the alosetron responses in both pivotal Phase III studies. Although we did not conduct any studies yet with relevant U.S. comparators, we do have two comparator studies from relevant European comparators.

The study you are looking at here which has recently been completed was a large, multi-center trial evaluating mubevrin [ph], which is one of the most widely used agents in Europe, versus alosetron. As you can see, alosetron was significantly superior to mubevrin.

DR. LAINE: So your expert IBS consultants do agree that 10 percent improvement is indeed clinically significant, as well as statistically significant?

DR. MANGEL: It sounds like you're asking me to speak for them.

Dr. Camilleri, would you have an opinion?

DR. CAMILLERI: I think one of the important issues here is that these trials have used a global response endpoint and the proportion of individuals that respond at that threshold endpoint is increased relative to the placebo-treated arm. The question you are posing is, is a 10-percent difference in the symptomatology different. And I think what Dr. Mangel has shown is that certainly for several of the endpoints that I saw on that slide, there was certainly a greater than 15-percent across the board for most of those symptoms.

So I think one has to distinguish between the proportion that reached the global endpoint in alosetron versus placebo group, where the sample size was appropriately chosen to show a 10- to 15-percent increment which would justify the prescription of this medication in this study population.

CHAIRMANHANAUER: While you're up there, Michael, Dr. Geller has a question.

DR. GELLER: In all the material I received, I didn't say that overall percent. Now, doing some quick averaging, I guess I would like you to tell me what the prime--rather than looking at the six percents, then, you really only should be looking at two, which is the overall three-month comparison in each of the trials, and those percents aren't given, although the p values are.

DR. LAINE: You mean--I have 17 and 9.

DR. GELLER: That's not right, that's not it. It's in the 50s, according to their analysis.

DR. LAINE: The difference?

DR. GELLER: The difference is, I think--well, quick--they have the data.

DR. MANGEL: Of course, I would agree, Dr. Geller, there are several different ways to look at it. When we look at the portion of weeks with adequate relief in--

DR. GELLER: I'm just asking for the primary

endpoint, the percent of response in each treatment group for each trial, which is not in the book, I don't think.

DR. MANGEL: You're looking for--

DR. GELLER: The primary endpoint--

DR. MANGEL: For the total number of months?

DR. GELLER: Yes.

DR. MANGEL: Okay. Could we have slide N-2 up?

DR. GELLER: That doesn't give--

DR. MANGEL: What this is is the number of months as a monthly responder for either zero, 1, 2, or 3 months on alosetron treatment versus placebo. Is that--

CHAIRMAN HANAUER: Is the question you're asking when was the primary endpoint measured?

DR. GELLER: The primary is three months.

CHAIRMAN HANAUER: Are you looking at multiple or--

DR. MANGEL: The primary endpoint is monthly responder for each of the three-month intervals. The primary endpoint was not the total number of months.

Could I defer to our statisticians on this because I'm clearly not answering?

Dave?

MR. McSORLEY: If you could put that slide back up, N-2, please? Dave McSorley, clinical statistics at Glaxo Wellcome. Could I have slide N-2 back up, please?

I think, Dr. Geller, what you were asking was that in terms of subjects who are monthly responders for all three months in each study. In study S3BA 3002, although the numbers aren't here, this was 41 percent, and this was 29. So there was a 12-percent difference in the proportion of subjects who are monthly responders for all three months.

And, similarly, in S3BA 3001, I don't recall the exact proportions. I believe it was--again, it was 41 percent versus 26, so I think it was a 15-percent difference in the proportion of subjects who were monthly responders for all three months. And I think that's what your question was, and that's what the p values represent, a comparison between the two treatment groups with respect to the total number of months, subjects for monthly responders.

DR. LAINE: Which exactly was the primary endpoint?

MR. McSORLEY: Yes.

DR. LAINE: Was it this or was it the--I thought it was the number of people with adequate relief, and the question is was it each month an endpoint or was it at three months, your primary endpoint?

MR. McSORLEY: Well, as you recall, the primary endpoint was the monthly responders. Since there are three months, our strategy for dealing with the multiple endpoints involved looking at the total number of months, so monthly

responder being a dichotomous endpoint; either you were or you weren't. Therefore, the total number of months could take on a value across all three months as either zero, 1, 2, or 3. That was our first test.

DR. LAINE: At each month?

MR. McSORLEY: Yes.

DR. LAINE: Okay.

DR. GELLER: The p value of whatever, .001 and .012, corresponds to the number of months, zero, 1, 2, or 3 of response compared in the two arms?

MR. McSORLEY: That is correct.

DR. GELLER: Thank you.

CHAIRMAN HANAUER: Dr. Senior?

DR. SENIOR: Would you clarify? I thought Dr. Mange1 said--and maybe the statistician will stay--said that if a patient left the study after responding in the first month, that response would be carried forward for the rest of the study, so that we therefore have credit for all three months. So if a patient had a response but withdrew for constipation, they would be counted as a three-month responder. Is that correct?

MR. McSORLEY: Yes. The last observation carried forward approach was applied on the monthly basis. Therefore, if you had an entire month missing, you looked at the data at the previous month and carried that forward.

DR. SENIOR: You could have two months missing.

MR. McSORLEY: That's correct. If you had any data at all in a month, if it was just one value, you obviously could not be a monthly responder, so you would be a non-responder for that month. So months in which there were partial data--the missing weeks in a month with partial data, those missing weeks were then assumed to be no response.

DR. SENIOR: I understand, but the critical number is the patients who were credited with responding for all three months, and that group includes people who weren't studied for three months and who may have left the study in the first month.

MR. McSORLEY: Right. I think the question you're asking is does the imputation--was that driving the results for the adequate relief? And let me assure that the imputation, according to the last observation carried forward approach, was not driving the treatment differences for adequate relief. In fact, at month one, none of the differences were attributable to the last observation carried forward approach because there was nothing to carry forward. Missing months were assumed to be no relief, so they were non-responders.

In addition, at months two and three, less than 1.6 percent of the treatment difference was attributable to

the last observation carried forward approach. Therefore, the last observation carried forward approach was quite neutral in estimating missing features with respect to adequate relief and was not explaining the significant treatment differences we've seen on the monthly responders or the total number of months analysis.

CHAIRMAN HANAUER: Dr. Geller?

DR. GELLER: I'd like to pursue the discontinued patients just a little bit. My first question--I work in cardiovascular clinical trials on the whole, and they are a lot larger than these and follow patients for a lot longer time. And I would be downright embarrassed to have this kind of discontinuation rate, so I wondered what actions you took so that patients would not discontinue.

MR. McSORLEY: If you recall--could I have slide R-49 from the core presentation?

This shows you the adequate relief data week by week, and although these are labeled weeks 13, 14, 15, and 16, during the follow-up when patients were discontinued, you know, they were encouraged by the staff at the site to continue answering the adequate relief question, calling in each week for up to four weeks. Of course, you know, you can't guarantee that people are going to do that if they withdraw, but what this shows you is that we did actually collect data for four weeks' follow-up for patients who

withdrew. And these data in each study show that there was no differential response once patients withdrew from treatment.

DR. GELLER: I was interested in during the treatment when you have various reasons for withdrawal, and one of them is, in fact, consent withdrawn--I was just wondering what kind of encouragement you gave patients who were not particularly reporting symptoms to continue taking the drug if they said, no, I don't want to continue this now.

DR. MANGEL: The only actual measure which was instituted as an effort to try to keep patients in were for individuals with four consecutive days without a bowel movement. They could have a brief interruption of alosetron therapy or in treatment, whichever arm they may be in, for up to four days.

DR. GELLER: Well, what if somebody said, I didn't take my pills, I forgot, I was out of town, I forgot to take them with me for a few days, and it was more than four?

DR. MANGEL: That is actually something different, Dr. Geller. The criteria of the drug holiday for up to four days was in response to four days without a bowel movement.

DR. GELLER: Right.

DR. MANGEL: Individual patient compliance of pills were not --except in the very large extreme, were not a

cause for removal of the patient from the study.

DR. GELLER: But what did you do to encourage the patients to stay in the study if they weren't exhibiting symptoms?

DR. MANGEL: Yes. The primary measure to encourage patients to remain in the study is, as you may recall, we collected data on the electronic data capture system. If a patient did not enter data for any specific day within the study, then a fax was automatically sent to the site of that patient. The site was instructed to call the patient to remind them to enter data to see if they were having any problems. Those were the only measures that were taken to encourage patients to remain within the study.

CHAIRMAN HANAUER: I have several questions and they are all in different directions. First is the endpoint. We heard from actually the public that the most important endpoint from their perspective was quality of life. Yet, by the SCL-90, there were no differences. What is your take on that?

DR. MANGEL: Yes. The SCL-90, Dr. Hanauer, is not a quality of life instrument. It's more a measure of distress. The SCL-90 is more measuring psychometric dimensions than quality of life parameters, per se. In our study, we did actually have a quality of life--we actually had two quality of life instruments, as well, the SF-36,

which is a generic instrument, as well as a disease-specific instrument, the obvious QOL.

In the United States, which is somewhat different from many of the European countries where statistical significance is all that is required for achieving--or recognizing that you've received benefit in quality of life, in the United States we also have to exceed a clinical hurdle which is known as the MMD, or meaningful minimum difference.

We have recently received our MMD data and are in the process of evaluating whether we achieved a clinical hurdle on our IBS quality of life data. We achieved statistical significance on eight of the nine domains in one study, nine of the nine domains on the other study for the IBS QOL. I should point out, though, that that may be misleading, as in addition to achieving statistical significance to achieve satisfactory quality of life benefit as far as a claim in the U.S., you must also achieve a clinical hurdle. We do not have those results to share with you. They were not included within the NDA.

How come the results were not included within the NDA? There are actually two reasons. One is the MMD instrument; we have just received the results from that. It was actually a separate instrument. It was administered in a 12-month-long study entitled S3B 3006. The instrument was

not included within the pivotal program.

CHAIRMAN HANAUER: Well, I guess we'll come back to that in a subsequent discussion because obviously you had preliminary discussions with the agency regarding the endpoint that you used, and that was the reason that you--I presume that's the reason that you came up with the current primary endpoint.

DR. MANGEL: Yes, at the end of Phase II.

CHAIRMAN HANAUER: And the agency didn't request any additional quality of life as part of the NDA?

DR. MANGEL: Well, I don't want to speak for the agency unless the agency wants me to.

CHAIRMAN HANAUER: Did you guys want any quality of life data?

DR. TALARICO: We don't have any regulatory criteria yet for accepting quality of life as a parameter.

CHAIRMAN HANAUER: Well, you know, from our standpoint, one of the issues is we kind of set the hurdle now, then, as their current primary endpoint. So, that's kind of setting a--it's going to set a precedent if we accept it as that primary endpoint.

DR. HOUN: We're open to comments on that primary endpoint, and I think in terms of quality of life, I mean if a company wishes to pursue that as another indication, you know, that is up to the company and further discussions with

the agency. Quality of life has been a difficult area in tool validation and meaning, and so it's not as clear-cut as maybe other endpoints and trials.

CHAIRMAN HANAUER: Dr. Wald, do you have comments on that just to get some follow-up? Are you satisfied?

DR. WALD: Well, I think it's a very important issue that you raise. One was talking about symptoms, and then you're breaking them down into primary and secondary endpoints. But, of course, the global issue is quality of life and I think that is what is important to patients. And I think it will be very helpful if we have the kind of data that hopefully will come forth that will show that. It makes sense that if you have improvement in symptoms, you should have improvement in quality of life, depending, of course, on what you are measuring.

One of the questions I wanted to ask goes back to a preliminary slide in which you indicated or asked patients what their most discouraging symptom was, and about a third talked about abdominal discomfort. I may have missed it, but do you have data that breaks down that to separate out those who view urgency or frequency of defecation to see whether those patients who indicated abdominal discomfort also had significant, or statistically significant improvement in the major cause of their problem?

DR. MANGEL: I would to rephrase your question,

Dr. Wald, just to make sure that I have it correct. You would like to know how individuals did on adequate relief by what was their most bothersome symptom, just to make sure I answer the correct question?

DR. WALD: Yes, but specifically for the group, the 36 percent or so--perhaps that's not true in all of the trials--who would indicate that abdominal pain was the primary symptom that caused them the most distress. If we just took that group and eliminated the others, how much of the improvement that you see in your data comes from that?

DR. MANGEL: There was about a lo-percent improvement on adequate relief for that population with alosetron treatment as compared to placebo. The statistical significance--actually, we didn't analyze it because what we're doing is we're taking. the population and then you've dividing it by the percent of people, or subcategorizing by the percent of people which had that specific most bothersome symptom, so you're starting to lose power. But we were looking for the trend to see how those people would do. We also--

DR. WALD: So, in other words, that subgroup had approximately the same amount of improvement difference-wise from placebo as did the rest of the population?

DR. MANGEL: Yes, and what we saw, Dr. Wald, is for the patients who reported urgency to be their most

bothersome symptom, they did quite well on adequate relief. For individuals who were diarrhea-predominant and reported bloating as their most bothersome symptom, they actually also did quite well on adequate relief. For those who were categorized as those with an alternating bowel pattern and bloating was their most bothersome symptom, they did not do well at all on adequate relief.

DR. WALD: I just want to focus on those who had abdominal pain, the 36 percent. The reference is 10 percent in those with diarrhea predominance and a similar amount with the alternating?

DR. MANGEL: No. I'm sorry. That number was for the diarrhea-predominant; it's on the order of about 10 percent. For the alternators, it actually was about 15 percent.

DR. LAINE: A smaller point. You know, typically, one gives approval for the population that was studied. You're asking for approval in people who have diarrhea, basically. It strikes me as basically the population you included was anybody who didn't have hard stool, basically. So it would strike as your endpoint is in those who don't have hard stool. And it may be a subtle difference, but that's why I say looking at IBS, perhaps, obviously you certainly had your investigators check whether it was diarrhea-predominant or not. But, in reality, you entered

anybody who had a stool greater than 2.5.

And the other problem is you didn't really talk about--it's not a problem--frequency, which is the other part of diarrhea or constipation, was not really an inclusion criteria. So, in reality, it was really only stool consistency that was an entry criteria. So it strikes me as what you would be asking for based on this study would be people who didn't have hard stools, IBS female patients.

DR. MANGEL: Yes. First, I would like to start my answer, we agree with you, Dr. Laine. Our entry criteria for bowel function were based on the stool consistency score being greater or equal to 2.5 on the 5-point scale, which is somewhere between hard and formed stool. The intent of that was, clearly, we thought patients who were very constipated would not benefit from a drug that tends to induce constipation. So, that is why we simply chose not to study those patients.

We did find somewhat of a disparity in the results of the 3001 and 3002 study with respect to how the alternating patients performed. In the 3001 study, as well as in the mubevrin study, which is the recent European study, the alternators all received benefit over placebo for adequate relief.

In the 3002 study, the alternators were much more constipated variety overall, and that was based on stool

consistency scores as well as stool frequencies. When we dissected out the alternators from the 3002 study who had a normal consistency and a normal frequency, they also received good benefit with alosetron.

So we agree that we did not study those patients who were constipated, and at screening we actually only had a stool consistency entry requirement, not a stool frequency.

CHAIRMANHANAUER: Following up on those lines, the most common side effect was constipation, and also the reason for withdrawal. Did you correlate the likelihood that the patients were going to complain of constipation based on their baseline stool consistency? Was that a factor overall?

DR. MANGEL: Yes. The overall rate of constipation in the alternators was approximately--when you correct for placebo because the placebo rate was 1 or 2 percent higher, was approximately 7 percent higher in the alternators than in the diarrhea-predominants, you know, so the alternators started with a lower frequency and a harder consistency than the diarrhea-predominant patients. So it's exactly as you predicted, Dr. Hanauer. Those who tended to be more constipated at study entry were more likely to develop constipation.

DR. RACZKOWSKI: I wonder if you could clarify one

of the summary slides that you had. It was slide number A-53--

DR. MANGEL: Could we have A-53, please?

DR. RACZKOWSKI: --where you indicated that alosetron provides significant and sustained adequate relief of IBS pain and discomfort. And the question I have is where the term "sustained" comes from because my understanding of what a monthly responder would be is someone who responded in two out of the four weeks of that month, or more, not necessarily contiguous weeks. Similarly, in your overall analysis when you're looking for monthly responders for two months, those don't necessarily have to be contiguous months. So what do you mean by "sustained" there?

DR. MANGEL: Sure. Could we have slide A-49 from the core, please?

The notion of monthly responders is, of course, more applicable to a regulatory environment than a clinical environment. We feel the data presented on the week-by-week basis which, of course, comprised the primary data to generate the monthly adequate relief responders, you know, may illustrate this point a bit better. And what you see is once benefit is achieved, a sustained response occurs on adequate relief.

DR. RACZKOWSKI: But that's not in any given

patient. You're talking about overall in the population.

DR. MANGEL: Yes. Okay, could we have--what we also did--and I will show it to you all; just pull up the slide. We also evaluated for individual patients, the patients who had at least two weeks of adequate relief for month for each of the three months, and individuals who had at least three weeks of adequate relief for each of the three months. So I believe this is addressing your question. So those are the individuals who would have at least, in that latter group, 9 weeks of adequate relief out of the 12-week study.

If you bear with me for just one moment, because this is an important issue, I will pull up that slide. Could we have in the C set slide number 27?

So what you're looking at here, and as you would anticipate because you've made your hurdle higher, that the relative percent of patients, the absolute percent of patients who would achieve adequate relief for at least three weeks per month for every month will be lower than two weeks per month for a month. But what you see with alosetron--you know, you see a similar delta between alosetron and placebo-treated patients. So this represents patients who have received at least three weeks per month for each month with adequate relief. And this, as well as the weekly basis, is some of the evidence for

sustainability.

We also analyzed transitional probabilities, such as the probability, once you have relief, of switching to a no-relief state, but more appropriately, once you have relief, of staying in a relief state. The transitional probability was approximately 80 percent. So once you're in relief, it's an 80-percent probability you're going to stay in relief.

DR. LAINE: As you got closer and closer to no pain, is it not true that--you didn't give all the data, but that alosetron and placebo were quite comparable for pain-free status?

DR. MANGEL: For pain-free days?

DR. LAINE: Yes. Well, actually, you presented it in two different ways, or it was presented in different ways, but the numbers weren't always given. No data was given for that.

DR. MANGEL: Yes, and I believe, Dr. Laine, you're referring to the pain-free day responders for the secondary endpoints, yes. And a pain-free day responder is actually, we believe, a very high hurdle. That represents individuals who had to have at least 50 percent of the days within a month of no pain at all, and we agree. I mean, that analysis only showed significant improvement at month three in the one study for virtually the absence of pain.

CHAIRMAN HANAUER: Dr. Geller?

DR. GELLER: I have some questions about the analyses you conducted. I understand that for your primary endpoint, you had first an overall analysis and then the three monthly analyses. I wonder if you had any system in place for sequential analyses when you were doing all these week-by-week comparisons.

The slide you just had up a few moments ago, A-49, is the first example where you have 17 weeks of data, counting week zero, and it looks like you conducted 17 hypothesis tests for each study. Was there any sequence rule in place for conducting the next test?

DR. MANGEL: I would like to refer to Dave McSorley again.

MR. McSORLEY: Our strategy for dealing with the multiple significance testing was --you're exactly right--we did test endpoints sequentially by pre-specifying the order for which we tested endpoints and then requiring significance before we proceeded to the next endpoint.

Specifically, on the week-by-week analysis, that was a secondary endpoint, a supportive endpoint to the monthly responders mainly to identify the onset and durability of the treatment effect. And those p values that are starred in slide A-49 are the raw p values and they are not adjusted for multiplicity. The multiplicity adjustment

again applied to the monthly responders, as the first test was the total number of months. And if that was significant, we primarily assessed the individual months to see which months were significant or responsible for the significant result on the total number of months, and then the weekly results were done as complementary to that to identify the onset and duration.

So the primary adjustment sequence was the total number of months, and if that was significant, then we looked at the other things as complementary and supportive and moved on to the secondary endpoints. So just let me show you how that all plays out in terms of our primary and ccey secondary endpoints.

If I could have backup slide N-46, what this slide shows is our multiple testing strategy involved the total number of months with adequate relief was the primary assessment for efficacy. And then if that was significant, tie proceeded to the secondary endpoints that were given in a pre-specified order--stool consistency, urgency, stool frequency, then bloating and incomplete evacuation.

And as you can see, in each study we were significant at p less than .05 for each of the endpoints. However, when we got to the bloating endpoint, it was not significant at the pre-specified interval, month one. So the testing--

DR. GELLER: Where was that in the sequence, bloating?

MR. McSORLEY: I'm sorry. Bloating was number four and it was not significant at the primary interval that was specified, which was month one. So testing then stopped at that point, and so this was the sequence for testing endpoints and the significance is seen there. Again, the whole rationale for testing in sequence is if we have p less than .05 for each of the endpoints, then the overall significance level is less than .05, so no adjustment is necessary.

DR. GELLER: But then on the question I asked initially on the weekly data, we do have 17 comparisons for each study for each of those weekly graphs.

MR. McSORLEY: That is correct.

DR. GELLER: Okay. Now, I have one last question regarding the multiple testing and it relates to slide A-58-

MR. McSORLEY: Could we have slide A-58?

DR. GELLER: --where you have the secondary endpoints broken down by months. So we have some different kinds of combinations here, so is there a sequential procedure in place here?

MR. McSORLEY: Well, for incomplete evacuation and bloating, that is a continuation of the pre-specified order

for the secondary endpoints.

DR. GELLER: But what about the months?

MR. McSORLEY: Well, the primary interval for assessment was month one, and that not being significant--these are just displayed to show how the results came out. So I think at this point--

DR. GELLER: So month one is not significant in any of those?

MR. McSORLEY: That's correct, and so these are primarily presented for supportive and descriptive purposes.

DR. GELLER: Okay, so now just let me get this straight. For the secondary endpoints, the months were specified in what sequence?

MR. McSORLEY: Month one was the primary interval.

DR. GELLER: And then?

MR. McSORLEY: And then weeks within month one.

DR. GELLER: And then?

MR. McSORLEY: Months two and three.

DR. GELLER: Combined or separately?

MR. McSORLEY: Separately. At that point, months 2 and 3 and weeks 5 through 12 were looked at, you know, as complementary or supportive purposes.

DR. LAINE: That wouldn't prevent you from going on to the next one, then?

DR. GELLER: Yes, indeed.

MR. McSORLEY: No, because the primary interval for assessment was month one.

DR. GELLER: But these have no significance in month one, all these?

MR. McSORLEY: That's correct.

DR. GELLER: Thank you.

DR. LAINE: So that means if, at month two, there wasn't significance, you could still go on to the next endpoint because of the fact that you were only looking at month one in the sequence, is what you're saying?

MR. McSORLEY: Right.

DR. LAINE: For instance, in the two-month adequate relief, you reached a p value that was not .05 at two months.

DR. GELLER: I think there was a sequential procedure in place, but it wasn't in place, in that there was a sequential procedure in place and then if everything went right, it followed. But if everything didn't go right, the remainder of the tests are still done. I think that's actually what we see here.

MR. McSORLEY: Oh, you're exactly right. All of the tests were done, but interpretation for whether it's inferential versus descriptive purposes, we followed exactly the pre-specified--

DR. GELLER: But nobody said this particular slide

was descriptive and not for inferential purposes.

MR. McSORLEY: I do think the title for the slide did say secondary endpoints.

CHAIRMAN HANAUER: Do you need more clarification?

DR. GELLER: I don't think so. Thank you.

CHAIRMANHANAUER: Dr. Berardi?

DR. BERARDI: I have two questions. I don't want to interrupt the momentum here in this direction and if you want me to, I can ask these questions later, but one of them has to do with potential drug interactions and the other one has to do with hepatic metabolism.

CHAIRMAN HANAUER: Go for it.

DR. BERARDI: The first question has to do with the potential for alosetron to have drug interactions, and I was particularly reading some of the information that was sent as background information. I wondered if you all collaborate on, in particular, the study that was done with theophylline because this drug is a known inhibitor of cytochrome p4501-A-2 [ph]. And I was curious as to was this a steady state or a single-dose study. Was AUC measured?

I know the data was given on blood levels, but I was wondering if one could elaborate on that for me, please.

DR. KOCH: Yes. Kevin Koch, Glaxo Wellcome, clinical pharmacology. It was a single-dose--I'm sorry--it was a repeat-dose study. We dosed for 15 days with

theophylline and then added the alosetron placebo 8 days into that. So we were looking at steady state blood levels of theophylline, and we didn't see any effect of alosetron in vivo.

DR. BERARDI: Was AUC measured?

DR. KOCH: Yes, it was.

DR. BERARDI: And you saw no differences in AUC?

DR. KOCH: No differences at all.

DR. BERARDI: And if you don't mind, could you talk a little bit more about the cisapride study, and I think you did haloperidol and morphorine [ph].

DR. KOCH: Yes; not morphorine, haloperidol, yes.

DR. BERARDI: Okay, and--

DR. KOCH: The cisapride study, as well, we looked at-- saw no effects on AUC blood levels.

DR. BERARDI: And that was the effect of alosetron on cisapride, or cisapride on alosetron?

DR. KOCH: Alosetron on cisapride.

DR. BERARDI: On cisapride?

DR. KOCH: Right.

DR. BERARDI: Okay. My second question is this drug is highly metabolized, and I was curious as to--I know that this probably isn't going to be a major issue for most of these women, but for the woman who has hepatic impairment of significance, do you have any information on or any

studies that have looked at how clearance would be altered in patients that are hepatically-impaired?

DR. KOCH: We did not study it, per se. In mild/moderate impairment, the literature shows very little effect on cytochrome p450. In severe impairment, the literature is a bit mixed. There are certainly decreases in l-A-2, which accounts for about 10 percent alosetron metabolism. So, there, we wouldn't expect to see much of an impact. There are some effects on 3-A-4 as well.

DR. BERARDI: And if I may, I just have one last quick question. I was just curious as to how compliance was measured in the study, or how did you define compliance first, whether it was 80 percent of all doses that were to be expected? I think you did pill counts, if I read it correctly.

DR. MANGEL: Yes, 80 percent.

DR. BERARDI: Eighty percent?

DR. MANGEL: Yes, and at that level for each month for both treatment groups in each study, it was greater than 90-percent compliance.

DR. BERARDI: Thank you.

DR. GELLER: Are you including the discontinued patients in that assessment or not? You must be excluding them because you had 20-percent discontinued patients and you can't have 90-percent compliance then.

DR. MANGEL: You know, compliance with pill count, as compliance with the phone system, would only be applicable to while the patient is still within the study.

'DR. HOUN: I just wanted Dr. Washington to describe the performance characteristics of her immunohisto testing.

DR. WASHINGTON: We did not test the antibody ourselves on other serotypes of E. coli. The paper that we used as a reference says that they contacted the manufacturer, who is here in Maryland, and by the manufacturer's report there is only weak reactivity with a few other serotypes of E. coli. So we have not tested it for cross-reactivity to other E. coli. We're relying on the manufacturer's report there.

DR. HOUN: If this is a commercially available antibody, then it is regulated under FDA and the laboratories that are performing the test have to acquire la independent laboratory characteristics from this test. Is your lab routinely doing this?

DR. WASHINGTON: No, we do not do this for diagnostic purposes. I was sent the antibody by the company and asked to perform the testing on these slides. But, no, we do not, and I don't know of anyone who uses this antibody routinely for diagnosis.

CHAIRMAN HANAUER: Dr. Laine?

DR. LAINE: Just a quick follow-up. On your case one, the 1996 case, it appeared that there was no significant inflammatory cell infiltration. You had the withering bland, as you said, and there was some erosion of the--or some lack of epithelium. Is that--

DR. WASHINGTON: Well, in one area it looked like the surface epithelium had stripped off. That's often artifactual. There was no neutrophilic response. There was a little bit of reactive change in the crypts, but they w&e not noticeably smaller. So I really do not think this is diagnostic of ischemic injury or even--I would not call it suggestive if I had that biopsy blind.

DR. LAINE: There certainly are times when you can't really say one way or the other whether something is ischemic or not ischemic.

DR. WASHINGTON: Sure, right.

DR. LAINE: So you wouldn't rule it out. You just wouldn't rule it in.

DR. WASHINGTON: I wouldn't totally rule it out. I just simply have no evidence for it in the biopsies. I'm relying on the gastroenterologist to sample abnormal areas.

CHAIRMAN HANAUER: Dr. Prizont?

DR. PRIZONT: A question; I think it's Dr. Mangel. I'm impressed by the number of E. coli infections you have here. My understanding is that enteropathogenic E. coli

usually is prevalent in enlisted soldiers, children, and so on. And the question I have is whether the slowing down of the motility by alosetron may predispose the infection with E. coli.

It is known that decreasing peristalsis in the case of ? , for instance, or in the experiments Shigella--I used to work in Shigella--that predisposed infection with pathogenic microorganisms. And I wonder if you can postulate about it.

DR. MANGEL: Yes, and perhaps, Dr. Prizont, I would comment on the first half of your statement and then answer the question as best we know it. The trigger for us to do aminohistochemistry looking for E. coli 0517:H7 was a paper published in the American Journal of Gastroenterology by Soo, et al, coming from Dr. Brandt's group, in which they retrospectively reviewed cases which were considered ischemic colitis. Of those cases, 27 percent were found to be E. coli-positive.

So, you know, that's probably the extent of the retrospective case review. So in that series, 27 percent of the cases were E. coli-positive. We believe our specimens are consistent with--two of the cases represent the E. coli infection.

In terms of the actual question, Dr. Prizont, I'm not familiar with any data one way or another in terms of

constipation predisposing to E. coli infection. I'm just not--I'm not aware either way.

CHAIRMAN HANAUER: Dr. Gallo-Torres?

DR. GALLO-TORRES: Thank you. These are questions for Dr. Washington. Did the case of infectious colitis occur in the middle of an epidemic, number one? Number two, are there results of cultures of the stools in these four patients, but especially in those two that you are labeling infectious colitis?

Number three, it wasn't quite clear to me how many cases did show infiltrated crypts.

DR. WASHINGTON: Just two cases.

DR. GALLO-TORRES: And the final question, please. Are you categorizing the cases as being exclusively ischemic colitis or exclusively infectious, or are you thinking of a mixture of the two entities?

Thank you.

DR. WASHINGTON: First of all, I don't know of any--we're talking about the two '98 cases that look, in my opinion, like they represent E. coli infection. I don't know of any particular outbreak at that time, but I think E. coli 0157 colitis is probably under-diagnosed because I think many pathologists don't recognize this mixed ischemic/infectious pattern and it simply gets labeled ischemic. And if it's in an older person, it may not get

investigated further.

You know, obviously, if it's in a 4-year-old and you have an ischemic-looking picture, you're going to think about E. coli, but in an older patient that might not be the case. So I don't know of any associated outbreak with these two cases.

What was the second question?

DR. GALLO-TORRES: The second question was do we have stool cultures and whether we have any results of these.

DR. WASHINGTON: Well, stool cultures--you have to notify the microbiology lab in many hospitals to look specifically for the serotype of the E. coli. If they just grow E. coli out on their McConkey agar plate or whatever, they're not going to regard that as a pathogen. So there has to be specific testing for the E. coli 0157:H7 serotype, and I do not believe those were done, although someone else may have more information on that.

DR. MANGEL: Culture was done on one of the two patients, Dr. Gallo-Torres.

DR. GALLO-TORRES: Which one was it for, please, what year?

DR. MANGEL: One of the '98 patients.

DR. GALLO-TORRES: '98.

DR. MANGEL: I'm saying culture was done on the

96 case and one of the '98 cases, and was read as negative by culture in each of those.

CHAIRMAN HANAUER: For--

MR. McSORLEY: For E. coli.

DR. GALLO-TORRES: For E. coli?

DR. MANGEL: Yes.

DR. GALLO-TORRES: Thank you. The third question was--

DR. WASHINGTON: There are some other rarer serotypes of E. coli that are associated with this hemorrhagic colitis, so simply testing for one serotype may not identify the rarer ones. I feel we don't really know the full spectrum of the clinical or the pathology of the disease.

CHAIRMAN HANAUER: Dr. Ferry?

DR. FERRY: There are other organisms, at least in children that have produced this hemorrhagic colitis as well.

DR. WASHINGTON: Sure.

DR. FERRY: And I guess my question is how specific is this pathology for this, and is this--I mean, can you clearly just by looking say there is enough ischemia here that it clearly differentiates this type from any other just infectious colitis?

DR. WASHINGTON: I think the ischemic pattern is

the--the mixed ischemic/inflammatory pattern is the pattern we associate most closely with E. coli 0157 colitis, but I can't give you any figures on absolute specificity for that. I think it is clearly not just an ischemic colitis. You know, ischemic injury is part of the spectrum of this disease, as the toxin damages blood vessels, is my understanding. So it's not surprising we have an ischemic-appearing injury to the colon. What makes me think it's infectious is the superimposed acute colitis in the intact mucosa which is not typical of the usual ischemic colitis, in my experience.

DR. LAINE: CBF can also cause, can it not, a similar picture?

DR. WASHINGTON: Right.

DR..LAINE: Was that ruled out in these people, C. dificile?

DR. MANGEL: C. dificile was also collected, Dr. Laine, in the same acute patients, and C. dificile was also negative in those two patients. I think, though, as stated by Dr. Washington, we would certainly conclude that a negative culture for C. dificile is much more reliable than a negative culture for E. coli.

DR. WASHINGTON: The test for the toxin, I suppose, is more reliable.

DR. WILSON: I have a question for Dr. Washington.

In your opinion, as an academic clinical pathologist, how would you have read these four biopsies certainly without going beyond your standard of care at your hospital?

DR. WASHINGTON: The '96 case I would have signed out as a non-specific reactive change, negative for acute and chronic colitis, no evidence of ischemia. The two '98 cases, I would have diagnosed as, you know, mixed ischemic/acute inflammatory colitis, and in a comment I would have said that E. coli 0157 infection should be clinically excluded, and say that although there are elements of ischemic injury in there, the pattern was not typical of classic ischemic colitis and infectious etiology was favored. The '99 case, I would have signed out as compatible with ischemic colitis.

CHAIRMAN HANAUER: Dr. Houn?

DR. HOUN: I just wanted to know if you read these blind.

DR. WASHINGTON: I looked at the slides as they came in without reading the laboratory reports that were supplied or any of the description. You know, I knew they were cases that had been considered ischemic colitis, but I had none of the clinical information in front of me as I looked at the cases.

DR. RACZKOWSKI: I wonder if there's any data on whether there are carriers, non-symptomatic carriers of E.

coli 0157 in an analogous situation to have group A beta hemolytic strep in the throat but not having strep throat.

DR. WASHINGTON: The pathology literature that I read refers, you know, just basically in the introductory portions to asymptomatic carriers. I don't know the data on that, but, yes, I believe it occurs.

DR. PRIZONT: Maybe Dr. Hanauer can answer this. We know from the point of view of ulcerative colitis, in enteritis, as well, that there is an association between viruses and bacteria and inflammation of the bowel. I'm not sure if this is in association, if the ischemic colitis started before the infection or the infection was a consequence of the ischemic colitis.

CHAIRMAN HANAUER: I'll give you a crack.

DR. WASHINGTON: I think I'll defer on that one.

CHAIRMAN HANAUER: Yes, we know--well, obviously it goes both ways, but most of the time we think that infections lead on to the other disease and that these are not secondary manifestations. But we're certain that it can happen secondarily. People with known ulcerative colitis can get Clostridium dificile, et cetera.

Well, I think I'm going to take a chairman's prerogative. My stomach is churning. I want to thank Glaxo Wellcome for their lucid and timely presentation. We're going to take a lunch break. We'll try and get back at 1:40

o we can start exactly at 1:45 for the afternoon session,
nd that's what we'll go for.

Thanks.

[Whereupon, at 12:45 p.m., a luncheon recess was
aken.]

AFTERNOON SESSION

[1:45 p.m.]

CHAIRMAN HANAUER: We're going to begin our afternoon session, now that Dr. Laine is here, and I'm happy to introduce Dr. Robert Prizont from the FDA who is going to give their perspective on the clinical aspects of the study.

DR. PRIZONT: Chairman, Members of the Advisory Committee, Ladies and Gentlemen, I was assigned the task to review the efficacy results of alosetron, a novel serotonin receptor antagonist in patients with a gastrointestinal functional disorder known as irritable bowel syndrome, or IBS.

In this brief presentation, I will point out relevant issues included or excluded from the study protocol. I will mention the actual disposition of patients enrolled in the clinical trials and will make observations on efficacy result issues as they relate to the indication proposed by the NDA sponsor.

Next slide.

Glaxo Wellcome proposes to indicate the use of alosetron for the treatment of IBS in female patients whose predominant bowel symptom is diarrhea, either alone or as part of an alternating stool pattern.

Next slide.

To support the claim of alosetron efficacy, the

sponsor conducted two pivotal clinical trials, abbreviated here as A3001 and A3002, and evaluated alosetron performance in IBS patients enrolled in a number of U.S. centers.

Next slide.

Both pivotal trials have an identical protocol with a design prospectively established as randomized, double-blind, and placebo-controlled, with a 12-week treatment period.

Next slide, the slide before that one, please.

This slide reviews some relevant issues included in the protocol. Women considered as candidates for treatment were diagnosed as having IBS by applying the guidelines to diagnostic criteria defined by a working team of experts in the World Congress of Gastroenterology, held in Rome in 1988, diagnostic criteria now known as the Rome Diagnostic Criteria.

In order to be eligible for enrollment, the IBS manifested in patients had to exhibit subjective symptoms, particularly IBS abdominal pain and, in addition, lower bowel symptoms had to reveal absence of constipation. As part of the methodology, the study protocol included a core scale to assess and define stool consistency.

Next slide.

Excluded from the protocol was a prospective definition of diarrhea and a stratification of IBS by types

or subtypes.

Next slide.

The last protocol issue relates to the prospective definition of clinical endpoints or clinical outcomes. The prospective primary efficacy endpoint was the adequate relief of IBS abdominal pain or adequate relief of IBS abdominal discomfort for at least two weeks per month. Relevant secondary efficacy endpoints were the proportion of pain-free days and improvement in lower bowel functions, such as stool consistency and stool frequency.

Next slide.

The next three slides show the similarities and differences in the disposition of patients enrolled in the pivotal trials. Between September 1997 and the summer and spring of 1998, enlisted centers randomized a total of 1,275 women diagnosed as having non-constipating IBS. 625 were randomized to trial A3001 and 647 were randomized to trial A3002.

Next slide.

There was a difference between pivotal trials A3001 and A3002 in their proportion of alosetron and placebo patients who discontinued prematurely. In trial A3001, 23 percent of patients on alosetron and 22 percent of patient on placebo discontinued or had to be discontinued prematurely from the trial. In trial A3002, 24 percent of

patients randomized to alosetron were premature withdrawals from the study, compared to only 16 percent of premature withdrawals in the placebo group. This difference was statistically significant.

Next slide.

In both trials, the reason for the high rate of premature discontinuation in patients treated with alosetron was the development of severe constipation. Between 62 percent to 69 percent of patients on alosetron developed this adverse reaction and had to be prematurely withdrawn from the studies. The issue of withdrawal due to constipation will be dealt in detail by the next presenter, Dr. John Senior.

Let's turn now to some relevant issues on efficacy ensuing from proposed label indication.

Next slide.

First is the issue of response to treatment, i.e., number of months with adequate relief of abdominal pain or adequate relief from abdominal discomfort. This slide, introduced by the sponsor as the first relevant comparison of treatment responses, shows the primary efficacy results in the intention to treat population of trial A3001. The column on the left lists the number of months with response. The alosetron and placebo columns represent the proportional responders who had either one, two, or three months'

response.

The comparison revealed that 41 percent of IBS women on alosetron versus only 26 percent of IBS women on placebo were responders for the three-month treatment period. As noticed in row two and three of the table, there was no difference between treatments in responders in a combined one or two-month treatment.

Next slide.

As seen in this slide, the favorable difference of alosetron over placebo in the proportion of primary efficacy responders to the combined three-month treatment was replicated in pivotal trial A3002.

Next slide.

This illustration is an amplified and detailed representation of monthly responders in the all-randomized patient population of trial A3001. Months are specified here as month one, two, or three. By prospective trial design, a patient could respond to either one, two, or to the three-month treatment. This slide displays eight possible patterns of response or no-response over the three-month treatment period.

Bars indicate the proportion of patients in each treatment group who displayed a particular pattern as defined from left to right. The bars on the left represent the proportion of patients who had no response to any of the

three-month treatment. The bars in the intermediate patterns indicate no substantial difference between the treatment groups. The bars on the far right indicate that treatments differed in the proportion of patients who achieved a response for the combined three-month period. This three-month period of response revealed a larger proportion of responders in the alosetron group.

Next slide.

The next relevant issue is the post hoc breakdown of the randomized IBS patient population in subtypes of diarrhea-predominant IBS and in alternating constipation diarrhea IBS. IBS subtypes are proposed as a label indication for alosetron treatment.

How was IBS diarrhea defined? As mentioned, the protocol did not define diarrhea. Simply, it included a numerical scale to score stool consistency in eligible IBS patients. This slide shows a clinical translation of the numerical scores of stool consistency. Scores of 1 and 2 represent very hard and hard stools and are consistent with the diagnosis for constipation; On the other extremes, scores 4 and 5 represent loose and watery stools and are consistent with a diagnosis of diarrhea. In the middle is the lonely score of 3, representing formed stools, stools consistent with normal bowel function.

Next slide.

IBS patients enrolled in trial A3001 and randomized to alosetron treatment, whether we consider the all-randomized population or the post hoc subtype of diarrhea-predominant, had scores of 3.4 or 3.5, perhaps considered as semi-formed stools, but certainly not consistent with a diagnosis of diarrhea.

Next slide.

These two squares illustrate the distribution of scores in the all-randomized population to trial A3001. The alosetron represents that between 75 percent to 80 percent of IBS patients enrolled in the trial had stool consistency lower than 3.7 scores, consistent with formed or semi-formed stools.

Next slide.

The other final element to consider in the definition of diarrhea is stool frequency. The Rome Diagnostic Criteria requires a frequency of greater than three bowel movements per day to include the diagnosis of diarrhea. Patients enrolled in the two pivotal trials had an average baseline stool frequency of less than three bowel movements per day.

Let's summarize now.

Next slide.

Glaxo Wellcome submitted data from two controlled clinical trials to support a claim of alosetron efficacy on

IBS. The trials enrolled 1,275 women with IBS. The protocol did not define IBS subtypes. Stool characteristics of enrolled patients did not meet the definition of diarrhea.

Next slide.

In this trial, alosetron 1 milligram twice a day given for a period of three months provided adequate relief of abdominal pain or adequate relief of abdominal discomfort.

Thank you.

CHAIRMAN HANAUER: Why don't we hear John Senior's presentation on safety and then we'll combine our discussions at that point.

DR. SENIOR: Good afternoon. We appreciate very much the elegant pharmacodynamic and physiologic reviews by Drs. Gershon and Camilleri, and the most interesting gender studies of Dr. Chang.

Now, as you've heard from Dr. Prizont, we considered this new drug to be a very promising treatment for at least some IBS patients. Really, no adequate, proved treatment has been available, and so we decided to review safety and efficacy concurrently to speed it up.

Next slide, David, please.

This is the primary safety database. It's pretty much as Dr. Mange1 described this morning. He told you

about the designs. These first two studies were the dose-ranging studies, the European and the U.S. dose-ranging studies. These were both placebo-controlled, so we went anywhere from zero, 0.1, 0.5, 1, 2, 4 and 8 milligrams twice a day, covering a reasonable range.

These are the two principal efficacy studies, also called pivotal, and this is the year-long study which really was just finished at the end of September and for which we have a first interim study submitted with the application, a second interim study which we've really just received, and a final report to be received later on. About five-sixths of the 2,800 patients were women.

Next slide.

Initially, there was concern about the possibility of arrhythmias, as has been seen with other types, particularly the 5HT4 agonists. But we did not see it. They did a good job, but I think pretty much assured us that arrhythmias were not a problem. There were some troubles with the animals in possible hearing loss, and that was disproved by audiograms in patients. However, we did confirm the sponsor's finding of constipation, and we discovered really a couple of new problems that we had not expected.

Next slide.

Let's talk about constipation first and the

evidence for it. Now, it was dismissed by Dr. Mange1 as a class effect, but to the patients it's a problem. As we see with the placebo group in the European study, 3 percent had constipation and 2 percent were withdrawn. The 0.1 alosetron twice a day really did not make much of a change in that, but when we got to 0.5 or 2, we saw significant increases in both constipation incidence and in patients withdrawn for it.

And when we looked at the higher dose-ranging study--next slide--at 1, 2, 4 and 8 twice a day, we see very significant increases in the number of patients reporting constipation and the number of patients withdrawn from study. These are very highly significant findings on alosetron. When we looked at the male/female ratio, we really did not see a gender effect on this dose relationship response of constipation.

When we plot the whole thing--next slide--here we have--adding in the principal efficacy studies, we had 834 people on zero dose, placebo, with about a l-percent incidence of people withdrawn for constipation. At 0.1 and 0.5, we had another 100 or so, and we saw a beginning of a rise in the number of people who were withdrawn for constipation. We had over 700 people on 1 milligram twice a day, and then smaller numbers at 2, 4 and 8 milligrams, but there is definitely a trend line for a dose-related and

common occurrence of constipation severe enough to cause withdrawal of a patient from the study or cessation of therapy.

Next slide.

In the principal efficacy studies, I looked at constipation at three levels; first, any constipation that was new in onset while on study drug; second, where it was bad enough to require interruption of treatment. So this is a subset of these. And then the third subset is even worse; they had to be withdrawn from study because of constipation. So each of these three levels shows a highly significant increase in alosetron in the population to be treated at the lose recommended to be used. These are very highly significant numbers.

In the next study, 3002, we really saw pretty much the same thing. And if we put the two studies together, because they are very eminently poolable--next slide--in the principal efficacy study we had over 600 people in the placebo and alosetron arms. Again, we see an average of about 28 percent showing constipation while on study drug. Thirteen, almost fourteen percent had to have treatment stopped for four days so that they could maybe have a chance to recover, all very significantly greater on alosetron than placebo, and about 10 percent versus 1 percent withdrawn from the study because of constipation.

So what can we say? Is it adequate to dismiss this as a class effect or should something be done about it? We'll leave that for the learned consultants of the Advisory Committee.

This problem was not expected.

Next slide.

This patient, whom you will recall had a biopsy that was non-specific, was a young woman 33 years old, a rather tall, not obese woman, not very well-educated, had not finished high school. She started alosetron, in one of the dose-ranging studies had 2 milligrams BID for only two days beginning back in July of '96. On the morning of the third day, she developed explosive diarrhea. She had first loose and then watery stools, 30 stools that day. They didn't find anything on physical exam in the emergency room of her local hospital.

They gave her a hyoscyamine preparation. It did not help her. The pain was worse. She came in the next day with peritoneal signs, rebound tenderness, rebound pain, and left-sided abdominal tenderness. She was scoped by the investigator, who found mucosal erosions in the left colon, and diagnosed ischemic colitis and did the biopsy which you saw shown by Dr. Washington. Now, the biopsy didn't show anything, but the patient certainly did. It took the patient almost--well, from July until October to recover,

and that case was reported to the sponsor in October of 1996.

Next patient.

Now, these two patients, the 41-year-old and the next one is a 38-year-old, had similar pain, abdominal pain with rectal bleeding. Seen in the ER, did not respond to hyoscyamine, admitted; segmental colitis. Biopsy showed what they thought was ischemic colitis, but is now being claimed to be E. coli 0157 hemorrhagic colitis.

And the next case is similar; again, rectal bleeding, crampy abdominal pain. Local doctor consulted, gave fluid and fiber; did not respond, pain worse. 3:oo a.m., she came in. This is not trivial. Colonoscopy showing sloughing in the mucosa. It was not attributed to study drug. The patient was withdrawn, and although the case report did not give much information beyond that, there were no more cases of rectal bleeding. Now, I will point out that we have not received any of the biopsies. We have not received even any of the reports of the colonoscopies or pathologies, so we are waiting to see this information.

Next slide.

Now, ischemic colitis has been around for probably a long time. It was reported in 1963, predominantly in older people, often after some event such as shock or digestive failure or aortic clamping, say, for an aortic

graft. And this was bad. This often caused transmural infarction, gangrene of the colon, perforation. And unless they were operated on promptly, they died.

Now, in more recent years, it is known that maybe a third of the cases occur in people under 50, and that things such as drugs may cause this--ergot agents, cocaine, pseudoephedrine. But not just them; efregens [ph] and danozol [ph] may cause this. These are not necessarily considered vasoconstrictors. This is characterized by crampy abdominal pain, diarrhea, submucosal hemorrhages that look like thumb prints on the barium enema. These people recover. They often do not show lesions in the small vessels, and certainly no occlusions of the inferior mesenteric artery. These are called non-occlusive ischemic colitis.

Next slide.

So we saw one case of whatever it was in the dose-ranging study. We saw another case in each of the principal studies. So we're looking at 3 out of 900, or about 1 in 300. Now, our statisticians tell us, basing this on a simple binomial expansion, that the confidence interval of that is anywhere from 1 in 1,500 to 1 in 100. So the estimated incidence of this may be as much as 1 percent when we get more data to look at.

Next slide.

So how can ischemic colitis be diagnosed, or hemorrhagic colitis, whatever it is? If you've already got abdominal pain or diarrhea to begin with, these are cardinal findings. They are unreliable, therefore, to detect this and confound the diagnosis. So probably rectal bleeding may be the best indicator of this and we ought to be watching for this very closely. Now, they did look a little bit at this.

Next slide.

Going back to the principal studies, these are my reviews of the sponsor's listing of adverse events in these studies. If they had known hemorrhoids or menstruation or known lesions such as fissures or whatever, I didn't count them. Maybe a little more in alosetron than in placebo of unexplained rectal bleeding, but certainly I agree that there were no further cases here of missed ischemic colitis.

Now, the third problem, just one case.

Next slide.

This is a woman who was withdrawn from the study because she had pulmonary edema as her serious adverse event the day after an endoscopic retrograde colangeopancreatogram [ph] . Now, I was curious and said, well, why is she having an ECRP done? So I looked back and said, oh, the drug had been stopped some time before because she had abnormal liver values, elevations of the enzymes after the first visit at

22 days, and ALT almost four times the upper limit, accompanied by a doubling of the bilirubin on the 50th day. The drug was stopped three days later when these results came back and she recovered promptly. That's nice, but what does our experience tell us about such cases?

Next slide.

The late Dr. Zimmerman noted many years ago, over 20 years ago in his first edition of his book, that when you have combined hepatocellular injury and loss of overall organ function indicated by jaundice, you're looking at the probability of mortality in 10 to 15 percent from liver failure, from drug-induced liver injury. This observation was restated by Hy Zimmerman posthumously in the second edition of his book just published in September, and has been confirmed over and over again by Dr. Robert Temple, of the agency, anecdotally but repeatedly in the years in between.

Now, we might call up, David, slide 29 so you can see what the data look like. Before you get to this, let's go to 29. No, 29; that's 30. There you go.

Can you see those numbers? The patient started out with normal enzymes, normal bilirubin, at screening. Study drug was started 27 February, '98. 20th of March, 22 days later, up went the enzymes, all three--AST, ALT and alk fos [ph] . But the bilirubin was still normal. A month

later, everything is abnormal. Her ALT is up to almost four times normal and the bilirubin has gone many times over what it originally was. And she's not jaundiced, but she certainly had a bilirubin problem.

Drug was stopped 3 days later, after 53 days of treatment. She they did follow her and she recovered very promptly. As you see, in 2 days it was already better, and in 11 days she was back to normal. And then they did the ERCP which showed nothing.

Let's go back to where we were, wherever it was, slide 22, David? This one, that's it.

So what does this mean in terms of safety concerns? From the patient's standpoint, this constipation is more than a class effect; it's a darn nuisance. I'm not sure that it's a good thing to go from normal stools to hard stools, which was the finding claimed to be an efficacy finding. And, certainly, it's not a good idea to get this whatever colitis, ischemic, hemorrhagic. There's not much to choose. Hemorrhagic colitis due to E. coli 0157 is not a nice disease. It causes not just a little rectal bleeding, but may cause hemolytic uremic syndrome, thrombotic thrombocytopenia perpia [ph], renal failure, and all kinds of bad stuff. So I'm not sure that's a good alternative.

Liver injury is rare, less than 1 in a 1,000, probably 1 in 1,200 here if we count all the patients. But

I don't think we can afford to ignore this either because of what has happened with other drugs when they get out in the market and are used in hundreds of thousands of patients, or more.

So we are then balancing our concerns. How can a patient with IBS and her doctor weigh the chances of a good probability of a modest benefit against a small probability of a serious adverse effect? That's a dilemma and that's the problem we're putting to you.

Dr. Hugo Gallo-Torres will summarize the issues raised by the efficacy and safety reviews.

DR. GALLO-TORRES: Good afternoon. My very brief participation this afternoon is to summarize for you efficacy and safety issues as presented to you by Dr. Prizont, reviewer of the efficacy data, and Dr. Senior, reviewer of the safety data, of alosetron.

Among the issues raised regarding the efficacy of alosetron is, one, efficacy was evaluated only in women. Efficacy was most pronounced in the diarrhea-predominant group in an analysis not pre-specified in the protocol. And, number three, treatment duration was limited to three months.

Next one.

We really did not raise this precisely, but we feel it's very important. Pharmacodynamic data were

generated mainly in men and at doses other than those proposed for marketing. We feel very strongly that drug metabolism has not been fully characterized. Regarding this issue, with us is Dr. David Lee, a biopharmacist from our division who will be happy to comment a little bit more on the pharmacodynamic issues. Incidentally, also in the audience are Dr. Hoberman and Dr. Friar, both statisticians, ready to answer questions regarding statistical issues, if needed.

Next one, please.

Now, regarding the safety of alosetron as summarized by Dr. Senior, among the issues raised are ischemic colitis is very important. It would not be expected in this patient population, women with mild to moderate IBS, or in clinical trials of that size. As you heard, one case of liver injury occurred with a pattern that predicts liver failure in 10 to 15 percent of such patients.

Next one, please.

One will have to wonder what will happen if one approved this compound when the conditions are no longer controlled, and so one will have to raise potential additional risks, such as uncontrolled settings, such as the drug being taken by sicker patients, longer use, other medications, concurrent diseases such as liver disease, variable follow-ups, and other risk factors such as, for

example, acetaminophen or the intake of alcohol.

Last one, please.

Finally, irritable bowel syndrome is very common, and many patients will seek relief of discomfort and inconvenience from IBS-associated symptoms. Uncommon or rare events may become serious public health problems when hundreds of thousands or millions of patients are exposed to the drug.

That's it. Thank you.

CHAIRMAN HANAUER: Does the Committee have questions for any of the FDA reviewers?

Let me begin with one regarding the safety issues. We looked at a database of only the 2,000 or so patients in the clinical trials that were reported, the pivotal trials. Yet, the sponsor has performed a number of other trials inside and outside the United States. I presume that the agency has had access to a larger database than what you've just presented.

John?

DR. SENIOR: Yes, Steve, but a lot of the studies were done outside the U.S., particularly in the early stages. They were single-dose studies. There were all kinds of pharmacodynamic studies, young men getting this dose in IV preparations. We didn't really consider those as germane to the way the drug is going to be given. It is

being proposed to be given for 12 weeks at a dose of 1 milligram. So we focused the safety database, which was approximately 2,800, on the controlled studies.

Now, we have an extra 800-and-some patients in this year-long trial that has just finished, and we have not yet had a full final report on that. In addition, there are several other studies underway on which we have no knowledge, no report, no data. So what we're reporting here, Dr. Hanauer, is what we have to look at that is germane to the proposed labeled use.

CHAIRMAN HANAUER: I was just going to follow up and ask Dr. Mangel, can you expand that database for us? Can you give us a total number of patients exposed at 1 milligram or above?

DR. MANGEL: Overall, Dr. Hanauer, for completed as well as ongoing studies--and the reason ongoing studies are important, of course--although the studies are blinded during the course of the treatment, serious adverse events do become known to us during the course of the study and if the investigator gives attributability, then the blind is broken on that.

I was wondering, as long as I'm up here--we actually disagree factual with some of the statements which were made and if I could provide some clarifications?

CHAIRMAN HANAUER: Clarification or rebuttal?

DR. MANGEL: Clarifications.

CHAIRMAN HANAUER: In either event, we're happy to hear them.

DR. MANGEL: Okay. In reference to the case 2829 of ischemic colitis in which it was reported that it took 11 weeks for the patient to recover, if you turn to page 52 of your briefing document, in the first paragraph, a clinical diagnosis of ischemic colitis was made. The patient improved and was discharged five days after admission. The follow-up visit with the patient was 11 weeks later. It did not take 11 weeks for the patient to recover.

The next point I would like to add clarity to--at least sitting back here, I believe that there is a misunderstanding. The data which we presented today was on the ITT or total population. This was not subgroup data as our primary efficacy data which were presented. Data in diarrhea-predominant individuals were referred to to illustrate some points or to answer some questions. The data which you saw today were strictly from the ITT population.

I believe there could be some lack of clarity from the wording of the proposed indication, and it's something certainly which we could work out in the future with the FDA. But once again, the data were not from the diarrhea-predominant subtype.

The next clarification which I would like to make is--and if I could see one slide, please, because we actually on October 25th submitted to the FDA the course of the LFTs for that one patient. Could I have slide E-91, is it, Chris? E-91, please. And what you are looking at is the LFTs for the patient which Dr. Senior was referring to, and as you can see, this patient's LFTs normalized while still on treatment.

DR. SENIOR: The case report does not say that. Now, if you have other information, please provide it.

DR. MANGEL: Dr. Senior, if you--

DR. SENIOR: The case report says she was withdrawn on the 53rd day, and those peaks were seen on the 50th day. Now, the drug was stopped before she was withdrawn. She was not on drug from day 53 until the ERCP was done, unless your case report is erroneous.

DR. MANGEL: Dr. Senior, on October 25th, additional information about this case was submitted to the FDA.

DR. SENIOR: On October 25th? This submission came in June.

DR. MANGEL: This question was brought up to us by the FDA at our 90-day meeting on October 6th. With all due diligence, we contacted the site. We were able to gather the information and submit the information in our October

25th submission to the FDA.

CHAIRMANHANAUER: Yes, Dr. Prizont?

DR. PRIZONT: I don't recall presenting data on diarrhea-predominant patients. I presented data on intention to treat. My point on the subtypes correlated to the indication, precisely what you said. I'm going to stop here, but, you know, I just want to mention that in the original submission you did include analysis of diarrhea-predominant and the alternating subtype patients. You didn't present it here today, but you did present that in the summation.

CHAIRMAN HANAUER: I just want to add two sentences of amplification to the potential issue for everybody because we're talking about a drug that has potential applicability to 10 to 20 percent of our population of women that the sponsors have described. And although the trials went for 12 weeks, what was presented to us was that the efficacy went back to baseline, was lost, once the drug was discontinued. And no one here would anticipate that this drug is just going to be used for 12 weeks, so we really should anticipate the potential for a significant exposure to the female population here.

DR. LAINE: Along those lines of those specific IBHI criteria, can the agency representatives tell us if those criteria were met in terms of the number and length of

evaluation? Anybody, anybody?

CHAIRMANHANAUER: Harmonization?

DR. LAINE: Right.

CHAIRMAN HANAUER: IHC.

DR. LAINE: IHC, whatever it is.

CHAIRMANHANAUER: CI, whatever.

DR. LAINE: CHI. I always get confused, whatever.

CHAIRMAN HANAUER: There's an international there, something.

DR. LAINE: Yes, international harmonization something.

DR. TALARICO: I think three months was selected as an adequate duration that would give us an idea of prolonged use of a drug which may be used for a much longer period of time, but not necessarily continuously.

DR. LAINE: But I thought those rules were "x" umber for "x" months, and they were like 6 and 12 months. mean, at other meetings we've been told about those.

DR. MANGEL: Yes. The ICH guidelines specify at east 300 patients for 6 months. As you saw this morning, e had 415 patients for 6 months. The ICH guidelines pecify at least 100 for 12 months. In the second interim nalysis, we had 187 patients for 12 months.

DR. LAINE: Thank you.

DR. RACZKOWSKI: And in terms of the total number

of exposures, the ICH guidelines recommend 1,500 patients be exposed to the drug.

CHAIRMAN HANAUER: Other questions from the Committee members for the FDA before we move on to the questions that we've been posed?

Everyone is very quiet here.

Statistically, Dr. Geller, you said you had some comments before regarding the statistical analysis. Were they solved by the agency's presentation?

DR. GELLER: Well, Glaxo probably has a slide of the imputation which is in the briefing book, page 70 on the middle of the page, and page 75 on the right-hand of the page, and it's the bottom table. It shows the number of positive imputations with the number of data missing. So, that would show--some people are concerned--I'm concerned about the percent of missing data, and this shows the effect of the imputation. And I didn't understand the table when I saw it in the book and I think everybody would benefit by understanding the imputation, the effect of the imputation on the final analysis by an explanation of that table.

MR. McSORLEY: Thank you. Yes, if I could have--Dr. Geller, we've also summarized the data that are presented in the table that you're referring to in the briefing document on page 75. It is also summarized on slide--if I could have backup slide N-12, please?

This slide shows the amount of adequate relief from monthly responders; that is, monthly responders for adequate relief in terms of a "yes," having at least two weeks of adequate relief for each month within each of the months for those patients who had missing data for the entire month. And as you can see, at month one in each study, there is no monthly responders being imputed for either study, and at months two and three, in particular in 3BA 3002, there is more monthly responders for adequate relief being imputed for placebo than alosetron.

In particular, the numbers then--the heights of these bars represent the percent of subjects in terms of actual numbers. There were, in 3001, 5 patients imputed as monthly responders out of the 309 patients in the alosetron group, versus 3 out of 317 on placebo. So in terms of a treatment difference for all patients on the percent of subjects who were monthly responders, that translated into less than 1 percent of the treatment difference being attributable to the last observation carried forward approach.

Similar findings are seen on month three where, for alosetron, 10 subjects who had missing months had adequate relief imputed for that month, versus 5 for placebo. So, again, 10 out of the 309 alosetron subjects, minus 5 out of 317 for placebo, yields 1.6 percent of the

treatment difference that could be attributable to the last observation carried forward approach. And that's the largest percent difference between treatments that is attributable by the last observation carried forward approach.

And, similarly, you see the same kind of thing in S3BA 3002. On placebo, you have 6 out of 323 at month two that are imputed with adequate relief, versus 6 patients out of 324 for alosetron, which is less than 1 percent of the difference attributable to adequate relief. And similarly for month three, there are 10 patients who have adequate relief imputed for month three, versus 8 on placebo, and so less than 1 percent of the treatment difference is attributable to the last observation carried forward approach.

DR. GELLER: If I understand the table in the book correctly, the difference between the table and the slide is that the table has denominators, and the denominators have the number of people at each month--

MR. McSORLEY: Who were missing.

DR. GELLER: --who were missing altogether.

MR. McSORLEY: That's correct.

DR. GELLER: And therefore the table in the book also tells you the number of imputations of zeroes, of non-response, as well.

MR. McSORLEY: That's correct. At month one, for all of the treatment groups, since there's actually nothing to carry forward for month one--

DR. GELLER: Right.

MR. McSORLEY: --all missing months are considered as no relief. So there are no monthly responders being imputed for month one in either treatment group.

DR. GELLER: Right, but what I see in this table now is that at month three--you've shown us figures, and the FDA concurs, that the effect is on the total three months. But when you look at this table, you see that in the first trial, 67 alosetron patients had imputed data, and 69 in the second trial.

MR. McSORLEY: Well, no. Sixty-seven had--that's how many had missing months.

DR. GELLER: That's right, so you imputed either zero--so you imputed 10 one's and 57 zeroes, so that the result at three months depends very highly on all that imputation in that sense; that is, the effect you see that there's response at three months depends on the fact that there were as much missing data as there are.

MR. McSORLEY: Not exactly. I think there is actually more response being imputed on placebo in 3002 at month three than on alosetron. So, in actuality--

DR. GELLER: In month three--

MR. McSORLEY: No--yes, that's true.

DR. GELLER: There's more response imputed for alosetron.

MR. McSORLEY: In 3002, there is more response imputed for placebo than alosetron. In 3001, yes, there's a little bit more response imputed on alosetron than placebo. 3ut with respect to the treatment differences in terms of all patients in both studies, when you take the difference between how many'were imputed as a "yes" for monthly responder in each of the groups and take that difference, .t's less than 1 percent of the treatment difference at month three is attributable to the last observation carried- the imputation approach. And what's in this table--

DR. GELLER: But there's a percent imputed as a no," and I'm just saying whatever the results are, the esults that look so good at three months, in particular, .ave a lot to do with the fact that 59 placebo patients and 7 alosetron patients on the first trial have values imputed ather than real data.

MR. McSORLEY: But the amount that are imputed as yes" is very small. The amount imputed as "no" is correct, nd since there are slightly more missing data on alosetron han placebo, imputing a "no" would actually tend to be onservative in terms of underestimating the treatment ifference as opposed to over-estimating it.

DR. PRIZONT: Can I intercede one minute, please? On that, I just wanted to respond, you know. I'm going to refer to A 3001, and as you remember, I showed a table with the specific combination of months. I mean, when we say three months, we don't know which one--or when we say two months, we don't know which one of the two months are. And in that case--and that was the statistician that did the analysis--patients with missing data were considered failures who were not carried forward in that particular analysis.

DR. GELLER: I'm not--

DR. PRIZONT: Is it more or less approximate, more or less the same percentage of difference or the same delta that, you know, they got with the LOCF? So just referring to A 3001. I think that 3002 overall is a little bit weaker study.

DR. GALLO-TORRES: Steve? I'm sorry, I don't mean to interrupt you, but I also would like to have Dr. Hoberman commenting on this. It's very important because he is very familiar with the data. I do not mean to interrupt you.

CHAIRMAN HANAUER: I'd just like to know is the data concerning or are you satisfied that we're not losing efficacy here?

DR. HOBERMAN: When I started reviewing this NDA, I was concerned that response was being carried forward. I

am a believer in LOCF analyses in many situations. This one seemed a little peculiar to me, so I did several analyses and my bottom line is that the imputation has zero to 1 percent effect on any decision made on whether alosetron is effective.

Any kind of imputation might slightly inflate, you know, the number of responders at three months. But whether or not you do my analyses which do not carry forward or the sponsor's, the percentage of patients at three months is virtually the same. The treatment effect is virtually the same.

Just one more remark. When Dr. Prizont presented those eight bars with the different patterns of response, the eight different possible patterns of response over three months, that was generated by me. And what I did was say if a person was not in the trial, they were a non-responder. When that data was analyzed, the results were consistent between the two trials, with no doubt about statistical significance.

DR. GELLER: Thank you. I have one more question. Given the primary endpoint of the trial and that you asked the question every week, you must have done an analysis of the number of weeks of response, with some assumptions about the missings. I'm interested not only in the comparison, but in the average number of weeks of response.

MR. McSORLEY: We did do an analysis using a generalized estimating equation analysis as a supplementary post hoc analysis to explore what was happening week by week in terms of a longitudinal analysis approach to that, and essentially it confirms what you see in the week-by-week figures for adequate relief at each week that early on-- well, in a model that had just simple main effects for treatment and week, the treatment effect was significant, and during the first four weeks when you did not see a significant treatment effect, there was an effect due to week.

But after that, for the second eight part of the weeks in which the curve stayed fairly consistent over the duration, there was no interaction effect between treatment and week. So it was consistent in terms of the weekly analysis looking at weeks in a longitudinal way.

DR. GELLER: Well, I just wondered if you did total number of weeks of relief, 12 weeks of data so you get an answer, rather than one to three you get an answer, or zero to 3, you get zero through 12.

MR. McSORLEY: We did not do an analysis of the number of weeks. I don't recall. Amy or Steve or Allen, do we have a backup slide for any--looking at the number of weeks or the proportion of weeks?

DR. MANGEL: I have the values for the proportion

of weeks. In the 3001 study, the proportion of weeks with adequate relief for placebo was 38 percent. For alosetron, it was 51 percent. For the 3002, the proportion of weeks with adequate relief for placebo was 42 percent. The proportion of weeks with adequate relief for alosetron treatment was 53 percent. Each of the p values were less than .001.

DR. GELLER: And that's with last--is that last observation carried forward on the missing?

DR. MANGEL: Yes, that was observed. That was the observed data.

DR. GELLER: Well, what do you do for people who aren't followed the full time? So are you making the non-response zero in that?

MR. McSORLEY: No, no. That's just looking at the proportion of weeks with relief.

DR. GELLER: So that's an on-study analysis?

MR. McSORLEY: That's correct. That would be the proportion of weeks with relief out of those weeks for which they answered the adequate relief question.

DR. LAINE: Can I ask a very quick question? Kind of like hepatitis, if you took this drug for a month or some period of time and you didn't respond, did you have any chance of responding in the second or third month; i.e., can se use non-response after a certain period of time as an

indicator you shouldn't go the full three months?

DR. MANGEL: Probably, Dr. Laine, the way I would answer that question best is that IBS is a multidimensional disorder. Alosetron produces improvement on multiple IBS-relevant dimensions. You know, a subset of that question might be what proportion of patients are receiving benefit on some endpoint, versus the proportion of patients on adequate relief.

As there is no obvious responder definition for changes in stool frequency or changes in stool consistency, we actually thought long and hard about that to make a responder--to answer that, to get at the notion, you know, what are patients receiving benefit on. I mean, you know, so all I can really comment on is for adequate relief the transitional probabilities, either staying with relief or no relief, staying with no relief, are about the same.

DR. LAINE: Do you have those data?

DR. MANGEL: It's about 79, 80 percent, also, right, Dave?

MR. McSORLEY: Yes.

CHAIRMAN HANAUER: Dr. Prizont showed his data that it was an all-or-none phenomenon, that they either responded for three months or they didn't respond because they didn't respond at one month. There were no--

DR. GELLER: That's what I was picking on earlier.

That depends on missing data. That conclusion depends on missing data.

DR. PRIZONT: But I mean we amplified that in the--we amplified that in the analysis by the statistician reviewer where the missing data was considered--

DR. LAINE: But these people all had active IBS when they were enrolled. It's kind of like an arthritis flare, if you want to study it; they all, in a sense, had disease for the two weeks. So, i.e., when they started they allegedly had the disease. IBS goes up and down, but if you took at the one-month non-responders and see what happened to them in the next two months, I guess that's what I'm really asking.

DR. MANGEL: I don't believe we have that analysis.

MR. McSORLEY: I wondered, Dr. Hanauer, if I could--right before the break for lunch, we were discussing multiplicity with Dr. Geller, and I wonder if we could come back to that to add--if I could have Dr. Gary Cook, who is a statistical--

CHAIRMAN HANAUER: Yes, only if you can do it in human terms that won't take more than a minute or two.

MR. McSORLEY: I believe that that would--I think that was an important issue and I think that we didn't have complete closure on that and I want to make sure that Dr.

Geller is comfortable with that.

CHAIRMAN HANAUER: Okay, if you can close it quickly in terms that we will generally understand.

MR. McSORLEY: Thank you, Dr. Hanauer.

MR. COOK: I'm Gary Cook, with the University of North Carolina. On the missing data issue, you asked a question about number of weeks. The GEE analysis, which has week-by-week analyses, when it fit in a main effect model with just time and treatment in the model, that gives you an average over all of the weeks and is effectively testing the number of weeks. So the significance of that analysis addresses your question about that.

The issue that you had about responders for all three months--what David McSorley was trying to indicate is that the number of patients who actually were imputed as responders for all three months is a small number. The number who were imputed as non-responders is indeed a larger number, mainly because a lot of them may not have responded in the first month.

In order to have this particular statistical endpoint have more interpretable clinical relevance, assessments were done of each of the three months, and also week by week, to show that the data that applied globally for all three months also was exhibiting the difference on a month-by-month basis, which it clearly did two out of three

times with p values below 0.05, and on a week-by-week basis which it did basically in all of the latter weeks, the weeks after week four for the most part. And so those were intended to be descriptive p values to help understand where the difference in the overall assessment of the primary endpoint was coming.

Now, the study did have a pre-planned assessment of secondary endpoints, and those are indicated here and they were, in order, stool consistency, urgency, stool frequency, incomplete evacuation, and bloating. And for them, the primary assessment was month one and they were tested sequentially. And if one proceeds basically to display number N-46, there was statistical significance in both of the studies for the first three of those.

Now, once you got to the fourth one--I'm sorry--tool consistency--this is the primary and then this is the three secondaries in month one, in their sequential order of testing; consistency, first; urgency, second; frequency, third. Now, the fourth one in the hierarchy corresponded to incomplete evacuation. That was not statistically significant, so no inferential statement has been made about that.

Now, it is true that on some of these other measures, key values below 0.05 were shown for some of the other endpoints, again to show where p values below 0.05

were descriptively obtained. But the only ones that are inferential are month one for these three secondary endpoints.

DR. GELLER: Okay. Now, just to make sure I understand this, back to the slide I asked about earlier, which is the secondary endpoint, it's slide A-58. It's about secondary endpoints in months two and three, and month three, right.

MR. COOK: All of those are descriptive. They have no inferential role. They are there--

DR. GELLER: I was told earlier that these were not significant in month one.

MR. COOK: And because they were not significant in month one, they were outside the inferential process because only month one was the priority. The five endpoints were assessed in month one.

DR. GELLER: Okay, so the slide you just showed before this overall--

MR. COOK: Those are the ones that were inferentially confirmed.

DR. GELLER: Overall?

MR. COOK: Overall, for month one because the second--go back to the previous slide, number N-44.

DR. GELLER: Yes, this one.

MR. COOK: N-44. What it says here was assess

change from baseline at month one first. If p is less than 0.05, then they would have assessed weeks one to four, and if all of them had been individually significant, they would have proceeded to the next endpoint.

DR. GELLER: And slide 46 is about what?

MR. COOK: Slide 46--

DR. GELLER: That's about one--

MR. COOK: --is month one for these three secondaries, all three months for the primaries.

DR. GELLER: I see.

MR. COOK: Go back to 44.

DR. GELLER: Okay.

MR. COOK: That was the plan. Forty-four was lobal test of total number of months of adequate relief as he primary, and the assessment was looked at month by month o identify the fact that months contributed individually to he global overall significance. The secondaries were then ssessed in this order, with month one being the primary.

CHAIRMAN HANAUER: Okay, we've got it. Thank you.

MR. COOK: And on the next slide--

[Laughter.]

DR. GELLER: Yes, we've got it.

CHAIRMAN HANAUER: Please. Thank you.

MR. COOK: I've tried to make it simple.

[Laughter.]

CHAIRMAN HANAUER: Was this made simple in advance? These were pre-defined endpoints--

MR. COOK: Yes.

CHAIRMAN HANAUER: --agreed upon by the agency before the study was started? Yes?

DR. HOUN: Yes.

CHAIRMAN HANAUER: Thank you.

Okay, we're going to go on to questions. We're going to forge ahead here. Does the Committee have any comments on the design, conduct, or further discussions regarding the analysis of the principal efficacy trials that we've just heard, 3001 and 3002? So what we're looking for, just as I said, comments on this.

Dr. Geller, you've got the mike. Any comments on the design, conduct, or analysis?

DR. GELLER: I'd just make one point about the endpoint, about the primary endpoint. It's not time-invariant, so if you had a patient who had a response in two weeks in month one and two weeks in month two and then dropped out, that patient would not have the same assessment as somebody who had four weeks of response in the first month and then no response and dropped out. So the endpoint has a peculiar property.

CHAIRMAN HANAUER: Other comments?

Dr. Ferry, in particular I want your comments

because a significant--you can maybe enlighten us on--we've heard the general incidence of irritable bowel, but certainly this affects children and we'd like your impact on the pediatric perspective.

DR. FERRY: The incidence of irritable bowel syndrome really probably varies by age. It's most clearly defined in adolescents, children 13 years and up, sometimes a little younger who have matured or are in adolescence. And it's pretty much the same disease, I think, and we would characterize it the same. It's not a very common problem in pediatrics, but it's definitely there, and its implications and its severity are, I think, very much the same as in adults.

In younger children, it's, I think, much harder to define. We see lots of children with abdominal pain; it's the number one diagnosis that comes into our clinic, actually, but it's almost always with a little bit of constipation, but very hard to define, very hard to treat. Some people would classify it as irritable bowel syndrome. Others would say it's not, that it's really something, you know, quite different.

The true incidence of pain and diarrhea in the younger children, I think, is pretty infrequent. I do believe there will be a real interest in using this drug in children, and perhaps at all ages, actually. We are

struggling with many patients we have no treatment for at all, not even a hint of treatment for children, you know, with pain. So I do believe people will use this in a variety of settings in children, and probably younger than adolescence, **probably** a younger age.

CHAIRMAN HANAUER: Do **we have data in--does the sponsor have any** data in children?

George Dukes?

DR. DUKES: Yes, George Dukes, Glaxo Wellcome. Actually, Steve, we have submitted a proposal to the agency to discuss with them a development program in pediatrics, where we intend to study age groups 6 to 11, as well as adolescents. And we will be negotiating the exact protocol with the agency to look at that, and hopefully starting the first of the year.

CHAIRMAN HANAUER: Is there any reason to expect differential metabolism in children than in adults?

DR. DUKES: I'll try to answer that, but Kevin may want to get up here. Our understanding is no. The enzyme systems that are used to metabolize alosetron are mature by age 6 and, in fact, are mature at a much younger age than that. So we do not believe there will be a difference.

CHAIRMAN HANAUER: Dr. Ferry, as long as you're here to provide advice, do you have any specific issues regarding the design and conduct as applied to adults as you

would apply it to children as far as endpoints are concerned or duration of the trial?

DR. FERRY: I don't have any concerns about duration of the trial. I think endpoints are going to have to be looked at, you know, very closely. You're going to have to rely on parents' evaluation of what's happening with children, and I think the endpoints may have to be a little bit more specific in terms of real changes rather than just kind of well-being. But I mean I think it's an important-- we need to do studies in children, so I'm very much in favor of it. I think the endpoints may have to be looked at a little differently.

CHAIRMAN HANAUER: Dr. Wilson, comments regarding conduct, design, and analysis?

DR. WILSON: No, not really.

CHAIRMAN HANAUER: Dr. Laine?

DR. LAINE: Well, just very briefly, in general, I think we see that--I'm generally okay with it. It does work. I certainly think this is going to be widely used. The concern, obviously, I have is what I expressed earlier. I mean, I think this is a--it's a significant and a real effect. It's a relatively modest effect in terms of using their primary endpoints, only about a lo-percent increase if we look at their primary endpoint at one month as compared to placebo.

CHAIRMAN HANAUER: That's efficacy. Design, control, and analysis?

DR. LAINE: That's analysis, too.

CHAIRMANHANAUER: How is that?

DR. LAINE: Okay, and--go ahead.

CHAIRMAN HANAUER: Any other?

DR. LAINE: No. I mean--

CHAIRMAN HANAUER: Are you happy with the endpoint, relief of primary symptoms?

DR. LAINE: I think, you know, obviously I'd actually want to have an instrument person confirm that they properly evaluated the instrument. It's a hard thing to do, but I think at least to a novice their evaluation in Phase :I and Phase III seemed a reasonable thing in terms of validating that it met other criteria of IBS as well.

CHAIRMAN HANAUER: Dr. Berardi?

DR. BERARDI: No additional comments.

CHAIRMAN HANAUER: Speak up, Dr. Wald.

DR. WALD: Well, I think that the method in terms of obtaining data, I think, has been quite innovative. I think it may even set the standard for future studies in a disorder which has no disease markers, which depends upon symptoms accurately obtained. And I think prospective data are the way to do it, so I would have to say that I'm very impressed with the way that the study was conducted.

I think the issue of three months is sufficient for efficacy. It does not answer the important questions that have been raised about using a drug which has potential side effects in a disorder which causes no mortality. so I think you have to set the bar fairly high when you're talking about a disease--or a disorder--I'm sorry--which itself has no mortality, which has a normal life expectancy.

So I think that we have to respect the information that has been presented to us in terms of some of the side effects that we've seen, and I think constipation will be a major issue to confront. This is a very potent anti-diarrheal agent and it's not going to be suitable for everyone. I would depend upon the statisticians to tell us whether the analysis has been done correctly, but I think given the nature of the population we've studied, I seem pretty satisfied with it. The effect is modest, but I think it has been definitely established here.

CHAIRMAN HANAUER: Again, we'll come back to efficacy, but I really want to push this panel, if anyone has comments, because we are setting a bar of efficacy based on relief of primary symptoms. And, again, as an IBS expert, is that going to be the bar that other compounds should reach?

DR. WALD: I think you asked a very important question before, as I told you at lunch, which is in a

disorder, again, with no mortality, the issue of quality of life is everything. And it would be especially important for us to confirm some of the primary efficacy endpoints with quality of life data. However you establish that with NSF-36 or a disease- or disorder-specific issue, this is a quality of life disorder, as we've heard from our patient advocates here, and for physicians. So I would look very--I would like to see that data before making a final decision.

CHAIRMAN HANAUER: Well, that's important because you're going to make a recommendation of approvability based on the data you have now, versus waiting on quality of life, and it can go either way. YOU can accept the data as given with or without quality of life.

Would you accept the data as--assuming the data is positive, would you accept that without quality of life for approval of the drug?

DR. WALD: Well, to borrow your analysis, if you had a situation where you could prove efficacy of data but quality of life was unchanged, I think we would all on this panel have to think very carefully about introducing a drug like this. If, on the other hand--and I think, to me, I would be very surprised if otherwise--if the quality of life data do confirm the primary efficacy data and the secondary, I think that would--I would anticipate that. I can't imagine why it wouldn't, unless there are so many people who

are so unhappy with side effects that that would negate the positive consequences. And that might be an issue to confront when you talk about a 20-percent or so incidence of constipation as a side effect, but I would be optimistic.

DR. LAINE: Just in terms of your question, I definitely think the endpoint should be symptoms, and I have no problem with that at all. I mean, the only question I raise is making sure that the instrument used to document the symptoms is acceptable. But I think that's completely okay. There are instances, by the way, where quality of life improves, but symptoms don't improve in some studies. So I think they are both important.

DR. WILSON: One question I have is have any other drugs been submitted to a quality of life measure previously as a measure of efficacy in any disorder? I mean, I just don't know.

DR. TALARICO: There is still some work done on the validation of the data that one collects on quality of life. For some conditions, it seems to be pretty acceptable. For others, it's more difficult.

DR. WILSON: No. I mean--

DR. TALARICO: But for a policy, we don't--

DR. WILSON: That's what I mean, before the FDA as a measure of efficacy and a measure of approval or reason for approval.

DR. HOUN: In the three divisions that I oversee, there hasn't been approved for quality of life.

DR. WILSON: So this would be the first.

DR. HOUN: This one doesn't have a quality of life--

DR. TALARICO: But it would not be exclusively on the quality of life.

DR. WILSON: I know, I know.

DR. TALARICO: Okay.

DR. WILSON: What I'm saying is that if we withheld for quality of life, that would be precedent-setting. Is that true?

DR. HOUN: I think for this drug, for IBS, yes, this would--this whole thing is precedent-setting.

DR. WILSON: No, but I mean for any drug.

DR. HOUN: Other drugs, like dealing with pain, there are pain-specific drugs like for arthritis that incorporate improvement in daily activities and are probably more leaning toward quality of life indicators.

DR. WILSON: But they're not doing global--global quality of life is a very different measure because that measures more than just--I mean because if you just say daily activities, with arthritis, it's like you're moving. You know, that's what you measure; you're moving. I mean, this is like--that's the same as measuring the number of

stools or whether you have adequate relief of pain.

DR. HOUN: I think in some of those assessments, they approach more global assessment of well-being improvement, not just of activities but overall relief of pain. But in this field, and in many.other fields in FDA, that has not been accepted.

CHAIRMAN HANAUER: Do those of you from the agency have any more specific questions regarding the Committee's assessment of the design, conduct, or analysis? Have we addressed your questions to this?

DR. TALARICO: I think here the Committee should know the primary efficacy endpoint and the secondary efficacy endpoint, put together somewhat in a global assessment.

CHAIRMAN HANAUER: Any other questions for us regarding conduct or analysis for this or subsequent trials?

DR. PRIZONT: I have a question. I mean, I included that in my review. I wonder if prospectively these trials were designed to assess adequate relief of abdominal pain or discomfort. The primary endpoint was that, and I wonder whether that alone encompasses all the symptomatology included in IBS based on the Rome Diagnostic Criteria.

I mean, we are talking about abdominal pain related to, associated with, or relieved by lower bowel functions. And I, for one--I'm not sure if I'm speaking on

behalf of the agency, but I, for one, I would like probably to include a more general endpoint, like adequate relief of IBS symptoms, and that's it. That encompasses probably all the symptoms.

CHAIRMAN HANAUER: So what's the question?

DR. PRIZONT: The question is what do you think about it.

CHAIRMAN HANAUER: Do I think--do we think--I and se think that--

DR. PRIZONT: You and everybody.

CHAIRMAN HANAUER: --the Committee think that the primary endpoint should be rephrased as adequate relief of symptoms or primary symptoms?

DR. PRIZONT: Right, IBS symptoms.

DR. LAINE: Pain and discomfort.

DR. PRIZONT: Right.

CHAIRMAN HANAUER: I'll throw that to Dr. Wald. How can they better ask this question, or is it adequate?

DR. WALD: I think that's a very difficult question to ask because the irritable bowel population is such a heterogeneous one in terms of its symptomatology. And what you're asking for with this particular drug is a very narrow indication; that is, I like your term the non-constipated IBS because we could argue what diarrhea means.

I think that you're really stating the same thing

as the primary and the secondary endpoints. We could be specific. I think I would prefer to be specific because I think we would need to emphasize, if we were to label this drug, that it's for a very select population with a very select group of symptoms. So I would try to be as specific as possible rather than to make a global statement because it seems to me that the irritable bowel syndrome is already too vague for many of us, and particularly when you get away from the super, super specialists in this area, it becomes even vaguer still. So I would try to be very specific and try to inform in terms of the labeling issue rather than make a global statement, although I understand what you're getting at.

CHAIRMAN HANAUER: Okay, moving on to the next question, was efficacy demonstrated in the overall population--well, was efficacy demonstrated in the overall population enrolled in the two clinical trials?

Dr. Geller?

DR. GELLER: I think so.

CHAIRMAN HANAUER: Dr. Ferry?

DR. FERRY: Yes, I believe so.

CHAIRMANHANAURR: Yes.

DR. WILSON: I think so.

DR. LAINE: Yes, and again just to make the point about just, I would say, hard stool or whatever other term

we use rather than non-constipated, rather than just the terms used here.

DR. BERARDI: Yes.

DR. WALD: Yes, for half of them.

CHAIRMAN HANAUER: Well, they are asking the overall population. You can divide it later. So who wasn't it demonstrated in, or which half was demonstrated?

DR. WALD: The half who got better.

[Laughter.]

CHAIRMAN HANAUER: Yes, so efficacy was demonstrated in those who improved. Specifically, they are talking about the overall population of irritable bowel. Was there one specific population that you can define in advance for labeling purposes that should be described, then?

DR. WALD: Yes. I would think it would be the non-constipated, what we would call diarrhea-predominant group. I'd have to agree with Dr. Prizont that there was no efficacy demonstrated for the alternating group and, by design, the alternating constipation diarrhea group. That was not statistically significant, and the constipated group was not studied. So, yes, for that specific population.

CHAIRMAN HANAUER: Well, there is an expansion of this in the subsequent component of our question, which is the sponsor is proposing indication for the treatment of

irritable bowel syndrome in female patients whose predominant bowel symptom is diarrhea, either alone or as part of alternating stool pattern.

Let's just ask, has efficacy been demonstrated in women with diarrhea predominance?

DR. WALD: Yes.

CHAIRMANHANAUER: Dr. Berardi?

DR. BERARDI: Yes.

DR. LAINE: Again, I want to make the point that that's again a post hoc analysis. I mean, to me, you'd look at the group that they entered.

CHAIRMAN HANAUER: Do you feel that--

DR. LAINE: Well, I'm trying to explain that you can't say that because with--I think the quick answer is yes, but you can't start breaking it down because that's not what they did. They did a study in people who had stools that were not hard and they showed efficacy. Then when they did a post hoc analysis, it seemed to be pretty much clear in the diarrhea and it was plus/minus in the alternators, but the alternators were a much smaller population as a post hoc analysis. So I have problems with breaking it down in terms of labeling. I mean, to me, you just say it was effective in people who didn't have hard stools, you know, and were women.

CHAIRMAN HANAUER: Well, let me ask again, has

efficacy been demonstrated in women with diarrhea-predominant IBS?

DR. LAINE: They didn't study that.

DR. WILSON: Yes. I think one of the points that we did harp on is irritable bowel patients do not have to have diarrhea, loose stools, everyday. If you have a score of 3.5, that means by definition you had to have some days that it was 4, okay?

DR. LAINE: But they excluded people with less than--excuse me--more than 2.5, whatever it was.

DR. WILSON: Right.

DR. LAINE: Less than 2.5; sorry. So they couldn't have people who had a mean really that was at all loose--at all hard, rather. I keep confusing.

DR. WILSON: Right, exactly, but what I'm saying is that so there were patients who did have some days that they had loose stools. So the bottom line is, yes, I think, in patients who were non-constipated.

CHAIRMAN BANAUER: Well, I didn't ask non-constipated. I asked has been demonstrated in diarrhea-predominant.

DR. LAINE: That wasn't your question.

CHAIRMANHANAUBR: Well, that is the question. We'll come to modification in a minute.

So your answer was yes?

DR. WILSON: Yes.

CHAIRMAN HANAUER: My answer is yes.

DR. FERRY: And my answer is yes, also.

DR. GELLER: Yes.

CHAIRMAN HANAUER: Okay. Now, I'm going to rephrase this. Has efficacy been demonstrated in women with IBS as part of an alternating stool pattern?

DR. WALD: I have to defer to Dr. Prizont. I think when you break the analysis, although post hoc and perhaps not the primary intention, there are insufficient numbers to make that determination. So I cannot say yes, so I will say no.

CHAIRMAN HANAUER: Thank you.

[Laughter.]

CHAIRMAN HANAUER: Dr. Berardi?

DR. BERARDI: No.

DR. LAINE: They didn't study it, so no.

DR. WILSON: I'd have to say no.

CHAIRMAN HANAUER: And I'd say no.

DR. FERRY: No.

DR. GELLER: No.

CHAIRMAN HANAUER: It sounds trivial, but I think my purpose in expanding that question is that the primary symptom was constipation and I certainly think that my own interpretation of this is that the therapeutic margin, as

modest as it is, definitive but modest, probably would be lost in that alternating group because of the risks of constipation, because the sponsor also concurred that those were the patients who were more likely to have constipation from the drug. So, that was purpose in dividing that out.

Question 3: The following events were seen in greater proportion of patients receiving alosetron: ischemic colitis, elevated liver enzymes, and constipation. We're going to have comments on each of those, so ischemic colitis.

Dr. Wald, any comments? What's your take on the ischemic colitis?

DR. WALD: I used to know what ischemic colitis is; I'm not sure I understand it now.

CHAIRMAN HANAUER: You used to know what IBS was until today.

[Laughter.]

DR. WALD: I never knew what IBS was.

I have to say that something happened with greater frequency in the patients who took the active drug than the placebo. It was something associated with an inflammatory response, perhaps of the colon, and I'm not sure I understand whether it's an infectious agent or what often passes in clinical medicine as what we call ischemia.

I certainly think some of the diagnoses are

improved, but I would like to be submitted to a panel of pathologists as unknowns in order to get an assessment of that. But I am somewhat concerned about the increased risk of that, without putting a label on it, and I'd perhaps not use the word "ischemic colitis," but non-specific or hemorrhagic colitis of some sort.

CHAIRMAN HANAUER: That's real helpful for a clinician.

DR. WALD: Well, it's vague, but--

CHAIRMAN HANAUER: They already have a non-specific condition, and there's a possibility of inducing another non-specific condition.

DR. WALD: Well, I thought I knew coming in that this was ischemic colitis. I think listening to the data, reading Dr. Brandt's comments, and so forth, I'm not sure we know what it is. But it is worthy of taking that data, the blocks, and so forth, and really looking at it, but in a blinded fashion. I would submit it to perhaps three or four pathologists with no axe to grind and tell them to tell us what it is without really implicating what happened.

CHAIRMAN HANAUER: Dr. Berardi, any comments on the non-specific colitiform disorder, colitic disorder?

DR. BERARDI: If Dr. Wald can't figure it out, I can't either. I too agree that there appears to me to be something happening. As to exactly what it is in terms of

ischemic colitis, I'm certainly not in the position, but I do think that this should be pursued further.

DR. LAINE: I agree it may be nothing, but it could be something, needs to be evaluated when the agency has to get the blocks and all the information and go over it more carefully to make a final decision.

DR. WILSON: I would agree as well. It's really unclear. Unfortunately, as a clinical gastroenterologist, it's a common kind of colitis or colitidy that one encounters where you never know what the real answer is, but it goes away.

CHAIRMAN HANAUER: I also agree that this is a potential problem. I'm not as optimistic as you are that an additional pathologic review is going to add clarity to the diagnosis, but I think that this ischemic-like colitis, with or without infectious component, has been seen more with this than was seen with placebo and it needs to be watched for.

Dr. Ferry?

DR. FERRY: You know, in pediatrics we don't have an issue where we really see ischemic-type colitis. I mean, we do see infectious colitis and we do see hemolytic uremic syndrome with very severe forms of colitis. And I came away with the impression that there is, you know, a strong possibility that this may be, at least in two of these

cases, something related to infection, and I think that really does need to be looked at more closely. So I have some concerns about it, but I came away with the idea that there's a good chance it's in infectious and maybe not ischemic.

DR. GELLER: I would like to see the slides read blindly, but also in addition to those slides, some others should be added in, so that there should be true blinded review.

CHAIRMAN HANAUER: Okay. What about the elevated Liver enzymes? Dr. Wald?

DR. WALD: Well, I guess I'm impressed by Dr. Senior's presentation. I think we have enough patients to show efficacy, but we certainly don't have enough experience to show hepatotoxicity. And, again, I think there's a high barrier to leap here on a disorder which is not itself associated with mortality. So it may be one case and it may be a fluke, but I think we have to respect it because of the temporal relationship with which the enzymes came up and went down, unless, of course, we get additional data that shows, in fact, the original information was perhaps incomplete, and that would be helpful. Apparently, there is such data or may be such data, but for now I have to be concerned.

CHAIRMAN HANAUER: Anyone have differing comments

than that?

DR. LAINE: My only additional comment is even if there was additional data, I don't say we should disregard hepatocellular injury, but I think that the issue of the 10 or 15 percent leading to fatal acute liver failure is really an overstatement and concerned me somewhat because this was somebody who had mild elevation transaminases and one slight elevation in bilirubin and was watched over 50 days. I think that's a far different case than what you were talking about, Dr. Senior, in the sense that if somebody has dramatic hepatocellular injury with very high transaminases and clinical jaundice, it is a much different situation.

In addition, that person would develop acute liver failure. This person was watched, and even if they were taken off the drug at day 50 and the liver tests came down afterwards, they had a lot of time to develop acute liver failure and didn't. So although I think we need to watch and I'd be concerned, I wouldn't want to be quite as alarmist in terms of suggesting, you know, that this scenario is suggestive of a high rate of acute liver failure and death.

DR. SENIOR: We can't predict it, of course, Loren, but as you say, I just think we ought to keep it in mind and not just ignore it.

DR. LAINE: I absolutely agree. I think we need

to keep it in mind, not ignore it. I just wouldn't be quite as alarmist with this particular case that was--

DR. SENIOR: Right. What Zimmerman was talking about was jaundice. We didn't have jaundice here. We had a 2.1 bilirubin. That's not jaundice.

DR. LAINE: I agree. That was my point.

DR. WILSON: I would agree with that, and also just pointing out that women do take a number of other drugs that have potential hepatotoxicity, NSAIDS, and so forth, and that's the only reason I'd take note of it.

DR. WALD: But if I can also--women are more susceptible to drug-induced hepatocellular injury, and since this is going to be exclusively in women, it must be respected.

DR. FERRY: I would agree actually with Dr. Wald. There may be more information that says these levels went back to normal before the drug was stopped. That would be very, very important, and I think we just have to watch this closely.

DR. GELLER: I think I have to defer on this one.

CHAIRMAN HANAUER: Constipation. Dr. Wald?

DR. WALD: Constipation is a very serious problem.

CHAIRMAN HANAUER: First of all, do you understand what it is yet?

[Laughter.]

CHAIRMAN HANAUER: We've confused you on everything else.

DR. WALD: Well, I think if anybody who has used ondansetron and granicetron [ph]--and talk to your patients--that's a major issue. This drug can produce constipation and it's a very potent anti-diarrhea1 agent. It's going to inhibit the use in some individuals. On the other hand, for those who have diarrhea predominance, it could be a very helpful drug. And I'm concerned it has to be mentioned, but I don't see it as a complication that should preclude it's being released.

CHAIRMAN HANAUER: Dr. Berardi?

DR. BERARDI: Yes. I too am concerned about it, and I also recognize that in the real world patients that have diarrhea-predominant that aren't getting efficacy at least immediately with this drug may, in fact--I can see them taking this with other anti-diarrhea1 medications, or even other medications that have a decreased motility effect. So, that could increase the potential for constipation, but I don't see that precluding using or approving this drug.

CHAIRMAN HANAUER: Dr. Laine?

DR. LAINE: I mean, I think we should make the point that the modest significant improvement was shown, despite this. So it was still shown even with the side