FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

Afternoon Session

March 4, 2013

1:00 p.m. to 5:00 p.m.

FDA White Oak Campus

Building 31, The Great Room (Room 1503)

White Oak Conference Center

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:00 p.m.)

Call to Order

Introduction of Committee

DR. JOHNSON: Good afternoon, everyone. If everyone could kindly take their seats. I would like to remind everyone present to please silence your cell phones, BlackBerrys, or other devices for which you have not already done so. I would also like to identify the FDA press contact for this meeting, Stephanie Yao.

My name is Julia Johnson. I am the chairperson for this advisory committee for reproductive health drugs. I will now call this afternoon session of the meeting of the Advisory Committee for Reproductive Health Drugs to order. We will start by going around the room and introducing ourselves. I know we did this, this morning, but we need to do so again. Let us go ahead and start on our left. Dr. Bockman. Or actually, I apologize. Dr. Soule.

DR. SOULE: I am Lisa Soule. I'm a clinical

team leader in the Division of Reproductive and Neurologic Products.

DR. ORLEANS: I'm Ron Orleans. I'm a medical officer in the same division.

DR. GUO: I'm Jia Guo, statistical reviewer at FDA.

DR. BOCKMAN: Richard Bockman, endocrinologist from Weill Cornell in New York.

DR. CURTIS: Kate Curtis, an epidemiologist from the Division of Reproductive Health at CDC.

DR. KITTELSON: John Kittelson, biostatistics, from the University of Colorado.

DR. ORZA: Michele Orza, consumer representative with Patient-Centered Outcomes Research Institute.

DR. CHAI: Toby Chai. I'm an urologist at Yale School of Medicine, New Haven, Connecticut.

DR. MONTGOMERY RICE: Valerie Montgomery Rice, dean and executive vice president, Morehouse School of Medicine, reproductive endocrinology.

MS. BHATT: Good afternoon. I'm Kalyani Bhatt. I'm with the Division of Advisory Committee

Consultants Management.

DR. JOHNSON: Julia Johnson, chair of OB/GYN, University of Massachusetts, and chair of this committee.

DR. ROSEN: Cliff Rosen, endocrinologist, Maine Medical Center.

DR. CLARKE: Bart Clarke, endocrinologist, Mayo Clinic, Rochester, Minnesota.

DR. ARMSTRONG: Deborah Armstrong, medical oncologist, Johns Hopkins.

DR. DOBBS: Adrian Dobbs, endocrinologist, Johns Hopkins.

DR. KEYES: Linda Keyes, patient representative.

DR. GILLEN: Daniel Gillen, Department of Statistics, University of California.

DR. SCHWARZ: Bimla Schwarz, from the University of Pittsburgh.

DR. GORDON: Keith Gordon, Merck, industry representative.

DR. JOFFE: Hylton Joffe, director of the Division of Reproductive and Neurologic Products at

FDA.

DR. JOHNSON: Thank you and welcome everyone.

For topics such as are going to be discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal for today's meeting is to be fair and have an open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a very productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their discussions about the topic at hand take place only with the open forum of this meeting. We are aware that the media is anxious to discuss these issues with the FDA, however, the FDA will refrain from discussing details of this meeting with the media until its conclusion.

Also, the committee is reminded to refrain from discussing the meeting topic during our break. Thank you.

Conflict of Interest Statement

MS. BHATT: I will be reading the Conflict of Interest Statement.

The Food and Drug Administration is convening today's meeting of the Advisory Committee for Reproductive Health Drugs under the authority of the Federal Advisory Committee Act, FACA 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

The agenda for this afternoon involves the

discussion of new drug application 204516, paroxetine mesylate, 7.5 milligram capsules, submitted by Noven Pharmaceuticals for the proposed indication of treatment of moderate to severe vasomotor symptoms associated with menopause.

This is a particular matters meeting, during which specific matters related to Noven Pharmaceutical's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Keith Gordon is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Gordon's role at

this meeting is to represent industry in general and not any particular company. Dr. Gordon is employed by Merck.

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationship that they may have with the firm at issue. Thank you.

DR. JOHNSON: Thank you very much.

We can now proceed with the FDA opening remarks from Dr. Hylton Joffe. I would like to remind public observers at this meeting that while this is a meeting that's open to public observation, public attendees will not participate except at the specific request of the panel.

Dr. Joffe.

Introductory Remarks - Hylton Joffe

DR. JOFFE: Good afternoon, everyone, and welcome back. This afternoon session, as you heard, is on paroxetine mesylate for the treatment of vasomotor symptoms, moderate to severe vasomotor symptoms, or hot flashes, associated with menopause. And some of the slides that I'll be presenting here are very similar to what I presented this morning. But this is a separate session, and there may be folks here who weren't here this morning, so I think they bear repeating.

So what I'd like to do over the next five minutes or so is explain why we decided to bring paroxetine to the advisory committee, again, give a brief overview of FDA's approach to developing treatments for vasomotor symptoms due to menopause, and ending with the questions that we're going to ask the committee to discuss and vote upon.

So why discuss paroxetine? Well, paroxetine is approved for other indications, psychiatric indications. And if it obtains an indication for the treatment of moderate to severe vasomotor

symptoms, that would potentially make this the first approved non-hormonal treatment for that condition. As I mentioned at the earlier session, FDA sees a lot of value in developing non-hormonal treatments because not all women can use the available hormonal therapies. With that said, FDA feels strongly that our approval standards should be met with regard to a positive benefit/risk assessment for the product.

As you will hear during the presentations, there were two phase 3 paroxetine clinical trials. Each had four co-primary efficacy endpoints, and one of those co-primary efficacy endpoints was not met in one of the trials. Also, at week 12, there was a statistically significant reduction in the frequency of symptoms, and the question is whether that's clinically relevant to the study participants or not.

Again, we used draft guidance from 2003, which talks about treatments for vasomotor symptoms. And over many, many years, we've applied these to products, both hormonal and non-hormonal

products that are being developed for the treatment of vasomotor symptoms. The link to the guidance is on the bottom of the slide.

Some selected recommendations from the guidance are shown on this slide. Again, we recommend randomized double-blind clinical trials of at least 12 weeks in duration. We recommend that women be enrolled with at least 7 or 8 moderate to severe hot flashes per day or at least 50 to 60 per week at baseline.

Then, for efficacy, we recommend the following four co-primary efficacy endpoints. These again are applied to moderate to severe vasomotor symptoms, and they look at the mean change in frequency from baseline to week 4, frequency from baseline to week 12, severity from baseline to week 4, and severity from baseline to week 12. Looking at two time points gives an assessment of durability of effect over time.

With regard to severity, this is the standard scoring we've used for many years. Mild hot flashes are those that cause a sensation of

heat without sweating. Moderate provides a sensation of heat with sweating, but the woman is able to continue her activity, whereas severe, there's a sensation of heat with sweating, and it causes cessation of activity.

Here's the formula that was agreed to by FDA and the applicant for calculating the severity score before the studies got underway. This is assessed at baseline and at weeks 4 and 12. Again, it takes into account the number of moderate and severe hot flashes, and it weights them with a factor of 2 for moderate and 3 for severe. For vasomotor treatments, we either use this formula, and we've also used a variation on this formula that takes into account mild symptoms at weeks 4 and 12. But as mentioned previously, this was the agreed-to formula between FDA and the applicant before studies got underway.

Two other topics I wanted to touch on again. These are not included in the guidance, but they are important. The first is clinical meaningfulness, and it asks whether any reduction

we see in the frequency of moderate to severe hot flashes, relative to placebo, whether that reduction is clinically meaningful to the study participants. We ask applicants to prespecify the support of analysis, and it comes into play if the reduction in frequency in the pivotal trials is found to be small but statistically significant. And by small, as you heard this morning, we talk about a reduction of about less than two episodes per day over placebo.

As you'll hear, paroxetine did meet a reduction in frequency that was statistically significant at weeks 4 and 12 and that this reduction was less than the two per day threshold. And that's why clinical meaningfulness then enters into the picture, and you'll hear the results from those analyses in a little while.

The other topic we're interested in is persistence of benefit. And as I mentioned this morning, this is being asked of all non-hormonal therapies to date, development programs to date. And basically, we ask companies to look at whether

the reduction in frequency of moderate to severe hot flashes persist out to week 24. Again, this is a prespecified supportive analysis, and this will be an analysis we'll look at with paroxetine as well, given that it met statistically significant reductions in frequency at weeks 4 and 12.

I'll just end with the questions we're going to ask the committee to discuss and vote upon. The first one is: Based on the prespecified analyses, is there sufficient evidence to conclude that paroxetine mesylate is effective in treating moderate to severe vasomotor symptoms associated with menopause? Please provide a rationale for your vote and, if applicable, any additional recommendations.

The second question asks: Based on the prespecified analyses, is there sufficient evidence to conclude that the change from baseline in VMS frequency is clinically meaningful to women? Please provide a rationale for your vote and, if applicable, any additional recommendations.

Then the last question asks: Is the overall

risk/benefit profile of paroxetine mesylate acceptable to support approval of this product for the proposed indication? Please provide a rationale of your vote and, if applicable, any additional recommendations.

With that, I will turn this back to the chair. And I want to thank everyone for coming, and I look forward to an interesting discussion.

DR. JOHNSON: Thank you very much.

Now, we can proceed with the sponsor presentations. As they prepare to speak, a reminder that both the FDA and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes it is important to understand the context of each individual's presentation.

For this reason, the FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships which they may have with this firm at issue, including consulting fees,

travel expenses, honoraria, and interests in the sponsor, including equity interests and those based on the outcome of today's meeting.

Likewise, the FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationship. If you choose not to address this issue of financial relationship at the beginning of your presentation, it will not preclude your speaking.

Thank you, and let us proceed with the sponsor's presentations. Dr. Lippman.

Sponsor Presentation - Joel Lippman

DR. LIPPMAN: Thank you, Dr. Johnson

Good afternoon. While vasomotor symptoms are not life-threatening, they are life-altering. My name is Joel Lippman, and I'm an OB/GYN who has dedicated my working career to women's health, starting first in clinical practice, and then working in industry to develop women's healthcare products.

Since 2008, I have been chief medical

officer and head of research and development at Noven Pharmaceuticals, a company whose foundation is in women's health, including hormonal treatments for vasomotor symptoms or VMS. We understand that women and clinicians need an alternative, another option to consider alongside hormone therapy.

On behalf of my colleagues at Noven, we are gratified to be here to work with this committee to bring a new treatment option to women with VMS. After this introduction, Dr. David Portman, a practicing OB/GYN and director of the Columbus Center for Women's Health Research, will present the symptom burden of VMS, current treatments, and the need for new treatment options. I will then review the clinically meaningful efficacy of low-dose mesylate salt of paroxetine or LDMP.

Dr. Brent Blumenstein is an independent biostatistician who was asked by Noven to review all the statistical work conducted on LDMP data and will discuss the association of the primary efficacy endpoints with multiple clinical outcomes. Dr. Blumenstein has published extensively, served

on multiple FDA advisory committee meetings, and is the former deputy director of the Southwest Oncology Group's statistical center.

I will then describe the safety and tolerability of LDMP. Dr. Elizabeth Lucini, the head of pharmacovigilance for Noven, will review the risk management plan. Finally, Dr. Portman will return to provide a clinical perspective on the patient-reported benefits of LDMP.

LDMP is a selective serotonin reuptake inhibitor, and it's mechanism of action for the treatment of VMS is thought to be related to the potentiation of neurotransmitters in the central nervous system, which impact regulation of body temperature control. The formulation is a 7.5 milligram capsule dosed once a day at bedtime without the need for titration.

The VMS dose of paroxetine, for which we are seeking approval, is lower than the therapeutic doses of paroxetine that are currently approved for psychiatric indications and are currently being used off label to treat VMS. Now, Dr. Portman will

discuss the patient burden of VMS and current treatment options.

Sponsor Presentation - David Portman

DR. PORTMAN: Good afternoon. My name is David Portman. I'm director of the Columbus Center for Women's Health Research and a practicing OB/GYN. I've received research grant support, honoraria, travel, and compensated for my time, but I have no financial interest in the company or the outcome of this meeting.

My clinical practice focuses on menopause. I prescribe hormone treatment for VMS, but over the last decade, I've seen growing resistance from my patients to hormone treatment. My patients and I need an other FDA-approved treatment option for VMS.

Vasomotor symptoms are frequent and disruptive, occurring at a time in a woman's life and career when her functionality and productivity are critical. By definition, a severe hot flash does not allow a woman to continue with her current activity. Sweating, which occurs with all moderate

and severe hot flashes, can be embarrassing at work and socially impact on quality of life. Night sweats and interrupted sleep not only impact the woman and her partner; awakenings are also often associated with decreased productivity during the day and reduced ability to function.

Hormone therapy is currently the only approved treatment option for VMS, however, it's not appropriate for all patients, particularly those with risk factors for cancer and cardiovascular conditions. Even after extensive counseling, many if not most of my patients decline to even initiate hormone therapy due to perceived risks and concerns. Some patients try over-the-counter and herbal remedies, which have no proven efficacy and unknown risks. We are left with no other evidence-based approved treatment options. As a result, we resort to off-label neuropsychiatric drugs, including paroxetine, but without a label, prescribing information, or definitive data to inform us.

Published results of limited

placebo-controlled clinical trials suggest that SSRIs and SNRIs may be efficacious, non-hormonal treatments for VMS. This forest plot suggests that paroxetine may be one of the most effective agents. The studies conducted by Stearns show that there is no dose response with regard to efficacy as evidenced by the lack of difference between the 10-milligram and 25-milligram per day doses, however, higher doses were associated with more adverse events and more discontinuations due to adverse events.

Of particular concern for mid-life women are weight gain and impaired sexual functioning, common side effects seen with doses of paroxetine approved for psychiatric use. According to the estimates from IMS Health, over 3 million prescriptions were filled for antidepressants to treat VMS in just the last year. Of these, 2.4 million prescriptions were for SSRIs. OB/GYNs account for 13.2 percent of total off-label use; PCPs, 52.6 percent.

There's a clear unmet need for additional approved treatment options, over than hormones, for

women with moderate to severe VMS. Such treatment options should be evidence-based and specifically labeled for VMS.

Now, Dr. Lippman from Noven will present the efficacy data.

Sponsor Presentation - Joel Lippman

DR. LIPPMAN: The efficacy of LDMP, administered once daily at bedtime, was established in postmenopausal women with moderate to severe vasomotor symptoms. In addition, patient perception of clinical benefit was also established.

The two pivotal phase 3 studies had a similar study design. Both were randomized, double-blind, and placebo controlled. After a 12-day, single-blind, placebo run-in period, subjects were randomized 1 to 1 to placebo or LDMP. Study 3 ended at week 12, where Study 4 extended to week 24. The study population were similar for both studies, except that in Study 4, 10 percent of patients had a prior psychiatric diagnosis.

These studies enrolled postmenopausal women

greater than 40 years of age who had at least 7 moderate to severe hot flashes per day or at least 50 flashes per week. Co-primary endpoints for both studies were mean changes in the frequency and severity of moderate to severe VMS from baseline to weeks 4 and 12. As per the statistical analysis plan, since the normality assumption was not met, median daily change in hot flash frequency and severity are reported. In addition to the primary endpoints, PGI-anchored receiver operating characteristic analysis in Study 3 and persistence of benefit at week 24 in Study 4 were prespecified supportive endpoints.

These studies also evaluated patient-perceived benefit using prespecified direct and indirect assessments. The assessments included patient global impression of improvement, changes from baseline in nighttime awakenings, climacteric symptoms, and daily interference of hot flashes. In addition to patient perception of improvement, the studies also collected data on clinician perception of improvement using the Clinical Global

Impression scale. There was no imbalance between the treatment arms with respect to demographic and baseline characteristics.

These studies included postmenopausal women with an average age of 55 years. Approximately 70 percent were Caucasian and 30 percent were African American. Twenty percent were surgically menopausal and 80 percent were naturally menopausal. The co-primary endpoint of change in frequency was significantly in favor of LDMP in both studies.

In Study 3, women taking LDMP had significantly greater reductions in median daily hot flashes compared to placebo at both week 4 and 12. The absolute change from baseline at week 4 for LDMP was 4.3 flashes per day and for placebo was 3.1. And at week 12, it was 5.9 for LDMP and 5.0 for placebo. The placebo-adjusted benefit in favor of LDMP is 1.2 at week 4 and .9 at week 12.

The results in Study 4 were also significant. In Study 4, women taking LDMP had significantly greater reductions in median daily

hot flashes compared to placebo at both week 4 and week 12. The absolute change from baseline at week 4 for LDMP was 3.8 flashes per day, and for placebo was 2.5. At week 12, it was 5.6 for LDMP and 3.9 for placebo. The placebo-adjusted benefit in favor of LDMP is 1.3 at week 4 and 1.7 at week 12.

At week 24, the results were also significantly in favor of LDMP. The co-primary endpoint of severity was assessed using the prespecified weighted average severity score, which is calculated by adding together the total number of severe and moderate hot flashes weighted with a value of 3 for severe and 2 for moderate and then dividing that by the total number of moderate and severe hot flashes. The result provides the average severity of an individual hot flash without regard for the number of flashes. The score always ranges from 2 to 3, and the score becomes indeterminate if the patient is a complete responder and has zero hot flashes.

In Study 3, women taking LDMP has

significantly greater reductions in the median daily hot flash weighted average severity score compared to placebo at week 4. At week 12, the difference favored LDMP but did not meet statistical criterion. In Study 4, LDMP showed significant reductions in severity score at both week 4 and week 12. At week 24, results were also statistically significant in favor of LDMP.

In order to better understand LDMP's impact on the overall patient burden, we performed an exploratory analysis, looking at the reduction and hot flash composite score, which provides an integrated picture of hot flash frequency and severity. The composite score is representative of actual patient burden. The score is the numerator of the previously discussed weighted average severity score.

The LDMP treatment arm had a significantly greater reduction in hot flash composite score from week 1 through week 12. This represents a substantial decrease in the patient burden that is clinically meaningful because there's a decrease in

both the frequency and severity of moderate and severe hot flashes.

Another exploratory analysis looked at patient burden by examining the treatment effect of LDMP on severe hot flashes only. Severe hot flashes by definition lead to disruption of activity. LDMP resulted in significantly greater reductions in severe hot flashes compared to placebo at week 4 and week 12 in both studies. In addition, the benefits of LDMP persisted out to 24 weeks.

In Study 4, the persistence of benefit was demonstrated by the 50 percent reduction rate in hot flash frequency compared to baseline. More patients treated with LDMP than placebo met the definition of persistence at week 24 and this met statistical criteria. Persistence of benefit can also be evaluated by looking at responders at week 12 who continue to benefit at week 24.

The lower left-hand quadrant reflects the patients for whom their week 12 change in frequency persisted to week 24. The majority of patients who

responded at week 12 saw a continued benefit at week 24. These reductions in the frequency of hot flashes were not only persistent but also clinically meaningful to patients. In our clinical trials, we asked patients directly and indirectly about their perception of improvement, and, consistently, patients answered that they benefitted from treatment with LDMP.

The patient global impression of improvement is a direct way of assessing treatment benefit. A greater proportion of patients on LDMP described themselves as very much better and much better, seen here on the left, compared to placebo; while fewer patients reported having no change or worse, seen to the far right, compared to placebo. Similar results were observed at week 4. This endpoint was only assessed in Study 3.

A responder analysis linking patients perception of improvement to reduction in hot flash frequency was conducted. For this analysis, a patient was considered as satisfied with treatment if they scored as much better or very much better

on the PGI. A higher percentage of patients on LDMP at both week 4 and week 12 had a clinically meaningful response. This was statistically significant at week 4.

Another direct way of assessing the clinical benefit of hot flash frequency reduction is by looking at the number of nighttime awakenings due to flashes. LDMP achieved significantly greater reductions in nighttime awakenings due to hot flashes at week 4 and 12 in both studies and also at week 24 in Study 4. There are multiple domains of climacteric symptoms, and the green climacteric scale assesses each of these domains and is an indirect measure of clinical benefit.

The GCS is a validated and self-administered questionnaire. The GCS showed greater reductions in vasomotor symptoms for patients on LDMP at week 12 in both studies. Results were similar at week 4. The clinical global impression of improvement was assessed in both Studies 3 and 4 and favored LDMP in both trials.

A higher percentage of patients on LDMP were

responders on the clinical global impression of improvement. Responders were defined as patients whose scores range from a little improved to very much improved. These results achieved statistical significance at weeks 4, 12 and 24.

Dr. Blumenstein, an independent statistician, will now discuss the exploratory analyses on the prespecified primary and secondary endpoints and the associations between the reduction and hot flash frequency in clinical outcomes.

Sponsor Presentation – Brent Blumenstein

DR. BLUMENSTEIN: Good afternoon. My name is Brent Blumenstein. I'm an independent biostatistician, and I've been compensated for my consulting time but have no financial interest in the company or the outcome of the meeting. I will discuss exploratory analyses used to evaluate multiple outcomes. Specifically, I will show that the frequency primary outcome relates to secondary outcomes in a way illustrating the clinical mean of LDMP across multiple domains.

The first method of analysis uses the outcome as a dichotomy; that is, as response versus no response. Thus, all outcomes will be on the same scale. Dichotomization methods used included the pooled baseline median, assessing the sign of changes, and using predefined criteria related to the nature of the outcome. A drawback of dichotomization is loss of statistical sensitivity, but this is an acceptable tradeoff.

Now, the measure of effect to be used in each outcome is the odds ratio; that is, the odds of response in the experimental arm divided by the odds of response in the control arm. Each outcome odds ratio is assessed for direction that greater than 1 favors LDMP and also assessed with respect to the information that comes from the width of its 95 percent confidence interval.

Since the effect size estimates are all on the same scale, a forest graph can be used to display the LDMP effect across broad range of outcomes. In Study 4, the preponderance of odds ratio estimates are to the right of 1; that is,

LDMP is favored, and therefore there's a broad clinical benefit, as suggested. The results for Study 3 are similar.

I will now focus on the global impression class of outcomes. The patient global impression was administered in Study 3, and the clinical global impression was administered in Studies 3 and 4. The clinical and patient global assessments are strongly associated despite them being assessed separately. The association is illustrated in Study 3 in this block graph for week 12. Agreement of patient and clinician impressions of improvement is clearly evident. The taller blocks running from front to back show the frequency of exact agreement between the patient and clinician impressions, and these cases are dominant. The same association is seen for week 4.

The global impressions are also strongly associated with the frequency primary outcome. In this dot graph, patients having a larger decrease in frequency also tend to report an impression of greater improvement; that is, a lower patient

global impression score. This kind of association was observed for the global clinical impression in both studies at all weeks. The associations illustrated for the global impressions can also be seen across a broad range of other outcomes, including nighttime awakenings, climacteric symptoms, and the daily interference of hot flashes.

Now, another method of confirming the general and broad LDMP clinical benefit is to perform a global statistical test. A global multivariate test assesses all outcomes simultaneously instead of one at a time. The O'Brien test procedure ranks each outcome across all patients regardless of arm, then a score is computed for each patient from these ranks as a simple sum of the ranks for that patient; then the arms are compared using a two-group T test on these scores. A small p value for the T test is evidence that the outcomes in one arm are generally shifted away from the outcomes of the other arm.

The O'Brien test p values are all small, as

can be seen in the table for 12-week results. Similar results are seen at other weeks. The first set of O'Brien tests, those in the first two rows, includes the primary outcome and the important other outcomes as seen previously in the multiple outcome forest graph. The second set of tests do not include the primary outcomes, and the p values are also small. The purpose of this second set of tests was to assess whether the global test was dominated by the primary outcomes.

Dr. Lippman will now return to conclude the efficacy presentation and describe the safety of LDMP.

Sponsor Presentation - Joel Lippman

DR. LIPPMAN: The efficacy of LDMP was demonstrated in two adequate and well-controlled studies. LDMP reduced hot flash frequency significantly at weeks 4 and 12 in both studies compared to placebo. Reduction in severity was significant for LDMP compared to placebo at week 4 in both studies and at week 12 in Study 4. Although statistical significance was not achieved

at week 12 for reduction in the weighted average severity score, when examined in the context of the totality of the data, there's consistent evidence of benefit at all time points.

Daily reductions in both frequency and severity were also significantly in favor of LDMP at week 24. A significantly greater proportion of patients on LDMP achieved a 50 percent reduction in hot flash frequency from baseline compared to placebo at week 24, demonstrating persistence of benefit. An association of the direct and indirect outcomes to frequency reduction show a convergence of data that provides compelling evidence of the clinical benefit with LDMP.

There were no new or unexpected safety findings observed in the LDMP clinical program out to 24 weeks. The LDMP NDA also relies on FDA's findings of safety for higher doses of paroxetine. Data presented is for the all-controlled studies' pool, which includes the phase 2 study and the two phase 3 studies. Of the nearly 1300 patients enrolled into the clinical studies, about half of

LDMP and placebo patients reported an adverse event.

The rates of adverse events leading to discontinuation were 4.4 percent and 3.3 percent, respectively. The proportions of patients experiencing at least one serious adverse event were 2.2 percent and 1.4 percent, respectively. There was one death in the LDMP clinical program. The patient died of an acute cardiorespiratory failure, and this event was reported by the investigator as not related to study drug.

The most commonly reported adverse events that occurred at a rate of 2 percent or more and at twice the rate of placebo were fatigue, nausea, and dizziness. These common adverse events occurred primarily within the first four weeks of treatment. Adverse events of special interest were based on the paroxetine label and patient or physician tolerability concerns with SSRIs.

There was one spontaneously reported event of suicidality in the clinical studies. This event was a suicide attempt in Study 4 in the LDMP arm,

in which a patient took an overdose of non-study medications, and this event was determined to be not related to treatment by the investigator. In the LDMP clinical program, suicidality data was prospectively collected using validated scales at scheduled clinic visits.

Study 4 and the phase 2 study utilized the self-administered Sheehan Suicidality Tracking Scale or STS. This instrument is known for detecting subtle changes that may be subclinical. Prior to the initiation of Study 3, FDA issued a guidance recommending the Columbia Suicide Severity Scale for the prospective assessment of suicidality in clinical trials. Study 3 used the Columbia scale instead of the STS. This is a rater-administered scale that is less prone to subclinical findings.

In Study 4, there was a numerically increased rate of adverse events based on scale-elicited suicidal ideation and behavior on LDMP using the STS. All of these reports were reviewed by the safety monitoring committee. In

Study 3, there were no treatment-emergent suicide ideations or behavior found on the Columbia scale.

The incidence of abnormal bleeding adverse events was similar across groups. Vaginal or postmenopausal hemorrhage was the most commonly reported event in both groups, with six subjects in each group experiencing this event. There were no clinically important findings with respect to GI or other bleeding events in the LDMP group.

There were 5 bone fractures reported in the clinical program, 4 events in 3 subjects in the placebo arm and 1 in the LDMP arm. In the LDMP studies, there were minimal discontinuation symptoms and no increase compared to placebo in the rates of sexual dysfunction or weight gain, concerns that physicians and patients have with higher doses of paroxetine in this population.

The DESS was administered within 7 days of the last dose of study drug. Approximately 15 percent of patients experienced new symptoms and the incidence of new symptoms did not differ much between patients in the LDMP and placebo treatment

arms. These results confirm that there is no need for tapering when discontinuing dosing.

The Arizona Sexual Experiences Scale was prospectively administered to evaluate the effect of LDMP on sexual functioning. These results showed that there was no difference between LDMP and placebo in sexual dysfunction. Weight was measured at every clinic visit, and the percent change in weight from baseline was less than 1 percent at week 4, week 12, and week 24 and were similar between groups.

The safety and tolerability of LDMP is favorable for the treatment of moderate to severe vasomotor symptoms. There were new or unexpected safety findings in the LDMP clinical program. The most common adverse events occurring more frequently in LDMP were nausea, fatigue, and dizziness. These events were generally mild to moderate and occurred primarily within the first four weeks of treatment. The LDMP profile builds on the well-established safety profile of paroxetine, which has been used for over 20 years

at higher doses.

Dr. Lucini will now review the risk management program for LDMP.

Sponsor Presentation - Elizabeth Lucini

DR. LUCINI: Good afternoon. I'm Elizabeth Lucini, and I'm the senior director of regulatory affairs and pharmacovigilance at Noven Pharmaceuticals. Noven is proposing a risk management process to identify and mitigate risks associated with the use of LDMP for the treatment of VMS. The elements of the risk management process will be discussed and refined with FDA. The LDMP clinical program identified no new or unexpected safety findings in postmenopausal women with VMS.

Paroxetine at doses of 10 to 60 milligrams for psychiatric indications has an established safety profile. Noven has developed a risk management plan to ensure the appropriate use of LDMP while focusing on the currently labeled paroxetine events. The elements of the risk management plan include the label, a medication

guide, pharmacovigilance with targeted follow-up, postmarketing surveillance, and an education plan.

Noven has adopted the class safety labeling for antidepressants, including SSRIs, in safety labeling for paroxetine in the proposed for LDMP. This label will therefore include all warnings and precautions from the paroxetine label. These include, but are not limited to, the boxed warning for suicidality and the warnings regarding abnormal bleeding, bone fractures, and use in pregnancy. The proposed LDMP label also includes the contraindications from the paroxetine label.

We understand that the division is discussing concomitant use of tamoxifen with the oncology division. Based upon those discussions, Noven will work with FDA to determine the best way to address the concomitant use of tamoxifen in labeling and in educational activities.

Noven has proposed that patients prescribed LDMP receive a medication guide which matches the warnings and precautions in the full label but presents them in patient-friendly language and

includes a list of symptoms that should be monitored for. In addition to pharmacovigilance activities, there will be targeted follow-up for adverse events of special interest, which currently include suicidality, abnormal bleeding, and bone fracture, and will be refined on an ongoing basis.

The goal of this targeted follow-up is to obtain as much relevant information as possible to enable a meaningful assessment of causality on the individual case level. These events are assessed for a signal by comparing the rate in a given time frame to previous time frames and against the background rate.

Additionally, Noven will conduct signal detection using FDA's AERS database and active surveillance using medical claims data. Active surveillance will better enable separation of a potential signal from the background rate, using a large healthcare utilization database containing real-world information. By performing active surveillance, the database will be used to collect case reports at defined periodic intervals in

defined groups, focusing on the AEs of special interest. Data on two groups of women with VMS will be collected, women receiving LDMP and women treated with other medications. Active surveillance will enable the identification of a new signal or the validation of a potential signal that was identified via pharmacovigilance.

Epidemiological studies and claims databases have shown an increase in bone fractures and depressed patients taking SSRIs. Despite emergent evidence of the importance of serotonin in bone health, the mechanism by which SSRIs increase fracture risk is not clear. Noven is prepared to conduct a study of sufficient power and duration to assess the effect of LDMP on bone mineral density and bone turnover markers with follow-up if needed to see if any negative effects are reversible.

The LDMP education and outreach program is focused on reinforcing potential safety risks described in the label and the importance of monitoring patients for them. Specifically, the education plan will target prescribers,

pharmacists, and patients, and will be tailored for each audience. The content will highlight the labeled risks, and it will also include information on drugs that should not be used concomitantly with LDMP.

The elements of the risk management plan as described will be discussed and agreed with FDA during the NDA review, and on an ongoing basis, Noven will assess the appropriateness of risk management activities in consultation with FDA.

Dr. Portman will now put the risks and benefits of LDMP into clinical perspective.

Sponsor Presentation - David Portman

DR. PORTMAN: My patients who come to me for help with their vasomotor symptoms for menopause need more treatment options, particularly non-hormonal treatment options. LDMP should be part of my armamentarium for treating VMS because of its demonstrated efficacy and offers a safety profile differentiated from hormone therapies.

In trying to determine the best choice for an individual patient, it will be important to

understand the benefits and risks of each treatment option to make an evidence-based treatment decision for each patient. At the same time, we need to understand the patient's own concerns and preferences. In order to help understand the risks and benefits of each treatment choice for a given patient, it's important to put the results of the phase 3 studies into perspective.

The relative benefit/risk of LDMP can be put in context with the only approved treatment for VMS, hormone therapy, by using the available data from the label and literature. Both hormone therapy and SSRIs have a very well defined safety profile within their respective classes. SSRIs have a boxed warning for suicidality, which I discuss in detail with my patients. With hormone therapy, I discuss the boxed warnings for the increased risk of stroke and venous thromboembolism, including DVT and PE, as well as breast and endometrial cancer.

In order to have a viable non-hormonal treatment option for VMS, it must provide

reductions in hot flash frequency that are clinically meaningful. In the phase 3 clinical trials, LDMP showed an approximate 59 percent decrease in frequency of moderate to severe hot flashes over baseline. To put this in context, in a Cochrane review published in 2009, hormone therapy averaged a 75 percent reduction over baseline across all doses, a greater reduction at the higher dose range, and roughly a 65 percent reduction at lower doses.

The experience of VMS is multifaceted. It requires a range of endpoints and patient-reported outcomes to adequately gauge clinically meaningful improvement. We now have convincing data that show that LDMP reduces frequency and severity of moderate to severe vasomotor symptoms. From my clinical perspective, great insight from the LDMP program relevant to assessing clinical benefit can be found in these data which show the beneficial effect of LDMP on multiple outcomes. The results of these outcomes favor LDMP with the majority of point estimates to the right of unity.

Patients presenting to me with VMS at the time of menopause also describe a range of climacteric symptoms. The green climacteric scale assesses these symptoms, and in the LDMP clinical trials, scores from this scale were associated with the co-primary endpoint of frequency reduction.

The GCS is a validated, self-administered questionnaire, evaluating common menopausal symptom domains and their severity and impact on the patient. LDMP was favored over placebo in the psychological and vasomotor domains. Importantly, there was no negative impact on libido, a common complaint among patients on higher doses of SSRIs.

As a clinician, these improvements in patient-reported outcomes and directional benefit on multiple menopausal domains is of extreme clinical importance to me since patients with VMS often have multiple concerns and complaints accompanying their presentation. In the hot flash related daily interference scale, the HFRDIS and the profile of mood states, POMS, which are both associated with the co-primary endpoint of

frequency reduction, also demonstrated a beneficial impact of LDMP on multiple menopausal symptom clusters.

In the HFRDIS at week 12, patients had less interference on LDMP in the social, leisure and enjoyment domains and in sleep and quality of life. Beneficial improvement with LDMP is further confirmed by the benefits seen on the POMS and patient domains, such as increases in vigor and activity and decreases in inertia. Along with the GCS, these patient-reported outcomes indicate that patients treated with LDMP had significant and clinically meaningful benefit in many aspects of their lives.

I've used paroxetine and other SSRIs off label at higher doses, so I was curious to see if this very low dose of paroxetine would benefit my patients with the most bothersome symptoms and requested a subanalysis be done of the patients that entered the study with the greatest burden of symptoms at baseline. I asked the sponsor to analyze the data from patients who had a baseline

GCS score greater than 12, a GCS vasomotor score of greater than 2, and patients who had baseline frequency of more than 10 hot flashes per day. The cutoff for GCS used in this exploratory analysis have been published in a recent article with desvenlafaxine and were defined as a way of identifying baseline bothersomeness VMS criteria.

There is consistent benefit across patient subgroups with all the point estimates favoring LDMP in this severely symptomatic patient population. I was pleased to see that the patients with the greatest burden had some of the greatest magnitude of benefit over placebo. As a clinician, I asked my patients how they're responding to treatment, about their impression of improvements, and actually assessed this in the study with the CGI as an investigator during the LDMP trials. Clinicians saw a consistent treatment effect of LDMP apparent at week 4 through week 12 in both trials, and through week 24 in Study 4. These differences were statistically significant at all time points in both studies.

The CGI reflects the exact sort of conversation that we have with our patients during office visits, especially outside of the clinic trial setting, deflecting a meaningful treatment benefit. The clinician's impression was corroborated by the patients' own impression of improvement, as seen with the PGI, and these results along with the improvement in multiple patient-reported outcomes illustrate the positive impact of LDMP treatment on patients' lives.

There's a clear need for FDA-approved non-hormonal treatment options for VMS. Low-dose mesylate salt of paroxetine at 7.5 milligrams taken once daily at bedtime has demonstrated significant reductions in the frequency and severity of hot flashes. These reductions translate into clinically meaningful improvements as perceived by patients and clinicians, and these improvements persisted up to 24 weeks with no diminished efficacy during the course of treatment.

Across multiple measures, LDMP demonstrated meaningful and consistent benefit over placebo.

LDMP was well tolerated with a low rate of adverse events and, importantly, the common side effects of weight gain and sexual dysfunction, known to be associated with higher doses of SSRIs, were not increased over placebo. Additionally, there's no need for titration or tapering with LDMP, which is not surprising, considering that the dose of LDMP is below the lowest approved dose of paroxetine, and yet can treat some of the most severely affected patients.

Significant numbers of my colleagues are prescribing higher doses of paroxetine and other SSRIs off label to treat VMS with no guidance, no active surveillance, and no label for VMS. What's most important to me is that the patients reported through the PGI that they've benefitted from treatment. Less important but still compelling, the clinicians in the study also reported patient improvement with treatment using the CGI. These results corroborated the patients' perception of improvement.

So given the consistent clinically

meaningful benefit and its safety and tolerability, LDMP has an overall favorable benefit/risk profile. It would be a welcomed addition to consider alongside hormonal therapies for VMS. These treatment options belong side by side. Let doctors and patients choose which is right for them. Thank you.

DR. LIPPMAN: In addition to the speakers you've already heard, we have with us several independent experts who are available to address questions. They are Dr. Gerard Sanacora, director of the Yale Depression Research Program; Dr. Annette Stemhagen, vice president of safety, epidemiology, registries and risk management at United BioSource; and Dr. Nelson Watts, director of Mercy Health's osteoporosis and bone health services in Cincinnati, Ohio.

Clarifying Questions to Sponsor from Committee

DR. JOHNSON: Thank you very much. I appreciate all the information provided. Now, we can proceed to clarifying questions from the committee. Shall we begin with Dr. Bockman?

DR. BOCKMAN: I have two questions. One is, you talked about -- looking at slide 67, it looks like there's a discordance -- unless I read this incorrectly -- between the severely affected, the GS score greater than 12 versus greater than 2, between Study 3 and Study 4. There does seem to be a better mean for Study 3, but not for Study 4.

Does that make sense to you?

DR. LIPPMAN: Yes. And I'd like to ask Dr. Blumenstein to comment on that.

DR. BLUMENSTEIN: Slide up, please. Well, this is showing lots of tests, and these tests weren't necessarily predefined. This is an exploratory analysis, so there's going to be some degree of wobble in the outcomes. And one shouldn't take the crossing of the null line -- in this case zero. One shouldn't take that to mean that there's lack of statistical significance in the sense that the primary analyses were analyzed. So, yes, there's what we interpret this as just wobble in the outcome across all these outcomes.

DR. BOCKMAN: Just a quick follow on that.

I mean, the conclusion that it was equally effective in severely affected versus less affected individuals was not different? The effect of the drug in hot flash reduction? I mean, in Study 3, it definitely looks like it's lower, but -- that's what I was wondering. But there's a difference between the two studies. And you say there's enough wobble in the data that you can't really make that distinction.

DR. BLUMENSTEIN: Well, I would say -- to answer your question directly, I would probably want to then model the pooled data for the studies in a model that included an interaction term for benefit by arm with study involved in that interaction.

DR. BOCKMAN: Okay.

DR. BLUMENSTEIN: And, quite frankly, I just haven't done that.

DR. BOCKMAN: All right. So this graph is not really addressing the issue that Dr. Portman raised.

Can I switch -- I would like to ask -- since

you do have an expert here, I wonder if Dr. Watts would like to comment on the fact that all the fractures that occurred, occurred in the treatment arm. There were three fractures.

So I guess my question is twofold. One is, is there some proven relationship between SSRIs and fracture? And two, is that just a lucky finding?

DR. LIPPMAN: Yes. Just to clarify, the three fractures were in the placebo arm.

DR. BOCKMAN: That's a better outcome.

DR. WATTS: So if we could have a slide up on the fractures to show that they were all in the placebo arm. And slide off, please.

My name is Nelson Watts. I'm an endocrinologist from Cincinnati, Ohio, with a long interest in osteoporosis and bone health. I've been paid for my consulting time, and my expenses have been covered, but I have no financial interest in the company, nor in the outcome of this trial.

I think it's instructive to understand that this lower dose of paroxetine mesylate, a selective serotonin receptor inhibitor, is taking on the

label of all SSRIs. And to provide that language, epidemiologic studies on bone fracture risk following exposure to some antidepressants, including SSRIs, have reported an association between antidepressant treatment and fractures. There are multiple possible causes for this observation, and it is unknown to what extent fracture risk is directly attributable to SSRI treatment.

Now, I did several systematic literature searches. I found nothing on paroxetine and fractures, nothing on paroxetine bone density or bone turnover markers. There is literature dating back over 30 years, showing that people with depression are at increased risk of fracture; that antidepressant drugs increase fracture risk further, and that includes SSRIs, and possible mechanisms might include hyponatremia or increased risk of falling.

There's been considerable interest in serotonin as a mediator of bone health. Gut serotonin has a negative effect on bone formation.

CNS serotonin through neuronal influences has a positive effect on bone formation and may reduce bone turnover. Having said that, there is no data that I could find on SSRIs in depressed patients that provides a convincing story. There are some cross-sectional and observational studies suggesting that depressed patients on SSRIs had lower bone density and perhaps faster rates of bone loss, but no studies of lower-dose SSRIs in patients without depression.

As stated, the sponsor is prepared to conduct a study that would assess whether or not this lower dose of SSRI in non-depressed patients has an effect on bone turnover markers or on bone density.

Slide up, please. So the plan would be to do a prospective double-blind, randomized trial over two years, looking at bone turnover markers and bone mineral density with follow-up if needed, so that if negative effects are observed, that it would be possible to determine whether or not those are reversible when treatment is stopped.

DR. JOHNSON: Thank you. Dr. Montgomery Rice?

DR. MONTGOMERY RICE: Dr. Bockman led Dr. Watts to my answer for my question, so he answered it all. That was it.

DR. JOHNSON: Thank you. Dr. Dobbs?

DR. DOBBS: My question refers to slide 50 on sexual function. So to say that 45 percent had no sexual dysfunction means that 55 percent had sexual dysfunction, which I would think is a little bit high for this age group. And I wonder how much depression is mixed in with your population and whether or not your drug is working on depression at all.

Also, my understanding is that the drug affects both decreased libido and orgasmic function, and I wondered if you could comment a little bit more on that.

DR. LIPPMAN: I'm going to ask Dr. Bhaskar, our executive director of clinical research, to comment on the scale.

DR. BHASKAR: Good afternoon. Sailaja

Bhaskar, clinical research, Noven Pharmaceuticals. So the Arizona Sexual Experiences Scale was administered in the study at week 4, 12 and 24, in both studies. And what we -- so the questionnaire collects about everything, including sexual experience, libido, and orgasmic experience. And what we found out was that the results are no different from placebo.

DR. DOBBS: That there was no difference? Can you repeat that again?

DR. BHASKAR: There was no difference compared to placebo. And the events that were noted were at a much lower rate than what is reported in the literature for higher doses of paroxetine.

DR. DOBBS: How much of the population was depressed at baseline?

DR. BHASKAR: In Study 4, there was 10 percent of subjects who were included who had baseline psychiatric conditions, and in Study 3, subjects with depression were excluded.

DR. DOBBS: They were not on medications,

but were they depressed by any other scoring? Was it measured?

DR. BHASKAR: We did measure the HADS at baseline to determine whether subjects were depressed at baseline, and we didn't see an increase in the HADS scores, which is the Hamilton Anxiety and Depression Scale.

DR. LIPPMAN: Could I ask Dr. Portman to come up and provide some clinical input to that response?

DR. PORTMAN: So the Arizona scale, the ASEX scale, was used to monitor, during the course of the study, any changes in sexual function because of the concern with higher doses of SSRI. The incidence, when you look at it, over 50 percent, people meeting the cutoff for sexual dysfunction, while it may seem high, Lohman in a seminal paper in 1999 from JAMA found 43 percent of women reporting some form of sexual dysfunction. So this 50 percent figure really is not beyond the realm of what we've seen reported in the literature.

DR. JOHNSON: Let me ask a clarifying

question. This is a modest decrease in dose from the lowest dose used for depression, but SSRIs are classically seen to affect libido in increasing anorgasmia. Can you explain why you think there was a different finding with this medication in your studies?

DR. LIPPMAN: Well, in terms -- paroxetine has non-linear pharmacokinetics, so the exposure of the patient -- well though, the dose is 25 percent less. In fact, the actual patient exposure due to the non-linear pharmacokinetics may be less than that, and that might explain some of what you're asking about.

DR. JOHNSON: Dr. Orza?

DR. ORZA: I have two clarifying questions from the background materials and one from the slides. You said that you had a plan to minimize the placebo responders, and that didn't seem to have worked. I was wondering if you could comment on -- you still had, despite that run-in period, a very high placebo effect.

DR. LIPPMAN: I'm going to ask Dr. Bhaskar

to come back and talk about our 12-day placebo run-in period, and what the intention was, and what were the results of that.

DR. BHASKAR: So placebo response has been reported in the literature with all VMS trials. With estrogen trials, with hormone-replacement studies, the placebo response was as high as 58 percent, but those studies did not have a run-in. Subsequently, Stearns, et al. have published papers with placebo run-in at the beginning of the studies, and they have reported a placebo response while including the run-in period as high as 43 percent. In our studies, we saw 46 percent, which corroborates what Stearns reported in her trials with the run-in period.

DR. ORZA: Then the second question was about the serious adverse events. There seemed to be disproportionately among the non-Caucasians. Is that true? I couldn't do the math, but --

DR. JOHNSON: I'm going to ask Dr. Lucini to come up and address that, please.

DR. LUCINI: When we look at serious adverse

events, it is a small number we're looking at. So perhaps another way to look at it is to look at all treatment-emergent adverse events by race, where there was a higher rate among African Americans subjects -- I'm sorry -- among white or Caucasian subjects.

Slide up, please. The rate of all treatment-emergent adverse events was higher in the LDMP arm with the white or Caucasian subjects, but the rates of cardiovascular and hepatic AEs were higher in the African American arm.

DR. ORZA: And then the last question -- I just want to be sure I'm reading the scale correctly on the severity score slides 21 and 22. Is that .01 and .02? And the scale is still 1 to 3?

DR. LIPPMAN: Which slide? Okay. Could you repeat the question, please?

DR. ORZA: Slide 21 and 22, the scale there is --

DR. LIPPMAN: Yes. Your correct. The severity score will always be between 2 and 3, and

the scale is correct. There were relatively small changes. If I could address that further, the hot flash weighted average severity score is really meant to determine the severity of a single hot flash. So to derive it, it's a weighted average of moderate and severe. You multiply moderate times 2 and severe by 3, and then you divide the numerator by the total number of moderate and severe hot flashes. And what you get out of that is the average severity of a single hot flash. It's always going to range between 2 and 3.

Next slide. Slide up, please. So that's the weighted average severity score. To assess patient burden, which really is a function of the amount of burden these symptoms are causing on the patient, we actually did an exploratory analysis looking at the composite score. And the composite score actually is the same numerator as the hot flash severity score, but it does not include the denominator. So it weighs a moderate flash as having a score of 2 and a severe hot flash of having a score of 3.

Slide up, please. So just to illustrate the findings you might get when using these two scales, let's say there's a patient who had 50 severe and 50 moderate hot flashes, so her average weighted severity score of a single hot flash will be 2.5 Now, if that patient is on treatment and has a response, and goes down to 1 severe hot flash, her actual severity score is 3.0, which went up. And if the patient's a complete responder, her score is indeterminate because the denominator can't be zero.

If you use the composite score, the same patient with 50 severe and 50 moderate hot flashes would have a composite score of 250. If that patient responded the same way and had one remaining severe hot flash, the score would be down to 3, and if the patient had zero hot flashes, the score would be to zero.

So each of these techniques -- and I want to show -- slide up, please. This just shows the information with the two scores on the same slide. And using the composite score, we achieved

statistical significance in Study 3 at both time points. Both scales, both scores, have their usage. The weighted average score helps understand the effect on a single hot flash, but the composite score really assesses the hot flash burden to the patient. And one other way to assess this is another exploratory analysis we did on actually a prespecified endpoint, which is looking just at severe hot flashes.

Slide up, please. So in Study 3 and Study 4, we looked at the drug effect on just severe hot flashes and found that in both Study 3 and Study 4, at all time points -- 4, 12 and 24 -- we had a significant effect versus placebo on severe hot flashes by themselves.

DR. ORZA: So I'm sorry. In slide 21 and slide 22, is that the composite or the --

DR. LIPPMAN: This is the median daily weighted scale. So this is the prespecified one that did not achieve significance at week 12.

DR. JOHNSON: Dr. Schwarz.

DR. SCHWARZ: I was interested in comments

about the non-linear pharmacokinetics, and I was hoping you could provide a little bit more background on how you got to the 7.5 dose as opposed to 10 or 5 rate.

DR. LIPPMAN: We got to 7.5 dose by examining the literature, and it was mostly literature by Stearns, et al. And she had done some studies, and it did not appear, on higher dosages looking at vasomotor symptoms -- and it did not appear to be a dose effect. But it did appear in her studies that there was an effect on tolerability, with lower doses having better tolerability.

So we wanted a dose that was below the dosages that were indicated for psychiatric illnesses to lessen potential confusion. And we even had some patients who were telling us that they felt bad about being on a drug that most people thought was for psychiatric illness. So that's when we came up with the 7.5 milligram dose. And we knew that the kinetics of paroxetine was non-linear; so even though it was only perhaps

25 percent dose less, the kinetics may have contributed to the actual exposure being even less than that.

We went into a phase 2 proof of concept study with that dose. And in phase 2, we found the efficacy with higher dosage and tolerability that didn't look different from placebo. So to us, that meant that that was a very good dose to take into phase 3, and that's why we did that.

DR. JOHNSON: Dr. Chai.

DR. CHAI: I have two questions. I'm not clear. Did you make subjects go off any psychiatric meds for Study 4? Because you had about 10 percent subjects. And then the second question is maybe for Dr. Sanacora about any concerns about patients who are on paroxetine that have to be prescribed a second SSRI for new onset depression, or other antidepression drugs, or other psychiatric issues that may come up; so multiple use of the same category of drugs.

DR. LIPPMAN: We did ask subjects to go off any psychiatric medication.

Dr. Sanacora?

DR. SANACORA: Yes. I am Dr. Gerard Sanacora, professor of psychiatry, Yale University, and director of the Yale depression research program. I have been compensated for my time as a consultant to Noven Pharmaceuticals and my expenses have been paid, but I have no direct interest in the outcome of this meeting or in Noven Pharmaceuticals.

I think the question specifically is are there any concerns that this drug may be used alongside another psychiatric drug. And, in fact, there's indications/warnings in PDR, in the package insert, that these drugs have very specific indications and contraindications for use with other drugs, such as MAOIs and others. And it should not be -- and it should be made very clear through patient education that this is an SSRI, and it is not indicated for the treatment of depression. So the concern would be no greater than any other drug, such as Zyban or Wellbutrin. Where you could be using the same drug for two

different indications, it should be made clear to the treaters.

DR. CHAI: Can I follow up? I'm concerned about using the same category, the same classification, for two different conditions, the additive effect of -- side effects, for example. So a patient could get an SSRI for depression, and then this mechanism, SSRI, for VMS. Is there a concern about the additive effects of same classification of drugs? Because, again, we don't know how long these patients are going to be treated for. And your experience, primarily, I'm thinking from a psychiatrist standpoint of treating patients with multiple agents in the same category.

DR. SANACORA: So these medications are used at very broad dose ranges, so from 20 to 60 milligrams, typically for paroxetine. So there is a broad range of doses that are used, and these medications are frequently used in combination. However, as I mentioned before, there are specific contraindications that should be made clear.

DR. LIPPMAN: I'd also like to ask Dr.

Portman to come up and comment from a gynecologist's point of view.

DR. PORTMAN: Should this become available to my patients for the treatment of vasomotor symptoms and it achieved its goal of reducing the symptomatology, and the patient returned and had new onset symptoms of depression or anxiety, then certainly that issue would be addressed. And should she need to go on a different medication for that specific disease state, LDMP most likely would be discontinued, and she would be treated accordingly for her depression.

Certainly, there are people who are treated with bupropion and this class of drugs together. That certainly is something that may be considered in this treatment population, but most likely if she was going to be going on a new psychotropic drug, would discontinue this and address her mental health issues. I don't see clinicians adding one drug on top of the other when that issue presents itself.

DR. JOHNSON: Clarification, Dr. Dobbs?

DR. DOBBS: Yes. So would you up the dose for a depressed a patient who you start at one dose and comes back complaining of depression?

DR. PORTMAN: Once the patient shows evidence of major depressive disorder, I would certainly most likely consult my psychiatry colleagues to let them determine what the best treatment course would be for that patient. I don't have any data on any other dose for this particular therapy. The low dose was specifically designed to minimize side effects. I'm not sure I want to increase it for that purpose and then increase side effects.

So if her depression became her primary problem, I would get assistance in that regard. I wouldn't double the dose. I would assume that the psychiatrist would find the right treatment that was right for her. If her vasomotor symptoms recurred, then that would be addressed in a different way.

DR. DOBBS: The company said that they based it on Dr. Stearns data. But when you did a dose

finding, and you went up to higher doses, did VMS symptoms resolve? You never really did that.

DR. LIPPMAN: We didn't do dose finding. The only dose we've studied is 7.5 milligrams.

DR. JOHNSON: Dr. Kittelson.

DR. KITTELSON: Yes, a point of clarification just on your slide CT-35. And in our background document, or briefing document, there's a figure 313. Are these the same? They don't seem to be -- well, they're not exactly the same. I guess I want to understand how they differ. So then I can go on to figure 312 from the briefing document, which gives a different impression. It's from Study 3.

DR. LIPPMAN: I'm going to ask Dr. Blumenstein to come up and discuss this.

DR. BLUMENSTEIN: I have the advantage of being able to see both simultaneously.

DR. KITTELSON: Oh, okay. Well, I may have them simultaneously.

DR. BLUMENSTEIN: I suppose you do, too, because you could have it opened. There's a

different set of outcomes that are displayed in there.

DR. KITTELSON: Yes. So in figure 313, at least for the first, the frequency response looks like it might be the same as the first-line frequency reduction. But the numbers, 101 and 183; in there, it's 223 and 61 -- I guess -- are they -- how are these different?

DR. BLUMENSTEIN: I will look in to this and get back to you with an answer.

DR. KITTELSON: Okay. But I guess my -- it seems like there are more outcomes here, and you get a different visual impression. But figure 312 in the briefing document is from Study 3. So do you have an analogous slide for Study 3? But it gave quite a bit different visual impression, which was there were a lot of things on either the wrong side of that line or certainly with confidence intervals that included 1 quite dramatically.

So that's my question.

DR. BLUMENSTEIN: Could I have the slide for Study 3? It should be around CT-35. Yes. You

were comparing --

Slide up, please. We don't have it yet. Study 3 does not have as dramatic -- slide up, please.

So this is the slide that matches the figure that you mentioned.

DR. KITTELSON: So that matches more my -- I was concerned about this picture in particular in the briefing document. I guess I just wanted to check that. I wasn't misunderstanding the two slides, because the Study 4 ones didn't seem to agree between the presentation and the document.

DR. BLUMENSTEIN: I will look into that, and we'll get back to you with an answer.

DR. KITTELSON: Thank you.

DR. JOHNSON: Dr. Clarke?

DR. CLARKE: For Dr. Watts, just a short question to clarify. In slide CS-48, it talks about a hand fracture in the treatment group, and then there's a foot fracture quoted in the placebo group. Are these truly carpal or metacarpal fractures, or are they finger or toe fractures, or

do we know?

DR. WATTS: I can't answer that.

DR. LIPPMAN: Dr. Lucini, do you have additional information on that, or do we need -- we can get that information.

DR. WATTS: That's all?

DR. JOHNSON: Dr. Bockman?

DR. BOCKMAN: Yes. I wondered about that, too. It looks like the severity of fractures in the placebo group was greater, so they were more active or more trauma associated with them.

But I'm going back to CE-18. And maybe this went by, but I still don't get it. And it has to do with the fact that just going on the study is a good thing in terms of hot flashes. Is there some explanation for that? What I'm talking about is the fact that the placebo group goes down quite dramatically, as does the treatment group, and the treatment group does a little better.

DR. LIPPMAN: There's a significant placebo effect.

Could I have the Cochrane slide back up,

please? And this placebo effect has been seen in these types of studies before. The studies were blinded. And I think perhaps -- slide up, please. This slide, again, establishes the placebo effect that was in our clinical studies, as well as what's been seen for placebo, and there is a significant placebo effect.

So I think you go on our drug, and you do get a reduction of hot flash beyond that of placebo, but it's meaningful. And what I'd like to do now is provide some additional information that needs to be considered in addition to the reduction and the frequency, but really how that correlates to other endpoints.

So could I please have the slide on -- slide up, please. So in terms of clinical meaningfulness, there is much data from our study which goes to the issue of clinical meaningfulness. And one is, when you start a patient on a drug, it's nice that you have therapy at a certain period of time, 4 weeks or 12 weeks, but what about maintaining that effect?

So, as you can see in this slide, in the left lower-hand quadrant, patients who respond to our product tend to continue to respond at week 12. Next slide up, please. And if you respond at week 12, you tend to respond at week 24. In addition to maintenance of effect, one of the real key important issues for women who have moderate and especially severe hot flashes is nighttime awakenings.

Slide up, please. So when you look at our studies -- we looked at nighttime awakenings, both Study 3 and Study 4 at all time points. And as you can see from this slide, LDMP is significantly better than placebo in terms of nighttime awakenings at all time points studied. And perhaps most importantly, we asked the patients, what do you think about your response through the Patient Global Impression Scale.

Slide up, please. And this was only done in Study 3. And as you can see here, at every time point, there are more patients on LDMP versus placebo in the category of very much better, and

there are less LDMP patients versus placebo in the category of no change or worse. And there are women who will tell you that I had one hot flash today and it was at the wrong time, and that really impacted me. But importantly in our study, we correlated that to other endpoints, including maintaining the effect, including nighttime awakenings, and including the patient global impression.

I'd like to have Dr. Portman come up and talk about the clinical global impression and some other clinical endpoints that made this data meaningful to his patients.

DR. PORTMAN: The placebo response in these trials is remarkable. I've conducted probably several dozen vasomotor symptom trials, and these are very consistent across the board. We can't give patients placebo. One, it's deceptive in this context. If we gave widespread placebos, I think it begins to be an ethical challenge. And we also can't give patients in a natural clinic setting, in a practice setting, the care that they get in a

clinical trial.

We can give them active treatment that will have a meaningful effect outside of that clinical trial setting because I do it all the time. I prescribe hormones. I prescribe these medications off label. The patient doesn't come back every four weeks, doesn't fill out a diary, doesn't talk to myself or my coordinator. And she comes back, and she has a meaningful response when I see her in 12 weeks or 6 months.

The patients in the clinical trial on placebo have the response that they do because of all the clinical care that they get. They get reassurance. They get constant coddling. And that I just don't think simply gets done in a natural practice setting. So even while we do this in clinical trials to make sure we have a treatment effect, I think that the meaningful treatment effect that we have with medications in our practices is quite different than the differential we see in clinical trials.

If we can put the slide up on my impression

and other clinicians' impressions. Slide up.

So part of what I do as a practitioner is I have a face-to-face interview with my patient. I ask are you achieving some relief. Has the severity of your problem improved? In fact, the clinical global impression is based on the impression of the severity of the patient's vasomotor symptoms; were they very much improved, much improved, or somewhat improved. And across all time points, there was a significant impression on the part of the clinician that the patient was improving on active treatment more than on placebo. Perhaps far greater than the absolute difference between hot flash differences.

Slide up. And this correlates very well with the patient's own personal, self-reported impression. So it's not just the investigator projecting onto the woman what he or she thinks she should be doing. But as you see in the box plot, patients who filled out their own personal impression, it correlates very well with what the clinician observed on their own as well. So that's

one sense of why I think that absolute differences in hot flashes may not be as critically important, but rather how the overall patient is doing perhaps much more so.

Another important thing that we look at -- slide up -- is not just a point in time measuring a differential in hot flashes say at week 4 and week 12, but it's vital that the patient has ongoing relief. So this exploratory analysis, this Kaplan-Meier curve, looked at patients who had three consecutive weeks of 50 percent reduction in hot flashes, and the distinction between placebo and active treatment is quite apparent very early on. And patients who had this three-week durable response on active treatment, 50 percent of the patients achieve that by two months and didn't reach that 50 percent of patients achieving that threshold in placebo at all during the trial.

So there really, I believe, is a differential treatment effect between the active treatment arm and placebo, which may be explained in the context of all this data a little bit better

than just simply looking at purely a placebo effect.

DR. JOHNSON: Thank you.

DR. BOCKMAN: Can I just do a quick follow-up? It's real short.

DR. JOHNSON: Okay.

DR. BOCKMAN: To Dr. Lippman's comment, there clearly is persistence of the placebo effect. And I guess my question is, can you actually do a crossover study when the placebo effect is so large?

DR. LIPPMAN: That would probably be somewhat challenging.

DR. JOHNSON: Did you have a clarification?

DR. KITTELSON: On the survival study, is it possible to relapse on that? This is the first time we've seen it, and I hadn't had a chance to -- that Kaplan-Meier curve that was just up, you can relapse. It was three weeks durable, but then you could go back again, right? So it's not a steady state. It's not like alive or dead.

DR. PORTMAN: Right.

DR. KITTELSON: Okay. Thank you. That's all I wanted to know.

DR. JOHNSON: Thank you very much. We appreciate your input, and we request that you stay available for questions in the future.

For the committee members who did not have a chance to ask their questions, there will be time after the FDA or later in the afternoon.

So now let us proceed to our presentations from the FDA.

FDA Presentation - Ronald Orleans

DR. ORLEANS: Good afternoon. My name is Ronald Orleans, and I'm the clinical reviewer for NDA 204516, which seeks approval for paroxetine mesylate capsules, 7.5 milligrams, for the treatment of moderate to severe vasomotor symptoms associated with menopause.

Here's an outline of my presentation. I'll give a short introduction to the NDA submission, including some regulatory history, then I'll give an overview of the phase 2 and phase 3 clinical studies. After that, the efficacy results will be

discussed by our FDA statistician, Dr. Guo. After her presentation, I'll return to discuss our safety findings.

Paroxetine is a serotonin reuptake inhibitor, and as such belongs to the SSRI class of drugs. The division's review of paroxetine was based primarily on data from the applicant's single phase 2 study -- we refer to it here as 002 -- and the two phase 3 studies, referred to as 003 and 004. Currently, paroxetine is not approved in any country for the VMS treatment indication. If it's approved in this country, it may be the first non-hormonal drug approved for treatment of moderate to severe vasomotor symptoms association with menopause.

Slide 4 reviews the history of paroxetine. Paroxetine, the active ingredient, was first marketed in the U.S. in 1992 as paroxetine hydrochloride. The current indications for paroxetine hydrochloride are psychiatric and are listed here. The current approved dosing for these indications ranges from 10 milligrams per day to a

maximum of 60 milligrams per day.

Pexeva, which is the applicant's product in tablet form and substitutes mesylate for hydrochloride as the associated salt, was approved for similar psychiatric indications in 1993. The proposed dose to treat VMS is 7.5 milligrams daily, which is lower than the approved psychiatric doses.

The product has a relatively long regulatory history. The FDA issued a draft guidance for the clinical evaluation of hormonal products for menopausal symptoms in 2003. Dr. Joffe has previously discussed this guidance. Through information requests in 2008, it was agreed that a mean reduction from baseline of at least 2 hot flashes per day in the paroxetine arm, greater than that of the placebo arm, would meet the definition of a clinically meaningful reduction in hot flushes. Methods of severity scoring were also discussed at that meeting.

At the end of the phase 2 meeting, a demonstration of persistence of benefit beyond 12 weeks was requested, as well as a formal evaluation

of suicidality. A special protocol assessment agreement was reached in 2011 for study protocol 003 prior to initiating the study. An SPA was not requested for the Study 004 protocol. In 2011, a responder analysis was agreed upon to demonstrate persistence of benefit in the 24-week Study 004.

This slide summarizes the phase 2 Study 002. This is a proof of concept study using just the paroxetine 7.5-milligram dose. No exploration of dose response was done in this study. The 7.5-milligram per day dose, which was used in both phase 3 studies, was based on published literature, showing no difference in dose response with regard to efficacy for VMS treatment in doses ranging from 10 to 25 milligrams. But there was a dose relationship for tolerability, so that a dose lower than the doses used to treat psychiatric disorders was chosen in order to achieve better patient tolerability. Data from this study was not used for the efficacy analysis but was used in the safety analysis.

This slide summarizes the two phase 3

clinical studies. In Study 003, the median reduction in frequency of moderate to severe hot flushes between paroxetine and placebo was less than 2 hot flushes per day. Therefore, the clinical meaningfulness of this reduction was further explored. Our statistician will discuss the concept of clinical meaningfulness and how this was used to evaluate efficacy in Study 003.

In Study 004, a secondary analysis was planned to assess the persistence of benefit at week 24 using a responder analysis. Responders were defined as those subjects who achieved a 50 percent or greater reduction from baseline in moderate to severe hot flush frequency at week 24 so that a difference in the responder rate between the active and the placebo-treatment groups would demonstrate a persistence of benefit. Our statistician will also discuss this in more detail.

Both phase 3 studies were very similar in design. Both studies were randomized, double-blind, placebo-controlled, multicenter studies in women with either natural or surgical

menopause. Both trials were conducted entirely in the U.S. An electronic diary was available throughout the day or night and used for daily entry of hot flush data.

Subjects were provided with definitions of mild, moderate, and severe hot flushes, which conformed to those previously specified in the FDA-VMS draft guidance document. As mentioned previously, the 7.5-milligram dose, which was used in both studies, was based on published literature, showing efficacy for VMS symptoms for doses ranging from 10 to 25 milligrams. The division agreed to the plan to minimize placebo responders by requiring subjects to requalify on the basis of VMS frequency and severity after the placebo run-in period.

Inclusion criteria were identical in both phase 3 studies. Hot flush frequency and severity inclusion criteria conformed to the entry criteria in our hormonal VMS draft guidance. That is at least 7 to 8 moderate to severe hot flushes daily or 50 to 60 hot flushes weekly for at least 30 days

prior to screening. Subjects were asked to discontinue any psychotropic drugs or hormone therapy prior to initiating the study. Exclusion criteria were nearly identical across studies. Both studies excluded prior SSRI or SNRI non-responders.

Regarding the third bullet, the phase 3 study subjects were generally free of any history of significant psychiatric disorders. Exclusion criteria for Study 004 were initially more liberal regarding time frames for a past history of psychiatric illness, but the protocol was later amended and tightened to exclude most subjects who had a history of psychiatric illness in their lifetime. Approximately 75 percent of subjects in Study 004 were enrolled under the original protocol that only excluded subjects with a major depressive episode within two weeks prior to enrollment, whereas 25 percent of the subjects were enrolled under the modified version that excluded subjects with a history of major depressive disorder any time in their life, and this was similar to

Study 003.

Although the division generally prefers no BMI restrictions in these types of studies to better reflect the general population of patients who may potentially use this drug, the restriction of a BMI of 40 or greater, that is, morbid obesity, did not seem unusually restrictive.

The definitions of the efficacy and safety populations were previously agreed upon. The mITT population consisted of all randomized subjects with a valid baseline, daily hot flush diary data, and who had taken at least one dose of study drug and had at least one day of on-treatment, daily diary data.

The safety population consisted of all subjects who took at least one dose of study drug and had at least one post-dose safety assessment. The numbers of subjects in the mITT and safety populations were very similar to the numbers of subjects who were randomized.

At this point, Dr. Guo will now talk about the efficacy evaluations.

FDA Presentation – Jia Guo

DR. GUO: Good afternoon. My name is Jia Guo. I'm the statistical reviewer from the Division of Biometrics III, Office of Biostatistics. As part of the FDA efficacy evaluation, I will focus on the analysis of the co-primary efficacy endpoints, supported endpoints, then highlight the summary of our evaluation.

The four co-primary endpoints are predefined as the change from baseline in daily frequency and severity of moderate to severe VMS at week 4 and week 12 for both Studies 003 and 004. The supportive endpoints include the clinical meaningfulness in Study 003 and the persistence of efficacy at week 24 in Study 004.

This slide summarizes the analysis method for the co-primary endpoints. For each endpoint, the applicant prespecified rank-ANCOVA analysis for the hypothesis testing. FDA agreed with this method. The treatment effect was estimated using the median difference in each endpoint between paroxetine and placebo groups. To demonstrate the

efficacy of paroxetine mesylate, the comparisons on all four co-primary endpoints must be statistically significant.

This table summarizes the analysis results of the co-primary endpoints. The fourth and the fifth columns show the median baseline and a change from baseline in daily VMS frequency and severity at weeks 4 and 12 for each treatment group by study. The last column is the treatment difference between paroxetine and the placebo groups.

At baseline, the median frequencies were about 9 to 10 per day and were very similar between treatment groups. For daily frequency, compared to the subjects in placebo group, the subjects in the paroxetine group reduced .9 to 1.7 more hot flashes at week 4 and 12 in the two studies. And the comparisons between paroxetine and the placebo and the reduction in daily frequency were statistically significant at both weeks 4 and 12.

The median daily severity was about 2.5 in both studies. In each treatment group at baseline, the severity score can range from 2 to 3 for

subjects who have at least one moderate or severe hot flash. At weeks 4 and 12, the reduction in daily severity in paroxetine group was a little bit more than that in placebo group by .03 to .05 in both studies. The comparisons between paroxetine and the placebo on the reduction of daily severity were statistically significant at both weeks, except at week 12 in Study 003.

Next, I'm going to present FDA analysis of clinical meaningfulness because the treatment difference in reduction in VMS frequency was statistically significant at weeks 4 and 12, but the effect was less than 2 per day. FDA has observed that the magnitude of the treatment effect of non-hormonal treatments in VMS frequency is less than that observed for standard-dose hormonal therapies. FDA requested this analysis to be conducted to ensure that such treatment effect is still of clinical benefit.

This analysis links the change from baseline in VMS frequency to a subject's perception of improvement in VMS, which was assessed by a 7-point

patient global impression questionnaire at weeks 4 and 12. Subject's response to the question can vary between very much better to very much worse.

This flowchart outlines the analysis procedure to evaluate the clinical meaningfulness. This analysis is done at weeks 4 and 12, respectively. First, regardless of treatment assignment, all subjects were grouped as satisfied and unsatisfied based on PGI response. FDA recommended that subjects should be considered satisfied with their treatment if their response was very much better or much better, and were considered unsatisfied otherwise. Then a receiver operating characteristic analysis was conducted with a satisfaction categorization to determine the threshold for a clinical meaningful reduction in daily VMS frequency.

Using the threshold determined in step 2, subjects were defined as responders or non-responders. Responders were defined as those subjects who achieved a reduction in daily VMS frequency greater than the established threshold.

In the last step, the proportions of the responder rate between paroxetine mesylate and placebo groups are compared.

This table presents the responder rates by treatment groups. At week 4, the estimated threshold value for change from baseline in daily frequency was -4. Subjects were classified as responders if their VMS frequency was reduced greater than 4 per day. Fifty percent of subjects in the paroxetine group and 37 percent of the subjects in the placebo group were responders. At week 12, the estimated threshold value was -5.3. Fifty-one percent of subjects in the paroxetine and 43 percent of subjects in the placebo group were responders. No adjustment for multiplicity was made for this supportive analysis.

Next, I'm going to talk about analysis of persistence of treatment benefit at week 24. In Study 004, the applicant preplanned a responder analysis to assess the persistence of efficacy at week 24. In this analysis, responders were defined as those subjects who achieved at least 50 percent

reduction from baseline in daily VMS frequency at week 24. Subjects whose reduction at week 24 was less than 50 percent or dropped out before week 24 were considered as non-responders.

The responder rates were compared using a logic model. FDA explored the treatment benefit of reduction of daily VMS frequency descriptively in Study 004 by plotting the median changes over time. Compared to week 12, the treatment effect appeared to be similar at week 24. In the mITT population, about 48 percent of subjects in paroxetine group and 36 percent of subjects in placebo group achieved at least 50 percent reduction in daily VMS frequency from baseline.

This table summarizes the results of efficacy evaluation by FDA. In the two phase 3 studies, the comparisons between paroxetine and placebo and reduction of daily VMS frequency were statistically significant at weeks 4 and 12. And the comparisons of the reduction of daily VMS were statistically -- on the reduction of daily VMS severity were statistically significant at all

weeks, except at week 12 in Study 003. In the supportive analysis to demonstrate clinical meaningfulness, the responder rates were higher in paroxetine group compared to placebo group at weeks 4 and 12. In the analysis of persistence of efficacy at week 24, the responder rate was higher in paroxetine group at week 24.

Dr. Orleans will come back to the podium to present FDA's safety evaluation.

FDA Presentation – Ronald Orleans

DR. ORLEANS: The evaluation of paroxetine safety was based on the database from the clinical development program and the postmarketing safety information from the approved Pexeva product. At the pre-NDA meeting, the division agreed that the pooling of the safety data from the two phase 3 trials and from the supporting phase 2 trial was acceptable. Safety data from the phase 1 pharmacokinetic study, Study 005, was not integrated into the data set because this study enrolled basically healthy women, and this study did not use a placebo or a comparator drug.

This slide lists the labeled safety issues associated with paroxetine. Regarding suicidality, The Pexeva label states that all patients being treated with antidepressants for any indication should be monitored appropriately. Serotonin syndrome has been reported with both SSRIs and SNRIs. Teratogenic effects occurring in the first trimester of pregnancy have been reported from epidemiological studies. Labeled precautions include risk of seizures, CYP2D6 inhibition, psychomotor restlessness, hyponatremia, increased risk of bleeding events, bone fracture, and worsening of glaucoma. The division was especially mindful of all these conditions when evaluating the safety portion of this NDA.

Subject disposition was similar across both arms of the phase 3 studies. For Study 003, the 12-week study, a similar percentage of subjects in both groups completed the study. The percentage of subjects who discontinued due to adverse events or serious adverse events were higher in the paroxetine group, 2.6 percent versus 1.3 percent.

In Study 004, which was 24 weeks, a similar percentage in each arm completed the study. The percentage of discontinuations caused by AEs/SAEs was the same in both groups but certainly higher than Study 003, perhaps because it was a longer study.

The one death that occurred in Study 003 was in a 55-year-old African American female who experienced a cardiorespiratory arrest 68 days after starting treatment with paroxetine mesylate. She died one day later, and was listed as having had two serious adverse events: coronary arteriosclerosis and cardiorespiratory arrest. She had a medical history of increased cholesterol and hypertension and had been taking benazepril, an antihypertensive, for about 15 years. She was noted to be hypertensive at her screening visit with a blood pressure of 146/86. Given the limited information, it was not possible for the division to determine if this death was drug related or not.

Thirteen non-fatal SAEs were reported in 13 subjects, about 2 percent in the paroxetine group

reported in 9 subjects; about 1.4 percent in the placebo group in the pooled safety database. This slide lists the 13 non-fatal SAEs that occurred in the paroxetine group. With the exception of the single death in the 003 study, the SAEs in the remaining 13 paroxetine subjects were all reported in the 24-week Study 004. SAEs in the 9 subjects in the placebo group were reported in both the phase 2 study -- 1 subject -- and in both phase 3 studies, 1 subject in Study 003 and 7 subjects in Study 004.

Six of the 13 SAEs occurred within the first 12 weeks of the study. All 13 of these SAEs resolved without sequelae. The main SAEs of concern, based on this listing, are suicidal ideation and suicide attempt. These occurred exclusively in the paroxetine group. These SAEs occurred in a population screened for depression and other psychiatric illnesses. A total of 28 subjects in the paroxetine group, 4.4 percent, and 21 subjects in the placebo group, 3.3 percent, had adverse events leading to study drug

discontinuation. So the percentage of discontinuations were slightly higher with paroxetine.

This table is a subset of all adverse events causing discontinuation and attempts to list only the discontinuations due to mood effects, which could possibly be related to paroxetine. It's interesting to note that even the most frequently reported adverse events resulting in drug discontinuation only occurred in two subjects. And that anxiety led to discontinuation more often in placebo subject than paroxetine subjects.

Events of concern were prespecified by the applicant in this statistical analysis plan as being of specific interest based on adverse events commonly reported for the drug classes of SSRIs and SNRIs. These included cardiovascular events, hepatic events, gastrointestinal and bleeding events, and suicidality events. Based on our review of the application thus far, no signals were detected regarding cardiovascular, hepatic, gastrointestinal, or bleeding events. The only

event of some concern was suicidality, which was prospectively assessed in all four clinical studies.

The term "suicidality" is defined to include suicide attempts, suicide behavior, and suicide ideation. Suicidality in these studies was determined in three ways: 1) either through the STS scale used in Study 003; 2) through the CSSRS scale used in Study 003, or; 3) through adverse event or serious adverse event reporting.

Suicidality detection overlapped, as some events were detected both as an AE/SAE and also through the suicidality instruments. It seems likely that relying only on adverse event reporting would result in under-detection of suicidality, but it is unclear to what extent relying on the screening instruments results in false positive reports of suicidality.

All treatment-emergent cases of suicidality reported in the phase 3 trials occurred in Study 004, which was at 24 weeks duration. One suicide attempt occurred. This was in a

50-year-old Caucasian woman who took an overdose of non-study medication in the setting of increased anxiety and depressed mood. This occurred on day 55 of the study. She was rushed to the hospital, treated, and released. She continued on the study drug for another month until the drug was discontinued.

The three SAEs of suicidal ideation all occurred after 12 weeks of treatment, but it isn't clear that duration of exposure is a relevant factor.

Potential suicidality is described in class labeling for all antidepressant drugs. Here are some summary points with respect to this application.

The incidence of suicidality in the clinical studies was found to be low, but the incidence was greater in women treated with paroxetine. The division sought consultation regarding the suicidality risk from the Division of Psychiatric Products. Their conclusions are listed on this slide. There was no higher rate of

discontinuations due to treatment-emergent suicidality.

The clinical studies submitted to the NDA do not demonstrate an increased risk of suicidal ideation or behavior for drug versus placebo in these study populations. Based on the exclusion criteria, the studies are not fully representative of the population who may use this drug. If the drug is approved for VMS treatment, ongoing surveillance was advised. And finally, labeling should include a suicidality boxed warning.

Overall, 50 percent of subjects in the paroxetine group and 47 percent of subjects in the placebo group reported at least one adverse event. This slide depicts the frequency of selected common adverse events in at least 1 percent of subjects and at a higher incidence than placebo. Adverse events we believe are unlikely study related, such as nasopharyngitis, bronchitis, urinary tract infection and the like, are omitted in this slide. AEs that occurred at a higher incidence in paroxetine subjects and are possibly drug related

are highlighted and include dizziness, nausea, fatigue, and mood swings. Overall, though, there doesn't appear to be any major differences in the incidence of common AEs between the treatment arms.

In the clinical trials, subjects were started on paroxetine mesylate without titration and were discontinued from the drug without tapering. A discontinuation emerging signs and symptoms checklist was administered 7 days after the last dose of study drug. Prior symptoms means a symptom which was present while taking study drug and continued into the post-drug 7-day period. Prior symptoms persisted in relatively the same number of subjects in each group, 405 and 414. In both groups, the symptoms were most likely to remain unchanged, but prior symptoms worsened in about 25 percent of the subjects who stopped paroxetine and 18 percent of those who discontinued placebo.

Based on this checklist, about 18 percent of the subjects on paroxetine and 14 percent on placebo developed new symptoms during the week

after discontinuation. Certain new symptoms, such as muscle cramps or spasm, restless feeling in the legs, and trouble sleeping or insomnia were reported in the paroxetine group at twice the incidence of the placebo group. Overall, though, there doesn't seem to be a need for tapering the dose when the medication is discontinued.

This review did not reveal any new or unlabeled safety issues relating to paroxetine mesylate. In summary, our conclusions regarding safety are these:

The overall incidence of serious adverse events, treatment-emergent adverse events, and adverse events of specific interest did not differ much by treatment arm. Central nervous system and mood-related adverse events occurred more frequently among subjects on paroxetine as did suicidality-related events, though at a low rate, and that, currently, labeling addresses the risk of suicidality. Thank you.

Clarifying Questions to FDA from Committee

DR. JOHNSON: Thank you.

We have about 10 minutes for questions to the FDA, although we will allow time for questions after the open hearings, as well. I'd like to start off with a question. If you would bring up slide 18, I would ask Dr. Guo.

Would you say that there is a significant effect --

DR. ORLEANS: Can you bring up the slide, Kalyani?

DR. JOHNSON: Would you say that there is a significant effect on clinical meaningfulness at week 12 on Study 3?

DR. GUO: So for this analysis, no multiplicity adjustment was done. So for week 4, we want to comment on the statistical significance for both weeks.

DR. JOHNSON: So is week 12 significant? Did you see significant improvement in clinical meaningfulness at week 12?

DR. GUO: Yes. As I just said, based on the responder rates, we do see higher responder rate in the paroxetine group. But based on the p value,

since this analysis was done at both weeks, and we did not control the multiplicity -- the type 1 error control was not done, so we will not comment whether this comparison was statistically significant or not.

DR. JOHNSON: Okay. Next, Dr. Curtis.

DR. CURTIS: I've been trying to sort through all of this clinical meaningfulness data, and I just wanted to clarify, was the only prespecified analysis on clinical meaningfulness the PGI data in Study 3? Is that correct?

DR. GUO: Right. This is prespecified.

DR. CURTIS: Okay. And then this is actually my question I had earlier for the sponsor as well. Given that this is sort of the main analysis of, and it's clearly an important endpoint, and also that persistence of benefit is a meaningful endpoint, but one was measured in Study 3 and one was measured in Study 4; can you tell us a little bit about the reasons for that and why this measure wasn't measured in both studies? And again, why persistence wasn't measured in both

studies?

DR. GUO: I think maybe the sponsor can comment on that.

DR. LIPPMAN: Albeit paradoxically, Study 4 actually started before Study 3. And we met with the FDA before we started Study 3, which was done under a special protocol assessment -- and we agreed upon the scale that was used for the ROC analysis with the FDA. But Study 4 was already in progress. We actually did have a different scale that we used to look at clinical meaningfulness in Study 4, but it was not prespecified by the FDA.

So I would like to have the NRS Study 4 slide up, please. So in Study 4, as I said, we did actually have a patient -- slide up, please. We did do a patient responder type analysis based upon the NRS, Numerical Rating Scale. And as you can see in this slide here, also LDMP had a benefit versus placebo, which treats statistical significance at most endpoints.

DR. JOHNSON: Dr. Orza?

DR. ORZA: A question for FDA about the

adverse event data. Table 10 in the background materials, and then I think it was slide 28, it did seem like the non-Caucasians were disproportionately represented in the adverse event data. I wondered if that was true and whether you looked for and found any differences in efficacy by race.

DR. ORLEANS: I'm sorry. I didn't understand the question.

DR. ORZA: Differences by race in either adverse event --

DR. ORLEANS: In terms of efficacy?

DR. ORZA: -- profiles or efficacy.

DR. ORLEANS: We didn't look at that, as far as I know. We didn't do the subset.

DR. LIPPMAN: So we did look to see if there is any evidence in a number of different subgroups by doing an effect modification analysis. So we looked at the effect potentially of race and age, as well as menopausal status and BMI.

Slide up, please. So you can see here this includes all the different subgroups looked at.

Could I please have the one just on the effect of Caucasian versus non-Caucasian? The forest plot? Slide up, please. So we did do an effect modification analysis looking at the effect of Caucasian versus non-Caucasian, Study 3 and Study 4. And most of the point estimates are to the left, favoring LDMP.

DR. MONTGOMERY RICE: Can you address the other part of her question, though?

DR. LIPPMAN: Pardon?

DR. MONTGOMERY RICE: About the side effects that seemed to be at a higher proportion.

DR. LIPPMAN: Thank you. So I'm going to ask Dr. Lucini to come back up and please discuss in terms of side effects, noticed any effect of race, please.

DR. LUCINI: Looking at the overall adverse event experience in the studies, we did note a difference in adverse event rates when comparing Caucasian versus African American patients.

Slide up, please. For all treatment-emergent adverse events, there was a

higher rate of reporting on the LDMP arm for Caucasian subjects, however, cardiovascular and hepatic adverse events occurred at a higher incidence in African American patients.

DR. JOHNSON: Dr. Kittelson?

DR. KITTELSON: Yes. I have a question about -- I guess the FDA slides. And the easiest place to get to it is slide 5 on the primary analysis with the ranked analysis of covariance.

Yes, there you go. We talked earlier about them, about rank-based inference and how difficult it might be, I guess, to get good estimates of a mean.

Did you do -- or did anybody do a classic least-squares analysis of covariance on this? One thing, the centers here are the differences. There's no confidence interval. Do you have a confidence interval on that so I can see the magnitudes of effect we can rule in or rule out? Or did anybody do that? Because it is -- I mean, a confidence interval on the difference between treatments on that last column there would be very,

very useful.

DR. GUO: Yes. FDA, we did a parametric ANCOVA analysis on the original data. And the treatment effect, which is based on the least-squares estimate, is similar to the median presented here. And the statistical significance does not change for all co-primary endpoints for all the -- in both studies.

DR. KITTELSON: But a confidence interval? You don't have the slide prepare. Or do you have the slide prepared?

DR. GUO: Right. We just used that parametric ANCOVA analysis as sensitivity analysis.

DR. KITTELSON: Right. Right.

DR. GUO: Rank ANCOVA was prespecified, so we did not report the confidence interval for the parametric ANCOVA analysis.

DR. KITTELSON: Yes, I understand. But the importance of a confidence interval around the difference between two groups is quite -- you know, it's sort of our standard way of looking at things. And when you go to the rank-based inference, it's

difficult, one thing, to see an -- I presume these medians in the median differences are not adjusted for any baseline value. Is that correct? They're just the actual medians in these groups?

DR. GUO: Right. This is just a median change for each group.

DR. KITTELSON: Yes. So if I were going to do an analysis, a parametric analysis of covariance -- which, by the way, is not dependent upon normality assumptions of the data itself, only of the estimates which should be defined in the sample size -- I would also have an adjusted magnitude in each of the two groups and an adjusted difference between them, and a confidence interval that would go with it. So I'm gathering we don't have such a thing easily accessible.

DR. JOHNSON: Did you have a brief comment?

DR. LIPPMAN: Yes. Thank you. Dr. Blumenstein can come up and discuss that a little further.

DR. JOHNSON: Briefly, please.

DR. BLUMENSTEIN: Slide up, please. So

these are the confidence intervals that you're requesting for the Hodges-Lehmann estimates, for the confidence intervals on the median. We also did parametric tests, and I can --

DR. KITTELSON: These will be adjusted for baseline value? Is that correct? Or baseline rank, some sort of way?

DR. BLUMENSTEIN: I believe that this particular graph is the difference -- just the difference without the covariate.

DR. KITTELSON: Okay. I think I do remember seeing them somewhere, and I likewise didn't see major disagreement between the analyses presented and the least-squares classic estimates.

DR. BLUMENSTEIN: I'm sorry. I didn't hear that last --

DR. KITTELSON: Oh. I said, I seemed to remember somewhere in these documents running across a similar kind of graph and deciding that there wasn't a grave difference between them. So I wouldn't want to leave the wrong impression with the committee, but you're confirming that, I

understand, with this. And FDA has also confirmed that there wasn't any grave difference. And the confidence intervals would have been nice to see, but this is the best we'll get, I think. Thank you.

DR. JOHNSON: I would ask the other members of the committee to hold your important questions. We will bring them to the FDA after the open public hearing. We now have a 12-minute break. Please be back at 3:30.

(Whereupon, a recess was taken.)

Open Public Hearing

DR. JOHNSON: We will now proceed with our open public hearings. Please be seated.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, as

a open public hearing speaker, at the beginning of your oral or written presentation to advise the committee of any financial relationship you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment for travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you not have any such financial relationship. If you do not address this issue with the financial relationship at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there are a variety of opinions. One of our goals today for this open public hearing is to

be conducted in a fair and open way, where every participant is listened to carefully, treated with dignity, courtesy, and respect. Kindly remember to speak only when recognized by the chair, and we thank you sincerely for your cooperation.

Now, let us begin with speaker 1.

MS. RYAN: Good afternoon. My name is Kate Ryan, and I'm speaking again on behalf of the National Women's Health Network, which does not take financial contributions from any entity with a financial stake in women's health decision-making.

The results of the LDMP trial show that it is also only moderately effective for the relief of menopausal hot flashes, with differences of about one or a little over one hot flash, less hot flashes, and only a .3 or 4 reduction in the severity of those hot flashes. As with the drug considered this morning, LDMP did not meet statistical significance for all of the prespecified primary endpoints, which is disappointing, though, again, we do recognize the placebo effect in these trials is also very strong.

We are, however, concerned about some aspects of the known safety profile of LDMP because of the population's new formulation it's intended to treat. Included in the current label, there's precaution about the drug interaction with tamoxifen, as well as a class-wide precaution about the association between SSRIs and bone fractures. These two warnings are of particular concern when you consider the women who might seek to use LDMP for hot-flash relief are also more likely to be at risk for these potential harms than people who might seek to use it for depression.

One of the groups most in need of non-hormonal hot flash treatments are women with estrogen-dependent cancers who cannot take hormones and may be taking tamoxifen, which causes hot flashes. However, LDMP is not appropriate for women using tamoxifen because there's evidence that it reduces the efficacy of tamoxifen when they're prescribed together. With regard to fractures, many women who will seek treatment for hot flashes may also have or be at risk for osteoporosis, and

therefore are also not good candidates for a drug that adds to their existing risk factors for a bone fracture.

LDMP carries these risks in addition to the risks of suicidality that is shared with gabapentin, the drug discussed this morning. For this morning's drug, we were willing to accept what we considered to be a very close benefit/risk profile of a minimally to moderately effective drug and a known safety profile, but with this afternoon's drug also being only moderately effective and, in our opinion, a more concerning safety profile.

We know that many women struggling with hot flashes do not want to use hormones, which leaves them without well-proven options for relief. We believe that a moderately effective drug could provide an important option for women at menopause if it were safe, and we again call for a closer look at the success of the placebo groups in both of these drugs, but given the committee's discussion and conclusion this morning, it would

not be consistent to recommend approval of this drug.

While we all want non-hormonal treatments, we are pleased that the committee is recommending the FDA hold to scientific standards that actually will meet women's needs. Thank you very much.

DR. JOHNSON: Thank you. Speaker number 2.

DR. CAROME: Good afternoon. I'm Dr. Michael Carome, deputy director of Public Citizens Health Research Group, testifying on behalf of myself, Dr. Sammy Almashat, and Dr. Sid Wolfe, our director. We have no financial conflicts of interest.

We strongly oppose the FDA's approval of paroxetine for treatment of moderate to severe VMS due to menopause because, 1) with respect to benefits, the phase 3 clinical trial has failed to demonstrate evidence of clinically significant benefits for paroxetine in comparison to placebo, and; 2) with respect to paroxetine, a psychotropic drug, given its risk, it has many well-documented risks that far outweigh the trivial benefits of the

drug for the proposed indication.

In terms of efficacy deficiencies, as seen in table 7 of the FDA background document, in the two phase 3 trials, the reduction in the frequency of moderate to severe VMS at week 12 from baseline with paroxetine versus placebo, although statistically significant was not clinically significant, -0.9 and -1.7 with a mean baseline frequency of 10. The one study that evaluated whether the reduction of frequency was clinically meaningful failed to show clinical meaningful changes at week 12, and the reduction of VMS severity at week 12 was not statistically significant in one trial and was trivial, -0.05 in the other.

In terms of safety problems, the current FDA-approved label for paroxetine lists multiple adverse reactions, some of them potentially life-threatening, including serotonin syndrome, which can cause coma or death, seizures or convulsions, manic episodes, hyponatremia, bleeding, and potential reduction in the efficacy of tamoxifen,

which is important because women with breast cancer or high risk of breast cancer who may be taking tamoxifen constitute a significant target population for this potential drug.

The label also lists common adverse events that led to discontinuation of paroxetine in clinical trials for other now approved indications that were twofold higher or greater than placebo, which included somnolence, insomnia, agitation, tremor, dizziness, and sexual dysfunction, including decreased libido on many trials.

Safety data from the phase 3 trials for this NDA revealed that suicidal ideation, suicidal attempts, depressed mood or elevated mood led to drug discontinuation in five paroxetine subjects and no placebo subjects. The FDA noted that these were plausibly related to the study drug.

Finally, a recently published review from the Nordic Cochrane Center found that withdrawal symptoms to SSRIs were very similar to those for benzodiazepines, and the paroxetine medication guide also warns that stopping Pexeva too quickly

may cause serious symptoms, including anxiety, irritability, high or low mood, feeling restless or changes in sleep habits, headache, sweating, nausea, dizziness, electric shock-like sensations, shaking, or confusion.

In conclusion, based on the sponsor's and FDA's analyses, paroxetine is at best marginally effective in treating moderate to severe VMS due to menopause, as changes from baseline to VMS frequency or severity seen with paroxetine versus placebo were not clinically meaningful. Given the absence of evidence demonstrating clinically significant benefits and the known risk of the drug, the high risk-to-benefit ratio for -- (mic timed out.)

DR. JOHNSON: Thank you. Speaker number 3.

DR. JENNINGS: My name is Dr. Mary Carol Jennings. I speak today on behalf of the National Research Center for Women and Families. I have no conflicts of interest, and I trained in obstetrics and gynecology at Boston Medical Center.

We can all agree that we need safer

alternatives to hormones. Paxil is widely used and available for depression and several other indications. The key questions today are whether there is clear scientific evidence that this version of paroxetine works for hot flushes, and, if so, do the benefits outweigh the risks?

As the FDA has clearly stated in their memo to you, the company reported a significant reduction in the frequency of hot flashes at week 4 but only in one study at week 12. And one of the studies did not show a significant reduction in severity of hot flashes through week 12.

What are the risks? FDA notes that the greatest risk is depression and suicide. Although patients were screened and depression and a long list of psychiatric conditions were exclusion criteria for most patients, the data clearly show that women taking paroxetine are more likely to have suicidal thoughts and behaviors than women taking placebo. This is true even on this very small does, the 7.5 milligrams. The CDC tells us that women between the ages of 45 to 54 have the

highest rates of suicide in the country. That's the same age group most likely to take a drug for hot flashes.

Again, the FDA must decide if the benefits of this drug for hot flashes outweigh the risks. The approval decision for hot flashes is different from that for depression or OCD because hot flashes are not fatal.

I also want to speak briefly on behalf of breast cancer patients who might consider this drug for hot flashes caused by tamoxifen. FDA scientists expressed concern that paroxetine's effect on the liver enzyme that processes tamoxifen may reduce effectiveness of this cancer drug. The benefits of paroxetine for severe depression may outweigh the risks, even for breast cancer patients taking tamoxifen, but the data to date do not prove that the benefits for hot flashes outweigh the risk for breast cancer patients, or for any other patients.

This drug is already available off label for women who want it and in generic form at a similar

low dose, making it an easier and less expensive option than the same drug, with a new name specifically approved for hot flushes. Given the risks, if the benefits are questionable, there is no reason to approve paroxetine for this new indication. Thank you.

DR. JOHNSON: Thank you. Speaker number 4.

MS. KELLEY: Good afternoon. I'm Kathy Kelley, here on behalf of HysterSisters, an online community dedicated to providing GYN medical menopause patient support. I have served as a consultant for Noven on an advisory board, received advertising support from Noven on HysterSisters.com, but I've received no financial support to be here today. Further, I have no financial interest in the outcome of today's hearing.

I represent the individual members of HysterSisters.com with almost 300,000 members. I represent women with DVT who cannot take estrogen therapy after an oophorectomy. I represent women who carry the BRCA gene. I represent breast cancer

patients. I represent women with endometriosis. I represent the multitude of women who will not take estrogen because they are worried about the possible health risks. I represent the multitude of women who will not take estrogen because they are worried about the possible health risks. These women are truly suffering from hot flashes that cannot or will not take estrogen replacement therapy for their hot flashes.

Last month in February, we conducted a survey of HysterSisters to learn attitudes about hot flashes and treatments. We had over 4500 respondents. Ninety-three percent stated that they suffered from mile to severe hot flashes. Utilizing comparative data analysis to overlap intensity of hot flashes with each of our questions, this is what we learned.

Over half of the members of the women with hot flashes do nothing about them. Three out of 10 women who experienced hot flashes do take estrogen. Women with severe hot flashes are more likely to do something about their hot flashes, but still only

3 percent take estrogen, and, conversely, over 40 percent report doing nothing.

Asking how do hot flashes affect your life, we found that 4 out of 5 women who experienced hot flashes say it negatively impacts their sleep. Over half of the women with the hot flashes say it negatively affects their mood. One out of 4 say their family life is negatively affected. Nearly 20 percent of women with hot flashes say it affects their relationships with their partners and spouses. Thirty percent say it negatively affects their sex life. When asked if they have concerns about taking hormone therapy, 4 out of 5 respondents say yes, they have concerns.

No matter the level of intensity of hot flashes, almost 2 in 5 say they've avoided treatment altogether for hot flashes. Nearly one-third focus on alternative treatments, such as supplements, herbs, or cold packs around their necks. When asked, 9 out of 10 women are interested in an FDA-approved, non-hormonal treatment for hot flashes.

The results of this survey of 4500 women demonstrate an unmet need in women's health surrounding hot flashes and menopause. These women are asking to have an FDA-approved medication to manage their hot flashes. Thank you.

DR. JOHNSON: Thank you. Speaker number 5.

MS. ROBSON: Good afternoon. My name is Michelle King Robson, and I'm the founder of EmpowerHER.com, one of the nation's leading women health communities, and I represent the voices of millions of women who come to Empower every single month. I have been a consultant with Noven, but I was not paid to be here today, and I have no interest in the outcome financially.

The estimated number of women who suffer from hot flashes in the U.S. varies anywhere from 30 million to over 40 million, and we even saw a slide earlier, 250 million. The reality is no one really knows. As I see it, that's problem number 1 for us.

I'm not here only as a leader in women's health but also as a woman who tried to manage by

own dreaded hot flashes, feeling firsthand the humiliation and embarrassment. Flashes, night sweats turn my life upside down. One or two less hot flashes for me would make a huge difference in my life, my daily life. "It's only hot flashes," is a grave misnomer when perpetuated by comedy routines and even our own doctors. But it's not just hot flashes. It's my health, it's women's health, and it's gravely underserved.

We ran a collective survey with HysterSisters, and over 6,000 women wanted a voice, many like me, embarrassed and ashamed. They too are having a hard time functioning. A lot of these women have moderate to severe symptoms, many afraid to take an FDA-approved hormonal treatment. They made it clear they want a non-hormonal option. These women suffer in silence.

There's been nothing regulated or approved by the FDA that isn't estrogen or is not a non-hormonal option, which in my opinion, these women are going -- and we see this all the time. They're going for non-traditional treatments, non-

traditional treatments that no one has ever approved, or looked at, or studied. I suffer, but not like the women I see on my site; not like Diane who suffered after having her estrogen blocked, hot flash after hot flash. Her clothes drenched and her life forever changes.

Then I talked earlier about my dear friend who text me after we started the study and told me about her friend who has ALS. So she suffers from ALS and is paralyzed from the neck down and could not be here and could not also take the survey. But she wanted me to tell all of you today that she suffers too from hot flashes and night sweats. And what's happening? Her husband Pete gets up at least three times in the middle of the night to change her sheets and adjust her covers, something a simple non-hormonal medication could help with.

You see, this isn't a life -- (mic timed out.)

DR. JOHNSON: Thank you. Speaker number 6.

MS. GIBLIN: Hello again. I'm Karen Giblin. I'm the founder of the Red Hot Mamas, which is the

largest menopause education program in North America. I have been a consultant for Noven in the past, however, I've not been paid to speak here today, and I've covered my own travel expenses here today. And I want to thank you, again, for allowing me to speak today on behalf of the impact of menopausal symptoms on women and the need for FDA-approved non-hormonal treatment options.

In 1991, I was serving as selectman in Connecticut. I had a total hysterectomy. I had severe hot flashes and night sweats. And this created a lot of embarrassment for me, especially when I was conducting a town meeting, where I would break out profusely in a sweat. My face would turn crimson red, and that would create a lot of embarrassment for me and a lot of anxiety while conducting a town meeting. They also occurred at night, and they disturbed my sleep. The next day I was fatigued. I was unable to concentrate. And this, too, was frightening because here I was managing the affairs of 21,000 people.

Women in my community began calling me,

asking me questions and sharing details about their menopausal symptoms. That's why I developed Red Hot Mamas, to help meet their needs. And today, we've worked in over 200 hospitals, and our programs are free to women, and thousands of women attend these programs each year. Well, many of these women consider me to be their voice of their concerns, so I'm going to share with you a few of those today. So let me read some quotes that are on our bulletin board.

The first quote I have is, "I've been having hot flashes and severe night sweats for the last year or so. I've been having them during the day at a rate of 2 to 3 an hour. They're so bad, I'm drenched in sweat. At night, I turn off the heat and open a window. There's a thermostat in my bedroom, and the temperature is in the 50's. I still have to throw off the covers and literally dry off with the ceiling fan on high just to cool myself down. This occurs too many times at night, and I don't sleep at all."

Women are concerned about how long their hot

flashes are going to last. Here's another quote. "I started having hot flashes when I was 38 years old. I'm now 53. I'm still on medication to control them." Now, I ask all of you, is this the answer we're seeking, a woman staying on hormone therapy for 15 years and over?

Hot flashes affect intimacy. Here's another quote. "My husband said last night, every time he wanted to come over and snuggle with me, the heat would radiate. I'd push him back. I said, 'It's a husband repellent.'"

Women at work have meltdowns. Here's another quote. "Today, I had a whole day of hot flashes, so many I thought I --" (mic timed out.)

(Pause.)

DR. JOHNSON: Thank you. Speaker number 7.

DR. GASS: Good afternoon. I'm Dr. Margery Gass from the North American Menopause Society. And in consideration of the committee, I'll not repeat my intro slides from this morning, only to say that I'm not here to discuss for or against any of the products being considered, only to highlight

the clinical challenge we face.

This afternoon, I want to share the consumer survey that we did expressly for this meeting. An invitation was sent to 18,000 consumers, a response rate of 7.7 percent, which is typical for these kinds of surveys, but over 600 comments went along with that. When we asked the key question, do women think there should be a non-hormonal prescription therapy, 89 percent, 90 percent average rounded up, said yes. And when we asked why, here were some of the responses: because of adverse reactions to hormone therapy, 30 percent; because of some women having contraindications, 37 percent; and an amazing 85 percent because of the perception that they are unsafe.

Eighty-eight percent of these women had hot flashes, and if you look at the pie graph here, you'll see that about 84 percent of them reported them as being moderate to severe. So this is exactly the target audience that these products would be on the market for. And how did they try to handle their hot flashes? They did lifestyle

changes, over-the-counter products, hormone therapy. Thirteen percent used compounded hormone therapy, other prescriptions, 11 percent, and some did nothing at all.

I want to share with you a few of the comments. I don't want to wear you out with the comments. Karen presented some very nice comments. I'll run through these quickly.

"I'm miserable, but now I'm unable to take HT because of a breast condition. This is a definite need for a safe, effective measure."

Each paragraph is a different woman.

"Menopause can be life-altering, and not in a good way. Between insomnia, mood swings, hot flashes, it can destroy your well-being, impact your relationships and day-to-day living in so many negative ways. Please help."

"My symptoms were so bad, I would have to pull over the car because of the sweat in my eyes and feeling that I had to get out of my skin and strip ASAP. This was a horrible journey for me of many years: weight gain, loss of mental acuity,

severe hot flashes, depression. I would not wish this on my worst enemy."

"I have Factor V Leiden. I've missed many work days and lower productivity due to lethargy, depression, sleep problems, night sweats from perimenopause. This is very expensive to businesses and very demoralizing."

"Still freezing my husband out of the bedroom."

And this is a message to me. "Emphasize not just hot flashes, but incontinence, bladder infection, atrophic vaginitis -- painful sex."

"The fan is my friend."

"I thought I was losing my mind, could not sleep."

"I continue to suffer greatly from hot flashes."

"At wits end. My doctors largely do not take this seriously and also think it's a short phase. For me, it's been seven years."

And one succinct comment. "Menopause is the pit of hell."

So what comments would I summarize here?

(Mic timed out.)

DR. JOHNSON: Thank you. Speaker 8.

DR. CARTER: Good afternoon. I'm Dr. Christine Carter, and I serve as the vice president for scientific affairs at the Society for Women's Health Research. I was asked to attend one advisory board meeting at the sponsor's treat, if you will, who picked up travel arrangements and a small honorarium. But I received no financial support to be here today, and I have no interest in the actual outcome financially.

Our organization, SWHR, is relevant to today's proceedings in that the society for 23 years has focused on ensuring not only that women participate in clinical trials, but that clinical trial results be analyzed and reported separately from men and women. In addition, you may not be aware, but SWHR sought and succeeded obtaining authorizations for the offices of women's health at all several of our federal agencies, including NIH, HHS, and the FDA. We continue to engage the

scientific community, policymakers, and consumers in dialogue to improve women's health and to increase the participation of women in clinical trials.

Today, I have a simple message. Women deserve choices. When the news hit 10 years ago from the Women's Health Initiative trial that menopausal hormones increased the risk to cardiovascular disease, pulmonary embolism, and breast cancer, thousands of women and their physicians decided that they could not or would not risk using estrogen to address the symptoms of menopause. Although the study population for this trial was considerably older than the menopausal age, the message was heard. Women and their physicians suddenly had far fewer choices to manage menopausal symptoms.

Interestingly, these very results were largely reversed and reframed years later when subsequent analyses were conducted, but the WHI investigators did little to inform the public of the subsequent findings. Many women began

experimenting with non-approved bioidenticals and/or supplements. Physicians used off-label drugs, et cetera, et cetera. And to this day, there remains considerable confusion.

We now have convincing data for non-hormonals. So this advisory committee has the opportunity to provide women and their physicians with a choice. Thank you for the opportunity to present.

DR. JOHNSON: Thank you. Speaker 9.

MS. FRENDT: You're all so serious in this room. You can tell I'm the one on the clinical trial. My name is Dawn Frendt, not paid. I have interest in this drug being approved but no financial. So I think that's what I'm supposed to cover. I have something to read, but I have to talk from my heart. And I'm not supposed to get emotional about it.

It changed my life. Twelve weeks, and it changed my life. Five years, hot flashes, waking up every hour and 15 minutes like clock work. I'm an outgoing person; still kind of comes through.

But I changed. I needed sleep anytime I could get it. So I pushed my family aside, and I went on the couch every moment I could get. Who you should be talking to is my family, my friends, my co-workers, my sister. I just gave it all up. I was too tired, too tired to deal with it.

Then I answered a phone call because my husband was out of work, and I need some extra Christmas money, so I'll pocket that money. But it was a life-changing event for 12 weeks; actually 13 because it worked a little bit afterwards. Never once. Never once did I ever have a hot flash when I was on that drug. I woke up the first night going, "Am I alive? What's happened here?" I slept the whole night through for 12 weeks, 13 weeks almost.

We've got to have something. I need it. If you don't approve for all the women of the world, approve it for me. I need the drug. I need to sleep. I need to be that person I was again. I've tried other drugs. I've tried everything over the counter that my girlfriends have suggested. I have

the washcloth and the cold water next to my bed, and it just doesn't work. I'm still waking up just tired, exhausted.

People have been very sweet to he, "Oh, how was your wonderful room?" I've never checked into a hotel room -- which they paid for -- alone. It was great, but I was up every couple hours with hot flashes. Those poor gals who cleaned the room, I've got to go back and forth in the bed because it was cold, as I had it down to 50 degrees.

I just need to be me again. I know there are lots of options out there. No side effects for me; none at all. I'm not saying that's -- "I had a little bit of depression." That's the thing I keep hearing here. I've learned so much; oh, we're depressed, we're depressed, we're depressed. We're depressed because we're sleep deprived, and then we don't want to eat because we don't feel like eating because we're too tired. We don't want to do things that bring us joy because we're too tired.

So I'm just begging -- look, I'm due in 29 seconds. I could just keep on going. But I'm just

begging you to just really, seriously take it into consideration. I've got a line-up of people that I've met. I just have told everyone, this is my answer, and I know it could be other people's answers, too. So thank you so much.

Questions to the Committee and Discussion

DR. JOHNSON: Thank you very much.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to addressing the tasks at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now begin our discussion portion of our meeting. I would ask, because we still have a list of questions both for the FDA as well as for our sponsor, to allow us approximately 35 minutes to allow those questions to be answered, then we will follow with the voting. With the voting, we will do what we did before and go around the room. We'll make brief comments as indicated as we vote

on the three questions at hand.

But now, let us begin with the discussion portion. I wanted to ask, Dr. Kittelson, did you get all your questions answered? I may have broken you off too quickly.

DR. KITTELSON: I think it's okay. But I did want to ask if there had been any evaluations of missing data. It's maybe 10 to 20 percent, and can anybody comment on the influence of missing data on the results or potential for that?

DR. LIPPMAN: Yes. I'm going to ask Dr. Blumenstein to come up and address that. And also, we have some additional information on a question you had asked earlier of Dr. Blumenstein as well.

DR. JOHNSON: You can proceed with the answers to those questions after the completion of this question.

DR. BLUMENSTEIN: Slide up, please. As you can see, the amount of data that was lost in 12 weeks is approximately a little bit more than 10 percent in both arms. In fact, the relative amount of missing data that didn't make it to

week 12 is reversed for the two arms. We also did extensive analyses to find out if the people who didn't make it all the way to 12 weeks were different.

Slide up, please. And so what this forest graph shows is the estimated mean for the change in frequency for those that dropped out of the study before week 12 versus those who had something close to week 12 or perhaps after. And as you can see, there's no evidence of a major difference in this primary outcome for these patients. We did extensive analyses on other baseline characteristics and other things of that nature, and we found no difference between those that made it to week 12 and those that did not.

DR. KITTELSON: Okay. Thank you.

DR. JOHNSON: And some points of clarification?

DR. KITTELSON: Yes. Thank you.

DR. BLUMENSTEIN: So you had asked about -- I forget the table number, but the multiple outcomes slide that we had showed

previously and the table number -- slide up, please -- and the table in the briefing book that was similar to this.

The difference is that the fourth line down is the response criteria that was the first line in the briefing book, and we added a few additional endpoints -- we added a few outcomes to this slide over that which was in the briefing book.

DR. KITTELSON: I see. So they were largely displaying the same information.

DR. BLUMENSTEIN: Yes, that's correct. In fact, I think -- I didn't do a line by line comparison, but --

DR. KITTELSON: I did see some that were exactly the same --

DR. BLUMENSTEIN: Yes, right.

DR. KITTELSON: -- so I was wondering why I was missing --

DR. BLUMENSTEIN: So, for example, the first line on this slide is a response criteria based on the baseline median as opposed to an individual patient showing a 50 percent reduction from

baseline.

DR. KITTELSON: Right. And so the analogous slide 4, Study 3, that's in the briefing document would be similar, and you showed us that, then, when you presented the last time.

DR. BLUMENSTEIN: Right.

DR. KITTELSON: So I can look at that as an interpretation of a similar result from Study 3.

DR. BLUMENSTEIN: Yes.

DR. KITTELSON: Okay. Thanks.

DR. JOHNSON: Clarification, Dr. Orza?

DR. ORZA: Do you have that figure for Study 3 and Study 4 combined? They were quite different.

DR. BLUMENSTEIN: Slide up, please. Our general impression is that Study 4 is stronger than Study 3. And in particular, this is true for week 12. And it helps explain why, for example, we might have missed the endpoint, the one endpoint that we missed on Study 12. So as you can see, point estimates for almost all the outcomes are to the right of the line, even at week 12 in Study 3.

DR. JOHNSON: Now, we are going back to the FDA questions. Dr. Armstrong?

DR. ARMSTRONG: I think this is primarily for the agency, but maybe for the sponsor as well. I think I probably reflect what a lot of people around the table are concerned about, which is that in these studies -- and it's not a criticism of the study because we know that the biggest effect is the placebo effect. And so trying to actually tease out what is the effect of the agent is difficult if you don't have that placebo effect. And we know that patients in studies -- and it was said they get much more attention. They are potentially being seen a lot more. They have potentially support because of that. And so, it's difficult for me to try and tease this out.

One of the things that I noted from Dr. Orleans' presentation was that -- one of the recommendations was for ongoing surveillance. So one of the questions is, does the approval process -- and again, I'm most familiar with the process in oncology drugs, but can it be done with

the caveat that further studies be done to look at this, to look at what we would call accelerated approval in oncology, where you really are required to get more data? Maybe not in a study situation, but to really try and get a sense of what the actual effect of the drug is in the non-study situation.

DR. SOULE: Yes. From a regulatory perspective, that really isn't something we can do in this case. And not to denigrate the importance of this disorder, but it is not a life-threatening condition. And it's really not being approved on the basis of surrogate endpoints, and those are some of the key factors for an accelerated approval.

DR. ARMSTRONG: Thank you.

DR. JOHNSON: Dr. Gillen?

DR. GILLEN: I'd like to just return back to this evaluation of clinical meaningfulness. And I think this is a question both for the FDA and the sponsor. The way the guidelines have currently been set up is to evaluate two -- I wouldn't call

them orthogonal but certainly different aspects of what we're dealing with, and that's frequency and severity. But all the clinical meaningfulness outcomes are kind of focused on frequency, and there hasn't been a look at severity in thinking about these things.

The dichotomization of the ROC curve, for example, is based upon frequency, and the sponsor actually produced some very nice plots showing a relationship between reported decreases in frequency and the PGI score. And I'm wondering if we have either reported frequencies -- reported distributions in terms of decreases in severity by PGI score or if we've also looked at, for example, clinical meaningfulness as it's attributed to severity as well, and what the importance is there.

DR. SOULE: Are you directing that to the FDA?

DR. JOHNSON: Are you directing that to --

DR. GILLEN: It goes both ways, so I think that you guys had come up with a formulation or an algorithm for defining clinical meaningfulness

based upon an ROC algorithm that strictly focused on frequency. And so I'm wondering if there's a concept of incorporating severity in there, if we think that that's an important aspect of an outcome.

DR. SOULE: Yes. That's something we'd certainly welcome feedback from you all on. To date, we have applied it only to frequency measures.

DR. GILLEN: And then from the sponsor's side -- so slide CT-37, again, shows the distribution of decreases in frequency as a function of PGI score and what patients actually scored themselves as. Did we look at severity there?

DR. LIPPMAN: It is true that most of those patient outcomes are correlated to frequency reduction. And remember, severity is a derived score. So at this point in time, I don't know that I can say that we have a separate analysis. Now, in our composite score, we certainly consider in the numerator the frequency and severity, and then

we weight them, and we develop a score. And that's why we think that's really a reflection of total patient burden.

But in addition to that, perhaps Dr. Portman can give some additional information on severity.

DR. PORTMAN: The FDA guidance does ask us to have patients identify at week 4 and week 12 severity and frequency, and that is currently the primary outcome. If you look at the Cochrane review, which I put up showing that there's a consistent placebo response across all studies, and the rates of response to hormone therapy, McClellan in that paper recognizes that one of the great variables in all those studies is severity. It's a highly variable score, doesn't have nearly the consistency of frequency. Perhaps it's easier to count hot flashes than grade them. We don't know why that is.

Could I have the slide up, please? So that's the reference, the Cochrane review, for your reference. The other scale that we used that identified severity is the Greene Climacteric

Scale. If I could get the bar graph from the Greene Climacteric Scale? And that is a rate of severity because when patients are asked -- the raw data, yes. Slide up. So while this doesn't ask patients to specifically to rate the severity of the single hot flash, it does ask the patient on a scale of 1 to 5 how severe various domains in these categories affect them.

So it indirectly is a measure of severity, and you see that the vasomotor domain is statistically significant. And I would use that as a surrogate for severity. And if we want to go ahead and put up the next figure.

This is looking at the GCS in just a different way, looking at all the domains based on percent maximum possible reduction. And if we do believe that the patients are giving us a view of what their severity of their symptomatology are, I think we do see a treatment effect, a clear treatment effect with the LDMP beyond placebo in all categories and across the study.

DR. JOHNSON: I'd like to ask a question to

the FDA. Could you actually bring up slide 29, CE-29? Your slide CE-29. Thank you.

I just wanted to make sure that I was clear on this. In the briefing documents, you did say that the clinical meaningful improvement was seen at week 4 but not at week 12. So am I correct in your assessment that clinical meaningful improvement was not seen at week 12? Is that correct?

DR. SOULE: I'll try this one. I think the difficulty with this is that it was not a prespecified primary analysis. So what we were reporting, although they're not labeled on this slide, are really nominal p values. I think you want to look at the totality, so I would look at both the responder rates and the p values. But we don't look at this as a strict statistical hypothesis test as we would with a primary analysis.

DR. JOHNSON: Yes, and I did hear that before, but I'm just -- to quote your statement on your overall summary of efficacy, I just want to

make sure I'm clear that the FDA's impression is that clinical meaningful improvement was not seen at week 12. Am I correct that that's your interpretation?

DR. SOULE: Yes. That's what we stated. Yes.

DR. JOHNSON: Now, I would like to look for the sponsor and ask you to compare your impression of the clinical meaningful improvement and the difference you would see between the slide 31 and 32 versus this slide 29, and tell me what the difference is in terms of interpreting clinical meaningful improvement.

DR. LIPPMAN: So I'd like to ask Dr. Blumenstein to come back up and talk about the ROC analysis.

DR. BLUMENSTEIN: Slide up, please. So I agree with the FDA about the interpretation of the p value for the ROC analysis. What we're showing here is just for the PGI, the bi-arm for Study 3. And this is the best we can do with respect to what the patient reports to us with respect to that

outcome dichotomized to show us a response.

DR. JOHNSON: What is this measuring?

DR. BLUMENSTEIN: The impression of improvement.

DR. JOHNSON: So the same 1 through 7 score?

DR. BLUMENSTEIN: Yes. I mean, as a way of explanation, the analysis that was done with the ROC -- using the ROC methodology resulted in a cutoff for the frequency. That was the whole purpose of going through the ROC methodology. Once you had the cutoff, then frequency was dichotomized based on that cutoff to be responder or non-responder. We also had other definitions of responder. That is, we had the 50 percent criterion. You saw also I did something with respect to whether the patient was above or below the baseline median for frequency response and so forth.

So one has many choices to make with respect to what a responder looks like. And if I can show the next slide, one of the more useful ways of looking at it that we found was in this cumulative

incidence graph. And what we're showing here is we've defined a durable responder as a woman who is experiencing a 50 percent or greater reduction for four successive weeks. And we have versions of this for longer definitions of response. And what we're showing here is that the women meeting this criterion of response; that is, including both achievement of a reduction and the durability of the reduction, is we're able to show it in this way so that you can see there's a difference between the arm and the women who achieve that.

If I could have the next slide up? So in this case, what we did is just simply changed it to be an 8-week criterion. And as you can see, the cumulative incidence lowered, that is, we didn't achieve as many women making that criterion. But we have the same rate, and we have the same flattening, and we have the same difference between the arms.

DR. JOHNSON: Thank you very much.

DR. KITTELSON: While this up -- sorry.

DR. JOHNSON: Clarification question?

DR. KITTELSON: Just while it's up, did they relapse?

DR. BLUMENSTEIN: Yes.

DR. KITTELSON: And does 8 week largely look like a cure? Can we think of it that way?

DR. BLUMENSTEIN: If I could have the Kaplan-Meier graph of the cessation of state of response? Slide up. So we did companion Kaplan-Meier graphs for those that did achieve the state of response. So this is not a randomized comparison, but this is showing how quickly a woman who has achieved a state of response ends that state of response. And so, as you can see, it isn't like immediate, and it appears as though there's roughly the same between the two arms, for those that achieved the response. Remember, there are more patients in the LDMP arm that achieves a response than otherwise.

DR. JOHNSON: More clarification comments on that question? Dr. Orza?

DR. ORZA: The first slide that they had up, can we get what the treatment difference is? It

shows bars, and it shows p values, but it doesn't actually tell us what the difference was between -- actually --

DR. BLUMENSTEIN: Are you talking about the cumulative --

DR. ORZA: Could we just see that for all the primary endpoints? There isn't any slide that just shows us what the actual treatment differences were for the primary endpoints.

DR. BLUMENSTEIN: Okay. Could I see the cumulative distribution for frequency at, say, week 12? That's not the slide.

One of the ways -- there becomes many ways of displaying the kinds of data that we've collected here. Slide up, please. And this is one way that we found to be useful and is coming into a more common usage in situations like this, particularly for patient-reported outcomes. And so, what you can see here is we call this -- the statisticians, we call this a cumulative distribution. And it's a little bit hard to understand, but it tells us the probability of

having a -10 percent or less by constructing a vertical line from the 10 percent point on the horizontal axis, up to where it intersects these two cumulative distributions. And then you can see how many patients -- what percent of patients had 10 percent or less, that is -- a 10 percent or more reduction that is a value for the primary endpoint of 10 percent or less.

Looking at it the other way, if you construct -- if you pick a point on the horizontal axis and then go straight out to where it intersects the cumulative distributions, you can see that's where patients receiving, say, 50 percent -- for each arm receiving 50 percent of a response, you can see what difference in the measurement would be by looking at the horizontal distance between these two curves.

So this is the kind of thing that we've assessed on multiple endpoints to be able to quantify and help us understand the degree to which these things work.

DR. JOHNSON: Thank you.

DR. LIPPMAN: Do we have a slide on absolute reduction that we could -- perhaps we'd give more information, if it's okay, for this question?

DR. JOHNSON: Very, very briefly, please.

DR. LIPPMAN: Okay. So what I'm trying to -- because I think you asked to give you a number so you could understand, perhaps, what the actual reduction of hot flashes is.

DR. ORZA: Just the basic, what is the actual treatment difference on the primary endpoints. We've seen everything but that. We've seen it in the FDA slides, but we haven't seen it in your slides. What is the difference in terms of numbers of hot flashes and degree of severity?

DR. LIPPMAN: Slide up, please. So here's the absolute daily reduction in frequency between the two groups in Study 3 and Study 4.

DR. ORZA: Right, but I have to do the math myself, right? I have to subtract 3.14 from 4.29. Do you have a slide that does the math for me, is what I'm asking for.

DR. LIPPMAN: Yes. Can you put the forest

plots up? Dr. Bhaskar will come up and discuss that.

DR. BHASKAR: So the difference in Study 3 at week 4 was 1.3, and for Study 4 at week -- for Study 3 at week 12 was .9. And the difference in Study 4 at week 4 was 1.3, and the difference at week 12 was 1.7.

DR. JOHNSON: Thank you. Dr. Curtis?

DR. CURTIS: I think I asked my question during the FDA session.

DR. JOHNSON: Dr. Montgomery Rice?

DR. MONTGOMERY RICE: I need just a little bit of clarity, and, FDA, you can answer this. I want to make sure that I understand. Based on your four co-primary efficacy endpoints, frequency at baseline, weeks 4 and 12, there was a yes, they met that. And then severity from baseline to week 4 was a yes. And then severity from baseline to week 12 was a no, based on the data that I saw.

Is that correct?

DR. GUO: Yes, you're correct.

DR. MONTGOMERY RICE: Okay. Now, those were

the prespecified agreements. But clinical meaningfulness was not a prespecified agreed --

DR. GUO: Analysis of clinical meaningfulness is also prespecified in the study protocol in the analysis plan, but it's a supportive analysis. So the study was not powered to detect a difference for the clinical meaningfulness. And also --

DR. MONTGOMERY RICE: Okay. So it wasn't powered for that. That's what I want to get to.

DR. GUO: Not powered for that. Only powered for the co-primary endpoints.

DR. MONTGOMERY RICE: And you had to have that difference of 2 hot flashes. Correct? You had to have some difference of 2 in order to go on to be qualified to do the clinical meaningfulness.

DR. GUO: No.

DR. SOULE: No. I'm sorry. Actually, the opposite. We use that as a supportive analysis if the difference over placebo is less than 2.

DR. MONTGOMERY RICE: Is less than 2.

DR. SOULE: Right.

DR. MONTGOMERY RICE: Okay. That's what I meant.

And then for the sponsor, Dr. Portman, I want to make sure I understand something. In you-all's submitting data, what you talked about here was that 4.5 million prescriptions -- paroxetine for approved indications, in the past you had 3.3 million for SSRIs to treat VMS. And of that, 2.4 were SSRIs, meaning none SNRIs, I assume, and 250,000 were for paroxetine. And the common dose was 20 milligrams to 40 milligrams.

So we had 250,000 prescriptions of this product in a higher dose. What were the others? I mean, because you've got 2 million other prescriptions that look like they're being treated for -- used for VMS also. Is that correct? Am I interpreting this correctly, based on what you-all put in here?

DR. PORTMAN: The IMS -- you can go ahead and put this slide up. This breaks down the prescribers' diagnosis and the various doses. So you can see there's a variety of doses, but the

majority of the doses were 20 and 40 for the prescriptions for VMS with paroxetine.

DR. MONTGOMERY RICE: But you've got a lot of other SSRIs being used to treat VMS. I'm just thinking about how we practice. So a patient comes in. She has hot flushes and she has depression. And I know you're going to tell me you're going to send her to a psychiatrist to get evaluated for depression. So let's clear that up. You went to a psychiatrist. He said an SSRI would be a good drug.

How do you decide you're going to give 7.5 or 10 or 20 if she's got hot flushes and that?

DR. PORTMAN: Well, right now, there's no guidance. It's based on people's review and interpretation of the literature. And I think that the message that has been sent is that higher doses are better. If the average dose that the GYN and PCP is prescribing is a 20- or 40-milligram dose, I assume they're doing that for the other SSRIs and SNRIs as well. And I think that what's helpful here is that we have seen that lower doses may be

as effective, better tolerated, and with some guidance, we might be able to keep an eye on safety signals as well.

DR. MONTGOMERY RICE: But we don't have any data that says that this lower dose is as effective as that 10 or 20-milligram.

DR. PORTMAN: We have no comparative data, no.

DR. MONTGOMERY RICE: Okay.

DR. JOHNSON: Thank you. We'll allow time for just two more questions after a comment by FDA.

DR. SOULE: I just want to clarify one thing, Dr. Montgomery Rice. You asked about our interpretation on the co-primary endpoints. Only one of the studies failed on the severity endpoint at week 12. So I didn't want to leave you with the impression that we thought both of them had failed.

DR. MONTGOMERY RICE: Just one of them.

DR. SOULE: Just one. Yes.

DR. JOHNSON: Dr. Rosen.

DR. ROSEN: I just wanted to ask the sponsor

and also the FDA about the discontinuation that was presented in slide 34. For the FDA first, was there a statistical significance to the fact that there was a much greater rate of recurrence of symptoms in those individuals who were treated with active drug versus placebo?

DR. ORLEANS: Not that I'm aware of. This is just descriptive.

DR. ROSEN: Descriptive. Okay.

And has the sponsor done any studies looking at post -- or discontinuation of the drug to see if this is a significant side effect? That is, once you stop Paxil, you actually would get more hot flashes?

DR. LIPPMAN: The DESS was actually done within a week of discontinuation.

DR. ROSEN: And is there any known effect from discontinuing SSRIs in terms of more rapid occurrence of symptoms such as hot flashes?

DR. LIPPMAN: That is not known at this time.

DR. ROSEN: I had one other comment. I just

want to make clear to the record that although Dr. Watts did mention that he didn't find anything about paroxetine in fractures, there are several meta-analyses showing an increased risk of fracture with long-term therapy of SSRIs; mostly in older individuals, but they range from a relative risk of 1.4 to 2. So there is definitely evidence in the literature now. Three meta-analyses and one registry study from Norway recently published showed this, so I wanted to make that clear.

DR. JOHNSON: Thank you. And our last question from Dr. Dobbs.

DR. DOBBS: A slide went up -- very quickly -- by the sponsor on efficacy between races. And it is as if the African American population had a poor response than did Caucasians. Did I interpret that wrong?

DR. LIPPMAN: Could I please have the slide up on the -- slide up, please. So this was the slide I presented, and the point estimates are all in the same direction.

One other way I could approach this is we do

have a pharmacokinetic study. It's a small study, but it was a single- and multi-dose study. And it actually had about 22 subjects, an equal number of Caucasian and African Americans. And, actually, when we analyzed the group separately, the curves matched, but the area under curve was actually a little bit higher amongst African Americans.

DR. DOBBS: Because here, only at 4 weeks does it show efficacy for the non-Caucasian; everything else, it crosses.

DR. LIPPMAN: I'm going to ask Dr. Blumenstein just to comment a bit further on that.

DR. BLUMENSTEIN: Yes, we did extensive modeling of the outcome with respect to multiple covariates. And of particular interest was the relationship that you see here between the racial status, either Caucasian or not or African American or not. We also involved BMI in that, and we weren't able to find any statistical evidence of an interaction that would explain what you see here. Another way of saying that is that there's nothing statistical here that this is consistent with

chance.

DR. JOHNSON: Well, I would like to thank all our members of our committee for your questions, and I would like to appreciate the FDA and the sponsor for the time and effort put into our answers.

Now, we will proceed with the voting questions. For voting questions, we will use our electronic voting system. Once we begin to vote, the buttons will flash and will continue to flash until you've completed your vote. Please press firmly with the button that corresponds with your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. When everyone has completed their vote, then the voting will be locked.

The voting will then be displayed on the screen, and the federal officer will read the vote for the record. Then we will go around the room and each individual will state their name and their vote into the record. If you have any comment that

is significant to make at that time, please feel free to do so.

Let's proceed with our first question. Based on the prespecified analysis, is there significant evidence to conclude that paroxetine is effective in treating moderate to severe vasomotor symptoms associated with menopause? If you would please vote.

(Vote taken.)

MS. BHATT: The voting results, yes, 7; no, 7; abstain, zero; no voting, zero.

DR. JOHNSON: If we could start with Dr. Schwarz.

DR. SCHWARZ: I voted no that I didn't think all the prespecified outcomes were demonstrated to be significantly effective, though I was impressed that some of them were close.

DR. GILLEN: Daniel Gillen. I also voted no, mainly for the magnitude of effects. And to be quite honest, the high variability in measuring severity that was coming up, particularly in the treatment arm during the 12-week, the 4 to 12-week,

is questionable to me. It's curiously been -- whether it was met -- I mean, I know that statistically it was met in one of the trials, but what that means to an actual patient is unclear to me still at this point.

DR. KEYES: Linda Keyes. Well, we know that the studies didn't meet all four primary endpoints. That's why --

DR. JOHNSON: Please state how you voted.

DR. KEYES: Yes. I voted yes. That's why we're here. But this one came awfully close, and I did think that the preponderance of evidence point towards modest-small, but probably a very real effect. I share Dr. Gillen's concerns about the magnitude of the severity effect.

DR. DOBBS: Adrian Dobbs. I voted yes. I value more the issue of frequency than severity. I agree that this probably -- it's very difficult to define severity. And I felt it was a modest effect, but, all in all, it's a reasonable safe option for women. And I thought the primary outcomes really were consistent and were found, and

it was only that clinical global that was a little questionable statistically.

MS. ARMSTRONG: I'm Deborah Armstrong. I voted no. It did not meet all the primary endpoints, particularly in 003, which was the study that was a subject of the SPA. And also, I think a low magnitude of the effect, and, as I stated before, the confounding influence of the placebo effect.

DR. CLARKE: Bart Clarke. I voted yes because I think the co-primary endpoints met criteria except for the one time, the week 12 in Study 3 for severity. And again, I value the frequency, I think, a bit over the severity, even though they're both valid endpoints. So I voted yes for this reason, and I'm still concerned about the magnitude of effect being very small.

DR. ROSEN: I voted yes as well, and I do --

DR. JOHNSON: If you could state your name.

DR. ROSEN: Cliff Rosen. I voted yes. And I value frequency and this one endpoint on

severity. I think the problem here -- and it's going to be the problem with any non-hormonal therapy -- is the placebo effect is so strong that it's going to be very difficult for any agent to meet those criteria. So I thought they came as close as they probably can ever come this close to, for question 1.

DR. JOHNSON: Julia Johnson. I voted yes. Along with others, I was concerned about the no-effect with severity in study number 3. And the difference between study number 3 and 4 were concerning to me, but having met 3 of the 4 criteria, I thought that it was reasonable to consider this moderate effect.

DR. MONTGOMERY RICE: Valerie Montgomery Rice. I voted yes. Any of us who are clinicians know that severity is very subjective, based on the environment in which the hot flush occurs. Frequency is either yes or no. And so I value that more so. And when you look at the effect -- and I believe it came very close. So when you look at the totality of the data, even though it was a

modest effect, I think it was beneficial.

DR. CHAI: Toby Chai. I voted no. My main issue here was the difference between the two studies in terms of they didn't seem to look similar. And I understand that it was very close in study number 3 for one of the variables. But I just thought that the overall evidence is that it was not balanced -- not all four the same effect.

DR. ORZA: Michele Orza. I voted no. I thought that the size of the effect was similar to the last drug we looked at in terms of frequency. And I thought that the severity was much less than the last drug and almost negligible.

DR. KITTELSON: John Kittelson. I voted no, primarily because of the -- by primary prespecified analysis, it didn't meet all four. The asterisk got put in. And agreeing with them in many of the other no comments, the asterisk gives -- I think, as noted, it's going to be very difficult for drugs to meet efficacy given current guidelines, and those are draft guidelines.

Perhaps it's time to revisit and try to

think about the relationship between severity and frequency and how those would be better addressed because I think the need is very clear, and perhaps the hurdle is set someplace that's difficult. Thanks.

DR. CURTIS: Kate Curtis. I voted no. And being almost at the end of the line, I don't have any additional reasons for voting no. I agree with the ones that were mentioned.

DR. BOCKMAN: Richard Bockman. I voted yes because I felt, in a very narrow way, they did meet the prespecified analyses statistically, but I think the difference is really very small and weak.

DR. JOHNSON: So in summary, reasons for voting yes included that there was some moderate effectiveness; that even though it barely met criteria, there was a significant placebo effect, and that would impair the ability to find a significant effect of any non-hormonal medication. Some concerns were variation in the results, especially the difference between Study 3 and

Study 4, and that, indeed, it met three out of the four criteria, not truly all four. So perhaps these are criteria that are too challenging, but an argument could be made that it did not meet the specified criteria.

So our next question, based on the prespecified analysis, is there significant effect to conclude that the change in baseline in VMS frequency is clinical meaningful to women? Please vote.

(Vote taken.)

MS. BHATT: The voting results, yes, 4; no is 10; abstain, zero; no voting is zero.

DR. JOHNSON: Let us again go around. This time we'll start with Dr. Bockman.

DR. BOCKMAN: I had to look how I voted.

(Laughter.)

DR. BOCKMAN: I preface my comment that there is such a slight difference, I think, between the placebo and the drug. But it's very clear that for some, it does make a difference. So I don't really know how to conclude. I'm sorry. I can't

justify my vote.

DR. CURTIS: Kate Curtis. I voted no, and I'll admit that I struggled with this one as well. But the fact that only one study had a prespecified analysis of clinical meaningfulness, which was significant at week 4 but was either not significant or not powered to look at week 12 -- and also, there was that large placebo effect, and that really counted for the difference between week 4 and week 12 -- was an increase in the placebo and really no change in the drug effect -- that led me to vote no.

DR. KITTELSON: John Kittelson. I voted yes for reasons that are hard to articulate. Primarily, if I look at the strict meaning of the question VMS frequency, it met those conditions. I also think there was a preponderance of evidence in the personal assessment of efficacy that was important and needed to be considered. And so I came down the yes side on this one.

DR. ORZA: Michele Orza. I voted no for reasons that are equally difficult to articulate.

And it did have to do with how the question is phrased because what we keep calling the placebo effect is actually -- you can get a 50 percent reduction in your hot flashes just from all the other things that they're doing. And so the question is really that additional 5 or 10 percent that you're getting from the drug; is that meaningful. And I didn't see a clear signal that that little additional percent, which is what we're talking about, was meaningful.

DR. CHAI: Toby Chai. I voted no. Also hard to articulate, but it's been articulated --

(Laughter.)

DR. CHAI: -- in some way or form or fashion.

DR. MONTGOMERY RICE: Valerie Montgomery Rice. I voted yes, and I based that on looking at frequency, the personal assessment data. And I looked at the data that looked at the responder rates at weeks 4 and 12, and then I looked at the persistence of the efficacy at week 24. And I know that women are looking for something that works

fast and that continues to work as long as they're taking the medication. And that was clearly shown in Study 004; the responder rate was higher in the paroxetine at week 24.

DR. JOHNSON: Julia Johnson. I voted no. I was concerned regarding clinical meaningfulness and the ability to demonstrate that using the mode that was provided by the FDA.

DR. ROSEN: Cliff Rosen. I voted no. I'm just not sure that there's clinical meaningfulness. And I'm really still troubled by the persistence of benefit from week 12 to 24 because placebo has it, as well as the active drug. And I think it's really hard for me to sort out what's happening in this study that's really different with the active compound.

DR. CLARKE: Bart Clarke. I voted no, mainly because of the small magnitude of effect.

MS. ARMSTRONG: Deborah Armstrong. I voted no as well. Again, as I said before, I think because the biggest effect here is the placebo effect, it's really hard to determine what part of

what you see, change from the baseline, is actually due to the drug and what's due to placebo.

DR. DOBBS: Adrian Dobbs. I voted yes. I have no problem with the placebo effect. I think it's real, the physiological effects that a placebo does that works in every single disease state. It was a slight difference above placebo here that I felt comfortable with that it would be helpful.

DR. KEYES: Linda Keyes. I voted no, largely because the significance of the effect declined between weeks 4 and 12. I think it is possible that there is an effect there, but I cannot say it has been demonstrated to be meaningful.

DR. GILLEN: Daniel Gillen. I voted no. I also agree that the placebo effect is real, but, again, my no vote really comes from the magnitude of the added effect of the drug relative to what the placebo effect is. For example, a .9 decrease relative to a 5 decrease in the placebo arm in Study 3 and 1.7 in Study 4.

Just while we're on this topic, since the

question really was phrased in terms of frequency, again, and we thought about this algorithm for defining clinical meaningfulness as this prespecified secondary analysis, if you will, I think if severity is going to be considered also as a co-primary endpoint, we need to consider what clinical meaningful severity changes are, actually. It seems to me that we can rationalize what frequency changes are because there was already a threshold that was made, and said, look, if it's less than 2, then we'll go to this other analysis and look at it. So we already have some concept there that we're making. We're putting a judgment on what clinical meaningfulness is, in decreases in frequency.

I think that thinking about going forward with this, a similar approach could actually be taken to come up with a composite for frequency and severity. Because you're basing it on an ROC curve now, a risk score can actually be developed across severity and frequency that can be used, then, to judge, based upon the patient's perception of

improvement on those two measures. And you could think about how to weight those two things.

Again, if you're going to think of them as co-primary endpoints, we need to consider what a clinical meaningful difference is on both of them.

DR. SCHWARZ: Bimla Schwarz. I voted yes, predominantly because I was impressed with the data presented as a composite score that combined both frequency and severity scores. I think that the reason we did placebo-controlled trials was to look at the difference between the placebo and the active treatment, and I think we're seeing a signal there.

DR. JOHNSON: Well, thank you to the committee. Just in summary, although it was hard to articulate, the overall thoughts were that there was limited clinical meaningfulness and that, indeed, the significance of the change was small. However, seen on the other side, severity is a difficult tool to measure, and their placebo effect is significant. There was also thought that, indeed, the data presented did appear that there

was long-term benefit and that potentially there is a positive use of this medication.

So now we will do our last question. Is the overall risk/benefit profile of paroxetine acceptable to support approval of this product for the proposed indication? Please vote.

(Vote taken.)

MS. BHATT: The voting results, yes, 4; no is 10; abstain is zero; no voting is zero.

DR. JOHNSON: Now, let us start again with Dr. Schwarz.

DR. SCHWARZ: Hi. I voted yes because I think there was some evidence of benefit. I'm not worried about the safety profile of this already FDA-approved drug, and think if we are worried, then the way to address that is to help women access a lower-dose version of it. And I do feel that the stigma of having it only labeled for psychiatric indication limits the number of women who are currently using this as an off-label treatment.

DR. GILLEN: Daniel Gillen. I voted no,

again, going back to the previous answer in terms of clinical benefit and looking at the magnitude of the treatment effect relative to the magnitude of the placebo effect, where there is no risk involved. And so that was what my basis of my judgment is.

DR. KEYES: Linda Keyes. I voted no. I think in this case, the magnitude of the benefit was quite small, and the risk profile appeared rather problematic. In addition, there is the possibility of off-label use at a dose that's very close to the dose presented here, and I did not feel that they adequately provided justification for the 7.5-milligram dose. So they haven't shown that this optimized the trade-off between risk and benefit. And so, it was difficult for me to see how this is superior to, say, a 10-milligram dose.

DR. DOBBS: Adrian Dobbs. I voted yes. I felt that there was, however small, a benefit above placebo, and it was safe, and it has a role for a subset of women. And I want to comment that probably the ideal study design for many studies is

an active, a placebo, and a do-nothing arm, but, obviously, those studies become very expensive.

MS. ARMSTRONG: Deborah Armstrong. I voted no. Concerns were not safety. I guess I would have been surprised if there were new toxicity or safety issues identified using the lower dose, and there weren't. It's the benefit part of the calculation, as evidenced by my two prior no votes.

DR. CLARKE: Bart Clarke. I voted no, agreeing with Dr. Gillen, basically.

DR. ROSEN: I voted no, based on my previous -- Cliff Rosen. I voted no, based on my previous rationale and the lack of strong support for an indication. I will make one comment, and that is that I do empathize with the yes votes because, in some ways, having an indication might allow us to have better surveillance over who's getting this drug and what is happening to it, and how it's being utilized, which we really have very strong difficult figuring out right now.

DR. JOHNSON: Julia Johnson. I voted no. Although the risk is small and I agree it doesn't

appear to be any different than the more standard doses of this medication, we have very little information about this dose. There isn't long-term surveillance to know, and we did see some effect on suicidal ideation. And I actually was somewhat concerned that there may be a greater effect than seen. Having said that, also a contributing factor, as already mentioned, is the relatively low effect on the patients who use it.

DR. MONTGOMERY RICE: Valerie Montgomery Rice. I voted yes. I was not as concerned about the safety, based on the information that I saw. I also think that, based on the numbers that we're seeing of prescriptions that are written, we have to be realistic about how medications are going to be clinically used when there has been some proven benefit. I thought the sponsor put forth a reasonable surveillance and follow-up program for us to monitor this further, as well as the appropriate warnings that would need to be considered and the follow-up. And I do believe that there is a role for non-hormonal therapy in

women with these moderate to severe symptoms.

DR. CHAI: Toby Chai. I voted no, based on my prior two votes, where I didn't think there was sufficient evidence on the prespecified analysis for the co-primary outcomes, and also the lack of clinical meaningfulness. And finally, I share some of the concerns over side-effect profile, suicidality and osteoporosis, and that's how I justified my vote.

DR. ORZA: Michele Orza. I voted no for reasons that have been well said by others.

DR. KITTELSON: John Kittelson. I voted no. In this case, the risks of the whole class, reinforced by the minor signals here, made me worry about a yes vote; that the benefits were not big enough to offset that. It might be in future work that better work on endpoints and combining severity and frequency into a more robust endpoint would help overcome some of those concerns. But at the moment, the risk and the class were too much to justify a yes vote.

DR. CURTIS: Kate Curtis. I voted no again,

based on my prior two votes, and the very modest effect and the lack of clarity around clinical meaningfulness.

DR. BOCKMAN: Richard Bockman. I voted yes. I think there's a very small beneficial effect from this drug. And I think it's widely used, and there's wide experience with this drug. And I think this very small dose is probably safe, and I think it's time to sort of legitimize its use.

Adjournment

DR. JOHNSON: Thank you very much. So in summary, the minimal effect of the medication was a concern. There was limited concern regarding risk but some raised regarding suicidal ideation. If indeed it had been approved, then it could be more closely monitored, and it would allow a non-hormonal medication to be available for patients. But overall, the benefits were minimal and did not outweigh the risks.

Thank you again for all of the comments from the team. I would now like to thank the FDA, as well as the sponsor, for your very hard work, and

to the committee for your careful attention of this issue. I would like to thank everyone, and we are adjourned.

DR. JOFFE: This is Hylton Joffe from FDA. I just want to echo a thank you as well to the advisory panel, to both applicants from both sessions today, to the presenters for the open public hearing. I think the discussion and presentations were very helpful, and we'll carefully consider what we hear today when we make our recommendations.

I also want to thank Dr. Johnson for facilitating very nicely a jammed-pack, two-session advisory committee meeting in one day. And also, last but not least, Kalyani Bhatt and Lisa Soule, who are behind the scenes and have played a major role in helping FDA prepare for this advisory committee today. So thank you.

DR. JOHNSON: You're welcome.

(Whereupon, at 5:03 p.m., the afternoon session was adjourned.)