study 351 and 301, either on a monthly basis, at month 1, month 2, and month 3, or at study endpoint, if you look at QA12, I think consistently you see a treatment difference of about 10 to 15 percent.

Again, it was not our intent in these studies to highly select a population, we enrolled a wide spectrum of patients into the study, and I think these results shown here adjusted, not laxative adjusted in 351, adjusted, not laxative adjusted in 301, I think in clinical practice, the type of benefit is this 10 to 15 percent, and if you go on to QA13, which is the monthly results, and again looking

across 351 and 301 monthly results except for month 2, one generally sees 10 to 15 percent response rate, and again, slightly higher if one is only looking at a female population.

We do feel that a 10 to 15 percent treatment difference in clinical practice, in a difficult disease to treat, for which there is no good alternative therapy, and which I hope you will agree is a safe drug, is a clinical meaningful benefit for the patients.

DR. HANAUER: Do you have a one-week response rate versus placebo?

DR. LEFKOWITZ: You mean at week 1?

DR. HANAUER: At week 1, because it seems that the overall long-term kind of peters out a bit compared to the early response, and I am wondering if this is a drug that works early because of its laxative effect on the primary endpoint.

DR. LEFKOWITZ: The results at week 1 in particular are generally a bit higher, and are about roughly 13 to 15 percent at week 1, but then they do tend to stabilize and remain persistent throughout the 12 weeks. The last four weeks are no different than, for example, week 3 to 6 or whatever.

So, I think that it is true that at week 1, you see more of an effect, but then it does stay persistent

throughout the study.

DR. O'NEILL: I still want to get back to the meta-analysis, Dr. Houn had asked me to address that.

So, these trials were only looked at once with regard to relative treatment effect, and that was at the completion of the trial, and the up-sizing of the trial had nothing to do with monitoring the trial in between.

DR. LEFKOWITZ: That is absolutely correct. We did no exploratory analyses of the data, other analyses of the data, yes.

DR. O'NEILL: Generally, with regard to the meta-analysis issue, I think it is appropriate to look at all of the data collectively, but I think there is a sequence to how the data came about, and I think that also needs to be thought about.

The first study might be considered, I guess, the study that define the endpoints for the further studies. 351 could be viewed as an exploratory study even though it was one of the identical design trials, but that was used to design the primary endpoints, I believe, for the other studies.

So, I think in that sense there is a sequence to this, and meta-analyses, if you are going to do a meta-analyses, you should really prespecify it in advance with all the conditions in terms of how it might be used for an

inferential purpose. That is not to say that isn't useful to get effect sizes in other things. That is why I asked you what the overall effect size was, which was around 6 to 7 percent.

But the other studies also, the individual studies seemed to be, on their face, you gave them the best shot in terms of the primary endpoint, powering them, and when you put under studies that are not significant in with the others, you have to ask was it but for power I would have found an effect.

I think that is what the issue is here. The dose titration study, I believe in some ways might have been your optimal shot, because you optimized in the titration arm the ability to maximize the responder, and that study seems to be a little different in design even though that is being combined in the other two studies.

So, I think there are some other questions with regard to dissecting the components of the meta-analysis that would like to talk about perhaps later on.

DR. LEFKOWITZ: If I could just make two points before letting Dr. Fisher respond. Again, the pooled analysis is just one of several analyses we would ask the committee to consider, and we are asking the committee to consider the totality of evidence across the three studies.

You know, in terms of the dose titration design,

it again was our intent to see if we could, in that study, see if predominants on 4 mg, we could optimize their response. In retrospect, perhaps it wasn't the best design in a study, such as irritable bowel syndrome, where you have varying degrees of severity, a disease that waxes and wanes, so I am not -- again, in retrospect, I am not sure that in this particular disorder that would be the optimal design, and I would submit that 351 and 301 are the studies that more show the efficacy of the product.

Dr. Fisher.

DR. FISHER: The primary meta-analysis, just to reiterate, in fact, both Gary Koch and I came in and sort of gave them the same advice, which was go with the original endpoints, which, of course, works against the -- you know that slide we had up there, the righthand one, used all the data, but nevertheless, for the 351, it used the original endpoints.

So, number one, that works against the studies, and it is also conservative in the following sense. I imagine later the clinicians will discuss what went on in 307, but one of the striking things about it is this particular sponsor decided to use the last four weeks, but actually, they looked quite good for two months, and then due to chance, due to design, due to whatever, things sort of fall part in the last four weeks, but that was also

included in the meta-analysis.

So, in that sense, what is done is conservative. It is true there is sort of a mixture of apples and oranges because you have some studies with 12 mg and some with 4 to 12, and I suggested the meta-analysis for primary evidence of efficacy.

Once you bring up efficacy, if you are talking about the best way to estimate the effect you get with a particular dosing regimen or something, then, I think there are much subtler issues, and then a lot of the things actually that have been raised in the FDA document start to come into play, but the first task obviously is decide is there substantial evidence of efficacy, because if the answer to that is no, then, we can just all go home, we can ignore safety, too, for that matter.

So, we did this to look at the overall program in a fairly conservative way, but trying to integrate all the data for primary evidence of efficacy.

DR. LAINE: Just real quickly, you did say this was a post-hoc analysis, this meta-analysis was post hoc, is that right, it was not prespecified?

DR. FISHER: Yes, we were trying to integrate the data across the three studies.

DR. HANAUER: Dr. Richter.

DR. RICHTER: Steve and Martin, I want to get back

to the drug is being proposed for people with constipation-predominant IBS, and what I am a little perplexed about is your inclusion criteria which has the Rome aspects to it, which again is based on a consensus of opinion rather than necessarily strong scientific data.

I was involved in Rome I, and somewhat involved in Rome II, but there you talk about bowel movements on an average of less than three a week, and then I am kind of surprised that when you get over to the demographics of your actual patient population, they don't really fit in, that is, their average number of bowel movements a week is five or more, and they tend to have not that firm of a stool.

I am perplexed there, and also the secondary issue I have is if you were to really stay with the Rome criteria of more severe constipation, have you had the opportunity to look at that subset, and those with more severe constipation, which you anticipate would have more pain, do they get a better response with your drug.

DR. LEFKOWITZ: I must admit we were initially I guess bit perplexed with the number of bowel movements per week, as well, which were about five to six. If you look at median bowel movements, there are perhaps four and a half to five, still perhaps higher than what you might expect.

However, you know, Rome criteria, which is 25 percent of the time less than three bowel movements a week,

and again number of bowel movements is not the only or perhaps the best measure of constipation.

In addition, patients could fulfill the other two of the three Rome criteria and get in. However, when we did look and if you go to QA77, what patients actually did over the four weeks -- and if I could have QA77.

[Slide.]

This is when we looked over their four-week baseline, and you can see that fully two-thirds of the patients either fulfilled the less than three bowel movements a week 25 percent of the time, or the hard or very hard stool, so one or the other was fulfilled almost two-thirds of the time.

There was also patients who did seem to have a diarrhea component of disease or perhaps an alternating component of the disease, and again our intent by not having strict stool consistency criteria, for example, would be to try to enroll patients who would likely get the drug in clinical practice, which is generally based on clinical history.

So, we do think that it was a generally constipation-predominant population with clearly some alternators in the disease. We actually did not look at people in terms of response rates who had a more severe constipation, we looked at people who had more of a

diarrheal component, either based on this group right here or based on a stool consistency less than 3.5. Those people tended to do worse or did not have differences from placebo, whereas, people who either had stool consistency between so-called normal, between 3.5 and 4.5 or more than 4.5, both those groups of patients had response rates higher than placebo that were similar between them.

DR. RICHTER: Let me clarify the point then. Then, for the ones with the more severe forms of constipation, when you did a post-hoc look at it, they seemed to respond as well as the ones with the milder form?

DR. LEFKOWITZ: Yes. We looked at it, it was based on stool consistency, we broke it with less than 3.5, 3.4 to 4.5, and then 4.5 being higher.

If you give me one second, I will show you the results. If you go to ESG125.

[Slide.]

Shown here, as you can see, about half the patients had stool consistency greater than 4.5. This accounted for 11 percent of the population. Again, these are pooled results across the three studies, so no treatment effect of less than 3.5, and a fairly similar treatment effect from looking across these patients here, intermediate stool consistency, and those with higher stool consistency.

DR. HANAUER: So, the more constipated, the less

of an effect?

DR. LEFKOWITZ: No, no, I am sorry, this is people with less constipation, less than 3.5 being the loose end of the scale, which is shown down here, 4.0 higher, 5.0 being somewhat hard. So, 3.5, 4.5 in the middle, 3.5 being less constipated.

DR. RICHTER: This is stool consistency, right?

DR. LEFKOWITZ: This is stool consistency, yes.

DR. RICHTER: Did you look at it for stool number?

DR. LEFKOWITZ: We only looked it for greater than three bowel movements a week, and those patients tended to do less well than the rest of the population. We didn't look at people on the lower end in terms of response rates.

DR. HANAUER: Constipation-predominant, why did you not look at the constipated patients?

DR. LEFKOWITZ: Well, I guess you are defining constipation strictly on bowel movements. I guess we felt that that entire population fulfilled constipation-predominant IBS in terms of the diagnostic criteria.

DR. HANAUER: I am sure you had a group of experts telling you that having constipation up to 25 percent of the time was constipation-predominant.

Maybe Dr. Wald, who we have talked about constipation before, is this really the group of patients that were enrolled in the study who clinicians considered

constipation-predominant?

DR. WALD: Well, I think that, strictly speaking, if you had constipation greater than 25 percent, but you had diarrhea 25 percent of the time or greater, you would be mixed. If you had constipation greater than 25 percent, but in all other respects, in those non-constipated intervals, you had what we would call normal bowel habits, we would, yes, call that constipation-predominant irritable bowel.

DR. HANAUER: Is this group of patients the ones in your practice who you consider constipation-predominant?

DR. WALD: Yes, I think that would be a fair statement. There are some that have occasional diarrhea, but that doesn't form the essence of their being, so to speak. As I say, it's a predominant, it's a strictly speaking definitional issue.

The issue with constipation and irritable bowel is I think the frequency of the deranged bowel habit versus what we would call the normal bowel habit, in the absence of diarrhea or significant diarrhea would then put them into this, plus, of course, the finding of pain, which distinguishes them basically from pure constipation or pure diarrhea.

DR. HANAUER: Dr. Wison.

DR. WISON: I just wanted to again clarify the definition of constipation because I think that from a

patient-driven diagnosis, the straining and consistency seems to predominate at least from some of the studies that we have reviewed more recently. Therefore, the number is one of the problems that I think physicians have always face that doesn't necessarily define constipation, at least that is my understanding.

So, from a patient-driven standpoint in studies in the elderly, and so forth, the character of the stool and the passage of the stool is more critical. I don't know if that is a fair assessment to the experts there.

DR. WALD: I am sorry. The microphone must be malfunctioning because I didn't catch your remarks at all except I could see you were looking at me, and I had a feeling you were talking to me.

DR. WISON: I was just going to say that the point that I thought Rome II, and so forth, was trying to focus on was the patient-driven definition of constipation as straining at stool and character of stool less than the number of stools. So, that was one of the points that was being raised, you know, in a clinical arena with our evaluation of constipation-predominant symptomatology.

DR. WALD: I think that is absolutely correct, Dr. Wison. The concept of frequency alone, if you use frequency alone as less than two, very few patients would be constipated, forget the irritable bowel issue. So, it

becomes what they call a satisfactory bowel movement or one that is truly a complete bowel movement.

So, frequency is one part of that, but it would be the frequency of a complete or satisfactory bowel movement.

DR. HANAUER: Dr. Surawicz.

DR. SURAWICZ: I have three questions, but I will ask them one at a time.

What is your definition of a laxative in the group that you said laxative or you excluded that?

DR. LEFKOWITZ: If you are asking what particular laxative, anything --

DR. SURAWICZ: No, what I want to know is whether that includes fiber and bulk, are you considering that a laxative?

DR. LEFKOWITZ: No, bulking agents were not used as part of the adjustment criteria. If people were on bulking agents, they continued bulking agents. That was not used as part of the adjustment for laxatives.

DR. SURAWICZ: Okay. You say that the low placebo rate was a high hurdle, and I know you tried to explain that later, but to me it seems like a low placebo rate would make it easier to show efficacy.

DR. LEFKOWITZ: I think whether or not a low placebo response helps to show efficacy really depends on he disorder and the variable being involved. I don't think it

is necessarily true that low placebo response -- I mean if you take it to the extent, I don't think complete relief in irritable bowel, at least where we are right now, is a reasonable criteria.

So, clearly, if we went to complete relief, you wouldn't expect it. There is examples in, for example, hypertension, if your criteria was a blood pressure of 80, you know, again, that is a stringent, so I think it really depends on the particular variable or the particular disorder, whether low placebo response rates will make it easier or harder.

I think the 30 percent that we saw when we changed is very much in line with I think more the recent trials and where one can detect treatment differences, not the 50 or 60 percent perhaps that had been reported in some earlier trials, but also not the very stringent, and that was what our data supported, and that is what we believe.

DR. SURAWICZ: But why did you call the low placebo rate a high hurdle, because you said that several times?

DR. LEFKOWITZ: I was only meaning to refer complete, considerable relief being a difficult -- it is only in a sense complete is higher than considerable.

DR. HANAUER: The endpoint was the hurdle, not the placebo rate.

DR. LEFKOWITZ: Yes. The endpoint was the hurdle, that is correct. That is correct.

DR. HAUPTMAN: Lawrence Hauptman, Novartis.

Let me address that point about the low placebo rate possibly making it harder to find the difference. We hypothesized 30 percent versus 45. The 15 percent that we hypothesized was in part due to what we thought we would need to get in placebo, the 30 percent.

The fact that the placebo rate turned out to be lower, say, 20 percent, had the difference been the same, had it still been 15 percent, you are right, it would have been easier to show a difference, but that may not be the case. The lower placebo rate in the face of what we thought we would expect might mean we weren't measuring what we thought we were measuring, and then the 15 percent that we thought we would see actually wouldn't be relevant.

Under that context of a stringent high hurdle, the difference in those terms could have been some number less than 15 percent, we have no idea. If it had been, say, 7, 8, or 9 percent, those same power calculations would have led to a smaller power, would have been harder to do it.

Just take a ridiculous example where it is virtually impossible, you set it so high that not only does the placebo rate come down to virtually zero, but then any treatment effect would come down to virtually zero, the

same, and it would be almost impossible to find the treatment difference. That is the context in which we expressed that.

DR. SURAWICZ: May I ask one last question about the placebo rate, and that is why does the placebo rate improve over time, and does that have any influence on your drug efficacy over time? Are the same factors possibly involved?

DR. LEFKOWITZ: It is hard for me to explain why the placebo rate increases over time. It was more so I think in 307 than the other studies, but the difference, as Dr. Hanauer said, well, at week 1, our difference was the greatest of any week. When you go beyond week 1, the difference from placebo stays fairly constant over the course of the study.

DR. HANAUER: Dr. Smith, did you have a question?

DR. SMITH: Yes, I do.

I would like to follow up on the placebo concept again. In any clinical trial dealing with an entity that has a psychosocial component, you anticipate a strong placebo response that can last variably three to six months.

But what I have a concern about is that the planners -- or have a question about -- is the people who planned and designed the study, knowing that there is a psychosocial overlay to irritable bowel syndrome, didn't

have a four-week washout period or pre-study period where all placebo responders are segregated out, and wouldn't that have made it easier to detect a true clinical difference, because in my second, if you want to use the word concern, is the statistical difference that you can document on slides versus the clinical difference.

DR. LEFKOWITZ: The issue of whether having a placebo run-in, then eliminating placebo responders was certainly one that we seriously considered in the design of the trial.

It has been almost the uniform recommendation of those who give recommendations, such as Rome II, not to have a placebo run-in in the trial, for several reasons, one being that it may actually select out non-responders to the drug; two, being it may not be real world in a sense because the psychosomatic part of it is the real world, and therefore it should be included as part of the trial.

I actually know of no recent studies that have done that. We did seriously consider it, but based on the consensus in the field, which is the recommendation not to have a placebo run-in, eliminate placebo responders.

DR. WOLFE: My question or comment was almost exactly the same, that psychosocial-related diseases do have these kind of responses. If you look at pain syndromes in general, placebo response rates seem to increase with time,

especially when you are giving the people the perception of getting more drug possibly.

But getting back to the design, you are right, a run-in can cause the problem of bias, but did you look at the patients four weeks after the drug was stopped and see what happened to these people, the people on drug, was their sense of well-being that much less than those who were on placebo?

The other thing is did you ever consider a cross-over design in which people could really then determine the effect and use themselves as their own control?

DR. LEFKOWITZ: Again, I agree. You know, as you said, heightened expectations may certainly have been more of a factor in Study 307 as you mentioned. In terms of a cross-over design, I think that is potentially fraught with some difficulties in terms of carryover effects and other things in this disorder.

I am sorry -- oh, in terms of the month withdrawal, while we continued to collect safety information 30 days after the study, we did not do a formal withdrawal. I think unless one really does a double-blind type of withdrawal, I think there is a very likely expectation that everybody after the study -- I think it would be hard to tease out what is going on once the study ends in an open-label fashion. We did not do a four-week formal withdrawal

period.

DR. HANAUER: I am going to give Dr. Laine the last question unless Dr. Ferry wants one, and then we are going to take a 15-minute. We will do it Dr. Laine and then Dr. Ferry, and then a break.

DR. LAINE: I noticed in your indications that you were seeking, it made no reference to gender. Clearly, you have a relatively small number of men. There are gender differences in response to therapy in general, in this disease perhaps, and you showed no even suggestion I guess that made that benefit men.

I was wondering why you were going for men and women, rather than just women, based on your data.

DR. HANAUER: I would like to come back to that because that is a summary type question rather than a methodology question.

DR. LEFKOWITZ: If I could just point out in response to that, if you do look over the study, the results are variable. You do see some effect, however, endpoint you don't. It is a variable response. I fully agree with the small numbers that we clearly have not demonstrated evidence of efficacy, and we would look to the committee for their recommendations.

DR. HANAUER: Dr. Ferry.

DR. FERRY: My question was really sort of a

clarification. You used the global assessment, and that sort of is the standard to try to come up with an answer for irritable bowel syndrome, but I mean a global assessment includes sort of a general category of well-being, it includes abdominal pain and discomfort and altered bowel habits.

If I am looking at the data correctly, the pain and discomfort aspect of it, looked at separately, wasn't that significantly improved across the three studies.

So, my real question is, I guess, are we looking at a drug that is basically altering bowel habits as its real efficacy or does it have something else on well-being other than bowel habits either centrally, and it seems like it is mostly altering bowel habits. Is that --

DR. LEFKOWITZ: I think, number one, certainly in a disorder like irritable bowel, it is very difficult to tease out the effects on bowel habits compared to pain, whereas, the primary, when we modified it with the overall integrative assessment.

However, if we can show QA41 --

[Slide.]

I do think we have shown a significant effect on pain.

[Slide.]

Shown here are pain scores on Study 301, baseline,

[Slide.]

DR. HANAUER: Now, the data that we are seeing here at 12 weeks, is that of the percentage of patients that are still in the study, or is this carried over, this data?

DR. LEFKOWITZ: No, these are patients who are still in the study, throughout the study.

DR. HANAUER: So, we don't have an overall proportion?

DR. LEFKOWITZ: No. We do have it study endpoint, for example, days with significant pain reduction, which was significant in 351 and in a positive direction for 301. If you just look at pain scores at endpoint, those are highly significant if you just look at pain scores at endpoint, but these results are shown for patients as they remained in the study.

If you go to QA43 --

[Slide.]

What we did here was a correlation between the change in abdominal pain score, reduction in pain compared to the change in number of bowel movements. As you can see, there is a lot of scatter here with fairly weak correlation between this rough measure of number of bowel movements and visual analog of pain.

I think, however, it is difficult to separate out the two.

DR. HANAUER: Okay. Here is the rest of the agenda. We are going to take a 15-minute break and reconvene at 10:45, and then we are going to complete your adverse events and summary, and then try to get the FDA in before lunch.

[Break.]

DR. HANAUER: Dr. Lefkowitz, do you want to introduce your next speaker?

DR. LEFKOWITZ: Prior to proceeding with the safety overview of tegaserod, the Agency has asked us to address two specific issues, finding of in the preclinical studies of carcinogenicity in mice and also an initial imbalance in the reporting of ovarian cysts.

Dr. Bentley will present the results of the preclinical studies.

Preclinical Findings

Philip Bentley, Ph.D.

DR. BENTLEY: Dr. Hanauer, members of the committee, ladies and gentlemen: I would like to briefly review the findings from the long-term toxicity studies.

[Slide.]

We performed carcinogenicity studies in rats and in mice. In the rat study, there was no indication of an increased tumor incidence in any organ. In the mouse study, there was a treatment-related increase in the incidence of

tumors in one organ, tumors in one site.

[Slide.]

If you look in details at the study, you can see that the incidence, in the small intestine, the incidence of adenocarcinomas was increase in the high-dose animals only, and that this increased incidence was associated with a mucosal hyperplasia which persisted during the treatment period.

I would like to draw your attention to the doses used in this study. The 600 mg/kg dose was exceptionally high. The animals had a 70-fold higher systemic exposure to the drug than is seen in the clinic, or based on a body surface area, a 240-fold excess of the drug.

In terms of current guidelines, actually, the 200 mg/kg dose, the middle dose, is more representative of the type of maximum dose used with 34 times the human exposure.

[Slide.]

We concluded from this study that treatment with high doses, treatment of mice with high doses of tegaserod caused an increased incidence of small intestinal tumors, which was associated by a sustained hyperplasia in the intestinal mucosa.

However, it is important to note that the high dose in these animals really exceeded what would be classed as the maximum tolerated dose for the animals when defined

in terms of a decrease in body weight gain. This is shown on the next slide.

[Slide.]

This shows the weight gain of the animals throughout the two-year course of the study. The top lines are the two control groups and the low-dose group. The white line is the mid-dose group, and the blue line on the bottom shows the body weight curve for the high-dose group.

It is apparent that the animals had a severe reduction in body weight gain. In fact, the body weight gain was only 33 percent that of the control animals.

The white line, the mid-dose group, is around 20 percent, which again more clearly fulfills the criteria for a maximum tolerated dose.

[Slide.]

So, the tumors were only seen in a single organ at very, very high doses, which clearly exceeded the maximum tolerated dose.

It is important to note that we have examined the mutagenicity of tegaserod in a variety of in vitro and in vivo tests. Particularly important were the different endpoints used - mutagenicity, chromosomal endpoints, and test for chromosomal damage in the mouse strain which was used for the carcinogenicity study.

All these mutagenicity tests were negative,

indicating that there is no mutagenic potential of the compound, which also indicates that the tumors must have arisen through non-genotoxic or epigenetic mechanisms.

The importance of that is that if the mechanism is non-genotoxic, it generally has a clear dose dependence with clear no-effect levels. So, you can clearly say at the doses it did not occur, there is a biological reason for it.

[Slide.]

The main driving force behind the tumors in this case is an induction of cell proliferation at the high doses by treatment of tegaserod. This slide shows the results of a 13-week study in which the cell proliferation in the intestine was examined by the incorporation of bromodeoxyuridine, and histopathologically, we examined for hyperplasia.

It is clear that there was at these doses an increased incidence of cell proliferation within the intestine associated with hyperplasia, but once treatment is discontinued, these effects reverse and are totally reversible, and after a four-week recovery period, that is, a four-week period with no treatment after the 13-week treatment period, there were no signs of hyperplasia or increased cell proliferation within the intestine.

[Slide.]

The conclusion then is that short-term treatment

of mice with high doses of tegaserod induces a reversible hyperplasia within the small intestine. A longer term treatment, as witnessed by the carcinogenicity studies, results in a sustained hyperplasia, particularly at the high doses, and this hyperplasia can then result in carcinogenicity.

[Slide.]

If we look at the processes involved, we have a sort of scheme here, going through cell division to the induction of hyperplasia, to the induction of tumors, and it is important to note that for each of these steps here, there are clear no-effect levels, so there are no-effect levels for the compound which don't induce cell division, there is a no-effect level then between the induction of cell division and hyperplasia, and you can have doses of the compound which induce hyperplasia, but do not induce sustained hyperplasia and do not induce tumors.

If we look at tegaserod, the no-effect level for the induction of sustained hyperplasia is 200 mg/kg. The no-effect level for the induction of hyperplasia is around 150 mg/kg, although this is not shown on that slide.

So, if we look at these doses which are involved then, the no-effect level again would be 200 mg/kg, we considered the doses involved. The high dose is 600 mg/kg was equivalent to 240-fold the human dose on the body

surface area basis. That is 70-fold the expected human exposure, but probably more important for a case like this, where we are looking at the effect directly in the intestine or the anticipated intestinal concentrations, in this case, we estimate that the exposure of these animals in the intestine itself, at the site of action, was 570-fold that estimated in the human situation.

At the no-effect level, we had doses of around 80-fold the human dose on a body surface area basis, resulting in a 34-fold excess of exposure, and local concentrations around 190-fold higher than expected.

I would like to point out again that this dose actually more correctly fulfills the criteria for a maximum tolerated dose than the higher dose, which clearly exceeded these criteria.

[Slide.]

Our conclusion therefore is that tegaserod therapy poses no carcinogenic risk for patients. This is based on the fact that the compound is not mutagenic, that the tumor incidences were only seen at a single site, which is again an indication there is not a genotoxic mechanism involved.

The mechanism involved is an induction is an induction of intestinal mucosa hyperplasia. No such hyperplasia was seen in studies of one-year duration in dogs or in the rat toxicity studies even though the exposure