FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

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ON BEHALF OF ELI LILLY AND COMPANY:

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RAJINDER JUDGE, M.D.
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MEIR STEINER, M.D.
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ALSO PRESENT:

SHERRY A. MARTS, PH.D.

C O N T E N T S

NDA 18-936(S), Prozac (fluoxetine hydrochloride)
ELI LILLY AND COMPANY
Indicated for the Treatment of
Premenstrual Dysphoric Disorder

P R O C E E D I N G S

(8:09 a.m.)

DR. TAMMINGA: I'd like to call this meeting to order. This is a meeting of the Psychopharmacologic Drugs Advisory Committee, and we've gathered to discuss an application, fluoxetine hydrochloride for the treatment of premenstrual dysphoric disorder.

First, I'd-like to have everybody at the table go around and introduce themselves so that the committee can refresh our memory with each other. Dr. Dominguez, do you want to start? I should remind people to talk directly into the microphone.

DR. DOMINGUEZ: My name is Roberto Dominguez from the University of Miami. I'm Professor of Psychiatry.

DR. ALTEMUS: I'm Margaret Altemus. I'm a psychiatrist at Cornell Medical College.

DR. HAMER: I'm Robert Hamer. I'm a statistician at Robert Wood Johnson Medical School.

DR. GELLER: Barbara Geller. I'm a child psychiatrist, Washington University in St. Louis.

DR. THYS-JACOBS: I'm Susan Thys-Jacobs. I'm the Director of the Metabolic Bone Center, St. Luke's Roosevelt Hospital and Columbia University, New York.

DR. COOK: Ed Cook, child psychiatrist, University of Chicago.

DR. PARRY: Barbara Parry, Professor of Psychiatry, University of California, San Diego.

DR. TAMMINGA: I'm Carole Tamminga. I'm a professor in the Department of Psychiatry at the University of Maryland.

DR. TITUS: I'm Sandy Titus. I'm with the FDA, the Advisors and Consultants Staff.

DR. WINOKUR: Andy Winokur. I'm professor in the Department of Psychiatry at the University of Connecticut Health Center.

DR. FYER: Abby Fyer, psychiatrist at Columbia University in New York.

DR. CHEN: Richard Chen, statistical reviewer, FDA.

DR. MOLCHAN: Susan Molchan, medical reviewer, FDA.

DR. LAUGHREN: Tom Laughren, team leader for Psychopharm at FDA.

DR. KATZ: Russ Katz, Director of the Division of Neuropharm, FDA.

DR. TAMMINGA: We're waiting for our consumer representative, Gaurdia Banister.

Sandra?

DR. TITUS: I'm going to read the conflict of interest statement regarding this meeting.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and the information provided by the participants, the agency has determined that all reported interests in firms regulated by- the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

A waiver has been granted to Dr. Robert Hamer. A copy of this waiver statement may be obtained by submitting a written request to FDA's Freedom of Information Office located in room 12-A30 of the Parklawn Building..

In addition, we would like to disclose for the record that Drs. Andrew Winokur and Carole Tamminga have unrelated interests in Eli Lilly which do not constitute financial interests within the meaning of the 18 U.S.C. 208(a) rule, but which could create the appearance of a conflict. The agency has determined, notwithstanding these interests, that the interests of the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned.

In the event that the discussions involve any

other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. TAMMINGA: Dr. Katz is the Director of the Neuropharmacological Drug Products Division.

DR. KATZ: Thank you. I'll just be very, very brief. I just really want to extend my personal welcome to the committee and thanks for the work you've done prior to the meeting and for the work you're going to do today.

I particularly want to extend a welcome and thanks to our three invited consultant experts, Dr. Altemus, Dr. Thys-Jacobs, and Dr. Parry, who have been gracious enough to come and help us out with their expertise.

Once again, you know we have asked you here to advise us on an application for a drug to treat an indication for which there are no approved treatments. So, the application presents some generic problems about how to study this indication as well as, we think, interesting

data-specific and application-specific questions.

So, I really just want to say thanks for coming. We look forward to an interesting discussion. I'm sure it will be, and with that, I'll turn it back to Dr. Tamminga.

DR. TAMMINGA: Thanks, Dr. Katz.

Dr. Laughren will begin now with the FDA overview of the issues.

DR. LAUGHREN: Good morning. I'd also like to welcome the committee back here.

As Dr. Katz mentioned, we're going to be focusing today on this application for fluoxetine in the disorder of premenstrual dysphoric disorder, but as Dr. Katz mentioned, given that there are no regulatory precedents for this indication, we would like to have some general discussion about this entity as an indication. Following that, we will have some specific questions about this application that we'd like to have discussed, and finally, as always, at the end of the day, we'll want you to vote on specific questions of safety and effectiveness for this application.

Now, whenever we consider a new indication, we like that indication to have some acceptance in community. We like it to be reasonably well-defined, and we like there to be some reasonably well-accepted diagnostic criteria.

Now, PMDD of course is mentioned in DSM-IV, but one potential issue for discussion is the fact that rather than being in the main body of DSM-IV, it's in an appendix. So, we probably ought to have some discussion of what the relevance of that is.

Secondly, as defined, PMDD has a lot of affective features, and so another question that naturally comes up is whether or not this is distinct from other disorders that are characterized by affective symptoms, such as, for example, major depressive disorder.

A third question that comes up is what is the relationship of PMDD to the broader category of PMS. Some have suggested that this is a severe subtype of PMS, and I think that merits some discussion.

Now, one issue which is really not the focus of today's meeting, but it would be useful to have some discussion on, is this question of whether or not this broader category, PMS, is a candidate for a new indication. The reason I ask that is that, as you are well aware, there are many companies who are interested in looking at this category, and so even if you were to accept PMDD as a reasonable candidate for a new indication, one question is whether or not this broader category of PMS would be a candidate for an indication.

Next I want to focus on some specific questions

that we'd like to have addressed with regard to this application. One issue has to do with the fact that the focus in these studies supporting this claim was focused primarily on affective symptoms as part of this larger syndrome. For example, in study 19, the visual analog scale, although it included 7 items, the focus was on the 3 mood items, and similarly for study 22, a 16-item visual analog scale, there was a focus on the mood-4. So, one question is whether or not it's appropriate to focus on that subset of a larger scale. In general, the issue is whether or not one should focus on a subscale when one has an instrument that's focused on a broader syndrome.

Ordinarily in psychopharm, for example, in depression or schizophrenia, in choosing a primary endpoint, one would focus on the total scale, such as the HAMD or the PANSS or the BPARUS. So, that's another question, whether or not these should be the primary outcomes in these trials.

Again, if one -would accept those as primary endpoints in those trials, what relevance, if any, would that have for the way the claim should be stated? For example, should the focus be rather on the total syndrome, should it be on the affective symptoms of PMDD?

Now, another issue that comes up is the manner of dosing. In this program, of course, with fluoxetine,

the dosing was continuous throughout the cycle. I'm sure you're aware of reports in the literature for other SSRIs where, rather than continuous dosing, dosing was during the luteal phase and, at least from those reports, appeared to show some benefit. So, the question is, what is the relevance from a regulatory standpoint of these different possible dosing strategies? Would that have any relevance for us in making a regulatory judgment about this application?

Another feature of this program was the' exclusion of patients who were taking oral contraceptives. One can certainly understand the rationale for doing that. There is some literature suggesting that oral contraceptives may in themselves have some benefits in the symptoms of PMDD. However, The impression one gets is that the data are not entirely consistent, and it may be that there's a population of patients who, even though they are taking oral contraceptives, still have PMDD. So, the question then is whether or not fluoxetine would have any benefits in that population that was excluded from these studies.

Similarly, one might have a question about whether or not fluoxetine has been shown to be safe in a population of patients taking oral contraceptives.

Another issue, as was the case last month with

PTSD, is that this program is relatively small in terms of the safety exposure. Of course, there is a substantial body of systematically collected data on patients taking fluoxetine for other disorders, and so again, a question as to whether or not one can extrapolate from that larger database to this population in terms of safety.

Another issue that also came up at our last meeting on PTSD is the question of the appropriateness of a crossover trial for a chronic psychiatric disorder. Now, we had that discussion last month, and everyone I think pretty much agreed that for that disorder, a crossover trial would not make much sense. Now, this is also a chronic disorder, but it has some unusual features that may lend itself to this design. In particular, there's a very predictable cyclicity with patients returning to baseline during every cycle. So, again, I'd like to have some discussion of whether or not that design is appropriate for this drug in particular, but also in general for this condition.

Now, this list of questions was not intended to in any way limit your discussion. Clearly, if you have any other issues that you think are important to discuss, please bring them up. This will be helpful to us not only in reaching a judgment about this application, but again, as you know, there's interest more generally in developing

drugs in this area. So, it would be helpful to us in advising sponsors on other development programs and then ultimately in making judgments about applications that we expect in the future.

As I said, at the end of the day, we'll want you to vote on these two questions. Number one, has the sponsor provided evidence from more than one adequate and we-ll-controlled investigation that supports the conclusion that fluoxetine is effective for the treatment of premenstrual dysphoric disorder? And has the sponsor provided evidence that fluoxetine is safe when used in treatment of this disorder?

And I'll stop there.

DR. TAMMINGA: Thank you very much, Dr. Laughren. You've done a good job in laying out the pivotal questions for the committee to consider.

But the next thing that we'll do is actually hear from Lilly in their presentation of the data on fluoxetine in the treatment of premenstrual dysphoric disorder. I'll turn this over to Dr. Gregory Brophy who will take charge of the Lilly presentation. Thanks.

DR. BROPHY: Good morning. On behalf of Eli Lilly, I'd also like to welcome you and express our appreciation to the committee for their contributions today, as well as for allowing us the opportunity to

present data substantiating the safety and efficacy of fluoxetine in the treatment of premenstrual dysphoric disorder.

As my colleagues will elaborate, PMDD is a serious disorder, one that can be clearly distinguished from other depressive disorders. It's also a disorder associated with significant morbidity as its symptoms characteristically can adversely affect the functioning, particularly the social functioning, of its sufferers.

I'd like to introduce our two primary speakers this morning. They are Dr. Jean Endicott. Dr. Endicott is the Professor of Clinical Psychology within the Psychiatry Department at Columbia University. She also serves as the Director of the Premenstrual Evaluation Unit at Columbia-Presbyterian Hospital. Jean has a longstanding clinical trial and clinical experience in this area as a PMDD expert. She'll focus her discussion today primarily on a lot of background information on the disease itself, in particular diagnostic criteria classifying as PMDD.

Our second presenter will be Dr. Rajinder Judge. Dr. Judge is the Medical Director within Lilly Neurosciences. Dr. Judge's presentation will be primarily on the clinical trials themselves, particularly focused on outcome measures, as well as the results of those studies, demonstrating the activity of fluoxetine in this disorder.

I'd like to ask, if possible, that since both of these presentations build upon each other, that if we could hold most of the questions until the completion of Dr. Judge's presentation, other than clarifying questions, I think some of the questions may well be answered in Dr. Judge's presentation.

In addition to these two presenters, we're also honored to have another PMDD expert and one of the principal investigators for the largest trial that Dr. Judge will describe, Dr. Meir Steiner. Dr. Steiner is Professor of Psychiatry and Behavioral Neurosciences at McMaster University and will also help us address questions this morning.

With that, let me turn the podium over to Dr. Endicott.

DR. ENDICOTT: Today I'm going to be focusing on the menstrual cycle and a condition that is exquisitely entrained with phases of the menstrual cycle, both the onset and the offset of the condition. The symptomatic phase is during the late luteal phase of the menstrual cycle, the period after ovulation. In some women, the symptoms start earlier, but the most severe symptoms are seen during this premenstrual or late luteal phase of the cycle.

After the onset of menses, the women, within a

couple of days, often the first day of the onset of menses; become asymptomatic. The syndrome, the disorder, goes away, and during particularly the mid-follicular phase of the cycle up to the time of ovulation, they're essentially symptom-free. This is a unique feature of this condition among the mental disorders.

Now, this is not a new condition. It is not something that we have discovered in the 20th century. Even in ancient history, there was literature that described severe changes in mood behavior that occurred just prior to the onset of menses. It was mentioned in early Greek literature that some women had a delay of menses and that pregnancy would be a cure for it, which is rather interesting.

By the 1930s, the term "premenstrual syndrome" was coined and was used to describe problems experienced by 15 women, and it was described very well. The description clearly fits the current diagnostic criteria by Dr. Frank in the Archives of Neurology and Psychiatry. Between ancient history and the 1930s, there were other mentions of severe problems with mood and behavior prior to the onset of menses in the medical literature, but he coined the term "premenstrual tension syndrome."

A great deal of work was done in the 1930s, 1940s, and 1950s, and by the 1950s, the term "premenstrual

syndrome" came into more common usage in recognition that it was not just tension, that there were other dysphoric mood states associated with the syndrome.

In 1983, NIMH convened a workshop on premenstrual syndrome, and this was in recognition that a lot of investigators were beginning to study the condition and were interested in coming up with some guidelines to help in the study of the condition. A number of different divisions within NIMH sponsored this workshop, and the workshop did yield some suggestions for criteria for premenstrual changes and premenstrual syndrome. The major criteria was the contrast between the mid-follicular phase and the late luteal phase in terms of severity and the nature of the symptoms.

In 1987, in response to advice of an advisory group, the DSM-III-R nomenclature group included specific criteria for late luteal phase dysphoric disorder in the appendix of DSM-III-R as a proposed diagnostic category needing further study. Of great interest and particularly relevant for this group is the content was almost identical to the DSM-IV criteria. The requirement that there be severe, marked dysphoric mood states was included, and in fact, the DSM-IV criteria adds only one symptom to the possible list, and I'll go into that later.

In the early 1990s, as a result of this, of

course, there was an explosion of research in the area looking at both treatment of the condition and also efforts to understand the pathophysiology.

By the early 1990s, the DSM-IV nomenclature committee had a work group called the Premenstrual Dysphoric Disorder Work Group to review literature up to that point in time, and the literature review, which is included in the DSM-IV source book, included literature up to 1993. The group worked together and with many advisors, and there was agreement among the group in their recommendations to the nomenclature committee on the suggested criteria and name of the condition. There was also very good agreement on the summary of the evidence and the written materials that were included in the DSM-IV source book.

There was some lack of consensus among the members of the work group regarding recommendations of the placement of the condition within the nomenclature. Some recommended that it be in the body of the nomenclature with the criteria. Others had some reservations for various reasons, and the nomenclature committee decided to put PMDD in the body of the nomenclature but to include the criteria in the appendix.

Now, how do we conceptualize PMDD currently? Currently it is thought to be in the upper range of the

broader category of PMS. That's partially because the work has not yet been done to decide whether or not there is a discontinuity between the conditions. But this is somewhat similar to the concept of depression. If you think of depression and general minor depression and major depression, there's no clear-cut pathophysiological cutoff, but most clinicians are very comfortable with thinking major depression as being different from minor depression or depression in general. So, currently PMDD is conceptualized as being at the upper range of severity of the broader category of PMS, but there are additional differences. It's not just the upper range of severity.

In premenstrual dysphoric disorder, the mood symptoms are prominent. It's the dysphoric mood symptoms that are prominent and are the primary clinical complaints of the women who are seeking treatment. They're not only prominent, they're severe, and they include particularly irritability, low mood, and anxiety.

There is functional impairment associated with these mood symptoms. The mood symptoms themselves are associated with functional impairment particularly in psychosocial relationships.

There are physical symptoms, just as there are with the garden variety PMS. Breast tenderness and bloating are there.

The prevalence in many studies have suggested that it's around 3 to 5 percent of regularly menstruating women. Some recent evidence suggests it may even be higher. It may be up to 8 percent. But these are women who are having regular menstrual cycles.

The symptoms appear regularly every cycle. During the week before menses, the premenstrual period, or the late luteal phase of the menstrual cycle, and they remit following the onset of menses.

Now, in contrast with the more general premenstrual syndrome, the physical symptoms tend to be most prominent, particularly again the breast tenderness and the bloating. Mood symptoms tend to be less severe. If they're there, they're no big deal. They don't bother the women that much. There's little or no functional impairment associated with the syndrome, and the prevalence, of course, is much broader, 20 to 80 percent.

Now, to go over the DSM-IV criteria, I want to stress a number of features.

First of all, this is a chronic condition. The criteria require that the symptoms occur in the late luteal phase of most menstrual cycles during the past year. Most women who seek treatment report that they have had it for years and that it has tended to get somewhat worse over time. The average in several studies has been around 8

years. Also, that it remit within a few days of the onset of menses, and this is an important differential diagnostic point.

There are 11 types of symptoms or groups of symptoms in the criteria. At least 5 of the 11 symptoms must have been present most of the time during each symptomatic phase, but at least one of those symptoms has to-be one of these first 4 dysphoric moods: depression, anxiety, affective lability, persistent marked anger/irritability. Now, the reality again is that most women who seek treatment may have one primary symptom, but they tend to have all of these, not just one of them.

The additional symptoms are decreased interest in usual activities, subjective sense of difficulty in concentrating, lethargy, easy fatigability, marked change in appetite. The most common is increased, but some women have decreased. Hypersomnia or insomnia, and the one added criteria was subjective sense of being overwhelmed and out of control. That's the only criteria different between LLPDD and PMDD. Therefore, any woman who meets the criteria for LLPDD would have met the criteria for PMDD as well. And then other physical symptoms.

So, you can see that the emphasis in these diagnostic criteria, at least five had to be present, or on the dysphoric mood changes and the associated features, the

physical symptoms are there, but they're not a major part of the criteria.

The criteria continue. The syndrome must markedly interfere with work, school, or usual social activities and relationships. It's not sufficient just to have the syndrome. There should be marked impairment and functioning.

It should not be merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, generalized anxiety disorder, dysthymia. So that part of the criteria is that you rule out another ongoing condition that could account for the symptoms.

And furthermore, the criteria required that the diagnosis be made provisionally until it is confirmed by prospective daily ratings, and those prospective daily ratings have to confirm the timing of the onset and the offset of the symptoms, as well as the severity of the symptoms, and the impairment during at least two consecutive symptomatic cycles.

Now, what about the impact on functioning? How is this a clinically significant syndrome or disorder?

First of all, a woman who develops the disorder, by age 26, may experience more than 200 symptomatic cycles between then and menopause, or 1,400 to 2,800 symptomatic days, depending upon the duration of her

premenstrual disorder. As I've mentioned, in the DSM-IV criteria the symptoms are severe enough to have a significant, clinically significant, impact on social, home, and occupational functioning, and I'll be illustrating that with some data in the next slide.

The social functioning is affected more than vocational functioning. Many of the women manage to push themselves, spend extra time, energy and effort on their vocational functioning, and it's in their social functioning, particularly interpersonal relationships with mate and children, in which it shows itself more.

Women with PMDD may report impairment of family and social activities at a level similar to that of depression. This is illustrated in this next slide in which women with major depressive disorder are compared with women with PMDD on these social adjustment scale, with the self-report scale developed by Myrna Weisman, in which there are a number of different dimensions measured. As you can see, the women with PMDD report impairment in functioning that is nearly equivalent to that, and in some cases is equivalent to that, of women with major depressive disorder, particularly social activities, marital activities, extended family, and parenting.

This is very important because some people say, well, it only lasts a week to 8 or 9 days, so it must not

be that impairing. Frankly, it is quite impairing and it occurs every cycle.

What do we know about the etiology of PMDD? Well, just as is the case with most mental disorders, we don't fully understand the etiology. However, we do know some things about it.

The most likely theories are based on observations of cyclic changes in ovarian steroids do cause dramatic changes in brain neurotransmitter systems, a number of them, including serotonin. What has been clearly established is that in women sensitive or otherwise predisposed to mood instability, the normal events of the ovarian cycle -- in other words, there's nothing wrong with the menstrual cycle -- the normal events of the ovarian cycle may trigger severe mood changes. And I'll be reporting some other information on that topic. So, this is one thing that has been clearly established. The exact mechanism the way the neurotransmitter systems are involved is not as clearly established, but a great deal of work has gone on and is currently going on in this area.

How is PMDD distinct from the other depressive disorders, particularly major depression and dysthymia?

Well, first of all, the mood disturbance is cyclical. It is very tightly linked to phases of the menstrual cycle. It has a highly predictable onset and

offset, not only by phases of the cycle, but within an individual woman, you will find that her onset and offset, relative to her circulating gonadal hormones, is very tightly linked and very consistent from cycle to cycle.

The most common chief complaint is irritability, Although the other symptoms may be there, the women who seek treatment tend to focus on irritability.

The cyclic occurrence of these symptoms cease during pregnancy and post-menopause. This is not the case with either major depression or dysthymia or the anxiety disorders.

Prevention or suppression of cycling gonadal hormones relieves the symptoms. Again, this is not the case with the other depressive and anxiety disorders.

Furthermore, hormone replacement therapy can provoke cyclic dysphoric changes in women who have a history of PMDD. This has been done in double-blind studies and is clearly established. This does not happen in women who have a history of major depression or dysthymia.

The HPA axis functions normally. in PMDD. There's no evidence that the HPA axis is abnormal in any way, and this is unlike the documented disturbances in major depression.

There is great symptom stability seen across

cycles. Again, this is in some contrast with studies across episodes of major depression in which there is somewhat less symptom stability. Here the symptom stability is very stable and very predictable for the individual woman.

And most important, recently in 1998, Ken Kendler published the results of a very large study of twins, comparing monozygotic and dizygotic twins, in which both premenstrual related symptoms, focusing mainly on depression, and lifetime major depression had been evaluated at least at two points in time. What he found was that both the genetic and environmental risk factors for these two conditions were not closely related. They were not shared.

There was a large genetic contribution for premenstrual mood changes but that was not accounted for by major depression, lifetime major depression, and this was a very important study in this area.

There are some other ways in which PMDD is distinct from the other depressive disorders. It's most likely to respond to the serotonergic antidepressants than to other antidepressants. As you know, in the comparison studies between the TCAs and the SSRIs, with major depression you don't find that distinction, It's a clear distinction here. The serotonergic antidepressants are

superior.

Furthermore, upon treatment, the symptom improvement in PMDD is very rapid, as shown within the first treatment cycle, even though the women have not been on the medication that long. This is in contrast with major depression and dysthymia.

The physical symptoms shown with women with PMDD are unique to that condition. Breast tenderness and bloating are the most common. This is rarely seen in women with simple dysthymia or major depression.

Upon treatment cessation, the symptoms return rapidly, and the reemergence is more predictable. It's quite predictable with PMDD. There have been a number of studies, two of which are summarized here, about the reemergence of symptoms after stopping treatment.

Dr. Pearlstein in 1994 published an article on after 1 year of successful fluoxetine treatment, 31 women, they discontinued treatment, and the PMDD symptoms, meeting criteria for PMDD, returned within two cycles in 30 of the 31 women.

Kimberly Yonkers did a study published in 1997 in which there was double-blind randomization from sertraline to placebo in women who had been on the medication 3, 6, or 9 cycles. So, the women did not know when placebo was going to be instituted. The rates of

recurrence were 66, 66, and 60 percent within a couple of cycles after cessation of the active compound.

Now, in recognition of the clinical significance of this condition and of the need to find effective treatments for it, a very large number of compounds and interventions have been studied. This is just a sampling. This is not exhaustive. Other compounds have also been studied.

The most work has been done with the SSRIs, and this is shown here in which there are 32 studies, published studies, with SSRIs. The greatest number are with fluoxetine, but there have been published studies -- the double-blind, placebo-controlled studies are-in the dark blue and the open-label trials are in the light blue.

31 of these 32 studies were successful, were effective. There was a single study with fluvoxamine in which there was no difference. There are some other issues about that study, but 31 out of 32 studies of SSRIs have shown the SSRIs to be effective in the treatment of PMDD.

So, in conclusion, PMDD appears to be a distinct clinical entity with exquisite onset and offset of timing and clinical features and other characteristics that occurs in 3 to 5 percent of menstruating women and maybe even more. It has clinical and biological profiles that differ from those of major depression. It is a severe

form, we think now, of the broader category of PMS that impacts normal functioning to a clinically significant degree.

It should be better diagnosed and treated. There are plenty of women who have not had the diagnosis made. There is currently no registered treatment in the U.S. for PMDD. And there is an unmet clinical need for safe and effective treatment for the psychological as well as the physical symptoms of PMDD. There is evidence that the SSRIs meet this need, and Dr. Judge will be presenting that data now.

Thank you.

DR. TAMMINGA: I'd just like to remind the committee that all the slides that are shown are in the navy book in front of you.

DR. JUDGE: Well, good morning. It's my pleasure to present to the advisory committee and to the FDA this morning.

As you heard from Dr. Endicott, PMDD is a disorder which causes suffering to many, many American women. The data I will present this morning on fluoxetine will show how highly effective fluoxetine is in treating the symptoms of PMDD.

Firstly, I will address the efficacy with respect to the PMDD studies, and I will focus on the key

symptoms of premenstrual dysphoric disorder, i.e., the mood symptoms, the physical symptoms, and the social impairment that accompanies these symptoms.

Secondly, as you know, fluoxetine is a drug which has been marketed for over 10 years, and the safety profile is very well established. I will, therefore, provide a succinct summary of the safety and importantly compare that to the overall fluoxetine safety database.

And finally, I will provide conclusions and dosing recommendations.

These slides show the listing of the published studies in PMDD for fluoxetine, firstly, the double-blind studies on the left and the open-label studies on the right.

The first three studies here comprise the application for fluoxetine in PMDD. Although these comprise the application, all of the studies in the literature are consistent with respect to the results for fluoxetine in efficacy and safety. They have all utilized the DSM-III-R criteria for LLPDD. As you heard from Dr. Endicott, as these patients conform to DSM-III-R, that means that they also conform to DSM-IV criteria.

Furthermore, all of these studies in the main utilized a dose of 20 milligrams daily, and that was considered an effective and. safe dose for patients with

PMDD.

Although these studies are open-label, there is some nice information that can be obtained from them, namely, for patients going out to longer than 6 months, as for the shorter-term studies, patients going out to even up to 20 months did show a maintenance of efficacy with fluoxetine. Furthermore, there was also evidence from these studies to suggest that when fluoxetine was stopped, even after the long term, there was very quickly a reemergence of symptoms following cessation of treatment.

Three trials, as I've indicated, comprise the application for fluoxetine in PMDD, and these are listed here below in more detail. These are studies C019, X022, and X037. For purposes of perhaps ease of communication, I will refer to these studies as studies 1, 2, and 3. All were double-blind, parallel-controlled. One was a crossover trial.

The efficacy measures utilized in these studies are listed here and spelled out in full here. For the first study, number 1, the visual analog 7-item scale was utilized as the primary outcome measure. For study number 2, x022, a 16-item visual analog scale was utilized as the primary outcome measure. For the third study, X037, an overall measure of improvement, the clinical global impression, was utilized as the primary outcome measure.

In addition to the ones I've just indicated, there were a number of other scales utilized in these studies, particularly in studies 1 and 2, the premenstrual tension syndrome. Both patient rated and clinician rated tools were also used in these studies.

There are a wide variety of scales utilized here. There is not a gold standard of scales that is currently utilized in PMDD studies, but all of the scales here are appropriate and are reliable in treatment and study of PMDD.

I'll just go into a little bit more detail. These slides list the scales that were used in these studies, the main scales across the top, and across here, down here, are the DSM-IV criteria for mood, for physical symptoms, and social impairment. The numbers listed here list the items of these scales which correspond to each of these symptoms as listed by DSM-IV. This shows that all of the scales used in these studies did employ items that correspond to the DSM-IV symptoms.

So, for example, if we look at the premenstrual tension syndrome scale, both the clinician rated and the patient rated, listed here are items that are part of these scales and that correspond to the mood symptoms of DSM-IV, as listed in DSM-IV, and then over here they also contain items which list physical symptoms and they also contain

items which list social impairment.

For the primary outcome variable in study 1, visual analog scale-7, again the items in this scale do correspond to the mood symptoms of PMDD. It also contains items corresponding to the physical symptoms of PMDD. It did not contain items corresponding to social impairment, but for that study, the PMTS scales were utilized. So, we can glean social impairment information from those scales.

With respect to the second study, the visual analog scale 16-item was used, and this scale contained items which corresponded to all of the symptoms as listed by DSM-IV, i.e., the mood symptoms, the physical symptoms, and the social impairment symptoms.

So, all of these scales utilized are appropriate and reliable to measure treatment change as 'listed for the core symptoms for PMDD.

Going on to the studies for PMDD, this slide lists the inclusion and the exclusion criteria for these studies. First of all, the studies obviously included females 18 years and over, and they had regular menstrual cycles.

All the patients did conform to a DSM-III-R diagnosis of late luteal phase dysphoric disorder, and as you heard from Dr. Endicott, as they conform to the DSM-III-R, they therefore conform to DSM-IV criteria.

They also had to have an adequate method of birth control other than hormonal. I'll make another comment on that a little bit later.

And they also had to meet criteria for protocol predefined symptom severity. For example, in study 1, patients had to exhibit during the prospective cycles, during which they were monitored for this baseline state, either at least a 50 percent change in the core items for the mood items for the visual analog scale, a 50 percent increase from follicular to luteal phase, or they could exhibit, for example, a 100 percent increase or more in just one of those items corresponding to the mood scales.

The exclusion criteria. Patients were excluded if they had serious health problems, and they were also excluded if they were on the following medications: any psychotropic, diuretic, or hormonal medication, including oral contraceptives. As you've heard and just to reiterate the point, it is essential to quite clearly delineate the effects of fluoxetine on PMDD. As you've heard, oral contraceptives can have some effect on PMDD symptoms. There's a variety of literature which shows an inconsistent and variable effect on PMDD symptoms, perhaps most often the physical symptoms, and for that reason, rather than introduce another variable into the study, it was felt prudent to exclude oral contraceptives.

Also, patients with concurrent Axis I diagnosis of other disorders were excluded as appropriate.

Going on to these studies in more depth now, the reference here on the corner of each slide indicates the study to which this refers. Study 1, C019.

This is the first study, study 1, C019. This is a double-blind, placebo-controlled, dose range-finding study. After the screening period here with two cycles, patients then entered a placebo single-blind period here, and this provided an adequate basis for prospective monitoring for the patients and adequate baseline measurements of symptoms.

At this point, patients who still met the DSM-III-R criteria for PMDD and importantly excluded placebo responders, patients were then randomized in a double-blind fashion at this point to receive either fluoxetine 20 milligrams a day, fluoxetine 60 milligrams a day, or placebo. For those patients who received 60 milligrams a day, they were put on 60 milligrams a day from day 1, straight off the bat. They did not have the ability to titrate up to this dose; 60 milligrams a day from day 1.

The study then continued for 6 treatment cycles, making this a long-term study.

Patients were seen during each cycle twice, once during the follicular phase and once during the luteal

phase.

The primary objective of this study, as you heard from the first speaker, was to assess the efficacy of fluoxetine in PMDD as measured by the luteal phase Mood-3 average of the visual analog scale -- and I will go into this in a little more depth later for clarity -- average change from mean baseline to mean treatment score.

Now, originally in the protocol, it did not specify the VAS Mood-3 specifically. It was enlisted as just the visual analog scale. As the study started, Lilly and the primary investigator for this study made an agreement that the most appropriate outcome measure for this protocol should be the VAS Mood-3. That was decided upon and confirmed in writing before the completion of the study, just after the study had started in fact.

In addition to the primary, obviously I will show you items, the second objectives of the study, further measurements for the efficacy of fluoxetine in PMDD pertaining to the symptom clusters for the mood items to the physical items and social impairment as measured by the visual analog scale and also as measured by the subtotals of the premenstrual tension syndrome rating scales, patient rated and physician rated, obviously, also an opportunity to assess the safety and tolerability of fluoxetine in PMDD.

This slide here shows the visual analog scale that was utilized in this study. Patients were asked to rate themselves on a scale 0 to 100, ranging from no symptomatology to extreme symptomatology here. The items in yellow comprise the core items for mood and, therefore, the primary efficacy analysis for this study. So, the primary items for mood here are item 1, calm and unruffled, going to tense, uptight, uneasy; number 2, happy, content, and energetic, going to extremely depressed, sad, apathetic, and lethargic. Item 7 measured irritability. There were three physical items score here: headache, bloating and tenderness, and breast tenderness. And item 4 looked at emotional lability, even-tempered to extreme mood swings. So, that's the visual analog scale 7-item.

So, the primary efficacy variable is the average of the three mood symptoms here highlighted in yellow: the average scores of dysphoria, irritability, and tension. And secondary efficacy variables included the VAS Mood-4 average, which incorporated the other emotional lability item here, also the average of the physical symptoms, and then the subtotals for mood, physical, and social impairment for the PMTS scale.

This just shows in depth the PMTS scales for purposes of clarity. The clinician rating scale is listed on the left on both slides,. and the corresponding items of

the patient rating scale, PMTS-P are listed on the right. So, overall the range for both scales is 0 to 36. For the clinician rating scale, there were 10 items which were scored from 0 to 4 for most of the items, apart from number 7 and 8 where the items are scored from 0 to 2. The corresponding patient rating scale simply asked the patient to respond a yes or no to each question. Again, the items here correspond to those items as per the clinician rating scale.

This is looking at the calculation of the efficacy measures in a little bit more depth. This is a pictorial representation of the follicular and luteal cycles in this study. The first two cycles are the baseline placebo cycles, and then the six studies are the six treatment cycles. F is follicular; L is luteal. As I indicated, patients were seen twice during each cycle, once in the follicular phase, once in the luteal phase, and at those visits patients were assessed in terms of their efficacy.

So, measurement of the average luteal scores here for these two placebo cycles provided the mean baseline score. The average of the luteal scores for these six cycles here provided then the mean treatment score, and the calculation of the overall efficacy measure was the mean treatment score minus the mean baseline score.

Now, originally Lilly did plan to analyze the percent change in the analysis plan. However, the percent change would have assumed a normality assumption. There were extreme outliers, which violated the normality assumption. And therefore, it was felt appropriate to look at the mean treatment change.

Going on to some characteristics of the patients in the study, these are the baseline characteristics, and these are listed in more detail in your briefing document supplied to you. But essentially the age of entry-for these patients in these studies was mid to late 30s. Importantly for the demographic variables listed here and also in your briefing document, there were no differences in the groups at baseline.

The average VAS Mood-3 follicular and luteal scores are represented here more visually. Importantly all three treatment groups, with respect to their scores, are similar at baseline. Moreover, as one would expect for PMDD, the luteal scores are higher. This is the mean score on the visual analog scale, VAS Mood-3. The luteal scores are higher than the follicular scores, the follicular scores indicating insignificant symptomatology, as one would expect with patients with PMDD.

This lists the patient disposition for the study with respect to the percentage of patients. Overall,

fluoxetine 20 milligram patients were the highest number of patients who completed the study. The highest percentage of patients completed the study were on fluoxetine 20 milligrams.

In terms of patients who dropped out for any reason, these are shown here. For the patients who dropped out due to an adverse event, more patients on fluoxetine 60 milligrams who dropped out due to an adverse events. There were a low level and similar level for dropouts with respect to placebo group and fluoxetine 20 milligrams. For lack of efficacy, as one would expect, a higher proportion of placebo patients dropped out due to lack of efficacy.

I'm going on to now show the efficacy measures by means of a series of bar graphs. In all of these graphs, fluoxetine 20 milligrams will be shown as orange, fluoxetine 60 milligrams will be shown as yellow, and placebo in green.

Moving on to the primary efficacy measures -- and, again, I will concentrate on the mood symptoms, then the physical symptoms, then the social impairment symptoms from each study.

First of all, the mood symptoms in the luteal phase. This looks at the mean reduction from baseline to mean treatment here, so the greater the reduction, the greater improvement in overall outcome.

This is the primary objective here, the VAS Mood-3. We see here there's a greater reduction with statistical significance for both fluoxetine 20 milligrams and 60 milligrams versus placebo here. If one looks at the individual items that comprised the primary outcome, VAS Mood-3, which is dysphoria, irritability, and tension, then one sees that indeed in each case fluoxetine 20 and 60 milligrams are statistically significantly superior in their reduction of symptomatology versus placebo in each case.

There does appear to be some numerical superiority for fluoxetine 60 milligrams versus 20, but the difference between the two groups was not statistically significant with respect to the two fluoxetine groups.

The results here are mirrored by the consideration of the results seen on the PMTS scales, both the PMTS-P, the patient rated scale, and the PMTS-C, the clinician rating scale. Again, showing the reduction from mean baseline, patients on fluoxetine on any dose, either 20 or 60, achieved superior clinical improvement versus placebo, and the difference between the active treatment groups and placebo did attain statistical significance. Again, some numerical superiority observed with fluoxetine 60 milligrams versus fluoxetine 20 milligrams, but the difference between the two fluoxetine arms was not

statistically significant in this case.

Moving on to the physical symptoms, again this looking at the visual analog scale, the overall physical average is shown here, again mirroring the mood symptoms, a statistical difference for superiority for the fluoxetine arms versus placebo. Then if one looks at the individual physical items which comprise the physical average, bloating, breast tenderness, and headache, one sees that it is the effects of breast tenderness and bloating which lead to the overall significance. There does not seem to be any difference between the groups with respect to headache. But as you heard earlier, bloating and breast tenderness are two of the most common symptoms in patients with PMDD.

Again, the effective results for fluoxetine in the mood symptoms and the physical symptoms here are also mirrored by consideration of the PMTS subtotals, for the PMTS-P and the PMTS-C. Again, a significant reduction for physical symptoms for both fluoxetine arms versus placebo, and again some evidence of numerical superiority with fluoxetine 60 milligrams versus 20, but the differences were not statistically significant.

Moving on to the social impairment. As I noted earlier, the visual analog scale from this study did not measure social impairment, and so we view the items from the PMTS-P with respect to social impairment. Again,

reduction from mean baseline for the PMTS-P and the PMTS scores showing a very nice improvement in social impairment for patients on fluoxetine 20 and 60 milligrams versus placebo, the difference between the active treatment arms versus placebo attaining statistical significance.

So, I've shown you the subtotal scores for the mood and physical symptoms and the social impairment. I just want to point out now that analysis of the overall scores for each of these measures, the overall visual analog scale 7-item, the overall PMTS-P, the overall PMTS-C. Also I showed that fluoxetine was statistically superior with respect to its effects on those scores versus placebo.

So, efficacy was seen for both fluoxetine 20 milligrams and 60 milligrams for all of the symptom clusters of PMDD.

Two pertinent questions at this point. How quickly was the efficacy apparent and what was the course of the treatment effect?

With respect to how quickly was the efficacy apparent, we viewed here the efficacy seen with respect to the mood symptoms and the physical symptoms at the first treatment cycle. So, remember, patients were asked to take medication from the first day of their menses. So, this is just after a couple of weeks of treatment. We see that

even at the first cycle, there is superiority for fluoxetine versus placebo in the mood symptoms and in the physical symptoms as shown here by the primary analysis of Mood-3 average and also the physical average on the visual analog scale. So, a very quick response to fluoxetine was evident.

With respect to the course of the treatment effect, this is shown here for the last observation carried forward for the primary analysis, the VAS Mood-3, placebo here, this line; fluoxetine 20 milligrams, the orange line here; and fluoxetine 60 milligrams, the yellow line here. So, this is looking at the mean reduction from baseline, and what we see is that up to 6 months, at each cycle, there is a statistical difference maintained between placebo and both of the fluoxetine groups, both the 20 and the 60 milligram groups, showing that the efficacy of fluoxetine is maintained for out to 6 months.

So, with respect to the conclusions in the study, both fluoxetine 20 and 60 milligrams a day were effective in the treatment of PMDD. Statistical differences were shown with respect to placebo, with respect to the primary objective, the VAS Mood-3, and the secondary objectives, and I also indicate there's also the consideration of the total scores as well. Efficacy was seen in all of the 'symptom clusters of PMDD. So, although

mood was defined as the primary outcome measure, it's also interesting to note that the mood symptoms, the physical symptoms, and the social impairment associated with PMDD all improved very quickly. Efficacy was demonstrated in the first treatment cycle and maintained for up to 6 months. There was some evidence that fluoxetine 60 milligrams was in general numerically greater than 20 milligrams, but the differences were not usually statistically significant.

Moving- on to the next study, this is study number 2, X022, and this is a double-blind crossover study. As was alluded to earlier, the disorder of PMDD comprises symptoms which are very closely entrained to the menstrual cycle. So, the predictable nature of these symptoms emerging cycle after cycle after cycle makes it a very predictable disorder with discrete episodes of disorder. Furthermore, studies would suggest that there is symptom stability across cycles. So, symptom stability being the rule rather than exception. So, these two characteristics of PMDD do make it an ideal disorder to study in a crossover design. This is also evidenced by the literature where a number of studies with various treatments have used the crossover design in order to study PMDD.

So, in this study after 3 cycles of screening and evaluation, patients were entered into this study.

Patients were either randomized to the fluoxetine arm or the placebo arm for 3 cycles. After this there was a 1-cycle crossover, l-month crossover, and then patients were crossed over to the other treatment, again for another 3 cycles here. For the fluoxetine arm, patients were started on 20 milligrams, and investigators, at their discretion, could titrate up in increments of either 10 or 20 milligrams, according to safety and efficacy, to a maximum of 60 milligrams.

Patients who entered here are listed here: 9 for the fluoxetine group, and placebo, 10 patients. Obviously, each patient acted as their own control. This enhanced sensitivity allows for relatively fewer patients.

Originally this protocol was intended to recruit 30 patients, but in an earlier analysis done for purposes of a scientific abstract, the investigator noted significant differences between the treatment groups and elected to stop the study at that point. It's important to realize that all of the patients who were recruited at that time were allowed to finish. That numbered a total of 19 patients. And moreover, the raters who were assessing the patients and the patients themselves, who obviously were assessing themselves on scales remained blind to treatment assignment, first, to minimize any kind of bias in this study.

The prime objective here was to assess the efficacy in the treatment of PMDD as measured by the average within-cycle change from follicular to luteal phase in the VAS Mood-4. So, there are differences here with respect to the outcome measures from the first study. Just to point out that patients did score themselves every day in this, they did do some measurements every day during this, study, and they did some measurements again for every visit. Again, they were seen for two visits each cycle, follicular and luteal phase.

So, I'm going to talk about this in a little bit more depth, but just to emphasize that the outcome measure here was the average within-cycle change from follicular to luteal phase, in the VAS Mood-4 subtotal. So, this is a 16-item VAS and the VAS Mood-4 subtotal comprised the primary efficacy outcome, and that comprised the mood swings, depression, irritability, and anxiety.

Again, the secondary objectives were obviously to look at the other items of the visual analog scale and the PMTS scales with respect to the other subtotals, the mood subtotal, the physical symptom subtotal, and the social impairment.

This slide shows the visual analog scale used in this study. So, this is a 16-item visual analog scale. Patients were asked to rate-themselves from no symptoms to

severe symptoms, and the symptoms listed in yellow again comprise the primary mood items, rapidly changing mood to mood very stable; item number 8, most sad ever to most happy ever; the irritability item, and the most anxious ever to most calm ever.

The other items that comprise physical symptom items are shown here: number 5, extreme breast pain; extreme bloating; and extreme physical discomfort. You see all the other items that were also in the scale.

This shows the daily rating form which also comprised one of-the secondary scales in the study. This form, obviously as the name implies, was rated daily by the patient and the patient rated the severity of each item on a scale of 1, none, to 6, extreme, the total score ranging up to 108. Listed here are those items which pertain to mood, the physical symptoms, social impairment, and there are a variety of other symptoms which were also scored on this daily rating form.

Now, just to go into the depth of how the efficacy analysis was calculated, again just to reiterate the primary outcome variable was the VAS Mood-4 subtotal. This is how this was collected.

The luteal score was the average of the patient's score for 7 days prior to the menses. The follicular score was the average of the patient's score

over the 7 days post-menses. Subtracting one from the other provided the within-cycle change, and this was averaged over 3 months of treatment to provide the primary patient treatment outcome measure.

Baseline characteristics, very similar to the first study. Most of the patients were Caucasian and the age of these patients were similar to the first study, mid to- late 30s. Importantly, consideration of the follicular scores here for the PMTS patient total for the PMTS clinician total, and for example, in the Beck's Depression Inventory, if you look here, the scores are very, very low in the follicular phase, indicating an absence of any significant premenstrual symptomatology, as one would expect with respect to the cyclicity of PMDD.

With respect to patient disposition, the majority of patients completed this study. Very few patients dropped out for any reason at all.

Again, I will go through the efficacy outcomes with respect to the mood symptoms, the physical symptoms, and then the social impairment.

Firstly, with respect to the mood symptoms. Now, here the scale is looking at average within-cycle increase. So, within-cycle increase from follicular to luteal, so indicating an increase in symptomatology. So, an increase in scores here would indicate an increase in

symptomatology and therefore deterioration in the patient's outcome.

For the primary outcome measure, the VAS Mood-4, the 4 items on the visual analog scale, you will note there's a greater increase with respect to the symptomatology seen in the placebo patients shown here in green, and this increase was statistically superior than the increase evident for fluoxetine patients. So, the fluoxetine patients improved with statistical superiority versus the placebo patients.

When-one sees the individual items which comprise the VAS Mood-4 items, again fluoxetine is superior with respect to placebo in each of these items, the mood swings, depression, irritability, and anxiety. And fluoxetine patients exhibited far less increase in symptomatology versus the placebo patients.

This was mirrored by consideration of the secondary outcome variables, the daily rating form, and the PMTS-P and PMTS-C. For both the DRF and PMTS-C -- that's the clinician rating and patient rating -- again, evidence of fluoxetine superiority with statistical significance versus placebo. For the PMTS-P, quite clearly there is fluoxetine superiority, but the differences did not attain statistical significance.

Going on to the physical symptoms with respect

to this study, again shown here are the physical average for the symptoms comprising from the visual analog scale. This shows the individual items which made up this physical average, and fluoxetine is highly effective with respect to placebo for breast pain, bloating, and physical discomfort, giving an overall highly statistically significant effect versus placebo on the visual analog scale.

Again, consideration of the secondary measures employed in this study further mirrored the evidence seen for the primary outcome measure in that for the physical symptoms, for the daily rating form completed by the patient, the PMTS-P completed by the patient, the PMTS-C completed by the clinician, statistical superiority for fluoxetine versus placebo in each case.

The similar results are evidence for social impairment with highly statistical significance for fluoxetine versus placebo with respect to the visual analog scale here, the overall social impairment. This comprised two items, work efficiency and social activity. So, this is important. It shows that the patients rates themselves as improving with fluoxetine with respect to their efficiency at work and their social activities.

Again, this is mirrored by the consideration of the secondary outcome variable. Patients rated themselves as improving with statistical significance over placebo for

the daily rating form, and for PMTS-P and PMTS-C, again quite clearly there is numerical superiority for fluoxetine, but the differences did not attain statistical significance here.

Going on to the same questions as we asked in the first study, when was the efficacy apparent and what was the course of the treatment effect, these two slides go to show some evidence for those questions.

First of all, again, entirely consistent with the first study, a consideration of the first treatment cycle, within-cycle increase, showed that for the primary VAS Mood-4 for the physical symptoms and for the social symptoms, all from the visual analog scale, at the first treatment cycle was exhibited a superiority for fluoxetine versus placebo, again entirely consistent with the first study.

The course of treatment effect is shown here just for one measure, the VAS Mood-4, which is obviously the primary outcome measure. For patients here for the purple, here we see here for the patients who started off the treatment with placebo. Now, scores higher on this graph indicate increase in symptomatology. Scores in the lower half of this graph indicate lower symptomatology. So, higher scores are considered bad for the patient.

So, for the patients who started off on

placebo, as indicated for the first 3 cycles, their scores are in the upper half of the graph, indicating significant symptomatology for these patients. After the crossover -- you see then the patients who then were crossed over to fluoxetine -- then their scores for the next 3 cycles were in the lower half of this graph, indicating improvement for the patients.

Exactly the opposite is evidenced for the opposing group. We see here for fluoxetine, the patients who started off on fluoxetine, their scores for each of these 3 cycles are in the lower half of the graph, indicating very little symptomatology for these patients, and after the crossover, when they were switched over to placebo, we see that their scores shoot up to the higher portion of the graph, indicating an increase in, symptomatology. So, a nice visual representation of the comparative effects of fluoxetine versus placebo.

Now, the crossover washout phase here was a 1-cycle duration, 1 month. As we appreciate, for fluoxetine, the half-life is relatively long and also contains an active metabolite, norfluoxetine. So, therefore, a reasonable question at this point is, were there any carryover effects, and if there were any carryover effects, what was the implication of that carryover effect with respect to the overall efficacy seen in this study? I'd

like to elaborate on those results.

First of all, with respect to the mood symptoms across the treatment cycles for this study. This is just looking at the VAS Mood-4 and another example of mood, the DRF mood subtotal. This shows that for the overall treatment effect for all cycles shown here, the overall value for fluoxetine versus placebo, was highly statistically significant, p, 0.002. This column here shows the possibility of the carryover effect. As you see over here with the p values of 0.9 and .26, there is no carryover effect- evident.

When one then moves on to the first treatment cycle, the results from the first treatment cycle only, we see here again for the same items the VAS Mood-4 and the DRF Mood subtotal. We see, if we look over into the carryover effect column here, .09, .12, then there is a suggestion of a carryover effect. But it's worth bearing in mind, again just to emphasize, we're looking at the within-change from follicular to luteal. So, in actual fact, a carryover effect present here would actually bias against fluoxetine.

So, in spite of that bias, when we look at the overall p value for the treatment effect at cycle 1, we see, in spite of the carryover effect, which is biased negatively versus fluoxetine, the differences between

fluoxetine and placebo still attain statistical significance.

Just to show the robustness of the scores in another manner, I'm now going to focus on looking at the first 3 cycles here. I'm going to show you results from just the first 3 cycles which really approximate to a parallel group study.

This is looking at the so-called first period analysis. That's the analysis from the first 3 cycles of that study. This is looking at a variety of measures with respect to the moods on the left side and respect to the physical symptoms on the right side.

For VAS Mood-4 subtotal, for DRF Mood subtotal, for PMTS-P subtotal, for PMTS-C subtotal, overall, whichever way you look at it, even in the first period analysis only, statistical significance is for fluoxetine versus placebo. And the same is evident for the physical symptoms. Again, just looking at the first period only,. statistical significance is for fluoxetine versus placebo.

So, in conclusion for efficacy in the study, a flexible dosing for fluoxetine in the range of 20 to 60. milligrams a day -- and the patients attained a mean dose of 27 milligrams in this study -- was effective in the treatment of PMDD. Again, we saw statistical differences superior to placebo with respect to the primary objective,

the VAS Mood-4, and importantly also the secondary objectives. Efficacy was seen in the symptom clusters of PMDD for most variables with respect to mood, physical symptoms, and social impairment. Just an overall analysis of the total scores for the visual analog scale 16-item, again, statistical differences for fluoxetine versus placebo.

Improvement, as demonstrated in the first study, was demonstrated in the first cycle and maintained for up to 3 months.

So, thus far, I've presented two well-designed, randomized, placebo-controlled studies that have shown fluoxetine is statistically significantly superior to placebo in the treatment of PMDD.

Moving on to the third study, this is X037, study number 3. This is a placebo-controlled, parallel study. Initially after the screening period here, patients, first of all, entered a single-blind placebo period here, after which they were randomized to receive either fluoxetine, bupropion, and placebo. Bupropion is a predominantly dopaminergic agent, and patients were randomized to 300 milligrams a day, as 100 milligrams three times a day, and fluoxetine 20 milligrams a day.

For this study, the CGI score was listed as the primary outcome measure. That was specifically the CGI in

terms of those patients who achieved a score of 1 or 2 was listed as the primary outcome measure. So, this is the percentage of responders, the percentage of patients who achieved a score on the CGI of 1 or 2, the primary outcome measure here.

As we see here, for fluoxetine patients in orange, there was quite clearly a trend toward significance; p, 0.07 for fluoxetine patients versus placebo. The differences did not attain statistical differences between fluoxetine and placebo, but you see that the percentage of responders between the bupropion and the placebo groups is very similar, so indicating perhaps, as Dr. Endicott had alluded to, some evidence of the serotonergic specificity for patients with PMDD.

When one considered any improvement on the CGI, a secondary outcome measures, scores of 1, 2, or 3 -- so, patients who listed any improvement when they scored 1, 2, or 3 on the CGI, and then the differences between the groups are statistically significant in that fluoxetine patients attained the greatest number of patients who were responders, with statistical superiority versus placebo. Again, essentially no differences between the bupropion and the placebo groups.

Consideration of the secondary outcome measures for this study in terms of the daily assessment of

functioning, the GAS scores, all showed similar results to the first outcome measures shown here in that the differences indicated some superiority for fluoxetine but not attaining statistical,significance. So, I'm not going to show all of those here.

So, two studies have confirmed the efficacy of fluoxetine in PMDD, and a third study has provided supportive evidence with respect to the efficacy of fluoxetine in PMDD. Importantly, the efficacy shown in these studies is entirely consistent with the other double-blind studies reported in the literature.

I'd like to move on to show you the effect size. As was evidenced in these studies, there were a variety of scales used because there is no one gold standard scale for PMDD. But it's also interesting to note that even when one makes a comparison of the effect size across the studies, you see a moderate to large effect size consistently for these patients. This is shown in the next slide.

So, effect size can be regarded as a unitless measure that can compare across different studies and different scales. Generally, the traditional thing is that patients with an effect size of 0.5 to 0.8 have demonstrated a medium to large effect of treatment.

Now, the circled shapes here are the primary

outcome measures. This lists basically the outcome effect size for study 1 and study 2. Study 1, the circles are the study 1 outcome measures for the mood items, the physical items here, and the social impairment. The primary outcome measure is this one, VAS Mood-3. For study 1, with respect to the 60 milligram arm, the black circle, that is the VAS Mood-3 here. For study 2, the primary outcome measure, the VAS Mood-4, is shown here. So, for the primary outcome measures for the first two studies, we see an effect size which is medium to very large, consistently for these studies for the fluoxetine groups. If you look at broadly the picture of effect for the other effect sizes listed here with respect to the other mood subtotals, the other physical subtotals, and the social impairment subtotals, one sees very broadly an effect size which is ranging from medium to large in the main.

So, overall in terms of efficacy, I'm going to conclude on the efficacy here. The PMDD studies were randomized, double-blind, and placebo-controlled. The study populations were appropriate and consistent, and the outcome measures were appropriate to measure changes in PMDD symptoms.

PMDD studies demonstrated the efficacy of fluoxetine in the range of 20 to 60 milligrams a day. Again, just to reiterate, 20 and 60 milligrams appeared to

be similarly effective, although there was some numerical superiority for 60 milligrams. And importantly, fluoxetine was effective in treating the symptoms of PMDD for up to 6 months. The efficacy of fluoxetine was also evident during the first treatment cycle in all of these studies.

Moving on to the safety, as I have indicated, the safety profile of fluoxetine is well-known. Hence, I will-provide a rather succinct summary.

First of all, with respect to the safety population in the PMDD patients -- and I will compare that to the overall fluoxetine safety database for the indications for which it has been approved in the U.S., that is depression, OCD, and bulimia, numbering almost 4,000 patients. I will also compare the safety profile of the patients with PMDD to a subgroup of this larger fluoxetine database, and that is the female patients aged 18 to 45 years which most closely approximates PMDD patients. That database is numbering almost 1,700 patients.

I will focus on study 1 in terms of the PMDD studies. Study 1, study 2, and 3. The adverse events collected here were spontaneously collected for study 1 as treatment emergent adverse events. For studies 2 and 3, the adverse events were collected in a different manner, and so it was difficult to merge the database with respect

to the adverse events. So, I'm going to concentrate on study 1 when I show you the adverse event profile for PMDD patients.

First of all, in looking at the overall study drug exposure for the PMDD safety population in total, the total days of exposure was over 27,000 for fluoxetine at any dose. Importantly, about 50 percent of this exposure was in the range of 151 to 220 days.

This is looking at study 1 and looking at the percentage of patients who reported one or more adverse events, as one would expect overall, a high level of reporting for the three groups and with more patients reporting adverse events in the fluoxetine arms versus the placebo arms. With respect to the patients who dropped out for any adverse events for this study; more patients dropped out in the fluoxetine 60 milligram arm as compared to fluoxetine 20 and placebo. No statistical differences in the patient dropouts in the fluoxetine 20 or placebo arm.

I just want to reiterate that the patients who were on 60 milligrams in this study did start on 60 milligrams at day 1. They did not have the ability to titrate up to that dose. So, from what we know about fluoxetine, it may be that if they had started on 20 and titrated up to 60 milligrams, this higher rate of dropout

would not be evident for patients as shown here.

This is also evidenced by the fact that when the dropouts did occur in the 60 milligrams, most of the dropouts were, in fact, in the first portion of the study, so fairly early on with fluoxetine treatment.

There were very few serious adverse events in this study at all.

This lists the most common treatment emergent adverse events in study 1 reported by at least 10 percent of patients taking fluoxetine. This is fluoxetine 20 milligrams, fluoxetine 60, on both slides. Overall, the pattern of reporting of adverse events for fluoxetine are what we would expect for what we know about fluoxetine. Importantly, fluoxetine 20 milligrams appeared to be very well tolerated with very similar differences, not statistically significant to placebo, for any adverse events of any clinical significance.

For patients on fluoxetine 60 milligrams, there were high numbers of adverse events reported and in some cases the differences between fluoxetine 60 and both placebo and 20 milligrams were statistically significant. As I stated earlier, the fact that these patients did start out on 60 milligrams from day 1 may have been a factor in this.

Now, these slides compare the most common

treatment emergent adverse events in the three databases that I alluded to. Firstly, for study 1, this is the incidence of adverse events for the fluoxetine groups. There is a combination of the 20 and 60 milligrams groups, and this is compared, first of all, to the approved indications database. These are patients with bulimia, depression, OCD, and then this is again compared to the approved indications females subgroup of that database, females aged 18 to 45. If you view overall the adverse events, the pattern of adverse events is as expected for fluoxetine, and importantly no unique adverse events were emergent which showed any uniqueness for PMDD patients.

In order to assess tolerability, it's perhaps pertinent to look at patients who had dropped out due to any adverse events. This shows patients who dropped out in study 1, study 19. We view that overall, first of all, for fluoxetine 20 milligrams the incidence of dropouts was low, and no one particular adverse event contributed in particular to a high level of reporting of dropout due to adverse event. Very few patients dropped out in studies 2 or 3 due to adverse events. So, again, the dropout here would be as one expected for fluoxetine.

So, in conclusion for safety, fluoxetine has been used in over 35 million patients worldwide and a very, very large safety database does exist for fluoxetine. I've

provided evidence to show its safety in PMDD patients and compared that with respect to the approved indications database. Also extensive post-marketing surveillance for this pharmacological agent has shown it to be a very safe product.

Fluoxetine patients with PMDD is therefore safe and well-tolerated and, importantly, clinically comparable to the known profile of fluoxetine with no unique events seemingly for the PMDD patients.

Fluoxetine 20 milligrams appeared to be better tolerated than fluoxetine 60. Overall fluoxetine 20 milligrams was as expected, well-tolerated and safe for PMDD patients.

I'll now provide dosing recommendations based on the efficacy and safety data that I have just reviewed. Again, just to reiterate, fluoxetine 20 and 60 were similarly effective in patients with PMDD. While fluoxetine 20 to 60 is safe for patients with PMDD, 20 milligrams did appear to be better tolerated than 60 milligrams. So, therefore, the optimal dose should be 20 milligrams for patients with PMDD, and some patients may, indeed, benefit by increasing their dose to 60 milligrams.

Before providing the concluding the comments, I'd like to address one of the questions that the FDA have raised with respect to the use of oral contraceptives.

I've indicated in these studies patients with oral contraceptives were excluded for the reasons previously alluded to in that they do have variable effects on premenstrual symptoms. Where they do have an effect, it seems to be on the physical symptoms, and that is inconsistent so. So, in order to clearly delineate the effects of fluoxetine in these studies, oral contraceptives were excluded. Nevertheless, for menstruating females, reports anything up to 30 percent of patients may be taking oral contraceptives. So, the question arises, does the combination of the use of oral contraceptives in combination with fluoxetine have any implications for efficacy or safety for that combination?

First of all, what are the potential for possible interactions from the pharmacokinetic point of view? Fluoxetine is metabolized primarily by the P450 2D6 enzyme system.. The oral contraceptives are primarily metabolized by the P450 3A4 enzyme system. Now, the effect of fluoxetine on the 3A4 system has been investigated by virtue of in vitro and in vivo studies. The in vivo studies, using the 3A4 substrates of midazolam and terfenadine, did not indicate any clinically significant interactions between the combination. So, this suggests that there is unlikely to be any potential for interaction between fluoxetine and oral contraceptives.

I'd now like to provide evidence from clinical data which further supports this. As I've indicated, there is a very large efficacy and safety database for fluoxetine with respect to other indications. So, although the PMDD patients did not have any oral contraceptives concomitantly, in the other indications, for example, depression, OCD, and bulimia, there were patients who did take oral contraceptives. So, by subgrouping those existing safety database with respect to efficacy and safety, it was possible to try and tease out any possibility of interactions between oral contraceptives and fluoxetine.

First of all, with respect to efficacy, just to reiterate, many of the women in the approved indications database were taking oral contraceptives. So, in viewing the efficacy of patients with depression, OCD, bulimia, and comparing it for those patients who did take oral contraceptives versus those that did not, there was no clinical evidence that concomitant use of oral contraceptives either augmented or lessened the efficacy of fluoxetine.

The same analysis with respect to the safety during clinical trials of fluoxetine, no drug interactions were noted for patients who were taking oral contraceptives.

Importantly, extensive post-marketing surveillance has not shown any evidence for interactions between fluoxetine and oral contraceptives. It's important to note that fluoxetine has been on the market for over 10 years. Also, a search of the literature yielded no case reports of such an interaction.

So, it would seem from the data presented, that oral contraceptives and fluoxetine can be used safely with respect to efficacy and no safety implications.

So, my concluding remarks. PMDD is a distinct clinical entity which can be differentiated from depression and other anxiety disorders. It can be considered a severe form of premenstrual syndrome that causes impairment of functioning. It's quite clearly inadequately recognized and treated at the present time. For fluoxetine in PMDD, three randomized, double-blind, controlled studies presented support for the efficacy of fluoxetine in PMDD. The results presented are entirely consistent with the numerous other published studies for fluoxetine in PMDD. Safe and well-tolerated at the recommended dose, and the dosing recommendation is appropriately supported by the data presented.

Thank you very much for your attention.

DR. TAMMINGA: On behalf of the committee, I'd like to thank Dr. Judge, Dr. Endicott, and Dr. Brophy for

their very well done presentation of the data set.

I'd like to suggest that we take a break and formulate questions, and following the break, the-committee will come back and address questions both to Lilly and to the FDA. We'll take a break and be back by 10:15 please.

(Recess.)

DR. TAMMINGA: I'd like people to take their seats so we can restart the meeting please.

The committee has now heard a presentation from Lilly about their indication. We've heard the issues laid out and many probing questions laid out by Dr. Laughren. Now, the committee will have a chance to ask questions to Lilly about the presentation of their data.

I would like to encourage not only the committee members, but also the advisors to satisfy every question, so to speak, to Lilly because after we come back from lunch, the committee will then talk about all the issues that came up about the presentation.

One more thing I need to remind the committee of. Unlike our last meeting, all the microphones are active all the time.

(Laughter.)

DR. TAMMINGA: So, if people would just keep that in mind.

There are a number of committee members who

have questions for Lilly about the presentation. I would suggest that Dr. Judge actually come up to the podium, if you do not mind, rather than getting up and going down all the time, and you can actually address questions from the committee. I did not mean to say that Dr. Judge had to answer these questions all by herself.

(Laughter.)

DR. TAMMINGA: But I suspect all of your Lilly will'help out anytime. Also, we might have questions for the rest of the Lilly people, but you can really moderate the response.

I might just take the chair's prerogative and ask the first question. Would you remind us, Dr. Judge, what is actually the half-life of fluoxetine and its major metabolite?

DR. JUDGE: The half-life of fluoxetine, 4 to 6 days. The active metabolite, norfluoxetine, up to 16 days.

DR. PARRY: I'd appreciate it if you could review on each of the studies you presented, the authors, the site of the study, and where it was published.

DR. TAMMINGA: If the person who's asking the question could just identify themselves for a minute.

DR. PARRY: I'm Barbara Parry, Professor of Psychiatry, University of California, San Diego.

DR. JUDGE: Study 1 was conducted in Canada in

7 centers and was published by the principal investigators, Dr. Steiner, et al. in the New England Journal of Medicine.

Dr. Schmidt was the primary investigator for the second study, X022, and that was conducted in that one center. That was published in which year, my colleagues can remind me. We'll get that information.

And the third study was conducted by -- the principal investigators were Terry Pearlstein, et al., and were conducted in two centers, the other investigator being Dr. Stone. That was published also a number of years ago.

DR. THYS-JACOBS: I'm Susan Thys-Jacobs, and I want to just ask a couple questions about study 19, which was the multi-center trial.

All the studies that you had presented are double-blinded and I'm assuming that the tablets looked alike. But in 19 there was placebo, 20 milligram dose, and there was a 60 milligram dose. When they went from single-blind into double-blind phase, how did you carry that out?

DR. JUDGE: It was one capsule. There was always one capsule for 60 milligrams, 20 milligrams, and placebo.

DR. THYS-JACOBS: It was one capsule for the 60.

DR. JUDGE: Yes.

DR. THYS-JACOBS.: Okay.

Another question for 19 was that you defined baseline scores as visit 3 and 5. Were the true baseline scores before entering the single-blind washout different or similar? Luteal mean scores.

DR. JUDGE: Dr. Steiner can perhaps elaborate on this as well. But for the patients, as they entered the screening phase, and then prior to that, the scores were similar, but I don't have the scores for that on hand.

Dr. Steiner, can you comment?

DR. STEINER: There's no difference in the baselines for the two or three cycles that actually screened the patients before they went into the single-blind assessment phase. The data that are used are for placebo nonresponders that entered into the randomizatjon.

DR. THYS-JACOBS: I have another question for 19. You showed the data at the first treatment through treatment cycle 6. At treatment cycle 6, however, at the 20 milligram dose, there seemed to be a diminution effect, not major, but there did, indeed, seem to be some decreased effect. Was that effect significantly different from treatment cycle 1?

And how do you explain the fact that there was a decrease of rapid decline in symptoms in treatment cycle 1 and then there seemed to be a gradual increase in symptoms by treatment cycle. 6? Do you think that women

over time become more tolerant to this drug?

DR. JUDGE: I'll make an attempt at answering that, and perhaps Dr. Steiner can also comment.

What's interesting at cycle 1 of that study, as you correctly noted, is a very, very robust and fast response, and it may be evidenced by the fact for the extreme relief experienced by these patients. Remember, they've had several cycles at that time of prospective monitoring, and it may be reflected in their extreme relief.

Now, that was a 6-month study and so, therefore, a long-term study. Also, it may be reasonable to assume that patients towards the end of the study are less able to reflect or relate to their baseline levels of functioning as they would earlier on in the study.

The important thing is that throughout the study 20 milligrams was statistically significant from placebo in the LOCF population.

DR. THYS-JACOBS: Well, that was the 'mean and at all cycles.

DR. JUDGE: At all cycles.

DR. THYS-JACOBS: No. My question was, was there a difference --

DR. JUDGE: Was there a difference between the last --

DR. TAMMINGA: One at a time please.

DR. JUDGE: My statistician, Dr. Brown, will attempt to answer that.

DR. BROWN: This analysis looks at the comparison of the treatment effect at the first treatment cycle to the last treatment cycle, cycle 1 versus cycle 6. These are, of course, just those patients that completed all the way through. So, it's just those patients that completed that 6-treatment cycle. We show the means and the standard deviations, of course, for the first and the last. It's just a basic paired t-test looking from the first to the last, and you can see for the within-group comparisons for the placebo and the 20 and the 60 milligram groups, there were no statistically significant differences between the first and the last. For fluoxetine 60 milligrams, it's a trend for a difference.

Now, looking at the physical, there was a difference between the first and the last for the fluoxetine 60 milligram group, but not the fluoxetine 20 milligram group.

DR. TAMMINGA: So, this is a completers only analysis.

DR. BROWN: Yes. This is only completers. That's correct.

DR. TAMMINGA: So that if you look at a

completers only analysis, it looks considerably different than the last observation carried forth, which is a slide that Dr. Judge showed.

Dr. Hamer.

DR. HAMER: I actually have lots of questions, but just one that's --

DR. TAMMINGA: Do you want the statistician to sit down or stand up?

DR. HAMER: I'm not sure who's appropriate to, answer this one.

Remind me again about what direction the scoring is; that is, let's look, for example, at fluoxetine 60, first cycle, 23.7; last cycle, 31.6. Does that mean they got better or they got worse?

DR. JUDGE: From baseline, the average follicular scores for fluoxetine 60, as in all of them, for VAS 3, was actually around 50. So, the mean here is -- this is 23, which -- and so the mean here is 31, which is slightly worse than 23. The lower the score, the better the patient.

DR. HAMER: So, here for the fluoxetine 60 group, they got non-significantly worse between the.first treatment cycle and the last treatment cycle. Right?

DR. JUDGE: This is a difference of 7 points on this score.

DR. HAMER: In many of the analyses that you presented earlier, you presented a lot of data in which one group had a number that was bigger than another'group and non-significant, but nonetheless, you pointed out to us that one was numerically different than another. Here you're choosing not to pay attention to that numerical difference.

DR.' JUDGE: I don't understand what you mean. We are paying attention in showing that to you. There is a numerical difference. Here the difference is from the baseline to the mean, to the mean, there is, for example, for the 20 milligrams, maybe there's a difference from here to here. The last treatment cycle is about 5 points and only about 7 points for fluoxetine 60 milligrams. So, it's not that great.

DR. TAMMINGA: Dr. Dominguez.

DR. DOMINGUEZ: Yes. This is an unusual application in that not only the total number of patients that were entered into the application, which was similar to the OCD application, but also from the fact that, as far as I'm concerned, at least 80 percent of the strength of the treatment effect is carried by one study. And perhaps you could argue 90 percent of it is carried by the 019 study, the other two studies being relatively small.

Was there an extension phase to the 019 study?

DR. JUDGE: There was not a formal extension phase to that study. Dr. Steiner can perhaps comment anecdotally on what happened to patients after that study, but there were no formal extensions to that study.

Dr. Steiner, would you like to comment?

DR. STEINER: In all sites, most of the subjects who were completers on fluoxetine requested to stay- on the drug and did so. We have informal or anecdotal evidence up to 1 year that women still were on the drug. I'm talking 20 milligrams.

DR. DOMINGUEZ: Was fluoxetine available in the market at the time that the study was initiated in May of 1990? And could this have influenced your retention rate? I am not surprised with regards to the lower retention rate with the placebo group and the 60 milligram group, but I am somewhat surprised at the low retention rate in the 20 milligram group since they seem to be doing so well. So, could the fact that the medication was already available in Canada at that time have influenced your retention rate? What are your thoughts?

DR. STEINER: I can only speculate. But the drug was available.

DR. DOMINGUEZ: It was available.

DR. STEINER: Yes. At the end of the study, the drug was available.

DR. DOMINGUEZ: At the beginning of the study, it was also available. Correct?

DR. STEINER: Yes.

DR. TAMMINGA: Dr. Judge, in this study number 19, could you review for us again the retention rate in the placebo and the 20 and the 60 milligrams?

DR. JUDGE: If we could go back to the primary analysis that shows the patient disposition for study 19 please.

Green, placebo; in orange, fluoxetine 20; and in yellow, fluoxetine 60. For fluoxetine 20 milligrams, about 65 percent of those patients completed the study. Remember, this is actually a 6-month study, which is a long-term study. As you would appreciate in doing studies with obsessive-compulsive disorder, depression, other studies, it's actually very difficult to keep patients in a long-term study. But nevertheless, 65 percent of them completed, and the completer rate in terms of placebo and 60 milligram arm ranged from 40 to 50 percent.

With respect to the dropouts due to adverse events, as you pointed out, it's higher in the 60 milligram group than the other groups. The dropouts due to adverse events between fluoxetine 20 and placebo was not statistically significant, and to be honest, with respect to other studies that we know for depression, OCD, or

whatever, it's not remarkably different. Again, remember, this is over a 6-month study.

As I pointed out, for fluoxetine 60 milligrams, patients were started on that drug at day 1, 60 milligrams at day 1. It would be more appropriate to start them on 20 and titrate them up, giving them a chance to tolerate the side effects. If that had taken place, the titration, one would in fact expected a perhaps lower dropout rate due to adverse events.

In terms of lack of efficacy, as we predicted, about 25 percent of placebo patients dropped out due to lack of efficacy.

DR. DOMINGUEZ: Yes. I appreciate the fact that this was a 24-week study and the OCD studies were 13 weeks. On the other hand, one could view it as a 6-cycle study versus a 13-week OCD study, and that the percentage of response in these trials was very similar to the percentage of response in OCD trials with regards to the active treatment and in comparison also with the placebo group. Basically you had no placebo effect here. You got no placebo effect in your OCD application.

So, since 80 percent of the patients in the 20 milligram OCD study completed the study, I'm a little bit surprised at 65 completing after 24 weeks. Just an observation.

And I wanted to relate that to the availability of the drug in Canada that some patients may have opted out of the study, either seeing insufficient response, and also based on the population that you treated, which was principally a college graduate population or higher education.

DR. TAMMINGA: Yes, Dr. Geller.

DR. GELLER: I just want to comment on comparing OCD to this disorder, that OCD bothers you every day of the month. This bothers you just part of the month and that might account some for the difference in dropouts.

DR. TAMMINGA: Additional questions for Lilly? Dr. Fyer.

DR. FYER: I just want to follow up somewhat more informally this observation because this is the main study that the efficacy depends on. The fact is that they start our randomizing 320 patients out of over 400, and then we end up with 172 patients at the end. I agree that it doesn't seem immediately obvious why that should be true despite the length of the study. If you look at the table about attrition, it doesn't look like there's such a much higher initial rate of attrition in the 60 milligram group.

So, what I'd like to just ask is just informally do the people from Lilly have any idea about why so many people dropped out in that study? Because in the

other studies, Dr. Judge made the point that very few people did drop out. Is it just because you have a more representative sample, you're going to have a higher dropout rate? Or is there something about that study? What were people's informal observations about that situation?

DR. TAMMINGA: Can you comment on this, Dr. Judge?

DR. JUDGE: Just on that point when you said there wasn't evidence of attrition early on in the study, there was in fact, and I think we have a slide to show in terms of patient dropouts due to adverse events for the 60 milligram arm versus the 20. You'll see that most of them did, in fact, drop out in the first two cycles. I'll just show you that, and the slide will show you that.

Thereafter, the attrition rate for fluoxetine 20, placebo -- placebo patients dropped out more towards the end. We show this here. So, this is the patient discontinuations due to adverse events by time. This is a number of patients dropping out. So, for fluoxetine 60, you see that in the first couple of cycles, the patients dropped out. Thereafter, it's a steady dropout, not particularly different from cycle to cycle, and it's fairly constant for the other two arms.

Do you also have the slide due to lack of

efficacy, the same slide? This is true for the lack of efficacy. As one would expect, for placebo patients, more patients drop out as the study continues over the course of time due to lack of efficacy.

In reviewing this data, I think overall the highest number of patients stayed in the study for 20 milligrams. When one looks at the attrition rate for some of the long-term studies for depression and OCD, there is quite a high attrition rate when you refer to OCD studies. The short-term attrition rates are obviously better than -- short-term attrition rates would be not as high as this study. This is a long-term study, and generally when one looks at long-term studies for all drugs, there seems to be a high attrition rate in general. But even so, 65 percent of patients on 20 milligrams were still remaining at the end of the study.

DR. TAMMINGA: Dr. Fyer?

DR. FYER: Yes. I don't want to get into a picky thing about 10 patients, but I think the important thing is that there's a continued steady drop-off. You have a very slight increase in the number of people on 60 milligrams in the first week, but then at every time another 10 percent of the patients are leaving the study. It's not just in the 60 milligram group. Again, I'd just like to ask you if you have some idea as to what was going

on in that study.

DR. JUDGE: Can I refer also Dr. Steiner here?

DR. STEINER: This is not unusual in PMS/PMDD that you lose at the end up to a third of your population, A.

B, this was a very labor-intense study. These women were with us for a year. They had to come twice a month, and some of them just gave up after a while. And the steady decline is really not unusual in these studies.

DR. TAMMINGA: There was some part of Dr. Fyer's question that would contrast the dropout rate in this study with the dropout rate in the next two. While you're up there, maybe you could just more specifically --

DR. STEINER: This was the longest and more labor-intense than the others. The requirements were different. We were bringing them in. They had to be, twice a month, in the clinic for up to 90 minutes, 2 hours sometimes. Canada is a big country. There are all not in the big cities. They're coming from far away. We had winters. All the stuff that you see under "other" is transportation, distance, and cold weather. And then you had to sort of drop them out because if they missed two or three visits, they were out.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: Related to this study, you

mentioned early on in introducing it that a decision was made to focus on the VAS Mood-3 as the primary outcome measure. I wasn't clear about the rationale for that choice. I wonder if you could elaborate on that a little bit.

DR. STEINER: If you recall -- we're talking the late '80s, early '90s -- the visual analog scale was a homegrown thing that we developed. At the time when we started working with Lilly, we did not anticipate, nor did we know that fluoxetine is going to be helpful for the physical symptoms. We thought that if we lumped together the 7 symptoms and if it doesn't work for the physical symptoms, we will actually wash out some effect on the other 3 major components. So, we picked irritability, dysphoria, and tension as the primary outcome. We left the lability out because some people questioned whether this is a unipolar or bipolar dimension, and we then separated them out.

But as you have seen, we have the same statistical significance for the 3 VAS. We have it for the 7 VAS, and we have it for the physical separately.

DR. WINOKUR: My other question. This now switches to safety, adverse events. Can you comment either from your specific studies that you talked about or other information in the literature about the occurrence of

hypomanic or manic symptoms in this specific population on fluoxetine?

DR. JUDGE: With respect to the occurrence and switch into mania for fluoxetine in general, there's a very low switch rate. That's evidenced by the clinical trial database. In fact, one of the few double-blind studies of bipolar depression with fluoxetine versus imipramine, evidenced again a nice treatment effect, without any increase in switch-over to mania versus placebo. So, that's for general fluoxetine.

For switch-over to mania in this study, there were no patients in the PMDD population that ascribed to or switched to mania.

DR. WINOKUR: If you scale it down from full-blown mania to more just --

DR. JUDGE: To hypomania?

DR. WINOKUR: -- manifestations suggestive of hypomania, I'm just wondering whether there's -- I'm focusing on this population because this is going to be a population that's going to be extending the use of this drug.

DR. JUDGE: Right.

DR. WINOKUR: And if there's any even clue of the potential for activation of --

DR. JUDGE: Yes.. From the studies in this

population, there wasn't any event that we'd say, oh, my gosh, this is happening.

Anecdotally perhaps Dr. Steiner can comment about his other experience or even Dr. Endicott.

DR. STEINER: The exclusion criteria were that they should not have an Axis I diagnosis. Therefore, we did not include bipolars. But we did not have hidden bipolar II's and we did not have a single switch in this study.

DR. WINOKUR: That's really what I'm trying to focus on is excluding the known bipolars. Is there any even hint? Because what we're really talking about now is extending this drug to a totally separate population not known to have bipolar, and that's why I think that's a crucial issue.

DR. STEINER: We did not witness one single case.

DR. JUDGE: And that was also evident for the other two studies.

DR. THYS-JACOBS: There was no placebo effect noted during the double-blinded study period 2 in this trial. Was there a placebo effect going from the screening period to study period 1? Was anything noted?

DR. JUDGE: Are you talking about study 1?

DR. THYS-JACOBS.: 19, yes.

DR. JUDGE: Can you repeat your question?

DR. THYS-JACOBS: There was no placebo effect noted during the double-blinded phase at all, and apparently that was being screened for during the single-blinded study. I'm asking was there a placebo effect noted during the screening period into the single-blinded phase?

DR. JUDGE: Yes, indeed. And Dr. Steiner will elaborate. But there were some patients who did drop out during the screening phase because they were placebo responders. So, a placebo effect was evident.

Dr. Steiner?

DR. STEINER: There were 12 placebo responders during those first two cycles and they were not randomized.

DR. TAMMINGA: 12 out of 320 or 12 out of 450?

DR. STEINER: out of 450.

DR. JUDGE: Remember, by this time in terms of the placebo effect, patients had really undergone several cycles of screening with respect to their diagnosis and prospective daily ratings. So, really --

DR. THYS-JACOBS: There were two cycles. We're talking about two cycles. There were two screening cycles. Is that correct?

DR. JUDGE: There were screening cycles, but even before then, patients in terms of their screening, that they brought patients into the study -- we're talking

about one would expect a fairly low level of placebo responders in this study because, for example, in depression or other studies, we don't prospectively diagnose patients by prospective measurements. This is unusual and I think serves to lower the placebo response in PMDD studies in general anyway.

In fact, the placebo effect noted here is not appreciably different from placebo effects noted in other SSRI studies in the literature.

DR. THYS-JACOBS: Most of the studies that I know of have a 25 or 20 percent to 30 percent effect. You're saying that in these studies, in the PMDD trials, there is no placebo effect?

DR. JUDGE: You saw that there was a placebo effect, and in fact for this study, as Dr. Steiner will comment as well, there is a placebo effect. The placebo effect is low which can be sometimes attributed to the screening allowed for these patients. But also remember, in general -- this study was conducted quite a while ago, and maybe as with other studies, maybe there may be a creep up of placebo effect due to other phenomena, as we see with OCD, as we see with depression. That may be evident, and maybe that's what you're ascribing to PMDD studies.

DR. THYS-JACOBS: No. Most of the published trials on PMDD and PMS have-shown effects of anywhere from

20 to 70 percent. So, how are you talking about 12 out of 300 patients going from the screening period into the study phase? That's a very small number.

DR. JUDGE: But there is no study that shows a 70 percent response rate for PMDD. When we talk about those high levels of placebo responses, we're talking about studies which really are not specifically PMDD but more often listed as severe PMS or PMS in general.

Dr. Steiner, would you care to comment on that?

DR. STEINER: Two things. I agree with Susan that -- we were very surprised. It was a low placebo response. Two things to say about it.

The literature is really not about PMDD. It's mostly about PMS, and there the placebo response was obviously much higher.

The other thing is that between the initial screening and the randomization, we have lost not only 12 placebo responders, we have also lost approximately 80 other patients which we were not able to document whether they were placebo responders and that's why they left us. They just disappeared for other reasons. So, maybe it was a little bit higher. But we have documented to date on 12 placebo responders who stayed with us and had to be told that they cannot be randomized because they're placebo responders. That's what I can report on. The others are

speculations.

I think that overall we had a very low placebo response because of the extremely rigorous inclusion criteria. This was the first time that that kind of rigor was actually applied. So, we excluded them before,they even were coming into the placebo phase.

DR. TAMMINGA: Dr. Temple.

DR. TEMPLE: Just a point of terminology. The placebo response is not measured in clinical trials. What you measure is the response in the placebo treated group, which is a mixture of true placebo response, that is, response to drug taking, and the natural history of the disease. This comes up a lot.

The idea that in depression the placebo response is 60, 70 percent I think is totally unreasonable and is a quirk of study design. You take people who are in the process of being at the worst part of a cyclical disease and then you put them in a trial, it's not surprising they regress toward the mean and do other things like that. But if they got a good history of regular monthly symptoms over many years, it doesn't surprise me at all that when you put them in a trial, nothing much happens because they're not regressing toward a mean. This is something they have.

So, these are very study-determined. I have a

sort of personal quest to not call these responses in the placebo group placebo response until somebody actually includes a no-treatment group, that is, someone who doesn't get any drug at all, and that is almost never done. So, we don't really know what the placebo response is here. We just know how the placebo group responds, which is not necessarily the same thing at all.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: After a number of years of doing this, I think I have a reasonably good idea of how to interpret these sorts of studies when the studies have been designed with rigorous protocols by pharmaceutical companies involving an end of phase II/pre-phase III meeting in which the design, the outcome measures, and the statistical analyses are planned and consultation takes place. It's less clear to me how to interpret studies whose purpose is registration when apparently that kind of process didn't take place here.

So, to help me understand this, could somebody from the pharmaceutical company please, in some sense, take me through the history of these studies, tell me whose idea they were, if indeed rigorous documentation, such as protocols that specify design, outcome measures, statistical analyses, in as much specificity as might take place in sort of the usual situation and to what extent

things like the switch apparently from a measure that consisted of a total of a full-blown set of visual analog scales to a measure that consisted of only a subset of them, of an analysis that switched from an analysis of percent change to an analysis that consisted of absolute change, even though, if you analyzed the data both ways, you get consistent results.

But there's in some sense at least the potential for kind of a hidden multiple comparison issue here which, thankfully for Lilly, is probably obviated by the fact that there was such a strong effect that we probably don't need to worry about it much.

But I would like to know sort of how these studies got designed and what role Lilly played, if any, in the design, funding, and execution of them.

DR. TAMMINGA: And your question pertains to all three studies.

DR. HAMER: It pertains to all three studies.

DR. TAMMINGA: Dr. Judge.

DR. JUDGE: Well, study 1 was a protocol designed collaboratively by Lilly and Dr. Steiner. The protocol was put into place and agreed by Lilly and by Dr. Steiner. It was Lilly monitored.

DR. HAMER: So, this is what we would call an investigator initiated study?

DR. JUDGE: Yes, and Lilly funded and Lilly monitored.

For the other two studies, they were conducted more independently. For study number 2, this was conducted under an independent IND, and number 3 was exempt from IND.

For all three studies, protocols and analysis plans were put in place by the investigators before the study obviously started. Lilly, when comprising their analysis plans -- it's important to note that all analysis plans were put into place and very strict audit and quality controls were done for each of the sites to ensure that the studies had been conducted to GCP standards, had'been conducted according to protocol, and with the exceptions that I've stated with the reasons for those exceptions. In all studies, we're confident that the quality of the studies is as one would expect, good quality, GCP conducted studies. Importantly, with respect to the analysis plans, which were prospectively put in place, before any of those Lilly personnel had information or unblinded to the individual patient information.

DR. HAMER: Well, then to move to the blinding issue, I got confused by the statement that apparently the crossover study terminated early because the blind was broken somewhere in the middle and then the investigators did an analysis, presented an abstract, and then decided

not to continue the study. Is that the case that the blind was broken part way through it?

DR. JUDGE: As you indicated, yes, but the blind was not broken to individual patient assignment to the raters who were rating the patients and, moreover, to the patients. As you remember, the primary outcome measure was patient-rated visual analog scale.

Now, when the analysis was done for that study, it involved very few numbers of patients. In fact, the investigator found a treatment effect and stopped the study. In fact, there were a number of other patients enrolled in the study at that time, and they were allowed to complete. That numbered a total of 19, as you saw.

DR. HAMER: I'll save other questions until later.

DR. TAMMINGA: Dr. Chen.

DR. CHEN: Let me add some questions for this topic here. Could you briefly describe the early termination for the second study? How many times you have unblinded the data, when you decided? Did the investigator decide, how they decided to terminate the study? Do you have that knowledge here for this?

DR. JUDGE: In addition to what I've just alluded to, it was an independent decision by the investigator to terminate the study at that time. But as I

said, if someone from my group can elaborate on how many patients exactly that analysis involved. But I said there were a number of other patients ongoing in the study. It wasn't that 19 had completed and then the analysis involved 19 patients. Only a fewer patient number had completed, and in fact when he found that statistical difference, he decided to terminate the study independently. Then the other patients who were already enrolled in that study were allowed to complete. As I said, the clinicians who rated the patients, the patients themselves remained blinded in order to minimize any bias in that study.

DR. TAMMINGA: Dr. Fyer.

DR. FYER: I just want to ask a clarification. So, that was an independent investigator study. Who were the clinicians versus the investigator that all this was kept --

DR. JUDGE: Well, as with any site, there is a principal investigator, and there are people who work with the investigator who are the study coordinators that are more involved in the actual screening of the patients, the rating of the patients week by week, and assessing them per protocol.

DR. FYER: I'm aware of how clinical trials are done generally. But what I'm interested in is, are you aware on a person-by-person-basis of exactly who knew and

who didn't know? Because very often, especially in smaller organizations, there's a lot of functional overlap.

DR. JUDGE: Yes. In fact, for that study -- and my team can correct me if I'm wrong -- it was mainly the other co-investigator for that study, Dr. Su, who was actually seeing more of the patients.

DR. FYER: And so, there was no communication about the overall outcome or any issues about patterns of side effects or anything of that nature.

DR. JUDGE: Not that I'm aware of. As I said, the audit on that study has been very meticulous in terms of quality assurance and quality control.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: Well, to continue Dr. Chen's question, I think maybe one of the things that might be related is, in the protocol, was this interim analysis that led to the early termination of the study planned?

DR. JUDGE: This was an unplanned interim analysis.

DR. HAMER: Do you know if there were other unplanned interim analyses?

DR. JUDGE: No, there were not.

DR. HAMER: So, if you think about spending your alpha in terms of sequential analyses, there was no adjustment for that here. .

DR. JUDGE: If I can ask my statistician to comment on this.

DR. BROWN: No, there wasn't an adjustment. But like we said, the investigator initiated this unplanned interim analysis at 10 patients, found a significant effect, and decided to stop the study, and continued the patients that were currently enrolled, so we ended up with 19 patients.

If we go ahead and use a penalty for an early look, say, an O'Brien-Fleming type of a spending rule, and adjust for those looks at the data at the 10 and the 19, we would still show a significance all the way through. That would be about a .01 nominal significance level we would be looking at at the 19 patient level.

DR. HAMER: Although since this is a post hoc use of an O'Brien-Fleming sequential rule, we really don't know how many interim analyses we should be adjusting for since they might have chosen to have done other interim analyses than the ones that they did.

DR. BROWN: Right. They might have chosen to do something else, but they did just do the one look at 10. So, you're right. It is a post hoc.

DR. TAMMINGA: Should we understand that Lilly looked into whether they did any other unplanned analyses and the answer is no?

DR. BROWN: That's right. No, they did not.

DR. HAMER: Although perhaps the blind to the raters was not broken, did the raters know that an interim analysis had been done and that the interim analysis apparently showed that fluoxetine was superior to placebo?

DR. JUDGE: There was, as I said, an abstract generated from that interim analysis. So, anyone who viewed that abstract would, in fact, know that that was the case. But remember, that was on a fewer number of patients. So, the abstract actually reported a fewer number of patients, but the actual end of the study involved almost a double number of those patients.

DR. HAMER: As long as I have gotten us onto the crossover study --

DR. COOK: Can I follow up on this one?

DR. HAMER: Yes.

DR. TAMMINGA: Dr. Cook.

DR. COOK: I really feel the need to know very specifically how this study was blinded because it just raises many questions if it wasn't blind to the investigative team. So, I really feel the need to have detailed knowledge of how this was blinded to where it could be relatively arbitrarily unblinded. Were the capsules identical? We have to get the details since it's at variance with usual practice.

DR. JUDGE: In terms of the blinding for this study -- and perhaps, Cathy, if you could comment on the actual capsules. Unlike the first study where there was one capsule for like 20 milligrams, 60 milligrams, and placebo, for this study there were, for example, tablets corresponding to 20 milligrams, 30, 40, 50, 60. And in each case, if there was a titration, there was a titration. So, for example, the number of placebo capsules would also increase as well. So, the blinding in terms of the numbers of capsules was exactly identical so physicians could titrate up according to safety and efficacy, and the titration would therefore involve, if it was placebo, a greater number of placebo'capsules; if it was fluoxetine, a greater number of fluoxetine capsules.

Even the principal investigator was blinded to individual treatment assignment.

And that interim analysis, the only one planned for that study, was undertaken on 10 patients. There were 9 other patients in the study at that time, and they were continued on. So, the final analysis involved 19 patients.

Cathy?

MS. SHULER: That's accurate with the exception of the fact that the capsules were in 10 milligram increments.

DR. JUDGE: Dr. Tollefson?