abdominal pain severity, because data in the literature suggesting that patients with more severe pain may be less responsive. So, that is the stratification that we did do.

But the 12 mg dose with data I could show you, there was no difference between mild -- we broke it into tertiles, and there was no difference. For the 4 mg dose, there seemed to be a difference with people with severe pain less likely to respond.

DR. WOLFE: That was pain only, though.

DR. LEFKOWITZ: That was pain only.

DR. WOLFE: Because the pain is just so difficult to quantify. Constipation, at least you can get some quantification.

DR. LEFKOWITZ: If you want to go to ESG125.

[Slide.]

This is a slide I showed before, and I am not sure that this fully answers your question, because we don't look at patients with very severe pain, but again, this was a small number of patients in the study who had stools 3.5 on the scale with 3 being somewhat loose. These are sort of the middle group, and half the population with the cutoff on 4.5. This was the data I showed you earlier.

I guess you might be interested in the people further out on the scale, but we didn't break out the data that way.

DR. WOLFE: Any statistical analysis of these patients?

DR. LEFKOWITZ: In terms of?

DR. WOLFE: Any statistical difference in --

DR. LEFKOWITZ: I mean clearly between here and here, they looked quite similar. We didn't run formal statistics on this data.

DR. HANAUER: Other questions to the sponsor from the committee?

[No response.]

DR. HANAUER: I want to handle a few questions that were left over from the statistical group before we go to the big picture questions that the Agency has asked the committee.

Going back to the statistical assessment, and the sponsor can address some of these questions, too, the first issue is that the summary from Statistics said that there was a significant treatment effect demonstrated in female patients in Study 301, that was supported by the post-hoc analysis in 351, but not replicated in 307.

What is the difference? Why was there no effect seen in 307? A treatment effect was not demonstrated for either dose in 307. I am asking you or the sponsor.

DR. WOLFE: No one knows. We can't give an answer, we can only speculate, but I think I have two

explanations why -- I don't think 307 -- first of all, the dose escalation I think just enhances the placebo response because if one works, three is better, so you are just actually help encourage those.

If you looked, they had a sharp rise, at least some of the data they had a sharp rise in improvement as they escalated, even placebo. So, I think that study right there really may have hurt them.

DR. HANAUER: Along those lines, were the number of tablets a day increased, or was the dose increased in dummy tablets?

DR. LEFKOWITZ: The number of tablets were kept constant, at two tablets twice a day. By study design, the patients were not supposed to know when they were being dose escalated. Clearly, the study coordinators knew because they had to give them the correct drug supply.

We certainly suspect that the patients did know that week before was the time of dose titration, however.

DR. HANAUER: You think they knew.

DR. LEFKOWITZ: Yes. That would be my speculation, speculation.

DR. WOLFE: The other reason is that from 4 to 12, regardless of the question of desensitization and tachyphylaxis being, yes, less common with partial agonists, it still does occur, and if you have a little bit of a drug

working, you up the dose at that point, you will not probably have the effect that you would have by starting off with a higher dose in the beginning.

So, it is all speculation, but again, I don't think there is a very good dose response curve demonstrated for this drug, and the doses may have actually, 4 and 12, as far as -- we can't measure acid secretion. I mean we don't have an objective parameter to measure here.

It makes it very difficult to really determine what is the optimal dose. You are looking at symptoms only. So, for that reason, 4 and 12 are going to be very similar in regard to the response.

DR. LAINE: I was going to ask actually, the sponsor, experts, or anybody else, the only trial that was clearly positive, 301, was done completely in Europe. 351 was done in the United States and did not achieve the primary endpoints, and 307 was done two-thirds in the United States.

Certainly, in other GI diseases, we have dramatic differences in responses between the U.S. and extra U.S. populations. Do we have data on IBS and differences that occur in different populations? This is again the only study that was positive was the European study without U.S. patients.

DR. LEFKOWITZ: As I showed earlier, what we

looked at were the demographics of the patients, the baseline characteristics of the patients, and they were almost --

DR. LAINE: That is not really the point. The point is do we have -- we have lots of, as we talked about at lunch, lots of peptic ulcer studies that showed marked differences between healing rates in the United States and Europe, H. pylori, I mean there is lots of different precedents for that.

I am not really talking about your study, because your study clearly did show a difference in response between -- or it seems to me at least -- between European and non-European, or European and U.S. studies.

What I am asking is are there other studies to show similar differences in responses depending on different countries? I mean there have been previous IBS studies either the Glaxo's information or other studies that we have had in the past.

DR. LEFKOWITZ: I can't comment on the other studies. I would just submit that my interpretation of the data is that the response rates in Europe and U.S. were overall quite similar, 301 and 351, the results were quite consistent between the two studies.

DR. LAINE: The only problem is 351 was really, you know, was positive only after you had already seen the

results, so I think we have to take that with a grain of salt or at least certainly not as a pivotal trial.

DR. LEFKOWITZ: I understand that, but what my point is, however, is that the overall response rates, the treatment differences in those two studies were actually quite similar.

DR. HOUN: The Glaxo experience was U.S. only for those pivotal trials.

DR. HANAUER: Other comments regarding that 307? Did you want to say anything about 307?

DR. SURAWICZ: No. It is just that I don't think the panel can answer why 307 wasn't successful. The company would. I think they have done an excellent job in their presentation and handling questions, and it is obvious that the placebo rate is -- the response rate is so high there. Why those things happened, I don't think we will ever know.

DR. HANAUER: The other question back from Statistics was whether or not the effect, has the effect of treatment on abdominal pain been adequately assessed, the specific aspect of abdominal pain.

Are you comfortable with the way that that was evaluated in these trials?

DR. LAINE: Are you asking how it was evaluated or what the results were?

DR. HANAUER: That was one of Sonia's questions.

DR. LAINE: I am asking to kind of clarify, are you saying do we think the scale that they used was appropriate or inappropriate, or are you saying that since it didn't achieve statistical significance, we don't think they have documented that they have abdominal pain relief?

DR. CASTILLO: I think the Division wants to know if it was adequately assessed.

DR. HANAUER: You mean is the instrument an adequate assessment?

DR. LAINE: I am not sure that we are the ones to say about the instrument. If the instrument is adequate, then, their endpoint was not significant in their trials. Their secondary analysis looked at that obviously, and gave different views, but they had a lot more data points there to show small differences being statistically significant.

So, I mean I would say that their primary endpoint of pain, if it was an adequate instrument, did not demonstrate abdominal pain relief, but on the other hand, I can't comment on whether that scale is indeed the proper instrument.

DR. TALARICO: The question was whether it was adequately represented in the study population, and from the result, is there any trend that indicates should that population be expanded, that efficacy may be demonstrated.

The other question that we would like an answer,

is the disease the same in men and female, is there a physiological -- as part of the IBS.

DR. LAINE: The men doesn't seem to matter anymore because they have already changed their proposed indication to female, so it seems it is really a --

DR. CASTILLO: I think the question is in the overall picture of constipation-predominant IBS, pain is an important clinical component of it, and has it been adequately assessed in these trials. I think that was what we were looking for.

DR. GALLO-TORRES: One is pain by whatever means isolated by itself, even by a VAS. That is one way of assessing pain alone. If one assesses pain as a component of a global parameter, that is really the core of the question, which one is more applicable and more useful, more meaningful, which would of the two approaches, and has the sponsor done the proper evaluation of pain.

DR. LAINE: Remember there was the one question that we accepted in the previous alosetron submission. Does somebody have that readily available, exactly what that question asked by way of comparison? That was a global question, if you remember, do you feel better. Did that specifically say pain or was it generally, how do you feel?

DR. GALLO-TORRES: There is a question with the alosetron included that were irritable bowel syndrome pain

and discomfort. That was a very meaningful type of question.

DR. LAINE: It said irritable --

DR. GALLO-TORRES: Irritable bowel syndrome pain and/or discomfort.

DR. LAINE: All I am asking I guess was that one that we accepted last time, was that specifically pain -- certainly, the Rome criteria still requires pain or discomfort as the primary reason for having a symptom in IBS with the constipation being -- and the other bowel habits -- being contributory.

So, I would think you would still want to make sure pain and discomfort it seems is still the number one issue presumably in irritable bowel syndrome, although patients certainly complain about all the other aspects of bloating and alteration of bowel habits, as well.

DR. HANAUER: Dr. Camilleri and then Dr. Wolfe.

DR. CAMILLERI: I was just going to provide the information, that the question in the other trial posed the following question: Have you achieved adequate relief of your pain or discomfort, and it pertains to the past week?

DR. HANAUER: Thank you. Dr. Wolfe.

DR. WOLFE: I wasn't here for the other one, but these people don't come here with isolated pain, it's a whole syndrome, and I think the pain question has been

looked at fairly carefully, but the overall quality of life question, I am not sure if that has been answered.

That is my biggest question. The other thing, too, when we see patients like this, some of these comments bring back nightmares or daymares. These patients, I rarely aim for a complete relief, so maybe the original questions have not been realistic, and partial relief on a scale may have been a better question to ask. What you do retrospectively is a different question all together.

DR. LAINE: It seems to me that I guess the question being asked, though, is if pain is indeed important, their primary and secondary endpoint of pain did not achieve significance except I guess in 301 with the higher dose.

However, when they did the secondary analysis of pain with the many data points, they did have significance, so the question I guess is if they didn't achieve it in their primary analysis of pain, is that important, is that one of the things you are asking?

In other words, if they don't achieve it in pain in two of the three studies.

DR. COHEN: I would just comment that when you look at it as a secondary efficacy variable over the course of the study, for one study 301, for 11 of the 12 weeks there was less pain, to me, in terms of measurement of pain,

and there is a whole science of pain reduction, that was clinically significant, as well as statistically significant.

I think the question that you are raising, was that enough to give the patient overall relief, and that is reflected in the global relief. I think if you look at the data both as a statistician and as a clinician, I think there is clinical relief of the major components of IBS as I presented it.

I think the question that you are asking is whether or not that is enough of a relief, and I think that is a very hard -- I don't know if anybody can answer that.

DR. HANAUER: Which brings us to the second question up there, which is behind us, are the therapeutic gains seen clinically significant, clinically meaningful.

DR. COHEN: I can answer that. I think that in a disease or a syndrome where there is nothing out there, there is no efficacious parameter, over the years in practice we have gone through all of the drugs including calcium channel antagonists, things that weren't even mentioned on Dr. Wald's slide, and nothing has had proven efficacy.

So, if you are looking at a margin of effectiveness of an agent, and it does relieve pain, it improves bowel function, I personally think it's clinically

meaningful, and the term that I used, I said it was a moderately effective drug for the relief of the pain and the constipation in this group of patients.

DR. LAINE: What I was going to raise, though, is that methodologically, you would think you would first look at your primary evaluation of pain, and when you looked at that, you didn't show significance.

It was when you started looking at your secondary evaluations, you did show significance -- excuse me -- you showed it in one trial with 12 mg, I don't mean to diminish that. Then, you started to show significance.

DR. HANAUER: Okay. But what you were asking early on, is a 0.2 --

DR. LAINE: Right, 0.2 on a scale of 6.

DR. HANAUER: -- meaningful, not significant.

DR. LAINE: Or can a patient even discriminate that.

DR. HANAUER: I think that is really the question at hand at the moment that the Agency wants to know, is whether the therapeutic gains -- we understand where they were statistically significant -- now, is that 0.2 or whatever percentage clinically meaningful.

Dr. Wald. We won't pay attention, but we will listen.

DR. WALD: I think if we get away from the

statistics, that what you have is a big dilutional effect. You have many patients who are getting better on the placebo, and then you have other patients who are not getting better either with placebo or the drug.

Then, you have about 10 percent of these patients getting better and accounting for the difference, which is only an average or a mean on those slides.

So, if you took the 10 percent and you took those averages of 0.2 or 0.3, you could be dealing in those 10 percent with 2 or 3, not 0.2 or 0.3.

So, it seems to me intuitively that for those patients who did experience relief beyond placebo, that those are probably clinically significant changes.

DR. HANAUER: Do you want us to poll the panel on these questions or no, you have got a sense on this aspect. Okay. Dosage, we are going to come to I think in the main questions. I think we are going to hit all of these in the main questions.

What I would like to do is take a 10-minute break now and then we will come back and go through the list of the questions of the Agency. We will definitely reconvene exactly at 3:00.

[Break.]

Discussion and Questions

DR. HANAUER: Setting a bit of the ground rules

for the questions, you have seen the questions, you should all take out of the packet, so the committee has the questions.

The ground rule that we have been asked to do is to address the questions as they stand. Now, we understand the sponsor, Novartis, has written another potential indication up on the board, which we appreciate their flexibility, but we are going to go back to what we were asked to assess from the data that was provided at hand, and then we can go back at the end of this and talk about modifying the statement of indication.

Quite specifically, the statement is that Novartis Pharmaceuticals Corporation has requested approval for Zelmac (tegaserod) Tablets for the treatment of irritable bowel syndrome in patients who identify abdominal pain/discomfort and constipation as their predominant symptoms. The sponsor recommends a dose of 6 mg po BID within 30 minutes prior to a meal.

So, the first question that the committee has been asked to ponder is:

1. Has efficacy been demonstrated in both men and women with constipation-predominant IBS? If not, in which gender was efficacy demonstrated?

I think let's just take the issue of men right now as a simple point.

Any discussion on the issue of whether or not efficacy has been demonstrated in men? Any discussion?

[No response.]

DR. HANAUER: We now go for a vote.

Has this been demonstrated to be effective in men?

Dr. Wolfe.

DR. WOLFE: No.

DR. HANAUER: Dr. Smith.

DR. SMITH: No.

DR. HANAUER: Dr. Richter.

DR. RICHTER: No.

DR. HANAUER: Dr. Buyalos.

DR. BUYALOS: No.

DR. HANAUER: Dr. Laine.

DR. LAINE: No.

DR. HANAUER: Dr. Ferry.

DR. FERRY: No.

DR. HANAUER: No.

DR. SURAWICZ: No. Men are different.

DR. WISON: No.

DR. HAMMES: No.

DR. HANAUER: Now for the tough parts. Okay. We are going to limit this then to women for our discussion.

Has efficacy been demonstrated in women with constipation-predominant IBS? Then, we will go back to

specifics.

DR. HAMMES: Yes.

DR. WISON: Yes, depending on our definition on efficacy.

DR. SURAWICZ: Well, I wasn't here in November, but I read the transcripts, and I understand that that drug had an efficacy of 10 percent above placebo, and that's the same here, so I think we have made that decision, and the answer is yes.

DR. HANAUER: Yes.

DR. FERRY: I am going to vote yes, too.

DR. LAINE: No.

DR. BUYALOS: No.

DR. RICHTER: No.

DR. SMITH: Minimal, yes.

DR. WOLFE: Equivocally, yes.

DR. HANAUER: This is not a plurality here. It is not necessarily democratic. This is an advisory committee, so they take advice as to speaks loudest.

Now, the question is assuming yes, which of the follow doses have demonstrated efficacy, and the options are 4 mg/day, 12 mg/day, or the titration?

Why don't we just discuss this point. Michael.

DR. WOLFE: The way it looks, the data looks, if I want to say yes, and I did, 12 mg would be the dose.

DR. HANAUER: Dr. Smith.

DR. SMITH: 12 mg.

DR. RICHTER: I go with 12 mg.

DR. BUYALOS: 12 mg.

DR. HANAUER: You can't say anything. You don't think it's effective, but I will let you comment, but not vote.

DR. LAINE: I think there is minimal dose response, but certainly in some studies, only 12 mg did make the primary endpoint, so 12 mg.

DR. FERRY: I would say 12 mg is the dose to go with. I think that was the closest, best response.

DR. HAMMES: I actually thought that both were fairly comparable, but I think that since we don't see any significant dose-related toxicity, I would say it is 4 to 12.

DR. SURAWICZ: I favor that, as well. I mean why use a higher dose if some people, even though it's a small number, would have response at a smaller dose, and then as a clinician, you never like to use your whole regimen at the beginning. You always like to start with something, and if it doesn't work, you can increase the dose and see if that works. So, as a clinician, I would be much more comfortable with Option No. 3, titrated dose regimen from 4 to 12.

DR. WISON: I would say that 4 in the initial dose

trials was an effective dose, and subsequently in the others, was not different, so I would go with 4.

DR. HAMMES: If our first duty is to do no harm, and given the great placebo effect, I would say start with 1, but I would go with the titrated regimen, start with 4. Why use 12 if 4 works.

DR. HANAUER: Do you guys want to follow up any of these?

DR. WOLFE: Can we discuss this?

DR. HANAUER: Sure. Now you say this.

DR. WOLFE: I am not sure if I agree with that. I understand the point, starting this thing 4 versus 12, but there are some suggestions that titrating may not work, may actually cause more problems.

Why not say 12 for a short period of time and then if you want to try, some studies in the future, so you maintain your patients at 4, certain patients that need maintenance therapy, go down, but if you wanted to use the analogy of patients with reflux disease, we don't use a lower dose of PPI and then go to a higher one. We start with the dose of PPI and then see if we can sometimes go to a lower one.

DR. HANAUER: Let me comment for a moment. We are not describing clinical practice here and what we should really be doing as an individual patient. What we are doing

is making recommendations for dosing, labeling for the Agency, and how you use the drug will be reflective on your experience and everything else.

DR. WOLFE: Then, I will go back to what the data did show. The data did show that titration to a higher dose was the weakest response of all, so I would really question whether we should really use titration as our parameter for dosing.

DR. LAINE: I mean I hate to be data driven on this committee, but, you know, if we look at their results, I mean the places where they did achieve response in 301 with relief in abdominal pain was the higher dose, and not the lower dose.

If we look at their non-pivotal 351 in retrospect, again, it was 12 mg. So, it would strike me, although I agree there is not much of a dose response, the one they have shown more likely to work is 12.

In addition, the only reason you use the low dose first is if you have concerns about cost, which we are not discussing, or safety, which I don't think we have seen any concerns about at the higher dose, or side effects, which I don't think we have seen any dose-related effects.

So, although typically, you know, we are taught to use the lowest dose first, if there is no safety, cost, or tolerability issue, I am not sure there really is any point

DR. LEFKOWITZ: For the abdominal pain, it significantly improved; for the SGA of relief, it did not.

DR. HANAUER: There is a little bit of confusion from everyone's standpoint of who really does get to vote, and the guests don't get to vote. You can vote, but it is not counted. So, I am going to ask Tom to recap the vote on those first things, so we know.

Do you want to go through them?

MR. PEREZ: On Vote No. 1 regarding efficacy in men, it was unanimous. Efficacy in women, there were two no's, the rest were yes. What doses demonstrated efficacy: 4, we had a vote of 1; 12, we had a vote of 4; titrate, 3.

DR. HOUN: Let's just identify the guests are our two OB-GYN experts.

DR. HANAUER: Dr. Smith and Dr. Buyalos.

DR. HOUN: I guess I want to clarify the vote on female. I had thought that initially, there were three no votes by Dr. Buyalos, Dr. Laine, and Richter. So, Dr. Buyalos' vote is not official.

DR. HANAUER: We won't confuse you anymore. We won't let them vote.

Next question. Comment -- and we will have discussion before we have a vote -- but comment on the following findings of the carcinogenicity studies.

First, mucosal hyperplasia and adenocarcinoma of

What I would like is the two OB-GYN consultants to comment first and then we will find out whether there is more of an opinion from the panel.

DR. BUYALOS: First off, ovarian cysts is a very generic term. It really doesn't mean anything to an OB-GYN per se. In the course of follicular genesis, cyst formations form, so there are a number of different studies in different mice and rat species, if you expose them to things such as androgens early in their gestation that allow these multiple nonspecific cystic structures on the ovary.

So, I don't find this troubling in the slightest.

DR. SMITH: I concur. I believe that it is a true finding in the female Wistar rats, but I would never want to equate the physiology of a female Wistar rat to human females, and I think that this is just a documented incidental finding with no clinical relevance, especially in light of the human data.

DR. HANAUER: Was the sponsor's spin on the ovarian cyst team in the clinical trial also adequate for you?

DR. SMITH: Absolutely.

DR. BUYALOS: Yes, it was.

DR. HANAUER: Is there any dissent or concern from the other panel members regarding the animal studies or the human studies with ovarian cysts?

making light of the, quote "diarrhea," but diarrhea is a huge clinical problem.

DR. WOLFE: As long as it goes away, as long as it stops is what I am saying, it stops right away.

DR. HANAUER: Right. What you are saying is the diarrhea that you have heard about related to the clinical trials is not a severe diarrhea that you are concerned about.

DR. WOLFE: Right, yes.

DR. HANAUER: Joel.

DR. RICHTER: I would agree, Steve. I think it tends to be a mild problem. It looks like only about 2 to 5 percent of patients are discontinuing the studies because of it, and apparently it looks like if you stop the medication, the diarrhea goes away.

DR. HANAUER: It looked like that alosetron, too, as far as the patient until marketing when we have seen some serious events.

Do you feel that what you have heard requires any postmarketing surveillance regarding the severity of diarrhea?

DR. LAINE: Could I just ask, Steve, were there any hospitalizations for diarrhea among these discontinuations?

DR. LEFKOWITZ: There were no serious adverse

events reported for diarrhea. There was also no electrolyte problems that the patients ran into due to the diarrhea.

DR. LAINE: So, no significant dehydration problem?

DR. LEFKOWITZ: That is correct.

DR. HANAUER: By the way, I am not trying to imply anything. I am just trying to get everything out early, so that we don't have to go through this, as they say, do this again next year.

DR. FERRY: Can I ask one more? Were there patients in the study you had diarrhea that it didn't resolve, or the ones that didn't drop out, what happened to the diarrhea?

DR. LEFKOWITZ: Most of the patients who had diarrhea in fact stayed in the study. The dropout rate was 1.6 percent for the tegaserod group, the incidence being 12 percent. Most patients either stopped the drug and then the drug was reintroduced and they were able to continue in the study.

DR. HANAUER: I just want to hear this again. No hospitalizations for diarrhea, no treatment for dehydration?

DR. LEFKOWITZ: Certainly no electrolyte abnormalities reported to us, and as far as we know, no clear-ups of the dehydration.

DR. HANAUER: Thank you.

DR. FERRY: I was just going to say that is important, I mean if we are talking about labeling later on, with what has happened to alosetron, if we want to be careful with this, it sounds like most of the patients in the study did stop the drug temporarily, it wasn't like they continued it and the diarrhea just went away, so that may be a consideration that we should address.

DR. LEFKOWITZ: Yes, 30 percent of the patients who had diarrhea within the first two weeks missed at least one dose of the drug. So, in fact, most patients were able to continue in the study, and the diarrhea would resolve.

DR. HANAUER: From the Agency, did we address that adequately for you guys? Yes? Okay.

The next issue relates to the lower abdominal pain and the laparotomy in a greater proportion of patients receiving Zelmac.

Any comments from the committee regarding this issue? Again, from the OB-GYNees, this is not troublesome to you? Anyone find a problem or a comment?

[No response.]

DR. HANAUER: Agency, Hugo, is there a concern?

DR. GALLO-TORRES: Some lingering concern about that in my mind. How often do you see surgical interventions in patients with IBS?

DR. HANAUER: That is difficult, because you have

asked the OB-GYNees, you are going to see the numerator, if you ask us, we see the denominator.

DR. SMITH: We are going to see a different population, but the general rule of thumb in OB-GYN is that of women who are presenting with abdominal and pelvic pain, abdominal pelvic pain chronic in recurrence, 40 percent is due to pelvic disease, 40 percent is gastrointestinal disorder, such as irritable bowel or chronic constipation. A tremendous number of these ladies go through laparoscopic procedures to diagnose it, only to find large, distended intestines and colon. So, the diagnosis of constipation is made with a perfectly normal pelvis.

Then, there is a bunch of other less common etiologies for the chronic pelvic pain that can range from urinary tract to pelvic floor triggers and musculoskeletal problems, but 40 percent of all abdominal pelvic pain that we see as OB-GYNs is actually constipation and irritable bowel.

DR. GALLO-TORRES: What proportion, more or less, of those patients have appendicitis?

DR. SMITH: A small percentage, because that would be short-term pain. Very few patient really are presenting with chronic appendicitis, so, you know, the one lady who came here had a background of chronic pain, but what was going on is that she had an acute appendicitis at that time,

unrelated to medicine. It was just an incidental occurrence during the study period, and that was also -- was that the 13-year-old? I am not sure.

DR. GALLO-TORRES: And a final question related to this. How many of those patients have adhesions as a previous history?

DR. SMITH: How many of those patients have adhesions?

DR. GALLO-TORRES: Yes, adhesions.

DR. SMITH: I think a fair number of the 40 percent who have pelvic pathology are going to be having abdominal pelvic adhesions as an explanation for the chronic pain, but the flip side is that an awful lot of patients with adhesive disease have absolutely no pain symptoms at all.

So, it is not a tight correlation at all between the presence and absence of adhesive disease and the presence and absence of chronic abdominal pelvic complaints, but my impression in reviewing the case reports is that I have no suspicion of a relationship between the medication and adhesive disease or a propensity towards having a laparotomy, and think that in some cases, personally, that it was treatment failure and breaking through of the medication and worsening of the irritable bowel syndrome that was the actual stimulus for the surgical intervention.

DR. BUYALOS: I would agree with that, and in fact, if you look at the algorithm for pelvic pain in gynecology, we have typically treated with medical therapies, oral contraceptives or non-steroidal, inflammatory type products, but as part of that algorithm, a diagnostic laparoscopy is frequently employed.

We are seeing a different population than gastroenterologists obviously, and the second thing is the histories are very muddy on the case reports that they have, but a substantial proportion of them were having prior one to two years beforehand, so I don't find it in the least concerning from that perspective.

DR. HANAUER: Thank you. So, I think you have a unanimous no conflict from the committee on this.

We are now going to some of the critical questions, which is, on the basis of your benefit-risk evaluation, which is going to be key word for tomorrow, do you recommend that Zelmac be approved for the indication requested by the sponsor, that I stated above, which is approval for Zelmac tablets for the treatment of irritable bowel syndrome in patients who identify abdominal pain/discomfort and constipation as their predominant symptoms?

For that indication, do you recommend approval?

DR. WOLFE: Is there a length of time attached to

that?

DR. HANAUER: What you saw is what you get. You don't have to answer now. That's a legitimate question, and there is no length of time assessed on that.

DR. WOLFE: I mean at least minimally, it should add in there short term. At this point, I think that is all we have seen. It doesn't say short term from what you just read.

DR. HANAUER: By "short term," do you mean three months, 12 weeks?

DR. WOLFE: That is what I just asked, but at least it should say short term. We will define what short terms means later on. I don't think it should be indefinite.

DR. HANAUER: This is a comment phase. You are not voting on it.

DR. WOLFE: I think it should be short term, and I would say 4 to 6 weeks right now is all I would say, because I think the benefit -- I didn't see the benefit really getting that much greater as time went on.

DR. LAINE: I would say you have to go with what the studies did, and although I didn't vote for it, I mean if you are going to approve it, you are approving it on the basis of the studies, so it seems to me you have to say 12 weeks, so you can't say more, you can't say less, it's 12

weeks.

DR. HANAUER: Do you have to say anything?

DR. HOUN: Or are you recommending other studies, the short-term study?

DR. HANAUER: We will come to that.

DR. LAINE: My view would be you would say that because I think nowadays you are trying to be, you know, you get the indication based on what studies you did, not on what we kind of assume. So I would probably -- I don't know that you want to approve -- if you don't say anything, then, that means you can use it for years and years, which people are going to do anyway, but I think it would be reasonable now, before further studies are done, just to go with what their trials were, so I would say 12 weeks.

DR. WOLFE: Is that what we are doing? We just took men out, and the study wasn't done to look at women only, it was done to look at people, and we just took men out and made it for women only.

So, I think we have the right to look at both the gender, as well as the length of time.

DR. HANAUER: Absolutely. You are here to make recommendations.

Other comments on this issue? Joanne.

DR. WISON: We are somewhat hindered in making recommendations of duration, because if we knew that

symptoms recurred immediately upon discontinuing the medication, then, we could make a recommendation for longer periods up to 12 weeks, but as it stands now, people got maximal response in shorter periods of time.

So, therefore, I would go with your recommendation for a shorter duration.

DR. HANAUER: So, do you have a recommendation regarding -- Dr. Wolfe said 4 to 6 weeks based on --

DR. WISON: Looking at some of the data, looking at what the response has maxed out, and it was somewhere like 4 to 6 weeks.

DR. HANAUER: Dr. Wolfe.

I will point out as a clinician, as well as a chairman here, once you put a duration on it, you are going to get all sorts of hassles from third-party payers saying that you have over-extended your duration.

Now, that is not the Agency's concern, but that's a clinician's concern.

DR. WOLFE: But the thing is where do you stop? You say, well, for 12 weeks, let's go on for 12 years.

DR. HANAUER: The point is do you want to really put in a term limit, do you want to have term limits on this indication?

DR. WOLFE: There is precedence to that. I mean this has been done for other diseases, as well. I mean

unfortunately, it was done for reflux disease, because it was treated like peptic ulcer for years and years, but with the proper studies, we realized that longer term treatment was necessary.

I don't think we have shown that here yet. We haven't seen trials beyond that, and the longer it is treated, 12 week starts to sound like more of a chronic use to me. I don't know. I arbitrarily said 4 to 6 weeks, it was arbitrary.

DR. HANAUER: I would just again in the discussion phase argue against that. To me, what we have heard the likely use is going to be intermittent by the experts, but if you put a 4 to 6 week term on it, your third parties are going to stop the treatment if you decide to reinitiate it or give it longer.

DR. RICHTER: Steve, I would go with what Loren was suggesting. Both he and I voted no on this, but based on the data, if you were talking about a recommendation --

DR. HANAUER: Well, you voted no, that it wasn't effective. You didn't say to approve it.

DR. RICHTER: I would give the length of duration of this as up to 12 weeks, because that is what your data is showing, and that allows you both options. You could use it for a shorter period of time if that's what the patient is telling you they only need it to, and it also protects you

from the third-party payers who don't want you necessarily to extend it indefinitely, and we don't have any definite date on this medication at this point in time.

DR. WOLFE: Once again, is that our job to worry about whether third-party payers are paying or not?

DR. HANAUER: Your job isn't, but I am being --

DR. WOLFE: I understand, you are being a clinician, too. We have the same trouble, getting all these letters from managed care.

I am thinking of other PI's that say effective therapy has not been demonstrated beyond a certain period of time. Have we demonstrated an effect beyond 4 to 6 weeks?

DR. HANAUER: Dr. Smith.

DR. SMITH: Well, I disagree that the common usage, speculation, of course, is going to be short and intermittent term. Patients call into the office. They will get a prescription by telephone, and they will refill it by auxiliary staff in the office.

If what happens in the primary care physician's office is anywhere similar to what happens in an OB-GYN's office, who will be prescribing this just as readily, one, the physicians will not have read the medical literature, they will go by whatever is being in service by the representatives from the company, and I would vote very strongly that it's approved for short-term treatment, and

you don't have to specify short term, and that the efficacy with prolonged treatment and recurrent treatment is not proven, and it is up to the company to establish the efficacy, as Dr. Laine said, with alternate forms of use, to say that it is okay to use it three times every two years or for 16 consecutive months, there is no proof, and I think that the Agency has a responsibility to protect the public from misinterpretation or embellishment of the true data.

The data itself is relatively weak, to begin with.

DR. FERRY: I am not too much in favor of limiting a time period. I think that complicates things for a lot of reasons, and I understand the concern about not really knowing long-term use, but this is a -- I mean it appears to be a pretty safe drug.

My guess is patients are going to want to use this, the ones that get some benefit, and I sort of hate to see it constrained that it only be used for three months. I do think there is some real merit in doing some follow-up studies to find out the true use long term, but I am not in favor of setting a time limit on it.

DR. HANAUER: Other comments regarding this? Yes, Dick.

DR. HAMMES: To put on my consumer's representative hat here, by all accounts, this is a chronic disease by definition, I guess. We are looking back 12

months to get them enrolled in it.

We have evidence that it is effective out to 12 weeks. We don't really know what happens beyond that, but we do have safety data out a year or more, I believe, and it is a very safe drug. So, I don't think we need to put any limit on it. We can state that it has been shown to be effective out to 12 weeks, but I don't think we need to limit it.

DR. WOLFE: I really disagree with that. I think the most you can say right now is 12 weeks. Whether you can go beyond that, studies have to be done to show efficacy beyond that time period.

This is again, and I hate to use the analogy of other disorders, but we have the acute phrase treatment and maintenance phase treatment, and this is a chronic disorder which is different from other chronic disorders, that this waxes and wanes much more so than other disorders that are chronic, and the short-term treatment may be effective in certain individuals, and they get treated pulse by pulse therapy instead of by chronic therapy, maintenance therapy.

DR. HANAUER: Joel.

DR. RICHTER: I just want to reemphasize what Mike says. I mean I don't see how you can extend efficacy data any longer than the study is. You can say this medication is safe for up to a year, but there is no placebo-controlled

efficacy data past the data that we have for 12 weeks, and I don't think you can make a recommendation past 12 weeks.

DR. HANAUER: We have time for labeling modifications, but the first question is, "On the basis of the benefit-risk, do you recommend that Zelmac be approved for the treatment of irritable bowel syndrome in patients who identify abdominal pain/discomfort and constipation as their predominant symptoms?"

Dr. Wolfe.

DR. WOLFE: Yes.

DR. HANAUER: No, you don't. You want it in females.

DR. WOLFE: Yes.

DR. RICHTER: No.

DR. HANAUER: Dr. Laine.

DR. LAINE: No.

DR. FERRY: Well, if we throw females in, yes. I wouldn't do it this way.

DR. HANAUER: So, do it this way, and then you can modify it.

DR. FERRY: So, it's no.

DR. SURAWICZ: I think I am missing what the controversy is here.

DR. HANAUER: Well, the controversy is the semantics of the labeling as is written up there. There is

other subtleties --

DR. WOLFE: If it's all people, I would think it was no.

DR. HANAUER: Would you agree with the labeling of Zelmac Tablets for the treatment of irritable bowel syndrome in patients who identify abdominal pain/discomfort and constipation as their predominant symptoms?

DR. SURAWICZ: Well, we have already talked about its lack of efficacy in men, so is that -- are we rehashing this again?

DR. HANAUER: No, we are voting.

DR. SURAWICZ: We are voting to approve or not approve? I vote to approve.

DR. WISON: I vote no.

DR. HANAUER: No.

DR. WOLFE: Steve, I will have to change my vote because I thought we were talking about women only.

DR. HANAUER: That is why I interrupted you.

DR. WOLFE: I say no.

DR. HANAUER: Okay.

DR. SURAWICZ: But we already talked about that.

DR. HANAUER: Yes, but now this is a vote.

DR. SURAWICZ: But we voted before.

DR. HANAUER: No, you voted whether you thought it was effective.

DR. SURAWICZ: And we were unanimous that it wasn't effective in men.

DR. HANAUER: Right, but we are sticking with that label, because we were asked to stick to it. Now, you can modify it if you would like.

DR. SURAWICZ: Great. Let's modify it.

DR. HANAUER: How would you like to modify it, Dr. Surawicz?

DR. SURAWICZ: For use in women.

DR. HANAUER: Any other comments on the labeling modification?

DR. WOLFE: Again, I think we have to come up with a time limit, and maximally 12 except things say short term in parentheses, as a compromise, 6 to 12 weeks.

DR. LAINE: I like up to 12, the way Joel said it, even if I voted no.

DR. HANAUER: Any other comments regarding the labeling before we come back to some of these individual amendments? I particularly have one, and that is, I am uncomfortable with the discussion of with the labeling that says, "For treatment of irritable bowel syndrome in patients who identify abdominal pain/discomfort."

My view is that the labeling should read, "For the treatment of abdominal pain and constipation in patients with irritable bowel syndrome." To me, that is a more

sensible labeling because you are treating symptoms and it is not treating a long-term disease.

That is what we have looked at, that is what the sponsor looked at.

DR. WOLFE: You may avoid, by doing what you are saying, you may actually avoid people just saying, well, here is another new drug, and we just go ahead and use it for IBS, and not pay attention that there is a difference of IBS.

DR. HANAUER: That is why I said it that way.

DR. WOLFE: I think you are right. It's commendable.

DR. SURAWICZ: The only concern I have with that is that if people don't read the entire sentence, and they are treating any abdominal pain and constipation with this drug, then, it is going to be a disaster.

DR. WOLFE: I don't know if it's going to be a disaster or not.

DR. SURAWICZ: Well, yeah, because you are going to be treating colon cancer and bowel obstruction, and all kinds of stuff that causes abdominal pain.

DR. HANAUER: My approach also separates it from the other drug, which is the treatment of irritable bowel syndrome in patients with diarrhea-predominant. Here, you know, IBS is IBS, whatever. I think that you are really

treating the symptoms of abdominal pain and constipation in patients with irritable bowel rather than treating irritable bowel syndrome in general.

DR. BUYALOS: Steve, is this a common phenomenon? What other chronic condition is a medication approved, which is gender specific? I am not familiar with that.

DR. HANAUER: Birth control.

DR. BUYALOS: I am talking about a chronic condition which affects both sexes.

DR. HANAUER: According to the sponsors and others, there is a gender difference in the affectation, in the incidence. As a matter of fact, alosetron, which is the other drug that was approved for diarrhea-predominant, was also only effective in women.

DR. BUYALOS: Maybe that was a power phenomenon also with the number of subjects in the study.

DR. HANAUER: Well, women have power, but that didn't seem to be the issue seriously.

The next question is what labeling recommendations -- we are in the process of addressing this, and I guess we should take different aspects of it. I presume everyone on the panel -- and I don't mean to vote for them -- agrees that this should be limited to women, right? So, the indication should have females in it. Any dissent regarding that?

[No response.]

DR. HANAUER: Unanimous that the labeling should discuss women.

I will just take them in order that they were brought up. The second is the term limits. Do you want to make a statement of proposal? Was your proposal short-term treatment?

DR. WOLFE: Short term use. It should say short term and then in parentheses take a week number. Again, there is going to be some arguments here, but I agree with Loren and with Joel, that it should really say up to 12 weeks, but looking at the data, I didn't see much effect over 6 weeks, but I don't have any objection to 12 weeks.

DR. HANAUER: Well, make a proposal then.

DR. WOLFE: Short term parentheses up to 12 weeks.

DR. LAINE: I agree.

DR. HANAUER: Loren has agreed already. George, comments?

DR. FERRY: I am still wondering what -- what does that mean actually? That means that a doctor prescribing this cannot -- I mean should not refill it after three --

DR. LAINE: No, because we don't set clinical practice. All it means is that like a representative can't perhaps go to the doctor and tell them that they should use it beyond 12 weeks.

DR. FERRY: How will it read? How does this translate into what would actually be written down? You should stop this drug at 3 months, you should not use it longer than 3 months?

DR. RICHTER: It would be no different than -- I just cannot conceive of giving an indication for a drug longer than you have the efficacy data and the study, and if you want to say, well, the issues are chronic disease, this is no more of a chronic disease than reflux disease. So, when the PPI's come out of the H2 blockers, we gave those drugs for 3 months, then, we would stop those, and then when the patient's symptoms relapsed, we would start them back until we had the maintenance data from the companies, and then we do maintenance therapy now.

DR. WOLFE: We actually started using it long term before that. We had studies in the literature showing long-term effects, but here we don't have any studies, and we have nothing in the literature suggesting this drug works longer.

Again, what people do in practice is their business, but we don't have data beyond that.

DR. HANAUER: Other comments? Yes, Dick.

DR. HAMMES: I still think by putting a limit on it, clearly, you are going to be making this unavailable via third-party payers, HMOs, or what have you, for people that

need it after 3 months, and I don't think there is any data to suggest that it was not effective after 3 months, and I really don't see any kind of data that indicates that we should be proactive and put that kind of limit on it, considering the effect that it is going to have on people that may need it.

DR. HANAUER: Of the voting members, how many feel -- just raise your hand if you feel there should be a short term up to 12 week information on it?

[Show of hands.] Six.

DR. HANAUER: Opposed to that?

[Show of hands.] Two.

DR. HANAUER: Two. And the opposition states no limit, no term limit, or you want to make a proposal or just a comment?

DR. HAMMES: I don't think it needs to be mentioned in the labeling.

DR. HANAUER: Timing need to be mentioned, Christina?

DR. SURAWICZ: No.

DR. HANAUER: The third aspect of the labeling was my notion of a label for the short-term treatment of abdominal pain/discomfort and constipation secondary to irritable bowel syndrome.

Additional comments regarding that?

DR. LAINE: Could we have the alosetron label read to us perhaps? In other words, how was it written in terms of diarrhea-predominant? I mean we could perhaps use that as a precedent.

DR. HANAUER: I don't need if you need a precedent or a fix.

DR. WOLFE: Steve, can you say constipation, abdominal pain type irritable bowel syndrome, because secondary to is -- associated with --

DR. HANAUER: I don't want to say type because I don't think that they have shown that it is really effective in -- that they can effectively type it is the problem.

DR. WOLFE: It is important, though, they are going to start using it in people who have an obstruction, an obstructing lesion of some sort without really --

DR. HANAUER: Contributed to irritable bowel syndrome. You don't have to accept it, you can oppose it.

DR. WOLFE: I like the idea, but I think we need some careful terminology here.

DR. HANAUER: So, the Agency will think through that terminology of how you want to modify it. I think you get a sense that there are different ways of saying this that may impact upon the usage and miss-usage.

Aside from the short term that Dr. Wolfe has already imposed, are there any other labeling

recommendations to reduce the potential risks of Zelmac, the potential risks being diarrhea, right? Is it necessary to black box diarrhea?

DR. WOLFE: List that as a side effect.

DR. HANAUER: As a side effect or a contraindication?

DR. WOLFE: Well, it's a contraindication and side effect.

DR. LAINE: I think it would be reasonable to, because of the constipation issue, with alosetron to be reasonable, not to black box it, but just to mention that patients with predominant diarrhea or with -- you know, we have to figure out the wording -- but who have diarrhea a significant portion of the time should not receive this medication, or something along those lines perhaps, at least now until we get further information.

DR. HANAUER: Or that diarrhea is the most common side effect. As a precaution? Tom wants to know. You guys can figure that one out, that is pretty straightforward.

Now, I think these are the really important aspects now. Dr. Houn, do you still care if operations are necessary, what proportion is acceptable? The committee really doesn't predict that that is going to be a problem.

DR. HOUN: Do you think there should be surveillance on that?

DR. HANAUER: Does the committee think that there should be surveillance regarding specifically the risks for operations in patients, exploratory surgery?

DR. WOLFE: Any question that came up should be watched carefully as far as I am concerned.

DR. HANAUER: Okay. If you should watch it, how should they watch it? Does this require a case controlled study? I think you heard from the OB-GYNees, and we know in our practice, that oftentimes women with abdominal pain associated with irritable bowel or whatever end up going to laparoscopy as a diagnostic maneuver, and if they are going to separate this as an issue of the background population of this group of people, is there a way that they should do that?

DR. WOLFE: There are postmarketing surveillance studies to do postmarketing surveillance.

DR. HANAUER: What study?

DR. WOLFE: Long term on patients on this drug open label. There are several studies that I could see being done in the future, and that is one of them, do an open label study, follow patients out, you know, follow patients who have been taking it out for a certain period of time.

DR. HANAUER: How would you ascertain then if whatever proportion of patients go through surgery is an

increased risk? These are the kind of things that they want to know, right? Aren't I getting to your points here?

DR. HOUN: Appropriate control group.

DR. HANAUER: What would be an appropriate control?

DR. WOLFE: People treated by other means, people treated with fiber only, people treated "in traditional ways." It can't be a double-blind, obviously, it can't be double-blind. It has to be a surveillance study of some sort in which people are relying on reports or else relying on -- I don't know.

DR. RICHTER: I think you are going to have to do some maintenance studies with this medication versus placebo, probably with the same study design that we use in ulcer disease or GERD. Get a group of people that have had a good response to the medication, and then at that point in time, over a year's period, randomize them to either maintenance medication or placebo unknown, and follow that group out for efficacy over a year, and also look at some of these other side effects because based on what we know, if you are going to use the weaker endpoint of some relief, you are going to have 40 or 50 percent of your patients staying in the study on placebo.

That will give you a pretty good idea then, over a year's period of time, as a control population for the

issues that are coming up.

DR. HANAUER: So, a maintenance trial for patients who have responded.

DR. RICHTER: Right, yes.

DR. WOLFE: I would stress, though, if we are going to use 12 mg as the dose, maintenance studies should be done at lower doses, as well, to see if a lower dose can maintain the patients once --

DR. HANAUER: So your concept is a dose ranging maintenance trial.

DR. WOLFE: Yes.

DR. HANAUER: Loren, any comments?

DR. LAINE: I agree with the idea of the long-term maintenance trial for killing two birds with one stone. Personally, if we do approve just 12 mg, would be happy just to have it 12 mg, so I don't think I see any reason to complicate things by going down to 4 mg maintenance.

DR. HANAUER: Comments on this end?

DR. WISON: The lowest maintenance dose possible would certainly -- since we will be dealing with young women, I would favor looking at the lowest possible doses.

DR. HANAUER: Other comments? Dr. Ferry, would like to try it on children?

DR. FERRY: I am so glad you brought that up. Thank you very much. As a matter of fact, there are some

issues in children that this drug might be very important for. I think there is still some confusion in children whether younger children actually have irritable bowel syndrome, but there are some very close similarities with chronic recurrent abdominal pain, which is often accompanied by mild constipation.

I think there are some very clear-cut indications to study this in children, because I think there is going to be a great interest in pediatric GI people finding some solution to a disorder we have absolutely no treatment for at all, that is very chronic and disabling in terms of time lost from school.

So, yes, I think pediatric studies, and I am thinking of the age between 5 and 12, not adolescents so much, but the younger children.

DR. HANAUER: From the pharmacokinetic and pharmacodynamic data that you have seen, do you think additional dose ranging studies are going to be necessary in kids?

DR. FERRY: I think they probably are. For one thing, just looking at the data presented for men, where the drug doesn't work, but the weights are considerably higher, so I think figuring out a weight/kg dose for children is going to be important, so, yes, there are going to have to be some dose ranging studies in children and

pharmacokinetics to prove just what really works, and also in a younger age group, the question is going to come up about the type of vehicle to deliver this drug, as well, whether it can be crushed, mixed in syrup, just whatever, so there are other important issues about how to deliver it.

DR. HANAUER: Do you think there might be gender differences in children as there are in adults?

DR. FERRY: I have no idea, although I will tell you, chronic abdominal pain is more common in girls in our practice than it is in boys.

DR. HANAUER: So, you would try to get an adequate sample size of both genders?

DR. FERRY: I would, yes.

DR. WOLFE: The prepubertal, too? Do you see the same thing?

DR. FERRY: With recurrent abdominal pain?

DR. WOLFE: Yes.

DR. FERRY: Yes, it is prepubertal, and adolescents tend to have a pretty, in my experience, typical adult pattern irritable bowel syndrome. Under age 12, this recurrent chronic abdominal pain has never responded to any of the medications that adults have used traditionally without any proof of efficacy. They don't respond to fiber, they don't respond to anticholinergics.

Our postulated mechanism is that there is a

heightened sensory reception in the pain fibers from the autonomic nervous system and from the gut to do this, which maybe makes this drug an even better drug for children.

DR. WOLFE: Would there be any reason to do some studies again men, using even higher doses, to see if men do require a higher dose?

DR. HANAUER: Do you think so?

DR. WOLFE: I think it would be worth a try. Again, the problem when we had that low a response rate and took that many that will show it, it is going to take more men to show it, and I think possibly higher doses.

DR. HANAUER: Let's ask Dr. Camilleri that, get him back into this. One issue is are we dosing high enough in men, does the peristaltic activity that has been demonstrated in the clinical studies, the nonclinical trials, is that the same in men as it is in women, or is there a gender difference regarding that?

DR. CAMILLERI: Regrettably, the sample size in those mechanistic or pharmacodynamic studies is too small to really tell, but I think the point raised by Dr. Wolfe is a very relevant one, as is the point by Dr. Ferry, that dose responsiveness is almost as important as adequate sample size in this case.

DR. HANAUER: Other comments? Michael.

DR. WOLFE: As long as Dr. Camilleri is up here,

is it worthwhile to get more convincing data? It is not going to make a difference in approval, but I would like to see really a cross-over design study to see again, just to add more information, although we may have it with the maintenance study, if we place certain people on drug, put them on placebo, and see what happens to them. That may answer the question and again kill two birds with one stone.

DR. HANAUER: That would also be addressed in the maintenance trial where patients are re-randomized, and you would see whether or not there is a "rebound" effect.

From additional studies, I would also recommend that the sponsor be a PRN versus a continuous use. My sense is that the majority of the physicians, the consultants are looking to use this for intermittent symptoms and allow patients to use it intermittently and assess the quality of life compared to those who are getting a placebo .

I think that would address the questions, many of the questions that we have asked.

DR. WOLFE: Is our charge also to make recommendations regarding, not advertising, but how the drug is promoted, because I don't think we should think give the impression to anybody that this is a replacement for fiber, for example. This is adjunctive therapy to people taking fiber.

DR. HANAUER: That certainly is an important point

since the patients in the clinical trials were treated, were continued on their fiber therapy.

Do you want to comment on that Lilia?

DR. TALARICO: In a way, yes, it would be an adjunctive therapy to whatever the other treatment for IBS, but I have another question. The modification in the labeling, mention was made for the use of this drug for current symptoms of pain and constipation rather than the pattern.

This would change the indication in the sense that it would limit to the time when the patient is actually experiencing the constipation.

DR. HANAUER: Right.

DR. TALARICO: What is the committee's suggestion?

DR. HANAUER: I think we agree with that. Again, one of the issues is we don't want to see patients continued on this necessarily through diarrhea, because that doesn't make sense.

DR. TALARICO: The discontinuation when the symptoms subside is one thing, but the initiation of the treatment only when currently, the patient is experiencing pain and constipation rather than the patient having IBS with the pattern or predominantly by pain and constipation.

DR. HANAUER: I think the bottom line is -- and I don't want to speak as a whole -- but my interpretation of

the data is that part of the reason that we see such a modest benefit is that it is a very heterogeneous group, and a lot of these people who are entered in the trials were what we would consider alternators rather than constipated patients. I see the most important benefit in the patients really who were constipation-predominant, which is not the patients who swing from diarrhea to constipation, who I can envision being one week getting Zelmac, the next week getting another drug.

DR. TALARICO: But again, when should the patient start the treatment or limit the treatment if the patient is diagnosed with IBS, predominant, characterized by pain and constipation, can faster treatment just based on the diagnosis and the pattern of the IBS or just because --

DR. HANAUER: I think that is an excellent question and let me try and rephrase louder, so the committee can hear this.

You are trying to ask can you really treat IBS consistently based upon a historical pattern.

DR. TALARICO: Exactly.

DR. SURAWICZ: I thought you were asking can you treat acutely or maintenance.

DR. TALARICO: Well, either way, when should the patient receive this if we limited the administration of the drug to 12 weeks because the trials were done with 12 weeks,

if we allow the patient to stop the medication when the symptoms have subsided, when should the patient start the treatment?

DR. SURAWICZ: I would go back to what I learned when I was a student on Surgery from our chief of Surgery, that you can't make an asymptomatic patient feel better, so I would opt for treating when there are symptoms, and not treating when they are asymptomatic.

DR. HANAUER: Unless you do demonstrate a maintenance benefit, until you demonstrate a maintenance benefit.

Joel.

DR. RICHTER: I like the last ramification that the company gave us, where they emphasize IBS patients who currently have a problem with constipation. I think that is the group we are talking about at least initiating this therapy for whatever period of time one wants to use it.

DR. TALARICO: That was the point

DR. WOLFE: As long as you are talking about other studies and what would help, I think, the company and help all of us are outcomes and cost analyses to show that treatment does not only make the patient feel better, which is very, very important, but also, as was shown in the very beginning, decreases days lost from work, increases productivity, and decreases all the indirect costs

associated with this disease.

DR. HANAUER: Yes, I was intrigued by the company saying that this was a $12 billion disease. My sense is that if this is improved, it is not going to be an $11 billion disease.

DR. RICHTER: I mean I would emphasize the same thing that Mike did. I really think these maintenance studies are going to be important because it allows you to look at a couple of things, and critical in the maintenance studies is going to be the use of some quality of life indicators to really see how these people are doing, and also attempt to do some type of a cost analysis data based on recurrent visits to physicians and studies being done.

DR. HANAUER: I agree.

DR. HOUN: Let me just summarize that the original Novartis proposal for it to be approved for IBS in patients who identify abdominal pain/discomfort and constipation as their predominant symptoms, I believe the vote was -- I have 7 no and 1 yes, is that correct?

However, in discussion of labeling, is it the committee's sense that should the indication change --

[Electronic interference.]

DR. HOUN: [Continuing] -- for people who currently have these symptoms, that with those kinds of changes, the committee is favorable for that indication?

DR. HANAUER: Any dissents to that? Yes.

DR. LAINE: I mean we have a dissent about the efficacy, but assuming it's being approved, I would agree with that, but the only thing I would want to make sure in that wording --

DR. HANAUER: Wait. You are the dissent. Given those stipulations --

DR. LAINE: I think it didn't change on my original vote, but given the fact that it is going ahead --

DR. HOUN: No, no, no. I think if you still feel that the benefit-risk ratio is unfavorable, because efficacy wasn't demonstrated, you should state that. I am just saying for those of you who felt the benefit-risk ratio is favorable, those are the kind of changes you folks are interested in.

DR. LAINE: Two comments. One, I mean I didn't change my efficacy vote, but the one point I would make, and that is I would just want to make sure that constipation has to go along with abdominal pain/discomfort.

I mean just the way you read it, I wouldn't want people to think they could use abdominal pain/discomfort or constipation. I mean it's really people who have abdominal pain/discomfort and also have constipation. So, I would just want that to be very clear in any labeling.

DR. HANAUER: Dr. Smith.

DR. SMITH: In the studies presented, all three of them, the mean age of the female patients was 43 to 45 years of age, which is really past the child-bearing age, but as you extend the utility of this agent, and it becomes available especially to OB-GYN physicians treating generally a younger age group, you are going to have the issue of pregnancy while taking the medicine become more important.

There was only a handful of pregnancies out of 2,000 patients, about 20 pregnancies perhaps, but as the age wear, and these ladies all had an average duration of the disease of 13 or 15 years, so you are going to see it being used in women in their late twenties and thirties, who are clearly of child-bearing potential, and that is going to be an issue that everyone is going to have to consider.

DR. HOUN: So, are you recommending a pregnancy registry?

DR. SMITH: I would think so, just as you have one for Prozac, the initial data showing that it was increasing the risk of miscarriage, and subsequent data showing no real increase.

DR. HOUN: Just a final issue was if the drug should be approved and the labeling was revised, there was some discussion and dissent in terms of should it be short term versus no statement of term, and that is how I think the committee --

DR. RICHTER: Didn't we vote on that issue, though, wasn't that issue 5 to 2 or 6 to 3?

DR. HOUN: Six to 2.

DR. HANAUER: Any other questions? I think we have been through your list. Anything else from the Agency that you would like to clarify from the committee, use us? Use us or lose us.

DR. FERRY: One other question I had that I don't think we addressed, but I was just wondering if we should consider making a suggestion in the labeling about if diarrhea does occur with this drug, that the drug be temporarily stopped.

DR. HANAUER: Makes sense.

Other comments? Joel.

DR. RICHTER: Are we going to do part (b) of 5?

DR. HANAUER: I assume we had done it because we modified the thing, but go ahead.

DR. HOUN: I think the people who voted no should suggest studies that would increase their confidence for efficacy.

DR. RICHTER: I mean I would like to see a single U.S. study, because this drug, we are the FDA or we are making advice to the FDA for the United States, a single U.S. study which shows efficacy without having to do a post-hoc analysis, and I personally think that should be done

with 12 mg, the higher dose, give you the best chance, and also use both a general assessment of pain, as well as a pain-specific score for your two primary efficacy points.

I am very bothered that we are talking about -- I am very sympathetic to a group that don't have any drugs available to them -- but when you are talking about an efficacy in the individual patient of only 1 to 8, to 1 to 15 women being helped, I would like to at least be able to say that there is a U.S. study done properly that shows this, and that would be combined with the European data to show that there is really true efficacy in the U.S. population.

DR. LAINE: I would concur obviously. I also felt that I wasn't convinced by the data as presented, and I would have liked to have seen one pivotal trial in the U.S. that really did document efficacy.

As I said, there was really only one trial that documented -- there was only one pivotal trial of 12 mg, and it did document efficacy in Europe, but not here. So, I would concur.

DR. HAMMES: Along those lines, I would really like to see a cross-over design, they are their own controls, try to get is placebo effect out of the way.

DR. RICHTER: I mean the literature -- and Michael and Arnie can comment about it, too -- the literature in

pain has been these cross-over designs never work, because they result in an adjustment of your pain scores. You never know how long of a washout period to have.

I think the best way to get at this long-term placebo response really is a maintenance, you know, trial, and then see what happens, but in the pain literature, they really try to stay away from these cross-over studies as much as they possibly can.

DR. HANAUER: With that, I would like to thank Novartis for an outstanding presentation and preparation and being able to address all the committee's questions.

We will adjourn until 8:30 tomorrow morning.

[Whereupon, at 4:12 p.m., the proceedings were recessed to be resumed at 8:30 a.m., Tuesday, June 27, 2000.]

CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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