levels of these animals were as high as those of the mice, so it suggests it was a species sensitivity in this case.

The initial effects in the mouse were reversible. There were no carcinogenic effects in the rat, and above all, the tumors were only seen at very high doses, and from the no-effect level for the tumors, there are very high safety margins.

DR. HANAUER: Does anyone on the committee have questions related to this? Dr. Wolfe.

DR. WOLFE: Quick question. Any work in isolated cell lines, any new mechanism of action proposed why you may see some effects in mice?

DR. BENTLEY: We haven't worked in isolated cell lines, no.

DR. HANAUER: And it is only small bowel mucosa, have you looked at colonic or gastric mucosa?

DR. BENTLEY: We looked at all the intestine, it's only in the small bowel and only at the very high doses.

DR. HANAUER: Thank you.

Review of Data on Ovarian Cysts

Bruce Carr, M.D.

[Slide.]

DR. CARR: Mr. Chairman and members: I was asked by Novartis to (a) review the adverse events reported as ovarian cysts with the use of tegaserod; and (b) to

determine if there is an increased association with the laparotomies due to gynecological and gastrointestinal indications in tegaserod.

[Slide.]

First, I will discuss the issue related to ovarian cysts. In review, the ovary is a dynamic organ with follicular growth and development occurring continually, so that at any given time, ovarian follicles or corpora lutea, which are the remnants of the follicle, are present in the ovaries.

Physicians and even gynecologists sometimes call ovarian follicles cysts, a term which may itself suggest a pathological condition, when, in fact, they are describing normal ovarian events and physiology.

Ovarian cysts are usually defined as greater than 4 cm and persist for a number of months, but the pathology and the treatment of ovarian cysts is not clearly understood.

[Slide.]

Now, this slide illustrates an ultrasound of an ovary and associated follicle, mature follicle. If a patient experienced abdominal pain and the physician ordered an ultrasound, the diagnosis of a cyst would be provided back to the physician, and he or she may consider the cyst to be the cause of the pain.

However, this ultrasound is an infertility patient of mine with a mature follicle one day prior to ovulation. The day the patient ovulates, the cyst, the follicle will rupture, and the patient may develop short-term, acute pain known as Mittelschmerz, but this is a normal physiological event.

Now, with this as background, we can proceed with the discussion of the cases of ovarian cysts.

[Slide.]

This slide illustrates my further analysis of nine adverse events, termed ovarian cysts, of which eight patients were being treated with tegaserod and one with placebo.

I divided these into those where the diagnosis was not confirmed or confirmed. In those cases that were not confirmed, the revised diagnosis, in fact, was a cystadenofibroma, which is in fact a benign ovarian tumor, a peritubal cyst, which is a cyst of the fallopian tube, which is probably a congenital defect of muellerian origins. A third case had no cyst found at surgery, and only pelvic adhesions, and the fourth I considered not confirmed was a patient who had abdominal pain where the adverse report was, quote, "ruptured ovarian cyst," but there was no evidence to document this either by examination or imaging studies.

In addition, there were five cases in which the

ovarian cysts were confirmed. Of these five, two in fact had history of prior ovarian cysts. Two of these patients were both on tegaserod.

One patient had prior ovarian cysts diagnosed, as well as adenomyosis and menorrhagia. The other case had a case of ovarian cysts on the left and right ovaries removed approximately three to four months prior to surgery and at the time of recurrent surgery we will discuss a little bit later, also had appendicitis of the appendix.

This leaves us with three cases of newly occurring ovarian cysts. One was placebo, which she had a diagnosis of polycystic ovary, which is an ovary with very small follicles, possibly a genetic disease.

An additional polycystic ovary was seen in a patient on tegaserod. This was confirmed by CT scan. Again, PCO is not a disorder associated with abdominal pain or development of large cysts.

One patient had a cyst or follicle that was diagnosed by a gynecologist that arose during a cycle, that regressed in a subsequent cycle.

[Slide.]

This slide illustrates the Phase II, the Phase II and III combined, as well as uncontrolled, long-term studies in female patients with ovarian cysts. Looking at the percent of patients in the combined Phase II/III studies,

the percent patients with cysts was approximately the same in the placebo, as well as in the drug-treated group.

In the uncontrolled, long-term studies, the percentage of patients with the cysts remains the same, but obviously, there was no placebo patients in this group, but this information is somewhat reassuring.

[Slide.]

Next, we evaluated the estimated ovarian cyst frequency in women aged less than 50 years, in the pooled Phase II/III and long-term studies.

The data presented here is presented as the estimated frequency per 1,000 women years. There is no significant difference between the groups.

[Slide.]

We also investigated the prevalence of ovarian disease or ovarian surgery at baseline. In the patients with previous ovarian surgery, the prevalence was similar in the placebo- and tegaserod-treated patients. In the patients with previous ovarian cysts at baseline, the prevalence was similar in the placebo and again drug treated-patients.

[Slide.]

In order to place these data in perspective, in a review of the literature, the prevalence of simple cysts and polycyst ovarian disease, which were detected by ultrasound

in asymptomatic healthy populations, was evaluated.

As seen in the postmenopausal patients, and in women aged 25 to 40 years, there was a similar prevalence of around 6 percent. This number appeared to be double, however, in adolescent girls.

[Slide.]

With respect to the preclinical studies with tegaserod, there appears to be no treatment-related ovarian cysts in the rat toxicity studies up to six months, dog toxicity studies up to 12 months, mouse carcinogenicity study or after reevaluation of the rat carcinogenicity study.

In addition, there was no histopathological evidence or hormonal perturbation in any of the studies.

[Slide.]

In summary, there is no evidence of a link between tegaserod and the development of ovarian pathology either by evaluating of the clinical studies, which I have just presented to you, or the preclinical/toxicology studies.

[Slide.]

Next, I will discuss the relationship between laparotomies in patients due to gynecological and gastrointestinal indications.

[Slide.]

I evaluated those women undergoing gynecological

surgery as shown in yellow. We can see that in patients where the ovarian cysts were not confirmed, that were on tegaserod, they had different etiologies and indications for laparotomies, which I had discussed previously - an ovarian tumor, a peritubal cyst, or pelvic adhesions, again, different etiologies.

In the confirmed patients on tegaserod, two patients, which I had previously described, underwent surgery, again with different etiologies.

The first patient had an indication for surgery that revolved around bleeding problems, a CT scan diagnosis of adenomyosis and ovarian cyst.

The second case had a diagnosis of ovarian cyst and possible appendicitis, and was proven to have appendicitis at the time of surgery, and a cyst was merely drained.

[Slide.]

The next slide summarizes five patients undergoing laparotomy for gastrointestinal indications. The first placebo patient had adverse event of appendicitis. Second, had a perforated cecum. The three patients on tegaserod had ileus, benign pancreatic cyst, and a small bowel obstruction, again different etiologies.

[Slide.]

The frequency of laparotomies by year in the NDA

database was evaluated. The frequencies per year appear to be similar in the Phase II and III studies with tegaserod and placebo, and in long-term therapy, placebo data is not available, but the frequency of laparotomies per year appears to be confirmatory of that observed in the Phase II and III studies. Again, this is somewhat reassuring.

[Slide.]

In summary, regarding tegaserod and laparotomies, in the study population a variety of different gynecological and GI disorders led to the laparotomies.

The frequency of laparotomies by exposure duration were similar for tegaserod- and placebo-treated patients.

There appears to be no obvious causal relationship or signal that tegaserod affects the frequency of laparotomies.

Thank you.

DR. HANAUER: Any questions from the committee regarding this? Yes, Dr. Houn.

DR. HOUN: Just a question on 5-HT_4 receptors. Have there been studies to see if they are located other than in the GI tract?

DR. CARR: We specifically did a research review of this, of the literature, and could not find any reports of these receptors in ovarian tissue.

DR. HOUN: Have you conducted those studies?

DR. CARR: No, I conducted a review of the literature, and there have been no reports.

DR. HOUN: And this wasn't studied by the company?

DR. CARR: No.

Safety of Tegaserod

Martin Lefkowitz, M.D.

[Slide.]

DR. LEFKOWITZ: I will now review the safety profile for tegaserod beginning with a review of the exposure, adverse events, laboratory evaluations, ECG, and overall summary.

[Slide.]

Over 3,500 healthy subjects or patients have been exposed to the drug at the time of the NDA submission, with a maximum daily dose up to 200 mg in healthy subjects.

Over 1,800 IBS patients received the drug for at least 85 days, and 302 IBS patients for more than 335 days.

[Slide.]

Serious adverse event reporting through the tegaserod clinical program was low, pooling the control studies in Phase II and III reporting frequency of serious adverse events was similar, exactly balanced, of 1.8 percent in the placebo and tegaserod groups.

Serious adverse events were reported in 4.1 percent in the long-term studies consistent with the longer

duration of the study.

[Slide.]

The reasons for discontinuation through the Phase III program is shown here, blue, placebo, red, 4 mg, here, the dose titration dose, and the 12 mg/day dose.

For the titration, the 12 mg/day dose, over all discontinuations were similar and 5 percent higher in the 4 mg/day dose. Adverse event, discontinuations specifically due to adverse events was slightly increased in the tegaserod groups compared to placebo, but were overall low.

Other reasons for discontinuation were low and generally similar between the groups.

[Slide.]

When we specifically look at reporting of any adverse events, that was balanced across the group with a slightly higher reporting of severe adverse events in the tegaserod group compared to placebo.

As mentioned before, serious adverse events reporting was low in the program, and discontinuation rates due to adverse events, as you saw previously, also low.

[Slide.]

Reporting of adverse events greater than 5 percent in the Phase III program are shown here, the two most common adverse events being headache and abdominal pain, placebo here, with similar reporting frequency of headache and

abdominal pain compared to tegaserod groups.

The single adverse event that was reported with a higher frequency was diarrhea, which was reported at about two-fold higher, 5 percent in the placebo group, 11 to 12 percent in the tegaserod group, without any dose relationship in the reporting of diarrhea.

Reports of severe diarrhea was approximately one-third in the tegaserod and one-third on placebo, and was about 2 versus 4 percent.

Other adverse events were all similarly reported between tegaserod and placebo.

[Slide.]

We then looked at the time to the first episode of diarrhea after day 1. This is day 2 to 7, and then over the next three weeks, month 2, and then month 3.

As you can see, most patients who had diarrhea early on in the study, this was generally due to the tegaserod with about half of the cases of tegaserod-induced diarrhea occurring within the first week, with then a slightly higher frequency of first episodes of diarrhea throughout the rest of the study.

The majority of these cases of diarrhea were single episodes with a median duration of two days and a mean duration of seven days.

[Slide.]

Shown here are the adverse events leading to discontinuation. Overall in the program about 1 to 2 percent higher patients in the tegaserod group discontinued compared to placebo.

Importantly, discontinuations due to abdominal pain was balanced between the groups. Again, the single reason that patients discontinued more frequently in tegaserod was due to diarrhea, 0.4, compared to 1.6 percent due to drug. So, although higher, a low discontinuation rate due to diarrhea. In the entire program, 2.1 percent of patients discontinued due to diarrhea. Discontinuation rates due to other reasons were low and similar in the treatment groups.

[Slide.]

We conducted a long-term safety study, a 12-month open label study, which utilized a dose titration design, of which 80 percent of the patients were dose titrated to 12 mg/day. 579 patients enrolled, and 304 completed.

[Slide.]

The adverse events seen in the long-term safety study was very similar with what was seen in Phase III, again headache and abdominal pain being the two most common adverse events, and an adverse event rate of diarrhea being reported at 15 percent.

[Slide.]

Reasons for discontinuations due to adverse events, again was compatible with the Phase III program. The discontinuation rates overall, 11 percent in the study, and those due to diarrhea, 4 percent over the 12-month study, and 3 percent due to abdominal pain and flatulence.

[Slide.]

We evaluated laboratories throughout the program. In Phase III, clinically relevant laboratory abnormalities in hematology and biochemistry values were rare and with similar frequency for tegaserod- and placebo-treated groups.

Liver chemistries, a 3-fold increase in ALT elevations was seen in 0.4 percent of tegaserod and 0.2 percent of placebo patients, with 3-fold elevations in AST of 0.1 and 0.1 percent in the two groups.

There were no simultaneous elevations in ALT/AST and bilirubin. There were no serious adverse events of hepatitis or elevated LFTs. The results in Phase II and long term were similar, showing no evidence of tegaserod-induced hepatotoxicity.

[Slide.]

We carefully evaluated the effects of tegaserod on the ECG both in preclinical studies, as well as in clinical studies. We conducted a series of preclinical studies both in vitro and in vivo, that showed no effects on the QT interval and specifically no effects on the delayed

rectifier current, which is the mechanism whereby cisapride is known to cause prolongation of the QT interval.

In our clinical studies, we conducted well over or we analyzed well over 10,000 tracings in the patients, shown here in Phase III. ECGs were recorded at baseline two hours after the first dose at a maximum concentration of the drug at month 1 and again two hours after dosing at month 3 or at study endpoint.

In the long-term study, patients had ECGs periodically over the course of the study.

All ECGs in Phase III and in the long-term study were centrally analyzed by an independent cardiologist with intervals evaluated by a SigmaScan technique, in which a jeweler's lamp is used to magnify the ECG tracing, and then the intervals are measured.

The results of this analysis showed no effects on the ECG, specifically no effects on the QTc interval or other ECG intervals, and no difference in arrhythmias between tegaserod and placebo.

[Slide.]

In summary, tegaserod at a dose of 4 and 12 mg/day was well tolerated with a similar safety profile between the 4 and 12 mg dose.

Diarrhea was the single adverse event with the higher frequency than placebo, and an overall

discontinuation rate of approximately 2 percent.

No effects were seen on the ECG or on laboratory parameters.

[Slide.]

Our overall conclusion is that the totality of the data demonstrate that tegaserod is effective in the treatment of irritable bowel syndrome in patients who identify abdominal pain or discomfort and constipation as their predominant symptoms.

Tegaserod at a dose of 12 mg/day improves the abdominal discomfort or pain, bloating, constipation seen in patients with irritable bowel syndrome. The drug has a favorable safety profile, and we believe presents a favorable benefit-to-risk profile for patients with constipation-predominant IBS.

At this point, should I take questions?

DR. HANAUER: Thank you.

Are there any additional questions for the sponsor from the committee? Dr. Laine.

DR. LAINE: Just while we are here I always forget, so I always ask the FDA officers this. The ICH criteria for number of patients long-term follow up, can somebody remind me of those, you know, how many patients for like one year, how many patients for -- maybe after lunch you can tell me.

DR. HOUN: Dr. O'Neill or Dr. Castillo for the ICH statistical long-term exposure study -- 100 for 12 months and 3 to 6 months, it is between 300 and 600. That is the recommendation.

DR. LAINE: Thank you.

DR. HANAUER: Anyone else on the committee? Dr. Wolfe.

DR. WOLFE: Can I ask a preclinical question, a pharmacological question?

DR. HANAUER: Yes, you may.

DR. WOLFE: I think Mike Camilleri might be the best person to ask that to.

This is a receptor agonist, and what is the signaling pathway?

DR. CAMILLERI: Yes. Thank you. The 5-HT_4 receptor is a G-protein related, 7 transmembrane domain receptor.

DR. WOLFE: Those receptors are notoriously prone to desensitization.

DR. CAMILLERI: That is an excellent point, Dr. Wolfe. One of the advantages of this particular compound is that it is a partial agonist, which notoriously are less sensitive to desensitization although, of course, there could conceivably be some.

DR. WOLFE: What about up-regulation of receptor

synthesis?

DR. CAMILLERI: I may have to ask my colleague, Dr. Pfannkuche, about up-regulation of receptor synthesis.

DR. PFANNKUCHE: Hans Pfannkuche, Novartis.

Maybe we can show a slide QA160, which very nicely explains what Dr. Camilleri already alluded to.

[Slide.]

With respect to desensitization, it is clear that it has been shown very often that with a partial agonist there is less desensitization tendency.

With respect to up-regulation, there are some hints based on findings with atrial tissue that during chronic treatment with beta blockade, that there might be kind of a higher response rate with respect to 5-HT_4 receptors, which are only located on atrial tissue, but this is rather preclinical findings.

DR. WOLFE: As a follow up to that question, in the animal studies, was there any tachyphylaxis observed?

DR. PFANNKUCHE: We did some subchronic studies on motility, of course, and we had a very slight tendency with respect to tachyphylaxis.

DR. HANAUER: Okay.

DR. LEFKOWITZ: It is now my pleasure to introduce Dr. Sidney Cohen for concluding remarks.

DR. HANAUER: One more question. Yes, Dr. Hammes.

DR. HAMMES: I am curious. There seems to be no dose response to the diarrhea effect. Is there any speculation on why?

DR. LEFKOWITZ: Although we did observe on those graphs a dose response in terms of bowel movements and stool consistency, those were the reports. I personally can't speculate on why, but it was 11 to 12 percent in 4 mg and 12 mg/day groups, and, in fact, dropouts overall were less in the 12 mg/day group than the 4 mg/day group.

It is still my pleasure to introduce Dr. Cohen.

Closing Remarks

Sidney Cohen, M.D.

DR. COHEN: Mr. Chairman, members of the Advisory Panel: I would like now to summarize and highlight some of the important features of today's presentations.

[Slide.]

First, let me remind everybody that irritable bowel still remains a very difficult to diagnose and to treat condition. There are no measurable serological or gastrointestinal motility markers of irritable bowel syndrome despite investigators looking over many years.

Therefore, we must rely on clinical syndrome, and it is a compilation of symptoms. Despite the discussions of the Rome criteria, I must remind you that you still come down to two important clinical symptoms - abdominal pain and

change in bowel habit, and those are the symptoms that bring the patient to see the physician, and those are the symptoms that we will look for, for relief

Irritable bowel syndrome treatment is empiric; there are no proven efficacious therapies for patients with abdominal pain, bloating, and constipation as their predominant symptoms. So, this is the background upon which today's presentation is given.

[Slide.]

Tegaserod is a unique pharmacological agent, and I want to highlight some of the points that Dr. Camilleri raised, that tegaserod addresses the clinical components in irritable bowel syndrome, the abdominal pain, bloating, and constipation.

It does this by stimulating the peristaltic reflect, augmenting aboral propulsion, and diminishes visceral sensitivity, reducing pain.

The peristaltic reflex is the physiological basis of motor function in the gut. The reflex was described by Bayliss and Stalling at the turn of the century, and describes how the gut relaxes distally and contracts proximally.

Tegaserod stimulates and augments this response, so it physiologically enhances movement through the gastrointestinal tract in the small intestine and colon.

Dr. Camilleri showed very nicely that tegaserod reduces the firing, the action potential firing of spinal afferent nerves, so it is a visceral analgesic in a disorder where you have increased visceral sensation or visceral hypersensitivity.

[Slide.]

The clinical trials that were presented recruited a largely unrestricted population of patients with irritable bowel who identified abdominal pain or discomfort and constipation as their predominant symptoms.

These patients are reflective of patients seen in common clinical practice, and my review of this material clearly indicates, pertaining to the question raised earlier, that this is a constipation-predominant group. It fulfills the criteria.

[Slide.]

Now, the primary efficacy variable was the global relief of symptoms, but as a clinician, as a clinical investigator, I remind you that specific symptoms of irritable bowel syndrome is what brings the patient to see the physician, it is what causes the patient to lose time from work, and this is abdominal pain with associated bloating and the constipation with its stool frequency and stool consistency changes.

[Slide.]

I took the opportunity, therefore, to look at those specific symptoms. In the study, they are secondary efficacy variables, but for a clinician, they are very clinically relevant and important.

What I did here was compile for Study 301 the individual symptoms, by week, removing the 4 mg dose, looking at placebo versus the 12 mg dose. The data is very impressive.

If you look at the pain score, by week, 11 of 12 weeks, consistently the patient had less pain. In addition, the patient had more bowel movements, as you can see here, so the two main features of this condition, pain and constipation, were affected in a positive way. The symptoms were relieved in 11 out of 12 weeks.

Additionally, the patients had less bloating by score over the weeks, and had improved stool consistency.

So, to me, as a clinician, these are very important data, highlighting the clinical symptoms that bring the patient to see the physician.

[Slide.]

When you look at the 351 study, the major supporting study, again, you see very similar findings, looking at pain, improvement in bowel function, bloating, and stool consistency. Week after week, the patient has improvement in all of these clinical parameters, the

secondary efficacy variables of the study, but the primary parameters that a patient witnesses and a physician sees in clinical practice.

[Slide.]

The 307 study was more difficult to evaluate. It was a dose escalation study, but I highlight here that looking at the individual symptoms, pain, constipation, bloating, and stool consistency, for many of the weeks you see clinical improvement. Taken together with the other studies, you see clear trending and you see clear improvement in these secondary efficacy parameters, the clinical symptoms of IBS.

[Slide.]

Now, this is the overall global relief, and looking at the three efficacy parameters - complete, considerable, and somewhat relief, and again I would like to highlight, by week, and you can see over the 12-week period, you see clinical improvement, the overall relief of symptoms in patients with irritable bowel for the 351, 301, and you see some improvement in the 307 study, but then with dose escalation, you see this rise in placebo response, making this a more difficult study to interpret.

I would emphasize here one of the questions raised, this is an appropriate placebo response for a clinical GI disorder where you are measuring symptom scores.

[Slide.]

When you look at the very high hurdle of complete or considerable relief, you see a much lower placebo response, and I think very much more difficult to achieve clinical efficacy, which is complete or considerable relief, but yet with some of the overall relief you still see points over the weeks of clinical improvement.

[Slide.]

So, in summary, Mr. Chairman, I would say that tegaserod at a dose of 12 mg, 6 mg BID, has been demonstrated to be effective in the treatment of abdominal pain, bloating, and constipation in irritable bowel syndrome. This effect is more dramatic in women.

Tegaserod is safe and well tolerated. Diarrhea is the only drug-related side effect, it is self-limited, and infrequently led to discontinuation of the drug.

[Slide.]

The overall conclusions here indicate that you have an agent with a unique pharmacological action that addresses the clinical components of constipation-predominant irritable bowel. The drug enhances the peristaltic reflex and decreases visceral sensitivity, leading to decreasing constipation and reduction in pain.

When you look at the studies by clinical symptoms, individual symptoms, you see a positive and significant

clinical effect in reducing abdominal pain, bloating, constipation, and stool consistency, the hallmark symptoms of irritable bowel syndrome.

When you look at global relief, you see that it is effective in providing overall or global relief of the symptoms of irritable bowel.

[Slide.]

My final bottom line is that in a clinical syndrome in which there has been no proven treatment, effective treatment, tegaserod is a strong first step in the management of constipation-predominant irritable bowel syndrome. This effect is most dramatic and most prominent in females.

Thank you.

I will now turn the podium to Dr. Lefkowitz for questions.

DR. HANAUER: Dr. Laine.

DR. LAINE: I was wondering if you could back to one of Dr. Cohen's slides, which is 351 with the four different graphs on it, and I would actually just ask Dr. Cohen -- it was like CO 4 or 5 or one of those -- but I guess it comes up to, as an example of that one, if we look at the pain score where there are significant differences, but as I remember, that is a 6-point pain score, is that correct?

DR. LEFKOWITZ: Yes, that is correct.

DR. LAINE: As I look at that, we are seeing again the point I made earlier, you have 800 and some patients or you have many patients with many data points, which may be giving this statistical significance because you have so many data points, but I would ask Dr. Cohen, as a clinician, does a 0.1 change on a 6-point scale really mean anything clinically to him.

DR. COHEN: I think this is a very difficult question to answer. As a clinician, if a patient can tell you week after week that they have less pain and improved bowel function, I think you have to take that as being clinically significant, and my conclusion is that this drug is moderately effective in reducing those symptoms.

DR. LAINE: I was wondering if the sponsor has information, you know, typically, you can look at perhaps the minimum discriminating difference, if you will, that a patient can actually distinguish, is there evidence that a 0.1 or 0.2 change, or 0.3 change on a scale of 6 is a clinically relevant interaction, something that a patient can -- I forget the right wording -- but is distinguishable by a patient, let's say?

DR. LEFKOWITZ: No, clearly, we don't have that information. I think the scores are used to show that the drug is having an effect on pain and bloating. We also

looked at abdominal pain in different ways. For example, we looked at the subject global assessment of abdominal discomfort and pain, where we did show consistent differences for the tegaserod groups compared to placebo.

We looked at days with significant pain. We also saw significant differences, so we tried to translate these pain scores into some patients' perceptions.

DR. LAINE: And not that you would have for secondary endpoints, but did you predefine any things that you felt were going to be clinically significant in changes in pain scores or the other scores, because, as you know, there are actually times when you have enough data points where something can meet your clinical equivalence criteria, but still be statistically significantly different, so I was just trying to separate those two out.

DR. LEFKOWITZ: Yes. No, again, these pain and bloating scores I think, as Dr. Cohen said, is difficult to interpret clinically. I think they do show that the drug is having an effect on pain, and I guess I would look to the subject global assessments as an indication of the patient's perception of response.

DR. HANAUER: And there was a correlation between the global assessment and the degree of improvement on the visual analog scales?

DR. LEFKOWITZ: I am sorry?

DR. HANAUER: You have them graded as somewhat relief, considerable relief.

DR. LEFKOWITZ: Oh, from the SGA of relief to the subject global, yes, the measures were highly correlated, yes.

DR. RICHTER: Martin, was there any attempt to look at quality of life in these issues because again you are getting to the aspects of pain which is very subjective, difficult to assess.

Is that contemplated by your group if you haven't already done it?

DR. LEFKOWITZ: As you recall, at least, number one, for our global relief endpoint, we did include trying to capture at least an element of that. The question both related to abdominal discomfort or pain, altered bowel habit, and overall well-being, so it was captured as part of that.

We did administer quality of life scales in this study as a tertiary variable. The scale used was not, and has not, been validated in controlled clinical trials for responsiveness. We saw, on that scale, significant increases on both placebo and on drug that were not different between the groups.

DR. HANAUER: Dr. Buyalos.

DR. BUYALOS: Yes, a couple questions. Number

one, since the benefit was demonstrated in women, and most of these women were on reproductive age, and a lot of women, the luteal phase of their cycle after ovulation frequently will have gastrointestinal symptoms, such as diarrhea or constipation, was that examined separately?

The next question I have is the impact of hydration and exercise. A lot of these patients were consenting to be studied, were they specifically instructed not to change their exercise or hydration patterns?

DR. LEFKOWITZ: Yes, patients were instructed to continue on their usual diet and exercise patterns.

I am sorry, I forgot the first question.

DR. BUYALOS: The impact of being in the luteal phase of their menstrual cycle.

DR. LEFKOWITZ: Yes. We did not collect information during the study on menstrual cycle. The incidence of dysmenorrhea was very low and balanced between the two groups.

DR. HANAUER: Dr. Talarico.

DR. TALARICO: The last slide before your summary, the complete and considerable disease responders, I have difficulty understanding the placebo curve.

Slide 10, I think.

DR. LEFKOWITZ: In Dr. Cohen's talk?

DR. TALARICO: Yes.

DR. LEFKOWITZ: CO10. I think clearly in 307, we have difficulty understanding the continued increase in the responder rate.

DR. TALARICO: Yes. I can understand the low starting, the rate of responder, since these are the two most rigid criteria of response, but I have difficulty understanding how they can, how the response can escalate with the placebo at such a rate.

DR. LEFKOWITZ: I guess perhaps over here, one is seeing some sort of --

DR. TALARICO: I would have started, I would plateau it at the system point.

DR. LEFKOWITZ: I am sorry? These are the placebo rates that we observed in the study. I don't know what I could say beyond that. Again, I think if you look at the entire relief score, the SGA of relief, one doesn't get this very high placebo response rate. These are fairly low rates, and I think they are more impacted by perhaps small changes in small numbers of patients.

If you look, for example, at percent somewhat relief, that is quite flat, if you go to the previous slide.

DR. TALARICO: Oh, yes, this, I can understand this one, but the one before, even though the numbers are -- it's the pattern that is very difficult for me.

DR. LEFKOWITZ: I certainly agree the pattern in

307 is difficult for us to understand.

DR. TALARICO: Thank you.

DR. HANAUER: Okay. Let's move on to the Agency's review.

DR. TALARICO: We have made a slight change in our agenda. Since all the preclinical issues have been addressed by the sponsor, we will omit our preclinical presentation and go right to the first one, which is the statistical, followed by the medical presentation.

FDA Presentation

Statistical Reviewer

Sonia Castillo, Ph.D.

DR. CASTILLO: Good morning, Committee, and ladies and gentlemen. I am Sonia Castillo, and I was the statistical reviewer for this product.

[Slide.]

Here is a list of the topics I will present today, so let's begin with a little bit of background. I would like to thank the sponsor for presenting such a great presentation. It makes my job a lot easier.

We are going to zip through the first couple of pages here.

[Slide.]

Here, we have a listing of all the three clinical trials studied for this product. I just want to note again

that in Studies 301 and 351, we had 4 mg/day group, 12 mg/day group, the placebo, and in 307, we had 4 mg/day and a 4 to 12 mg/dose titration group and placebo. Also, in Study 307, after four weeks on treatment, all patients were either titrated or mock titrated depending if they responded to treatment or not.

[Slide.]

Here is a little bit of background again. As the sponsor has mentioned, Study 351 was completed and analyzed first. The results of the protocol-specified analyses were not significant.

This led to a change in the definition of a responder to treatment. When this change was subsequently applied in a post-hoc analysis, the data gave significant results and led to protocol amendments for Studies 301 and 307 although they were still blinded.

Therefore, we have two studies in which the analysis presented is prospective. Those are 301 and 307, and one in which it is post-hoc, which is 351.

[Slide.]

The original protocol for all three studies had one primary efficacy variable, and that was the subject global assessment of abdominal pain and discomfort. It called for an enrollment of 591 intent-to-treat patients.

[Slide.]

Here is what the variable looked like. You heard the question before. Patients on a weekly basis were asked, "How much of a problem was your abdominal discomfort/pain over the last week?"

What they did is they put a slash somewhere on this 100 mm VAS, or visual analog scale, as to how they felt. The definition for responder to this variable was greater than or equal to 20 mm and greater than or equal to 40 percent reduction in the mean visual analog scale at study endpoint, which was defined as the last four weeks on treatment compared to the baseline value.

DR. HANAUER: If you would go back to the last one, because this is somewhat unclear I think to everybody. There were four assessments in the last month, right, this was a weekly VAS score.

DR. CASTILLO: Weekly VAS score.

DR. HANAUER: So, is the one that counted the absolute, the fourth of the third month? You only counted the 12? Do you understand what I am saying? If this is done weekly, and you are looking at the endpoint for the last four weeks, were they looking at the endpoint of the absolute last determination?

DR. CASTILLO: No, the four last weeks.

DR. HANAUER: Averaged? The four last weeks were averaged.

DR. CASTILLO: No, you took -- yes, average, the four last weeks compared to the baseline value, yes.

DR. HANAUER: Thank you.

[Slide.]

An amendment was submitted prior to the start of all the studies. In this amendment, the subject global assessment of relief was added as a second primary efficacy variable.

Now, the sponsor added the second efficacy variable because they considered both the subject global assessment of relief and the subject global assessment of abdominal discomfort/pain as clinically relevant outcome variables of irritable bowel syndrome, but the sponsor did not know whether either was more important than the other. This amendment also called for enrollment of 693 intent-to-treat patients.

[Slide.]

As you have seen before, here is the subject global assessment of relief. The questions that patients answered every week in terms of how they felt their overall well-being, symptoms of abdominal discomfort and pain, and altered bowel habits, and they had to choose from the five answers down there, listed in yellow, completely relieved, considerably relieved, somewhat relieved, unchanged, or worse.

[Slide.]

Definition of responder for this variable was a patient who fulfilled the following four criteria. You had to have complete or considerable relief at least 50 percent of the time at study endpoint, and that was the last four weeks on treatment.

In addition, this definition took into account the number of days with laxative use, which had to be less than five, less than or equal to five, and no laxative use during the last 28 days of treatment. Duration of exposure to study medication be at least 28 days, and had to have at least one post-baseline subject global assessment of relief.

Just recall that laxative use is allowed for purposes or rescue during the entire study period, and in addition, bulking agent use was permitted during the entire study.

[Slide.]

As I mentioned before, after the post-hoc analysis of Study 351, another amendment was submitted prior to breaking the blind Studies 301 and 307.

In this amendment, the definition for responder for SGA of relief was modified. At first, it was just this component, complete or considerable relief at least 50 percent of the time at study endpoint.

An addition component was added, which was

complete or considerable or somewhat relief 100 percent of the time at study endpoint.

The Division considered this change clinically meaningful. In addition, the subject global assessment of relief became the only primary efficacy variable, so we went from two to one, and the subject global assessment of abdominal discomfort/pain was changed from a primary to a secondary efficacy variable.

The Agency would appreciate the committee's view on changing the subject global assessment of abdominal discomfort/pain from a primary to a secondary efficacy variable, since it was considered a clinically relevant outcome.

I am going to present the results for both the subject global assessment of relief and the subject global assessment of abdominal discomfort and pain.

[Slide.]

This table seems a little busy, but I will simplify it here. On the left here we have results for the primary efficacy analysis when using the original definition of responder, and on the right is when we have the new definition just to see what happens to the responder rates.

As you can see, adding the extra category of somewhat relieved across the last four weeks of study, for example, in Study 301, the responder rate for the 4 mg group

went from 28 percent to 39, the 12 mg went from 27 percent to 38, and placebo, 20 percent to 30 percent.

So, the effect was you increased the responder rates.

Using the original definition of responder, you see that none of the treatment differences were statistically significant in all studies.

In Study 301 -- we are going to focus now on the new definition of responder to SGA of relief -- in Study 301, both the 4 mg and 12 mg showed statistically significant results, a treatment difference of 9 percent or about 1 additional responder for every 11 patients treated, a treatment effect of about 8 percent of the 12 mg group, or about 1 additional responder for every 12 patients treated.

In Study 307, neither of the treatments were statistically significant, and for Study 351, recall that for the protocol-specified analyses -- I have blocked them off right here -- none of the results were statistically significant.

In the post-hoc analysis, we get statistical significance for the 12 mg group, and that was 12 percent or about 1 additional responder for every 8 patients treated.

[Slide.]

Here is a quick overview of the subject global assessment of abdominal discomfort/pain. In all studies,

across all studies, there was not a statistically significant difference seen, and, in fact, in Study 307, the treatment difference was negative, which means that the active treatment was numerically worse than placebo.

[Slide.]

So, what we can conclude from these analyses are as follows. For the subject global assessment of relief, a statistically significant treatment effect was demonstrated in Study 301 for the 4 mg and 12 mg doses and supported in a post-hoc analysis of Study 351 for the 12 mg dose, but not replicated in Study 307.

For the subject global assessment of pain, a statistically significant treatment effect was not demonstrated across all three studies.

This gives two questions that we would like the committee to consider. One is why is efficacy not shown in Study 307 for either dose, and which, if any dose, is effective.

[Slide.]

By regulation, the Agency investigates efficacy by gender. Here are the results that we get. On the lefthand side, we have the results for males. As you can see, in all studies, none of the treatment differences were statistically significant, and they were either close to zero or negative. For those that are negative, those are

the ones in yellow here, that just shows you that the active treatment was worse than placebo, numerically worse than placebo.

We will go over to female patients here. Study 301, we had a significant difference for both the 12 mg and the 4 mg dose groups, 10 percent for the 4 mg, which is about a additional responder for every 10 patients treated, for the 12 mg, about 11 percent response rate or a treatment difference which is 1 additional responder for every 9 patients treated.

In Study 307, again, we see no statistically significant results. For Study 351, these analyses -- recall these are the post-hoc analyses -- we get a statistically significant result only for the 12 mg group, which is about 15 percent or 1 additional responder for every 7 patients treated.

[Slide.]

From these analyses, we can conclude that the treatment effect results are mixed in female patients, that efficacy in male patients is not clear, and that clinically, the results for female and male patients may indicate a difference in the pathophysiology of constipation-predominant irritable bowel syndrome between the genders.

[Slide.]

I just want to briefly make the statement, and Dr.

Joseph will further address this issue, that changing the subject global assessment of abdominal discomfort/pain from a primary to a second efficacy variable is of clinical concern because pain is an important clinical component of irritable bowel syndrome.

Also, its assessment via the subject global assessment of discomfort/pain, which was at one point in time a primary efficacy variable and then became a secondary, did no show statistical significance across the three studies.

[Slide.]

I am going to talk about taking into account laxative use in the analyses. The sponsor presents additional analyses -- and these additional analyses are all analyses done by week and by month that were not subject global assessment type of analyses -- that do not take laxative use into account when defining a responder for subject global assessment of relief and subject global assessment of abdominal discomfort/pain.

The Division does not agree that laxative use can be ignored, because the protocol-specified definition of responder takes laxative use into account, and laxative use is taken into account because it affects bowel habit in abdominal discomfort.

So, consequently, these additional analyses are

not consistent with the protocol-specified definition of a responder. You are using two different definitions of a responder or you are using two different ways of analyzing how you respond, one with laxative use and one without. So, it is kind of confusing how you would interpret or combine the results on that basis.

[Slide.]

I am going to quickly go through a couple of reasons why not to pool to demonstrate efficacy in these studies.

As presented by the sponsor, pooling of the studies to investigate the presence of a treatment effect did show statistical significance. There was a 6 to 7 percent treatment effect or 1 extra responder for every 14 patients treated. But each study did not show statistical significance on its own.

You will recall that Study 301 showed significant results for both treatment groups, Study 307 did not show significant results for either treatment group, and Study 351 showed significant results for the 12 mg group after a post-hoc analysis.

For pooling to demonstrate efficacy is not appropriate in this situation because the pooled analysis was not prespecified in the protocol. Also, the design of Study 307 is different. It included a 4 to 12 mg titration

group, and that is not the same as a 12 mg group.

Also, because we have these different dose groups in the three studies, we have different endpoint interpretations. Study 307 evaluates a fixed dose group and a titration dose group. Studies 301 and 351 evaluate two fixed dose groups.

Also, the dose titration done in 307 was based on the original definition of responder, which was complete or considerable relief 50 percent of the time, while the pooled analyses used the new definition of responder, which adds the component "somewhat relieved" 100 percent of the time. So, that is confusing, as well.

It is necessary to use consistent definitions of responder throughout an analysis.

[Slide.]

Also, pooling is not necessary in these studies because each one is adequately sized to show efficacy on a study by study basis. In fact, the intent-to-treat sample size at study completion was larger than planned, and as you can see here, more than 15 percent in all three studies.

Also, pooling gives no replication of the study results.

[Slide.]

In summary, we can say that a statistically significant treatment effect was demonstrated in female

Raymond Joseph, M.D.

DR. JOSEPH: Good afternoon. I am Dr. Joseph. I am the medical officer who reviewed the Zelmac NDA.

[Technical difficulties.] As you see, I have no slides, which will make today's discussion very short.

[Laughter.]

Basically, as we have talked about all morning, one of the advantages of going last is that a lot of the slides that I was going to cover have been covered, so there will be partially a review and we can speed through them.

[Slide.]

Again, the proposed indication as we have been talking about all morning, the treatment of irritable bowel in patients who identify abdominal pain/discomfort and constipation as their predominant symptoms, abdominal pain and constipation.

[Slide.]

Quickly going over the Phase II studies, basically, Studies 251 and 202, the double-blind trials, the first study randomized 547 patients in 45 sites in North America and Europe, essentially, a dose-ranging study from 1 mg/day, 4 mg/day, 12 mg/day, and 24 mg/day for 12 weeks.

Study 202 essentially randomized 123 patients at 16 sites in Europe and Canada. It incorporated a dose-titration phase with 4 dose levels of tegaserod or placebo

for 20 weeks.

[Slide.]

In essence, Study 251 showed that basically, 1 mg/day was essentially equal to placebo in effect. The 4 mg dose appeared to be the most effective dose. No dose response was seen over the range from 4 to 24 mg/day.

Study 202 showed that there was an increased response rate observed during some of the dose-titration from 4 to 12 mg. With the results of these studies, it was noted that the 4 and 12 mg were the doses to be chosen for the Phase III trials.

[Slide.]

Again, these have all been gone over. What the three studies have in common are that they were all placebo-controlled, double-blind, with levels of 4, 12, 4-week lead-in, 12-week treatment period.

The difference was the dose titration from 4 to 12 at 1 month in the 307 study.

[Slide.]

First, talking about Study 351, which was the first of the Phase III trials to be completed. The protocol prespecified analysis failed to demonstrate any efficacy. So, subsequently, the definition of responder has been changed, as we have mentioned today, to include somewhat relief 100 percent of the time.

The SGA of abdominal discomfort/pain was changed to a secondary efficacy variable.

Post-hoc analysis incorporating the above changes demonstrated efficacy for the 12 mg dose level only.

These things led to the protocol amendments for Studies 301 and 307.

[Slide.]

Here are the three studies dealing with the SGA of relief. The darker color shows the post-hoc analysis Study 351, Studies 301 and 307. As you can see, for the SGA of relief, the 12 mg dose only is statistically significant in the 351 study, and both doses, as has been mentioned earlier in the 301 study, and neither dose in 307.

[Slide.]

So, basically, our efficacy issues amount to pain was not adequately assessed as an efficacy endpoint. Overall difference between drug and placebo group is 8 percent. Efficacy in males is not established, and the potential effect of laxatives. I will talking about each of these in turn.

[Slide.]

With regard to abdominal pain, pain of course is an essential component of IBS. When analyzed as a component of the SGA of relief, which as you know encompassed well-being and altered bowel function, it was statistically

significant in Studies 351 and 301.

However, when analyzed independently, no statistical difference was seen in Studies 301 and 307.

[Slide.]

Again, looking at the three studies for the SGA of abdominal pain/discomfort, no statistical significance in 351, borderline perhaps in 301 for the 12 mg dose, and no statistical significance in 307.

[Slide.]

Overall efficacy, around 8 to 11 percent. The effect of gender in this study group certainly would be up for discussion, and are these results clinically meaningful, also a point of discussion I would believe.

[Slide.]

Efficacy in males. The study included 15 percent males. The response to Zelmac in males was not different when compared to placebo. The lack of differentiation from placebo may be due to inadequate sample size, or it may give rise to the question whether the disease is different in males.

[Slide.]

With regard to the laxative use, in the clinical trials, laxative use including bulking agents was allowed. The use and timing of the laxatives may influence the response of the SGA of relief.

The groups were similar in qualitative consumption between groups, however, quantitative differences were not assessed and may be affecting outcome in constipation study patients.

[Slide.]

In summary, the overall efficacy is shown in one of the studies, 301, for both the 4 and the 12 mg dose levels; Study 351 showed efficacy for the 12 mg dose level only; efficacy was not replicated in Study 307.

Efficacy in males again not demonstrated.

Laxative usage may have had an effect on efficacy.

[Slide.]

Turning to the safety aspect of the presentation, this is a slide just showing the most frequently reported adverse events in the Phase III studies. Again, headache, abdominal pain, diarrhea, nausea, flatulence, et cetera, diarrhea being the only adverse event that was twice as frequent as placebo, 11.7 versus 5.4.

These results were similar when you looked at the Phase II or the long term in terms of the types of side effects and their numbers.

[Slide.]

When you pool both the Phase II and Phase III studies, again, you see similar sorts of side effects, and again the diarrhea 2.1 percent versus 0.6 percent. The rest

are fairly similar in both placebo and tegaserod groups.

[Slide.]

A slide just showing the duration of exposure in the long-term studies, "n" being 675, so with one-day exposure, 100 percent of that 675 received it. When you get down to about 270, it is 48 percent, and at the one-year level, it is 27.4 percent.

[Slide.]

Safety in general. Approximately 72 percent of the Phase III patients experienced one adverse event. Only diarrhea was statistically significantly different from placebo, 11.7 percent versus 5.4 with a p-value less than 0.0001.

The adverse events were only marginally greater in tegaserod groups versus placebo overall.

The serious adverse events incidence was equal to tegaserod, roughly the 1.8 percent with placebo, and their profiles were similar.

[Slide.]

There was one death in the study. In Study 301, a patient with a 14-year history of depression committed suicide on day 36 of the drug. Her mother had also committed suicide.

There were 5 severe adverse events in tegaserod that were possibly related to the test medication, 2 cases

of abdominal pain, 1 case of gastritis, 1 case of supraventricular tachycardia, and 1 case of hypoglycemia.

[Slide.]

The diarrhea, which is roughly defined as greater than three bowel movements per day with a loose, watery consistency and a sense of urgency.

Syncope was noted in tegaserod patients, eight tegaserod patients versus one in the placebo. The p-value was not significant.

Further details about the type of syncope or what other associated findings, I don't really have at this point.

"Ovarian cysts" is in quotation marks because originally it was thought that there were eight cases of ovarian cysts in the tegaserod group and one case in the placebo group.

[Slide.]

Now, back to the diarrhea. The incidence again, as stated, was highly significant. In alternators, the incidence actually went up to 21 percent from 11.7. By "alternators," we mean the patients who were judged to have alternating constipation and diarrhea.

Discontinuation secondary to diarrhea was 2.1 percent in tegaserod versus 0.6 in placebo, and that p-value was 0.002.

Fifty percent of the diarrhea occurred during the first week, a lot of it occurring during the first day. We haven't identified any contributing factors or protective factors.

DR. HANAUER: Where did you find the alternator term? In alternators, how was that term defined or how are you defining that term, or where are you finding that terminology in the study?

DR. JOSEPH: Oh, that came in the sponsor's material that was given to me, and the value for 18 to 36 percent was what they determined that fit the definition of equal to 25 percent of the time, diarrhea, loose stools, that sort of thing, so they were considered to be alternating constipation and diarrhea.

DR. HANAUER: Can we clarify, again, where did that come from, was that from the baseline period, was that from the --

DR. JOSEPH: This was at baseline, the 18 to 36 is the way I understood it from the material submitted to me.

DR. LEFKOWITZ: I can clarify that if you would like. We tried to look at people who may have had an alternating component to their diarrhea in several ways, one being based on the history that they gave and the Rome criteria, at least one of those three diarrhea criterias. That was 36 percent of the population.

At least in our calculations, the diarrhea rate in those patients were 14 percent on drug, 6 percent on placebo, and we also looked at patients who had greater than three bowel movements or watery, loose stools during the baseline at least 25 percent of the time.

In those patients, it was 5 versus 17 percent, and then in the category I showed you earlier, with low consistency of less than 3.5, we had 5 versus 18 percent in terms of diarrhea rate.

So, those were different ways we looked at people who may have had an alternating component. I could show those slides later if you would like.

DR. HANAUER: Maybe we will come back later because I think it is confusing us because of the entry criteria, which was supposed to be constipation-predominant, but that included people that were predefined?

DR. LEFKOWITZ: No, these patients were not predefined. Our indication is constipation-predominant. Some of these, because the disease varies over time, over the month of baseline, we looked at people who may have had, through one reason or another, perhaps a diarrheal component, as well, so those were the numbers in the data that I gave you.

DR. HANAUER: Not for now, but for later, can you look at just the patients who were constipation-predominant

excluding the alternators for your analysis?

DR. LEFKOWITZ: Sure. In other words, I think it would be the converse of those groups that I gave you. I could show you two slides later perhaps that would clarify that.

DR. HANAUER: Hugo.

DR. GALLO-TORRES: Are we saying that these are alternators during the course of the trial, but they were not identified as alternators by previous history? These patients had a 10-year history of IBS, right?

DR. LEFKOWITZ: Yes.

DR. GALLO-TORRES: They behaved as alternators even though they were randomized as constipation-prone patients, is that correct?

DR. LEFKOWITZ: The criteria that was constipation-predominant, because IBS, obviously, one, as was shown in one of the earlier slides, people can change over time, so over that month baseline, we did look at patients, as I just described, who may have had some symptoms perhaps that would also be consistent with a diarrhea component.

They were not predefined or prerandomized. Whether one wants to use the word "alternator," I am not sure, perhaps just people who during baseline may have had a component.

DR. GALLO-TORRES: Was that definition based on one-month data, one-week data, daily data, how did that definition of alternator come about?

DR. LEFKOWITZ: We did not -- and let me be clear -- we do not suggest that we have efficacy or studied alternating disease. We studies constipation-predominant disease based on the Rome I criteria at the time, ensured that they had an element of abdominal pain for randomization, I think similar perhaps to what would be done in clinical practice, and they were randomized.

We simply looked at people who, over the four-week baseline period, we looked at some of their symptoms and just wanted to look at them to make sure that they would not run into trouble perhaps who may be prone to diarrhea.

We also performed a safety study in diarrhea-predominant, which we could share with you at a later time if you are interested in that study, as well.

DR. GALLO-TORRES: Thank you.

DR. HANAUER: I am sorry to interrupt your presentation, but these are things for clarity.

DR. WISON: I guess the one question was during the screening period, if data presented itself that the person was perhaps diarrhea-predominant or principally an alternator, were they then rejected from randomization? I guess that is the critical question that one would have.

DR. LEFKOWITZ: Sure. Based on clinical criteria, the investigators were to evaluate patients, and if they were felt to have diarrhea by clinical criteria as opposed to strict number of bowel movements and stool consistency, but if they were felt to have diarrhea at least 25 percent of the time, they were not to be randomized into the study.

Now some patients may have, based on their diary, recorded a certain number of bowel movements who fulfilled the criteria, but the investigator did not feel that they had diarrhea that would exclude them from randomization.

DR. HANAUER: Again, later on, can you show us how many people were assessed at baseline and then excluded before randomization, so we get an idea of how many people really were dropped before they were randomized?

DR. LEFKOWITZ: It was 21 to 27 percent, but we could show you the breakdown, sure.

DR. JOSEPH: So, as I was saying before, we haven't identified any contributing factors to the diarrhea or protective factors per se.

In the long-term study 209, the incidence was 14.6 percent diarrhea and leading to discontinuation in about 3.5.

[Slide.]

Talking about the ovarian cysts, as I stated earlier, originally, we were given the data that there were

nine cases of ovarian cysts in the tegaserod group and one in the placebo.

Of note, the patients who went to the operating room, there were five cases in the tegaserod group and none in the placebo.

[Slide.]

The patients undergoing surgery, all five cases were on the 12 mg/day dose, three were from the long-term study 209, one for each from 307 and 351, none from the placebo group.

[Slide.]

I am just going to quickly go through these five cases that went to the OR.

The first case as a 50-year-old white female with a 10-year history of ovarian cyst. She had no abdominal pain. She underwent elective surgery performed on day 334 of drug.

The surgery revealed a benign tumor, and no cyst. So, we felt obviously that this was not associated with the test medication.

Let's go to the next case.

[Slide.]

Case No. 2. A 45-year-old white female, had a past history of hysterectomy. She did experience abdominal pain. She went to the OR on day 261 of drug. Her surgery

consisted of a bilateral salpingo-oophorectomy, and her postoperative diagnosis was adhesions, and there was no mention of a cyst.

[Slide.]

Case No. 3. A 37-year-old black female with a past history also of hysterectomy. She experienced abdominal pain on day 100 of drug. CT scan revealed a 2.7 cm right ovarian cyst. The surgery, due to continued pain, was performed approximately five weeks later, and that consisted of a right salpingo-oophorectomy, lysis of adhesions, and appendectomy.

The pathology in this case showed a 1 cm peritubular cyst, adhesions, and a normal appendix.

[Slide.]

Case No. 4. A 35-year-old female. She presented unknown. We have no idea whether she had pain, et cetera. Her surgery occurred on day 306 of the drug. Pathology consisted of multiple ovarian cysts, including a 3.5 cm partially luteinized follicle cyst, and adenomyosis of the uterus.

[Slide.]

Last case. A 13-year-old white female. She also had a past history of bilateral ovarian cysts. She presented on day 87 of drug with a right-sided abdominal pain.

The surgery was a laparoscopic resection of the right ovarian cyst, thought to be around 4 to 5 cm, and an appendectomy. The ovarian cyst seen at surgery was lysed and drained.

The pathology report showed early appendicitis.

[Slide.]

In summary, the relationship between the drug and ovarian cysts is unknown, although when we looked further at the data, it appears not as worrisome as the 8 to 1 that we originally saw.

Three of the five previous cases had pelvic surgery. Adhesions were seen in two, one had early appendicitis.

The pharmacologic effects of the drug - perhaps may be not causative in terms of ovarian cysts, et cetera, but is there something in the smooth muscle contracting activity of this affecting a hollow viscus perhaps in the pelvis that might be calling attention or focusing attention to pain in the lower abdomen. This, I believe would be a subject for discussion later.

[Slide.]

After another case was uncovered of ovarian cysts, I don't know because the case is still blinded, a 43-year-old female who had a tubal ligation with reversal about three years later. She was diagnosed with ovarian cysts via

a sonogram on day 23 of drug.

This resolved on its own with her menstrual cycle and she was discontinued from the trial due to nausea and flatulence that had nothing to do with the cyst.

[Slide.]

When you look at 301-E-01 and 307-E-01 are extended studies of 301 and 307. The incidence of diarrhea in 301 extended went to 15 percent with a 3.5 percent discontinuation rate, and in 307 extended study, it went to 24 percent with a 5.1 discontinuation rate.

[Slide.]

With the follow-up 120-day safety data, appendicitis, in the NDA, there was the one case, the 13-year-old female that I showed earlier. In the safety update, there were three cases - a 34-year-old female who had had three doses, a 44-year-old female who was on day 71, and 56-year-old female on day 224.

[Slide.]

The adverse events occurring more frequently in the tegaserod group - syncope with a nonsignificant p-value; diarrhea with a highly significant p-value; the ovarian cyst issue, the significance of which is unclear at present; and the relationship of Zelmac to risk of abdominal pathology leading to surgery is unknown, and I think that would be a subject for discussion later.

That's the end. Thank you.

DR. HANAUER: Any questions for the FDA?

DR. LAINE: Just to get a clarification and confirmation about the dropping of the primary efficacy endpoint of abdominal pain. Your report stated that this wa done after the results of 351 were known, is that correct?

DR. TALARICO: Yes.

DR. LAINE: I was just wondering how come or what was the reasoning behind the decision to allow, so to speak, or to drop that primary efficacy as an endpoint. Were there kind of methodologic issues? I mean they talk about the problems with VAS, I guess, in their handout.

I mean the first one, you were arguing I guess the overall relief issue you were suggesting or they were suggesting was too stringent. Was there something about the abdominal pain that made you want to drop that as an endpoint, as well, primary endpoint? I wasn't clear on that. Anybody can address that.

DR. GALLO-TORRES: Rather than we answering that question, I would like to ask the sponsor to reply to that, please.

DR. LEFKOWITZ: In regard to the abdominal pain, first, I think it may be helpful just to back up a little and review where our two primary efficacy variables came from.

As I mentioned before, there was both lack of consensus in the medical community and at the Agency. In consultation with the Agency, we were first recommended to use an endpoint of abdominal pain. Subsequent to that, we were recommended to use an overall relief measure. That is where the second efficacy variable came from. We thought it best, therefore, to use both as the primary efficacy variables.

I don't think by making an issue of abdominal discomfort as secondary means that we don't consider abdominal pain an important component of IBS. Clearly, we do, clearly, the altered bowel habit is an important component of IBS.

What we were faced with was an evolving field in terms of IBS. At the time that we knew the results of 351, there were recent recommendations related that the overall integrative measures should be the primary outcome measure in IBS. In addition to that, it would be very -- and I think we were able to come up with what we thought was a reasonable modification of that primary efficacy measure and make it both clinically relevant and we thought potentially more sensitive, whereas, in a visual analog scale, there were issues about trying to redefine what a responder is, so we thought it best at that point to continue with the overall relief as a single primary outcome measure, which

was the overall integrative measure now consistent with what was being recommended in the field, and to use the SGA of abdominal pain as a secondary measure as one of the components of IBS.

Clearly, too, however, we fully realized that this would increase our statistical power with less multiple comparisons giving the two doses and the two primary endpoints. But whether it is a secondary or a primary, I think the point being we showed significance in overall relief with abdominal pain, showing favorable effects at least in 301 with a significant p-value.

So, that is sort of our take.

DR. LAINE: I guess I am just trying, because, I mean there may be a fine line, but, you know, a change of primary endpoint is a fairly big thing obviously in a large clinical trial, and I guess the question is, is it because it didn't work or is there really good methodologic reasons to change it.

I mean you can argue that in your first one, you documented because your placebo rate, that, you know, it was too stringent, and it was perhaps reasonable to change. I am just wondering if you have the same kind of, you know, methodologic excuse, if you will, to change it.

It just looks convenient to drop it, obviously, if it didn't work in the first study, and I just wanted to have

more justification, I guess, for dropping it.

DR. KOCH: Gary Koch, statistical consultant from the University of North Carolina.

The methodologic technical reason for dropping the second endpoint was that in Study 351, with two doses and two endpoints, and for those two endpoints, success would be declared if there was significance on either one of them.

There was not a rule of having to have significance on both of them. It was a significance on either one of them. What that created is four comparisons. So, if there was only an effect on one endpoint at one dose, the p-value would have had to be below 0.05 divided by 4, 0.0125.

So, one had a situation in which the criterion for significance would have been 0.0125 if only one of the endpoints was sensitive and only one of the doses was efficacious.

So, when the analysis of Study 351 was completed, the assessment identified a way to come up with only one endpoint, so that multiplicity adjustments only had to be made across the two doses, that is, if only one of the doses worked, the p-value criterion would have been a p less than 0.025.

Assessment of how to produce a more sensitive endpoint was more feasible on the SGA of relief rather than

on the one for abdominal pain/discomfort or even a composite of relief with pain and discomfort.

Relief was emphasized because in some sense it incorporated pain and discomfort, and because of the way the categorical scale was structured, it lent itself more favorably to bring in patients who had somewhat relief 100 percent of the time as a fairly good response, and the information on that was shown in the presentation.

But the main reason why it was moved from primary to secondary was to reduce the extent of multiplicity in multiple comparisons, so that when the assessment was done in the next two studies, it basically done with a method where there were only two comparisons at the primary level that had to be taken into account.

DR. LAINE: Just so I have the timing of everything that went on right, I understood, though, that that first amendment, which was done before the studies were done, was done in order to increase the sample size to allow for these multiple comparisons and do have the two primary endpoints. So, that was initially already factored in, is that correct?

DR. KOCH: Well, my understanding is yes, the original sample size increase when the second point was added, based on the assumption that the treatment effect was at a 15 percent level difference, did allow for that.

Now, if the true treatment effect is closer to 10 percent, then, of course, that kind of additional stringency means that you cannot incorporate the multiplicity adjustment. So, if the true treatment effect is closer to the 10 percent than it is the 15 percent, you can't handle a multiplicity adjustment that pushes you down to 0.0125, but you certainly can accommodate one that pushes you to 0.025.

DR. LAINE: So, was 15 percent chosen as a clinically meaningful difference, and did that clinically meaningful difference change to 10 percent, or what was going on with that?

DR. KOCH: Well, I think the sponsor is better able to answer that.

DR. LEFKOWITZ: Again, sizing of studies based on a 15 percent difference is what we had expected to see in our Phase III studies based through experience. I don't think one can interpret what one sizes a study on as to what is clinically meaningful. I think that is a clinical term based on a benefit-risk of safety and efficacy.

As I mentioned before, if you really look -- and that is based on an intent-to-treat analysis conservative approach -- if you really look at in what was an unselected population, if you really look at the month to month, the laxative, nonadjusted responses, you consistently are at 10 to 15 percent.

If you would like to look at the female population in particular, then, you are much closer to the 15 percent treatment difference.

DR. HANAUER: We are going to break for lunch for an hour and reconvene at 1:30, but I want to put a slight charge to the sponsor, to Drs. Camilleri, Wald, and Cohen.

One of the problems we are having to deal with is that we are looking at a drug for irritable bowel for constipation-predominant, and the Rome criteria have been described, and similar to the last application we were reviewing months ago for alosetron, that was taking a patient population that were diarrhea-predominant, we are seeing overlaps of patients where the diarrhea-predominants with alosetron are having significant complications of constipation.

You are presenting a group that are constipation-predominant with the most obvious complication being diarrhea. We would hope from the committee to be able to come up with some guidances, guidelines, recommendations to how to select the population that is going to get the best benefit from the drug with the least likelihood of side effects.

So, I want you guys to come up with some descriptions of how we or the clinical world should be allocating this drug to those specific groups, do the Rome

criteria help, is there any recommendation that we can eventually give, but that is for after lunch.

So, enjoy your lunch and we will see you at 1:30.

[Whereupon, at 12:30 p.m., the proceedings were recessed, to be resumed at 1:30 p.m.]

AFTERNOON SESSION

[1:35 p.m.]

DR. HANAUER: Good afternoon. To give you the lowdown for this afternoon, we are going to begin with the open public hearing this afternoon, and then we will move back to the questions that we had asked the sponsor to address, and then discuss the questions that the Agency has asked the committee to address.

At this point, I would like to invite Nancy Norton up to speak on behalf of the International Foundation for Functional Bowel Disease. Welcome back.

MS. NORTON: Thank you.

DR. HANAUER: Did we do you good the last time?

MS. NORTON: Oh, I think so, yes.

Open Public Hearing

MS. NORTON: Before I begin, I would just like to say that I am here on behalf of patients and that my expenses have not been supported by any particular pharmaceutical company.

Members of the Committee, thank you for the opportunity to appear before you today. I am the founder and president of the International Foundation for Functional Gastrointestinal Disorders and establish current chairman of the Digestive Disease National Coalition.

The IFFGD addresses the needs of individuals with

functional gastrointestinal disorders, irritable bowel syndrome being the most predominant one.

As the founder of IFFGD, I began the organization in 1991 when there was no specific medical treatment offered to patients living with irritable bowel syndrome. It wasn't until the mid-1990's that we saw a stronger interest in the functional GI disorders and IBS in particular.

As you heard today, irritable bowel syndrome is a chronic complex of symptoms, affecting as much as 20 percent of the population. Symptoms include abdominal pain, bloating, constipation, diarrhea and fecal soiling. These common dysfunctions strike people from all walks of life and result in a significant toll of human suffering and disability.

Irritable bowel syndrome represents one of the most common conditions encountered by gastroenterologists and general internists. It accounts for 20 to 50 percent of all referrals to gastroenterology clinics. Approximately 70 percent of individuals with IBS in the community are female, with the incidence being reported as high as 90 percent in medical centers.

In the U.S. Householder Survey of Functional Gastrointestinal Disorders, Prevalence, Sociodemography and Health Impact, Drossman reported individuals with IBS will miss 13.4 days of work annually as opposed to the 4.9

national average. IBS alone has recently been called a multi-billion dollar problem by the gastroenterology community.

Survey data by Talley reflect that patients with IBS incurred an annual health care bill of $742 (1992 dollars) compared to $429 for those without the condition.

Data also reveals that there is an increased risk of unnecessary abdominal surgery correlated by IBS patients.

Hysterectomy or ovarian surgery has been reported in female patients with IBS as high as 47 to 55 percent and has been performed more often than in comparison groups.

One of our goals has been to move the research field forward to provide a better understanding of the pathophysiology of IBS and the underlying mechanisms with the hope that one day better medical management and treatments will be available to treat patients with IBS.

We are making progress. We are seeing the development and approval of drugs designed specifically for the treatment of IBS. I think it is important to recognize that the spectrum of symptoms that an IBS patient faces can range from severe constipation to severe diarrhea, or perhaps alternating between the two, all the while dealing with the pain that accompanies irritable bowel syndrome. It is difficult to imagine the impact of IBS without personally experiencing this chronic disorder.

If these drugs are found to be safe and effective, I would urge you to make them available to the patients who so desperately need them.

The toll of IBS is on the individual's quality of life and discomfort, affecting almost every aspect of their life. Each day presents itself with uncertainty, not knowing if their day will be plagued by bowel symptoms or not.

The World Health Organization has defined Quality of Life as being "not only the absence of disease and infirmity but also the presence of physical, mental, and social well being." Quality of life may also be defined as an individual's overall satisfaction with life and one's general sense of person well being. It also includes their functional capacity and their own perception of disease.

Health Related Quality of Life includes: physical function, somatic sensation, psychologic state, and social interactions that are affected by one's health status.

Health related quality of life indicators are subjective. Their validation lies primarily with the patient.

Eisen, Locke, and Provenzale report gastroenterologists spend 50 percent of their time caring for patients with functional bowel disorders. These disorders do not have mortality or physiological endpoints,

thus, the evaluation of health related quality of life becomes critically important.

Patrick, Drossman and colleagues developed the IBS Quality of Life Measures that distinguishes symptoms, functional states, perceived quality of life and social disability components. Their results confirmed that IBS has a broad and significant impact on a person's quality of life in addition to the disease activity and symptom impact.

At IFFGD, we talk to tens of thousands of individuals who live with IBS and there is a constant theme that we hear from women and men. They consistently confirm the isolation that many IBS sufferers experience.

Partly, this is because IBS is very difficult for most people to discuss. Many patients believe it would help if they could talk about their condition and share their experiences. But the reality for them is that even mild symptoms can be very embarrassing to discuss.

More severe symptoms like unpredictable pain, urgency and bowel incontinence are close to unmentionable for many sufferers. Interviews with IBS patients consistently reveal that few talk about their symptoms with anyone else. Indeed, many patients go to great lengths to hide from others their condition and their own distress.

What does distress feel like if you have IBS?

If you are a person with constipation-predominant

IBS, chances are your distress and pain will increase with each day that passes that you do not have a bowel movement. The feeling of fullness and bloating, the pressure that begins in your rib cage, the distention in your stomach, the ache through your midsection, the cramping in your intestines causes you to double over in pain.

Each day that passes that you are not able to evacuate, you find yourself straining to have a bowel movement. We all know that continual straining to have a bowel movement may eventually cause more severe problems in the future, like rectal prolapse, which may result in fecal incontinence and ultimately surgical intervention.

For the IBS patient, the pain and discomfort is now, and they need to relieve that pain.

We see so many messages about constipation and diarrhea through the media that I think that people often lose sight of just how severe these conditions can be when you are faced with them as a chronic condition.

Who stops to think about the fact that IBS patients with constipation are afraid to leave their home or be in a social situation because of continual gas and bloating that they experience with their constipation?

There is little compassion when it comes to understanding bowel disorders and the impact that they have on people's lives.

IBS affects not only one's professional life, but also their personal life as well. It is difficult to plan trips, to eat in a restaurant, or even go shopping. Friendships, intimate relationships, and one's sex life are affected by it. There is no spontaneity in life for the person who lives with IBS.

There is a quiet anxiety, an anticipatory response to perhaps what will be next. One may be depressed at times feeling that their life is out of control or at the very least that their life is controlled by their bowel.

We live life from the edge of the room never willing to truly participate to the fullest for fear of having to find the quickest way out. There is a loss. There is lost potential.

IBS is invisible to others, but it affects every aspect of our life. Who would know our pain and oftentimes the shame that we feel except those who are closest to us. There are times when we feel very isolated because of our IBS.

There is a loss of spontaneity when symptoms may intrude at any time. Plans made often need to be changed. IBS is unpredictable. One can wake up in the morning feeling fine and within a short time encounter abdominal cramping to the point that you are doubled over in pain and unable to function.

The unpredictable bowel symptoms may make it next to impossible to leave home. For those of us who are attempting to manage our symptoms in the workplace and in social settings, we may find ourselves stranded in public restrooms until we feel some sense of security around our bowel. Public restrooms become a nightmare for us.

IBS patients are to be credited for the personal strength that they find each day to even just walk outside the door and into life while attempting to manage their bowel.

Few of you here today had to think about your bowel management program. You most likely came today with little thought, if any, as to are the public restrooms close at hand, how long would the taxi ride be from the hotel, where was your seat on the airplane, is it an aisle seat or a window seat.

These are just the little things that most of us don't give a second thought to. The person with IBS is thinking all the time about logistically how do they get through the day. For many people with IBS, the risk of leaving familiar surroundings is just too great. Their life is truly diminished little by little.

If there is any question in your mind as to the need to provide medical treatment to millions of individuals who suffer from IBS, please, let me share one more

experience with you.

On January 27th, Camille Grammer, who suffers from IBS, appeared with her husband Kelsey Grammer on the Today show with Katie Couric, on behalf of IFFGD. The foundation received over 12,000 phone calls from people looking for help. The 12,000 people who called are just the tip of the iceberg of those who need help. Today, you are in a position to provide it.

Many of those people expressed how alone they felt. They were looking for someone to tell them that there is a reason to be hopeful for their future and that medical science is working to find answers for them.

You are here to make recommendations on a potential new drug treatment for IBS that may provide relief for a significant proportion of the IBS population.

If Zelmac is shown to be safe and effective, it will represent a significant step forward in providing treatment for sufferers of IBS.

Thank you.

DR. HANAUER: Thank you.

Does anyone have questions for Ms. Norton?

[No response.]

DR. HANAUER: Thank you, Ms. Norton.

Are there any other public comments before we move ahead?

[No response.]

DR. HANAUER: We left before the break with me trying to pose a question back to the sponsor and the consultants as to whether or not we can really classify patients adequately into the different subtypes of IBS, and I would be interested if Dr. Wald would like to comment on that.

Responses from Novartis

DR. WALD: Yes. Could I have QA178.

[Slide.]

We obviously gave considerable attention to your request and tried to clarify for whom this drug might be used and on the basis of the data that we have. So, we would indicate once again that it is indicated for the treatment of female patients with IBS defined as abdominal pain/discomfort, and altered bowel habit in whom constipation is the current predominant symptom.

The issue of constipation was one that we carefully thought about and our response is based in large part by the Rome criteria, a consensus of experts who have talked about constipation, and with the growing realization that what our patients mean about constipation is often different than what physicians think of, and therefore, the old, very narrow definition of infrequent bowel movements is really inadequately to describe what patients mean when they

say they are constipated.

So, we would define constipation as a current decrease in bowel movements, below the accepted number of three per week, passage of hard or difficult to pass stools, excessive straining at defecation, and we might choose greater than 25 percent of the time, which is Rome or whatever the clinician's definition, or a sense of incomplete evacuation.

Any one of those or combination would be acceptable as a definition of constipation as we clinically understand it.

DR. HANAUER: Now, going back to the clinical trials to support this indication, are these the patients who were entered into the trial, did they meet these criteria for constipation?

DR. WALD: I think that is an important question that was raised by Dr. Joseph and perhaps even misspoken by us. If I could have the fourth slide on my presentation for the overview, which would be the Rome II criteria, but we can use Rome II and Rome I as examples of what I am talking about to make the point.

[Slide.]

I would remind those of us talking about constipation that according to the Rome criteria upon which this study entry was based, that what we are talking about

is the preceding 12 months in which there are at least 12 weeks or more, again need not be consecutive, of which abdominal discomfort or pain is associated with two of the three features that we have talked about.

Therefore, it is conceivable that an individual undergoing a four-week baseline trial prior to entry could have what we might call diarrhea, yet, would still fulfill the criteria which were based upon the clinician's evaluation using very specific criteria.

While for the individual patient, that clinician might choose not to use a drug like tegaserod at that point in time, we would anticipate that this patient would revert, if you will, back to their constipation-predominant disorder for which they were being enrolled.

So, I don't think we have alternators in our studies, those who we can tease out, and so forth. I think that all of the patients that were in this trial fulfilled the criteria, which was based upon the preceding 12 months prior to entry into their study.

In other words, the four-week trial at baseline does not invalidate the previous year's pattern upon which these patients were classified. I think we all as clinicians here know that patients will vacillate back and forth, sometimes having diarrhea, sometimes having normal bowel function, but their predominant pattern will be what

we what we have defined as constipation-predominant IBS.

DR. HANAUER: Thank you. You are a good politician.

Yes, Dr. Wison and then Dr. Wolfe.

DR. WISON: I guess one question that I have then, what was the goal of the four-week period theoretically?

DR. LEFKOWITZ: The goal of the four-week period I think was twofold: one, to establish baseline comparisons to compare the treatment effect to, and I think, two, is to get the patients used to filling out the daily diary and the study conditions.

DR. WOLFE: I want to try and word this properly. Is constipation sort of a moving target, and if you are using the strict definition of at least 12 weeks during the previous 12 months, but the slide before you stated that the patients had constipation at that particular moment in time, then, they could really enter the study without really having constipation at that time?

DR. WALD: Yes, I think that is correct, that even though they fulfilled the definition, in that four-week period they could exhibit what we might define as diarrhea predominants. That was not to invalidate your diagnosis according to Rome criteria.

Rome is very strict in terms -- it is not for the day to day or individual care of a patient, it is to enroll

patients into studies that are hopefully more homogeneous than in the past, and also it is useful for large epidemiologic studies which, of course, are often based upon recall. So, there are limitations, as well as advantages, of using Rome criteria, or any other criteria for that matter.

DR. HANAUER: But for the Rome criteria -- and please correct me if I am wrong -- they are established for the diagnosis of irritable bowel syndrome, but have they been established for the subcategorization into the three types that you are speaking of and that you we have been alluding to?

DR. WOLFE: And also really, this is a question regarding the use of this drug, is this drug really going to be a drug used long term, or is it better for people who actually have an exacerbation of their symptoms for the short term?

DR. WALD: Which question should I answer first?

DR. HANAUER: Answer mine first.

[Laughter.]

DR. WALD: You know, that is a very good idea. Now, what was your question?

[Laughter.]

DR. HANAUER: With the Rome criteria to establish diagnosis of irritable bowel syndrome, but we are moving on

now in a previous submission and this submission for a specific subcategory of IBS, and do those criteria really allow categorization?

DR. WALD: Well, if you look specifically at Rome, there is a diagnosis for irritable bowel, and then there are subcategories for things like functional constipation, functional diarrhea. The use of constipation-predominant and diarrhea-predominant, I think is historical in an attempt to further subdefine, recognizing that there are patients will either go back and forth, the so-called alternators who have 25 percent of this and that, or those who may have some diarrhea, but still are predominately constipated.

The issue is validation, of course. Not all in this room I am sure agree with Rome or all of its subcategories, but it is probably the most recent and best attempt to bring some order out of chaos, and so we accept the limitations of Rome.

I don't think we ought to hold to it hard and fast, but in the alternative and what we had before, I think it is a quantum jump and the studies that are now being done on fixed criteria, such as this, although they will never be perfect in a disorder in which you lack a biologic disease marker, well, sure, we have been advanced compared to what we had in the preceding 20 or 30 years.

Of course, it is a moving target. Now, the issue of constipation, and is it a moving target is what you wanted to know -- you know, for clinicians, there are patients who will good weeks and bad weeks. The reason for doing, in my own opinion, 12-week trials is to try to tease out placebo response rates and to make sure that whatever effect you are seeing is durable.

In the marketplace, in the clinician's office, I am sure that doctors will use this drug very differently, recognizing that IBS is episodic, that there are periods of time, perhaps weeks or months, in which you want to use the drug, and then backing off.

So, I don't think that this study seeks to define how it will be used, simply that it could be used for certain defined patterns, and it remains for others to then determine, and then the postmarketing surveillance, if we should come to that, how the drug would be used.

I myself would imagine using it for only a few weeks at a time in many patients who are episodic, but not using it for a full 12 weeks.

DR. HANAUER: I think actually what we are trying to do is help everyone understand the problem and actually help to understand some of the data from the trial, and that is my impression that we are dealing with a disease that does -- I agree with you in everything you have said -- that

does tend to be cyclic and that the problem that we are confronted with is giving a constant medication for three months at a time is going to even out those cycles, and that is why we don't see as prominent a difference as the sponsors would have predicted in the beginning.

On the other hand, there may be a way to, and what we are trying to do, is help the Agency come up with -- and the sponsor -- come up with an indication that would be clinically useful for those who are going to be prescribing the drug and the patients, Ms. Norton and her group, who are going to be taking the drug.

One of the concepts that I might throw out is that it is not necessarily the concept of the phase of the disease. As you mentioned, you might only give this during the constipation phase of irritable bowel rather than constantly for a period of time, but I don't want to consume the conversation.

DR. WALD: Just as a clinician now, just looking at the data, I would probably be remiss if a patient who had constipation-predominant symptoms came into my office with two weeks of diarrhea, and then I gave a drug whose potential side effects would be diarrhea. I think I would wait until they were unhappy and telling me that they weren't having a bowel movement again.

DR. HANAUER: Dr. Richter.

DR. RICHTER: Steve, let me follow up on this with Arnie, and Mike may want to answer this. As I understand the Rome, this definition is more so for the clinician. I mean this is your ultimate recall definition.

Your patient comes in the office to see you or I. They are complaining about constipation. You take a history. You get constipation and pain. You try to get some type of a quantification from their history over the last year what they have been.

I am not sure how accurate that is, but right now we know that is about the best that we can do. So, this kind of puts you into a global group, this patient looks she primarily falls into a constipated type of IBS.

But then doesn't your lead-in phase, doesn't this baseline phase, shouldn't it allow you to really quantify and qualify that more accurately? That is what I am bothered about by the demographics.

I have no problem that this is IBS pain, it's just describing this as IBS constipation pain that bothers me, because again, of the demographics of the patients, the number of bowel movements they are having, the fact that only a third of them have hard stools, and yet the stool consistency score, which averages 4.7, is somewhere between neither loose nor hard or somewhat hard, which is about what I have every day.

[Laughter.]

DR. RICHTER: But the point that I am making, though, is that your baseline characteristics of this is really your hard endpoint for what your patient group is that goes in, not the recall based on 12 months, because I have problems even with recall based on a week, because that recall based on a week, they may be feeling good those last two days, and they are going to say every day they have been feeling well.

DR. WALD: I think your points are very well taken, and we all know the limitations of recall versus prospectively applied data, both in constipation and in IBS, and perhaps most disorders that we deal with.

The only way to invalidate the diagnosis based on recall, if we use Rome, is to prospectively follow individuals for a year, and that, of course, would be logistically impossible.

You would have to show that in the next year, after you decided that you wanted to enroll these people, that they for a year fulfilled their criteria of constipation-predominant. You can't do that.

So, we accept the limitations that a month may not be representative, but even perhaps there are people who miss-recall, but I think it is the best we can, and besides those patients I believe are rather evenly divided amongst

the placebo and the active drug thing, so you hope by unbiasing, blinded studies, randomization, that you try to even that out.

But again I would emphasize that Rome is useful for a clinician often to avoid misdiagnosing IBS, but it has not been validated as an office practice tool for that patient who walks into your office and where you are deciding does this person have IBS or not.

It is best suited for large-scale epidemiologic studies and the kinds of studies that we have had presented here in the fall and now again here, and with its limitations.

DR. HANAUER: Michael.

DR. CAMILLERI: May I take the liberty for a couple of minutes. I think that a number of very good points have been made, and one of the reasons why the clinicians at lunchtime came up with the added concept of current predominant constipation is really fueled by the comment that Dr. Richter just made, that if you look at the mean consistency and frequency data, you actually dilute out the interesting and significant message that we have seen this morning, and I would just like to reiterate three points very rapidly on the slides.

[Slide.]

The first is QA77 indicating that in that four-

week run-in period, which Dr. Richter is telling us is a nice way to enrich our study population and characterize it, there are 60-something, almost 70 percent of patients who fulfill criteria either for frequency or hard or very hard stool. Therefore, the majority of these patients in fact prove to have the constipation-predominant irritable bowel syndrome currently in the context of the study.

[Slide.]

The next point I would like to bring to your attention is ESG123, and here what we are going to see is the influence of current in the four-week run-in period, stool consistency, ESG123, and stool frequency, and what we see here is that if patients have more than three bowel movements per week, there is no efficacy of the medication or if they have loose stools.

On the other hand, in these 2,000-odd patients, if they have less than three bowel movements a week or absence of loose stools, you will see the efficacy of the medication grouped across the three studies, and a similar result is also shown on 125, but I won't waste the committee's time.

The point I think that clinicians at lunchtime would like to bring to the attention of the committee is that it is the current symptom of constipation defined not necessarily by frequency, but by consistency, difficulty with stool passage, excessive straining that would suggest

that this medication has an added benefit, and indeed, by meeting all of the stool data, as Dr. Richter predicted, or as you predicted, Mr. Chairman, there is actually a dilution of the effect of the medication.

Thank you for your attention.

DR. HANAUER: Before you go -- so, your patient takes the drug and gets out of the constipation phase. The studies have shown continuation of it. Is that what you are going to do in practice?

DR. CAMILLERI: Mr. Chairman, you obviously know that in the context of a clinical trial, one is bound by the need to fulfill the trial criteria. Clearly, as Dr. Wald indicated earlier, and I am sure Dr. Cohen will suggest after I have moved away from this microphone, I suspect that we will all recommend that for patients who seem to be going into remission, it would be appropriate to suggest a drug holiday and stop the medication, but I defer to his --

DR. HANAUER: But your indications and the marketing, hence, the marketing of this appear to be as if it would be given as a continuous course over three months, was showing three-month data on that.

The issue is should labeling be modified -- I am putting it back to you guys, and eventually we will come to this -- should labeling be modified, so that it should be used during a phase or to treat the symptoms of.

DR. CAMILLERI: It is often established clinical practice among people who see a large number of these patients, that when the patient goes into remission, you would obviously try to withdraw the medication, and I think that the only way in which the label can be written presumably is as it relates to the way in which the clinical trial was performed.

DR. HANAUER: Right, but as you pointed out in the very beginning, 80 percent of these patients are seen by primary care physicians, not gastroenterologists, who are not the sophisticated nature of you or your colleagues or many or some of us at the table here.

DR. CAMILLERI: I think you for that compliment. Nevertheless, I do have a lot of confidence in our primary care and general practice colleagues, and I think we should defer to your committee to help in the decision as to how this medication would be given, and I think it would be consistent with what you and I as gastroenterologist clinicians do in our practice.

Thank you.

DR. HANAUER: Thank you.

Dr. Cohen.

DR. COHEN: Can I please have that 178 slide back.

[Slide.]

I would just comment. I think there is a great

deal of confusion here. The Rome criteria are very good for doing large population-based studies, and is also very valuable for the clinician to identify clinically the patient with the irritable bowel syndrome, and not only has clinical diagnostic criteria, but it has exclusion criteria, and it is being widely adapted by, for example, the American College of Physicians are recommending that this be used for the identification of patients with irritable bowel.

Indeed, now, you have asked the question, Dr. Hanauer, about the indication, and I think this indication, as stated here, carries a lot of important components. First, treatment of female patients with irritable bowel syndrome, and the definition of abdominal pain and altered bowel habit with constipation being the predominant current symptom, and the word "current" is critical, and the word "predominant" is critical in that definition.

The patient may have had in the prior 12 months or 20 years have had other components, but that when that patient presents, the patient then identifies the type of syndrome that they have current, predominant symptom of constipation, and then at the lunch table, we discussed the definition of constipation, which cannot be a narrow definition that we were going down or the pathway we were pursuing at the presentation this morning.

It has to be defined clinically. A decrease in

bowel movements, hard, difficult to pass stools, straining at defecation or feeling of incomplete evacuation.

My sense is that the clinician will treat this drug until the patient goes into some sort of clinical remission, and in some patients it would be a 12-week period, in some people it is going to be a long-term therapy. It is not going to be on-demand therapy.

So, I think the definition as you charged us here, the proposed indication is encompassing of the kinds of patients that I believe we would like to see be treated with this medication.

DR. LEFKOWITZ: Mr. Chairman, if I may just make a couple points. One of the reasons that we conducted our trials this way, that is, based it on clinical history, is that we can answer the question what happens when patients are treated with this drug who are liable to have diarrhea intermittently, how will they do on the drug. Otherwise, I would be standing here today without an answer to that question, and I could tell you in our Phase III trials, the incidence in diarrhea was about 3 to 1, 15 percent versus 5 percent in these patients.

As I mentioned before, we also did a study in diarrhea-predominant patients, which had very similar results, but we saw no serious adverse events, very low discontinuations, so we were able to answer that question,

and that was one of the reasons we approached it that way.

If I may also just take the liberty, based on that statement, which showed in female patients, if I could show Slide QA18 --

[Slide.]

I just wanted to again show the results in female patients as the magnitude of effects certainly came up. Here is the total population in 351, female patients in 301, female patients in 301, not much difference in 307 again on the SGA of relief, and in the next slide, 19 --

[Slide.]

Shown here are the monthly results. These are patients again remaining on the drug in practice, and in 301, the prospective endpoint in 301 and the SGA relief, you do see response rates around the 15 percent mark.

Further, if I could have Slide ESG31 dealing with the issue of abdominal pain in women --

[Slide.]

Shown here are the results of abdominal discomfort/pain in women at endpoint, fully adjusted values, intent-to-treat analysis, Study 351, a 9 percent difference, Study 301, a 10 percent difference, and let me point out that even if the SGA of abdominal discomfort was retained as a primary endpoint, in Study B301, this result would be statistically significant in the female population.

Thank you.

DR. WOLFE: One question that was brought up before by Joel was are we convinced that the decrease in pain was due to an improvement in constipation, and that could be answered by certain studies, I am not sure if they were done in the past or not.

If this is a drug which blocks afferents, then, by doing distension studies, balloon distension on this drug, you should be able to have better tolerance toward distension. Was that done?

DR. LEFKOWITZ: We performed one study in visceral sensitivity using a 4 mg dose, looking at rectal distension, and in that study we did not see an effect on visceral sensitivity. I might add, however, these small studies, which used a lower dose, and I don't know that is a particular best model to look at visceral sensitivity in man.

DR. WOLFE: In women.

DR. LEFKOWITZ: Yes.

DR. WOLFE: No 12 mg doses at all?

DR. LEFKOWITZ: No, we did not.

DR. SMITH: This may seem a bit facetious, but why don't we market placebo? You have a 40 or 50 percent response rate in the first two weeks, when some of the daily symptom calendaring, and if we are looking for a treatment

that addresses the syndrome, to recognize that it is a syndrome that has both psychological, psychosocial, and physiologic parameters that are distorted and affecting success and failure, but how does the placebo work, and why does it work so very well?

DR. WOLFE: We actually have been using placebo for many years because a lot of the drugs we use for IBS have never really been tested, and many of them are very old drugs, which have been used historically.

DR. WALD: That was exactly the point I was going to make, that we already are using placebo. If we define a drug that we are using, prescription or nonprescription, has never been more effective than placebo, and that is the story of irritable bowel syndrome.

How placebo works and why placebo works is unclear. Certainly, the concept that placebo works best is psychoneurotic individuals is probably not correct. Placebos are more likely to work in people who want to get better than people who don't, and whether that is working on endorphins or other kinds of things, we don't know, but that has been the experience of all clinically based entities where there is a huge response.

One might even conclude that in certain cases of inflammatory bowel disease, peptic ulcer, that placebos have a certain heal rate as well. So, it is a very potent tool

to use as long as the placebo that you are using doesn't carry with it any significant side effects.

DR. HANAUER: There are ways. These studies did not show the placebo was better than no treatment.

DR. COHEN: But I would comment that going back in gastroenterology when we had our first drug, the first H2 antagonist, that was a very prominent finding, and people were astounded at the very strong placebo response in GI trials for diseases where you actually had an organic lesion like a duodenal ulcer or a gastric ulcer, patients with esophagitis, and it seems to be consistent in gastrointestinal syndromes and diseases, and somewhat different than other disorders like cardiovascular and pulmonary disease, but I think you can ask the same question for many of the treatments that we have in GI.

DR. RICHTER: For anyone in the Novartis group, this is a three-month study. We have defined IBS as a disease which cycles and has to at least have 12 weeks of whatever your predominant pain complaint is or constipation complaint.

Can we get some evidence of prolonged efficacy past three months from your long-term studies, particularly your patients that have been in there a year, how does their response at six months and a year compare to their three-month response, does that continue? You see an acute

response and then abate some, does that plateau and stay plateauing?

DR. LEFKOWITZ: Yes. As you pointed out, we only have control data after three months. In the long-term study, those patients who actually complete the study, and using a response definition in that case of complete/considerable relief in this open label study, approximately 65 percent of patients had a response at the end of 12 months.

If you look at patients who had a response -- and clearly, people have dropped out of the study -- if you look at patients who were responders at month 3, and then what happened to them over the 12 months, 60 percent of those patients remained in the study and were responders at month 12, with approximately 20 percent of the patients having dropped out and 20 percent of the patients being non-responders.

DR. RICHTER: What that is signifying, Martin, is that even over that year's period of time, then, you have people that are not responding or dropping for other reasons. So, you are continuing actually, if anything, this drug doesn't plateau its effect out, this drug does have a falling decline in the efficacy over a year's period of time.

DR. LEFKOWITZ: No, I am not sure one can conclude

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DR. RICHTER: Well, you said at the end of three months, that that represents -- the question I am asking, if at the end of three months you get 100 percent responders --

DR. LEFKOWITZ: Correct.

DR. RICHTER: Then, what are those 100 percent responders doing at the end of a year? If they are not in the study at the end of the year, I consider that a non-responder.

DR. LEFKOWITZ: I understand that. The answer again is that 60 percent of those patients at month 3 are in the study, at month 12, unresponders, but clearly, we do not have a placebo control. I would submit if we did have a placebo control, you would certainly potentially see a difference. So, I think 60 percent of patients with irritable bowel syndrome maintaining a response in a waxing and waning disease is I think fairly reasonable.

DR. HANAUER: I am just pondering your last statement because I am not certain that you have shown maintenance of a response over a period of time, and that would be if we get into very subtle differences here, between the difference of maintenance of a response and intermittent treatment of this, which is what you are hearing most of your consultants and the members at the table thinking the way they would use it.

DR. LEFKOWITZ: Yes, we did look in our clinical trials of patients who responded at month 1 and what proportion of them remained responders at the end of the study, if you are interested in those data.

DR. HANAUER: Sure.

DR. LEFKOWITZ: That is in the ER file. That would be ER8.

[Slide.]

Again, these are people who were responders at month 1 to the drug, and then in 351, 301, 307, as you can see, most patients, whether on placebo or on the drug, more here in 351 on the drug remained responders at endpoint with similar rates across the three studies.

So, it was a persistent response, but it was also largely a persistent response in the placebo patients, as well.

DR. WISON: Just one point, though. You don't have any of the data for once people stopped, whether they returned to their baseline or whether that response was maintained, is that correct?

DR. LEFKOWITZ: That is correct, in a controlled fashion we did not collect that data, yes.

DR. TALARICO: Do you have any evidence if there is any rebound phenomenon when patients stopped the drug?

DR. LEFKOWITZ: I am sorry?

DR. TALARICO: Any worsening of the symptoms when they discontinued the drug?

DR. LEFKOWITZ: Again, we did not keep this patient in the study, but we did not get any reports from the sites. We collect safety after 30 days in these patients, and have had no evidence of that.

DR. HANAUER: There must be follow-up data on these patients in some way for safety, I presume, I haven't seen serious adverse events in the next months, that they became obstipated and needed surgery or anything like that?

DR. LEFKOWITZ: No, that is correct. We collect serious adverse events at least for 30 days, and often get reports well beyond 30 days, and we have gotten several serious adverse events in the population both on placebo and drug following completion of the study.

DR. HANAUER: Does the Agency have data on, for instance, an adverse event, such as constipation, 30 days afterwards, was that submitted in?

DR. LEFKOWITZ: Sure, we submit all serious adverse events that are reported to us.

DR. HANAUER: Other questions from the committee? Dr. Hammes.

DR. HAMMES: Do you have any data on duration of effect, single dose duration of effect, or how long after stopping you have a duration?

DR. LEFKOWITZ: You mean a single dose study in terms of --

DR. HAMMES: Well, we know that when things bind receptors, some of them can be insurmountable and stick around for a week or until new receptors are made. What does this drug behave like at the receptor?

DR. LEFKOWITZ: I think perhaps Jim McLeod might be able to give some information from some of the healthy volunteers or other studies.

DR. McLEOD: Most of our data is on control because we are usually looking at pharmacokinetics, but we did several control trials with placebo. What we observed was similar to Marty's during the multiple dose situation where most of the gastrointestinal adverse events, and since we are not looking at an effect, we are just looking at adverse events, occurred on the first and second day.

Then, we saw very few over the ensuing two weeks, which was the longest period that we dosed in the control situation where we intensely gathered this information.

We did a series of studies where we looked at the pharmacokinetics in a cross-over manner, so we would administer the drug, a single dose predominantly or one or two doses, and then we would bring them back either a week later or some period thereafter.

The effect again occurs when the drug is

readministered, so we do see a number of increased bowel movements on the first day of readministration a week later, and then subsequently, we have done three, four, or five cross-overs like this, so in terms of the effect, this receptor or its physiologic consequences seems to recover within a week.

DR. HANAUER: Dr. Ferry is kind of quiet, but I will use his prerogative. IBS and constipation are common in children. Do we have data at all in children?

DR. FERRY: That is what I was looking for. You had one 13-year-old patient with ovarian cysts. I don't know how many other children you had in the study.

DR. LEFKOWITZ: In Study 351, the age limit was 12. Although we didn't go to pediatricians, we tried to find GI sites who had told us that they dealt with a lot of adolescents. In fact, we only enrolled I believe it was three adolescents into 351. We have submitted a proposal to the Agency for a pediatric study that is under discussion right now.

DR. WOLFE: I am forgetting what was asked and what was presented. Do you have any data to tease out or to stratify according to the real severe constipation versus the mild constipation, looking at response rates, was there any difference?

DR. LEFKOWITZ: We looked at data based on