DR. TOLLEFSON: My name is Gary Tollefson, President of Neuroscience at Lilly. I want to just say a few words so that we don't make this more complicated than it perhaps is.

This was an independent investigator initiated trial. However, it was done under conventional double-blind methodology, as you would expect with any clinical trial.

Now, it happened at mid-course with the patient numbers that you have seen that the primary investigator opted to look at a group level for whether or not there was a treatment effect. The primary investigator, as you heard, saw a very robust treatment effect between the two groups, and for ethical reasons elected to terminate the study at that point. So, the patients that were represented as study 2 patients were patients randomized prior to an unscheduled interim analysis, and given the robustness of the treatment effect -- you might recall the slide showing overall treatment effects -- the investigator felt that it would not be prudent or ethical to continue prospectively in light of the drug/placebo difference that he saw.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: I'm now puzzled, as usual. You're saying that they did an interim analysis after 10 patients.

For ethical reasons, they decided to terminate the study. There were patients in that study then at that time currently assigned for placebo, but ethically it didn't bother them then to continue those patients on placebo double-blinded to the end of the study.

DR. TOLLEFSON: The patients that had been initially randomized to the trial were followed throughout the entirety of the trial. Thus they provided the basis for the interim analysis. Once that analysis was done, no additional prospective patients were enrolled to go up to the initially targeted patient sample of 30. So, in other words, no additional randomizations occurred after the interim. The interim was based on those patients previously randomized which was the study cohort you saw.

DR. HAMER: Right, but the ethical concerns were not sufficient to terminate patients on placebo in the trial rather than continue to give them placebo for the rest of the trial.

DR. TOLLEFSON: Yes. You remember the crossover design, and it was felt that the value of the additional scientific information that would be generated via the crossover was justifiable in order to continue patients through the rest of the trial. However, based on the phase I data, separation between drug and placebo, it didn't make a lot of sense to repeat that by enrolling

additional patients in the eyes of the investigator.

DR. TAMMINGA: But the decision was made on an efficacy basis, not on a side effect basis.

DR. TOLLEFSON: That's correct by the PI.

DR. TAMMINGA: Dr. Temple.

DR. TEMPLE: No one obviously approached us to see whether we thought it was ethical to continue to randomize people to this non-lifesaving treatment. I'm appalled at the idea that someone thought it was ethically imperative to stop the study because of this. That would imply you couldn't do more studies in this disease, which is really a garbled view of what's ethically necessary. But nonetheless, it seems to have happened.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: I just had a question about the interim analysis. It was done on 10 people. Are those the 10 people who at the time had completed both arms of the trial, or did it include data from all the 19 that were enrolled in their various periods and states?

DR. JUDGE: It included data from 10 patients.

DR. KATZ: Who had completed?

DR. JUDGE: Yes.

DR. COOK: I still haven't had my question answered in terms of how this blind could be broken in terms of the security of the blinding codes, et cetera.

This seems to have been relatively arbitrary. It obviously wasn't being kept separate from the investigator for the investigator to be able to do this analysis. I just need assurances that we know the blinding was secure.

DR. JUDGE: Investigators and all the raters in this study were blind to the individual patient assignment to drug. It is not uncommon to do interim analyses, as you know., for studies to delineate a group effect.

DR. COOK: But if they're blind, they can't do the analysis.

DR. TAMMINGA: Are you asking the question, Dr. Cook, who was allowed to be unblinded?

DR. COOK: Yes.

DR. TAMMINGA: Who was allowed to be unblinded in this study? Do we know that? Was that prospectively determined?

DR. JUDGE: I don't know specifically the names of those people, but the people who did the analysis were not involved in the conduct of the study in terms of rating the patients or ascribing treatment and seeing them from cycle to cycle and providing them with treatment, monitoring the adverse events, and rating their scales. So, those raters, which are specifically those who saw the patients, were not the ones who completed the statistical analysis. The statistical analysis was done by

statisticians who were not part of the rating cohort of that study, and in fact patients themselves who rated themselves on the primary outcome measure were also kept blind to their individual patient assignment as well.

DR. TAMMINGA: Are you worried, Dr. Cook, that people might have taken other peaks at the data?

DR. COOK: It just seems non-standard. It is true-that the patients are rating themselves, but it is certainly possible if anyone-working with them or involved in the study knows who is on which, then you violate the basic principles of blinding. That's my real concern.

DR. JUDGE: And that was obviously a concern for Lilly. It's a necessary requirement that a study is blinded and kept blinded to the raters of that study, and in comprehensive audit, absolutely comprehensive, a very meticulous audit, assurances were made and received with respect to the blinding of this study.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: You probably believe that you've already answered this. Maybe you have. But we've heard that the PI took a look at the data. Now, did the PI have anything to do with evaluating patients? Was that person involved in the conduct of the trial?

DR. JUDGE: No. The principal rater of that study was Dr. Su. In fact,. the authors of that study were

Su and Schmidt, and Dr. Schmidt was the person whose name is on the abstract. Dr. Su actually was more involved with the patients from a day-to-day basis, and he was at that time not privy to the individual patient assignment, as I've already alluded to.

DR. TAMMINGA: Dr. Fyer.

DR. FYER: I guess what makes me a little uncomfortable about this is the smallness of the operation. What we're talking about is a 19-patient trial with two physicians involved in a relatively small sort of organization.

I think I would feel a lot more comfortable if the sponsor had just presented the data saying, look, this is what happened. We had two doctors. One was the PI. They decided to take a look at the data. We don't really know to what extent these individuals communicated or the ethos or sort of cultural environment in a small clinic, which all of us at this table have worked in this kind of environment, might have contaminated this data. But the fact is that the effect at 10 patients was very robust, and we looked into it. We're inclined to think that this didn't occur. That kind of straightforward thing I think would be a lot more reassuring than what's sort of going on here.

The other thing that I would just raise as a

point is if there was a robust treatment effect at 10 patients, did the sponsor consider just presenting that straightforward data about which there could really be no questions at all? Even though it's a smaller n, in fact we're dealing with a very small n overall.

DR. JUDGE: Firstly, I do apologize if you felt that it wasn't straightforward. I was trying to give straightforward answers to these questions in that this study was conducted by one center. And, yes, it's relatively small compared to the other study. Patients acted as their own control, so providing enhanced sensitivity. So, in crossover studies in general one would expect smaller patient numbers.

The individuals involved in this study are very well established in terms of their research field.

But in terms of our assurances, we also wanted to assure ourselves before coming to you guys that, indeed, the data was collected in a manner that is conducive to GCP standards and to assure ourselves of the highest quality for the data. So, regardless of anything else, we did assure ourselves with very meticulous comprehensive audit that went on at both sites, including the other sites in the other studies as well. All three studies involved comprehensive audit from Lilly personnel, which was also ascribed by also independently conducted audit as well.

So, regardless of that, we actually did a lot to assure ourselves of the study in terms of the quality and the integrity of the data.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: But good clinical practices don't usually include an unplanned interim analysis, do they, by the investigator?

DR. JUDGE: Good clinical practice assures the safety and benefit for those patients done in a double-blind way per protocol. And, yes, there was an unplanned analysis in this-study, as you heard, and that was unfortunate, but we've tried to explain to you the reasons why.

DR. TAMMINGA: Dr. Parry.

DR. PARRY: First a comment. It would just be helpful for purposes of references to have copies of the published papers.

But I was interested in whether there was a difference in primary outcome measure as a function of site. As I recall, Meir Steiner's Canadian study, there weren't differences as a function of site, but were there in the Stone-Pearlstein study?

DR. JUDGE: In the Stone-Pearlstein study, the publication did cite the CGI as an outcome measure, and it involved the CGI 1 or 2 as the primary outcome measure.

For Dr. Su-Schmidt, for the second study, X022, the publication -- it was difficult to ascertain from the publication, if you just viewed the publication in the cold light of day, it talks about the DRF and the VAS Mood-4 as relevant outcome measures. We will have copies of that. We could provide them to you perhaps during lunch, and the FDA have been provided with copies of the publications.

DR. PARRY: But I mean, not the measures but the change scores. Were there differences as a function of where the study was conducted in the primary outcome measures, whichever primary outcome measure was used? Whether it was western Canada or eastern Canada or New Jersey or New York.

DR. TAMMINGA: Is your question about the number 1 Steiner study? Was there a site effect?

DR. PARRY: As I remember, there wasn't.

DR. JUDGE: If we're talking about the individual site effect for seven centers in Canada, we've got some information on that and my statistician will take you through that. Dr. Brown.

DR. BROWN: For the primary efficacy variable, the VAS Mood-3, there was, in fact, a site by treatment interaction. This graph here shows the results by site for the VAS Mood-3. Again, green is placebo, and orange is 20 milligrams. Yellow is the 60 milligrams. We can see for

sites 3 through 7, the dose response is quite similar. Remember that the placebo going above the 0 mark means that the placebo group, in fact, got worse. So, the dose response is quite similar.

And it appears that the interaction was being driven perhaps by sites 1 and 2 where you can see in site 1 the 20 milligram dose group responded better, in fact, than the 60, which is not consistent across the other sites. In investigator site number 2, the 20 milligram group did not respond as well, in fact, as the placebo group.

DR. HAMER: Were there particularly small numbers of subjects at sites 1 and 2?

DR. BROWN: Here are the site-by-site patients entered and randomized. So, sites 1 and 2 are a little smaller, but about the same size as sites 6 and 7. Sites 3, 4, and 5 were the biggest sites, but the spread was pretty good among them.

DR. TAMMINGA: Dr. Dominguez.

DR. DOMINGUEZ: Do you have a similar breakdown as far as discontinuations between sites?

DR. BROWN: No. I'm sorry we don't have that. Well, there are completers there, but I don't have discontinuations for a particular reason by site.

DR. DOMINGUEZ: For specific reasons per site.

DR. BROWN: No.. Sorry.

DR. THYS-JACOBS: (Inaudible) or entered treatment. You have 400 --

DR. BROWN: Pardon me. What was the question?

DR. THYS-JACOBS: 405 patients entered. I thought the definition of entering was the treatment phase. So, this is screening.

DR. BROWN: That's screening, and then the numbers there, the 108, 104, and 108, those sum to the 320 randomized.

DR. THYS-JACOBS: What was the difference when patients actually entered treatment phase in terms of numbers? Do you have that data?

DR. JUDGE: Patients who entered the placebo, fluoxetine at randomization numbered 108, just over 300, 320. So, that's the difference between 405 as the patients went to screening.

DR. TAMMINGA: Do you have additional questions on this issue? Any additional questions for Dr. Judge? Dr. Chen.

DR. CHEN: I have one more question about the study number 2. So, could you tell me about the resource? It seems to me today you are real clear about the randomization scheme and the interim analysis, but it seems to me when I reviewed the study, the application, the document said it depends on the investigator's decision.

It was not very clear in the submission.

But two weeks ago, we asked the same question about the early termination of study 2. At that moment, we didn't get it answered. But it seemed to me our question what's the resource -- within two weeks everything becomes clear to you.

DR. JUDGE: No, indeed. You're referring to the telephone conference that we had with the FDA, that Lilly had, to understand our presentation, whether you felt that our presentation was suitable. We asked you to comment on our slides. You said to us that it would be important for us to provide additional information on various questions, and one of them was the use of oral contraceptives. One of them was with respect to this question, and one of them was with respect to study 19 in terms of the primary outcome measure.

We didn't really go through, at that time, all of the answers, but we did undertake to provide to you in a few days some of how we would elaborate on it today, which we did just a few days after that telephone conference. So, today you find we understood and then we provided all these answers to you today in terms of your request to us for all of those questions at that time.

DR. CHEN: So, are all of those, what you mentioned today, documented.

DR. JUDGE: Yes, indeed, they are.

DR. TAMMINGA: Dr. Laughren.

DR. LAUGHREN: One of the concerns about SSRIs as a group is an effect on sexual dysfunction. That wasn't something that was looked at specifically in these trials, but I did notice, as you were going through the various rating instruments, that the PMTS did have one item that looked at sexual drive and interest I believe. Do you have any data on that specific item?

DR. JUDGE: If we could bring up those. Dr. Steiner would like to comment before we bring up those slides as well.

DR. STEINER: We actually started to look at the data just a few weeks ago not because of this, because we were interested in looking at it. If you look at our baseline data for that particular question on the PMTS, you see that women rate sexual dysfunction premenstrually as part of the symptoms of PMDD. They're not interested in sex. It's not a very specific question. It just asks are you interested more or less or not at all. So, you see that their baseline, their normal, is during the follicular phase and then they score high during the late luteal phase because they're not interested in sex.

What we have done is we have then looked across the six cycles of treatment; and there was no change in

this course during the follicular phase. This was continuous treatment with fluoxetine 20 and 60. It was no worse than during the follicular phase in terms of what they score on sexual functioning, and there is an improvement, an overall improvement, in that question during the late luteal phase. So, overall we have not seen that in this particular population Prozac caused sexual dysfunction.

I have to say that we're now looking at how many actually we lost or how many were dropped out of the study because of-sexual dysfunction, and I believe that there is a total of 5 subjects.

DR. TAMMINGA: Dr. Steiner, could you be more specific about when the improvement occurred in the luteal phase, what percentage of that of the follicular phase -- how high did it --

DR. STEINER: It's not back to the same normal baseline, but it's halfway there.

DR. TAMMINGA: Dr. Parry.

DR. PARRY: I want to address the issue of suicide. Many of these'patients may actually present with suicidal ideation. So, it is a potentially lethal illness. There has been some, though maybe erroneously, association with fluoxetine and suicide. I was wondering were patients with suicidal ideation excluded from studies, and if not,

was that targeted? What was the effect of treatment?

DR. JUDGE: In general, patients with significant coexisting other illnesses, generally medical, were excluded and, as you heard, also patients with other Axis I diagnoses were excluded.

Now, specifically in terms of patients presenting symptoms, I'm not aware from the data that we have in these studies, that anyone presented with a suicide attempt as a presenting symptom. I can tell you that from these studies, all of the studies, there was no one who attempted suicide, and I think it's pertinent at this point to perhaps ask Dr. Tollefson to comment in the overall Prozac and the suicide question because, obviously, it's very important.

DR. PARRY: But it's also suicidal ideation --

DR. JUDGE: Well, remember, the scales that were used -- in this study, for the big study, Dr. Steiner's study, for the Su study, there was a Beck's Depression Inventory scale that looked at, in the follicular phases of that study -- the Beck's is the Beck's, and we saw nothing significant in the follicular phase indicating that in the follicular phase the patients had very, very low levels of symptomatology. You're looking at a score of around 4 on the Beck's, which is really, really very low.

In terms of Dr. Steiner's study, study number 1, there was no instrument that captured the suicidal ideation per se, as one would expect, for example, in the HAMD.

Dr. Tollefson, if you could comment on the --

DR. TOLLEFSON: Well, I think that when we look at spontaneous events in these clinical trials, a suicide attempt or a completed suicide would register as a spontaneous event. None of those were observed in the clinical trial, to answer your question. I think that is consistent with our overall meta-analysis across not only depression but OCD and bulimia where see certainly a higher emergent rate in patients randomized to placebo than we do on active therapy. In fact, active therapy in other indications at least is associated with a reduction in suicidal ideation, as measured by HAMD item 3. Those were gender indicated.

We did not have specific suicide indices built into these prospective studies, so one would have to just really rely on the adverse event data, of which there was no evidence of a suicide attempt. There was one drug overdose with cocaine. That is the only event that would map to "overdose" in the entire cohort.

DR. PARRY: I think it argues for using the Hamilton or some'other scale. I think it argues for using

the Hamilton or some item that assesses that in future studies.

DR. TAMMINGA: Dr. Judge, would you -- Dr. Steiner, do you want to say something?

(Laughter.)

DR. STEINER: They were screened for major depression, and if they had major depression, including suicidality or not, they were excluded. So, they were not included. But that is not to say that we have not screened them for that.

DR. TAMMINGA: Thank you.

Dr. Judge, the committee would note that the dosing throughout these three studies is continuous. Certainly there is some question about whether dosing needs to be continuous or whether it can be intermittent. I would wonder whether you would like to comment on that, and also if you could give us some indication of whether Lilly is continuing to pursue, in Lilly-sponsored studies, additional questions in this area, if would be helpful to the committee.

DR. JUDGE: Thank you.

If you could bring up my slide with respect to intermittent dosing. I've tried to attempt to note the considerations with respect to intermittent dosing on one slide.

Intermittent dosing. Certainly there have been anecdotal reports that would indicate intermittent dosing may be effective. I think in order to explore this fully, there are various considerations that one has to think about.

First of all, in respect to safety, when we talk about intermittent dosing, as I would understand you, something like 10 to 14 days perhaps of drug before the onset of menses. Firstly, does the intermittent administration of fluoxetine, or indeed any other agent, subject that patient to repeated typical adverse events month after month after month. As you appreciate with fluoxetine, there is a diminution in the adverse event profile with time. If you administer intermittently month after month, does that subject the patient to a continuous high level of adverse event reporting?

Furthermore, we know that fluoxetine with its longer half-life -- patients don't really report discontinuation symptoms, but perhaps patients on the maybe more shorter half-life agents may, in fact, report discontinuation symptoms. So, that's important to establish that.

With respect to efficacy, also there's a question of compliance. Will patients comply to treatment that they perhaps have to -- will they find it easy to take

treatment for a few days in the month rather than every day?

Importantly, this question of kindling. Is the possibility of kindling phenomenon -- is that going to take place in these patients? I think that's also important.

With respect to fluoxetine, there is one pilot trial with intermittent dosing with fluoxetine. Again, Dr. Steiner did this trial. This is an open label, single-blind trial in which patients were administered 14 days of fluoxetine treatment prior to menses, and this was compared to continuous dosing 20 milligrams throughout the cycle. There was some evidence of a similar response for both groups of patients.

However, it's worth noting that that was not randomized appropriately. In terms of the patients who had a past history of depression, they were given the continuous trial of 20 milligrams of fluoxetine, and patients who did not have a past history of affective disorder were administered intermittent fluoxetine. So, that is an open trial, but nevertheless to your other question, yes, Lilly is pursuing other intermittent studies.

In the literature, all of the SSRIs, it's fair to say, have the largest body of data for continuous dosing, roughly at around the same dose that is also

applicable to the depression population.

DR. TAMMINGA: Could you be specific about what Lilly is doing to address these considerations?

DR.'JUDGE: There are studies underway with intermittent dosing for fluoxetine.

DR. TAMMINGA: Lilly-sponsored studies.

DR. JUDGE: Indeed.

DR. TAMMINGA: Dr. Temple.

DR. TEMPLE: It's not easy to have a discontinuous study of Prozac because 14 days after you stop, with a 14-day half-life, you still have half the same amount of long-acting metabolite on board, which raises the larger question which I know will come up later, but you need to address it too.

Is this a sensible approach to an intermittent disease? You basically are on Prozac. You didn't find any abnormalities with sexual function. It's not quite clear to me how hard you looked. But there are consequences to being on an SSRI all the time. So, the committee is going to address that later, but you may want to comment on it in advance.

DR. JUDGE: With respect to fluoxetine, continuous dosing of fluoxetine, as one attributes to PMDD, as well as other disorders, we know that fluoxetine at a dose of 20 milligrams, which seems to be the optimal dose

in this population, is very safe and very well tolerated. There is very long-term experience and a large body of evidence which relates to fluoxetine with respect to that.

I think the question is more around intermittent dosing. Yes, indeed, fluoxetine does have a longer half-life, but nevertheless, if patients are given intermittent dosing from day 1, do they have enough time then-to reach that steady state in order to have high levels when patients are off dose?

Furthermore, these other safety questions would also be still relevant, and that is ongoing in terms of clinical trials. And there are also pertinent questions to other treatments that are being studied for intermittent dosing. So, the questions are more around intermittent dosing I think than relate to continuous dosing. I think we're fairly comfortable with particularly the safety profile for fluoxetine in continuous dosing. Even though the disorder is just intermittent, as you say, many disorders are intermittent with respect to intensity of symptoms, but nevertheless, a longer-term approach prevents their reemergence and relapse of those symptoms.

DR. TAMMINGA: Dr. Temple.

DR. TEMPLE: Usually you don't know when a disease is going to relapse. So, you have no choice except to treat continuously. This is a little different. You

know exactly when it's going to happen.

DR. TAMMINGA: That's what Dr. Endicott emphasized in her presentation.

Dr. Fyer.

DR. FYER: Sort of two comments. First, on your response, Dr. Judge, I think that there's a big difference between a drug being overall safely tolerated the way these kinds of databases are put together and the question of individual people taking a drug for a very long period of time and it having effects that impact their life. It may not be medically dangerous. I would like to feel that the sponsor, in undertaking to get this kind of indication, would really take that seriously in terms of labeling and how they advertise and promote the drug because we're talking about women who might conceivably take this for a very long time.

The second comment I have is actually a question to Dr. Steiner. I was glad to hear that the reason for your dropouts -- it seemed to me that it was just a very hard study to do and that there wasn't something odd going on with the drug.

But the question I have is that in most of the studies we have mean scores as opposed to responder outcome. In the one study where we had the CGI used, in fact the 1's and 2's -- it was a small study and there

weren't significant differences. I wondered if you could give us from your clinical experience some idea as to whether we're dealing with a situation like OCD where even the people that get better don't get completely better or very few of them do, or if we're dealing with a situation like major depression or panic disorder where a large proportion of the responders are really better, you know, just-in terms of risk-benefit ratios, things like that.

DR. STEINER: As old as I am and have been in this field, this is the first time that something works. This is the first time that the clinic got flowers from husbands --

(Laughter.)

DR. STEINER: -- because we treated something that sort of restored life in some of these households. This is not something to sneeze at. I don't care about statistics. I'm telling you that clinically this was so impressive that it was almost unbelievable.

You were asked who was driving this study. We had 10 or 12 patients that we piloted before we went to Lilly and we said, this is the first time. I have worked with a lot of other compounds. They were all as good or as bad as placebo, and really nothing works after works after three or four cycles. This was the first time that something worked. We went to Lilly and we said we must do

that properly.

DR. TAMMINGA: Dr. Steiner, did all the patients get a little bit better or did all the patients get totally better?

DR. STEINER: Most of the patients got totally better. I'm talking about the completers.

DR. FYER: How would you comment on the third study where they did do CGIs and they didn't find for the 1' and 2's? Remember, 1 is completely and 2 is slightly.

DR. STEINER: I wasn't involved in that study and I don't think that I should be commenting on it.

DR. FYER: Somebody else?

DR. JUDGE: Again, for that study, there was clearly a trend towards significance, .07. When one looked at the overall CGI any improvement, then there was a statistical separation. Again, there were small numbers of patients in that study which might have accounted for some of the lack of significance. But generally the results are entirely consistent with the efficacy noted in the other studies.

DR. FYER: Respectfully, I just submit that if in fact all the patients got all better, you couldn't have seen that kind of CGI outcome. I don't know what happened, but that's not consistent.

DR. TOLLEFSON: -1 think it might be useful if

we put the CGI response slide up for you to take a look at. Again, remembering it's a very small sample size, which increases the hurdle for showing a p value less than .05. If you look just at treatment effect size, you look at the 20 to 60 milligram fluoxetine arm, you're seeing a response rate on CGI 1 or 2 that is in excess of 50 percent. I would argue that's as good as any response data, schizophrenia, depression, OCD, that we see in the literature.

If you then expand it a little bit more to include 3, you see now that we're approaching 90 percent plus who had CGI improvement with fluoxetine, and despite the small sample size, there's a very robust statistical separation between fluoxetine and placebo. You can see that there is a very strong differentiation from that of bupropion.

So, I would argue that that's a fairly impressive response rate with CGI, statistics aside for a moment, at either of the score of 1 or 2, which a priori was the primary outcome, or scores 1, 2, and 3 as a secondary analysis.

To Dr. Laughren's earlier question, which I'm not sure was fully answered, we do have the sexual functioning item from the PMS scale that we could up for you. I think that might provide some light on the issue of

either improvements or, alternatively, deterioration in function between drug and placebo.

Go ahead, Rajinder.

DR. JUDGE: This is looking from study 1 for those patients during the study who 'scored on the PMTS patient rated scale. So, this is looking at those patients who had sexual drive increased or sexual drive decreased. For the placebo group, these numbers are 58 and 51 percent, respectively. For the fluoxetine group, roughly around 50 percent each group, and for the fluoxetine 60 milligram arm, again roughly around 50 percent each group.

So, it seems from the data here that, overall, sexual drive could increase or decrease with respect to any treatment, and also that the differences between fluoxetine and placebo were not statistically significant as noted here.

DR. TAMMINGA: Dr. Laughren.

DR. LAUGHREN: Is this follicular phase or luteal phase data?

DR. JUDGE: This is luteal -- at any time, at any time during any visit. And patients were scored in follicular and luteal visits, so this is at any point in that study they could have sexual drive increased or decreased.

In fact, this is consistent with other studies

with fluoxetine where we note that patients -- if you just flick on to the second carry-on in this file, with the overall depression database patients improving or not improving. It's the last slide in this file.

So, this is looking at a meta-analysis of several studies with fluoxetine. It looks at another parameter, the SCL-58, and looking obviously at females only*. We see that for overall fluoxetine database, indeed, some patients do worse with the use of fluoxetine on fluoxetine or placebo. Nevertheless, some patients' sexual dysfunction remains the same, but some patients actually do improve and a greater number of patients do improve on fluoxetine versus placebo.

So, I think the sexual dysfunction question in terms of what we know less about the PMDD population, we know less about how these patients are at baseline, how is their sexual function at baseline. That's really information that is not very clear at the moment.

DR. TAMMINGA: Yes, Dr. Altemus.

DR. ALTEMUS: Do you have any data about anorgasmia? Because that's really the main side effect. Would that have been picked up in any of the measures?

DR. JUDGE: If we could go back to the first slide of this file, the overall treatment adverse events for all three studies. Specifically they're items relating

to sexual dysfunction in each of the three studies. For study number 1, anorgasmia was reported in 0 placebo patients, in 1 fluoxetine patient in 20, and again a similar number for fluoxetine'60 milligrams.

For decreased libido, again small numbers of patients reported decreased libido in this trial, as you can see here. Highest numbers for fluoxetine 60, **but then** again we're talking about 8 patients, which is 7 percent. The p value was not statistically different for the placebo versus fluoxetine in these groups.

In these studies you see perhaps a higher level of reporting, but it's more important to note that the way that these adverse events were not just spontaneously -- they were not just treatment emergent. They were any adverse events collected at any point. So, one would expect a higher level of reporting.

Again, most importantly to note, the differences between fluoxetine and placebo were not statistically significant for any measure. That's the data that was evident from these studies, the PMDD studies.

DR. TAMMINGA: Dr. Laughren.

DR. LAUGHREN: One comment on these data. In all cases you're relying basically, I think, on spontaneous reporting of those events, and you may see a different picture if you have sensitive scales designed to look at

sexual function.

DR. JUDGE: Yes, indeed. The interesting point would be also again to exploit such scales at baseline as well to see what the baseline level of functioning was.

DR. TAMMINGA: Any additional questions from the committee for Dr. Judge or for Lilly?

(No response.)

DR. TAMMINGA: Thank you, Dr. Judge.

Before we break for lunch, we have one person who has requested a time in open hearing to speak on this particular topic, I'd like to ask Dr. Sherry Marts from the Society for Women's Health Research to come forward and give her remarks.

Also, I would ask, if you would, in the spirit of disclosure, to indicated whether or not you actually get money, your organization gets money, from Lilly, and give us an idea of what percent of your finance of that might be.

DR. MARTS: My name is Sherry Marts. I'm Scientific Director for the Society for Women's Health Research, which is a Washington-based advocacy group dedicated to improving the health of women through research. We were founded in 1990 when we brought national attention to the need for research on conditions that affect women not only solely because they're women but also

differently from men or more often than men.

I would like to say that we do get support from Eli Lilly. They have been a longtime supporter of our efforts, and they provided a grant for the consensus roundtable on PMDD, which I'm going to talk about today. This was convened by the society in 1998, and a peer-reviewed summary of that conference was published in the Journal of Women's Health this past June. I have a few copies of it. Unfortunately, I didn't get the speaker's guidelines in time, and I only brought four copies. But if you're willing to share, I'd be happy to hand those out.

The group that assembled for that conference included experts in psychiatry, psychology, gynecology, and epidemiology. This conference report was published as a peer-reviewed paper, as I mentioned. Among the conclusions of that conference are that PMDD is a distinct clinical entity with a clinical picture that is not a typical picture for depression, mood, or anxiety disorders, and in particular, internal tension, anger, and irritability are characteristics of PMDD.

The key differences between PMDD and other disorders is the clear onset and disappearance of symptoms, both linked to the menstrual cycle. There's considerable stability in the course of PMDD from cycle to cycle and over time in the absence of treatment.

The conference noted that PMDD is a chronic condition that in some women can worsen over time. Age of onset varies and it can be any time after regular menstrual cycles are established.

PMDD differs from other disorders in. that there may or may not be comorbidity with other mood disorders, and unlike in depression, in PMDD the hypothalamic-pituitary-adrenal axis often functions normally. Blocking the menstrual cycle, as happens in pregnancy, can eliminate PMDD, but has no effect on other mood disorders, and after pregnancy, symptoms return once the menstrual cycle is reestablished.

Finally, the consensus conference concluded that there is biological evidence for the involvement of the serotonin system in PMDD.

Now, I want to say that the society does not have expertise in the evaluation of therapeutics. I'm not here to encourage or discourage the approval of any particular pharmaceutical agent for treatment. We gladly leave those decisions to the experts.

But we want to emphasize that PMDD is a severe, often debilitating disorder that is distinct from premenstrual syndrome. PMDD's symptoms.significantly interfere with a woman's life, preventing a sufferer from functioning effectively at work and at home.

We're concerned that this disorder may go unrecognized, undiagnosed, and untreated in many women. Among the barriers to diagnosis and treatment are the stigma that may be attached to a condition associated with the menstrual cycle. There's still a negative connotation against seeking treatment for something that's just in your head or just PMS. The admission that treatment is needed is seen as a weakness. Because this condition is not well understood, physicians may not recognize the signs and symptoms or know how best to diagnose PMDD by distinguishing it from mood disorders.

The possibility of a medical treatment for this disorder is heartening and it's evidence that women have succeeded in bringing attention to this condition to their health care providers.

We as the Society for Women's Health Research are committed to reducing the stigma of diagnosis with PMDD and committed to educating women that PMDD can be diagnosed and treated and that symptoms are, as I said, not just part of being a woman or all in your head. We encourage women to consider all treatment options and to insist on treatment that is effective and appropriate to the severity of their symptoms. We encourage the members of the advisory panel to consider the significance of this disorder for the approximately 5 percent of menstruating

women who suffer from it.

Thank you.

DR. TAMMINGA: Thank you very much, Dr. Marts.

Although Dr. Marts was the only person who requested a spot for remarks, this is the open public hearing part of the meeting, and I'd like to ask if anybody else has any statement to make.

(No response.)

DR. TAMMINGA: In that case, I think we ought to break for lunch. I would like people to come back promptly at 1 o'clock, and at that time the committee will have a discussion both about the diagnosis and about the efficacy and safety questions.

DR. TITUS: There is a table reserved for you in the restaurant, and I would like to caution you that the conversation needs to be about weather and neutral topics. The topic we're discussing -- you need to come back here and do it publicly.

(Whereupon, at 11:55 p.m., the committee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:03 p.m.)

DR. TAMMINGA: I'd like to reconvene the meeting.

The committee is now in the committee discussion and deliberation portion of our meeting. I'd like to focus our discussion on the items that Dr. Laughren raised for us this morning about the questions that the FDA has of this indication, both of the indication and of the drug, and remind the committee that the question that Dr. Laughren would like some discussion of, first of all, is the general question regarding PMDD as a new indication. With some more specific questions, Dr. Laughren asked about the relevance of the DSM-IV appendix status for PMDD, PMDD as a distinct disorder, distinguished from MDD, the relationship of PMDD to PMS, and as a follow-up question, the possibility, although we're not considering a drug for this today, the related question of PMS as a candidate for an approved indication.

So, I'd like us to start this afternoon meeting's deliberating about these kind of things. I would actually invite our consultants, who are experts in this area, to perhaps take a lead-off in the conversation. Dr. Parry.

DR. PARRY: Well, I think that the studies that

were presented this morning and most other studies that are accepted for publication use the criteria for premenstrual dysphoric disorder. There was a lot of deliberation going into making those criteria. The term "premenstrual syndrome, PMS" is amorphous and ill-defined. There's no definition of it. So, to say that one is a subset of the other or how it's differentiated I think is really a moot point.

I would strongly advise against fluoxetine being considered for use in this amorphous term PMS because the studies that the decision will be based on do not use -- specifically and go to a lot of trouble to define criteria for PMDD. So, we really don't have information on this amorphous, ill-defined PMS. So, I think we should confine our focus of attention on the studies and even treatments to the very carefully and very rigorously defined premenstrual dysphoric disorder. It's more rigorous than most other psychiatric disorders. The terminology that's used in the DSM-IV was based on pooling studies from across the country. So, I think given that background, the focus should be on premenstrual dysphoric disorder.

DR. TAMMINGA: Dr. Thys?

DR. THYS-JACOBS: I think PMS is a definitive and distinct disorder. Women who have had it -- and I

would say across the board, there are about 70 to 80 percent of premenopausal women who are suffering with premenstrual syndrome. So, I think it's a very distinct disorder.

DR. PARRY: What's the definition?

DR. THYS-JACOBS: I think it's been defined as an occurrence of physical and affective mood symptoms that occur during the luteal phase of the cycle, as distinct from the follicular phase. Now, exactly what that ratio is in terms of symptomatology -- is it a 30 percent increase? Is it a 50 percent increase? Is it 100 percent? We all know that premenstrual syndrome exists, it's a luteal phase disorder, and we know that these symptoms indeed occur.

Is PMS distinct from PMDD? Now, there is a definition in the DSM-III and the DSM-IV that cites specifically that five out of a lot of these symptoms define PMDD. I think it's fine. I think for a woman who has the very severe end of the spectrum -- and I don't see any difference between PMDD and PMS, not at all. In my practice and in my research, I don't see any distinction between the two. What I do see is that the women who come in who have PMDD indeed have a prominence of affective symptoms. Are they more symptoms than physical symptoms? I don't find that, not at all.

But I do agree that it is a distinct disorder.

It's distinct in terms of defining it from other depressive or other mental or mood disorders.

DR. TAMMINGA: You're talking about PMDD.

DR. THYS-JACOBS: PMDD and severe PMS. I do not consider them as different. Not at all.

DR. TAMMINGA: Dr. Altemus?

DR. ALTEMUS: I imagine that if this is approved, in the general public and in primary care, people aren't really going to know how to diagnose PMDD, and it will probably be used very widely for anyone with any premenstrual symptoms at all.

DR. THYS-JACOBS: I think the criteria are pretty well spelled out in terms of the DSM-III and DSM-IV. I think women know what PMS is. I don't think there's any question about it. The people that I speak to who are seeing these women, the gynecologists, the primary care internists, they all know what PMS is. They all know that it's a group of these symptoms, whichever symptoms you want to define, that occur specifically during this phase of the menstrual cycle, the luteal phase of the cycle, and remits with menses or the follicular phase. That is PMS.

Is PMS distinct from PMDD? No, it is not. It is not different.

DR. ALTEMUS: Well, I don't think we can make the leap that the drug is effective for PMS. I mean, there

have been two studies in PMDD. Even though you intuitively think that it will be effective for PMS.

DR. THYS-JACOBS: I'm not saying that. I'm not saying that this particular drug --

DR. TAMMINGA: We're really just talking about the diagnoses now just as a starter.

DR. THYS-JACOBS: -- should be indicated for premenstrual syndrome. When I think of premenstrual syndrome, I think of the global syndrome and I think of the physical and the affective, the water retention symptoms and the pain symptoms. I think of the whole global syndrome. I think what we've seen is that we have defined PMDD mostly as an affective syndrome with these particular group of symptoms, and this drug is or is not effective for this particular group of symptoms in this disorder. Is it effective across the board for the entire syndrome? We haven't seen that.

DR. PARRY: What's your operational definition in terms of severity of symptoms? They do make a distinction between major depressive disorder and depressive symptomatology. So, I think not only in terms of the nature of the symptoms -- and you specified timing, but what about severity?

DR. THYS-JACOBS: I think the timing makes the syndrome. There's no question about it. It's the timing

during the luteal phase. That's why it was late luteal phase dysphoria and premenstrual dysphoria. It's the timing of the syndrome that makes this different from major depression and all the other mood disorders. There's absolutely no question this disorder remits, subsides, ends with the beginning of menses, period. So, it's the timing. Whatever symptom you want -- it could be cravings, it could be pain, it could be depression -- any symptom you want that occurs during this luteal phase of the cycle and recurs, you have PMS.

DR. 'PARRY: Well, but again it's severity. Would you use fluoxetine to treat a little bit of breast swelling?

DR. THYS-JACOBS: I'm talking about PMS not versus PMDD.

DR. PARRY: Yes, but what are your severity criteria for PMS is what I'm asking.

DR. THYS-JACOBS: There's no severity. It's the timing of those symptoms that occur during the luteal phase of the cycle.

DR. ALTEMUS: But you're saying it's a disorder.

DR. THYS-JACOBS: It's a disorder. It's not a disease. It's an occurrence of symptoms, whatever group of symptoms the woman has for that particular phase of the

cycle.

DR. ALTEMUS: Would you say 80 percent of people have this disorder?

DR. THYS-JACOBS: Yes, absolutely. I think 70 to 80 percent of women who are walking around have suffered at some point in their life with PMS. There's absolutely no question. If you're out there and you're seeing women on a daily basis, yes, there are women out there who are suffering with this syndrome.

DR. TAMMINGA: Let me focus this discussion, if you would, for a minute on PMDD since the question on the plate -- we have sort of a minor question about PMS, but the major question on our plate is the PMDD question, the suitability, if you will, of the PMDD as a diagnosis and as an indication for drug treatment.

Good, Dr. Dominguez.

DR. DOMINGUEZ: I would like to ask the consultants, taking a step back from the discussion that just happened, why was LLPDD not elevated in DSM-IV to a distinct disorder? We learned from Dr. Endicott that there was a lack of consensus in that area. What were the major issues that drove this lack of consensus? Can the consultants or perhaps even Dr. Endicott enlighten the committee as to why?

DR. PARRY: Well, from my view, as Dr. Endicott

indicated, there was consensus on the-nature of the symptoms. I view it that was a political decision, not a scientific one. But the concern was that if it was put in the main body of the text, it would implicate all women as having a disorder, even though it specified that based on the estimates we had from studies, only 5 percent of women met criteria, but the concern was that it would stigmatize women. So, I'm happy to hear other comments, but I think it was primarily a political decision, not a clinical or scientific one.

DR. TAMMINGA: Why was the diagnosis changed from LLP -- whatever that was -- to the PMDD?

DR. PARRY: Well, it was first listed in the DSM-III-R as late luteal phase dysphoric disorder because the attempt was to define it as carefully as we could into the luteal phase of the menstrual cycle. But I think it was changed to premenstrual dysphoric disorder because late luteal phase dysphoric disorder was a bit cumbersome. It got referred to as L squared PD squared, and the premenstrual terminology was more user friendly.

DR. DOMINGUEZ: So, if the issue was political, as you say, then this disorder is going to remain in the appendices of future DSMs forever and ever? I think it is worded as studies that need further research and further verification. What else has to happen in order for this to

rise to a clear Axis I category?

DR. PARRY: I think the majority of the people who were on the board wanted it to go in not under the appendices, but the board, because of a few dissenting opinions and because of the public controversy, overrode that. So, my view would be we made a little bit of progress just getting it in, and I would hope that the next step would be to put it in.

Would you share that, Jean?

DR. TAMMINGA: Dr. Endicott.

DR. ENDICOTT: Dr. Parry and I were both on the work group that were advisory to the nomenclature committee, and it was fairly apparent from day 1 of that work group or advisory group that there were going to be issues around this political issue and that there was going to be some disagreement on the ultimate recommendation. But the group was able to work together very well on the subset of criteria and on the evidence to support those criteria.

There was a desire on the part of the nomenclature committee to have some kind of consensus recommendation, and they finally accepted that there was not going to be a consensus from our group. So, they were presented with the evidence.

As Barbara said, both in the advisory committee

and in the overall nomenclature committee, most of the people were in favor of moving it up from the appendix. But there were other issues going on, and this is always a committee kind of decision in a general setting in which political issues do get considered.

DR. TAMMINGA: Dr. Laughren.

DR. LAUGHREN: Let me try and clarify the question that I'm interested in having answered. Actually there are two questions.

One has to do with this entity PMDD and whether or not that's a reasonable clinical entity to focus on as a claim, an indication in labeling. In terms of this application, that's the only entity that we're focusing on because that's what they studied.

The second question really relates more to our advising other companies who are interested in this area and what to tell them about broader claims that they might be approaching. There is some interest in looking at this broader entity of PMS. My question is, separate from your answer to whether or not you think PMDD is a reasonable entity, is this broader entity something that, in a sense, is ready for prime time in terms of an indication? Is it well enough defined? Is there a consensual agreement about what the diagnostic criteria are so that a company could reasonably run a development program and submit an

application for this more diffuse claim? That's really the question.

DR. TAMMINGA: So, I'd like to hear from both the consultants and the committee members in response to each of those questions, addressing the first question about PMDD first and then the broader question about PMS.

Abby, do you want to go first?

DR. FYER: Sure. Actually I guess I would take it from the other point of view. What is it about this disorder that makes you feel that it might not be something viable to address as an indication for a drug treatment? Usually we look at epidemiologic data, we look at distress and impairment, et cetera, we look at distinctness from other disorders. It may be slightly different in some aspects from others, but I guess I'm missing the point. Maybe it's a little new in the history of the explicit definition of the disorder, but not really much different than panic which had a similar long history unofficially and then came into --

DR. LAUGHREN: Actually my own bias is in favor of what you said, that this entity is reasonably well defined. Really more my question has to do with this broader entity of PMS and whether or not that's a candidate for drug development. The questions I have listed here. Whether or not this entity is distinct from depressions,

say, major depression, I think that has largely been addressed, but other committee members may want to weigh in on that. But really, my main question has to do with future development programs for possibly this broader entity of PMS and whether or not that's a reasonable course for companies to be taking.

DR. FYER: You mean whether or not it's reasonable to advise people to develop indications for PMS.

DR. LAUGHREN: Right. Is PMS at this point well enough defined, well enough accepted in the community, and does it have enough agreement about diagnostic criteria that companies could reasonably go down that path and submit applications for that entity?

DR. TAMMINGA: Well, we've had two answers from our committee. One is yes and one is no. So, why don't the two of you restate your opinions, and then the rest of the committee can comment?

DR. THYS-JACOBS: I think PMS, premenstrual syndrome, is a distinct, defined disorder. There is absolutely no question that what makes this group of symptoms with this disorder or this phenomenon different from any other affective or any other disorder is the occurrence of these particular group of symptoms during the luteal phase of the cycle. I can't stress more to you that I really believe it. We have all recognized this for

centuries. It has been spoken about, written about by historians. We've defined it.

I think there was, indeed, a National Institute of Mental Health consensus that defined a 30 percent increase from luteal to follicular phase, that you had to know that there was a difference in scores, in visual analog scales, that there was, indeed, this difference of symptoms during the luteal phase to the follicular phase of the cycle.

So, we know what it is. We've defined it basically as a group of symptoms that occur. It's phase-related. It's temporally related to the menstrual cycle.

DR. LAUGHREN: Are you talking about PMS or are you talking about something called severe PMS?

DR. THYS-JACOBS: I'm talking about premenstrual syndrome, PMS.

DR. LAUGHREN: So, you're not making -- earlier you were talking about --

DR. THYS-JACOBS: No. I am not making any distinction in terms of severity, no, because I believe and my research has shown that, that the occurrence of premenstrual symptoms is abnormal. It's like being pregnant. If you're pregnant, you're pregnant. If you're a little pregnant, you're 1 month pregnant, versus 9 months pregnant. It's the pregnancy that makes the difference in

terms of the reproductive cycle.

What I'm saying to you is that the occurrence, the presence of symptomatology during the luteal phase of the cycle is not normal.

DR. TAMMINGA: Dr. Temple.

DR. TEMPLE: Couldn't the relationship between these two terms be described as PMS is the larger term, and when-the dysphoric symptoms are particularly prominent and are also premenstrual and have the appropriate timing, you call it premenstrual dysphoric disorder?

DR. THYS-JACOBS: Yes. I look at it that way.

DR. TEMPLE: So, one is perhaps a subset of the other.

DR. THYS-JACOBS: Yes. Yes.

DR. TEMPLE: And the way you get into a trial of premenstrual dysphoric disorder is you meet the criteria for those.

DR. THYS-JACOBS: You focus more on the affective --

DR. TEMPLE: If someone wanted to do PMS more generally, then they would be focusing on whatever the symptoms that happen to accompany this person's premenstrual syndrome, but they might even not have a dysphoric disorder. They might just be bloating or something. But you'd say that's still PMS, but no one

would say that's premenstrual dysphoric disorder because they're not dysphoric.

DR. THYS-JACOBS: Right. I definitely agree with that.

I should actually qualify this. What I look for is a difference between follicular and luteal phase. When I treat a woman who has premenstrual syndrome, what I look for after treatment is the equalization between luteal and follicular mean scores. That's what I look for. It doesn't have to be absent. I like to see absent symptoms. So, when I even tell you the presence, that's not really right. It's not the presence. It's the increase in symptoms during the luteal phase compared to the follicular phase. That's what I look for. I look for the decrease in luteal phase symptomatology, those mean scores -- or you could use a visual analog scale -- between one phase of the cycle and the other, and I look for the equalization between these phases. Then I say, yes, this woman is adequately treated.

DR. TAMMINGA: Dr. Hamer has a comment.

DR. HAMER: No. Actually, as usual, I'm just confused. Did I hear you say at one time that 80 percent of women had this and then at another time that it was abnormal?

DR. THYS-JACOBS: Yes.

DR. HAMER: I just wanted to make sure I heard that.

DR. THYS-JACOBS: Yes. I think 70 to 80 percent of women are suffering with premenstrual symptomatology.

DR. HAMER: Then why isn't that normal?

DR. THYS-JACOBS: Well, it depends on what norm-al is. If somebody comes in and says, I feel wonderful and their vitamin D level is 0 and then you start'treating them, and they say, wow, I've never felt better, what's baseline, what's normal? I don't have the answer to that question.

DR. TEMPLE: It's like asking whether presbyopia is normal or not. It's a matter of definition. Everybody gets it, but the lens isn't working anymore.

DR. TAMMINGA: The committee would like to hear from both Dr. Parry and Dr. Altemus about the broader question of PMS and the suitability, if you will, of PMS as a diagnosis.

DR. ALTEMUS: Well, I think PMDD is definitely well defined, and that's definitely an indication.

I have a more conceptual question I guess. For a drug to be approved, does there have to be a disorder with diagnostic criteria? I'm just thinking of, say, pain medication. Do we approve pain medications for arthritis?

Does there have to be a severity criteria for the drug to be accepted?

DR. TAMMINGA: Maybe Dr. Laughren can answer or Dr. Katz can answer this question.

DR. ALTEMUS: I think the problem with PMS is there's no severity criteria, like 80 percent of women have some symptom. I'm wondering for a drug to be approved, do we have to have a defined disorder with diagnostic criteria, or is it possible to have, say, a pain medication approved that works for all different severity of pain? Do you know what I'm saying?

DR. KATZ: Well, you could have a pain medication approved I suppose for all different severities, and they are. But pain is something that everybody understands. I mean, it's commonly accepted that pain is a syndrome, if you will, that's commonly understood. Everybody knows what you mean when you say I have pain, although there are different types of pain, of course.

The question here that Tom is asking, that we'd like to hear what everybody has to say about, is, is PMS so well-defined, so clearly understood by the community and accepted as a bona fide diagnosis in the community so that we could reliably identify people who have PMS, know what their symptoms are, and that there would be a common understanding so that we could write a label that says,

this drug is approved for patients with PMS?

DR. ALTEMUS: Well, if you wanted to do that, you'd have to have severity criteria, and the way you're describing it right now is there are no severity criteria. It's just symptoms.

DR. THYS-JACOBS: No. I'm not --

DR. KATZ: I don't know exactly what you mean by severity criteria, other than everything is on a continuum. First you're normal with anything and then eventually you're abnormal. So, I guess in some sense any disease state is defined almost by a severity criteria.

DR. TEMPLE: You could use presence or absence, that kind of thing.

DR. ALTEMUS: I guess what I'm saying is I think right now PMS is in the same sort of realm as pain, that it's a subjective report, and there really aren't diagnostic criteria, for what's the severity of bloating or discomfort that's defined as PMS.

DR. TEMPLE: You could develop one, and in fact you have to develop one or you won't be able to detect improvement. So, make a visual analog bloating scale and check it out and see if people -- it's subjective anyway. Actually nobody gave weight change measurements with this drug, which I meant to ask about and forgot to. But they're subjective symptoms. There are always ways to

develop a scale for those things. People do it when they're forced to because they want to study a drug usually.

DR. ALTEMUS: No. I agree there are scales. But right now, I'd say for PMS, as it's generally understood, there's no diagnostic criteria.

DR. KATZ: Well, then how do you know somebody has it?

DR. ALTEMUS: It's like pain.

DR. TEMPLE: But I think we heard this. They have cyclical symptoms of one kind or another and they vary, that come at that time, --

DR. KATZ: Right.

DR. TEMPLE: -- and are not there otherwise.

DR. KATZ: Right, but the question is if you're developing a treatment for it, do you study people who only have bloating, only have breast tenderness, who are dysphoric? That's what we're asking.

Ordinarily when we consider an application for an indication, the indication is something that is generally recognized as being a bona fide, reliably identifiable entity by the community so that people know what Parkinson's disease is, people know what major depression is. It's well understood what those things consist of.

Here the question is, how do we define PMS? Does the field in general believe that one definition as opposed to another is acceptable? That sort of thing.

DR. TAMMINGA: Do you have another comment, Tom?

DR. LAUGHREN: Well, I guess another question that I have, and this is really a more subjective thing. It's true that we approve drugs for something like pain or for nausea which are conditions which people understand. You don't have to have, in a sense, diagnostic criteria.

I guess my question is here what we're talking about is committing patients with this entity to possibly decades of treatment, of continuous treatment, with a drug which has some risk associated with it. The question is, if this entity is so vaguely defined that it exists in 80 percent of menstruating women --

DR. THYS-JACOBS: I can't imagine that you're saying that this is vague. I think it's very clear-cut. I think it's cyclical. It's recurrent. There's a group of symptoms that are increased during the luteal phase of the cycle. I cannot see that as vague. If this group of symptoms.is increased by 30 percent, 50 percent, 100 percent compared to the follicular phase of the cycle, for me that is a definition of what this syndrome is all about. I don't think you really have to say does this person who

is suffering with premenstrual syndrome have this particular symptom. No, we don't look at that.

You have to go back in history and realize that there have been clearly over 150 symptoms that have been associated with this syndrome. We've come down to maybe we've agreed to maybe 15, 17, or 20 symptoms. Do you want to look at the whole syndrome? That's fine. What I look for is this group of symptoms that occur and it's the change from the follicular phase, and that's the definition. I think that's clear. That is not vague.

DR. TAMMINGA: Dr. Parry, do you want to weigh in on this question? This is the PMS question.

DR. PARRY: Well, to try to go back to the original question, I do think that the disorder, premenstrual dysphoric disorder, as defined in the DSM-IV, has substantial evidence for clinical viability, the nature of the symptoms being primarily affective in nature, the severity of the symptoms.

When the DSM was initially developed, the definition of psychiatric disorder was that condition which causes symptoms of distress as well as a certain amount of impairment in social or occupational functioning. Now, for research criteria, we may use a cutoff score, but as with any other psychiatric disorder, it has to impair some aspect of social, occupational, or even school functioning,

as Dr. Endicott reviewed this morning.

Then the other nature of the diagnostic criteria is the distinct timing of the symptoms in relationship to the menstrual cycle. Many women may have cyclic mood symptoms, but they may bear no relationship to the timing of the menstrual cycle. And retrospective reports on that are notoriously unreliable. So, a prospective documentation of symptoms I think is critical in making the diagnosis.

So, not only the nature, the severity and the timing of the symptoms have been, I think, very carefully described in the premenstrual dysphoric disorder, but the associated features of the course of the illness, its inheritance patterns have also been described, and also its relationship to other psychiatric conditions and differential diagnoses. So, I do think that premenstrual dysphoric disorder is a well-defined, viable clinical entity.

I do not think that premenstrual syndrome is a defined clinical entity, and I think that there would be a great risk in trying to develop a drug treatment for a very, what I consider, ill-defined syndrome. It would be comparable, in my view, to taking someone with -- let's say, developing a drug treatment -- all the work that has gone into defining depression. Granted, major depression

may be a'spectrum illness and needs to be differentiated from grief or just feeling cranky or having some irritable symptoms. But I don't think it's advisable to develop drug treatment for something that's not a disorder that you could get recurrent pain syndrome, you could get very minor symptoms, and to use a drug treatment to mitigate those symptoms I have to say I think would be very inadvisable.

DR. TAMMINGA: Dr. Geller.

DR. GELLER: I think it will help if we make a distinction between what men accept and what women accept as commonly accepted entities. I don't want to be disrespectful to the meeting, but if this were a Perry Mason show, I'd ask all women who think PMS doesn't exist to raise their hand.

I think there is such wide clinical acceptance that I think that really is not so much the issue as the definitional issues in terms of being scientists. We don't have good measures that distinguish what the impairments are with PMS from non-impairments. The challenge to the companies who want to use this as an indication would be to do what Dr. Temple just said, develop instruments that are validated and reliable that can measure PMS symptoms, and then you can define an entity. From that, you can go on to drug treatment.

DR. TAMMINGA: Barbara, the difference between

like an entity or a diagnosis, that PMS is in your point of view a diagnosis, as well as commonly accepted entity.

DR. GELLER: I think what we generally do is we make things a diagnosis if they produce impairment, and I think until we have validated, reliable. scales that show what the impairment is, we ordinarily don't call it a diagnosis. The experts are telling us that at this point in time, those scales don't exist for PMS.

DR. THYS-JACOBS: No, that's not correct. There are scales for premenstrual syndrome.

DR. GELLER: Well, if there are scales and you can show --

DR. THYS-JACOBS: That's absolutely not correct.

DR. GELLER: -- the severity, then I'm misunderstanding Dr. Parry and I need correction. I thought you were saying at this point in time you didn't feel that severity of PMS symptoms could be measured in a way that would be appropriate for drug studies.

DR. PARRY: Oh, no, I did not mean to imply that. I think that the scales that were reviewed this morning -- the visual analog scale has been found to be one of the most sensitive markers, and it is a requirement to meet criteria for premenstrual dysphoric disorder that ratings be done on a daily basis over 2 months.

DR. GELLER: Right. No, for PMS, not the PMDD.

DR. PARRY: No. I'm talking about premenstrual dysphoric disorder. The symptoms that were listed this morning that are in the DSM-IV are listed by frequency of occurrence based on reports made at least five different centers across the U.S.

DR. GELLER: Dr. Parry, I think maybe we're having definitional problems. I don't think anybody listening to Dr. Endicott and the other presentations this morning has doubts about PMDD being a distinct entity where you can show severity in symptoms. My understanding is the FDA wants to know about the broader question of PMS, and here it sounds like there's a difference of opinion about how distinct an entity that may be in terms of what we can measure with rating scales.

DR. TAMMINGA: I'm hoping that Dr. Endicott might be willing to weigh in on this question. Even though you're not on the committee, we'd love to hear from you.

DR. ENDICOTT: I think I find myself falling kind of in the middle in the sense that I do think that most women know what PMS is and that they could give us a description. We could just tap any woman in the room and most of the men also could give us a clinical description of PMS that we would all nods our heads and say yes. However, when it gets to the issue of whether all PMS is a

disorder or not, that's where I do part company with Dr. Jacobs.

I think of it along the lines of a continuum ranging from just perceptible changes usually in physical symptoms that maybe get worse and worse and involve more and more symptoms, and at some point along that continuum, it becomes bothersome enough for the woman herself and for her mate or her children or her coworkers that treatment is warranted. Certainly all of us who do studies of PMDD do have women that we don't put into our formal protocols because they don't meet our most stringent criteria for PMDD, but they do have moderate to severe PMS that is causing them problems. We tend to sedge them over into another protocol or treat them openly because they have sought treatment for a condition that they have identified and that our prospective ratings show exist.

So, where is that cut-point along this continuum between what is just a phenomenon that is somewhat bothersome but not necessarily worthy of treatment and at what point is it severe enough that a woman wants treatment, needs treatment, and is willing to put up with the side effects that go with most treatment?

I think that there's always this issue. It comes up with everything else. How much pain do you have to have before you take an analgesic? How bad does your

headache have to be? How bad does your cold, sore throat, or flu have to be before you decide I got to do something about this?

So, I do think of PMS as ranging from something that nobody would seek treatment for or think is worthy of much attention, all the way up into PMDD.

DR. TAMMINGA: And that cut-point in your opinion does not occur at the point of diagnosis of PMDD?

DR. ENDICOTT: PMDD is a stringent diagnosis. There are certainly women who want to do something about their PMS that is just below the threshold of PMDD. But the idea that every woman might want to pop a pill or something -- even women with PMDD, a lot of them say, well, isn't there anything else I can do, lifestyle, vitamins, diet, exercise? Are there other things I can do so that maybe I won't need to take medication? So, for any woman there is always this issue of the balance between whether or not they want to take a medication or not and how severe it is, how much pain it's causing in their lives, and how much impairment it's causing.

So, we do see women who don't quite meet our criteria for the studies, but certainly are severe enough to warrant treatment.

DR. TAMMINGA: Thanks.

Other comments from the committee or its

advisors? Dr. Fyer.

DR. FYER: Following up on something Dr. Endicott said, years ago when Dr. Endicott started her studies, I remember having a conversation with her about starting the prospective follow-up. The thing that really struck me was the number of people who self-reported for PMS who did not turn out to have menstrual related symptoms.

I guess in terms of Dr. Laughren's question about drug companies using PMS as an indication, I think that it would be particularly important to make sure people get the right kind of care, that the prospective assessment be built into anything anybody does, and also the issue of, if people don't have that particular menstrual related thing, to begin to characterize the other things people have and what other kinds of treatment may be useful for them, and sort of see it as an opportunity to identify other treatment responsive syndromes that are troublesome to women.

DR. PARRY: In that line, I think there was a study done a while ago, the De Jong study at the NIH, that looked at women who came in complaining of premenstrual symptoms. They looked at the group in whom the diagnosis was confirmed versus those in whom the diagnosis wasn't confirmed by these daily prospective ratings. In the group

that was not confirmed, a majority of those, like 80 percent, had other psychiatric diagnoses, the most frequent of which was major depressive disorder. It was, I think, maybe less stigmatizing to think that they had premenstrual symptoms when they really had major depressive disorder.

DR. TAMMINGA: Additional comments, thoughts? Some of the committee hasn't spoken up.

DR. THYS-JACOBS: I just want to mention that most of the clinical trials on PMS have criteria of 2 months of prospective documentation of symptoms, and their criteria varies from trial to trial. Some people have used a 30 percent, some people have used a 50 percent. The majority of the studies have ruled out depressive disorders. So, the trials are there, and I think PMS, as it stands, in research is a distinct entity.

There are, indeed, a number of women who come in and say that they have symptoms, and when you prospectively document their symptoms, it's not what it turns out to actually be. But when you document for two menstrual cycles and you show that there's a luteal phase increase in their symptoms, that's what they have.

DR. TAMMINGA: Dr. Cook?

DR. COOK: I was just going to say I can't speak because I only have one X chromosome.

(Laughter.)

'DR. COOK: No.

But I did want to raise the issue, however, that although people are saying women would know what PMS is, most of the objections that have not been represented, other than to describe them as political, particularly have to do with PMS and are raised by women, not men.

So, I think the discussion has covered that there would be some risk in developing an indication for PMS, but if someone wants to go for the broader indication, I think the FDA should seek some input from those who had enough impact to keep what to me sounds like a very clear disorder, PMDD, out of the body of DSM-IV. I think that those are people that should be heard from. I don't necessarily agree with them. I just would suggest that that be included.

DR. PARRY: One risk factor I just thought of. For example, given the cyclicity of the symptoms, one very important differential diagnosis is women with rapid cycling mood disorders, and giving something like fluoxetine or other antidepressants can potentially exacerbate the rapid cycling. I think that would be one very strong indication. And 90 percent of patients with rapid cycling mood disorders are women, and it would be one of the very adverse consequences of not having a careful diagnosis.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: I'd also like then in my role as an advocate to do the same thing I did last time, which is strongly urge the FDA to, as it usually does, be very careful in writing the labeling for exactly that reason. As this will probably largely be prescribed by primary care physicians, gynecologists, they really do need to be sure to eliminate rapid cycling disorders so that they don't inadvertently give an SSRI to them.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: I'll jump in and make a comment. That was the direction of some of my questions earlier. I think I want to also distinguish just missing women who may have rapid cycling from the need to really focus down on the potential effects of the SSRIs or other antidepressants for the treatment of PMDD or other menstrual cycle related entities because we are talking about a cyclic mood disorder. And now we're talking about potentially applying these drugs that we know in other populations have a potential to induce mania or hypomania, as is the case for other symptoms or problems that have been talked about, such as sexual dysfunction. We know that sometimes symptoms have to be explicitly looked for rather than just kind of observed as adverse events. So, I think that future research studies might build in specifically

assessment of hypomanic type symptoms.

DR. TAMMINGA: Additional comments about PMDD as a diagnosis or about PMS as a disorder?

(No response.)

DR. TAMMINGA: If not, I think we should move on and talk about the appropriateness of the mood scales, of the VAS Mood-3 and the VAS Mood-4, in the data that we' heard presented today by Lilly.

Dr. Parry, you already mentioned something about this, that the visual analog scale was the single most appropriate scale. Maybe you could launch a discussion of this.

DR. PARRY: I was just referring first, in general, that the visual analog scale has demonstrated reliability and validity not just in terms of premenstrual dysphoric disorder but in depression and other disorders.

I think that the thing that you want to check is that these women are turning in their scales every week so that they're not retrospectively filled out.

I think in evaluating studies, it's important to see sometimes -- some of the earlier studies done just might have only a scale of 1 to 3, no symptoms, some symptoms, severe symptoms. I think the advantage of at least like 100 millimeter line visual analog scale is it gives the subject a whole range of symptoms and allows for

individual variability in completing these scales.

I think that the ones that were used in these studies were very adequate. There was one case where they linked I think happiness or mood and energy which may or may not be associated. But for the most part, they tapped into the main symptoms of depression, anxiety, rapid mood shifts, and irritability. Thanks to much of the work of -- Jean Endicott has developed the other scales -- it's quite adequate. They have been used extensively, and I think it's important to have both a clinician monitored -- as well as a subjective and an objective assessment built into the scales.

But I'd again like to point out compared to other psychiatric disorders, the daily ratings, at least for 2 months to get into the study, is more rigorous than we have for most other disorders. So, overall it doesn't mean there's not room for improvement.

DR. TAMMINGA: Dr. Thys?

DR. THYS-JACOBS: I would definitely agree. The VAS scale has been used extensively for not only PMS but for PMDD, and the fact that it was Mood-3 versus Mood-4 I don't think is really of any major consequence.

DR. TAMMINGA: What about using a subscale of the VAS rather than the total VAS score? We heard from Dr. Steiner this morning about the rationale for doing that.

DR. THYS-JACOBS: I don't think it makes that much of a difference because those symptoms that were chosen really are very much reflective of the total PMDD scale.

DR. PARRY: Yes, I do think they're much more like same amoeba, different pseudopods. So, they do correlate but I think it is of interest to go back, at least from a research point of view, and look at the subtypes of symptoms. Now, that's an area for development which specific subtypes of symptoms to do an item analysis to respond to specific interventions, physical versus emotional symptoms, for example.

DR. TAMMINGA: Dr. Laughren?

DR. LAUGHREN: Can I try and clarify again the specific question that I had? I thought I heard Dr. Steiner say earlier, expressed perhaps some surprise that fluoxetine had as robust effects as it had on physical symptoms, as well as, of course, the affective symptoms. I'm wondering if in retrospect -- and again, this has to do with our advising other companies in their development programs -- if you would have focused on that affective subset or if you would have focused on the total scale as your primary outcome in that trial. Again, the question is for future companies, should we advise them -- given the findings that we're seeing here, should the primary outcome

be the total scale or should it still be the, affective subscale?

DR. TAMMINGA: 'We could ask Dr. Steiner to give us his opinion on that.

DR. STEINER: Each line on a visual analog scale is its own scale. You can look at it that way. There are studies were you use one line of a visual analog scale and that is your rating scale. The fact that we picked seven lends itself to the fact that we were able to analyze it in total, which we did, which was statistically significant, lends itself to take the three major emotional behavioral symptoms that we wanted to analyze, and then separately the physical symptoms.

If you look at what's available in the literature for other SSRIs, it looks as if all of them work for both the emotional and the physical symptoms. So, if I were to advise to you guys, I would say take a combined visual analog scale.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: Yes. We'd be very interested in the committee's view of this whole question of the effect on the physical symptoms. Certainly it wasn't expected, and I suppose one possibility is that it's entirely an artifact, if you will, of the primary affective effect of the drug. I gather there were no objective, quote/unquote, measures

of bloating or weight gain or this sort of thing that were examined. I gather that's true. Maybe that's not true. If there are objective --

DR. JUDGE: We have information on weight.

DR. KATZ: Okay, well, that might be useful to look at because this will have impact if the drug were approved or might have an impact on the label and what this should be indicated for, just the affective symptoms of PMDD or the entire syndrome.

DR. TAMMINGA: Because presumably there are some people who have just physical symptoms of PMDD --

DR. KATZ: Right.

DR. TAMMINGA: -- while emotional symptoms --

DR. KATZ: Well, not of PMDD I gather by the diagnostic criteria, but of PMS.

In fact, it will be interesting, of course, to look and see if there were any work done on the effects of the drug in women who just had physical symptoms.

So, the whole question of the effect of the drug on the physical symptoms I think is very important for us to hear what the committee has to say.

DR. PARRY: I would just like to point out there was a study. I believe it was in the archives. Now, this is not PMDD but depressive symptoms in the general population. When you looked at somatic symptoms of

depression, a good portion of those were reported by women. So, now, it may not be the case in this disorder certainly, but some of the somatics being a depressive equivalent I think is a distinct possibility.

DR. TAMMINGA: Dr. Temple.

DR. TEMPLE: But my understanding is -- someone tell me if this is wrong -- that you can see cyclical weight changes and actual edema, at least in a fraction of the population. So, those presumably wouldn't be the result of your improved mood if you could show a difference in those things.

DR. PARRY: I think there is documented evidence of fluid and electrolyte changes with the menstrual cycle. I guess I was being more broad about symptoms other than just weight gain and fluid retention.

DR. TEMPLE: It would be extremely interesting to see if a drug that's known primarily at least as an SSRI had an effect on those things which certainly would have been a surprise to us.

DR. TAMMINGA: Perhaps, Dr. Judge, you could give us whatever data you have on the objective measures of physical symptoms.

DR. JUDGE: I'll take your points about weight with respect to two discrete questions. Firstly, overall weight changes in the groups per se. And the information

here is -- this is a summary of changes in weight from two of the studies. We were able to glean information on weight changes from baseline to end point. What we see is for the placebo group, overall there's a mean change of a gain of .2 kilograms. For the fluoxetine patients, overall there was a mean loss of 0.4 kilograms.

So, individually within the groups, if you looked at the next slide please, in terms of patient numbers who had potentially clinically significant changes in weight -- and that is, patients who had neither a 7 percent increase or decrease in weight -- we see overall for placebo very few patients exhibited any such parameters, and for fluoxetine a few patients again, but more than placebo, did exhibit either a weight gain or a weight loss. But overall the percentages were very low, 7 and 9.5 percent, respectively. Those differences were statistically different from placebo. So, that's the summary of changes in weight with respect to fluoxetine.

Now, overall in terms of your question with --

DR. TEMPLE: What you're really interested in is the difference between the follicular and luteal phase.

DR. JUDGE: Yes. That's what I was going to say in terms of the discrete question with respect to the --

DR. TEMPLE: We already know fluoxetine can

affect maybe weight.

DR. JUDGE: Yes. I was going to say with respect to your other question, especially for those patients who had bloating as a reported symptom, we don't have that information.

DR. TAMMINGA: Dr. Altemus?

DR. ALTEMUS: I'd just add that at first I was really surprised by that information that bloating went down, that those symptoms improved. But when you think about it, we don't really know what's mechanistically wrong, like what's going wrong in these women, but they have normal shifts in hormones but they have a very exaggerated response mentally to those shifts in hormones. Certainly there are mild changes in appetite and metabolism and fluid electrolytes with the cycle. So, when you think about it that way, it's not that surprising if they overreact to the hormone changes in terms of mood, that they'd overreact in terms of appetite or metabolism too.

DR. KATZ: The question is whether or not the drug is having an effect on those independent of its effect on -- you may not be able to tease this out, but since they are subjectively reported, if a person is feeling better from an affective point of view, there might be less attention paid to these other physical symptoms or they might feel as if they're lessened when in fact objective

measures may show that they're not lessened. That's the question.

DR. ALTEMUS: Yes. We were talking about this at lunch. I'm not even aware of a study in normal menstrual cycle that shows weight changes. I'm not sure that's ever been documented. It's a really common complaint, but I don't think it has been shown.

DR. TAMMINGA: Dr. Endicott.

DR. ENDICOTT: There are two issues here.

In terms of weight gain, a couple of studies that have tried to actually document the subjective feeling of weight gain have generally not done so. What they have found is a redistribution of water, not an actual increase, the idea that the bloating is not necessarily from water retention, but from a redistribution of water so that the subjective weight gain may well be response to that.

Now, on the other issue about whether if you improve the dysphoric mood changes you automatically get a reflected improvement in the physical symptoms, at least in one of our published studies of a drug, unnamed, we got very good changes in irritability, depression, and anxiety with no changes in the physical symptoms. So, it is possible to demonstrate changes in the dysphoric mood symptoms without changes in the physical symptoms. In fact, the women often said,' well, I still have my physical

symptoms, but that's no big deal.

DR. TAMMINGA: Dr. Steiner.

DR. STEINER: I think that bloating and the sense of bloating is more subjective than the breast tenderness. My surprise was that the breast tenderness -- and maybe it should not be a surprise -- is a pain and you're giving an SSRI. The bloatedness is also something like Jean said. When we tried to measure whether there was a change in weight, there isn't, although there is this complaint in the sense of bloatedness. But the breast tenderness is really an eye-opener. These women say I don't have that pain anymore, and I think that that is a drug effect.

DR. PARRY: SSRIs and other antidepressants do increase the pain threshold.

DR. TAMMINGA: We've been kind of discussing around the issue of whether the indication should be for the affective symptoms of PMDD or for the whole syndrome, however one might define that, of PMDD.

Dr. Fyer.

DR. FYER: Well, this is not at all my area of expertise, but it sounds to me, from what people have been saying, is that we really don't know about the actual effect on the physical symptoms, and that it would be premature to put in labeling something we don't know.

Rather, it seems to me that it would be very nice if the sponsor would undertake the responsibility of doing some well designed studies to address that question. It would be, I think, a help to everybody.

DR. TAMMINGA: Other comments? Dr. Temple.

DR. TEMPLE: What should they do?

DR. FYER: What should --

DR. TEMPLE: Well, they had physical symptom scores of the usual kind. Do you have a thought about how they could tease that out further?

DR. FYER: Well, like I said, I do anxiety disorders, so I'm not a measurement expert in this area.

But I think Dr. Katz' comment was well taken. We don't know to what effect what we're seeing is the result of mood changes, and it seems from what Dr. Endicott just said that, in fact, there's not all that much known about what actually physiologically goes on. I think it would be very helpful to everybody to do studies in which they actually looked at weight changes, luteal versus follicular phase of the cycle, during the drug treatment, as well as before, and to try to characterize that.

DR. TEMPLE: I suspect that's true. I guess my nervousness about it is that we don't usually expect that someone will solve a dilemma that's existed for 20 years before they can get a practical claim that they improve it.

DR. FYER: Well, no. Wait a second.

DR. TEMPLE: So, one has to balance what's reasonable.

DR. TAMMINGA: Dr. Cook.

DR. COOK: My concern is that it's new for them to really raise this. They had almost wanted to take it out in the design of these studies. So, even if they don't need to do more, they certainly need to test the hypothesis a priori.

DR. TAMMINGA: Dr. Fyer.

DR. FYER: I'm a little surprised to hear Dr. Temple take that position because I think when we talk about the real world, where drugs are prescribed, I think somebody raised the point before that much of the prescription for this indication is going to be in non-psychiatric settings by GP's where there is a predominance of managed care and limited time. I really think you want to be careful about somebody saying they have breast tenderness premenstrually and then being put on long-term fluoxetine. Before we get into that kind of situation, I think some experimental data would be useful.

DR. TEMPLE: That seems to me an important but different question. What level of symptomatology should make you want to go on an antidepressant for many years is a very important question. .

But, for example, the things that occur to me is they could find a population that doesn't have any obvious psychiatric component and see if they improve.

DR. FYER: Yes. That would be an excellent --

DR. TEMPLE: So, that's one thing.

You could also look within the trial to see whether people who have better response on mood also have a better response -- this is after the fact and it wouldn't be as convincing, but that's another thing they might do. They could look to see if there's a correlation between improvement on one and improvement on the other. That wouldn't be definitive, obviously.

I'm just trying to think of what they could do. But I would say nothing in this database would suggest a claim for treating those conditions alone in the absence of the dysphoric disorder. So, I don't think anybody has been thinking about that.

DR. FYER: But I think the other issue is to what extent the labeling reflects the idea that a whole syndrome -- where there's the implication that people who don't have predominant'dysphoric symptoms will respond to this drug. I think that's where the sort of gray area issue for labeling comes in.

DR. TAMMINGA: Of course, that wasn't tested here at all. The only thing that was tested here was

whether -- it only looked at the population of people with dysphoric disorder, and then we're kind of wondering about the status of the physical symptoms, and that's really less' clear. But for sure, we're not looking at any data of people who had no dysphoric disorder but PMS and had only physical symptoms.

Would Lilly like to suggest what studies they're doing? There has been some question in the committee about what studies Lilly might be currently doing that would address these kinds of questions.

DR. JUDGE: I just want to make clear that the application is for fluoxetine in PMDD, premenstrual dysphoric disorder. The question was raised as to what other studies Lilly are doing with respect to PMDD and specifically intermittent dosing. These are currently the two multi-center, multi-national studies that are ongoing, taking place in Europe and in the United States.

Firstly, a randomized, parallel, placebo-controlled study comparing two doses of fluoxetine intermittently and that is defined as 14 days prior to the onset of menses in approximately 250 randomized patients, and this will involve many, many more patients screened, but randomized will be approximately 250 patients.

Secondly, there is another study ongoing, randomized, parallel, placebo-controlled study comparing

infrequent monthly dosing of fluoxetine with an alternative formulation in approximately the same number of patients.

These are also again in PMDD patients, not specifically with one or two physical symptoms or PMS, specifically PMDD.

DR. TAMMINGA: Dr. Judge, in either of these studies, do you have objective measures of physical symptoms?

DR. JUDGE: Again, as we considered with a group of leading researchers in PMDD/PMS, it was felt that the scales currently used in the trials, namely the visual analog scales, namely PMTS, and perhaps one or two other scales, were indeed good scales in order to measure the appropriate outcomes with respect to physical symptoms and mood symptoms.

As you saw from the studies presented this morning, the secondary objectives of measuring physical symptoms was, indeed, stated as a secondary objective measure. Indeed, consistently the effect was found for physical symptoms, and we hope to find consistent effects in the ongoing studies as well.

DR. TAMMINGA: Dr. Fyer.

DR. FYER: It's really interesting that Dr. Endicott just got up and said that when the objective studies have been done about weight gain, what they found

is redistribution. Yet, you're doing these new studies, and the design of the study is not really addressing what's apparently known in the field. It might be nice to take these things into account.

DR. JUDGE: The studies that I've talked about are Lilly's commitment to further the work in PMDD with respect to intermittent dosing. The question was raised earlier, is it appropriate to pursue intermittent dosing?

With respect to weight change, I think that's a very important question. Is weight an appropriate symptom to study? We won't know that from these studies. That's a different question for which we have not put a study in place. Perhaps it's more appropriate for that study. I don't know that someone would have a special interest in that and do that. I'm not sure. But the studies ongoing are the ones that I've listed here. I think that's a very important and nice question, but it's not particularly going to be addressed by these questions.

DR. FYER: Yes, that's exactly my point, that it isn't going to be addressed. I think it would be nice if it were.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: In the existing 019 study that was Dr. Steiner's study, you saw the subjects once during the luteal phase and once during the follicular phase. Did

they get weighed each time?

DR. JUDGE: No, they did not get weighed each time. They got weighed infrequently, and definitely at baseline and endpoint, but not during every visit.

DR. HAMER: In the new studies, are they being seen both during the follicular and luteal phases, and are they being weighed?

DR. JUDGE: Again, there would be infrequent measurements of weight.

DR. PARRY: The inherent problem, though, of course, is that other things can affect weight, particularly diet and carbohydrate craving, which you'd have to control, and that's one of your outcome criteria for PMDD symptoms that you're trying to monitor.

DR. HAMER: Sure. Just asking about weight is asking about, in some sense, result not mechanism. But it would be nice to design in weight measurements at those places, as well as perhaps some physical measurements, various sorts of circumferences and things like that, so you could look for this redistribution of water.

DR. TAMMINGA: Dr. Altemus?

DR. ALTEMUS: If women on their rating forms are feeling significantly less bloated with the treatment, I don't think we would deny them the treatment because they don't actually have a physical change in weight. It's an

interesting mechanistic question, but it really is not relevant to whether this should be an indication for the drug.

DR. ENDICOTT: I'd like to comment. Weight gain is not part of the criteria for PMDD for the very reasons that have been mentioned, that the studies suggest that it is feelings of bloatedness that are part of the criteria but not weight gain, which is one of the reasons that I don't think any of the studies are focusing on weight gain per se because the really careful studies that have been done looking at that issue have found evidence of redistribution, not of actual gain.

DR. TAMMINGA: So, the physical symptoms that we're talking about could more precisely be called perception of physical symptoms rather than what we might really document with weight gain.

DR. ALTEMUS: Right. Like somatic symptoms in depression. People would complain of more aches and pains that improve.

DR. PARRY: You can always look at the item analysis on the Hamilton of either subjective or objective measures of weight change.

DR. TAMMINGA: This may be a good time to transition into the discussion of continuous versus intermittent dosage, especially since we've seen that Lilly

has two current studies now, one in intermittent and the other one in infrequent dosing. Any comments from the committee or from its advisors on that?

DR. PARRY: Well, I think the jury is still out with the luteal phase dosing. There are some preliminary reports.' I think to me probably one of the primary determinants may be the half-life of the drug. I think that was mentioned earlier., So, I think to put this forward, it would be best -- I think to put it on luteal phase dosing at this point I think would be premature.

DR. TAMMINGA: Dr. Thys?

DR. THYS-JACOBS: I agree.

DR. TAMMINGA: It would be --

DR. THYS-JACOBS: Premature.

DR. TAMMINGA: Premature to suggest luteal phase dosing.

DR. THYS-JACOBS: Right. There's not enough evidence at this point in time to advise luteal phase dosing.

DR. ALTEMUS: I think it's also not just the half-life of the drug but how long-lasting the changes are in the brain, that it may take several weeks to reverse once you've been on a drug for 2 weeks. That intermittent dosing might work for regular depression.

DR. PARRY: That's why we have patients off

fluoxetine for at least a month before they enter studies.

DR. TAMMINGA: Dr. Katz?

DR. KATZ: I don't think we're asking whether or not we should write labeling that says you should give it just during the luteal phase or however often. The question 'is given that it is an intermittent condition and that the presumption that you might be able to just treat this with intermittent dosing maybe even a couple of doses -- who knows -- whether it's appropriate to approve it with chronic dosing, in other words, whether this is something that is -- it's a benefit-risk question, whether it's worth having women on this drug chronically for a condition that occurs just intermittently for a relatively brief period of time. That's the question.

DR. TAMMINGA: The data that's in front of the committee is only continuous data.

DR. KATZ: Right and the question is whether or not you think that is appropriate to approve the drug on the basis of that. Is it worth it? Or should they do more studies that further define? Now, it is invariably true that we almost never know, when we approve a drug, the perfect dosing regimen. We only know what people studied. The question here is, should they study more before we approve it, or can you live with this?

DR. TAMMINGA: Dr. Altemus.

DR. ALTEMUS: I don't think so just because I don't think we put that burden on other disorders. You could say, well, can you give medication half as often for major depression? I think just because it appears during 2 weeks or a week of the month, I think it's pretty unlikely that -- well.

DR. PARRY: Yes, I would kind of echo that, that this is a recurrent, periodic illness and that the medication may work as a mood stabilizer. To recommend anything less, than that, we just don't know if that's going to have the same efficacy until that's demonstrated.

DR. TEMPLE: That's not the question.

DR. COOK: No, but I would add something, that until you have evidence that the intermittent dosing is both efficacious and safe, I don't think one should presume that it's safer to give it in an intermittent manner. These drugs have been tested for safety largely in a chronic manner, and as alluded to, I wouldn't use the word "kindling," but sensitization changes from this sort of dosing pattern wouldn't have the safety behind them.

Now, with fluoxetine, of course, you have the problem is anything truly intermittent, but as you're asking a more general question about SSRIs, hitting it just a few times a month may not be the best paradigm for long-term safety. We don't know. It's intuitive that it's

worth trying, but the data has to be there.

DR. TAMMINGA: Dr. Temple.

DR. TEMPLE: No one thinks we could approve an intermittent regimen that hadn't been studied. This goes to the fundamental question of the approvability of a chronic treatment for an intermittent disease where, in this unusual case, you actually know when the disease is going to occur.

DR. THYS-JACOBS: This is not a disease. It's a disorder.

DR. TEMPLE: Whichever. But you know when what you're treating, however you will care to define it, is going to occur.

It really goes to the fundamental question of whether a drug with a half-life of 14 days if the best way to treat this or an appropriate way to treat this. In asking that question, I want to be very clear I'm not offering an opinion. It's just something that ought to be discussed. That's all. I'm not saying that we are horrified by that idea. It might be the best thing in the world for everybody.

DR. TAMMINGA: Dr. Winokur?

DR. WINOKUR: Well, this is a disorder that we've heard, I think, convincing evidence is associated with a good deal of morbidity and distress, and I think we

can evaluate data from studies that have been done to form opinions about efficacy and safety, tolerability, acceptability in this context and then consider alternative approaches to treating when such data come along. But I don't see anything that is a barrier to our rendering an opinion about continuous treatment for a disorder that is discontinuous, but has significant implications. We've heard a lot of testaments to that effect.

DR. TAMMINGA: Dr. Geller.

DR. GELLER: There was mention in the material we got of a sertraline trial that was discontinuous. Is there more information on that? Did people get withdrawal when it was taken away and stuff?

DR. TEMPLE: I don't think we know yet.

It's also possible new information will emerge later that will cause people to reconsider what the best approach is.

DR. GELLER: I was wondering if specifically there was more information about the sertraline study at this point in time.

DR. TEMPLE: I don't think we do.

DR. TAMMINGA: We don't have it on our table.

DR. PARRY: The analogy that just comes to mind is lithium, recurrent mood disorder, and I think that there's substantial evidence at this point that for a

recurrent mood disorder that lithium works better the longer you leave it on them, and there are actually risks of taking them off. I might see that as the closest analogy to address that.

DR. TAMMINGA: If you don't mind my interrupting you, I'd like to ask you the question in the case that Dr. Temple proposes that in PMDD this is a predictable cyclic -- I mean, mania is not predictably cyclic, but this is clearly predictably cyclic -- would you still hold the same opinion?

DR. PARRY: Yes. Well, first, mania may be a rapid mood cycling. In most cases it is, but in not all cases is PMDD predictable. Of course, as soon as you enter them in the study; they don't get their symptoms.

DR. ALTEMUS: Also, I think it's premature to think that because it's cyclic you should give the drug when the symptoms appear. To really prove that, I bet you could give the drug during the follicular phase every 2 weeks and they may respond just as well. What I'm saying is it's premature to think that it should be given during the luteal phase just because that's when the symptoms appear.

DR. TAMMINGA: Additional comments? Dr. Fyer?

DR. FYER: I think that's an excellent point. We don't know the pathophysiology. I think Dr. Parry

referred to the possibility that it's acting as a mood stabilizer, and we don't know the important point of entry really is when people are clinically ill. It might be the week before.

DR. TAMMINGA: The data we have on the table are continuous data, and we've seen Lilly present that it's, in fact, doing a couple of different intermittent designs. so, we'll have some confidence that additional data will be coming.

I guess the question would be whether Lilly wants it to be continuous dosing because it uses more drug. That's not the right way to think about it.

DR. KATZ: No. I think Dr. Temple put it well. It's simply a question of is it appropriate to approve a drug for chronic use when the symptoms occur predictably intermittently. That's the question. We're not bringing an opinion to the table. We're simply asking the question is that an appropriate type of treatment for this sort of disorder.

DR. PARRY: Well, yes. I think the other consideration is if it's not treated in its initial stages, which may be a follicular phase or early on -- and I think there's data to support this, at least in PMDD -- it can get worse over time, I think the point that Dr. Cook was making, that it can exacerbate symptoms.

DR. TEMPLE: Part of the problem is it's hard to know how to even talk about this. With a drug with a half-life of 24 hours, you could ask the question, when do we have to treat, because then you could treat for the week before, the week before and during, you could modify your regimens and actually ask the question. With a drug with an active metabolite whose half-life is 14 days, you can't even ask the question. You're treating chronically whether you like it or not, and the only question is how much to give.

But just from my point of view, I thought what Dr. Winokur said was, look, you can look at the benefit, you can look at the consequences, and you can make a judgment about whether the consequence of being on Prozac a lot for a long time, which is obviously something that happens to a lot of people in this country, is worth it in view of the benefit of preventing these symptoms. I think that's what we're trying to --

DR. PARRY: The risk of no drug treatment and drug treatment.

DR. TAMMINGA: Dr. Laughren.

DR. LAUGHREN: Let me just give an example. There are drugs for chronic conditions that are given intermittently. Methotrexate is given once a week for treating rheumatoid arthritis. So, there are examples.

That's clearly 'a drug where you would want to limit the overall exposure., So, you would want to find a regimen that involved the least exposure to that drug to get a benefit. So, that's really the question. Is there a more optimal dosing strategy that works that gives a benefit and limits the risk?

DR. TAMMINGA: Dr. Fyer.

DR. FYER: Yes. I think this is a very . interesting question, but I think it comes down to sort of pragmatic issues. I think what you're seeing on the committee is a reflection of that. The sponsor and other people in the literature have demonstrated efficacy using a certain -- or made a strong case for that using a certain approach, and that certainly seems better than leaving people in distress. Anything else is going to be more of a question.

I think this almost becomes political in that would I personally think that it would be best that all sponsors be required to invest time and effort to find the optimum approach that has the least risk, et cetera. Yes, I definitely would.

Has that and is thatgoing to happen in the current climate in this country? I doubt it.

So, I think if you want to know is it best to do it that way, of course, it's best to do it that way, but

what's actually going to happen?

DR. LAUGHREN: We simply wanted to raise the question here for two reasons really. Again, this is a condition where the symptoms are cyclical. They're not present continuously. And secondly, there is a suggestion, I don't know how well established, that the possibility of intermittent dosing may be of benefit. That's not established yet. I totally agree with that. So, the question is whether or not there should be encouragement to look at more optimal dosing strategies for this condition.

DR. FYER: I personally think there should be encouragement in all kinds of disorders. What you're saying, Dr. Laughren, is that because of the particular pattern of appearance of the symptoms, this particular question gets raised. But in fact, since we don't know pathophysiology of most psychiatric disorders, one could legitimately raise that question about most of them.

DR. TAMMINGA: Dr. Laughren, is the data that the sponsor presented about the studies that are ongoing encouragement to the FDA or --

DR. LAUGHREN: We've not seen any data from any other studies.

DR. ALTEMUS: I think just one final point about that. From what we know about how antidepressants work, it's not an immediate relief of symptoms when you

take it. So, I think it's almost counterintuitive that you would expect it to work within those 2 weeks.

DR. LAUGHREN: Except that in this condition, it appears to have a fairly rapid response compared to its rate of onset in depression.

DR. ALTEMUS: Do we know, though? Is it within 2 weeks? It was a month.

DR. TEMPLE: It works 3 weeks later.

DR. ALTEMUS: But the question is does it work in the first week. Is there any evidence of that?

DR. TAMMINGA: Your question is, does fluoxetine work in the first luteal cycle?

DR. ALTEMUS: No. It has to start if you start on day 14, would that --

DR. TAMMINGA: Oh, we don't have those data in front of us. The only data that was presented to us this morning was when the treatment was started in the follicular stage, yes, there seemed to be a clear response that first cycle. The major response really occurred.

DR. ALTEMUS: So, by then they've been on it for 3 weeks by the time they get to their symptomatic period.

DR. TEMPLE: And that's not from the antidepressant.

DR. ALTEMUS: Right;

DR. PARRY: On the visual analog scale data, how soon do the ratings start going down?

DR. JUDGE: All patients starting dosing on the first day of their cycle, first day of menses, and what we saw for all those studies was that at the first cycle, which is usually roughly around 2 weeks after beginning of dosing, 2 to 3 weeks, that they did have a significant effect. Remember, the visits were done from cycle to cycle and the patients were seen follicular, so I can't answer that question whether at the first week, if we looked at the first week, whether there would be significance at that point.

DR. PARRY: But the VASs were done daily.

DR. JUDGE: That was not analyzed for purposes of today.

DR. TAMMINGA: I think we'll just have to wait till your luteal dosing studies are finished and look at those data.

If there aren't any more comments on the intermittency of dosing, I'd like to direct our attention to the use of oral contraceptives along with fluoxetine in this condition. The oral contraceptives were excluded from this study. They're certainly commonly used in the age range of people who would be treated for this disorder.

Do oral contraceptives do something promising

in this disorder and would we say that fluoxetine is both effective and safe in PMDD people who are using oral contraceptives?

DR. PARRY: I think one of the reasons obviously that oral contraceptives are excluded is because oral contraceptives in and of themselves can induce an atypical depression. They also have physical side effects. So, they have to be excluded. I just don't think we have the data to answer whether they can be used concomitantly.

If you look at what predicts onset of premenstrual dysphoric disorder, if you look at clinical demographic features, many women have previously been on oral contraceptives and some had dysphoric mood symptoms in relationship to that. Is that data different?

DR. TAMMINGA: So, PMDD does occur in women who use oral contraceptives.

DR. THYS-JACOBS: Yes, it can definitely occur. In fact, the evidence is either way. Some of the studies show that the OCPs can actually increase affective symptoms and diminish physical symptoms. What the data is on the SSRIs in combination with the OCPs I'm not sure.

DR. TAMMINGA: We saw some data this morning, not in PMDD, but in other treated populations, of oral contraceptive use along with fluoxetine, and the safety data looked with and without oral contraceptives looked

straightforward.

DR. ALTEMUS: And the response data too.

DR. TAMMINGA: Right, response data.

Dr. Winokur.

DR. WINOKUR: Yes. I would just reiterate I think thought Dr. Judge's review of these issues this morning was very on target. First of all, I think it would have been significantly complicating and confounding to have the presence of OCs in these studies, and then the second issue is potential risks of combining fluoxetine with OC use. I both agree that there's a pretty substantial database outside of PMDD for us to extrapolate to. I can't think offhand of any reason why we'd expect there would be different safety risk issues. I agree that the potential drug interactions, which are nontrivial with some drugs, are not, to my knowledge, a significant concern. I felt that that was quite thoroughly addressed in the presentation.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: It seems there are two aspects of these questions. One is to help the FDA write appropriate labeling, if this drug is approved, based on the studies that have been done. There have been no studies done, at least among the three we've been shown, in women on oral contraceptives. You might consider that you should then

write labeling saying that this shouldn't be used in women taking oral contraceptives because we have no evidence.

On the other hand, virtually every depression trial that I've ever run, or for that matter, almost any other trial, has excluded people who are suicidal, and we give antidepressants to people who are suicidal all the time. Most of the antipsychotic trials have excluded people abusing drugs, and we give antipsychotics to drug abusing psychotics all the time.

DR. TAMMINGA: Bob, we saw data this morning of fluoxetine given to women taking oral contraceptives.

DR. HAMER: But not for PMDD.

DR. TAMMINGA: Right, we didn't see PMDD plus oral contraceptives.

DR. HAMER: Right. But the point I'm trying to make with the discussion of suicidality and depression and so on is that that does not stop the FDA. The FDA does not then write labeling saying we haven't done clinical trials in suicidal people, so don't give the drug to suicidal people. They should sort of use the same kinds of judgments in this context too.

The other issue is whether to encourage or discourage, in further clinical trials or in other clinical trials, the use of oral contraception as an exclusion criterion. And I don't have any thoughts on that.

DR. TAMMINGA: A more naturalistic design.

Do you want to say anything about that, Dr. Laughren?

DR. LAUGHREN: Many parts of the population are left out of typical development programs. Now, hopefully what we see in a development program is that as you move from phase II into phase III, more heterogeneous populations are enrolled and you are including patients who have other disorders or taking other medications and so forth.

Really what we want a sense from the committee about on this issue is how important is this exclusion for this drug for this indication for labeling. It's likely if you think it's not a critical issue, that the extent of our modification of labeling -- we might say, in describing the clinical trials, simply that patients taking oral contraceptives were excluded. There wouldn't be any restriction on its use, simply a simple statement that that part of the population was excluded.

DR. TAMMINGA: I would feel comfortable with that, especially since we already have data in women with oral contraceptives, even though they don't have PMDD.

Any other opinions on this? Dr. Temple.

DR. TEMPLE: Just to launch an advertisement, I would say as a general matter, we agree with what was said,

that in phase III, as drug development progresses, exclusions should drop off, if possible, to nothing, and you should look at the consequence of the interaction, not avoid it. One of these days I'm sure we're going to write something to that effect, but I think there's a growing appreciation of that. In some areas, like exclusion of the elderly and things like that, there is considerable progress, but we all believe that should be much more general and that, in general, trials should include everybody who might get the drug.

DR. TAMMINGA: It's a good point to always make. I think I agree with you that it is becoming more widespread.

What I would like us to do is to proceed into a discussion of the specific studies that were presented. We addressed a lot of questions this morning to Dr. Judge and to the rest of the people in the sponsor's group about these studies, the size of the studies, the dropout rate, the single study that had a crossover design, the investigator initiated nature of the studies. I'd just like to open this phase up for some discussion of the committee and hear people's comments on any aspect of this that they think is important.

I bet Dr. Hamer could launch this part of the discussion.

DR. HAMER: Yes, and I'm going to launch it by saying that I'm really bewildered. I know how to behave when I look at a set of clinical trials submitted as part of an NDA whose purpose is registration, that the sponsor designed, managed, supervised with prespecified endpoints negotiated with the FDA. I know how to trust the results of those trials.

In a set of trials that was much more loosely, in some sense, organized and evolved, I'm not sure I know how to behave with these results. This is the intersection of science and regulation, and so it's not just a scientific interpretation.

For example, it's unclear to me how many other trials there are out in the literature involving fluoxetine and PMDD. I have actually been looking through the material and if it's in there, which it probably is, I just can't find it. But why these three trials that we're told about?

Again, in the usual NDA, there's half a dozen, a dozen, or whatever phase II trials that I don't pay any attention to because they were small and they were dose-ranging and all that sort of stuff. What I pay attention to is the negotiated-out phase III trials. Here I don't know what to pay attention to, and I don't know if there's stuff that I don't know about that I should be paying