attention to. So, I'm very bewildered.

DR. TAMMINGA: We're asked to pay attention to the three studies that were presented, 1, 2, and 3.

DR. HAMER: What we're actually asked is, is there evidence from adequate and well-controlled trials that the drug is safe and effective? I don't know that we're asked simply to attend to these three trials.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: Well, the point about there being perhaps many other trials that are negative is a good one, and I'm sure the sponsor has been through the literature and we can probably hear about that.

The question of relying on trials that were not supervised or conducted by a commercial sponsor, when those are submitted under NDAs, is not an infrequent one. There certainly is plenty of precedent for our approving a drug on the basis of a trial that wasn't conducted or supervised by a commercial sponsor who submits the application. We do require in those case, almost invariably, that we get the complete information, the protocol, and that the study be as well conducted and designed, prospective protocol, as if it were run by the company. So, there's certainly precedent for our relying on such trials if they're well done, if they're appropriately designed, and we have the data.

DR. TAMMINGA: Dr. Fyer?

DR. FYER: Yes. Could we address the other question? Because I'm just not familiar enough with the literature. Are there in fact other negative trials? And has the FDA conducted a literature search?

DR. TAMMINGA: We did actually see a slide this morning from Dr. Judge. Maybe you'd like to catch us up again.

DR. JUDGE: These are the other double-blind studies that have been conducted in PMDD for fluoxetine. Besides this, there are also a number of open studies which I won't show here.

For all of the other studies not part of the submission, there is no negative study for fluoxetine in PMDD. We've also attempted to try and find unpublished studies, obviously because there tends to be publication bias with respect to negative studies. We've also tried to look for negative studies with respect to fluoxetine in PMDD, and we could not find any as part of our attempts.

So, for example, Menkes was a study in New Zealand. Ozeren's study was a study in Turkey, and Wood and Stone were also studies in the United States of America. They all comprised patients with a diagnostic category of DSM-III-R and therefore of DSM-IV, as you heard earlier. The duration of the treatment cycles ranged from

2 to 3 cycles, and all utilized 20 milligrams daily. All were positive with respect to the efficacy of fluoxetine in PMDD.

What the open studies showed was further evidence for that for out longest, showing that perhaps fluoxetine is effective much, much longer out, and also the fact that when patients stopped treatment, even after several months, that there can be very quickly a reemergence of symptoms after stopping treatment. That's the summary of the open-label studies.

DR. TAMMINGA: Do you want to speak to why you chose the first three as part of your NDA?

DR. JUDGE: Yes, indeed. We attempted to find the data for all of the studies, but for these studies here, we were limited in terms of, first of all, access to that data, sometimes lack of cooperation from the site for whatever reason, and also sometimes for missing data, for example, substantial missing data that was available. So, we did attempt to go back to all of this data in order to provide a comprehensive listing. But this is the three that we felt were of adequate quality, controlled, and we had access to that data. We had investigator cooperation and we could show to you.

DR. TAMMINGA: Questions, comments for Dr. Judge? Yes, Dr. Temple.

DR. TEMPLE: When you say they were all positive, what do you mean, that they were in the right direction or that they attained nominal significance or what?

DR. JUDGE: All of these studies, the other ones listed here, for example, the two crossover and parallel design, with respect to the publication, the primary objective listed in that publication, there was significant evidence for fluoxetine with statistical superiority versus placebo.

DR. TAMMINGA: One of the things that we're used to seeing from data sets that don't have otherwise large safety databases is large n's. In this particular study, the n's are not as large as what characteristically we're used to seeing. We saw this morning the presentation of effect sizes, and the effect sizes were impressive. But still, the overall number of patients is not great.

Dr. Dominguez.

DR. DOMINGUEZ: Yes, not only the small n sizes in the other two studies, but the variability of the inclusion and exclusion criteria. For example, the use of a structured clinical interviews in some of the trials versus just the clinical interview to exclude Axis I diagnosis.

The failure to obtain a urine drug screen at

the beginning of the trial, knowing that benzodiazepines can be helpful for these individuals, and knowing that at least at some time during the trial, a number of patients did report using benzodiazepines at times, but that was just a listed report. One cocaine overdose.

Again, not knowing the race and ethnic background of the individuals in the larger trial. Not knowing what previous treatment they had had for PMDD and what had worked and what had not worked.

So, it's the variability in inclusion and exclusion criteria which makes this set of studies much harder to interpret.

DR. TAMMINGA: To some extent, you're really agreeing with Dr. Hamer, that these are studies that are more investigator initiated than drug company initiated.

DR. DOMINGUEZ: And they're valuable, but again that variability one has to always adjust for.

DR. TAMMINGA: One of the things that I'm wondering how to measure is the effect sizes that were reported in studies. I wouldn't mind hearing from some of our consultants about that. It would make me think that there is some consistency to drug response despite all the variability that you're bringing up, that there's a consistency and a rather sizeable drug response in order to get effect sizes like that:

DR. PARRY: Well, I know when the DSM-IV was putting together the database, we looked at different calculations of effect size, and no matter which way you looked at the data, you pretty much got the same phenomena. So, I think that it has been a pretty robust response no matter which technique has been used.

DR. THYS-JACOBS: Effect sizes actually varied from study to study. Most people use a 50 percent response as a real response rate. Some studies in PMDD and PMS actually looked at the visual analog scale scores and looked at the difference. Not all studies actually looked at effect size.

DR. TAMMINGA: Any more discussion about the designs of the studies that we had presented? Dr. Temple?

DR. TEMPLE: Well, I'm a little curious about some of the conversation. Obviously, I think Dr. Hamer shows great wisdom in thinking that the only really credible trials are the ones we help design.

(Laughter.)

DR. TEMPLE: And it's hard to disagree with that.

(Laughter.)

DR. TEMPLE: At least sometimes we've had the view that studies that use somewhat variable entry criteria and yet still get the same result add to the database, and

that replicating the identical finding over and over again is perhaps somewhat less interesting than replicating it in a variety of settings. I guess I think I at least partly believe that, but I'd be interested in the discussion.

Of course, in general, the more medicines that people might be taking that you don't know about, the more they interfere with showing anything. So, in a sense, even that-lack of knowledge is a sign of robustness, although also simultaneously makes you nervous.

But I'd be interested in a little more of that. The fact that they were different environments I wouldn't say discourages me too much.

DR. TAMMINGA: Slightly more naturalistic one might think.

DR. TEMPLE: Well, and there was a certain trend in that direction.

DR. TAMMINGA: Crossover design, Dr. Hamer?

DR. HAMER: It's another reason to be skeptical. Crossover designs really are a can of worms because they're complicated by carryover effects, sequence effects, a variety of things like that. In this particular design, the fact that with a drug whose principal active metabolite has a half-life that's probably at least 2 weeks and then to have only one menstrual cycle in the middle as your recovery, when, in fact, at least in depression we

know that fluoxetine requires a number of weeks to even start working and furthermore, a number of weeks to wash out, is troublesome.

On the other hand, the statisticians and Dr. Judge were absolutely right. In this particular trial, whatever carryover effect there was would have tended to inhibit the ability to show a difference between fluoxetine and placebo rather than exaggerate it, and thus the fact that they did, indeed, show a difference is reassuring. But I still don't like them.

DR. TAMMINGA: I would agree really with Dr. Temple about the what I would call more naturalistic design of this group of trials and still seeing a robust drug response is impressive from my point of view.

I was troubled, if you will, to use your word, Bob, about the low n. But then I sort of looked back at the data when I was studying it before the meeting. Although the n is 19, there's really 2 or 3 cycles per person in order to add up, if you will. So, if I were doing, for instance, rat studies, we might count that as an n of 28 or something like that. We have multiple repetitions in the same person of this phenomenon we're observing.

DR. HAMER: They're not independent of one another.

DR. TAMMINGA: Excuse me?

DR. HAMER: They're not independent of one another, the multiple observations from the same rat or the same person. So, they're not each another degree of --

DR. TAMMINGA: Oh, for sure. But they're a within-subject replication which is impressive.

Dr. Winokur.

DR. WINOKUR: I just wanted to ask Dr. Hamer a follow-up question on his comment to help me understand better. I understand the general reasons for caution about interpretation of crossover studies, but it struck me in initially looking at the data that in this case with the unique feature of this disorder with the repetitive pattern with what struck me as being a fairly solid design of starting with placebo and fluoxetine and then going the other direction and the results tending to support an impact of active drug treatment in whichever sequence, with all of that sorting out, that actually seems to be a persuasive argument. So, I'm wondering in this case whether that's a particularly appropriate use of this design, or am I statistically not tuning into something?

DR. HAMER: No. In this case, in some sense, the things that could have gone wrong with this crossover design would have tended to obscure the drug-placebo difference. So, the fact that there still was one was

nice.

But on the other hand, there are plenty of other reasons not to like crossover trials in general and including prospectively before you did this, this one. One is the difficulty of having a long enough washout period in the middle to know that you really are washing out not just the drug but the effect of the drug because, for all we know about things like receptor proliferation and those sorts of things, there may be a whole lot of things that need undoing over a long period of time.

The other is that if anything goes wrong in a crossover design, like you have dropouts partially through, so you don't wind up with people doing the entire, full design, you may wind up with only the first period analyzable, in which case you now have simply a parallel group design with a tiny n.

Again, in this case, it's reassuring that they analyzed just the first period data and found a significant difference because, if you want to, you can sort of disregard the entire crossover part of the design, and you still have a supportive study.

DR. TAMMINGA: Any other comments or concerns or extended discussions people would like to have about the design of the protocol of the data sets that were presented to us?

(No response.)

DR. TAMMINGA: Any other issues that people would like to bring up about the data that were presented to us that speak to the question about efficacy or safety?

DR. COOK: I have one comment, and that is this disorder would presumably start at menarche and they limited the beginning to age 18. Now, it would be one thing to suggest this will never be given to someone under 18, but Dr. Parry has said that this is a sometimes progressive disorder in which it's not clear why one would withhold treatment until age 18. Obviously, these are challenging risk-benefit issues, but I don't see justification for not having studied adolescents, recognizing that they have reasonable expectation that there will be off-label use in adolescents.

DR. PARRY: Well, except that generally physical symptoms predominate during adolescence and you don't see the mood symptoms until -- in most studies, the average age is 30s. Between like 30 and 38 is the mean age of symptoms, and they may have been there for 5 years. But you usually don't see severe mood symptoms during adolescence.

DR. HAMER: Speaking as the father of three people who used to be adolescents, I would say that it would be pretty hard to tease out mood swings due to

premenstrual dysphoric disorder from the normal mood swings that are part of adolescence.

DR. PARRY: That's why you need to 2-month prospective documentation.

DR. COOK: I have to object to that one because the same thing was said about major depression in adolescence and even pre-adolescence. So, particularly because you have the timing with the menstrual cycle here, you could make that distinction.

But I'm impressed by the age of onset except weren't there a lot of 18-year-olds? In other words, it seemed to me there were some young adults being treated, and the 18-year-old cutoff was arbitrary.

DR. GELLER: I just wanted to say, as the other child psychiatrist here, that we are beginning to tease out mood disorders from normal adolescents. I think this goes back to the comments that Dr. Winokur was making that the labeling here has to really stress differentiating this from rapid cycling mood disorders. I think without separate study of the adolescent population in this regard, that's going to be hard to do because a common presentation of bipolar disorder in this age group is to rapidly cycle. A lot of those people come in clinically and the parents tell you their child has a menstrual disorder. I think this is just an age range that is ripe for study and for

separate study.

DR. TAMMINGA: So, the committee would certainly like the sponsor to understand that we see studies of this disorder and this drug in adolescents as important.

DR. GELLER: Yes.

DR. TAMMINGA: Do you want to say that more strongly, Dr. Cook?

DR. COOK: I wanted to raise the issue. I hear now age of onset is different. My concern is exactly what Dr. Geller says. In largely primary practice, will this be used off label for this. So, on the one hand, it should be studied. Until it's studied, I think there should be strong cautions about its use off label.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: Yes. I'll just let you know. We now have regulations that require sponsors to study drugs in a pediatric population, and they can try and make the case that for any of the particular subpopulations, the condition doesn't exist. But to the extent that it does exist, they're required to do it, and they have to make a commitment. If those data don't come in with the specific application, they may have to make a commitment that they will do it and time lines are imposed and all that.

DR. TAMMINGA: So, we can be confident that

you'll receive those data.

DR. KATZ: At some point.

DR. TAMMINGA: Yes, Dr. Geller.

DR. GELLER: I think this has to be built in in some way either to post-marketing surveillance or people applying for other kinds of funding to look at the off-label use in the younger population because from what we're seeing as child psychiatrists, it's going to be used when other diagnoses are more likely.

DR. TAMMINGA: Yes, Dr. Dominguez.

DR. DOMINGUEZ: Another area for further investigation that we have heard very little from this application is issues of predictors of response. For example, I think the agency may want to look at certain associated features of PMDD that, although may occur rarely as part of the disorder, may serve as predictors of response, for example, psychotic-like features during the worst time in the luteal phase, suicidality, and concomitant substance abuse.

The issue of adding the feeling of being overwhelmed and out of control to some of the rating instruments I think would be important as well because it has been my experience, at least clinically, that you do find a set of patients with this disorder where that is the prominent feature, along with the effect of instability

that they present with, that is the most disturbing to them. Yet, I don't think that was probed at all in the data that was presented.

DR. TAMMINGA: Dr. Fyer.

DR. FYER: I just want to make two sort of comments that concern me, given the small sample size. That has to do with what's going to happen if and when this whole thing takes place. It seems to me there are two issues.

One is that the sponsor has gone over this whole issue about safety. I think that generalizing to the Prozac or fluoxetine database, it's sort of clear that we aren't going to have serious, unexpected things given the age and sex distribution of many people on Prozac is the same as for this requested indication.

On the other hand, the idea this is a chronic disorder, there's a high relapse rate, people are going to take this for a long period of time, I would really feel a lot more comfortable if there were a serious commitment from the sponsor to look carefully at quality of life issues. For example, in the FDA's review, it was pointed out that a certain subset of women gain weight continuously on this. That can be a serious health issue as well as a quality of life issue. It would be nice if systematic studies addressed exactly how can people deal with this and

are there alternative strategies that might help that kind of thing, as well as issues of sexual desire.

The other thing is that it would be in the sponsor's power, if the drug were to be granted an indication and marketed, to do post-marketing studies that would actually look at how the drug was being used and to see if there were consequences that might not be in the best interests of women in this country. I would think that if an indication were to be granted, that a request or a requirement from FDA that such work be done, given the widespread nature of syndromes related to this requested indication, would really be very helpful.

DR. TAMMINGA: Dr. Geller.

DR. GELLER: This is another child psychiatrist type comment. Can the labeling include something to the effect that if underlying conditions are found, they should be treated before treatment is initiated just for PMDD?

DR. TAMMINGA: This is a question to the people who design the labels.

DR. GELLER: Well, it's not looking for a specific answer, but that kind of thinking, that at least it would encourage people to think if they're going to give it off label. Dr. Hamer was just asking me, who's going to give it to the adolescents? Is it going to be the gynecologist or the pediatrician? Pediatricians are now

giving lithium. They won't think anything of giving Prozac for a menstrual disorder. Perhaps if there were something in the labeling pointing out that underlying conditions should be treated first, we might head off some of the --

DR. TAMMINGA: Well, certainly in the studies that were presented, only people who lacked other conditions actually got into the study. So, you're really suggesting that something be included in labeling that's consistent with the study data that were presented.

DR. GELLER: Right.

DR. KATZ: Certainly there's precedent for putting statements in labeling about it's off-label use, but usually when there's an affirmative finding that there is a safety problem in whoever those people are or there's evidence that it doesn't work in those people, those are the two circumstances I can think of where we 'put statements in labeling about off-label use.

DR. GELLER: I wasn't suggesting this is off-label use. I just meant for all age groups that there be some statement that emphasizes that we really don't have data on what happens if you treat an underlying condition first. As usual, the sample that was studied was relatively pristine in terms of comorbid disorders that occur commonly when you have PMDD. I'm going back again to Dr. Winokur's emphasis on people who may be having a

bipolar depression, getting the drug for that and then having an exacerbation of their bipolar phase.

DR. WINOKUR: Actually, since you mentioned that again, let me make sure. That was only part of what I said, not to have the other part left out. I'm also concerned about inadvertently discovering a new phenomenon, which is people who don't have formally bipolar disorder that is just not detected, but have a different form of cyclic mood disorder, namely PMDD, in whom a small subset but not yet detected or appreciated might be stimulated in the hypomanic or manic direction by a drug like fluoxetine. Again, we don't have any data yet to suspect that to be the case, but I think that from other clinical experiences, that's a lesson that we've learned to be very cautious about. I think if it is going to get out there more widely in a broader population, that's one area that we don't really have adequate data to judge in my opinion.

DR. TAMMINGA: Dr. Parry.

DR. PARRY: There's just one safety issue, and this is not what was brought up this morning. But in reviewing the materials I was sent, I just thought the description of the use in pregnancy could have been more specifically delineated. For example, there's the Pastuszak study and the Chambers study. Though there's no major teratogenic effects, the fact that mothers who are

taking fluoxetine, their children are in the intensive care unit and they had more respiratory distress and lower birth weight and that kind of thing, I thought for safety reasons should be given attention.

DR. TAMMINGA: Except that PMDD is not a disorder that occurs in pregnancy, so there would be no reason to treat it during pregnancy.

DR. PARRY: Yes, but you have to address that in a labeling issue, and if a woman becomes pregnant and she's on it, that's part of the presentation.

DR. TAMMINGA: Any more comments of any kind about the issue in front of us? Dr. Katz?

DR. KATZ: Yes, I have another question before you vote. It's sort of under the heading of maybe a theoretical labeling question again. You know we're obviously very interested in labeling, and you may just advise us to do the usual good job that we do. And I appreciate that in advance.

(Laughter.)

DR. KATZ: But I'd just be interested in some of your thoughts on the following.

Suppose that you have concluded or do conclude that there is evidence of effectiveness. It's possible I suppose to see that effectiveness as just really fluoxetine's antidepressant effect, and that in some sense

it could be considered a global antidepressant in that it has been studied up till now in major depressive disorder. Now it's being studied in a considerably different disorder but that has primarily an affective component. And right now the drug is approved as an antidepressant and then the labeling describes in whom it has been studied, major depressive.

One theoretical option, I suppose, for labeling would be to leave the indication as an antidepressant and then list after what's currently listed, which is it's been studied in major depressive disorder, and now say, well, it's also been studied in another sort of depression-like syndrome, as opposed to giving it its own PMDD claim. I just wonder what people think about that.

DR. PARRY: Well, I think it's important to recognize that premenstrual dysphoric disorder is categorized as a major depressive disorder, N.O.S.

DR. KATZ: Well, that's sort of what I'm asking. In other words, again if you find it's safe and effective, we could choose to label this as a specific treatment for PMDD in addition to its current indication, or we could subsume under its currently existing indication. That's the question I'm asking. I'm interested in your views on that.

DR. TAMMINGA: Dr. Geller.

DR. GELLER: Just educate us. What would be the down side of doing that?

DR. KATZ: Well, it would imply a couple of things. Number one, that PMDD is a type of depression, a type of depressive disorder, and it would imply that the drug is sort of a global antidepressant and it works in any setting in which a patient happens to be depressed, whether it's major depressive, whether it's a cyclical entity, perhaps even others which haven't been studied.

So, I don't know that there's a down side or an up side. We are going to have to deal with this question, and I'm just interested to know what people think.

DR. PARRY: I can just see, women who have premenstrual dysphoric disorder often don't like to acknowledge that this is a major depression. I'm just trying to think ahead about the potential consequences.

On the other hand, if you just propose it specifically for premenstrual dysphoric disorder, I guess my concern would be that any woman with any kind of minor, cyclic physical symptom that may or may not be related to the menstrual cycle might see this as a panacea.

DR. TAMMINGA: Dr. Laughren.

DR. LAUGHREN: Except that in writing labeling, we would rely very heavily on the diagnostic criteria for PMDD to describe the type of patient who would be a

candidate, including functional impairment as part of that. So, we would work very hard to avoid that possibility.

DR. PARRY: Yes. I'm just thinking of the potential abuses that may occur irrespective of that.

DR. TAMMINGA: Dr. Cook?

DR. COOK: Yes. I would be much more comfortable with a PMDD labeling. I think that's what we were-here to discuss, and I think that actually there's probably confusion out there in terms of PMDD being just depression. I thought there was data presented -- and certainly the epidemiology that isn't all that was presented today -- to suggest that this is a distinct disorder. This would not be like saying it works for melancholic depression as well as other depression. So, I think this would be reasonable with the caveats that this is not PMS treatment, but PMDD, to have it distinct.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: I think we've heard a lot of comments from the experts and from the general committee that recognize PMDD to be a discrete and recognizable, diagnosable entity. I think increasingly in our field and in communication to more family practitioner types, we've been trying to emphasize precision or care in diagnosis prior to treatment. So, I think that going from data and having discrete, delineated syndromes as a guide to

treatment rather than encouraging the older pattern of very broad spectrum triggers for treatment is really something we're trying to encourage. I would much more see the specific indication as being in that dimension.

DR. TAMMINGA: Dr. Fyer.

DR. FYER: I agree with what has been said about the diagnosis.

I think that there's an additional educational issue which I think is positive, but I am concerned about what Dr. Parry raised. I have a question for the FDA people, and that is, to what extent is it within your power, in addition to just labeling about PMDD, to actually structure interactions between pharmaceutical representatives, et cetera so that there is real education about this sort of limitation, as opposed to something that's on a package label someplace that a lot of people don't read?

DR. LAUGHREN: The promotion has to be very closely linked to what's in the label. So, to a great extent, that does control the level of promotion that can go on outside of labeling.

DR. FYER: Somehow, though, we all know that in the long run there seems to be an enormous amount of what's called off-label usage, and maybe again something that could be considered is some post-marketing survey aspects

to see because I think there is a widespread potential here for something that I don't think anybody is particularly interested -- at least people in medicine probably not interested in having unnecessary expense and side effects and maybe missing things that would be treatable by other perhaps psychotherapeutic interventions.

DR. LAUGHREN: Again, I share that concern. As I said earlier, we'll go to great lengths to try and define the population that we think are candidates for this treatment. Beyond that, it's hard to know what FDA can do. We don't, of course, regulate the practice of medicine, so we can't control off-label use in that sense. But we will try and write labeling that directs clinicians to what we think is the target population.

DR. FYER: You could possibly also ask the sponsors to participate in some post-marketing assessment of exactly what's going on.

DR. KATZ: I don't know if we could, and even if we could -- let's assume we learned that there was a lot of off-label use going on. It's hard to know what we would be able to do about it.

DR. FYER: Publish it so that people are aware that that's going on --

DR. KATZ: Well, a lot of off-label use is published. People think it's a good idea.

DR. FYER: Some of it is.

DR. KATZ: Well, right, right.

DR. FYER: Yes, and some of it isn't.

DR. KATZ: We could even in labeling put, just as another thing that's possible to do, a patient package insert in there which also tells the patient that this is for PMDD. It's not for mild symptoms of PMS. Now, whether or not that's actually going to affect people's behavior is another patient, but you can attempt to inform the patient as well as the prescriber.

DR. FYER: I mean, there is a trend, especially with the Internet, for increasing amounts of consumer sort of self-awareness and stuff. So, something like that might in fact be useful.

DR. TAMMINGA: Dr. Temple, did you want to log in?

DR. TEMPLE: Well, do I recall correctly that this will have special packaging, a different name, et cetera?

That really does open the possibility of a patient insert that is targeted to the population. It reminds them that they should think about whether they want to be on a chronic drug and that their symptoms are severe enough to warrant it. That very situation is one of the conditions in which we believe patient labeling is

important, where there's a decision that the patient really needs to participate in actively. In this case, you don't have to label all of the uses of Prozac. You can just label this one perhaps.

So, we'll think about that. Special packaging and labeling is a point of some controversy internally I should tell you.

DR. TAMMINGA: Unless there's further discussion, I would suggest we move ahead to a vote. Although we've certainly appreciated all the comments of the consultants, the consultants won't vote on the final efficacy and safety questions.

So, the first question that the committee will want to vote on is, has the sponsor provided evidence from more than one adequate and well-controlled clinical investigation that supports the conclusion that fluoxetine is effective for the treatment of premenstrual dysphoric disorder?

I think we just ought to go around the room. Maybe we'll start with you, Dr. Dominguez.

DR. DOMINGUEZ: I believe that there are some limits to the generalizability of the data that was presented with respect to race, with respect to ethnic groups. Essentially the patient samples that we have been presented today are in non-minority whites, and it appears

from the sample that clearly the drug is effective for the indication that is proposed. I think that this is a clearly distinct disorder. So, it should be labeled as such for this disorder.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: As uncomfortable as I am with the set of studies that wasn't generated in the usual way, yes.

DR. TAMMINGA: Dr. Geller.

DR. GELLER: Yes, with the proviso that the FDA do its usual outstanding job of writing the labels to take into account the discussion.

DR. TAMMINGA: Dr. Cook.

DR. COOK: Yes.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: I vote yes.

If I can editorialize for a minute, I'm incredibly distressed about the circumstances of the second positive study that we had to consider with the investigator unilaterally interrupting the study. I realize that that was not at all Lilly's doing. I think the data that we are left to consider are overall convincing enough. But I think it's an extremely dismaying circumstance, and I think it's the kind of thing that really can interrupt the progress of the kind of science that we need to make these kinds of decisions.

DR. TAMMINGA: Dr. Fyer?

DR. FYER: I would vote yes with two provisos. One, Dr. Geller's and that be taken seriously. I'd like to say that I also found this circumstance distressing and I found the sponsor's presentation of the data from that trial distressing. I would hope that in the future such things will be dealt with in a much more straightforward fashion in sort of due respect to the members of the committee and the public.

DR. TAMMINGA: And I vote yes as well with many of the same caveats as people have talked about before, but having some interest in the more naturalistic kind of data that we saw today.

The second question. Has the sponsor provided evidence that fluoxetine is safe when used in the treatment of PMDD?

Dr. Dominguez?

DR. DOMINGUEZ: Yes.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: Yes, attending in particular to the sorts of things Dr. Winokur has talked about.

DR. TAMMINGA: Dr. Geller.

DR. GELLER: Yes.

DR. TAMMINGA: Dr. Cook.

DR. COOK: Yes.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: Yes.

DR. TAMMINGA: Dr. Fyer.

DR. FYER: Yes.

DR. TAMMINGA: Dr. Tamminga, yes.

I think we've had a day and an afternoon where we've discussed an important issue, both an indication and a drug. We've discussed perhaps, at least for our group, a new style of data, if not necessarily for groups in general. And we've taken a vote and concluded the meeting.

Thank you all very much.

(Whereupon, at 3:15 p.m., the committee was adjourned.)