DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

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8:00 a.m.

Hilton Hotel
The Ballrooms
Gaithersburg, Maryland

P A R T I C I P A N T S

AVISORY COMMITTEE REPRODUCTIVE HEALTH DRUGS

Linda C. Giudice, M.D. - CHAIR
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Jonathan Tobert, M.B. [Industry Representative]
Lorraine J. Tulman, R.N.. D.N.Sc.
[Consumer Representative]

Teresa A. Watkins, R.Ph., Executive Secretary

CONSULTANTS AND GUESTS

SGE Consultants (voting)

Joanne F. Dorgan, Ph.D., M.P.H.
Diane F. Merritt, M.D.
Steven Nissen, M.D.
Donald L. Patrick, Ph.D.
Martha Solonche [Patient Representative]

SGE Consultants (non-voting)

Adrian S. Dobs, M.D.
Julia r. Heiman, Ph.D.

FDA PARTICIPANTS

Julie Beitz, M.D.
Donna Griebel, M.D.
Scott Monroe, M.D.
Daniel Davis, M.D.
Lisa Soule, M.D.

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. GUIDICE: Good morning. Would everyone take their seats, please? Thank you.

I'm Linda Giudice, and this is the reproductive Health Drugs Advisory Committee Meting to the FDA. And today the committee will discuss the new drug application, the testosterone transdermal system, Procter and Gamble, indicated for the treatment of hypoactive sexual desire disorder in surgically menopausal women receiving concomitant estrogen therapy.

I'd like to first remind the audience and committee members to please put your cell phones on silent or vibrate so that the proceedings are not interrupted. And I'd like to begin this morning by going around the table so that each of our committee members may introduce himself or herself. Please give your name and your affiliation, and then we will move on with the program.

So I'd like to start on this side, please.

DR. BEITZ: I'm Julie Beitz, I'm the Deputy

in Office of Drug Evaluation III.

DR. GRIEBEL: I'm Donna Griebel. I'm the Deputy in the Division of Reproductive and Urologic Drug Products.

DR. SOULE: I'm Lisa Soule, Medical Officer in the Division of Reproductive and Urologic Drug Products.

DR. MONROE: I'm Scott Monroe, Clinical Team Leader, Division of Reproductive and Urologic Drug Products.

DR. DAVIS: Dan Davis, a medical reviewer in the Reproductive Drug Products Division.

DR. MACONES: George Macones, Department of OB-GYN, University of Pennsylvania.

DR. HAGER: David Hager, Obstetrics and Gynecology, University of Kentucky and Central Baptist Hospital, Lexington, Kentucky.

DR. TULMAN: Lorraine Tulman, School of Nursing, University of Pennsylvania, Philadelphia.

DR. BURNETT: Bud Burnett, Urologist on staff at Johns Hopkins in Baltimore.

DR. DICKEY: Nancy Dickey, Family and

Community Medicine, Texas A&M University System Health Science Center.

DR. GIUDICE: I'm Linda Giudice, reproductive endocrinologist at Stanford University.

DR. WATKINS: I'm Teresa Watkins. I'm the Executive Secretary with the Advisors and Consultants staff.

DR. LOCKWOOD: Charles Lockwood, OB-GYN, Yale University.

DR. LEWIS: Vivian Lewis, reproductive endocrinology, University of Rochester.

DR. LIPSHULTZ: Baylor College of Medicine, urology.

DR. SOLONCHE: Martha Solonche, patient representative, New York City.

DR. PATRICK: Donald Patrick, Social and Behavioral Sciences and Health Outcomes, University of Washington.

DR. NISSEN: I'm Steve Nissen, and I'm a cardiologist with the Cleveland Clinic.

DR. MONTGOMERY-RICE: Valerie

Montgomery-Rice, reproductive endocrinologist, Meharry Medical College, Nashville, Tennessee.

DR. HEIMAN: Julia Heiman, Kinsey Institute, Indiana University.

DR. TOBERT: Jonathan Tobert, Tobert Medical Consulting, and the University of Oxford, England.

DR. GIUDICE: Thank you.

Ms. Teresa Watkins will now read the conflict of interest statement.

Conflict of Interest Statement

MS. WATKINS: Thank you.

The following announcement addresses the issue of conflict of interest, and is made as part of the record to preclude even the appearance of such.

Based on the submitted agenda for the meeting, and all financial interests reported by the committee participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of

interest at this meeting, with the following exceptions.

Because Drs. Adrian Dobs and Julia Heiman has past involvements with Proctor & Gamble related to the product under discussion, the Agency has decided to limit their participation.

Dr. Julia Heiman may participate in the committee's deliberations. She is, however, excluded from voting.

Dr. Adrian Dobs is permitted to give a presentation to the committee and to answer questions directly related to her presentation.

We would like to note that Dr. Jonathan Tobert has been invited to participate as a non-voting industry representative, acting on behalf of regulated industry. Dr. Tobert's role on this committee is to represent industry interests in general, and not any one particular company. Dr. Tobert owns Tobert Medical Consulting LLC.

In the event that the discussions involve any other products or firms not already on the

agenda, for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

Thank you.

DR. GIUDICE: Thank you.

Donna Griebel will now give her welcoming statement and comments.

Welcome and Comments

DR. GRIEBEL: [Off mike.] Good morning everybody. Can you hear me?

Now can you hear me? I'll lean.

I'm Donna Griebel. I'm the Deputy Director--as you've already heard--of the Division of Reproductive and Urologic Drug Products. The Division would like to welcome you all here today--both committee members and guests--and we

would like to express our gratitude to you all for traveling all the way to Washington at a very busy time of the year to consider the application that is before us.

As you have already heard, the NDA is for testosterone transdermal system. The proposed indication is for the treatment of a subtype of female sexual dysfunction called hypoactive sexual desire disorder. And it is specifically for a sub-group of women with this disorder, which is surgically menopausal women who are being treated with estrogen therapy.

This application, if approved will be the first product that will have been approved for female sexual dysfunction.

I'm getting tired of leaning.

And the Division did designate this review a priority review, which means it was given a six-month review clock. We did so because there are no products approved for female sexual dysfunction, and a product that successfully treats this disorder could have a major impact on a

woman's quality of life.

In your review of the FDA's background document--and hen you hear the FDA's presentation today you will conclude that the FDA concurs with the applicant, Procter & Gamble, that they have shown a statistically significant difference associated with treatment with TTS in the primary efficacy endpoint of interest, which is the number of satisfying sexual events.

However, we do have questions about whether the statistically significant change that was produced by TTS, and the proportion of women who experienced this improvement relative to placebo is a clinically meaningful difference.

Analysis of efficacy is but one piece of a risk-benefit analysis. You also have to look at the safety data, and you have to evaluate the safety data base for its adequacy.

The Division factored its experience with the impact of the outcomes from the Women's Health Initiative studies in their approach to evaluating the safety data in this application. The Women's

Health Initiative studies were very large, randomized controlled trials, prospective studies, that were powered to show important differences in safety outcomes. They led to changes in product labeling for products that are intended for treatment of menopausal symptoms in post-menopausal, and they reinforced an initiative to be sure that the lowest effective dose of these products has been defined.

The results of the WHI studies became available after launch of the studies that you will be seeing presented today.

We've invited additional experts to sit at the table today and participate in the committee's deliberations. They include Dr. Donald Patrick, who has expertise in evaluating health-related quality of life instruments and endpoints; Dr. Julia Heiman, who's director of the Institute; Dr. Steven Nissen is a cardiologist; and Dr. Diane Merritt was to join us today. She's an OB-GYN from Washington University.

The Division has invited two guest

speakers to participate. They will be making presentations on issues relevant to assessing risk associated with hormonal products in post-menopausal women.

Dr. Adrian Dobs is a professor at Johns Hopkins University in endocrinology and metabolism. She will join us later this morning to summarize the existing clinical evidence in the literature of potential safety issues associated with testosterone use in women.

Our second guest speaker, Dr. Judith Hsia, is a cardiologist at George Washington University. She was a lead investigator in the WHI studies. You will hear the FDA mention WHI over and over again this morning and clearly we do believe that the data from these studies are relevant to today's discussion--for a number of reasons that include: number one, if TTS is approved, it will be approved for the population that was studied in this application, and that is surgically post-menopausal women who are taking estrogen. This implies that women who take TTS will also be taking estrogen, as

well. And, presumably, they will be taking the products chronically.

WHI demonstrates that millions of women can be exposed to a drug for a well-accepted off-label use, such as estrogen for prevention of cardio-vascular disease, and only when studied in a large, randomized controlled trial do we find that the drug is not effective for the presumed benefit, and is actually associated with substantial risk.

WHI also drives home some very important practical issues. If you want to shoot for the ideal study design to evaluate such risks--and that is it takes enrollment of a lot of women to get those answers. There are also hypotheses for the safety outcomes from the WHI studies that may be applicable to the data that you're reviewing today.

It's important for you to remember that the guest speakers are only available to you for dialogue and interaction between the committee members and the guest speakers when they're at the podium. So we would like to remind you to be sure and ask your questions that you would like to ask

of them while they are at the podium.

Quickly, reviewing the agenda: Dr. Hsia will actually be our first speaker, and we'll open the meeting today. She will be followed by Procter & Gamble's presentation of the data. There will be a break, followed then by Dr. Adrian Dobs.

FDA will follow Dr. Dobs, and we'll close the morning with the open public hearing speakers.

After lunch we will return and the committee will have an opportunity to ask clarifying questions of the applicant, Procter & Gamble, and the FDA. And then you'll transition into discussion of the FDA's questions, and we'll vote on those questions.

When you're listening to the presentations this morning, please keep the questions in mind. And I'll briefly run through them.

[Slide.]

The first is an efficacy question: "Do the efficacy data represent clinically meaningful benefit above that of placebo for surgically menopausal women with hypoactive sexual desire

disorder who are taking concomitant estrogen?"

Uh-oh. I am now missing two of my questions.

[Comments off mike.]

I wasn't a good Boy Scout and didn't come prepared to the podium.

The second question is with regard to the safety database: whether there's been an adequate number of women exposed, and whether the duration of exposure is adequate; whether the duration of exposure with the placebo control is adequate--with the bottom-line question: "Is the exposure, the total number of women treated, and duration of treatment adequate to demonstrate long-term safety?"

The third question is a three-part question. The first is: "a) Are the safety concerns or unanswered questions associated with use of TTS in combination with estrogen that need to be studied; for example, questions about cardiovascular or breast cancer outcomes, or questions about risks and benefits in populations

who are likely to use this product off-label?"

If you answer yes to that question, we would like you to be sure to state what your concerns are, what questions you have.

Part c) of the question is: "Should these concerns or questions be studied prior to approval of the product?" If you believe that these questions need to be answered prior to approval, we would like to know what studies you would recommend, what the design would be, what are the endpoints, who's the population.

If you think that the product can be approved and that your questions could be answered appropriately after approval, we would like to know what the study designs would be and, specifically, we would like you to comment on the applicant's proposed claims-based cohort study.

And now the question that I do have--question number four--it's a short one but an important one: "Are the efficacy and safety data adequate to support approval of TTS?"

Next, I would like to introduce Dr. Judith

Hsia from George Washington University, who will speak today about the WHI, and assessing risks of hormonal therapies in post-menopausal women.

Assessing Risks of Hormonal Interventions

DR. HSIA: Well, it's a pleasure to be here, and I appreciate being able to speak first, because the Women's Health Initiative steering committee is meeting downtown today and, as you know, if one is not present, there's a risk of having undesirable tasks assigned.

[Laughter.]

So I want to try to avoid that.

So I'm here to talk about approaches to assessing risks and benefits, and what we've learned as a consequence of the WHI.

[Slide.]

I'm really going to sort of briefly cover four areas: biomarkers; observational studies; randomized trials; and looking at intermediate outcomes.

[Slide.]

So, if you think about estrogen, there are

many biomarkers. One which was studied early and often was lipids. So if you look at LDL--the bad cholesterol--in the lower left here, you can see that starting two years before menopause there's a steady increase in LDL and currently, the HDL--the good cholesterol--is falling. And it was known that estrogen would improve this profile.

[Slide.]

Here's data from the Women's Health Initiative estrogen-progestin trial. What is shown is the difference between the active E+P and the placebo groups with regard to change in the biomarker from baseline to year one.

So if you look at the LDL cholesterol, you can see that falls 12 percent--which is a good thing. The HDL increase 7 percent, which also a good thing. Triglycerides go up, which is not good thing. Glucose and insulin both fall, which is a good thing. And blood pressure goes up, which is bad. So that you end up with a mixture of desirable and undesirable characteristics, and it's hard to know what the overall balance is going to

be with regard to risk and benefit.

So a great many observational studies have been undertaken to try to assess the relative risks and benefits with hormone therapy.

[Slide.]

This is a summary from an analysis that was published relatively recently by Joy Manson and co-authors in the New England Journal. It sort of summarizes the observational literature so that for breast cancer there was thought to be an increase in risk with E+P, which was associated with duration of therapy. There's a 25 percent reduction in hip fracture. There was a 45 increase in stroke; a doubling in the rate of pulmonary embolism; and a 39 percent reduction in the risk of MI and coronary death.

And it was on that basis of these type of studies that women had been being prescribed post-menopausal hormone therapy for coronary prevention for many years.

[Slide.]

So at the time the WHI hormone program was

designed, that was the data was available, and it was on that basis that the design was developed. So it was anticipated that the benefits would include coronary prevention. And although stroke looked like it was increased, in those observational studies, people didn't really quite believe that. They thought if it prevented coronary disease it would prevent stroke as well. So this was sort of a question mark.

It was thought it would increase breast cancer risk, and venous thromboembolic risk. It would reduce hip fracture and possibly overall mortality. So that was the plan.

[Slide.]

As the trials were conducted there were two arms. It was stratified presence of a uterus so that women who had no uterus were randomized either to conjugated estrogens alone or placebo; and those who had a uterus were randomized to CEE with daily medroxy-progesterone acetate or placebo.

These were the sample sizes that were built into the design. And let me just point out

that in order to achieve randomization of 27,000 women, that 373,000 women were screened--which is, you know, a significant proportion of the age-eligible population of the country.

[Slide.]

Now, if you just look at the E+P trial--for which the data is fully complete and has been published--in reality there was a 24 percent increase in the risk of coronary heart disease. The stroke data--there was a 31 percent increased risk in stroke; venous thromboembolism was doubled. There was an increase in breast cancer. There was a somewhat unexpected reduction in colorectal cancer, which was statistically significant. Hip fracture was reduced.

And there was ancillary study called "WHIMS"--the Women's Health Initiative Memory Study--in which women who were 65 or older at study entry were invited to have annual mini mental status exams, and if those scores fell below a certain level, then they went on and had subsequent testing and clinical evaluation for cognitive

impairment. And almost everybody who was offered participation in the ancillary study did participate. And WHIMS demonstrated a doubling in the rate of dementia if one was assigned to active hormones.

[Slide.]

now, there's been a lot of discussion in looking at the WHI data about the relationship between relative risk and absolute risk. So these are the absolute risks with E+P. It's per 10,000 woman-years. And I think of that as 2,000 women treated for five years, since that was the duration of follow-up at the time the trial was stopped for safety reasons.

So if you treat 2,000 women for five years, there will be 30 heart attacks or coronary deaths in the placebo group, and 37 in the active treatment group; so an excess of seven heart attacks or coronary deaths associated with E+P therapy.

Now, the trial, as a sort of study policy, does not characterize any of these differences as

large of small. You know, it's in the eye of the beholder, and we just put the data out there so that health care providers and women can make an informed decision--for the first time.

If you look at stroke, there were 21 strokes in the placebo group for 2,000 women for five years, and 29 in the active treatment group. And you can see similar numbers across the board.

For breast cancer, there were 30 breast cancers in the placebo group, and 38 in the active treatment group. And you see, actually, the dementia numbers are in some ways are the most dramatic.

[Slide.]

So, after the results became available, the balance had shifted from what was anticipated, so that on the benefit side, there was a reduction in fracture--of both hip and total fracture--and a reduction in colorectal cancer. And the risks included increase in dementia, coronary heart disease, stroke, venous thromboembolism and breast cancer. So the trial was stopped 3.3 years early,

for these reasons.

[Slide.]

Now, if you go back to the Manson, et al., analysis in the New England Journal--this is just a reproduction of those numbers. And if you put the WHI E+P numbers up alongside, you can see that actually the observational studies were quite predictive, as far as breast cancer was concerned. The hip fracture numbers are relatively similar. The stroke numbers are relatively similar. The venous thromboembolism numbers are really identical. And the only thing that's off is coronary heart disease.

So the question is: why is it? And one of the things they tried to address in their analysis was what some possible reasons might be.

[Slide.]

Some of it might be due to the "healthy user" effect, where women who choose to take estrogen in those observational studies--you know, the way they're conducted is like the Nurses Health Study, they fill out questionnaires, "Are you

taking estrogen?" And then they follow them along and count up how many heart attacks people have. And women who choose to take estrogen are known to have other healthy practices, like they exercise more, they're leaner, they ate more servings of spinach and so on--and that these things, although they're adjusted for in the models, you don't know everything that you need to adjust for, and you don't have the data on everything that might be relevant. So that's one problem.

Another is compliance bias. The women who are taking their hormones might also be adherent to other healthful behaviors like taking their blood pressure medicine, or whatever.

It was thought--this is a relatively new idea--that there might be outcomes identification bias, where their health care providers thought that if they were taking estrogen that that symptom they had couldn't possibly have been a heart attack, and therefore they were under diagnosed for the outcomes that they may have had.

And there may have been incomplete capture

of early events, where women who had adverse events while taking estrogen stopped their hormones before they joined the study.

[Slide.]

So, now what is the potential impact of adding progestin to estrogen, which has relevance to the topic today?

[Slide.]

If you look at the outcomes from the Women's Health Initiative estrogen-alone trial, compared to the E+P trial, you can see that they are similar in some ways and different in others. So that if you look at coronary heart disease, rather than a 24 percent increase in risk, actually it's neutral: estrogen-alone is neutral with regard to heart disease risk.

Stroke, increase is relatively similar. There is also an increase in venous thromboembolism, although it's not as marked. Breast cancer actually is neutral with estrogen alone, whereas it's increased with E+P.

The colorectal cancer benefit appears to

disappear. Hip fracture is prevented by estrogen-alone, and there is an increase in the rate of dementia.

So, it does appear that there are some impacts of adding progestin to the regimen.

[Slide.]

If you compare the absolute risks of estrogen-alone in the upper panel, with E+P in the lower panel you can see, for one thing, that the characteristics of women who've had a hysterectomy differ from those of women who still have a uterus, so that the placebo event-rate is higher. These scales are the same.

So the placebo event-rate is higher for women with estrogen-alone. They have more hypertension, diabetes, greater body mass index, and so on, and this is an issue. However, we have done analyses to try to assess the impact of this on the difference between the trial outcomes, and it does not appear that this accounts for them.

But you can see, for instance, the absolute increase in the number of strokes here was

8, and the absolute number--an increase in strokes--here is more like 11 or 12. So there are some differences in the absolute event-rates.

[Slide.]

So if you look at the balance of risks and benefits with estrogen-alone--which was a 6.8-year follow-up at the time the trial was stopped early because of the increased risk of stroke and dementia--the benefit is fracture reduction; it was neutral with regard to breast cancer and coronary heart disease, and there was an increase in dementia, stroke and venous thromboembolism.

[Slide.]

So the impact of adding androgen to an estrogen regimen may be difficult to predict, and may differ among the various types of progestins or androgens that may be studied.

Now, the alternative to carrying out a big randomized trial that may require screening 300,000 subjects to get your enrolled population, is to do studies of intermediate outcomes.

[Slide.]

And there are number of different measures that can potentially be used. This is coronary calcium, which is assessed using a fast CT scan. It's about 500 bucks. So it's a cheaper study to do. It's non-invasive, and may potentially have utility.

Carotid ultrasound is another approach that one can take to evaluating drug effects or intervention effects without waiting for hard clinical outcomes.

And a third possibility is coronary angiography, or--since Dr. Nissen is in the audience--coronary ultrasound.

And there has been some investigation using these intermediate outcomes, which is really summarized here.

[Slide.]

There have been a limited number of estrogen trials with intermediate outcomes. There have been three angiographic trials, funded by the NIH; two used conjugated estrogen, and one used estradiol. And they all showed no benefit or harm

with post-menopausal hormone therapy. So, on the one hand, they didn't show protection the way the observational studies did, but on the other hand they did not demonstrate the harm with the combination E+P that was observed in the randomized trial with clinical outcomes.

For carotid ultrasound there's been one randomized trial using estradiol that did demonstrate benefit, and that may be considered to be consistent, in some sense, with the estrogen-alone coronary outcomes, but it's not consistent with the stroke outcomes, because there was an increase in stroke in the estrogen-alone trial which--you know, if you think carotid ultrasound should be more predictive of stroke--would not be consistent.

And there actually is no estrogen trial data with coronary calcification.

The advantages of these trials are that, you know, they're much cheaper to do. You can do them with a sample size of 400, rather than 16,000. And they can be done in a shorter period of

time--maybe three years rather than six. So the advantages are considerable--if you think that the data are going to be predictive.

[Slide.]

So, just to summarize: the approaches that can be taken to evaluating risk are, I think, basically four. There are biomarkers--which I think have very limited utility, because they're likely to give a mixed picture, and you're not sure how to interpret those results. There are observational studies which, I think, have been demonstrated to be not reliable for assessment of coronary risk, although possibly they may be reliable for assessment of other types of risk. And the other thing is that, of course, suitable cohorts may not be always available.

And then there are randomized trials, with intermediate outcomes, which may potentially be useful, but their predictive value is still somewhat suspect.

And there are randomized trials which, of course, are the gold standard, but are expensive

and take a long time to undertake.

So, I'll close with that and--am I supposed to take questions?

DR. GIUDICE: We have time for just a few questions.

Yes, please?

DR. NISSEN: Judy, thank you for a very lucid presentation. I had a couple of questions.

One is: what is known about the use of estrogen, or estrogen-progestin, in women who have existing coronary heart disease. That's question one.

And question two is: using something like Framingham Risk Score, is there an interaction between the baseline risk and the risk of adverse--or increases in event rates in women who receive hormonal therapy? Can you predict any of this, using something like Framingham?

DR. HSIA: Well, let me take your first question first.

The HERS trial randomized women--which I was principal investigator for--randomized women

with documented coronary disease to conjugated estrogen with medroxy-progesterone daily, or placebo, and demonstrated an increase in coronary events in the first year--really, the first six months--following randomization. And thereafter, the curves came together and there was no risk or benefit over longer-term therapy.

And the angiographic trials of course--the three of them--all included exclusively women with some coronary disease, and were neutral. But they were smaller, and there may have been a power issue.

With regard to whether risk characteristics at baseline can predict safety, we have done sub-group analyses looking not at the Framingham score because, actually, although we have blood on everybody, we don't have laboratory measures on everybody for cost reasons. But if you just count up risk factors, and look at women with--you know, with or without more or less risk factors at baseline, it does not help you predict. There's no interaction between that and outcome.

And if you look at the women in the randomized estrogen-alone and E+P trials who had prevalent coronary disease at baseline--which was only a few percent--they had the same relative risk as women who did not.

DR. GIUDICE: Any other questions from the committee?

[No response.]

DR. GIUDICE: Okay, thank you very much.

DR. HSIA: Thank you.

DR. GIUDICE: We'll now proceed with the sponsor presentation. And the first speaker is Dr. Joan Meyer, who is Senior Director of New Drug Development at Procter & Gamble.

Sponsor Presentation

Introduction

DR. MEYER: Good morning. In addition to being Senior Director of Drug Development at Procter & Gamble, I'm also the Global Project Leader for the Testosterone Transdermal System Project.

Today we'll present data to you on the

testosterone transdermal system. We've been granted the trade name Intrinsa, which I will use from now on, because it's easier to say than testosterone transdermal system.

So what is it?

[Slide.]

Intrinsa is a patch. It delivers 300 mcg a day of naturally occurring testosterone, and the patch is changed twice weekly.

Our proposed indication, as you've heard, is for the treatment of hypoactive sexual desire disorder in surgically menopausal women on concomitant estrogen therapy.

So what is hypoactive sexual desire disorder?

[Slide.]

Well, this is a recognized medical condition that affects many women. It has both ICD and DSM codes.

There are three key elements to HSDD that are very important to keep in mind, especially when considering the clinical relevance of this

condition. One is: the woman has a decrease in sexual desire. This leads to a decrease in sexual activity, and satisfying sexual activity. This, in turn, causes the woman personal distress. So these three things are very important: the desire, the decrease in satisfying sexual activity, and the increase in distress.

It affects all aspects of a woman's life, as we can show you today; her health, well-being and her relationship with her partner.

So what else will we be showing you today?

[Slide.]

After I give you a brief background of the project, Dr. Johna Lucas, the Director of Clinical Development at Procter & Gamble, will share with us the clinical efficacy data, and she's show you the highly significant improvements achieved by Intrinsa in all the endpoints that were measured, including desire, activity and distress.

Then, Dr. Leonard DeRogatis, the Director of the Johns Hopkins Institute for Sexual Health and Medicine, will show us the clinical relevance

in these data to the women who participated in the trials.

Then Dr. Lucas will return to share with us the safety data, and show us the favorable safety profile we saw in the clinical studies with Intrinsa.

Then we'll hear from Dr. Glenn Braunstein, the Chairman of Internal Medicine at the Cedars Sinai Hospital at UCLA Medical School. He will share with us the data from our clinical trials on the levels of testosterone, other hormones that we measured, and discuss their implications for safety.

Dr. Jan Shifren is an Assistant Professor of Reproductive Endocrinology at Harvard Medical School. She will put these data in context for us, and she'll show us the impact HSDD has on women's lives, and discuss the medical need for a drug like Intrinsa.

Then Dr. Michael Steinbuch, who is the Director of pharmacovigilance and Epidemiology and Procter & Gamble, will go over with you our

comprehensive Phase IV program that we've designed to follow the long-term safety of Intrinsa.

Finally, I'll return to wrap-up and share concluding remarks with you.

But, also available for discussion today, we have a variety of experts, both within and outside Procter & Gamble, to discuss any questions or data that you'd like additional information on.

[Slide.]

I just want to go over briefly the clinical development program for Intrinsa. And it's important to remember that this is, indeed, the first drug for the treatment of hypoactive sexual desire disorder. We worked closely with the agency, through our development program. We followed the FDA guidance on the female sexual function drug development, and we also did a variety of studies to design our Phase II and Phase III programs.

[Slide.]

As you can see from this list, we did dermal safety studies, PK studies. From these

studies we determined the optimal site for patch application. We did dose-ranging studies. And we also looked at the effect of route of estrogen administration on the data.

Our Phase III program consisted of four large, double-blind randomized placebo-controlled studies: two of these in surgically menopausal women. And these are the data we'll be sharing with you today. Two of these are in naturally menopausal women, one of which is just completing.

We will present safety data today from these studies to round-out the safety picture of what we know about Intrinsa.

But we also did some additional studies to further understand the benefits of this treatment. Again, because it's a new therapeutic area, we had to do some non-traditional studies. And we had significant input and interaction with the agency to develop these.

[Slide.]

The currently available instruments that are out there were not considered fully appropriate

really to measure the three key aspects of HSDD--desire, activity and distress. So we developed three now instruments to measure these aspects, and we validated these in four separate clinical studies.

We also included, in our Phase III surgical menopause program, a couple of additional studies. One is a blinded withdrawal, that showed that the patch is indeed having the desired pharmacological effect. This was covered in your briefing book, and we won't be discussing it in the formal presentations today, but we'll be happy to answer any questions that you might have on that.

Also, as part of the Phase III surgical menopause program, we conducted to establish what level of change in these instruments was meaningful to the women in the study. And Dr. DeRogatis will discuss this with us this morning.

We've also done a lot of safety work. We've evaluated the safety of Intrinsa in several different ways. We've collected adrenergic adverse events in a very systematic way during the studies,

and we've also collected spontaneous reports.

We've continued to extend the Phase III studies, and we are now into year three of three of these surgically menopausal studies.

We've held two scientific advisory groups, one to discuss what do we currently know about the safety of long-term use of testosterone, and the other was on breast safety and testosterone. An outcome of the latter study was another special study that we did in conjunction with the Karolinska Institute. And Dr. Braunstein will discuss these results.

Also, as you'll hear from Dr. Steinbuch today, we've proposed a comprehensive Phase IV safety program.

But now I'll stop telling you what we're going to tell you, and get started on the data.

I'd like to introduce Dr. Johna Lucas, Medical Director at Procter & Gamble.

Phase III Clinical Efficacy Data

DR. LUCAS: Good morning. I will now present the efficacy from our Phase III surgical

menopause program, using the 300 mcg per day testosterone patch.

[Slide.]

I will show you how the drug increased not just our primary, and important secondary, sexual function endpoints, but every sexual function endpoint that we measured--and most of them in a highly significant manner.

[Slide.]

I want to begin by talking about the instruments we developed, and explain how the therapeutic goals that were important to patients became our primary efficacy endpoints. I will describe our Phase II and Phase III surgical menopause program, and then I"ll present the Phase III results.

[Slide.]

Because no tools existed to measure sexual desire and distress associated with low sexual desire in women with HSDD, we developed three multi-national validated instruments for the assessment of sexual function. We consulted with

more than 100 physicians and sex therapists to get their perspective, in addition to our validation program with patients.

Our instruments are: the Sexual Activity Log. It is a weekly diary that quantitates the numbers of sexual events; the numbers of orgasms, and the numbers of satisfying sexual events, for both intercourse and non-intercourse activity.

The PFSF--or Profile of Female Sexual Functioning--is a 30-day recall inventory that evaluates seven domains of sexual function.

The PDS--or Personal Distress Scale--is also a 30-day recall that evaluates the distress associated with low sexual desire.

The development of these three instruments is the subject of two publications.

[Slide.]

First, to discuss the profile of female sexual function and the PDS. We began by speaking to more than 250 women who reported having normal sexual functioning prior to the removal of their ovaries, and had experienced a substantial of

sexual desire, which they found quite distressing, after their surgery. We used their own specific words to generate items to be used on our measurement tools.

These interviews generated 450 items. We categorized the items by content; removed the items that were, for example, redundant, slang, had compound concepts, or were not representative of the general reading level. We kept 83 items that retained both content and meaning in six languages, with both forward and backward translation.

We then tested the ability of these items to discriminate women with HSDD from their age-matched control women who described themselves as well-functioning sexually, with normal sexual desire. We tested these in three trials.

[Slide.]

This took us down to 37 items for the PFSF, and 7 for the PDS. These items were then tested in a fourth validation trial, comparing, again, surgically menopausal with HSDD to age-matched control women. Both the PDS and all

domains of the PFSF discriminated between surgically menopausal with HSDD< and their age-matched controls.

[Slide.]

In parallel to the development of the PFSF and the PDS, we developed the Sexual Activity Log--or SAL--which is a weekly diary. We developed the instrument with further interviews, revision and retesting to confirm that it captured all activity; that it avoided double-counting; and that it could be easily and universally understood by all.

The SAL also discriminated well between surgically menopausal women with HSDD and their age-matched controls

[Slide.]

Our surgical menopause program for Intrinsa consisted of two Phase II trials to determine dose, and two Phase III therapeutic trials. All were of similar design, with an eight-week baseline period, and a 24 week treatment period to measure efficacy and safety.

In all trials, patients were on concomitant estrogen, and required to meet similar inclusion and exclusion criteria.

In the Phase II trials, 300 mcg per day was found to be efficacious as well as safe, and established to be the appropriate dose to take into Phase III.

The Phase III trials included a safety assessment of up to 12 months.

[Slide.]

Our Phase III program included two concurrent multinational trials of more than 500 patients each, which we refer to as SM 1, and SM 2. These two trials had similar numbers of sites, geography of sites, inclusion and exclusion criteria, visits and procedures.

[Slide.]

In choosing endpoints for the Phase III trials, desire, distress and satisfying sexual activity were all important endpoints to understand the treatment effect of women with HSDD. Benefits in each of these areas are essential to achieve a

relevant treatment response. In keeping with the FDA's draft guidance for female sexual dysfunction, we chose "satisfying sexual activity" as our primary endpoint. We pre-specified "desire" and "distress" as key secondary endpoints--not only because patients reported this as their primary therapeutic goal, but because they comprise the definition of hypoactive sexual desire disorder.

After showing you these key three endpoints, I will show you additional endpoints from the PFSF that are also relevant for a meaningful treatment effect, since they too reflect the other important losses that patients with HSDD identified.

[Slide.]

Inclusion criteria were designed to ensure that patients had HSDD associated with their surgery; that is, patients had considered themselves to have normal sexual functioning prior to their surgical menopause, and had experienced as substantial decrease in sexual desire, and

accompanying distress, after their surgery. It was also important that patients be on estrogen, and in a stable monogamous relations with the partner there most of the time.

[Slide.]

Exclusion criteria were designed to rule out other causes of low sexual desire, either physiologic or psychologic. Exclusion criteria were also designed to exclude patients with conditions or medications that could confound efficacy, or for whom testosterone might be inappropriate.

[Slide.]

This schematic shows the number of patients that were screened--about 1,700; who were randomized--about 1,100; and who completed--about 870. This represents about 80 percent of patients completing the double-blind portion of the trial. About 96 percent chose to enter the open-label period of the trial, and of those, 76 percent completed the 12 months.

[Slide.]

Data will be shown in this format, with the first two columns representing SM1, the second two columns SM2, placebo testosterone, placebo and testosterone.

The completion rate of 80 percent was similar in both arms, in both trials. Of the 20 percent who discontinued, reasons for dropping out were very similar between studies and treatment groups. Of importance, drops for adverse events were similar at about 8 percent, regardless of the study, for testosterone or placebo arm.

[Slide.]

Patient characteristics were also very similar between studies and arms. Mean age was 49, with about 80 percent of patients being between age 40 and 59. The average length of relationship was about 20 years, and patients on average had been surgically menopausal about half of that.

About three-quarters of patients were on oral estrogen, and about a quarter of patients were on transdermal estrogen.

[Slide.]

Patients were also balanced at baseline with regard to disease characteristics. This baseline sexual desire score of about 20 corresponds to patients' reporting "seldom" interested in sex. The personal distress score of about 60 translates to patients "often" being distressed about their lack of interest in sex. Baseline satisfying sexual activity was about 3 episodes per four weeks.

Now, to review the results of the Phase III trial.

[Slide.]

This graph shows the man change in total satisfying sexual activity experienced by patients with treatment at 24 weeks. Yellow represents testosterone treatment; blue, placebo treatment. Improvement seen with testosterone compared to placebo were highly statistically significant in both studies.

At the bottom of the slide--to help you understand how the patients experienced their change in satisfying sexual activity, I have

provided you with a percent change from baseline in the respective arms. On average, in the two trials, we see that the change experienced with Intrinsa treatment was about double that seen with placebo.

[Slide.]

Here, you see the changes in sexual desire at 24 weeks for both Phase III studies. Again, there was a highly significant increase in sexual desire with the use of the testosterone patch compared to placebo. Averaging over the two studies, the increases seen in placebo were about 24 percent. AS you know, this magnitude of placebo effect is commonly seen in behavioral studies. On the other hand, patients who were treated with Intrinsa experienced, on average, a little more than 50 percent increase in sexual desire--again, roughly double that seen with placebo.

[Slide.]

This graph shows you the changes seen in distress. Distress associated with low sexual desire is the hallmark HSDD. Distress

significantly decreased with Intrinsa treatment compared to placebo in both trials.

Patients receiving testosterone treatment reported approximately a 65 percent decline in distress compared to their baseline.

In addition to assessing sexual desire, distress and satisfying sexual activity, we also pre-specific all other domains of the PFSF as endpoints. Recall that these domains reflected the other important losses that women with HSDD complained of and said they would like to have corrected.

[Slide.]

Shown here is SM1. With Intrinsa therapy, patients experienced an improvement in every domain of sexual functioning over placebo; that is, they had an improvement in arousal, orgasm, improvement in sexual pleasure, reduction of sexual concerns, improved sexual responsiveness, and improved sexual self image.

[Slide.]

Here are the results of SM2. Improvements

were very consistent to that seen in SM1. Again, all PFSF domains improved significantly with testosterone therapy compared to placebo.

[Slide.]

This graph shows increases in the other sexual activity endpoints measured on the Sexual Activity Log. Not only were satisfying sexual episodes increased within Intrinsa treatment--which I showed you previously as our primary endpoint--but patients treated with testosterone also experienced significant increases in numbers of sexual episodes and in numbers of orgasms.

Note here, with the Sexual Activity Log, we are assessing numbers of orgasms, while with the PFSF domain of orgasm, we were assessing the ease and reliability of orgasm.

[Slide.]

In summary, after listening to what was important to women with HSDD, we developed and validated instruments to measure clinically meaningful endpoints. Both of our pivotal trials showed strong and consistent efficacy using these

rigorously developed instruments.

Surgically menopausal women with hypoactive sexual desire disorder experienced a significant increase over placebo in sexual desire and satisfying sexual activity. They also experienced a significant decrease in distress associated with their low sexual desire. All three of these endpoints are critical to assessing a relevant treatment response in this clinical condition.

Patients further experienced benefits in sexual arousal, orgasm, pleasure, sexual responsiveness, sexual self image, and a decline in sexual concerns. Patients also had increased number of sexual events, and numbers of orgasms.

The consistent significant improvement in all areas of sexual functioning identified by patients as important demonstrates the clinical meaningfulness of Intrinsa therapy to these women with HSDD.

Dr. DeRogatis will now provide additional perspective on the clinical relevance of these

results.

Thank you.

Clinical Relevance of Treatment Effects

DR. DeROGATIS: Good morning.

As the Director of the Johns Hopkins Center for Sexual Health and Medicine, I see and treat a full spectrum of patients with sexual disorders. I also have a strong professional interest in the methods and techniques determining clinical relevance of the results of clinical treatment trials.

Dr. Lucas has shared with you the efficacy results from the Phase III trials. Now I'd like to speak with you about the clinical relevance of those results.

[Slide.]

To begin with, I'd like to emphasize that the results from the Phase III clinical trails implicitly speak to clinical relevance in a number of ways. First, recall, as Dr. Lucas pointed out, all of the endpoints for both the Phase II studies and the clinical relevance study are derived

directly from conversations, interviews, etcetera, with patients who expressed their concerns, experiences and what was important to them. Instruments developed in this way, by the very nature of the process, have clinical relevance for the patients.

Second, the decrease in personal distress indicates in a very direct manner the impact that the testosterone patch treatment had on the patients' feelings about heir disorder.

Third, the fact that all of the PFSF domains--not just desire--show improvement with testosterone patch treatment gives us confidence that there is a meaningful treatment benefit associated with the patch.

In addition to this implicit evidence from the Phase III trials, the sponsor also did a formal Clinical Relevance Study which employed the anchoring technique, and I'd like to tell you more about that now.

[Slide.]

The anchoring technique for examining

clinical relevance is very well established through broad use in numerous disciplines of medicine. Advantages of the method are that it's readily understood. Perhaps the most important advantage involves the fact that it's patient-based; it utilizes direct questions of the patient as to the patient's perception of clinical benefit. These patient perceptions of benefit are then tied, through statistical analyses, to the major study endpoints. The statistical analysis in this case is Receiver Operating Characteristic Analysis--or ROC analysis.

The results then define meaningful change, in terms of what are referred to as "minimum clinically important differences," which helps to establish clinical relevance.

[Slide.]

What you're looking at now is a model of the anchoring technique that was used to relate patient perceptions of meaningful benefit to changes in major outcomes measures in the Phase III trials. The Clinical Relevance Study essentially

had three stages. In the first stage patients were queried directly as to their experience, or not, of what they perceived to be a meaningful benefit. Those that answered "yes" were indicated as "responders," those that answered "no" were indicated as "non-responders."

In step to, these data were then utilized in receiver operating characteristic analysis, with each of the three main study endpoints: the PFSF, the SAL and the Distress Scale.

Third, each endpoint MCID score was then applied back to the total Phase III population to establish proportions of responders and non-responders in the Phase III trials.

In addition to the anchoring technique, we also asked patients if they wanted to continue on the treatment. This is a very telling question in regard to patient's perceived benefits. And as we'll see a little later, the results were quite interesting.

[Slide.]

Let me tell you a bit more about the

details of the Clinical Relevance Study. The Clinical Relevance Study was performed during a two-week period immediately subsequent to the 24-week double-blind randomized trial. 132 women from the Phase III trials were the sample for the Clinical Relevance Study. All of the interviews were done by a single female interviewer to reduce variability--potential variability--across interviewers.

The interviews began with rather open-ended questions about experiences in the clinical study and prior to the clinical study, and progressed to more specific questions about perceived benefits, if any, on the part of the patient.

The specific question for the anchoring analysis was: "Overall, considering everything we've talked about today, would you say that you experienced a meaningful benefit from the study patches?" Patients answered either "yes" or "no."

Subsequently, when the blind was broken, we learned that 52 percent of the patients on

testosterone, and 31 percent of the patients on placebo indicated they had experienced a meaningful benefit or were responders. Now, these rates of response are actually fairly typical of a number of areas in which clinical trials are done in medicine. They're comparable to the rates we see in irritable bowel studies, in incontinence studies, in studies of depression, and so were not unusual and really not unexpected.

Following the relevance question concerning benefit, these data were then utilized in the ROC analysis to essentially determine responders and non-responders.

[Slide.]

Focusing on this distinction for a moment, this table contents the mean change from baseline in the responder and non-responder group in major study outcomes.

As you can see, they're very different. If you take satisfying sexual activity for a moment, we see a mean change of 4.4 satisfying sexual activities per month on the part of the

responders, and a fractional 0.5 change for the non-responders.

In terms of sexual desire, there's a 21 point increase in sexual desire in the responder group, which translates into moving them from "seldom" feeling sexual desire, to "sometimes" feeling sexual desire--which, by the way, is the modal frequency for women in this age group.

Distress also shows a dramatic shift in the desired direction: almost 37 point reduction in distress in the responder group. And, again, this translates into feeling personal distress "often" to feeling personal distress "seldom." So, some fairly dramatic results in our responder group.

[Slide.]

Now let me share with you an ROC analysis--okay? And let me talk about this just briefly for a moment. What we see in our ROC analysis is a vertical axis which has our true positives on it. Our horizontal axis has false positives. And the ROC curve is actually the entire distribution of changes from baseline on

this outcomes measure--in this case "satisfying sexual activity"--in the sample.

Now, where the white diagonal from upper-left to lower-right intersects the ROC curve is the point of optimum discrimination; that is, the value that optimally correctly assigns responders and non-responders, and minimizes false positive and false negative errors. This value for satisfying sexual activity, is 1.11 satisfying sexual activities a month.

It's a little difficult to conceptualize fractional sexual activities. And so the sponsor decided to modify this value a little bit to "greater than 1," thereby retaining the accuracy of the result, but sparing us the difficult task of trying to conceive of fractional sexual activities.

ROC analysis has a summary statistic associated with it that tells us, essentially, how good the discrimination was--in this case, between responders and non-responders. This is referred to as the "area under the curve"--AUC coefficient--which on this particular analysis is

.77.

Now, this is very good, since experts in the field believe that .80 is actually an excellent discrimination. Analogous analyses were done for sexual desire and for personal distress. The coefficients in those instances were .77 and .78, respectively.

So, we wind up with excellent discrimination in our constellation or set of outcomes measures.

[Slide.]

Now, lets look at our anchoring model with all the data filled in.

Over on the left we see our information on patient perception of meaningful benefit: 52 percent of those on testosterone, and 31 percent of those on placebo have a meaningful benefit. These data, when integrated with ROC analysis produce these optimum cutting scores--or MCIDs--which, when applied to the Phase III population generate these proportions of responders--okay?--on each of our study outcomes measures.

Now, the three main points to be made here are the following: first, these percentages are approximately equal across the three major study endpoints; second, each shows a statistically significant advantage for the active treatment; third, the Phase III results or rates of responders are very analogous to the rate of responders we saw in the Clinical Relevance Study.

[Slide.]

Now I'd like to share one final set of results from the Clinical Relevance Study involving interest in continuing treatment. In this graph what we see is that 80 percent of those who indicated they had a meaningful benefit also indicated that they probably or definitely would continue treatment with the patch if it were available. Conversely, an approximately equivalent proportion of individuals who did not experience meaningful benefit indicated they would not wish to continue treatment with the patch.

Now, these results are an important measure of clinical relevance because they help

confirm that the patients' assessment of meaningful benefit is truly valid in terms of intended behavior, not simply perception.

[Slide.]

So, in summary, what did we learn from the Clinical Relevance Study?

First, we learned that significantly more testosterone patients than placebo patients experienced meaningful benefit.

Second, anchoring, using minimum clinical important difference values, confirms similar proportions of responders in the Phase III studies.

Third--and perhaps most importantly--these results are consistent across all study endpoints: sexual desire, satisfying sexual activity, and personal distress.

[Slide.]

So, in conclusion, I think I have to conclude that a consistent pattern of outcomes shows strong evidence of a clinically meaningful benefit, which translates into observable clinical relevance. Both as a clinical scientist and a

practicing clinician, I would conclude that these data strongly support the sponsor's contention that the efficacy outcomes achieved by the testosterone patch are, in fact, clinically relevant.

Thank you.

Phase III Clinical Safety Data

DR. LUCAS: Now to turn to safety.

[Slide.]

As we started to plan the safety evaluations to be included in the surgical menopause program for Intrinsa, we identified these areas of potential concerns for testosterone in women. We reviewed the literature for known androgen effects in animals and humans, including hyperandrogenism in women, and adverse effects reported with androgen treatment in men.

We also consulted with experts knowledgeable in two areas where there was less literature: high dose androgen used in female-to-male transsexuals, and androgen abuse with athletes and body builders. We then sought to assess each one of these areas in our safety

evaluations.

[Slide.]

Recall--as I told you earlier--the SM trials--SM1 and 2--were essentially of identical design: six-months double-blind, followed by open-label. Baseline health risks were balanced in the treatment arms and across trials.

The primary safety data I will present are from the double-blind portion of the SM1 and SM2 trials--seen here in brackets--since, as you know, a placebo-control offers the best opportunity to determine a drug effect. I will also show you dat on patients who dropped from the study during the open-label period--which you see here in white. Finally, I will present double-blind adverse event data from the still ongoing natural menopause program. These data are very similar to those seen in the surgical menopause trials, and provide the opportunity to see double-blind data with up to 12 months of testosterone exposure.

[Slide.]

1,800 patients in the Phase II and III

treatment trials have been exposed to 300 mcg per day testosterone or greater. Over 1,300 patients have received at least six months of therapy, and over 600 have received over 12 months of therapy. This represents an exposure of more than 14,000 months, or over 1,000 patient years to the 300 mcg per day testosterone patch in post-menopausal women.

[Slide.]

I will show you the safety data in this order, starting with adverse event profile, weight and vital signs, laboratory evaluations, and, finally, breast cancer.

[Slide.]

The numbers of patients reporting AEs overall--in both Phase III studies--were similar between the active and the placebo groups, and between the two trials. About 75 to 80 percent of patients had at least one health occurrence during the six-month period. The small number of serious adverse events, and dropouts due to adverse events, were consistent between active and placebo

treatment, and between the two studies, as well.

No deaths occurred in the SM1 trial. There was one death in the placebo group of the SM2 trial.

Looking at the most common AEs about one-third of patients reported an application-site skin reaction, including mild redness or itching at some time during the six-month trial. About 75 percent of these reports were considered "mild." Application site reactions were not higher in patients receiving patches containing testosterone. About 3 percent of patients dropped out because of these site reactions in all of the arms.

[Slide.]

Now, to look at these known androgenic effects with ADs and clinical assessments.

In the testosterone-treated arms, 94 percent of the androgenic AEs were assessed as "mild." 78 percent of patients reporting androgenic AEs experienced only one of them during testosterone therapy. Further, time to even was not different between the active and

placebo-treated groups for any of the androgenic AEs.

[Slide.]

Acne was evaluated in two ways: clinical assessment and AEs. Clinicians were trained in the use of the Palatsi scale to evaluate patients for facial acne at scheduled visits. About 98 percent of patients in both active and placebo groups had no positive change in their acne score.

Looking at acne AEs--which were reported by both physicians and patients--there were no differences between active and placebo in SM1. In SM2 there were fewer reports of acne in the placebo group than in the testosterone treated group.

[Slide.]

Facial hair was also evaluated in two ways: clinical assessments and AEs. We also trained our investigators to use a modified Ferriman-Gallwey scale to assess facial hair growth. With these evaluations, we again saw no difference between active and placebo in SM1. In SM2 we did see a mild increase in active over

placebo, primarily in chin-hair growth.

Patient-reported AEs mirrored the objective evaluations for facial hair growth, with no differences seen in SM1, and higher reporting with testosterone in SM2.

[Slide.]

Now, to look at the less common androgenic AEs--investigators specifically asked patients about hair loss and voice deepening at regular visits. Answering "yes," as well as spontaneous reports, were included as AEs. Again, we saw no differences between groups in SM1, and a slightly higher incidence in SM2 in the active group over placebo.

The one reported case of clitoromegaly in SM2 was reported by phone after 12 weeks of therapy. This was not confirmed by physical exam. She withdrew from the study and, when contacted five weeks later, she reported the condition had resolved.

[Slide.]

This slide shows the withdrawals due to

androgenic AEs. Please note that some patients reported more than one androgenic AE, so this represents an overall withdrawal rate due to androgenic AEs in the two trials of 1.2 percent, and 1.8 percent in the testosterone arms.

[Slide.]

We also looked at other adverse events that could be important to this population. We looked at breast tenderness and hot flushes to confirm that we were not potentiating estrogenic adverse events, and saw no increase with testosterone therapy.

AEs of weight gain were examined and were minimally higher in the testosterone-treated groups.

[Slide.]

When we looked at weight gain objectively, we saw a similar small difference. Mean weight gains of about 1/4 of a kilogram--or - pound, compared to similar mean weight losses of about - pound in the placebo arm were seen. We also examined vital signs and saw no change from

baseline in mean systolic or mean diastolic blood pressure in either SM trial, in either arm.

[Slide.]

We also looked at other adverse events that were reported in the male testosterone labeled products. We saw no difference in anxiety, edema or aggression.

[Slide.]

Because we saw liver function testing AEs in the testosterone arms only, we evaluated each of these patients individually. This represents six patients, which I would like to tell you about.

Of the six, two of the patients had isolated bilirubin AEs--increases. Both patients wree just at the upper limit of normal, and increased very minimally at 24 weeks.

Four patients had transaminase increases. Three of the four had mild increases, with less that two times upper limit of normal. Of these three patients, two patients remained on testosterone therapy, and their levels returned to normal. One patient was still mildly

elevated--just above the upper limit of normal--after completed 52 weeks of therapy, and when she was examined after completing the trial, and off testosterone, remained just about the upper limit of normal where she had been before.

The final AE--the patient with a moderate transaminase elevation--her ALT went from 9 to 91, her AST went from 12 to 94--she also returned to normal while remaining on testosterone therapy after she discontinued chetachinasol, a drug known to be associated with elevated liver function testing.

[Slide.]

When we examined liver function testing overall, we saw no difference in the mean changes from baseline in any parameter of liver function testing--as shown here--for either placebo or testosterone. When we looked for outliers, no difference was seen between treatment arms for any parameter.

[Slide.]

Now, moving on to hematology, there was a

small--very small--clinically insignificant mean increase in hemoglobin and hematocrit, seen in both testosterone groups. This averaged about - percent of hematocrit, and about 1/6 gram per dL of hemoglobin.

[Slide.]

To confirm this was of no concern to patients at highest risk for polycythemia, we evaluated all patients on testosterone therapy with this scattergram. Baseline hemoglobin levels are on the x-axis; 24-week hemoglobins are on the y-axis. Therefore, for a patient who did not change, her dot would fall on the 45 degree line. Generally, we saw no large increases.

Of particular concern, though, are patients who started off with a high hemoglobin at baseline. These patients, like patients generally, show no evidence of concerning increases.

[Slide.]

Now to talk about assessing changes associated with cardiovascular risk. We've already talked about blood pressure and weight; now to talk

about carbohydrate and lipid metabolism.

To assess carbohydrate metabolism, we measured fasting glucose, fasting insulin, and HbA 1c. As you can see here, mean increases were not different in the testosterone and placebo-treated groups in either trial. When we looked for outliers in each of these parameters, there was no difference seen between the treatment groups.

[Slide.]

Additionally, no drug effect was seen on any parameter of the lipid profile that we measured, either: total cholesterol, HDL, LDL, or triglycerides. Again, outliers were not different in the two treatment groups for any of these lipids measured.

[Slide.]

We also evaluated changes in coagulation. Here you see mean changes in laboratory evaluations for clotting. Again, we saw no evidence of adverse changes with testosterone therapy.

[Slide.]

We also looked at women who were at

potentially the highest risk for cardiovascular risk, with four adverse laboratory changes.

When we looked at 150 women who were positive for at least three of these five criteria, that included obesity; adverse lipid profile or on a lipid-lowering agent; hypertensive or on an anti-hypertensive; or had elevated fasting glucose--our best surrogate for metabolic syndrome in the trials.

We found no evidence of more adverse laboratory changes in this subpopulation.

[Slide.]

Here we see the AEs reported in the open-label period of weeks 25 through 52, and the extension, 53 through 78. Patients who were on placebo for the first six months, and then on open-label the second six months are noted "P->TTS," and as they enter the second year, "P->TTS->TTS."

Patients who were randomized initially to testosterone, and then went into open-label testosterone are noted "TTS->TTS," and then, again,

"TTS->TTS->TTS."

During the open-label period, patients with up to 12 months of exposure in the TTS->TTS group showed only minimal differences in overal serious AEs or withdrawals due to AEs, compared to patients who were having up to six months of exposure in the P->TTS group.

Incidents of AEs were similar in the week 53 to 78 extension to those seen earlier with up to 18 months of exposure.

Average withdrawal rates due to androgenic AEs were also very similar, regardless of exposure up to 18 months.

[Slide.]

Looking at some of the same parameters in the natural menopause population, we see a very similar picture to what we just saw in the surgical menopause. NM1 is the six-months double-blind trial. NM2 is a one-year--52-week-double-blind trial.

This trial is still ongoing, so that this data is interim data. You will notice that the

numbers are not equal because this reflects a one-to-two randomization.

Like surgical menopause, about 70 to 80 percent of patients in natural menopause--regardless of arm--experienced an adverse event during the study. Serious adverse events and study withdrawals were very similar for patients with placebo and active treatment. Two deaths occurred from motor vehicle accidents in NM1.

Breakthrough bleeding AEs were numerically lower with testosterone treatment in both natural menopause trials.

[Slide.]

The natural menopause trials also give us an opportunity to see androgenic AEs with up to 12 months of exposure in a double-blind trial situation. Minimal differences in androgenic AEs were seen between the active and placebo trials in NM1--with the most differences seen in acne and hirsutism.

Additional blinded exposure of up to 12

months in NM2 did not appear to increase the incidence of reported androgenic AEs compared to placebo, or compared to six months exposure in NM1.

[Slide.]

Looking specifically at withdrawals due to androgenic AEs, minimal differences were seen between the active and placebo arms, with similar rates to that that we saw in the SM trials. Additional blinded exposure of up to 12 months in NM2 did not appear to increase withdrawals due to androgenic AEs compared to placebo, or to six months exposure in NM1.

[Slide.]

The final parameter that I would like to discuss is breast cancer. We performed mammograms in all patients over 40 years of age at entrance and at on year, or exit, if it was greater than six months.

In our overall program of 2,200 patients, four patients have been diagnosed with breast cancer; one DCIS, and three invasive cancers. All were in the surgical menopause program, and all

were initially randomized to placebo. Remember that in our Phase III program, patients received testosterone therapy in the open-label second six months, regardless of what they were randomized to initially.

[Slide.]

We evaluated these four cases. Case 1, we saw in Phase II, and she did not receive any testosterone. Case 2 was a 63-year-old who presented with an axillary mass determined to be metastatic adenocarcinoma, after she received five weeks of open-label testosterone therapy.

[Slide.]

Case 3 was a 56-year-old who was diagnosed with tubolobular carcinoma after 37 weeks of testosterone treatment. Her diagnosis was made after findings seen in her baseline mammogram became more prominent.

Case 4 was a 50-year-old patient who was diagnosed with ductile carcinoma in situ after 24 weeks of testosterone therapy.

This diagnosis was made based on a new

mammographic finding.

[Slide.]

The number of breast cancers observed in our clinical program is not unexpected and, based on calculations of expected rates, based on our number of women and their risk profile. Further, detecting breast cancer only in patients who received the least amount of testosterone because they were initially randomized to placebo, is not consistent with an association with testosterone.

Also, in patients who have received open-label testosterone for up to a second year of exposure, no additional breast cancers have been identified.

[Slide.]

In summary, after examining safety evaluations in more than 1,300 women for six months, and 600 women for a year, we found overal AEs, serious AEs, and withdrawals due to AEs were generally similar in the active and placebo-treated groups.

Small increases in androgenic AEs and

assessments were seen primarily in one surgically menopausal trial. Mean weight gains over placebo of about a pound were seen at 24 weeks. And, except for a very small increase in red-cell mass, no changes were seen in any mean lab parameter, or evidence of adverse changes in outliers of any lab parameter.

So, in conclusion, in surgically menopausal women with HSDD, the 300 mcg per day testosterone patch was very well tolerate. No serious safety concerns have been identified to date. In both Phase III surgically menopausal trials, we continue to monitor patients receiving open-label therapy, most now in their third year of therapy with no further safety signal being seen.

The safety changes which have been identified are generally mild, were rarely associated with withdrawal, and can generally be easily diagnosed and easily monitored by the patient herself.

Thank you. And now, Dr. Glenn Braunstein will address hormone delivery.

Phase III Hormone Data

DR. BRAUNSTEIN: Good morning.

I'm an endocrinologist and clinical investigator with over 30 years of experience in treating women with hyperandrogenic disorders, as well as androgen insufficiency.

Dr. Lucas has shown you today that the testosterone transdermal patch is both safe and efficacious. But one of the concerns that we clinicians have is the potential impact of long-term exposure to androgens administered therapeutically.

So my role is to examine the hormone levels achieved with Intrinsa, and to show the relationship between the androgen levels and the efficacy, and especially the safety parameters. Hopefully, my presentation will provide additional reassurance that the transdermal testosterone system is safe and efficacious.

[Slide.]

Here is my agenda. To put the levels of testosterone achieved with Intrinsa into

perspective, I will first review how testosterone circulates in the blood, because it is important to realize that not all the testosterone that is in the blood is available to the tissues. It is also important to understand that one of the main determinants of how much testosterone is available to the tissues is the level of sex-hormone-binding globulin--or SHBG. Therefore, I will show you the effect of Intrinsa on the levels of SHBG, as well as testosterone.

Then I will show how the free testosterone levels correlate with the efficacy parameters and the safety parameters in patients receiving Intrinsa.

And, finally, I'll also address some specific safety issues concerning estrogen-related target tissues: the breast and the uterus.

You will see that the median levels of free and bioavailable testosterone achieved fall within a physiological reference ranges for pre-menopausal women; that there is no accumulation of testosterone over 12 months of therapy; that the

testosterone levels correlate with the efficacy parameters; and that there do not appear to be any many hormone safety issues with Intrinsa.

[Slide.]

This is a diagram of how testosterone circulates in the blood. Approximately 98 percent of the total testosterone in the blood is bound to serum proteins, and the major protein is sex-hormone-binding globulin, or SHBG, to which approximately two-thirds of the testosterone is bound. This binding is very tight and, basically, the testosterone on SHBG is unavailable to the tissues.

Approximately a third of the testosterone is bound to albumin. And this albumin-bound testosterone is very loosely bound and may diffuse off of the albumin and enter target tissues.

Only about 1 to 2 percent of the total circulating testosterone exists in the free or biologically active state. And we refer to the combination of the free and the albumin-bound, weakly bound, testosterone as being bioavailable.

[Slide.]

To put the testosterone levels in perspective for you, we have established a reference range, shown by the dotted lines on the right side of the screen. Note that at the present time there are no accepted reference ranges for androgens in women. Testosterone levels in women vary widely. There is an age-related change, with the levels peaking in the 20s and then declining. There is a diurnal variation, with levels being higher in the morning than in the evening. And there's also changes throughout the menstrual cycle, with levels being highest at the mid-cycle time.

We elected to use a range based upon 161 women aged 18 to 49 years, who had multiple blood samples attained across the menstrual cycle, and the hormones were measured and the levels averaged. Since this is a range that women achieve naturally during their reproductive life, we felt that the androgen levels within or near this physiological range would be safe.

On the next several slides, I will show you the free, bioavailable and total testosterone levels, before and after Intrinsa therapy. Because the levels achieved in both the SM1 and SM2 trials were virtually identical, we have combined the results for easy presentation. However, the individual results are shown in the briefing book, and I'll be happy to discuss the results during the discussion period.

[Slide.]

So we will begin by looking at the free testosterone levels as shown here. And that's because these are the most important levels, as far as the cells in the body are concerned.

The circles represent the median hormone levels, while the whiskers represent the 10th and 90th percentiles.

The baseline free testosterone levels were, as expected, at or below the lower limit of the reference range in both the patients who were assigned to placebo, and those randomized to the testosterone system. This was what was expected,

since these are all women who had undergone surgical oophorectomy, were receiving estrogen, and had hypoactive sexual desire disorder.

At the end of 24 weeks, the median level of free testosterone in the patients on Intrinsa had increased into the reference range, while there was no change in the placebo group. And, very importantly, the levels were very similar at 24 and 52 weeks in the Intrinsa group, indicating no continued accumulation of testosterone over time.

[Slide.]

Similar results were find for bioavailable testosterone, which again represents the combination of free testosterone as well as the loosely bound albumin testosterone. And, again, there was no significant accumulation of bioavailable testosterone between 24 and 52 weeks.

[Slide.]

This slide shows the total testosterone data. And, although the median total testosterone levels achieved with Intrinsa were above the reference range--in part, due to the relatively

high levels of SHBG, which I'll show shortly--it is important to emphasize that this was not seen as a cause for concern because the free and bioavailable testosterone levels--the ones that are most important as far as the tissues are concerned--were in the reference range for a majority of the patients.

We also found that the total testosterone levels did not change between 24 and 52 weeks.

[Slide.]

Median levels of serum SHBG were stable over a one-year period of time, and they were all at the upper limit of normal for the reference range, reflecting the fact that three-quarters of the patients in the study were receiving oral estrogens, while one-quarter were receiving transdermal estrogens.

[Slide.]

Now let's look at the correlations between testosterone levels and the efficacy parameters.

This slide shows the consistency of results across the Intrinsa clinical studies. We

find statistically significant correlations between the changes in free testosterone and the changes in the efficacy parameters, including total satisfying sexual activity, desire, and a decrease in personal distress.

Very similar correlations were also found for bioavailable testosterone and total testosterone.

This finding is also consistent across all of the trials. We have pooled the Phase II trials, as shown initially. We have pooled the Phase III trials, and also in the NM1 trial--the natural menopause trial--the results show a tremendous amount of consistency.

Now let's look at the changes in androgen levels and safety parameters.

[Slide.]

We will examine the effect on estrogens, either through aromatization to testosterone--aromatization of testosterone to estradiol, or displacement of estradiol off of SHBG

by testosterone. We will also look at the effect of Intrinsa on estrogen-responsive tissues, including the breast and the endometrium.

We will show the relationship between the reported androgenic adverse events and the observed androgenic effects to she testosterone levels, and we'll show you the results with the free testosterone correlations and clinical laboratory measurements.

Although the data linking estrogen use to breast cancer is unclear, the relationship between unopposed estrogen use and endometrial hyperplasia and neoplasia has been established. Therefore, it was important to examine the effect of Intrinsa on the serum estrogen levels and on estrogen target tissues--including the breast and the uterus.

[Slide.]

As shown here the serum total estradiol levels were similar in patients who received placebo and those who received Intrinsa, and there were no changes through 52 weeks on Intrinsa. The levels were identical between those on placebo, and

those receiving Intrinsa.

Similar results were found for free estradiol in the serum, as well as serum estrone. Thus, there does not appear to be any major increase in aromatization--at least as assessed by levels in the serum.

Currently available data would also indicate that aromatization does not appear to be an issue in the tissues either, as we'll summarize on the next slide.

[Slide.]

A study was carried out at the Karolinska Institute in Sweden, in which women who had not undergone hysterectomy, and who were receiving estrogen and norenthindrone were randomized to receive either placebo or 300 mcg ga day of transdermal testosterone through the patch system. They underwent mammograms and fine-needle aspirations of the breast, both at the baseline state and after six months of therapy. The results showed that there were no differences between the two groups in respect to mammographic breast

density, or in breast epithelial proliferation.

There was, however, a significant decrease in the stromal cell proliferation in patients receiving transdermal testosterone. And this is important because the stromal cells are major source of aromatase enzyme activity in breast tissue.

In addition, preliminary analysis carried out on paired endometrial biopsy samples--that's approximately 300 samples--obtained from women in the Natural Menopause Study were examined. And two cases of endometrial hyperplasia were found. Now, that study is still blinded, and therefore we don't know whether the samples were obtained from women who were receiving placebo, or receiving transdermal testosterone. But even if we assume that both patients were receiving transdermal testosterone, that would give an incidence of approximately 1 percent of endometrial hyperplasia, which falls within the FDA guidance for estrogen-progestin combination products.

So these results are consistent with the

lack of any estrogen-related side effects relative to placebo observed in the safety data presented by Dr. Lucas.

Now we'll turn to the androgenic side effects.

[Slide.]

Although the androgenic adverse events in each of the Phase II and Phase III studies were not different between women on active therapy versus placebo, we pooled the results from the Phase II and the Phase III trials on surgically menopausal women in order to examine the issue with a larger group of patients.

We used a trend test to look at the incidence of androgenic adverse events against the highest pre-testosterone level measured in each of the women. The only statistically significant finding was with facial hair. This was also borne out with the combined observations of the investigators at the different trial sites. Importantly, there were no specific associations between androgen levels and acne, alopecia, voice

deepening, or clitoromegaly.

And, in a similar manner, we examined the relationship between changes in the laboratory parameters and the maxim free testosterone obtained in each of the women. And these were examined across both the Phase II and Phase III studies, which were combined.

These laboratory parameters included tests of liver function, lipid analysis, carbohydrate metabolism, hematology values and clotting factors. These parameters were chosen because they had been associated with abnormalities with the use of pharmacologic doses of testosterone, based on literature studies carried out in both men and women. And, again, the changes for patients within the highest decile of free testosterone, compared to placebo, were small and clinically insignificant.

[Slide.]

So, in summary, surgically menopausal women with hypoactive sexual desire disorder had low testosterone levels at baseline. 300 mcg a day

of transdermal testosterone increased the concentrations of free, bioavailable and total testosterone, with no evidence of continued accumulation over 12 months of dosing.

Serum concentrations of total and free estradiol, estrone, and SHBG were not affected bu Intrinsa administration over the year of study.

Higher exposure of free and total testosterone was not associated with clinically significant laboratory changes.

[Slide.]

Intrinsa raised the median free and bioavailable testosterone levels to within the pre-menopausal reference range that we established, and these correlated with an increase in the number of satisfying sexual events, the increase in sexual desire, and a decrease in personal distress.

Based upon the currently available hormone data, the one-year safety profile of Intrinsa shows no cause for concern. Higher free testosterone levels are associated with small increases in facial hair in the pooled trials, and the

appearance of such androgenic effects would allow the patient to make a personal risk versus benefit decision.

Thank you.

It's now my pleasure to introduce Dr. Shifren.

Hypoactive Sexual Desire Disorder Medical Need

DR. SHIFREN: Good morning.

As a gynecologist and director of the Vincent Menopause Program at the Mass General Hospital, I see many women with sexual concerns after menopause.

Hypoactive sexual desire disorder is the most common sexual problem that I see in my practice. It's a particularly poignant problem for our younger patients who've had their ovaries removed. After removal of the ovaries, a woman loses almost all of her estrogen, and approximately half of her testosterone. We have many options available for estrogen replacement, but currently there are no approved testosterone products to treat our surgically menopausal women who present

with sexual dysfunction post-operatively.

Today, I'll tell you about the negative impact that HSDD has on menopausal women, and talk also about why I'm an advocate for a low-dose testosterone patch.

Let me begin by describing some of the research that helps us understand HSDD.

[Slide.]

The Women's International Study of Health and Sexuality--or the WISHeS Study--was specifically designed to better understand HSDD in women, as available studies didn't completely capture all important aspects of this disorder--in particular, distress. This was a self-report survey of more than 4,500 women in the United States and Europe between the ages of 20 and 70. I'll be discussing a U.S. sub-population of 520 surgically and naturally menopausal women with partners.

This survey used three validated instruments: the Short Form-36, a measure of overall health status; and the Personal Distress

Scale; and Profile of Female Sexual Function.

So what did these studies teach us?

[Slide.]

Well, we learned that women with HSDD do engage in sexual activity. As these data illustrate, partner-initiated sexual activity is constant for women, whether they have no or normal desire. But, importantly, women with HSDD are significantly less likely to initiate sexual activity. This confirms that focusing only on the frequency of sexual activity can be misleading when trying to understand the sexual experience of women with HSDD.

[Slide.]

Not surprisingly, we also learned that sexual desire correlates with a woman's overall level of satisfaction with her sexual life. This graph shows that women with less desire were less satisfied with their sex lives. Women with higher desire scores were more satisfied overall.

[Slide.]

With respect to the effect of low desire

on couples, for women, sexuality typically exists within the context of the important relationships of their lives. As you can see in this graph, sexual satisfaction and relationship satisfaction are intricately related for women. Women who are less satisfied with their sex lives are significantly less satisfied with their personal relationships or marriage.

[Slide.]

As we see in these data from WISHeS--and as my patients tell me often--the distress women feel with HSDD extends beyond their loss of desire. Compared to women with normal desire, women with HSDD report feelings of low self-esteem, shame and failure. My patients often are very upset regarding the impact that their low desire has on their relationships. And, of note, nearly 90 percent with HSDD report feelings that they're letting their partner down.

[Slide.]

It's important to realize that HSDD not only affects a woman's sexual health, but is

associated with overall diminished health status. The WISHeS investigators used the Short Form-36--a well known and validated measure--to measure study participants' general health status. Compared to women with normal desire--in green--women with HSDD were significantly more likely to report decreased physical function, general health and vitality. They also reported lower levels of social functioning, emotional and mental health.

The SF-36 scores we saw in women with HSDD are very similar to scores seen in people with other medical conditions, such as arthritis or diabetes.

Now we have an understanding of HSDD and the impact this has on a woman's life. But why does it happen?

[Slide.]

Female sexuality is a complicated interplay of physiology, psychology, interpersonal relationships, and socio-cultural influences. As a reproductive endocrinologist, my focus is on the physiologic factors that affect a woman's sexual

health. When a woman presents with HSDD, the first thing I do is rule out non-physiologic causes, as these couples often benefit from education, counseling, sex-therapy and lifestyle changes.

Physiologic factors, including medical, neurologic, gynecologic and urogenital problems all may have a negative impact on healthy sexual functioning. For example, I've seen many menopausal women in my practice with vaginal atrophy and dysprunia associated with estrogen deficiency. For these women, sexual arousal and response often improves greatly after starting vaginal estrogen therapy.

[Slide.]

But the most common physiologic cause of HSDD that I see in my practice is androgen insufficiency--often associated with oophorectomy. As you can see in this study, removing the ovaries of both pre- and post-menopausal women results in an approximate 50 percent decline in testosterone levels. Many studies over the past 20 years have shown significant improvements in sexual desire,

response and intercourse frequency in surgically menopausal women treated with testosterone. But no testosterone product currently is available for treating our surgically menopausal patients with HSDD.

So what are physicians and patients doing?

[Slide.]

Unfortunately, we're using products that have been formulated for men, putting women at risk for receiving high doses of testosterone. Compounded products, with limited quality control and dosing consistency, also are being used.

As you can see, in 2003, approximately 20 percent of total prescriptions for branded male testosterone products were actually written for women. And in that same time period there were over 1 million prescriptions written for compounded or generic testosterone products, for women.

These data show the need for a quality testosterone product specifically formulated for menopausal women, with proven efficacy for all aspects of HSDD.

[Slide.]

Before concluding, I'd like to address a concern that some of you may have regarding the clinical meaningfulness of the changes in sexual function that we saw with testosterone patch treatment.

An increase of about two satisfying sexual events per week may not seem like a lot, but for women whose baseline activity level is only three events in a four-week period, this increase represents an important change.

In addition, desire scores increased on average by approximately 11 points, that means that women went from "seldom" having desire closer to "sometimes" having desire. And, most importantly, patients' distress scores decreased 23 points with treatment, which means went from being "often" distressed about their lack of desire in sex, to "sometimes" being distressed. And this represents a clinically significant change for women.

It's also important to remember that these are mean changes with treatment. Some women had

little benefit, while others had much greater improvements in sexual activity and desire. As you may recall from Dr. DeRogatis' presentation, responders had greater increases in all aspects of sexual desire, activity and distress measured in this study. In addition, women who derive little benefit from treatment are unlikely to continue therapy.

[Slide.]

So what I see as a clinician, and what we've shown you today, is that HSDD is an important medical condition that has an important impact on women's lives. Low-dose transdermal testosterone treatment is a meaningful treatment option for patients with HSDD, as it improves all aspects of this disorder.

Intrinsa also is a much-needed option for patients and physicians who currently have no approved therapies with demonstrated safety and efficacy with which to treat our patients.

Thank you.

The next speaker will be Dr. Michael

Steinbuch.

Phase IV Long-term Safety Plan

DR. STEINBUCH: Good morning. My name is Michael Steinbuch, and I'm responsible for pharmacovigilance and epidemiology at Procter & Gamble.

Let me begin by saying that P&G is committed to monitor the long-term safety of Intrinsa. We believe we can best accomplish this by conducting a prospectively designed observational safety that will be comprehensive in its design, and have the necessary data to detect a possible safety signal faster than any other method.

[Slide.]

As you've heard from Dr. Lucas, despite extensive and systematic patient monitoring during the Phase III program, there were no serious safety signals that merit specific follow-up. Nevertheless, we plan to monitor women exposed to Intrinsa for longer periods of time.

[Slide.]

In addition to routine post-marking surveillance and Phase III extension studies, we considered three options to address the long-term safety of Intrinsa: observational studies; randomized controlled trials; and patient registries. Each of these options has advantages and disadvantages.

We carefully evaluated all options and now believe that the best way to generate timely long-term safety data is through a rigorous, prospectively-designed observational study.

[Slide.]

Observational studies offer several advantages. They provide a robust method for rapid signal detection in a real-world setting; an opportunity to study large numbers of patients' the ability to adjust for potential confounding variables; and the opportunity to evaluate all patients that fill scrips for Intrinsa.

[Slide.]

The FDA reviewed an earlier version of our proposed Phase IV observational study. The agency

raised a couple of issues regarding the potential limitations of such a study. FDA questioned whether data in women over 65 would be captured when post-menopausal women treated with Intrinsa shift to medicare; and, whether the study would provide adequate power to detect an excess risk of safety events of interest with women in this age group.

However, in our clinical trials, where we actively recruited women ages 20 to 70, the women over 65 represented only 2 to 3 percent of the study subjects. As you just heard from Dr. Shifren, women are currently using various forms of prescription testosterone. Among the 30,000 female testosterone users in our proposed study database, only 3 percent are over 65. Also, the disenrollment rates are comparable, whether they are younger or older than 65.

Partly in response to FDA's response, we updated our study design. I'll show later that the updated study will be powered to detect potential safety signals.

Now, let's take a look at what we're proposing.

[Slide.]

We plan to contract with Ingenix, the research affiliate of United Healthcare, to conduct this research. Ingenix LabRx is a large, comprehensive insurance claims database. It represents approximately 5 percent of the U.S. population. It covers a range of health care services, and includes hospital, physician, pharmacy and laboratory data.

United Healthcare has an open formulary. In this multi-tier system, virtually all prescription drugs--including drugs for sexual dysfunction--have at least partial reimbursement. As a result, drug usage will be captured in the database.

Upon IRB approval, Ingenix will validate endpoints by identifying and reviewing all relevant records. About 85 percent of those are available for abstraction, and 90 percent of all medical claims are processed within four months.

United Healthcare has a stable enrolled population, with 85 percent per year. In addition, Ingenix has an experienced research staff and a proven track record with studies of this type.

[Slide.]

For example, the FDA has accepted numerous observational studies using the Ingenix database as a method to assess product safety. This database has demonstrated utility across a range of drugs and study endpoints in post-marketing safety studies. These include allergic reactions and GI outcomes, among others.

[Slide.]

The objective of our study is to compare event rates in Intrinsa users versus non-users, using a prospective cohort design with three-to-one matching. Matching variables will be carefully selected, and may include a propensity score, which is a proxy for overall health status. Appropriate matching minimizes biases between groups.

We propose the study be conducted for a period of five years. All patients exposed to

Intrinsa will be included in the analyses. Of note: there are no exclusion criteria. Endpoints of interest will include both cardiovascular and cancer events.

Let's take a closer look at the Ingenix database.

[Slide.]

There are 10 million patients in the database; of those 600,000 are menopausal, and 135,000 are menopausal women taking estrogen. Based on estimates of HSDD disease prevalence from the literature, we expect approximately 19,000 potential users of Intrinsa. Assuming 30 percent of these women fill a prescription for Intrinsa, there would be about 5,500 Intrinsa-treated patients in the first year following launch.

[Slide.]

To provide estimates of the size of the patient population and power to detect safety signals over the course of the five-year observation period, we needed to make certain assumptions. For example, we have assumed a fixed

rate of 5,500 new patients per year; a .15 percent event rate per year for cardiovascular events--as was observed for the 50 to 59-year-olds in the WHI study; a 50 percent discontinuation rate per year; 15 percent disenrollment per year; an alpha of .05, and a one-sided test, which has more power to detect a safety signal.

[Slide.]

Given these assumptions, if a major safety signal emerged, we would be able to have 82 percent power to detect a relative risk of 1.9 as early as two years post-launch. AS person-years of observation accrue over time, our ability to detect smaller differences will increase.

[Slide.]

We recognize that observational research encompasses a broad range of techniques, and varies greatly in terms of their robustness. We've proposed an approach that will maximize its value as a signal detection method. This comprehensive design will have a number of components not typically found in observational research. These

include a collaborative protocol development with external experts and FDA involvement and approval; a blinded medical expert panel to adjudicate events ascertained from medical record abstraction. And, importantly, an independent safety review board will be established with no P&G participation or representation on the board. The independent board will be responsible for identifying possible issues, as well as analyze, interpret and report results to FDA and P&G.

Initial data will be available at 18 months post-launch. Results and analyses will be available for review about two years post-launch.

[Slide.]

In addition to observational studies, we considered randomized controlled trials and patient registries.

[Slide.]

Randomized controlled trials are idea for testing hypotheses and determining cause and effect. They offer the advantage of random allocation of study subjects, which minimizes

confounding. However, RCTs such as large simple trials are typically conducted in restricted patient populations, based on a set of inclusion and exclusion criteria.

The reality is, they may not reflect actual use of the product in the marketplace. We believe the major issues with a randomized safety trial for Intrinsa are recruitment, retention and adherence to treatment. In the WHI, for example, the participants were presented with a potential for a cardiovascular benefit, and yet 80 percent refused randomization.

As you heard this morning, RCTs are very large, and would require screening extremely large numbers of women. In our clinical trials, we enrolled 1,200 women from 100 sites in six months. Based on this experience, an RCT would take several years for patient enrollment, and five more years for follow-up.

We believe these factors would be major barriers to executing an RCT and detecting a signal in a timely fashion.

[Slide.]

While patient registries have the advantage of allowing the study of large numbers of exposed patients in a real-world setting, there is no practical method to identify a relevant comparison group.

[Slide.]

Procter & Gamble Pharmaceuticals will monitor the long-term safety of Intrinsa and will continue working with the FDA and Ingenix to refine the study plan.

Ingenix's robust infrastructure will be instrumental in executing a successful observational study.

Our approach is novel, in that we plan to implement the study at launch. We will have input from external experts to help us design the study, and we'll have this independent safety review board to execute, analyze and report study results to the FDA.

We believe this is the best study design for detecting a possible safety signal quickly, and

we're committed to making this happen.

Thank you for your attention, and I'll now turn the podium over to Dr. Meyer.

Closing Remarks

DR. MEYER: For my wrap-up, what I'd like to do with you is go over the questions that the FDA posed to you this morning. Due to time considerations, I'll be happy to answer any questions on our plan to maximize the safe use of Intrinsa with physicians and patients during the discussion period this afternoon.

The first question: The first is an efficacy question: "Do the efficacy data represent clinically meaningful benefit?"

Yes. We assessed three related but independent endpoints, all critical in HSDD. They're concordant but they're not redundant. They measure different aspects of the disease. These efficacy assessments were patient-centered. The patients told us the results were relevant. And independent observers confirmed these results were relevant. And the statistics told us these results

were relevant.

The primary endpoint and all the secondary endpoints were highly statistically significant. The results were consistent across studies and across endpoints.

In addition, the randomized withdrawal trial that we ran reinforced that the pharmacological effect of the drug was better than that of placebo.

Question 2: "Is the patient exposure adequate to demonstrate long-term safety?"

Yes. As Dr. Lucas showed you our exposure table, we have over 14,000 total patient-months of exposure--and these data are from June, when we were preparing our 90-day safety update for the agency. We have an additional 180 women in the surgical menopause program with 12 months of exposure; an additional 100 women to include in the 18 months of exposure. We currently have 80 people already in year three of the surgical menopause extension.

Because of the study that we're finishing

up enrolling, looking at the patch in women not on concomitant estrogen, one year from now we will have an additional 2,500 patient years of exposure to 300 mcg of Intrinsa.

Question 3: "Are the safety concerns or unanswered questions that need to be studied?"

Well, as you are all aware, it is not uncommon to have unanswered safety questions at approval. As you think about this relative to Intrinsa, it's important to keep in mind thus far we have seen no significant safety signals. And there's substantial experience already, in the real world, with concomitant androgen and estrogen use. Testosterone is not a new drug.

Importantly, we have committed to a strong, independent post-marketing safety study to be put in place at launch. Also we welcome the opportunity to hear more ideas from the committee and the agency about how to strengthen our labeling to address safety issues.

Number 4--this is an easy one for you: "Are the efficacy and safety data adequate to

support approval of the transdermal testosterone system?"

Yes. We feel very strongly that the efficacy and the safety data are adequate to support approval of Intrinsa to provide women with HSDD and their physicians this important treatment option.

Thank you for your time.

DR. GIUDICE: I'd like to thank the sponsor for their presentation this morning.

We're scheduled to take a break, but before we do, for those who are going to participate in the open public hearing, please be sure that you have registered outside, and please do this before the end of the break, otherwise you will not be able to participate in the open public hearing.

So we will take a break, and let us return, please, at 10:15. Thank you.

[Off the record.]

DR. GIUDICE: Back on the record.

Please take your seats and we can continue

with the morning session. Thank you.

We will now continue with the FDA invited speaker, Dr. Adrian Dobs, who's professor of medicine from Johns Hopkins University, who will be talking on safety of exogenous testosterone in women.

FDA Invited Speaker

Safety of Exogenous Testosterone in Women

DR. DOBS: Good morning. My name is Adrian Dobs, and I'm an endocrinologist at Johns Hopkins.

And when discussing the safety issues, it's really important to think that we're not talking only about testosterone, but also its metabolites.

[Slide.]

Testosterone is reduced through 5-alpha-reductase to dihydrotestosterone, and it's likely the DHT that has the effect on facial and body hair, scalp hair loss, acne and hirsutism.

It could also act directly on muscle, bone, causing virilization with clitoromegaly, brain and sexual function. And then it can be

aromatized to estrogen, and estrogen is likely acting directly on the breast and the uterus, and on the bone, brain and libido.

[Slide.]

So, what I'd like to do today is go through with you, as an outline, of what are the safety concerns with testosterone administration. A lot of this has been derived from a review article we just published in the Mayo Clinic Proceedings, which is in your packet for the committee members.

So what I'd like to discuss is the androgenic effects, cardiovascular effects--particularly lipids, vascular reactivity, glucose tolerance and hematopoietic. Then I'd like to discuss the endometrial and breast effects, and finally try to come up with some kinds of recommendations.

[Slide.]

When discussing the androgenic effects, the main three androgenic effects is that of acne, hirsutism, and virilization. The usual clinical

presentation of this is acne, increased hair growth, clitoromegaly, temple baldness and lowering of the voice. Testosterone is involved in thickening of the vocal chords, that's why men have lower voices than women.

In general, one would say that at higher doses these are extremely common. At low dose of androgen replacement, it's probably more rare or mild. It has been shown as a mild effect--of acne and hirsutism--in some of the studies with methyltestosterone.

In general, I would make the statement that it is dose and duration dependent, and most of these effects are reversible. The "most" would refer to temple balding. It's unclear if that will be fully reversible, or the clitoromegaly may take years to see any kind of resolution. But the acne and the hirsutism in a period of months will probably resolve.

[Slide.]

This is a study looking at hirsutism scores with a methyltestosterone done by Elizabeth

Barrett-Connor. And she looked at varying combinations of estrogens with testosterone. Here's androgen, a low dose. Here's androgens at a high dose. And in the light orange color is the percentage of subjects who claimed that they got worse by taking a high dose of androgens.

So you see there's a trend there that actually was not statistically significant. So that hirsutism and acne would not be surprising observations in women taking testosterone.

[Slide.]

Now, a large concern is obviously cardiovascular effects, and here there really is a great deal of question.

First, to begin with, this is an example of a study looking at the relationship of endogenous hormones to cardiovascular risk. And this is looking at the odds ratio of developing a cardiovascular event, compared to the four quartiles of hormones. So here is testosterone in green, adjusted for risk and the free androgen index. And what you could see here is that

individuals who are in the fourth quarter--the highest quartile--of androgens have an increased risk of developing some kind of cardiovascular event. And this is data from the Women's Health Study.

So there is this interesting relationship between endogenous hormones.

So what is the specifics of this?

[Slide.]

Well, there have been a few studies looking at testosterone in women. Generally, with all androgens, there's a clear significant reduction in HDL cholesterol. It's likely neutral on LDL, and it does result in a lower of triglycerides. The reason for this is probably the first pass through the liver, and the changes in hepatic lipase.

The data from women state that it's very dependent on the route of administration--that is oral testosterone will have a greater effect than transdermal, and also the type of testosterone--whether or not its methylated or an

anabolic steroid.

In general, aromatizable androgens--that is, testosterone that's converted to estrogen--have a neutral effect.

[Slide.]

This is some of our data looking at changes in lipids with a methyltestosterone, and as you can see, there's a pretty impressive decline in the HDL cholesterol, as there is a decline in the triglycerides.

[Slide.]

However looking at Shifren's data, there was really very little change across all the lipid parameters when used in a transdermal preparation.

[Slide.]

Now there's also questions about vascular reactivity. This has to do with endothelial dysfunction. It has been found to be an earlier marker of cardiovascular disease; that is the stiffness may predict the development of cardiovascular disease. This has been studied in small non-invasive publications, looking at

flow-mediated vasodilatation. And it turns out that epidemiologically, there is a decline in this flow-mediated dilatation in women as they go through the menopause.

The best way to study this is by looking at brachial artery reactivity. And this has been done by looking at endothelial independent dilatation, which is a glyceryl trinitrate induced kind of a procedure.

[Slide.]

So this is just one example of a study, looking at the effects of testosterone on vascular reactivity in women. This is flow-mediated dilatation before and six weeks after testosterone, to show that there was increased flow. This is the control group, and this is women that were given a type of nitroglycerin that would vasodilate. And there is a statistical increase in vasoreactivity.

There's some mixed data on this. I would probably make the statement that testosterone has a very minimal effect on vascular reactivity, and perhaps it could be beneficial.

[Slide.]

Plasma viscosity is of great concern when discussing cardiovascular effects. We know from epidemiological studies that increased plasma viscosity is a risk factor for cardiovascular disease, and does predict coronary artery disease development. The physiology here is not very clear. It seems to be affected by fibrinogen and triglycerides. And the only thing I could say is there's just been a few small studies evaluating this, and in one study they did show that there's actually improvement in viscosity when women were given testosterone.

[Slide.]

When it comes to hematopoietic factors, we've known for many years that testosterone is involved with erythropoiesis. It, in men, can be associated with polycythemia, and polycythemia is a risk factor for cardiovascular disease.

In looking at some large epidemiological studies with increasing hematocrit, there is an increase in cardiovascular risk.

The mechanism for this is that testosterone is involved in stimulating production of erythropoietin, and also in erythroid colony units. In men, it's very clear that testosterone can cause erythrocytosis. This is dose-related. It's area-under-the-curve-related, so that men who have been given injectable testosterone are much more likely to be found to have increase hematocrits. In men given transdermal types of testosterone, there's essentially very little problem.

In women, few studies have been done. In a study of 22 young women using a testosterone implant there was no effect on clotting factors. And you heard some data earlier this morning about the new transdermal compound.

Essentially, I could not find any reports of true polycythemia in women.

[Slide.]

Now, glucose metabolism is clearly a risk factor for cardiovascular disease, but for hyperglycemia and hyperinsulinism. There's very

little data here. There seems to be no evidence of changes in fasting glucose or in insulin sensitivity, although I would say there's little data in both men and women.

I think the big caveat to this is what we're learning more and more about, which is that of polycystic ovarian disease and metabolic syndrome.

[Slide.]

This is just some data from Shifren looking at glucose and insulin across groups. And there was no difference. This is just looking at fasting studies.

The big problem and the big question here is that there seems to be a fairly consistent relationship between endogenous testosterone and cardiovascular risk. When we're talking about polycystic ovarian syndromes or metabolic syndrome, metabolic syndrome is being increasingly recognized as a risk factor for the development of cardiovascular disease. In this situation, it's noted to have obesity, hyperinsulinism,

hyperandrogenism, and hyperlipidemia.

The mechanism for the hyperandrogenism in this complex of metabolic syndrome and PCO is not very clear. I've just written down one postulate, and that is the hyperinsulinism stimulates testosterone production from the ovary, and this works to decrease SHBG, and that works to increase free testosterone.

So I think of challenges that are ahead is really to determine what is the relationship here of testosterone, metabolic syndrom, PCO, and how to put this into context. Is it testosterone per se that's having a cardiovascular risk, or is it its metabolism to estradiol?

[Slide.]

I'd like to next talk about the potential side effect of endometrial or breast effects. Again, from endogenous hormone levels in epidemiological studies, there seems to be a relationship between hormones and the development of disease. So this is looking at the odds ratio of endometrial cancer, by quartiles of steroid

hormones in post-menopausal women. And the green is estradiol, and blue is testosterone. And you see here that women with increasing doses of endogenous hormones will have an increased risk of developing endometrial cancer.

[Slide.]

There's been several reports of hyperplasia and cancer with the use of high doses of testosterone. Most of this data comes from women who were given high doses of testosterone for transsexualism. This may not be applicable in this particular discussion. But clearly in that population when the serum testosterone level gets into the level of a male level, that testosterone will be aromatized to estrogen and run the risk of unopposed estrogen and the endometrium.

With low doses there is essentially no cancers that have been reported. There has been, in one study, endometrial hyperplasia that was seen in one of 107 women given methyltestosterone. But it was also seen in one of 111 women given estrogen. So there clearly will be this issue of

unopposed estrogen in women who have a uterus and might not be taking progesterone.

In one study there was a 6 percent incidence of cystic endometrial hyperplasia. And in another study, though, they did study vaginal cytologies. And these were all stable throughout the course of the study.

[Slide.]

Breast cancer risk is something that needs to be discussed. Epidemiologically it's similar to the endometrial data in that there seems to be a relationship between high endogenous testosterone and breast cancer.

With hyperandrogenism itself, it seems to be related to the association with metastasis. The physiology here, it's been postulated to be due to the fact that there is androgen receptors that are found in 50 to 90 percent of breast tumors. This testosterone therefore may act directly to stimulate breast epithelium, or it may be aromatized and therefore it's the estrogen that's acting on the breast tissue.

In women there have been no reports of breast cancer that came from exogenous testosterone treatment. We did hear this morning some cases of active and placebo-treated women.

[Slide.]

now, there are some other possible effects, but these are really very mild, but I'll just mention them in passing.

In men given alkylated androgens there's been associated hepatotoxicity and hepatic adenomas. This has not been the case with transdermal testosterones. In women, there's essentially no evidence of abnormal liver functions, either with pellets or transdermal.

There's a theoretical risk of some fluid retention with testosterone, but really not in the doses used even in men, and certainly no one would expect it in the doses for women.

[Slide.]

There's a great deal of question about anger and hostility. This is a very difficult parameter to measure. Some studies have asked

questions like "Do you have an interest in smashing things?"

[Laughter.]

So it's really a very tough parameter to get one's hands around.

And the physiological explanation would be that there are certainly androgens and estrogen receptors in the brain. In men, there's some questionable data--I mean "questionable" because of the study design--to say that there may be a relationship between testosterone and violent behaviors. I really question this data. In the clinical trials done in men, even given high doses of testosterone, it's been very hard to elucidate whether or not there's any relationship here.

And in women there was one study that showed that there was some increase in hostility scores in women given high doses. I think, in general, this is not a clinical problem. We generally live in a fairly controlled society.

[Laughter.]

So, I'd like to end up with talking about

some recommendations.

[Slide.]

I would say there are some absolute contraindications for the use of testosterone, and this would certainly include pregnancy and lactation, endometrial cancer or any unexplained vaginal bleeding, and breast cancer.

There might be some relative contraindications, as well. And that would be moderate to severe acne or hirsutism, androgenic alopecia, sever insulin resistance, and anyone with an anger management disorder.

[Laughter.]

[Slide.]

These are some recommendations. Obviously, there will be lots of discussions about this if and when things go further. But these are some monitoring that I would recommend, in that acne and hirsutism should be evaluated at each visit. Virulization should be evaluated at each visit. Anger and hostility can be asked at each visit.

Breast exams and serial mammograms should be done conscientiously--likely following strictly the recommendations, and be done annually.

It's important to ensure that women treated with testosterone should have regular OB/GYN exams, and if there's vaginal bleeding this should be discontinued. Obviously, this is the assumption that if a women has an intact uterus and is taking testosterone.

Hematocrits should be evaluated, I think, after the first three months and then, likely, annually.

Serum lipids--because transdermal has very little effect on serum lipids--can really be done as indicated.

And measuring of serum total testosterone I think is extremely important to ensure that the levels do not get very high since, as I've stated before, the side effect profile for testosterone is related to the type of testosterone, the route of administration, the dose used, and the length of time that the women is being treated.

I might recommend that women be evaluated at six weeks, and then I'd put question marks about whether or not this needs to be done every six months thereafter.

[Slide.]

So I think there are several remaining questions about the safety of testosterone therapy. With more women being treated for longer periods of time there will be questions about the long-term effects on androgenic signs and symptoms.

Conceptually, there is still a lot of question about the overlap of endogenous testosterone versus exogenous treatment and cardiovascular risk, and how this relates to such things as abdominal obesity in the metabolic syndrome.

The other remaining questions have to do with the use of testosterone alone versus being done in combination with estrogen and progestins. And really my last point that I think is of importance is better evaluation for the risk of breast and uterine tissue.

Thank you very much.

DR. GIUDICE: Thank you, Dr. Dobs.

I'd like to point out to the committee that this is now an opportunity to ask Dr. Dobs any questions, because there will not be an opportunity later.

Dr. Emerson?

DR. EMERSON: Have there been any studies that looked at the relative balance of estrogen versus testosterone and whether that's predictive? Or has it always just looked at testosterone levels versus estrogen levels?

DR. DOBS: They've basically been looked at separately, although various combinations of free androgen index, free testosterones. And the issue of measuring free testosterone in women is a difficult one. It's difficult enough in men, but the assay and the level of detection for women can be quite problematic.

So--no, I'm not aware of ratio differences as much as the absolute numbers.

DR. GIUDICE: Yes.

DR. NISSEN: I wonder how much is known about triple therapy--that is, estrogen, progesterone and testosterone. You know, whenever a drug gets out on the market there tends to be off-label use, etcetera. So we need to have some understanding about whether anything is known about that?

DR. DOBS: Well, triple therapy is what had been used in the Intrinsa data, in that most--in one of your studies--didn't you have--right--where they did use progesterone in women that had a uterus on board--sorry. That's a terrible way of phrasing that.

[Laughter.]

I meant estrogen on board--then being given progesterone. And the data was about the same there.

So there is a small study in which there's triple therapy--which would have to be recommended if a woman has her uterus and is being given estrogen and being given testosterone. She would have to take progestin.

DR. GIUDICE: Dr. Rice, and then Dr. Lockwood.

DR. MONTGOMERY-RICE: I raise a question--a concern--about the duration effect. I think what they share with us is that we're looking at low doses of testosterone. However, we know that when we look at our low-dose trials of estrogen---particularly, I'm thinking the Hope trial, when we looked at .3 mg of CEE, and that first year we saw minimum cases of endometrial hyperplasia. And in the second year we saw more cases of endometrial hyperplasia, even though we didn't see an increase in estrogen levels.

And so should we be concerned here about a duration effect, even in the presence of these low doses of testosterone?

DR. DOBS: Well, there's really no good data for this, because the only long-term treatments of testosterone have been with higher doses, and mainly in transsexuals. Goren, in Amsterdam has very nice data on uterine hyperplasia in that population.

So it's really hard to say what will be the long-term effect. There doesn't appear to be a cumulation of testosterone in the skin, as an example. But I think the issue of dosing is extremely important, and monitoring of doses.

I mean, I treat a lot of men with hypogonadism and testosterone, and their levels can be all over the place when given any kind of transdermal testosterone--whether it be patches or gels, there's a great amount of variability. And I think that might be the case here, when testosterone is going to be used in larger numbers of women is: what is the likelihood that the women will get to testosterone levels above the normal range?

So that's why I feel strongly that does need to be monitored carefully.

But if we're talking about greater then--I think they have two-year data--there's really very little that's out there to suggest there would be a problem on safety.

DR. GIUDICE: Dr. Lockwood.

DR. LOCKWOOD: I have a comment--and I apologize, Dr. Dobs, for having my back to you--

DR. DOBS: Yes, where are--oh, I see. Okay.

DR. LOCKWOOD: I can't twist my head around 180 degrees.

My comment is that we've also looked at the endometria of women that have been exposed to high doses of testosterone in preparation for transsexual surgery. And the marked effect that we've observed is decidualization, which suggests that the predominant effect is actually more pre-gestational than estrogenic.

So, you know, I'm not sure I would be convinced one way or the other about the risk of endometrial cancer--particular at very high doses of testosterone. But there may be individual variations in that response, depending on the level of aromatization and so forth.

My question to you is that there is a fairly, now, long experience with the use of danazol in women with mastalgia and fibrocystic

disease, etcetera, and the question--and I don't know whether you have the answer to this or whether, in fact, anyone does--but since that's a natural group to look at in terms of the risk of androgen-induced breast cancer, is there any evidence that such therapy is associated with a higher rate breast cancer?

DR. DOBS: That's an interesting question, and I've never heard of a case of breast cancer with the use of danazol. But I don't know about breast biopsies or any intermediate changes that might occur. I think that's an interesting question.

DR. GIUDICE: We have time for one more question.

Dr. Stanford?

DR. STANFORD: I was just wondering if you are aware of any data on androgen levels or insulin levels in women with PCOS who have undergone oophorectomy?

DR. DOBS: Well, I could--no, I was going to answer that--there are certainly a few taken

with PCOS, and they lose weight, or be given a medication to affect this, the insulin levels, they will drop their testosterone levels. So this could be modulated.

The oophorectomies wouldn't be done. Years ago, when it used to be called Stein-Leventhal syndrome, and there was wedge resections performed at that time, the testosterone levels did drop. And that's probably why they were able to get pregnant, and why it worked, is they were taking out a mass of the ovary, and that resulted in normal hormones and ovulation.

DR. GIUDICE: Thank you very much.

Going on now with the FDA presentation, our first speaker is Dr. Daniel Davis who is a medical officer in the Division of Reproductive and Urologic Drugs, and he will be talking on efficacy findings and issues.

FDA Presentation

Efficacy Findings and Issues

DR. DAVIS: I'm Dan Davis, and I'm one of two primary reviewers for this application. I

reviewed the efficacy data, and Dr. Lisa Soule reviewed the safety data.

My talk this morning will focus on the efficacy data and the efficacy issues.

[Slide.]

There are three important points that are listed here on this slide. First is to note that this is the first application the FDA has ever received for a female sexual dysfunction indication. The division did have our draft guidance for female sexual dysfunction, which was written in May of 2000 for helping to evaluated this application for hypoactive sexual desire disorder.

The second point is the issue of the relatively small treatment effect seen with testosterone treatment. The division agrees with the sponsor's analyses that the endpoint changes associated with testosterone were statistically significant compared to the placebo effect. But the key issue for us is really the clinical significant of the findings.

The primary endpoint, as already stated, was a change in satisfactory sexual events--noted in my presentation as "SSE." And the two secondary endpoints were sexual desire and personal distress.

Small mean changes were noted in all three endpoints. And relative to the testosterone treatment--we'll note it as the "TTS" in this presentation--there was a strong placebo effect that persisted throughout the two six-month blinded trials.

The third point regards the findings of the applicant's study for determining the minimal meaningful clinical change in the endpoints that will be discussed briefly a little later in the presentation.

[Slide.]

The FDA Draft Guidance for sexual dysfunction, and the Division's advice were very closely followed by Procter & Gamble. As noted earlier, in the applicant's presentation, they developed three instruments across different cultures and languages to assess three different

efficacy endpoints, namely: satisfactory sexual events, desire and distress that was associated with HSDD. The two placebo-controlled Phase III trials of six months' duration were completed, and each with over 500 subjects. And a clinical study to determine the magnitude of change in these three endpoints that would be clinically meaningful to the individual woman herself was performed.

[Slide.]

The key inclusion and exclusion criteria are summarized here. All of the women were surgically menopausal and on stable doses of estrogen. As noted earlier, approximately 77 percent of the women were on oral estrogen, and 23 percent on transdermal.

The diagnosis of acquired HSDD was made primarily by answering "yes" to five questions that are listed on the next slide.

All of the women were in good general health, and did not have major medical or psychiatric illnesses. And there were no specific serum testosterone criteria for inclusion or

exclusion.

[Slide.]

The five questions are listed here. I'm not going to read them, but they were used primarily for the diagnosis of acquired HSDD. The women themselves--as opposed to a clinician or a sex therapist--answered the questions, so that this was purely determined by the individual women. In essence, the subjects has a satisfying sex life before surgery, followed by a decrease in desire and activity after surgery, that cause them personal distress and a wish to have an increase in their sexual desire and activity.

Data from the Sexual Activity Log--which is abbreviated as SAL in some of the applicant's presentations--and the baseline scores on the two instruments for measuring desire and distress were not part of the entry criteria for the study.

[Slide.]

The primary endpoint was, as noted before, the change from baseline in satisfactory sexual events per four weeks. The individual's sexual

activity was recorded retrospectively each week on the Sexual Activity Log, and was collected at the clinic sites every month.

The secondary endpoints were the mean change from baseline in the Personal Distress score, and the mean change in the sexual desire score. The two instruments that were used to measure these endpoints had questions about how the individual felt over the previous 30 days. Each instrument was completed at baseline, and weeks 4, 8, 12 and 24 of the Phase III trials.

The answers then, from both of these instruments, were normalized to a scale of 0 to 100 points. And I think it's extremely important to remember that. So we're talking about a scale of 0 to 100 points.

A decrease in the distress score meant less distress, and an increase in the sexual desire score meant an increase in sexual desire.

[Slide.]

This slide summarizes the findings for the primary endpoint of satisfactory sexual events. On

average, the baseline SSEs for all subjects in the two trials was three satisfying events--which is shown, really, in this column: an average of about three events. The range is noted here.

A the end of the treatment period the TTS group increased by approximately two SSEs--that would be change, the change of 2 in basically the 1.6, compared to the placebo group, which had a change of the 1 and .7 events per four weeks.

The difference was shown by the applicant to be statistically significant. The clinical significance, however, of this mean increase from three to five events, and the difference of one event, placebo, compared to testosterone treatment is not clear to the Division.

[Slide.]

The secondary endpoints, the mean change from baseline in personal distress is summarized on this slide for the two trials. On a scale of 0 to 100, the mean baseline score was 65--approximately--here for all participants. And this corresponds, on average, to an answer of

"often" to the questions related to distress.

A decrease of 16 to 18 points was seen with placebo--that is here, 16 and 18 points--and a decrease of about 24 points was seen with testosterone treatment. The difference between the testosterone response compared to the placebo response in both trials, with 6 to 7 points on a scale of 100. So here's the difference of testosterone, compared to placebo.

We are not sure of the clinical significance of this change from baseline, and the relative difference between the placebo effect and testosterone effect on personal distress.

[Slide.]

The same concern is seen in the next slide, with the other secondary endpoint, for sexual desire.

The overall mean score was 21--mean baseline score, yes, was approximately 21 points on this 100-point scale. The placebo group increased an average of 6 to 7 points, while the testosterone group increased 11 to 12 points.

The difference between testosterone treatment and placebo is approximately 5 points in the first study, and 5.2 in the second study. And this is on a scale of 100.

Once again, the clinical significance of this small numeric change is the issue.

[Slide.]

The next slide simply shows a summary of the overall events. It just shows, for SSEs, just your change, placebo from baseline. And I really don't need to make any more comments, except that it's showing that there is one more satisfactory sexual even per four weeks; five more points on the desire scale of 100 points, and six to seven point greater decrease in the distress scale of 100 points--when we compare the placebo effect with the testosterone effect.

[Slide.]

To put these findings into perspective, I will now show data collected by the applicant for age-matched normal women with no female sexual dysfunction, and with a normal sexual desire.

This slide comes from basic data collected by Procter & Gamble early in their development program, at the time of the initial validation of their endpoint instruments. Data was collected from over 300 women with HSDD, and was compared to over 250 "normal" age-matched controls.

[Slide.]

The data presented here shows the "normals" for 146 U.S. women, and it's shown in the blue bars. So we have a baseline of SSEs of 12 events per four weeks; for desire, the baseline of "normal" women is 65 for desire; and for distress, it's 5 points on a scale of 100.

The Phase III data of the combined trials of all the women is also shown on this slide. So, for SSEs our baseline was 3, and with testosterone treatment increased to 5 for the SSEs. For desire, our baseline was 21 points and increased to 33, with a normal of 65 and a baseline here for distress was 65, and then that decreased to 41. Again, the normal is at 5.

Although there was a clear treatment

effect with both placebo and testosterone in the two Phase III trials, we can easily see that the testosterone effect over the six months of treatment did not return to the values of the normal age-matched women, as determined by the applicant.

[Slide.]

This entire study was covered very nicely by Dr. DeRogatis earlier. It summarizes the study performed by the applicant to determine a meaningful change in the endpoints as defined by the women themselves.

All of the 132 interviews were done within two weeks of stopping treatment. But the subject and the interviewer were blinded to the actual treatment received during the treatment, and the key question--I won't read it again, because DeRogatis showed it to you--but "--did you have a meaningful benefit from the study patches?"

Of the women receiving TTS treatment, 52 percent felt they had a meaningful benefit, while 31 percent of the women on placebo felt they had a

meaningful benefit.

The Receiver Operating Characteristics analysis was then used to determine those changes that best separated the group of women that felt they had a meaningful benefit from those who felt there was no benefit.

And the final results on that analysis showed that these were the minimal meaningful treatment changes, namely: greater or equal to 1.1 sexually satisfying even per four weeks; a desire score change of 8.9 or greater on the scale of 100; and a distress scale decrease of 20 or more in the distress score of 0 to 100.

The main importance, however, of this study was so that then these values could be used to perform a series of responder analyses, as shown on the next slide.

[Slide.]

I'm really just going to focus on the first set of bars here, because this was the primary endpoint for the study; that is, the satisfactory sexual events. And the responder

analysis--and this is for all of the subjects in the Phase III studies combined--so this is over 1,000 women--showed that the mean responders for placebo was 30 percent of the placebo women, compared to 44 percent of the testosterone women.

If the parameters are changed to greater than 2 SSEs or 3, we see a slight lowering of the bars. But what is important is that the difference between placebo and testosterone treatment range from the 12 to 14 percent; and specifically, this is a 14 percent difference here.

[Slide.]

In summary, the clinical efficacy findings show a small but statistically significant testosterone treatment effect seen in the three efficacy endpoints. There was a mean increase in the TTS users of one more satisfactory sexual event per four weeks, compared to the placebo response for four weeks.

For the secondary endpoints, the distress score decreased 6 to 7 points more with testosterone, compared to the placebo effect, on a

100-point scale. And the desire score showed a difference of 5.1 units, comparing placebo to the testosterone treatment.

For the responder analysis of the primary endpoint "satisfactory events," there was a 14 percent difference in the number of events per four weeks for testosterone treatment compared to placebo.

These changes in the testosterone treatment do not approach the normal values seen in the age-matched women without hypoactive sexual desire disorder as determined by Procter & Gamble and shown in slide number 11.

We look forward to the Advisory Committee's input concerning the clinical significance of these efficacy findings.

This concludes my remarks. And next we'll hear from Dr. Soule on the safety findings.

Safety Findings and Issues

DR. SOULE: Good morning. I'm Lisa Soule. I'd like to highlight some points raised in our safety review of the two Phase II and two Phase III

studies on transdermal testosterone in surgically menopausal women.

[Slide.]

High level concerns about safety of this product are two-fold. The adverse effects of long-term or chronic use of this product cannot be characterized from the current safety database. Events of potential concern may have a long latency from exposure to occurrence.

Also, the addition of testosterone to estrogen may increase risks of estrogen-associated adverse events such as breast cancer and cardiovascular disease--as is seen when progesterone is combined with estrogen. And it's worth noting again that the target population--surgically menopausal--will be concurrently using estrogen, a product with known risks, and may potentially use it on a long-term basis.

Current guidelines on the use of estrogen products are discussed on the next slide.

[Slide.]

Recommendations from the FDA and professional societies concerning the use of hormone therapy have changed significantly since publication of the Women's Health Initiative findings. And you can see the FDA boxed warning recommends that estrogen and E+P products be prescribed at the lowest effective doses, and for the duration, consistent with treatment goals and risks for the individual woman. And, similarly, the American College of OB/GYNs says the lowest effective estrogen dose should be used for the shortest possible time to alleviate symptoms, and further recommends that use should be reassessed annually.

[Slide.]

Review of the literature on testosterone use in women suggests a spectrum of risks. Some are documented to occur with some certainty at doses like the TTS patch, such as androgenic adverse effects: acne, alopecia and hirsutism. Others are not clearly or consistently found, but are suggested from data on women with endogenous

hyperandrogenism, such as changes in lipids, hypertension. And, finally, there are very limited data addressing the outcomes of greatest significance, such as increased cardiovascular morbidity and breast cancer.

[Slide.]

In evaluating the safety database from these studies, we must consider the extent to which results obtained from the study population can be generalized to the target population for this product. For example, African-Americans make up 13 percent of the U.S. population, but only 6 percent of the study population. We do know that African-American women are more commonly surgically menopausal than Caucasian women, but the prevalence of HSDD in African-American women is not known.

In addition, there were small numbers of older women in the trial. And, finally, women who may be at the highest risk for cardiovascular morbidity were either under represented--such as African-Americans and older women--or were completely excluded from these studies, as is the

case for women with existing diabetes or cardiovascular disease.

[Slide.]

In reviewing the safety database for TTS, the following safety endpoints were of particular interest, because they bear on specific areas that are potentially of concern in considering chronic use of testosterone in women. These include adverse events related to the use of TTS and to the duration of exposure to TTS; laboratory data that may reflect cardiac risk; changes in blood pressure and weight; and occurrence of breast cancer.

Before discussing safety outcome data, I want to show you some data on testosterone levels that were obtained in the women in these studies. Although, as you heard earlier, mean testosterone levels remained within the range for reproductive-age women, a significant proportion of the treated subjects had level of free and bioavailable testosterone above this range.

[Slide.]

This slide shows the proportion of

subjects with free testosterone values outside the upper limit of normal range, which is 7.3 pcg per ml for reproductive-aged women, aged 18 to 49. The percent shown here are for placebo subjects--shown in red here--and women on TTS for varying durations.

The green bars show subjects who were on TTS throughout the duration of the study, and had blood sampling done at the noted weeks here.

The purple bars are the subjects who were initially on placebo back here in the early part of the study and then switched to TTS. So at these points all of these women are on TTS.

It can be seen that virtually no placebo subjects had levels outside the reproductive-age range. At weeks 52 and 78, there was very little difference between groups, according to their duration of TTS. But you can see that almost a quarter of the women on TTS for longer than a year developed free T levels beyond the range for reproductive-aged women.

[Slide.]

And here's the similar data for bioavailable testosterone which, as you've heard, comprises both free and albumin-bound testosterone. And, again, virtually no placebo subjects are beyond the reference range.

And within subjects on testosterone, there's not a great difference according to the duration of testosterone. But here, up to 43 percent of women who used TTS for up to a year developed bioavailable T beyond the reference range.

[Slide.]

As you see, the trial design is complex, with different arms receiving different durations of testosterone exposure. So before I present any more data, I'd like to try to clarify how the subsequent data will be presented.

This figure shows the movement of subjects through the different phases of the trials, and the TTS exposure that each group received at the various phases. And what these "durations" here are. The N's in each box, shown here, are the

number of women who entered that phase.

The data presented from here on will primarily compare even frequency between women on placebo and women who received between 0 to 6, 6 to 12, and 12 to 18 months of testosterone. These exposures to TTS did not necessarily occur in the same phase of the trial, as the exposure of women who were initially randomized to placebo--this line here--and then went on to TTS always lagged six months behind those who were initially randomized to TTS.

The events to be reported on each slide from here on occurred in the study phase corresponding to the exposure interval for each group. So, for example, events reported for TTS subjects with up to six-months exposure occurred here in the double-blind phase, while events for the placebo-to-TTS subjects with the same amount of exposure occurred over here, in the open-label phase.

[Slide.]

Some adverse events show an increased

frequency in women who received TTS compared to subjects on placebo, including androgenic adverse events overall, as well as the individual components: acne, hirsutism, alopecia and voice deepening. The percents shown here are the percent of subjects at each of the three phases of the study who experienced androgenic events. They are grouped by the total duration of TTS exposure that the subjects received.

Androgenic adverse events overall occur more frequently in TTS-exposed subjects than placebo subjects, but don't show a steady increase with increasing duration of exposure. Some adverse events did occur with increased frequency, though, as duration increased.

[Slide.]

For example, alopecia. And here you can see, starting with placebos and no exposure, that the rate of these events increases as the women are on longer and long durations. And, remember, these events are not cumulative but, rather, show the occurrence of new cases of alopecia in each of the

three phases. And each phase, remember, is about six months long.

Since the associate of androgenic adverse events with the use of TTS seems clear, the relationship between free T levels and the occurrence of these adverse events was explored.

[Slide.]

The incidence of androgenic adverse events are examined here according to quartiles of free testosterone obtained during the double-blind phase. And the T values used here are the maximal values obtained at either the week-12 or the week-24 sampling.

There appears to be an association between higher levels of free T and greater frequency of acne and hirsutism. And, as you hear this morning, there was only a significant trend test here for hirsutism.

But if you look at acne, you can see that the women in the upper two quartiles--that is, women above the median--do appear to have higher rates than placebo women or women down here in the

lower two quartiles of free T.

In hirsutism, you can see more of an exposure response, which may plateau up about the third quartile. And if you look at the ranges of the third quartile, you can see that these are still below the reference range for reproductive-aged women.

[Slide.]

In contrast, alopecia and voice deepening do occur more frequently among TTS than placebo subjects, but don't seem to increase with higher free T levels. And it may be that these events occur where a threshold free T level is exceeded.

[Slide.]

Getting back to our risk spectrum, I want to review some data bearing on possible impact of TTS on cardiac risk factors. We're concerned about the potential impact of TTS on a number of cardiac risk factors and, as you've heard, several of these are believed to be linked in a common pathophysiologic process, and form a constellation known as the "metabolic syndrome"--which is an

independent risk factor for cardiovascular disease.

There are several diagnostic schemes, but generally the components include glucose intolerance, dyslipidemia, hypertension, and central obesity.

A community-based study of 16,000 mean and women found that the free androgen index was statistically significantly higher in women with metabolic syndrome, and also found that the prevalence of metabolic syndrome in African-American women was twice that in Caucasian women.

Let's look at the lipid data first.

[Slide.]

While, on average, lipid values showed little mean or median change, over the course of the studies some parameters were of concern in terms of percent of subjects who developed values outside the normal reference range. This slide demonstrates the proportion of subjects with abnormal values on LDLs and triglycerides. These labs were measured in all three phases of the

trials. The placebo group is in red.

Abnormal values were defined at the levels shown here. So, for LDL, above 160 mg/dL; for triglycerides, about 250 mg/dL--but, additionally, required that subjects have an increase from baseline of greater than 30 percent. So women who entered the trial with elevated lipids may not even be represented here. And thinking back to the metabolic syndrome criteria that you just saw, 3 to 4 percent of these subjects may meet the triglyceride criteria for the dyslipidemia component.

Virtually no subjects developed abnormal HDL levels in these trials, and the mean and median changes were neutral, or even showed a slight increase from baseline for HDL.

[Slide.]

Although, as you heard, mean glucose levels were similar between treatment arms during the double-blind phase, the change from baseline in glucose level appears to increase with duration of TTS exposure. And here you can follow the trend in

the groups, characterized by their initial randomization. So here are women on placebo at the beginning, and you can see that they have a slight drop in their glucose levels. But as they go on to six months and then 12 months of TTS, you can see that the glucose levels are rising.

Similarly, here are subjects receiving TTS in the beginning of the trial and, again, as their exposure increases, so too does their glucose level.

[Slide.]

Insulin was measured only during the double-blind and open-label phases, and not in the extension phase. The mean increases in the TTS-exposed subjects at both time periods--and again, remember, both of these, even though we have red coloring, are on TTS in the open-label--exceeded those down here in the placebo subjects.

Although the changes in these markers of carbohydrate metabolism are small, these small trends may be magnified when the full target

population, including who may already be glucose intolerant or insulin resistant, is exposed to TTS.

[Slide.]

Fibrinogen is an independent risk factor for coronary artery disease. The lab value was also assessed only for 12 months in the double-blind and open-label phases. The data on mean change from baseline is suggestive of an increase with TTS exposure for six to 12 months. And the median change data are similar.

The effect of TTS on blood pressure was also of interest as a risk factor for cardiovascular disease, as a component of metabolic syndrome, and in regard to the occurrence of hypertension as an outcome in itself. In the double-blind period, hypertension was recorded as an adverse event for 1.3 percent of placebo subjects, and 2 percent of TTS subjects.

A 2002 meta-analysis of 61 studies conducted by the Prospective Studies Collaboration in the U.K. found a two-fold increase in deaths from vascular disease and ischemic heart disease in

40 to 69-year-olds for each increase of 20 mm in systolic blood pressure, and 10 mm in diastolic blood pressure.

[Slide.]

And here you can see: a rise of 10 to 19 mm occurs in 5 percent more subjects who received TTS for 6 to 12 months, as compared to the placebo subjects.

[Slide.]

Similarly, there are 4 percent more subjects who had rises of diastolic blood pressure from 10 to 19 mm in the group who received TTS for up to six months, as compared to placebo subjects.

We don't have data that could speak to the issue of central obesity, but we can look at the changes in weight over the course of the studies.

[Slide.]

Although weight gain appeared to occur at higher frequency with greater TTS exposure, so too did the equivalent amount of weight loss.

[Slide.]

A short-term clinical trial database can

provide only limited information about risks with longer latency, and a significant background incidence; for example, no MIs occurred in these trials.

In regard to breast cancer, epidemiologic studies have suggested that androgen levels in women may be linked to the risk for developing breast cancer. And, similarly, there have been studies suggesting that increased insulin levels may increase breast cancer risk. Some authors have suggested that androgen's potential role in breast cancer risk may be through its impact on insulin resistance.

[Slide.]

This slide describes the four cases of breast cancer that occurred in the trails--as you've previously heard. But given the dual exposures to estrogen and to testosterone--all aside from this one placebo subject--and the relatively short duration of testosterone use--5 to 37 weeks--there are insufficient data to assess the causal role of TTS. And this highlights the

limited ability of short-term clinical trials to answer questions of causality, particularly in a population with a moderately high background incidence of the outcome of interest.

[Slide.]

The current safety database is unable to answer many questions about the safety of TTS for several reasons.

First of all, placebo-controlled data is available only for six months, and even long-term exposure is limited to 12 months--in under 500 women, and 18 months--in 127 women. And, as you've heard, women with diabetes and cardiac disease were not studied.

For naturally menopausal women, our concerns would include safety of TTS in women who retain their uterus, and the known risks of estrogen and progestin, which might be used for greater duration by women using the TTS than they would otherwise be.

[Slide.]

Procter & Gamble has a number of studies

in progress that will provide some additional useful data, and these include--as you've heard--the surgically menopausal studies: currently 321 subjects have entered this extension phase, which is in year two of what will be, ultimately, a three-year extension. In addition, the two placebo-controlled studies you've heard about in naturally menopausal women, there's a six-month study completed, and a 12-month study close to completion, each enrolling about 400 women. And of these naturally menopausal studies, 281 women have enrolled in safety extension phases.

These studies will also ultimately provide 293 paired endometrial biopsy samples.

And, finally, there's in progress a study of the TTS patch being used alone in women who are not taking estrogen or system estrogen-plus-progestin--although they are allowed to use vaginal preparations. And this study has a projected enrollment of 750 women in three arms, which are placebo, a dose of 150 mcg a day--half of what we're hearing about here, as well as the 300

mcg per day dose.

[Slide.]

As you've heard, Procter & Gamble has proposed a post-marketing pharmacovigilance study. And, briefly, to review, they propose to do a prospective cohort study in a claims database, with three-to-one matching of current and recent users with control subjects, planned outcomes, including cardiovascular disease and breast cancer; endpoints to be adjudicated by a panel of medical experts blinded to treatment exposure; and they propose that the first analysis will be available at 24 months post-launch.

Further, they estimate that their power to detect cardiac events occurring with a relative risk of 1.5 will reach 85 percent by year five.

[Slide.]

We have a number of concerns about the utility of this proposed plan, however.

First of all, to answer safety questions, does a claims database and cohort study provide the same level of evidence as a randomized

placebo-controlled trial?

We're concerned that the project sample size is inadequate. A study powered to detect a relative risk of 1.5 for cardiovascular disease may miss important but lower risks. And, just to remind you, the risks seen in the WHI estrogen-plus-progestin study were on the order of 1.2 for total cardiovascular disease, 1.3 for breast cancer, and 1.4 for stroke. And to detect risks of this size, a sample size of almost 17,000 was needed.

In addition, we're not given any information on the power to detect an increased risk of breast cancer.

We're also concerned that events with long latency may not be detected. And, again, in the WHI E+P study, breast cancer rates did not diverge until year four, suggesting that the effect of hormone exposure may not manifest above the background incidence until that time.

In addition, we're concerned about recruitment goals, which have not been met

previously using this database. And we're also concerned about turnover in plan coverage. And although you've heard that this plan retains 85 percent per year, when you take that out to year five you can see that you're retaining only 44 percent of the original population.

[Slide.]

The WHI had far-reaching effects on our assessment of risks associated with long-term hormonal treatment. We learned from this that the data was discrepant from that we'd previously known from observational studies, and that reinforced the value of prospective, randomized controlled studies of adequate duration to be able to define attributable risk.

And, ultimately, WHI indicates the need to give heightened scrutiny to hormonal therapy in post-menopausal women.

[Slide.]

To summarize the issues we must consider: the sample size and duration of treatment is inadequate to exclude serious risks, including

cardiovascular disease and breast cancer, with this treatment; and the population studied is inadequate to identify important risks in naturally menopausal women using estrogen and progestin, and in sub-groups at higher risk for cardiovascular morbidity.

We look forward to your discussion and assistance in resolving these issues and the efficacy issues raised earlier by Dr. Davis.

Thank you.

DR. GIUDICE: Thank you, Dr. Soule. And the committee will have an opportunity to ask questions of both of the FDA presenters after lunch this afternoon.

Open Public Hearing

This is now time for the open public hearing. And I have a statement, first, to read regarding this.

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, FDA encourages you--the open public hearing speaker--at the beginning of your written or oral statement to advise the committee of any financial relationship that 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 of your 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 do not have any financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you, however, from speaking.

So I'd like to begin with the open public hearing speakers. I would like to advise the

presenters to please state your name and your organization. Presentations will be strictly limited to three minutes--and we have a timer up here. The light will be green for the first two minutes and 30 seconds, then yellow for the remaining 30 seconds--and this will be the warning to conclude your talk. And the light will turn red at the three minute mark, at which time the microphone will cease to work.

[Laughter.]

So I'd like to call now--with that proviso--Ms. Lisa Martinez, please.

MS. MARTINEZ: First, I'd like to state that the Foundation just received a $4,000 charitable donation from Pfizer.

Now, on that point--good morning. I'm Lisa Martinez, a nurse and an attorney, and the executive director of the Women's Sexual Health Foundation, an international non-profit organization based in the U.S.

Our primary mission is to educate the public and health care professionals in the area of

female sexual health, including FSD.

We have heard from many women and their partners relating to female sexual health problems. These stories are heart-wrenching, and have a common theme: women are devastated, suffer in silence, feel very much alone in their journey to find the right answers, care and treatment; and wish that their sexual health would be taken seriously.

For women in relationships, this impacts not only them but their partners, who often feel equally helpless and devastated.

Sexual problems are not an easy subject to discuss. Women may feel embarrassed, and yet they don't give up. Some have gone for years looking for help from various providers, sometimes with success and sometimes not. It's not unusual for us to hear that women have been told by their provider that their problems are all in their head, or that a hysterectomy or bilateral oophorectomy could never be he physical cause of sexual health difficulties, and that any such problem would be

purely psychological.

The Foundation believes that a multi-disciplinary approach should be used to address sexual health problems. This would include both physical and emotional assessments.

As part of this complete approach to women's sexual health complaints, a serious effort must be made to determine if there are physical causes, such as hormone insufficiencies. Health care providers need to follow well-recognized workups that will leave no stone unturned, so that treatment plans are specifically targeted at the underlying causes of sexual dysfunction. Consideration should be given to pharmacologic and counseling.

Currently, there are no FDA-approved treatments for FSD, and providers are using off-label medications that have not been studied in women under FDA oversight.

There is a need for such treatment, including testosterone. But, more importantly, FSD is a serious health issue, and not just a lifestyle

issue.

Thank you.

DR. GIUDICE: That you for your comments.

The next presenter, Mark Klein.

DR. KLEIN: Yes, I am a Procter & Gamble shareholder and a physician.

If we balance Intrinsa's unimpressive modest results from very short-term studies, against my estimate that 50 to 80 percent of all the Intrinsa sold will be abused by non-menopausal girls and women--including some pregnant and nursing--it's a no-brainer: this is too dangerous to license for any use.

Over a decades time we could be looking at many tens of thousands of girls, women, fetuses and newborns permanently injured by anabolic steroids. There is no way to avoid such abuse. Once approved, Intrinsa will be available off the internet, off-label and on the black market.

In my 40 years of medicine I have never, ever seen government action prevent abuse of a hot, popular drug.

As the manager of a large asset family investment office holding Procter & Gamble, I feel major losses--like what happened to us with Wyeth's phyn-phen, and Merck's Vioxx. They happened because today's very weak FDA allowed these companies to cut scientific and ethnical corners. Almost as certainty, Intrinsa will result in mass tort class actions that could drive Procter & Gamble into bankruptcy.

I suspect there are many very savvy, seasoned long-term investors like myself unwinding big pharma holdings. I've reduced ours over the past two to three years from 15 percent to 6 percent.

The core problem is the big pharma's willingness to sacrifice scientific integrity to make their earnings numbers. And this is sure the case with Procter & Gamble.

As an investor and trustee for family accounts, I will sell our Procter & Gamble should Intrinsa be approved. The potential lawsuit risks for the company are so great that, in my opinion,

as a fiduciary, holding Procter & Gamble violates the prudent-investor rule.

In conclusion, I believe Intrinsa is the most hazardous non-narcotic drug ever presented for FDA approval. I urge it to be rejected for any use. And, if approved overseas, banned from sale in this country under threat of severe criminal and civil sanctions.

I have one word of advice to Procter & Gamble. I am personally absolutely shocked that you have gone into this business. We are in the business of selling soap, we are in the business of selling implicit promises not overt promises. And I hope you keep in mind, "Hell hath no fury."

DR. GIUDICE: Thank you for your comments.

The next presenter is Rosalyn Washington.

MS. WASHINGTON: Good morning. My name is Rosalyn Washington, and I have no financial affiliation with Procter & Gamble.

I am a wife, a mother, and a woman who suffers from low libido. Almost 10 years ago I had a hysterectomy with removal of both of my ovaries.

This surgery--which, in my opinion, is performed far too frequently on thousands of women in the U.S. on a yearly basis--robbed me of my sexual desire.

Unless you have experienced the lack of sexual desire you cannot completely understand the feeling of frustration and sense of inadequacy I have. When I learned of this research being conducted to help women with low libido I jumped at the chance of being a volunteer for the clinical trial study.

Overall, my experience in the study was an excellent one. I did not grow a mustache or a beard or develop large muscles. My voice did not deepen, and I did not grow hair on my chest.

However, there was a noticeable increase in my libido. I had first-hand experience with the positive effects of the Intrinsa testosterone patch, as a participant in the clinical trial studies, and I would like to experience those feelings again.

It is a known fact that women are much

more complicated than men. In a lot of cases our libido is directly linked to our emotions and mental state of mind. But this is not always the case. Physical factors, like a hysterectomy can affect libido by removing the ovaries which produce testosterone in a woman's body.

Intrinsa is a drug therapy that I believe the studies have shown to be effective in raising the levels of testosterone in a woman's body with little or no side effects.

It is my hope that Intrinsa receives FDA approval and be made available countless women like myself, who are seeking a solution for our sexual dysfunction.

A healthy and satisfying sex life is important to a woman's physical and mental well-being. I believe Intrinsa will help restore the level of hormones necessary for me to once again have a healthy sex life.

Thank you.

DR. GIUDICE: Thank you.

The next presenter is Kathleen Kelly.

MS. KELLY: In 1982 my mother died of ovarian cancer, setting in motion ready-made decisions for me and my sister with ovarian cancer familial risks.

My name is Kathy Kelly. In the summer of 1998 I had a hysterectomy and a bilateral oophorectomy. I searched on-line and found very little that was helpful to me, so I gathered materials, resources and added a discussion board, and launched a website called "Hyster-Sisters."

Now, over six years later, Hyster-Sisters is the largest on-line hysterectomy community, with over 55,000 members.

The Hyster-Sisters site is neither anti-hysterectomy, nor pro-hysterectomy; rather, it is a on-line community of women who give and receive support for hysterectomy decisions and recovery.

The Hyster-Sisters have sent me today to share their stories with you.

Many members recover from their surgery and head back into their lives without much

fanfare. For others, they return to our site months or even years later, in search of additional support for new health issues. Predominantly, they return in search of support for hormone therapy, many complaining of a missing libido.

And while we have thousands of personal posts from frustrated members regarding their loss of desire, time constrains me only to share with you a few.

A 47-year-old woman wrote: "Since my hysterectomy, I've tried all forms of hormone therapy and some herbal treatments. I'm beginning to wonder if it's simply impossible to get back my libido."

A woman in Arkansas wrote: "I have a check-up appointment with my OB/GYN next month, and my husband is going with me so we can talk about my libido. What is wrong with me? I am 24 years old. I love my husband. Has anyone else experienced a change in libido? How do you go about correcting it?"

A 43-year-old woman in Southern California

wrote: "Prior to my surgery my libido was tremendous. My husband and I have had 25 years of awesome sex. My husband has been very, very patient with me. We have tried just about everything, but to no avail."

The Hyster-Sisters have sent me, because it is our hope that the medical community find better treatment so that the hysterectomy is truly a last resort. But for those hundreds of thousands who have had an oophorectomy, we would like hormone options to better restore what we have lost.

Our next generation of women is depending on us.

The Hyster-Sisters have sent me to ask that you approve this drug--the testosterone patch--as one option for the libido needs of the surgically menopausal woman.

Thank you.

DR. GIUDICE: Thank you.

The next presenter is Leonore Tiefer.

DR. TIEFER: First slide, please.

My name is Leonore Tiefer--no money, no

way.

AS a psychologist with over 30 years of teaching, research, awards and publications in sexuality, I see today as a perilous moment in the history of women's sexuality.

Next slide.

[Slide.]

A few random credentials, which I offer because this is the first women's sexuality drug that the FDA has ever reviewed--and there is no sexuality drug committee. Input may be useful from someone who has spent decades immersed in issues of sexual nomenclature, measurement, motivation, behavior and biology.

Third slide, please.

[Slide.]

Here are my concerns--and I have handouts on these points, since you can only say just so much in 180 seconds.

The Intrinsa trials are grossly inadequate to assess the risks of extended steroid hormone treatment. And I hope we don't have to go through

another HRT scandal to learn this again. That's point one.

Point two is that assessing sexual experience is subtle and complex and arbitrary. Experts in sexology agree that there are numerous ways to define and measure desire and satisfaction. Methods chosen in every study must be closely examined for what they leave out, as well as what they include.

Point three: these Intrinsa trials excluded women with medical problems, relationship problems and life stress. It's no wonder it took 52 trial sites to find a meager 1,095 subjects.

How representative are these carefully selected subjects of the millions P&G is hoping to interest in it's new medicine?

Which brings me to point four: Intrinsa is not a glass of Chardonnay, and yet we have already seen that it may well be promoted, with a giggle and a wink, as the female Viagra.

Not so. This is a steroid hormone women must continuously take for weeks before getting an

effect. Yet P&G's promotional materials encourage the attitude that millions of women are walking around under-androgenized, in danger of imminent sexual withering away. It's a revival of menopause as a deficiency-disease, only this time it's testosterone riding to the rescue.

Fourth slide.

[Slide.]

So here are my recommendations.

First, postpone the application until there are longer studies on more appropriate populations.

Second: if women with low desire are testosterone-deficient, we must have an affordable assay to measure that deficiency, and there is none now.

Third: good sex research should always have a qualitative component.

And, finally, the FDA's DDMAC needs to carefully monitor the P&G materials for bias and boundary violations.

Last slide.

[Slide.]

I am representing a large group of experts who couldn't be here today.

Thank you very much.

DR. GIUDICE: Thank you.

Our next presenter is Wayne Shields.

MR. SHIELDS: Hi. My name is Wayne Shields. I'm president and CEO of the Association of Reproductive Health Professionals.

Thank you for holding this hearing and inviting us to be here today.

We are a 501(c)(3) organization, and we do receive support from foundations and companies, and we have in the past received unrestricted grants from Procter & Gamble.

It's important to know, I think, that ARHP has been around a while, and that ARHP is a medical organization of over 12,000 health care providers, multi-disciplinary, mostly OB/GYN and family practice. We have researchers and on-the-ground practicing clinicians.

On behalf of our members I'm glad to be

here today.

I also have to say I realize I'm a guy, and this conversation is about sexuality. I do represent mostly a female constituency. But I think the topic of sexuality is key, and it's under-addressed in America. So this is a great forum, and thank you for providing that opportunity.

ARHP is an organization accredited by the ACCME, and we provide CME for health care providers, and other credits. And we advocate for evidence-based research. And we support the availability of a wide range of safe and effective and appropriately used treatment options on women.

I'm here today to support this application, if it's appropriately used--and I know you'll have that discussion. And I'm here today to let you know that we believe this medication is appropriate for enhancing sexual desire in a very particular subset of surgically menopausal women.

We do support--and this is important for us in our mission at ARHP--careful clinical

screening to ensure that this medication is given only to appropriate candidates. I think that that's key.

In the past, sexual health research has focused mostly on men's sexual health, as you know. We feel it's important that female sexual health be represented more prominently. And while men have benefitted from a number of products and the ensuing attention on their sexual disorders, this is an important conversation and an important product, because it allows a forum for conversation about female sexuality, and their very unique and very different sexual disorders.

We support focusing on the sexual health of women. We see the introduction of a safe and effective medication for women as a great opportunity to be able to discuss, in an evidence-based and appropriate manner, female sexuality to enhance health care provider communication with patients.

We believe that hypoactive sexual desire disorder is a real condition, and that surgically

menopausal women who suffer from it deserve a range of treatment options, whether they be behavioral or medical. Many women with HSDD can benefit from counseling and lifestyle adaptation and other non-medical treatments--very true. Let's talk about that more. But there remain some women for whom a safe and effective medical intervention such as this one will be of benefit.

And we think this is especially relevant for surgically menopausal women.

The data and research we have examine indicates that while it's not appropriate--

[Time expired. Microphone turned off.]

[Laughter.]

DR. GIUDICE: Thank you.

The next speaker is Karen Hicks.

DR. HICKS: First slide, please.

[Slide.]

I'm Dr. Karen Hicks, a sexual health educator and founder of the Dalkon Shield Information Network--with no financial relationship to the company.

I'm here to request that approval of the Intrinsa patch be delayed until relevant safety issues have been fully reviewed and documented. Drug safety issues and scrutiny of the FDA have dominated the business news lately, due to the Vioxx scandal and risks of antidepressants for children. Today, as you deliberate the dawn of a whole new class of sexual medicines for women, it's time to consider some new precedents for considering the safety issues relevant to a drug like Intrinsa.

Next slide.

[Slide.]

I raise four questions: One, what is the safe dosage for individual variations among women who may be very different from women in the clinical trials, particulary with regard to ages, differing weight profiles, general health status and possible ethnic backgrounds?

Two: what is or isn't know about the long-term use of this drug? In the clinical trials, subjects used Intrinsa for time ranges

between 14 and 24 weeks, yet it's intended to be used continuously over the long term, and possibly for years.

Three: what potential adverse reactions has ben anticipated, and what might likely unanticipated outcomes be? Experience with testosterone in pill or injectable form, and other reproductive hormones prescribed to women, include cancers of the breast and other tissues, liver ailments, excessive facial hair growth and skin problems--to name a few.

Four: how will problems in prescribing and dispensing be prevented or minimized. Based on the excitement being generated in the press for this drug already, I predict that off-label use with soon follow.

Next slide.

[Slide.]

This week's Journal of the American Medical Association has two relevant editorials. The first speaks to the weaknesses of the current post-marketing surveillance process at the FDA.

The second explores the potential for conflict of interest in the evaluation of suspected adverse drug reactions.

The journal editors recommend that an independent entity located outside the FDA be given primary authority for this task. The Vioxx and Dalkon Shield IUD scandals hinge on the long suppression of information on dangers they posed to their users.

Next slide.

[Slide.]

I off five recommendations for setting new precedents.

One: admit full disclosure of the clinical trials to the public.

Two: initiate a user registry under the purview of the FDA to all users who volunteer to be kept informed.

Three: upload all documentation on efficacy and safety to the FDA website and announce the URL and telephone numbers widely on pharmacy patient package inserts and information sheets.

Four: if warranted, contact all users early through pharmacy databases about discoveries of dangers relative to this drug's use.

Five: include label warnings about duration of use beyond the length of the clinical trials.

Next slide.

[Slide.]

The public perception, reflected by substantial press coverage, already suggests that Intrinsa is "Viagra for women." I find this notion distorted and disturbing. This treatment is not equivalent in manner or duration of use. It acts on different body systems and has different effects.

Please consider these recommendations as you deliberate today.

Thank you.

DR. GIUDICE: Thank you.

The next presenter is Jean Koehler.

DR. KOEHLER: Hi. I'm Dr. Jean Koehler. First of all, I want to let you know that I was a

paid consultant in the persistence of benefit phase of the Intrinsa trials, and am currently a paid regional consultant with Procter & Gamble, and a long-term stockholder.

Additionally, I'm a paid consultant for Ortho-MacNeill Pharmaceuticals.

It is because of my clinical experience, and experience interviewing women on Intrinsa, that I felt the need to take te time out of my practice to be here today, at my own expense, to support the approval of this product. I am a licensed marriage and family therapist, and certified sex therapist in private practice. Additionally, I'm a faculty member at the University of Louisville School of Medicine, and have held both of these positions since 1976.

I am also the immediate past president of the American Association of Sex Educators, Counselors and Therapists--or AASECT. With over 2,100 members, AASECT is the oldest, largest certifying organization of professionals in the sexuality fields. While AASECT does not endorse

any particular product, I have been authorized by the organization to support the kind of research that is being presented here today.

In my own professional opinion, as a sex therapist and medical educator for over 28 years, I also see a great need for this product. Female hypoactive sexual desire disorder is not only one of the most common presenting complaints in psychotherapist and physicians offices, it also has been the most difficult of all the sexual dysfunctions to treat successfully.

While I have successfully treated many psycho-social causes of this disorder, my multiple years of experience tell me that without concomitant testosterone therapy, psychotherapy and relationship therapy has failed with women whose testosterone levels remain low.

I'll give you just one of many examples of positive use of testosterone in my practice.

The nine-year marriage of my client--whom I'll call "Laura"--was about to break up because she had totally lost her sexual desire and

willingness to have sex, after a good previous sex life with her husband. Her free testosterone levels were very low, and her husband as so sexually frustrated that he was becoming emotionally abusive.

After the combination of psychotherapy and testosterone replacement therapy restored her drive, Laura reports two years later, on follow-up, that she is still using her prescription, and that her marriage has more than stabilized, and she reports no adverse events. She now enjoys sex again, and two little children were spared the trauma of impending divorce.

Similar reports came from the women I interviewed in the persistence of benefits stage. And not only did they notice important increases in desire and function, but improved and increased emotional closeness with their partners.

So the importance of this product is not just about one more sexual experience per month. It's also about a generally improved quality of life for these women.

The patch will no doubt only work for a carefully selected group of women, but as a woman and as an advocate for patients like Laura, I maintain they deserve--

[Time expired. Microphone turned off.]

DR. GIUDICE: Thank you.

The next presenter is Anne Kasper, and I'm making these remarks, prepared by Breast Cancer Action, on behalf of both Breast Cancer Action, and Our Bodies Ourselves.

Both organizations work in the public interest, and do not accept funding from the pharmaceutical industry as a matter of principle--and neither do I.

Breast Cancer Action opposes approval of the proposed indication for NDA-21-769. While reduced libido and vaginal dryness are serious concerns for women with breast cancer who are put into menopause by chemo treatments, the solution does not lie in the approval of this therapy, which has only been briefly evaluated, and not in populations of women who may be at increased risk

from hormonal exposures due to their cancer history.

We recognize that the proposed indication of this NDA is for women whose menopause is surgically induced, but we are deeply concerned about the enormous potential for off-label use of the therapy in inappropriate populations.

It is now widely accepted that breast cancer is largely a hormonally driven disease. Most of the known risk factors for breast cancer have to do with lifetime exposure to endogenous hormones--particularly estrogens. The skyrocketing incidence of breast cancer--and the Women's Health Initiative results on hormone replacement therapy have raised concerns about the implications of exogenous hormonal exposures as well. While much remains unkonw about the etiology of breast cancer and other hormonally driven women's cancers, there is great concern that any treatment that interferes with the eodocrine system will ultimately stimulate some aspect of cancer development. Breast Cancer Action therefore urges that all women at risk for

breast cancer--and the agencies charged with protecting their health--proceed with extreme caution before pursuing hormonal treatments of other medical conditions.

For women who have already been diagnosed with breast cancer, this caution cannot be stated too strongly. A very recent study published in September in the International Journal of Cancer indicates that high serum testosterone levels predict a greater likelihood of breast cance incidence.

The drug application is based on a small, six-month trial. Yet we know from both the Women's Health Initiative and the experience with DES that the long-term effects of hormonal therapies may not be known for many years. Approval of the NDA will lead to one more instance when women become guinea pigs in an uncontrolled experiment that may have serious implications for their long-term health.

Thank you.

DR. GIUDICE: Thank you.

The next presenter is Sidney Wolfe.

DR. WOLFE: I'm Sidney Wolfe of the Public Citizen's Health Research Group.

Is an increase in approximtely one sexually satisfying encounter a month--not from zero to one, but approximately from four to five--worth the possibility of an incrased risk in breast cancer or a coronary heart disease?

Is the FDA actually considering the approval of this product?

I was interested to hear Dr. Davis' skepticism--I think is the proper way of raising it--as to what clinical significante there is in going from four to five sexual encounters a month, or having an increase of just 5 to 6 points more than a placebo on a scale of 100, in terms of sexual desire.

What is known is that there's a fairly good consensus among epidemiologist who work in the area of endogenous--or body-produced--hormones and breast cancer risk, that increasing levels of the common estrogens and adrogens such as testosterone are associated strongly with increasing levels of

breast cancer risk. This is best illustrated by a recent pooled analysis of nine high-quality prospective studies which were published in 2002 in the Journal of the National Cancer Institute. In the pooled analysis, the risk of breast cancer for post-menopausal women increased by approximately two-fold, with a quadrupling of blood testosterone levels.

In the data on the transdermal patch--which you saw some of this morning--the average blood level of testosterone in these 18 to 49-year-old women rose from a pre-treatment level of 176 nanograms per liter, to 797 nanograms by week 52. This is a 4.5-fold incrase in blood testosterone levels by 52 weeks, which is slightly higher than the four-fold increase in blood testosterone levels in the pooled study mentioned above that was associated with a two-fold increased risk of breast cancer.

Other concerns about the chronic use of testosterone, as mentioned by the FDA, is the increased risk of coronary artery disease. A study

entitled "The Relationship Between Serum Sex Hormones and Coronary Artery Disease in Post-Menopausal Women," found "--evidence of a positive relationship between the serum free testosterone level and the degree of coronary artery disease in women." And, again, in this study there was a four-fold increase in free testosterone with the patch.

Decreased sexual desire is a very complicated problem, as discussed by Dr. Tiefer today. There is little question that a large proportion of women with this complaint respond very well to counseling that may reveal underlying problems, such as a history of being sexually abused, current unstable or unhealthy relationships, depression, or other causes better dealt with directy rather than being glossed over with a testosterone patch.

The journalist H.L. Mencken has said that for every complicated problem there is a simple solution--which is usually wrong."

I urge you and the FDA to reject the

application for approval of the testosterone patch.

And, in closing, I have no financial conflict of interest.

DR. GIUDICE: Thank you.

The next presenter is John Grossman.

DR. GROSSMAN: Good afternoon. I want to thank the FDA and the panel for allowing me to participate in this important process that will serve the interests and advance the health of women.

My name is Dr. John Grossman, and I am professor of Obstetrics and Gynecology, Microbiology and Tropical Medicine, Prevention and Community Health, and Health Services Management and Leadership at the Geroge Washington Univeristy. I'm also the Executive Vice President of the Society for Gynecologic Investigation.

For the record, my comments do not reflect the positions of either of these organizations. I am here, rather, today to present my own perspective, based on being a practicing gynecologist in Washington, D.C. since the mid

1970s.

I have no personal financial relationship with the sponsor of this product, nor with their competitors. And I have no financial interest in this product or any comparable products.

My 29-year practice has become what my father, who was a founding Fellow of the American College of Obstetricians and Gynecologists, and a medical practitioner for 46 years, would have called "a mture practice." As years have gone by, I have had the good fortune to have my patients place increasing trust in our professional relationship. And during this period, I have learned that many women have problems with sexual intimacy for a variety of reasons. Perhaps one of the most difficult problems to quantify and to treat is diminished sexual drive.

My interest and concern about this issue prompted me to request a copy of the product briefing document that has been submitted to this panel. My review of the information currently available leads me to believe that Intrinsa is safe

and effective for increasing satisfying sexual activity in these women who have had hysterectomies, and I believe it could potentially benefit some other groups of women, as well.

I becan my medical education during the sexual revolution of the 1960s Even then, I would never have envisioned a time in America when television commercials would address what we currently call "erectile dysfunction." Relatively recently, health professionals have expressed concerns about gender bias, and the public has strongly supported gender equity in all areas of life.

I believe that Intrinsa safety and effectively increases sexual desire and the frequency of satisfying sexual activity, while reducing sexually-related personal distress. And I urge the panel to recommend approval of this product, not only to provide gender equity in issues of sexuality, but also to address the needs of my patients, and those of many other women who might not otherwise be heard.

Thank you.

DR. GIUDICE: Thank you. The next presenter is Lenore Pomerance.

MS. POMERANCE: Good morning. I have no financial relationship with Procter & Gamble.

My name is Lenore Pomerance. I'm a psychotherapist in Washington, D.C., and work with mid-life women and their partners on menopause, sexual relationships, and healthy lifestyles.

The approval of Intrinsa is premature until long-term data have proven its safety.

What short memories some of us have. 28 months ago the Women's Health Initiative halted its unprecedented trial of estrogen and progestin because risks outweighed the benefits for post-menopausal women.

The study was undertaken to test whether the estrogen preparations that millioins of women had already been taking for over 30 years helped or harmed them. If we knew then what we know now, would we have let doctors and drug companies convince us that menopause was a disease? Would we

have let ourselves be fooled into believe what Dr. Robert Wilson--who claimed in his book Feminine Forever--that "menopause is a hormone deficiency disease, curable and totally preventable, and that every woman, no matter what her age, can safety live a fully-sexed life for her entire life?"

The cure for this disease was "hormone replacement therapy," replacing what had been lost. And those 30 years saw efforts to make HRT reverse the ravages of old age, from wrinkled skin and weak hearts, to addled brains.

The results of the WHI have taken the "R" out of HRT. Researchers and practitioners don't talk of "replacement" anymore. The new term is "HT," and it is to be used only for menopausal symptoms of hot flashes and vaginal dryness, for the shortest time, and in the lowest dose possible. The new guidelins are not based on proven safety, but on women's wilingness to live with the risks.

Getting rid of the "R" is a backhanded way of admitting that menopause is a natural condiiton; a physiological process that every woman will

experience if she lives long enough. Many women are never bothered by the physiological changes. Some even welcome them.

In my practice, women for whom menopause is a crisis are often experiencing other life-changing events like divorce, widowhood, dying elderly parents, children leaving home, retirement.

Does history have to repeat itself? Will Intrinsa become the Premarin of the 21st century? I don't believe for a minute that Intrinsa prescriptions will be confined to surgically menopausal women with low libido.

The FDA has approved off-label prescribing, but it must foresee that, as happened with the Viagra boom, this new drug will be requested by many people on whom it has not been tested. Believing that it's safe, these women may well become the guinea pigs of the 21st century.

Let's not let that happen.

Thank you.

DR. GIUDICE: Thank you.

The next presenter is James Simon.

DR. SIMON: I'm Dr. James Simon. I'm a reproductive endocrinologist from Washington, D.C.. I'm not speaking as past president of the North American Menopause Society, I'm speaking as a practitioner.

My conflicts or potential conflicts are listed for you in my handout.

Slide--could I have the next slide?

[Slide.]

This is a concerned physician's view of the subject, and I'm representing myself and only myself.

Next.

[Slide.]

The issue before the panel really is: is low sexual desire really a clinically important problem? And what about the risks.

Next.

[Slide.]

in this study from Laumann, oftentimes brought into question, they found in a large cohort 32 percent of women experience low sexual interest.

And I say--this is from 1999--they have been criticized by this high number.

Next.

[Slide.]

A recent study, published only this year, looked at 29 countries, with 27,000 men and women, aged 40 to 80, and defined sexual dysfunction as "frequent or persistent problems." Those problems studied in women were--most importantly apropos of this application--lac of sexual interest.

Next.

[Slide.]

In this study, 65 percent of the women were having sex. The most common dysfunction was lack of sexual interest, found in 21 percent of the women, similar to their previous findings. They concluded, overall, that overall 39 percent of all women in their study--remember, they studied 27,500 men and women--had at least one sexual dysfunction.

Next.

[Slide.]

Another study, looking at safety--and,

importantly, most women make the decisions about hormones and safety of hormones based on the issue of breast cancer. And in this study, recently published in Menopause by the group at NIH, they looked to see if testosterone could protect--could protect--against the added risk of standard hormone therapy already mentioned by previous speakers. This was a retrospective, observational study of a small cohort of women, average age 56 years, and they were studied for 5.8 years. Outcomes were the incidence of breast cancer.

Next.

[Slide.]

They found, actually, that in women on testosterone, the risk was 238 per 100,000 women-years, lower than--not higher than--lower than women who were in the WHI, lower than women in the Million Women Study. And, in fact, consistent with women who had never used hormones.

Their conclusions were: the addition of testosterone to conventional therapy for post-menopausal women does not increase and may

indeed reduce the risk of breast cancer. These same investigators found this in pre-clinical scientific experiments.

[Time expired. Microphone turned off.]

DR. GIUDICE: Thank you.

The next speaker is William Petok.

DR. PETOK: Good morning. I have no financial relationships with the producers of this product.

Good morning, members of the Advisory Committee. Thank you for allowing me time to share some of my thoughts about the TTS.

I'm Bill Petok, a psychologist and a sex therapist in private practice. I'm also the Chair of the Mental Health Professional Group of the American Society for Reproductive Medicine. In addition to my clinical activities, I also teach obstetrics and gynecology residents at Baltimore's Sinai Hospital, specifically about human sexuality.

As you are aware, sexual dysfunction in American women occurs at a significant rate. HSDD is the most frequent problem I see in my clinical

practice, and the problem most frequently seen by the physicians that I teach. It is also one of the most difficult problems to treat because it can have many determinants.

In addition to the problem that HSDD presents for an individual, this disorder can also have an impact on relationships in which sexual interaction is a vital aspect. Low desire on the part of one partner can lead to frustration and dissatisfaction for both. Some of the women that I treat report they do not understand why they have lost interest in sexual interaction with their partners, especially when other aspects of their relationship are good. The partner can be at a loss to understand the changes in relationship, as well.

It is important to note that not all HSDD is hormonally related. AS I said before, it can have many determinants that include the quality of the relationship and other psychological factors. It is a complicated problem that requires a careful analysis and intervention. When hormonal factors

are implicated as part of the etiology, as for surgically menopausal women, testosterone supplementation can be an effective therapeutic addition.

Over the years that I have treated sexual dysfunctions, I have had many women report their physician has prescribed testosterone in one form or another. Frequently, the prescription is offered as a cream that is to be applied topically. Often the directions given to the patient are less than adequate, and she asks me why she isn't getting a result that increases her desire level.

She may be unclear in her understanding of whether she is to use the product just prior to sexual relations, daily, or with some other frquency. A delivery system that makes sense and has little room for misinterpretation would be useful to these and other patients. I believe the advantage of a product like the TTS is that it is easier to apply and therefore less likely to be misused.

I have two reservations--not so much about

TTS as about how it is reported in the press or promoted.

One, I'm concerned that this product will be inappropriately described as a "female Viagra" and be viewed as a cure-all for all female sexual dysfunction of any kind. The researchers have been careful to describe its success with a specific group of women: surgically menopausal women who are on a stable dose of estrogen, and who are in long-term established relationships.

It would be inappropriate to generalize these findings to a wider group of women.

Second, I am concerned that women not have expectations that are out of line with reality. This is not a cure--

[Time expired. Microphone turned off.]

DR. GIUDICE: Thank you.

The next presenter is Raymond Rosen.

DR. ROSEN: Can I have my slides, please? My first slides, please?

[Slide.]

Okay. Thank you.

I'm Raymond Rose, professor of psychiatry at Robert Wood Johnson Medical School. I've been a psychologist and sex researcher for approximately 30 years.

I serve as a research consultant, and have received research support from P&G, Pfizer and Solve Pharmaceuticals.

I'm here representing myself, and my travel expenses wer paid by my department.

Next slide, please?

[Slide.]

I want to use my brief time to just to comment on two important documents. One of them has been discussed quite a bit today, and that's the FDA Draft Guidance document on FSD from 2000. The other document hasn't been mentioned, but I think is quite important, which is a consensus document that a number of people here participated in in 2001.

Next slide, please.

[Slide.]

Just to begin with a few comments about

the guidance document. This is available on the FDA website.

Next slide, please.

[Slide.]

And the guidance document , which is very important--for people who haven't read it--covers four areas of sexual dysfunction in women: as has ben mentioned, inhibited or hypoactive desire is the most common area. The guidance document indicates how these are defined. And I think the sponsor's done an excellent job in following those guidelines.

Next slide, please.

[Slide.]

in terms of clinical trial endpoints, which has been a majoar area of discussion today, it's important for us to understand that the satisfactory sexual events aspect of it really comes from that guidance document. And the sponsor has really done everything they can to meet those guidelines.

Many of us in the field believe that,

particularly in the area of sexual desire disorders, satisfactory sexual events is not necessarily the optimal primary endpoint. And I want to urge all of us to move beyond that. I have spoken to members of the FDA and, hopefully, we'll be moving past that.

Nonetheless, I think the sponsor has shown great consistency in the effects across differenet endpoints.

Next slide, please.

[Slide.]

Just to comment quickly on the Princeton Consensus Conference--about 16 international experts, many of whom are here today, participated in this meeting in Princeton in June 2001.

Next slide, please.

[Slide.]

Of importance, we defined female androgen insufficiency. It's discussed and defined at great length.

Next slide, please.

[Slide.]

And we identified four important etiological sub-types, the most important of which, of course is the ovarian sub-type, including oophorectomy or effects of radiation.

I recommend this document because it provides very clear guidelines for diagnosis and classification of androgen insufficiency in women. And I hope that this document and other similar guidelines will be used in further developing this product if it's approved.

Thank you.

DR. GIUDICE: Thank you.

The next presenter is Amy Allina.

MS. ALLINA: Thank you. I'm here from the National Women's Health Network, which is a nonprofit organization that works to improve the health of all women by influencing health policy and supporting consumer decision-making. We accept no financial support from pharmaceutical companies or medical device manufacturers.

I'm going to talk primarily about my concerns about the limitations of the data. But

putting those limitations aside for a minute, I do want to acknowledge that it appears Intrinsa offers some benefit to the women in whom it's been studied. And the need in that group is real, so the chance to provide real help to women with the problem of low sex desire is hard to pass up.

As women's health advocates, however, we can't consider this product in a vacuum, and neither can the FDA. The world changed when the Women's Health Initiative revealed the long-term negative health effects of hormone therapy. And a six-month study of a testosterone patch that would be the first drug of its kind may have seemed adequate before, but it's not today.

Women who might stand to get a benefit from the testosterone patch also need to know about its long-term effects on their healht. In the wake of the WHI, it's appropriate and necessary to exercise special caution about long-term hormone use without long-term safety data.

The patch hasn't been studied for an adequate period of time to find out whether it

might increase risk of breast cancer. Some early indication might have come from a mammographic study but, as FDA noted in its medical review, there are several limitations that make it difficult to determine what effect the testosterone patch might be having on breast tissue.

The short-term that P&G has collected so far are also not able to provide reassurance about the effect of their product and risk of heart disease. The events occurring in the extension phase, which FDA noted, could reflect cardiovascular events are potentially important. Although there is no placebo comparison for the extension phase, the average age of women in the combined trials was 49. So these problems can't simply be dismissed as expected background.

The fact that lipid profiles were similar in the testosterone and placebo groups isn't adequate reassurance, since lipid levels failed to predict the the cardiovascular problems that were eventually found to be associated with hormone therapy in the WHI.

In addition to these long-term safety concerns, I want to urge FDA and all of you to balance the benefit that the testosterone patch might offer to a small group of women, with the health risks it may pose to many more.

It would be naive and irresponsible, I think, to pretend that this drug will only be promoted anda prescribed to women who are exactly like those in the trials.

A cursory scan of health websites and books that deal with sexual health issues shows that the recommendation of testosterone for treatment of women's sex problems is not directed solely to those women. It includes advice to younger women, including women in their reproductive years--which raises a whole new set of questions, for example, about the effect of testosterone on future fertility.

Even the company's proposed patient information leaflet blurs the line somewhat, defining Intrinsa

[Time expired. Microphone turned off.]

DR. GIUDICE: Thank you.

The next presenter is Neil Goodman.

DR. GOODMAN: My name is Dr. Neil Goodman. I'm speaking today representing the American Association of Clinical Endocrinologists, where I serve as Chairman for Reproductive Endocrinology.

The American Association of Clinical Endocrinologists is a professional medical organization with over 5,000 members throughout the United States and 70 foreign countries. ACE is devoted to the enhancement of the practice of clinical endocrinology, and the betterment of care for patients with endocrine diseases.

ACE supports the approval of the new drug application for the transdermal testosterone system from Procter & Gamble for the treatment of hypoactive sexual desire disorder in surgically menopausal women receiving concomitant estrogen therapy.

As you've heard, menopausal women frequently experience low sexual desire, which can cause substantial distress and negatively affect

quality of life. Representing about a third of post-menopausal women, surgically menopausal women, in particular, experience a greater degree of sexual dysfunction than any other group of menopausal women.

For more than 20 years scientific research has supported the use of testosterone for the treatment of female sexual dysfunction in surgically menopausal women. However most studies have been limited in the number of participants and the duration of treatment. In addition, there has not been a form of testosterone--which should be emphasized here--that gives women a simple and patient-friendly means of delivering physiologic levels of testosterone. The testosterone transdermal system is the first such testosterone product that has proven to be both efficacious and safe for the treatment of the hypoactive sexual desire disorder through randomized controlled trials. These are statistically significant, based on the information provided to the FDA.

It is the opinion of ACE, in reviewing the

study submitted to FDA by Procter & Gamble, that the transdermal testosterone system can achieve imporved sexual functioning at physiologic levels of testosterone, with a minimal incidence of adverse effects. This opinion is based, in part, on the extremely comprehensive and well-validated instruments for the measurement of female sexual dysfunction that's been developed by Procter & Gamble. These instruments, which include the Profile of Female Sexual Functioning, the Sexual Activity Log, and the Personal Distress Scale, are mandatory for proving efficacy of testosterone therapy. And I believe that these instruments have proven their effectiveness, and have been validated in the studies you've seen today.

The statistical analysis is highly significant, taking into account the number of women studied and the duration of treatment. Based on these studies, combined treatment with estrogen and transdermal testosterone has proven to induce increased motivational aspects of sexual behavior, not just frequency but, in fact, the desire and the

impact of orgasm in sexual intercourse.

ACE believes that the scientific data provided to the FDA is sufficient to prove efficacy and safety of the transdermal system, and should be approved without further studies.

Thank you.

DR. GIUDICE: Thank you.

The next presenter is Doug Ronsheim.

REV. RONSHEIM: Thank you very much for giving me the opportunity to speak.

I am the executive director of the American Association of Pastoral Counselors. It is a national counseling organization of licensed and credentialed professionals providing clinical services to individuals, families and couples.

The membership also attends to spiritual and faith issues which clients might wish to address in the context of care.

Professionally, I'm a licensed marriage and family therapist, a Fellow in the American Association of Pastoral Counselors, a clinical member and approved supervisor in the American

Association of Marriage and Family Therapy, also a Presbyterian minister, and have had a previous faculty appointment at the University of Pittsburgh Medical School Department of Psychiatry.

I initially became aware and interested in the topic of hypoactive sexual desire disorder as it was presented in a variety of counseling sessions with couples. Decreased sexual desire usually was not the presenting problem, but often emerged during the sexual history that sexual incompatibility post-surgery was a stressor--and for good, understandable reasons, and not due to any long psychiatric history.

The stress was due and exacerbated, may time, because the couples' previous sexual relationship had been quite satisfactory. In addition, awareness related to this has emerged in this past year in conversations with Dr. Larry Nelson, who does research at NIH at the other end of the reproductive spectrum, with premature ovarian failure, where women often, at an early age, for inexplicable reasons, lose the functional

capacity of their ovaries.

HSDD has intra- as well as inter-personal ramifications which can be significant. Dr. Nelson's research has shown that the loss of one's capacity to give birth to children, in addition to decreased sexual desire, is a double loss for them. A high preponderance of these patients exhibit varying degrees of depression and anxiety.

What is common here is a theme of loss. Interpersonally, decreased sexual desire is bound to affect a marital relationship, even though both spouses understand that this is caused by a medical or physiological reason, it can be experienced personally, and can be a factor for increased marital stress.

Having a resource for the treatment of HSDD can be a significant benefit and assist specifically in the improvement of a woman's sexual response and the general improvement of one's marital relationship which could again embrace a natural, more responsive sexual relationship.

The importance of addressing HSDD is not

only to curtail an already difficult and frustrating malady, but preventing the potential of the further spiraling down of intra- and inter-personal functioning, and decreasing the chances of the co-occurring development of the symptoms of depression and anxiety.

Thank you.

DR. GIUDICE: Thank you.

And the final presenter is Kim Wallen.

DR. WALLEN: Hi. I'm Kim Wallen from Emory University, and the Yerkes National Primate Research Center. I have no financial interests in any of the drug companies involved in these studies.

I do have an interest in female sexual desire, and my primary research interest is in how hormones affect female sexual desire in non-human primates. And there, I think, are some parallels to humans.

As a researcher who's studied this for over 25 years, i was not surprised by the minimal effects that Intrinsa produced in women. These are

not striking effects, and part of the reason, I think, is because this is an example of a drug that is prematurely coming to closure on something where we don't understand the basic science.

Having looked at the literature in humans on androgen insufficiency, I think it is quite unconvincing that we understand what is the hormonal basis of female sexual desire.

My concern of approval of this drug--besides the potential health risks of this drug--is that it will prematurely close the investigation of understanding how female sexual desire is influenced by hormones. There certainly are many factors that affect female sexual desire, but hormones are one of them, and we need to discover what the basic mechanism is. And I think it is quite clear from the data that Procter & Gamble submitted for this application that they don't know what the mechanism is. And I think from the other published literature, it's clear we don't know what the mechanism is.

So I would urge the committee to not

approve this because I think it is a premature drug that simply does not solve what is a very important and critical problem that we need to understand. And it is important to resolve this issue. But this is not the answer.

DR. GIUDICE: Thank you.

I would like to thank all of the presenters for their thoughtful comments.

And Ms. Watkins has a statement to make--please, before we leave for lunch.

MS. WATKINS: I'd like to remind the committee that, in the spirit of Federal Advisory Committee Act, and the Sunshine Amendment, that discussions about today's topic should take place in the forum of this meeting only, and not occur during lunch or in private discussions.

We ask that the press honor this obligations of the committee members as well.

We'll break for lunch now and reconvene at 1:15.

Thank you.

[Off the record.]

DR. GIUDICE: Back on the record.

Would everyone please sit? And would all of the members of the committee please take their places around the tables?

[Pause.]

This afternoon we will first begin with questions from the committee, initially to the sponsor, and then we will have questions to the presenters from the FDA. And then we will address the questions directly that were given to us by the FDA, and give them our recommendations.

DR. GIUDICE: So I'd like to open this up now to members of the committee. And--yes, and for those members who came in a little late, if you wouldn't mind introducing yourselves. This is not to point the finger to show that you were late--

[Laughter.]

--but just to familiarize everyone with who you are.

Dr. Emerson.

DR. EMERSON: I'm Scott Emerson. I'm a biostatistician from the University of Washington

in Seattle.

DR. GIUDICE: Dr. Stanford.

DR. STANFORD: Joe Stanford, family physician from the University of Utah, Salt Lake City.

DR. GIUDICE: Dr. Dorgan.

DR. DORGAN: I'm Joanne Dorgan. I'm an epidemiologist at Fox Chase Cancer Center in Philadelphia.

DR. GIUDICE: Thank you. And Dr. Merritt did arrive, but she's not in the room right this minute.

Questions from the Committee to Sponsor and FDA

DR. GIUDICE: So, I would now like to open the committee questions, and if you would just raise your hand and--Dr. Emerson? Please.

DR. EMERSON: I guess--I don't know how you want to interleave these, or if you want subject matter questions, or whatever--but one of the first questions I have is for Dr. Braunstein, who presented reference ranges for the testosterone levels in normal women.

Could you tell me what those reference ranges represent? It was like around slide 83 of your presentation.

DR. BRAUNSTEIN: Sure. 161 women in the reproductive age range, having normal menstrual cycles, not receiving any hormones at all, gave multiple samples across the menstrual cycle. So they weren't weighted towards mid-cycle time, or luteal phase, or follicular phase. So they were across the menstrual cycle.

Each individual's--the results from each of those samples for an individual was summed, and then the data was averaged. And these lines represent the lower 2-1/2 percentile and the upper 97-1/2 percentile.

DR. EMERSON: Okay. Then I just want to bring the committee's attention--slide 84, for example--while those reference ranges are for the central 95 percent of the data, those whiskers are the central 80 percent of the data. And we do have, in our materials, tables of how high the maxima actually go.

But the concept of what is being presented here is not at all comparable to the reference range, in terms of--that the central 95 percent would be a much, much higher range. In fact some of those measurements go up to 100 or so.

DR. GIUDICE: Dr. Nissen. And then Dr. Montgomery-Rice.

DR. NISSEN: Although I'm a cardiologist and here, I think, primarily to look at the cardiovascular issues, I did want to ask a couple of questions about efficacy.

The main one I want to understand is: you've gone to a lot of trouble to validate tools for assessing this. But what I didn't see anywhere in here--and I'd be interested in whether you can provide us with any information--on what the effect is of non-hormonal interventions; that is, if you take women with this disorder, and you give them counseling, you give them other kinds of supportive therapies that don't involve giving a systemic hormone, how much improvement, on the same scale, do you get?

You know, we saw about a 5 percent increase, for example, on one of your scales. Well, I'd like to know what that is for non-hormonal interventions. And if anybody can answer that I think it would be very helpful to me to put this efficacy into the context of the safety issues.

DR. MEYER: Although we did not ever test our scales in any other type of interventional therapy, I think Dr. Jan Shifren can give us some additional perspective on the efficacy of other types of interventions.

And one thing I did want to mention--as Dr. Shifren will reiterate--is the Intrinsa patch is not for everyone. As she has already told us, there are other types of therapies that are appropriate and have worked for women prior to androgen therapy.

DR. SHIFREN: I am not a sex therapist. I'm a reproductive endocrinologist. And certainly, for women with non-physiologic causes of HSDD, other interventions, such as counseling, sex

therapy, education, and lifestyle changes can be very effective.

What's important to realize is that the women in our trial--and, again, it was a select group of women. These are the women we would like to see the patch used in--all had healthy sexual functioning before surgical menopause, and reported significant decreases in desire and activity associated with distress, following surgical menopause.

To be entered in the study these women couldn't have depression or relationship conflict, or all of the other things that the other non-pharmacologic interventions are so effective at treating.

DR. NISSEN: I don't think you answered my question, though.

My question is: what do we know about whether those therapies are effective, and what is the magnitude of their efficacy? You have a drug therapy here, and there are other therapies out there. And so I need more information to

understand how large is this efficacy in relation to what can be offered women via conventional, non-drug therapies.

DR. SHIFREN: I think it really depends on the cause of the sexual dysfunction. There are studies that make it clear that counseling and sex therapy are very effective therapies, and they should be used widely. But when you select a group of women for whom the major issue is, let's say, surgical menopause, those are less effective.

The other thing I did want to point out is that our placebo-treated women--it's hard to say that was a placebo. Wearing a non-testosterone-containing patch is a very active intervention. And in some ways, the response in the placebo-treated women may almost address your question. These women were receiving active counseling by the physicians and the nurses that they saw regularly at the study site. They were wearing a patch, which was a clear reminder to both the patient and her partner that she was concerned about her sexual activity, that it distressed her,

and that she was committed to making it better.

So that just being in the non-testosterone treatment arm was an active intervention.

DR. GIUDICE: Dr. Montgomery-Rice.

DR. MONTGOMERY-RICE: I want to go back to slide 83-84, where Dr. Braunstein compared it to some data that Dr. Soule presented for the FDA. Because I'm confused--and maybe, Scott, you can help me interpret this.

When I look at slide 84, and it talks about his median free testosterone level, and we are still talking about a level of 7 picagrams, it doesn't appear that there are that many subjects. But you're saying that that is 80 percent of the subjects had a level that was greater than that.

So would that correspondent, then to what Dr. Soule is saying, where she points to data in slide 8 of her presentation, that more than 35 percent of the people were beyond this median value of 8.6

DR. EMERSON: So, if I could clarify what I was trying to get across--in the "normals" that

line that is drawn at 7, only 2-1/2 percent of normals are above that line. In the larger study--you know, we have 500 subjects in this--they have 10 percent of the subjects above the top whisker there.

And so we're seeing that there's something--and what Dr. Soule presented would be representative numbers, suggesting that between the dashed line and the top whisker might be 10 to 15 percent of the patients. And then another 10 percent are above that top whisker.

But the point I was trying to make is that this graph is actually quite misleading, in trying to give the impressing that most of the measurements--that the difference between the normal range and what they observed isn't that great, when they're using two different measures there.

DR. BRAUNSTEIN: In actuality, at any time, the patients on testosterone, about 15 to 20 percent or so were above the upper limit of the free testosterone level here. Again, this is a

reference range: young, pre-menopause women--young women. And we're using that just to show you that the majority of women fall within that range. Some will go above that range--but, certainly, not so terribly above the range that one would get serious concerns.

For instance, when Dr. Dobs was talking about the therapeutic doses that are used in women who are transgendered to males, they receive very large doses, and the levels are quite a bit higher. If you look at female athletes that are abusing androgens, the levels are substantially higher.

DR. EMERSON: Well, but the scale--if you went up to that 97-1/2 percentile on that--I can't say exactly what it is, but your maximum, in the 24 week is closer to 100. Okay. So the scale of that.

Now, again, maybe the majority of patients aren't up there, but some patients have very, very high levels of free--

DR. BRAUNSTEIN: Yes, there were a total of 11 patients that had a level of 21 picagrams per

ml. And of those 11 patients, there were, I believe, 7 who had androgenic adverse events, primarily hirsutism. And there were no other significant adverse events--no liver function abnormalities, kidney function abnormalities, etcetera. Again, they were androgenic types of adverse events--the types of things you would expect with very high free androgen levels.

And if we look at the highest decile--the highest 10 percent--really, there's no statistical difference if you look at the women who were in the highest decile versus those who were on the placebo.

DR. EMERSON: Where you sample size is already down to--

DR. BRAUNSTEIN: The sample size, the upper decile is small.

DR. EMERSON: And the other thing that I would also like to point out on this is that you had significant dropout in your patient population. 20 percent of your patients dropped out during the initial six months. And then at each stage, as you

went from the 6 months to 12 months, 12 months to 18 months, more patients dropped out. And so actually the highest level that you observed in free testosterone was in an intermediate measurement. And we can imagine that perhaps that patient dropped out because of that high level--perhaps not. We don't have that information. But that's something to keep in mind.

DR. BRAUNSTEIN: Well, in actuality, there was no relationship between when the highest level was found--because it could have been found at any time the bloods were sampled during the trial--versus when the androgenic adverse event, for instance--if one appeared--did appear.

Could I have that last slide, please?

Just to show the point in the upper decile--this is 6-99--you can see that in the comparison to the placebo group, the patients in the upper decile of free testosterone, 10.3 percent had acne, versus 7 percent in the placebo group; 3.5 alopecia, versus 2.7; 5.2 facial hair versus 5; no voice deepening versus 1.7.

So, again, the reference range--and your point is very, very well taken--but the reference range is just to provide you sort of a baseline sense of security. This is not being--you know, we aren't talking about this as a replacement therapy. This is a drug therapy--but to show you the relative levels of androgens achieved with Intrinsa versus the normal physiologic range in reproductive women was the purpose for establishing this reference range.

DR. EMERSON: Do you know whether the patient who had a measurement at 107.7 at 24 weeks is represented in the 52-week population where the maximum was 63?

DR. BRAUNSTEIN: I don't know that.

DR. EMERSON: Thank you.

DR. BRAUNSTEIN: But we can find out and come back to you on that.

DR. GIUDICE: In order: Dr. Lipshultz, Dr. Dr. Dickey, Dr. Judice, Dr. Stanford, Dr. Hager.

And we will go around the table.

[Laughter.]

So--Dr. Lipshultz.

DR. LIPSHULTZ: Yes, I have a question.

We see, repeatedly, a comparison of the TTS-treated to the placebo-treated. But I'm interested in Dr. Davis' slide, in which he showed the frequency of satisfactory sexual encounters over a four-week period, comparing the placebo to the treated to the normal. And my question is: if these people had a normal sexual relationship prior to the oophorectomy, and following oophorectomy they had androgen replacement therapy, why are they not going back to their pre- to their normal--quote "normal"--state. If the answer is androgen replacement, then why aren't they back to normal, rather than back to one increased encounter in a month?

DR. MEYER: Well, if I could have slide 252, please--although I don't know what their normal level may be.

But what this shows you is "total satisfying activity," "desire" and "distress." Here's the baseline level of the women in our

study--in the surgical menopause study. Here's the normal level that we got from our instrument validation studies in total satisfying activity in a four-week period.

The self-identified responders from our clinical relevance study got about 50 percent of the way back to the normal women--these are different women--but the normal women in the validation.

DR. LIPSHULTZ: Exactly, and my question is: what is your hypothesis, if this is due to something related to the oophorectomy, and you're replacing what you think is the target hormone, why wouldn't they go back to the validation level?

DR. MEYER: Because these are different women. Although we did not ask them what their normal level was. They could be back at their normal level.

The women who are self-identified responders in this study had a mean satisfying--an increase in satisfying sexual activity of 4.4 activities per month. So that's one per week.

DR. LIPSHULTZ: Right. But I think--

DR. MEYER: So that would get them back to seven per month, which might be their normal, although that is lower than the women in the validation study.

DR. LIPSHULTZ: But isn't it important for you to have that data? I mean, as to what you consider normal sexual activity for that group of women? Otherwise, as was pointed out by several people from the audience, that, you know, the androgen may not totally explain what's going on here, or else you would expect to see a normalization.

DR. MEYER: And Dr. Shifren can address this. But I think another important thing to look at is the distress. So, again, it's not just the activity, but--

DR. LIPSHULTZ: I'm not disagreeing that the patients are better. My question is why aren't they back to normal if the answer is androgens. They should say, "I feel exactly the way I did before because you've replaced my androgens."

DR. SHIFREN: I may be able to help a little bit here. I was not involved in the U.S. validation study. But I can tell you, from my typical healthy sexually functioning menopausal women, 12 events in four weeks is actually quite a lot. That's three times a week, and that's actually more than what we consider the typical average for even pre-menopausal Americans.

So I can't really speak to the validation study and normalization. But I think it's very important to realize: this isn't blood pressure. And there actually is no "normal." And it's actually normative that as couples age, with both duration of the relationship and aging, that frequency declines, but satisfaction can remain very high.

So there's not really a good correlation, for most couples, between frequency and satisfaction, and distress. The very first thing I say to almost all of my patients when they come in with sexual complaints is: "Let me start by saying there is no 'normal' frequency or set of behaviors.

And that the typical American experience has very little to do with Sex in the City. And if you are comfortable in your relationship, and it's working for you and your partner, that's all that matters. And if it means that you're doing non-intercourse events because your husband has erectile dysfunction, but it's a loving, close and intimate relationship and you have no concerns, there's nothing to treat."

So a lot of what I do is really validating for women that there is no "normal" for sexual function. The most important thing is that it's working for the woman, and that there's no associated distress.

DR. GIUDICE: Dr. Dickey.

DR. DICKEY: I'm going to change gears a little bit. I have a question for Dr. Steinbuch. I think that's how you pronounce it.

I'd like a little more information about the proposed long-term safety plan. It would appear that you're going to collect your

information from claims data. And I'm a little concerned about privacy issues, and a little concerned about whether claims data are actually going to give you the kinds of information that we've heard about through the morning, in terms of risk factors.

DR. STEINBUCH: Yes, with regard to privacy issues, the Ingenix database--as I described earlier--is comprised of all of these claims of patients throughout the United Healthcare System. And there really is no privacy issue there in regards to the fact that every report that we get is de-identified. So there's no--we can't identify any individual per se. At least our company.

Ingenix, when they go after the medical records for abstraction, it will be their company employees who would be actually going out and getting the information. So there really shouldn't be an issue there.

And, as I said, we're going well beyond claims, because we're going to be contracting with them to actually go after medical charts for review

of all relevant events of interest.

DR. DICKEY: And there's no privacy issue there?

DR. GIUDICE: This is an issue, I think, that needs to be further discussed--the whole issue of HIPPA. And I think what Dr. Dickey is getting at is can you explain to us exactly what the process is, so that patient privacy is not violated.

DR. STEINBUCH: I think it would be best if Dr. Alec Walker, who's here in the audience, who represents--he's a senior vice president of Ingenix. Perhaps he could address this issue with regard to how it works in the United Healthcare System.

Dr. Walker?

DR. WALKER: We have a number of FDA-mandated post-marketing safety studies--Alexander Walker, Senior Vice President, Ingenix.

We have, I believe, five of these studies going on now. They are HIPPA compliant. They are

done under IRB approval.

The data are manipulated in a de-identified fashion, to the extent that they can be. Then, at the last minute, if you have a potential event that you want to look at from the claims data, then it's de-identified to the extent necessary to go to the medical record, and it comes back.

DR. DICKEY: So, patients will give permission to participate in the study?

DR. WALKER: No. Under HIPPA, with an IRB approval--or, indeed, for an FDA-mandated study--you don't need individual informed consent. You do need the IRB or privacy board to examine the protocol and procedures to verify that there's adequate confidentiality in force and maintained.

DR. DICKEY: Thank you.

DR. GIUDICE: I have two questions. One has to do with the data and the analysis. And perhaps Dr. Meyer can answer this.

Have any of the data been analyzed with regard to BMI, because it appears that there's one

dose, and women--a large range of BMI. So can you give us any insight into that?

And the second is that there have been several comments about potential risks g with regard to breast cancer and cardiovascular disease. And in our briefing documents I did not see any pre-clinical data. And I'm wondering if you could share with us any insight into that?

DR. MEYER: Certainly. With respect to BMI--and we did break out these data by sub-groups, and I think they are in your briefing book--but in women with a BMI less than 25, between 25 and 30, and greater than 30, the data were essentially the same--the response on sexual desire. And for satisfying sexual activity, the women in the highest BMI group--that greater than 30--the response was slightly less--the median response was slightly less than those in the lower BMI groups.

DR. GIUDICE: And what about free testosterone in those groups?

DR. MEYER: Let's see, I think Dr. Braunstein--I don't know that we broke--we can

check. We'll look and see if we broke out free T by BMI.

DR. GIUDICE: Okay.

DR. MEYER: And with respect to non-clinical data in breast cancer, Dr. Mike Winrow is our non-clinical toxicology specialist, and has done an extensive literature review of all that's known on the non-clinical data of testosterone. And although-- there are lots of in vivo and in vitro studies that he can address that have looked at that.

DR. WINROW: Thank you. If you look at the labeling on current testosterone products, they're all labeled as potential carcinogens. That's based on data generated by the International Association for Research on Cancer, based on rodent studies with very high doses, many of them administered to neonates, over a period of years.

There's no doubt that at very high doses, in rodents, that can occur.

The more interesting data--and this is fairly recent data, and it follows from the

discussion that came this morning on the work being done at NIH--if you're looking at rodent data you're dealing with intact animals, estrus cycle not menstrual cycle, and all the other complicating factors--and extremely high doses.

What's being done at NIH, and published by Dr. Demitri Kakis, is shown on slide 644--if you could show that, please. And in this study, they've used probably the best model that could be used, which is an ovary-ectomized Rhesus monkey. And what they've done ovary-ectomized Rhesus monkeys, and then supplemented those animals with either estrogen--in the second line down--or with estrogen-progesterone, or estrogen-plus-testosterone.

I realize the numbers are small, but recognize that using Rhesus monkeys is not a trivial event these days. Their intention was to replace these hormones at levels that would mimic the pre-ovary-ectomy levels. So they are within a reasonable range of normal for both non-human primates and primates.

What they were looking at was proliferative response in breast tissue, which they were using as a marker for potential carcinogenicity.

It's a short-term study. But, at the same time, the numbers are quite interesting. They used this KI-67 antibody, which picks up an antigen that only is produced in proliferating cells. And with hormones, continuous cell proliferation is a requirement for the development of cancer. And so you normally see hormonally-induced tumors in tissues that respond in a proliferative way to the particular hormone under consideration. So if you get a lot of testosterone, you'll get prostate cancer--as an example.

And, as you can see here in these female Rhesus monkeys, the controls had KI--that's a percentage of cells that are proliferating--of about 8 percent. If you--following ovary-ectomy, if you then administered estrogen, that number shot up to 30.

So, administering estrogen to

ovary-ectomized monkeys produces a very significant increase in cellular proliferation in breast tissue. If you added progesterone to that--very little difference; not surprising because the progesterone's really there to address endometrial issues. If you added testosterone, however, that level dropped to 16.7, which--while the number is small, statistically it's no different from control. But, of course, as I say, the numbers are small.

So, adding testosterone to ovary-ectomized monkeys, in the presence of estrogen, significantly reduced the level of proliferation produced by estrogen alone, and moved them back towards normal.

The other things that this group have done along the same lines, they ran another study where they administered flutamide to intact Rhesus monkeys for a period of six months. So what they're doing there is block testosterone chemically, but leaving all the other hormones alone.

In that case you get a doubling of

proliferation in breast tissue. You've removed the testosterone, which is no longer offsetting the proliferative response of the estrogen, and so proliferation rate goes up--in the absence of testosterone.

Two other studies that they've run, and looked at other biological endpoints, they've shown that in these testosterone-treated animals, you can get a reduction in the expression of the oncogene MIK, and you can also see a change in the estrogen receptor alpha-beta ratio away from the ratio that's considered of concern for breast cancer.

So in these small studies, using ovary-ectomized Rhesus monkeys, all the data point towards testosterone not having a proliferative effect, or not raising the level of concern for breast cancer. In fact, it's the exact opposite if you look at the numbers.

And it was on the basis of this work that they did the clinical study in the Australian population which was published fairly recently.

So, you've got those two different sets of

data.

DR. GIUDICE: Thank you.

Now, starting over here with Dr. Stanford.

DR. STANFORD: Two questions--the first one, back to the reference range for free testosterone from the 161 pre-menopausal women.

You mentioned hat hey were only women with regular cycles. Was there any other effort to exclude those that may have indicators of metabolic syndrome? My concern is that if you just take 100 women off the street and look at testosterone levels, some of them may have unhealthy levels, because some estimates are that PCOS with hyperandrogenism may be around 10 percent of the population.

So we may not have a healthy range, perhaps. I wondered if any other exclusion criteria were applied to those 161 women. That's my first question.

DR. MEYER: And I would like--Dr. Braunstein can address the exclusion criteria, and then Dr. Ricardo Azziz is with us, and he's an

expert on PCOS and normal androgen levels in women. And I would like him to come up and address what is normal and not a normal androgen level in women.

DR. BRAUNSTEIN: Actually, the inclusion criteria was that they had normal menstrual cycles--ovulatory menstrual cycles. So if a woman with PCOS was in there, it would be one who was having normal ovulatory cycles.

I do think, though, since this issue of PCOS has been raised--and that condition is different from the model of giving back testosterone to oophorectomized women, I think it would be important to have Dr. Azziz address that issue.

DR. AZZIZ: Just as a disclosure, I own no stock and I was not a participant in these clinical trials. I'm simply a consultant as an androgenexist I direct the Center for Androgen Related Disorders at Cedars-Sinai Medical Center, and I'm faculty at UCLA.

There's a number of concerns and questions that the committee has brought up very well, and I

think these need to be addressed. One was the issue of polycystic ovary syndrome as an example of an androgenized patient.

I need to make sure that the committee understands that polycystic ovary syndrome has an underlying insulin resistant syndrome etiology. Over 70 percent of the patients with polycystic ovary syndrome are insulin resistant, and our research, and that of others, indicates that it's a cell-signaling defect that actually causes--a cell-signaling defect in the insulin-signaling pathway that causes PCOS.

So polycystic ovary syndrome is actually not a very good example of a hyperandrogenic effect. And one of the things that I think is important to not bring up is not to mix in the insulin-resistant syndrome or PCOS in this discussion.

In fact, androgens have very little impact on glucose metabolism in and of themselves, which is why they're not the etiology for the insulin-resistance in PCOS.

Secondly is the issue of androgen levels in normal women. It is important for the committee to understand that androgens, as opposed to--say--thyroid are not regulated very closely in a human body. You can quadruple or actually increase the androgen levels 10-fold in humans--and that's males and females--and LH levels, which are the primary responder, do nothing. They change absolutely nothing--which is why, in humans, the normal range of androgens in males can go from 150 nannograms per dL to 1,000 nannograms per dL. And these are all normal males here in the audience, and the same thing for women.

So one of the reasons that the levels of "normal" which were presented as a normal example are so wide. And absolutely correct--Dr. Emerson--that, in fact there are a number of patients that are above this--quote "normal limit" is that, in fact, physiologic effects of androgens do not correlate directly to the levels; and, in fact, there's a wide variability in androgen levels in the normal population.

Evolutionarily, there has been no pressure to select people with high or low androgens, otherwise women, of course, would be extinct, and so on and so forth.

[Laughter.]

And it is not the case.

So it's important for the committee to understand that this is not regulated like thyroid. Androgens go up, LH goes down. That is not the case in humans.

The last one is the issue of a "normal" population. A number of issues have been brought up related to what is a "normal sexual function," and why--and Dr. Lipshultz brought up very clearly--why isn't it that these people didn't become "normal."

I should point out that part of what we do, of course, is look at normal sexual function. And part of our center looks at androgen deficiency. 49-year-old women--couples--who are in their 50s do not, on average, have 12 intercourse encounters a month. The vast majority of surveys

of sexual function in the United States today put the number of intercourse activities--or acts--in normal couples in their 50s at between 1-1/2 and 2 encounters per week, which is somewhere between seven and eight per month.

In the validation study you had to recruit people who were willing to talk about sex. And that may have biases the--quote--"normalicy." So it's not actually proper to actually compare the small population of people used in the validation study in this study to the response. We need to look at the response of our patients here to what is normally assumed to be normal in the U.S. population. And in 50-year-olds, that's somewhere between seven and eight encounters a month.

I don't know if that answers some of the questions.

DR. STANFORD: Thank you.

My second question was for Dr. Steinbuch about--if I gathered correctly, you're estimating that you'd capture about 5,500 women would be prescribed Intrinsa in the Intrinsa in the

long-term safety monitoring plan.

What are you projecting that they would be prescribed Intrinsa for? Would these all be surgically menopausal, or would you be mixing surgically menopausal and naturally menopausal women? And how would you address that issue?

That's one of a number of issues, I think, about this safety monitoring which are really key to understand--whether it would be adequate.

DR. STEINBUCH: Yes, the 5,500 estimated number of Intrinsa users per year is a combination of both surgical and natural menopause women. And that's actually one of the advantages of the observational setting, in that all women who would be prescribed this medication would be included in the analysis, and there would be no group that would be precluded from inclusion in the sort of full statistical analysis at the end of each time period.

DR. STANFORD: Okay. So maybe I could ask just one other question.

Would chart reviews be done on all of

those women? What's the trigger for a chart review? You mentioned having the company from United Healthcare go back--Ingenix, I think, go back and do the chart reviews.

What would be the trigger for that?

DR. STEINBUCH: As I indicated, there would be a three-to-one match, and the chart review would be triggered by any one of the events of interest that will be ultimately determined by the panel would be involved, and the independent safety review board. And then once that final decision has been made, any of those events would trigger a medical chart review--throughout the system.

DR. GIUDICE: So just to follow up with regard to the patient population, it will be surgical menopause, natural menopause, with and without a uterus? And therefore the treatment will be Intrinsa alone? Or also estrogen and also progestin? I mean, what's the plan?

DR. STEINBUCH: Yes--well, the plan is to, as I said, bring all women who receive Intrinsa scrips--whoever they may be. In terms of the

matching criteria, there would be some very careful consideration to do appropriate matching and for perhaps stratifying by if they're estrogen only, or estrogen-plus-progestin, that might be a reasonable thing to match on, for example.

DR. GIUDICE: Dr. Hager, did you have a question? And then Dr. Macones, and then Dr. Rice, and then Dr. Lewis.

DR. HAGER: I have three fairly brief questions.

Regarding the anchoring technique--and I'm not an epidemiologist, and don't claim to understand that well--but as I understand it, you evaluated data and you had a fairly significant dropout that increased as you progressed through the study. You used the anchoring technique, and you used the last available interview among those who dropped out to go back and recapture that information. Is that correct?

And in so doing, do you have information from those individuals before you recaptured that information? Do you have data up to that drop-out

point? Because you had such large drop-outs--without extending that to 24 weeks? If a patient dropped out--a subject dropped out at 12 weeks, you captured that information and extended it out to 24 weeks--is that correct?

DR. MEYER: That's correct. We used the last observation carried forward.

DR. HAGER: Okay--so do you have the data without that extension?

DR. MEYER: Yes, we do. And when we looked at both ways, the very conservative LOCF method to get the proportion of responders. And Dr. DeRogatis showed you--what?--that was about 51, 31 percent.

When we take out the people who dropped out and do just the protocol analysis, we get the same--

DR. HAGER: Okay.

DR. MEYER: --effect.

DR. HAGER: Okay. And can you tell me why the African-American and Hispanic population was under represented in this study?

DR. MEYER: Yes--it's notoriously difficult to try and recruit a sufficient number of minorities into all clinical studies that are truly representative of the patient population. And we knew that going into this. And we were aware of the data in African-American women on hysterectomy. So we took extra care to try and recruit as many minorities as possible. For example, we did a patient recruitment in the media, and we would target media that targeted various minority populations. We talked to minority investigators. We took as many steps as we could think of to recruit minority populations. And 6 percent is not representative of the U.S. population--although better than a lot of clinical trials I've been involved with.

But, again, we chose sites with access to large numbers of African-Americans and Hispanic people. We had all our instruments translated into U.S. Spanish. We ran ads in the media--again--that targeted minorities.

And so one of the things that we're doing

at P&G is we have an ongoing effort to continue to try and increase our ability to recruit minorities into our clinical studies.

DR. HAGER: So are you concerned about the long-term follow-up in those sub-populations?

DR. MEYER: Well, again, with the large observational study, if we move forward with that, these minorities, if given a prescription, will be able to be followed, and in larger numbers.

And the other thing that we have done is also we have discussed our plans with a variety of, for example, African-American clinical researchers--OB-GYNs--to try and understand our data in the context of these patient populations.

DR. GIUDICE: Dr. Macones?

DR. MACONES: A question for Dr. Steinbuch, please.

I actually have two questions. First, to follow up on Dr. Hager's point--the UHC data that you're going to be using, can you tell us about the ethnic background of patients that are included in that data set? Is it a very generalizable group?

DR. STEINBUCH: The Ingenix database?

DR. MACONES: Yes, I'm sorry--from your agency.

DR. STEINBUCH: Yes, it is, actually. We've looked at some comparisons to the U.S. Census. And demographically, they're reasonably comparable.

DR. MACONES: My second question was about your sample size estimate for your post-marketing study, which you had on your slide number 120.

And my concern is that just at first blush, I thought that a study of 5,500 patients was going to be pretty small to look at some of the events that you're going to be interested in.

And it made me wonder about some of your assumptions. And the one that struck me the most was your event-rate per year of .15 percent. And I believe you said that that was based on WHI data for cardiovascular events in women who were 50 to 59. Is that right?

DR. STEINBUCH: That's correct.

DR. MACONES: That's a curious choice,

because I think in your clinical trials about half of the patients were less than 50.

So I wonder why you chose an estimate on the older population, rather than being more conservative, choosing perhaps a lower event rate, having a bigger study, with more power and more precision in the older patients.

I mean, I look at this now and I could predict it's going to be a negative, under-powered study. And that's a concern.

DR. STEINBUCH: Actually, the event rate that we used was the lowest that was possible within the WHI. As the FDA has indicated, they've been using the WHI as sort of an anchor for this. And we thought that was the best that we could do.

If you could please put up slide 691?

[Slide.]

This slide shows, broken out in the WHI, broken out by decades here, and when we look at--and this is for the estrogen-only arm--you could see that this is about where the line is for hazard ratio of 1. In the 50 to 59, most

of--either at or below 1 for this younger group.

Now, with regard to what the FDA has shown and shared is I believe they've been using the E+P for the full 50 to 79 year age group. And so, since our mean age was about 50, this was the closest that we could get using WHI, that would actually be the closest estimate.

Does that make sense?

DR. MACONES: It does, but I disagree with it. Again

DR. STEINBUCH: Okay.

DR. MACONES: I mean, the issue is that you're going to have no power to look at events in younger women, and that's likely to be half of the population.

I mean, again, based on the enrollment in your clinical trials, which the mean age was 50, which roughly means that about half of the people were less than that. And you're just not going to have a lot of power to look at those patients. And if you had a bigger study--again, power to look at events in younger patients--you're going to have

lots of power to look at event rates in the older population.

DR. LOCKWOOD: But to be fair--I mean, we don't want to get into a debate about WHI--but if you look at the data--and the argument's been made that, in fact, it may be protective in that younger age group. Look at the odds ratios--or the hazard ratios that are presented there. They're not quite significant, but there's certainly a strong, strong tend toward a protective effect between 50 and 59.

So I think, to be honest, that the group that you're thinking may have to be much larger to detect a potential adverse event in fact might be the opposite. It might be protective and it might be additively protective.

DR. MACONES: I think the point is "might be." And we don't know the "might be."

And I think for charged issues like this, I think we're better off being conservative and designing a bigger study rather than taking a chance and designing a smaller study that might miss an important effect.

But I appreciate the point that you make.

DR. GIUDICE: Dr. Dorgan.

DR. DORGAN: First of all, on this question--could you tell us what the power to detect increased breast cancer among these women would be?

DR. STEINBUCH: Yes.

Could you please put up slide 507?

[Slide.]

And as was mentioned earlier with regard to latency, I would direct your attention--the event rate here was again using WHI, 50 to 59 year age; .3 percent per year. All the other assumptions were the same as before, with regard to disenrollment, etcetera--discontinuation. And getting down to the four to five year, which I think is the most reasonable place to be looking here, we have an 84 percent power at four years to detect a relative risk of 1.4 with regard to breast cancer.

DR. DORGAN: Okay. I have another question that's based on the information in the briefing

book. In the briefing book it states that "--epidemiologic studies examining the relationship between endogenous testosterone and breast cancer risk have yielded equivocal results." And the reference for this is the Endogenous Hormones and Breast Cancer Collaborative Group paper in 2002.

Now, as a co-author on that I was kind of surprised by this interpretation of the findings.

I brought a copy of the manuscript with me. Testosterone was very strongly, actually, related to breast cancer risk in these women. Women in the highest quintile of testosterone levels--and this is within the normal range for post-menopausal women. So it's much lower than what we're talking about here.

Women in the highest quintile were at two-fold--let's see exactly--2.2-fold increased risk of developing breast cancer. This was highly significant. And the trend was also highly significant. With increasing levels of testosterone, risk increased significantly, going from the first quintile is the reference of 1, to

the second quintile of 1.3, to the third quintile of 1.6--up to as high as 2.2 in the fifth quintile.

Again, I want to say that these levels are endogenous levels in post-menopausal women. They are much lower than the levels that we're looking at here.

When we're talking about the concern for the women whose levels are above the 90th percentile--based on that graph you keep looking at, bioavailable testosterone. When we're focusing only on the women whose levels are above the 90th percentile for pre-menopausal women, I think we're missing the point.

The women who are even at the median, they had levels, based on some of the data that you provide us, that were three, four and sometimes five-fold higher than your control placebo group. This could translate into an increased risk of breast cancer in this group as a whole, of maybe 70 percent going up to--it possibly could even go up to a doubling of risk.

Could you comment on that?

DR. MEYER: Dr. Robert Reid, Chairman of the OB/GYN department at Kingston will comment on this.

DR. LOCKWOOD: On that, could I ask you a question?

DR. DORGAN: Sure.

DR. LOCKWOOD: Did your study adjust for potential confounding from BMI?

DR. DORGAN: We didn't adjust for BMI, but we did actually adjust for estradiol, because of concerns that the testosterone--this is endogenous levels, we were concerned that there might be--the testosterone levels might be just elevated secondary to estradiol, and all the effect might really be due to estradiol.

But when we did that--

[Pause.]

--sorry, I have to flip through here--okay--and this is looking at a doubling, as opposed to looking at quintiles.

So, if testosterone was looked at unadjusted for estradiol, a doubling of

testosterone was related to a relative risk of 1.42 for breast cancer. So it's about a 40 percent increased risk of developing breast cancer. It was statistically significant.

Estradiol, on its own--the doubling of estradiol--was related to--had a relative risk of 1.31--or a 31 percent increased risk.

When you include both testosterone and estradiol together, the increased risk associated with the doubling of testosterone was decreased a little to 32 percent; whereas the increased risk associated with a doubling of estradiol was decreased to 18 percent. So it's not being explained solely through estradiol.

DR. LOCKWOOD: I guess the big issue, though, would be if these patients are obese they're likely to have both elevated estradiol and testosterone levels, and to be at higher risk, independent of either, for breast cancer because of the obesity. It increases aromatase activity, potentially, in the breasts themselves.

So, you know, I hear you, but the

potential for confounding is so great that it does call into question those--

DR. DORGAN: I disagree. I think that--I don't know where you're coming--most of the association of obesity, we have shown in subsequent work, we can explain a lot of the association of obesity with breast cancer risk by effects on serum estradiol levels. And since we have adjusted for estradiol in these analyses, I think that it's showing that what appears to be a significant independent effect of serum testosterone with breast cancer in post-menopausal women.

Whether this effect is due to aromatization of the testosterone in the breast, we don't know. But I'm saying that these data surely don't suggest that the results are equivocally--epidemiologic studies that look at associations show a very significant and strong association of serum testosterone levels with breast cancer risk in post-menopausal women.

We don't know if they're causal. You would need a clinical trial to establish that.

DR. GIUDICE: Yes--please let's have a response.

DR. REID: May I enter the foray?

I don't think we have a clear answer to the question you've raised. I mean, the criticism of studies that have looked at a single isolated testosterone value in people who subsequently went on to develop breast cancer have been challenged based on problems with the assay sensitivity in the range for women, because it's at the low end of the assay. The fact that it's a single value, and there may be variations due to a variety of different life events and stresses.

The issue about aromatase activity in the breast--and biopsy studies around breast cancer have shown that there's often very high aromatase activity in the quadrant where the cancer is compared to other quadrants of the breast that don't have a cancer. So local effects may be much more profound than what you see in the circulation.

So it's a finding that merits consideration and concern, but, you know, the other

types of data that we see, for example, in Rhesus monkeys, showing an inhibition of proliferation, is just the opposite. And it's very reassuring in that context.

And I can't comment more than that on that specific issue. I could make some comments about relative risk and some of the other things that affect breast cancer risk if it's of interest, because I've heard a few things presented about--the WHI is constantly being cited here, and we heard a number of explanations for why the observational data did not match the randomized clinical trial data for cardiovascular disease. But the one explanation we didn't hear put forward--we heard about volunteer bias, and health user bias and so on--there's been a lot of discussion in the literature about the fact that women who were involved in the WHI, many of them were several years to many years post-menopausal. And probably the biggest difference between observational and randomized trial in that circumstance that would explain, to a large degree,

the cardiovascular outcomes is, in fact, the difference in age of the populations. There are observational studies from Nurses Health Study was in women who were 50 years of age or younger. And WHI, as you know, two-thirds of them were over 60 in the combined arm. In the estrogen-only arm, 50 percent of them were 70 or older when the study was closed.

So that's a very old population compared to the younger women. I think it's a point that maybe is lost in some of the discussion.

Would you tolerate a couple of slides? To clarify it? Or not--it's up to you.

DR. GIUDICE: Io think we need--we have many other questions, and we need to move on.

DR. REID: Okay.

DR. GIUDICE: So--in the queue--thank you--is Dr. Rice, then Dr. Lewis, and then Dr. Tulman--and others.

DR. MONTGOMERY-RICE: I have a couple of questions.

One of the things I want to make sure I

understand, that in the questionnaire where you ask about the satisfying sexual activity, that "satisfying" was being used as an adjective, meaning that were the women asked, well, did they have a sexual activity? Did they have sexual activity and maybe it wasn't satisfactory? Or did they only have the option to check that they had a satisfying sexual--

DR. MEYER: No, they had the option for both.

DR. MONTGOMERY-RICE: So they did have the option for both.

DR. MEYER: Activity and satisfying activity--

DR. MONTGOMERY-RICE: Okay, so--

DR. MEYER: And we also, in the instrument validation, took great pains to make sure that these women understood what a "satisfying sexual event" was. It's not handholding. And we validated that in the--

DR. MONTGOMERY-RICE: Okay. So, but when women said they had a satisfying sexual experience,

you took the mean--used means for your baseline and for your increases. So this 1.9, or whatever we're seeing, is a mean over all of--so how would an individual have rated that if that one increase in the number of sexual events was satisfying to them? Was that enough for them to rate that they had improvement?

And I ask that question because when I look at Dr. De--ahh-

DR. MEYER: Dr. DeRogatis?

DR. MONTGOMERY-RICE: Right--in his slide number 43, when you asked this question of interest in continuing the treatment, if this was a meaningful experience for them, and that a large percentage of them got 1 point of that increase in activity made a difference, how am I to interpret when I see 70 percent "definitely not," or 60 percent "definitely." Tell me how I am to interpret that, if these people really rated--they had the option to rate whether they had sexual activity, or whether it was satisfying? Why weren't more people interested in continuing?

DR. MEYER: Oh, actually, what this shows on this graph--in the white are the women who reported no meaningful benefit. Now this--again, the data were blinded to everyone when this question was asked of them. So these are the women who were the non-responders. So most of them--if you look at the first "definitely not" or "probably would not," 95 percent of these women would not use this patch.

If you look at the women who reported having a meaningful benefit, using the cut-off that we used, a similar number--about 95 percent--90 to 95 percent of these women have said that they probably or definitely would be interested in continuing treatment.

DR. MONTGOMERY-RICE: And then the people who are in the light blue, who would definitely not, those were mixed--some of those on placebo, and some of those were--or all of these are treatment people?

DR. MEYER: All of these are women who said they had a meaningful benefit. So some of them--

DR. MONTGOMERY-RICE: No, no.

DR. MEYER: --some are placebo and some are treatment.

DR. MONTGOMERY-RICE: Okay. So what percentage of the people who were "definitely not" and "probably not" were the people who received the patch?

DR. MEYER: The definitely and probably would--this is about 51 percent of the women who were on the patch. So it's about 49 percent are going to be in the white bars that had no meaningful benefit.

DR. MONTGOMERY-RICE: So 49 percent of the people who were in this study, who were on the--49 percent of the people using the patch--

DR. MEYER: In the clinical relevance study.

DR. MONTGOMERY-RICE: In the clinical relevance--did not say they wanted to--they probably would not continue treatment.

DR. MEYER: Yes. Well--no, this is placebo also.

DR. MONTGOMERY-RICE: Okay. Well I'm going to ask the question again. I want to make sure we're clear about this.

What percentage of the people in the "definitely not" and "probably not" were people who used the patch?

DR. MEYER: What percent of these--

DR. MONTGOMERY-RICE: Yes.

DR. MEYER: It's about 49 percent.

[Comments off mike.]

DR. RODENBERG: 49 percent of the people on active therapy--I have numbers to address your question, maybe not completely, the way you're asking it. But let me see if this addresses your question.

49 percent of the women on active therapy stated that they would probably not or definitely not use the patch. 64 percent of the people on placebo therapy stated that they would definitely not, or probably not use the patch.

Does that answer your question?

DR. MONTGOMERY-RICE: Yes. Thank you.

DR. GIUDICE: Dr. Lewis?

DR. LEWIS: I have a couple of questions. One has to do with the instrument that you designed. And I think that certainly it helped to make the study population very well-defined--which I think it was well-defined in this case.

But I would like you to address a concern that it will lead to less stringent selection of candidates for this treatment when it reaches the general population; that is, if it's already being touted as a female Viagra in the general press, how many physicians, and how will physicians be educated to select a proper population with hypoactive sexual desire disorder? That's one question.

And the second question really is for our committee consultant. Could you comment on a correlation between testosterone levels and hypoactive sexual--or sexual dysfunction in a menopausal population? I'm really only aware of the Australian study, which showed no correlation between testosterone levels and sexual dysfunction.

And that was like a population-based study in Australian women--maybe a couple thousand women, something like that.

DR. MEYER: Okay, let me first address the educational plans that we have to ensure that patients and physicians understand how to maximize the safe use of the patch.

If I could have slide 707 projected, please?

[Slide.]

We have several plans. We have both a package insert that we have tested with physicians for clarity of understanding; that they understand what this patch is indicated for, and how to use it. And we have a patient information leaflet. Again, it's tested which surgically and naturally menopausal women to ensure that they understand how to use the patch, and who it's intended for.

We're also developing tools to help both clinicians and patients understand and recognize HSDD, and for clinicians to diagnose HSDD and identify appropriate patients. And these are

based, in part, on the five questions that we used in our clinical study to enroll the patients--again, to ensure they had desire, they had the surgery, they lost desire, and they're distressed about it.

So we have--we're targeting both the patients and the physicians for this.

We also have a web-based educational program in development for physicians on the appropriate use of the product; the prevalence of HSDD; and the clinical implications. And, for example, one way that we are ensuring that physicians get training in HSDD and the appropriate use of the patch is if they would request a sample to be sent to them they will have to fill out a questionnaire on the disease--successfully fill out a questionnaire, I should add--so that we can be sure that they understand that these are for the right people.

The other aspect of this education program is to facilitate the dialogue between patients and physicians, because it's not always occurring now.

Physicians don't have treatment options all the time. We've done a lot of research with physicians, and a lot of them don't discuss it with their patients because they can't do anything anyway. So what's the point? A lot of patients don't really know whether or not what they're feeling is normal, hence the Hyster-Sisters website, which I think has helped an awful lot of people.

So this is to facilitate dialogue between patients and physicians so that everybody knows who should have the patch, and who should not.

And the other thing that we're doing is a CME program supported by unrestricted grants to educate physicians on female sexual function.

DR. LEWIS: But your post-marketing follow-up is with a mixed population. It's not just with the surgical menopause patients.

DR. MEYER: Right. And we also will have educational tools for naturally menopausal women, contingent upon that.

DR. LEWIS: Okay. Thank you.

DR. GIUDICE: In the queue--

DR. MEYER: Oh, there was a second question--

DR. GIUDICE: Oh, I'm sorry. That's correct. Yes. Dr. Heiman.

DR. HEIMAN: Yes, I can make just a couple of comments on the--you were talking about endogenous levels in post-menopausal women, not necessarily surgical menopausal?

So, these correlations typically--they're often not significant. And there's actually going to be a couple new studies coming out shortly that I actually can't comment on at the moment.

But they are not significant. Typically, DHEA, believe it or not, tends to be more correlated with desire.

But there are subgroups of women for whom it's--you know, that's really the problem with this area, from our side of the fence. Number one, the definition of sub-groups of low sexual desire, of which there are sub-groups. There are, but they haven't been clearly identified. And, number

two, the subgroups of women for whom low testosterone actually is correlate: who are they? How are they different?

So I'm not sure the question has been finally answered, even with the new studies that aren't quite out yet coming out.

DR. GIUDICE: Thank you.

DR. MEYER: Oh--Dr. Shifren would like to comment on that.

DR. SHIFREN: One thing--if I could have slide 500 projected, please. This will show you some of what we're up against.

[Slide.]

Here are the levels of free testosterone in women with low libido and women with normal libido. And these are from our surgical menopause population validation studies. And you can see the extensive overlap in free testosterone between these groups.

[Comments off mike]

The libido in oophorectomized women? Well, as they're trying to pull that up I'll just

describe the study. But basically, as a reproductive endocrinologist, I was very interested in trying to find some data that showed us that physiologically, testosterone is important for libido. We clearly have treatment studies--many before the Phase III studies you've seen today.

But what do we have as background data/ And, really, the best studies to look at are those in which women have had their ovaries removed. And, of course, you need to use hysterectomy, because the majority f women who have oophorectomy have concurrent hysterectomy.

So this is a very nice slide out of Sweden, where they basically send questionnaires to a group of women who had undergone hysterectomy at one institution. They then asked the women, "Since your hysterectomy, tell us if your libido is the same or better or worse?"

And what you can see is that regardless of whether women received estrogen therapy or not, if you compare women who underwent bilateral oophorectomy at the time of hysterectomy, to women

who did not undergo oophorectomy at the time of hysterectomy, you can see that women who underwent oophorectomy concurrently were significantly less likely to say that libido was same or better, or were significantly more likely to say that libido was worse.

So I think this is one of the true more natural experiments that does show that for menopausal women--for surgically menopausal women, the testosterone produced by their ovaries really does affect libido.

DR. GIUDICE: Thank you. Dr. Tulman.

DR. TULMAN: Yes, thank you.

Do you have--and I don't know whether this is for Dr. Shifren or for Dr. Braunstein--you've shown us the testosterone levels for pre-menopausal women. You've shown us testosterone levels through the placebo group and the baseline treatment group for women with HSDD who are, by definition, post-menopausal.

Are there any norms you can show us for women who are naturally menopausal, and their

testosterone levels, and how they might differ from women with HSDD?

[Pause.]

And I have a part two of the question.

DR. BRAUNSTEIN: [Off mike.] I don't have a slide for it, but--

DR. TULMAN: Well, can you tell me?

DR. BRAUNSTEIN: [Off mike.] Yes--

DR. TULMAN: I can't hear. I don't know if anyone can hear you.

DR. BRAUNSTEIN: Yes. Levels were very similar in the natural menopause versus surgical menopause. They were both at sort of the lower level of detection even with an assay that is highly well validated by FDA standards against GC tienna mass spec.

DR. TULMAN: And these are women both with HSDD and women who report their sex lives as being satisfactory?

DR. BRAUNSTEIN: No, specifically these are the women with HSDD.

DR. TULMAN: How does that compare with

women whose--

DR. BRAUNSTEIN: There's a lot of overlap. So if you look at the women in the validation study with normal sexual function, they tended to have, on the average, about 1 picagram per ml of free testosterone levels higher than similar women who had been oophorectomized.

DR. TULMAN: Okay. So that--and I guess my part two of the question goes back to some basic theory which one of the people asking the question at the public forum part of the meting asked: how does the theory--or where is the theory, or what is the mechanism for testosterone to produce the effect of improving a woman's sex life?

DR. BRAUNSTEIN: Well, there is certainly pre-clinical animal data that shows that if you remove ovaries and give testosterone there's increased sexual activity. In regards to humans, some of the best studies on the effect are te ones that were carried out by Dr. Cherlyn Gelfand--and Dr. Gelfand's here--looking at women before and after oophorectomy, and women who either received

placebo, estrogen, testosterone alone or estrogen plus testosterone, and showing that those on placebo dropped down; those who were maintained on testosterone stayed up as far as libido.

Now, as far as the theory of where it works, there's a couple places that testosterone works. One, I think--if I'm not mistaken, Dr. Heiman's group has shown that there's increased vaginal blood flow with testosterone administration.

But probably most importantly, there are receptors--there are androgen and estrogen receptors in the brain. And testosterone probably works primarily by increasing desire. It's not a female Viagra. Viagra works mechanically on the erectile function in the male. This is more of something that works centrally on desire. And I think the desire goes up, and then sexual activity goes up.

DR. TULMAN: And what part of the brain is that in?

[Laughter.]

DR. MEYER: The highest concentration of steroid receptors in the brain is in the area known as HTSM--hypothalamus thalamus septum and midbrain area--and it's long been shown that, especially in the hypothalamic area, this is where sexuality lies. You can lesion that area and get Kleuver-Bussey-like syndrome and things like that. And that's where these receptors primarily are.

DR. GIUDICE: Dr. Patrick.

DR. PATRICK: Yes, I have some questions for Dr. DeRogatis.

The first one has to do with--I'd like to sort of compare your slide 42 on the clinical relevance results--the summary of the MCID with Dr. Davis' slide 14, which is the summary of the results, and just make sure I understand, since it's very hard to relate the responder analysis to the change scores.

First, in the anchoring study--if I understood this correctly--that a single question was asked on whether they found the change to be--they found a change, and they found the change

to be meaningful.

DR. DeROGATIS: A meaningful benefit.

DR. PATRICK: And cognitively, that's a pretty difficult task. Did you do any debriefing?

DR. DeROGATIS: I'm sorry, I didn't understand your question.

DR. PATRICK: Did you do any debriefing of how women thought through that question? Did the perceive a just-noticeable difference and then call it "important," or did they--how did they know a change was "meaningful?"

DR. DeROGATIS: Ahh--I think it was--the question had to do with clinical benefit: "Did you experience a meaningful benefit?"

DR. PATRICK: Okay.

DR. DeROGATIS: I don't know that they were--and if I'm wrong there's someone who can tell me this--I don't know that they were debriefed about the details of that.

DR. PATRICK: Okay.

DR. DeROGATIS: However--

DR. PATRICK: So it all sort of hinges on

that one question.

DR. DeROGATIS: Well--yes, that's right. But--and that--you know, there are many approaches to clinical relevance, and the anchoring, and all of them--there's not a definitive approach. All of them have strengths and weaknesses.

DR. PATRICK: Right.

DR. DeROGATIS: And perhaps, if there is a weakness in the anchoring approach, it's the reliability of that single question, and that playing an important part.

However, I think it's important to recognize for clinical relevance, I think there's a little confusion about it, clinical relevance is predominantly established--it's an individual patient characteristic, and it's predominantly established by proportions of responders--as opposed to comparisons of means, which is the basis for statistical significance.

And so once the MCID is established in an optimal fashion, then the magnitude of difference can appear small to anyone, but it's actually the

proportion of responders. And the significant difference between those proportions that is the basis for clinical relevance statement.

DR. PATRICK: Right. But the clinical trial results, with the statistical significance are still changes in mean group scores. And we have to be able to interpret those, as well as a responder analysis. And if I understand the results, we have a change of just about one event in four weeks from a baseline of three events to four events.

DR. DeROGATIS: No, it's actually two events; that is, the treatment group changed two events, making it really a 66 percent change--

DR. PATRICK: Yes, but I'm interested in--

DR. DeROGATIS: --and the placebo group--

DR. PATRICK: --taking away the placebo effect here.

DR. DeROGATIS: Yes, well then it's one--

DR. PATRICK: That's right.

DR. DeROGATIS: --it's one event, but still a 33 percent change.

DR. PATRICK: Okay.

DR. DeROGATIS: And I--no, go ahead.

DR. PATRICK: And then with the distress, that's 6.7 units, and with desire, that's 5.1 units. And that's what we're left with: the difference between treatment and placebo.

And I think that the instrumentation in this study was really well known. The validity studies are really well done.

And our issue is interpreting those mean group scores. And although the responder analysis gives us a little bit of a hint there, I wonder what you would say to: if I took that difference in your meaningful benefit versus no meaningful benefit and applied it to the mean differences, which is taking the difference between two groups and applying it to a change score--and I wasn't quite sure about the validity of doing that, although that's what one of the slides from Dr. Davis does.

If that's the case--I mean, how--is that fair to apply the MCID?

DR. DeROGATIS: On hundred-point scales--and now this is a little Kentucky windage, because I don't have actual data, although there are some very recent reports--Guy Att and his group, and Sloan and his colleagues have both done reports in which they have used as example hundred-point scales. And this technique that they're talking about is referred to as "effect size empirical rule checking." And I won't bore you all with the details of that because everyone will fall asleep.

But, in fact, they wind up with magnitudes of change that are only slightly greater--I think they're in the range of seven or something like that--as opposed to the five and six here.

So it's on the edge. But, again, I'm flying by the seat of my pants.

DR. PATRICK: Well, the Dyatt approach is actually using the anchoring approach, but it's using it with a 15-point scale and not a "yes/no." So it's actually from a minimally big change to a great deal of change.

DR. DeROGATIS: But in his review he contrasts--

DR. PATRICK: Right--back to the distributional approach. But we're not talking about distributional approach, because that was not presented in our briefing package.

We don't know the SEM, we don't know the center deviation difference. So I don't want to get into that.

But my question is: is it fair--because this is the important thing for me--to say that the difference between the TTS and the placebo was one event per four weeks; your minimally clinical important difference was one--okay. So you win on that.

DR. DeROGATIS: I'm with you so far.

DR. PATRICK: But for distress, it was greater than 8, and we got a difference of 7--so that we're just on the margin there.

Is that fair to do?

DR. DeROGATIS: No, I don't think it is.

DR. PATRICK: That what I wanted to know.

DR. DeROGATIS: And let me tell you why.

DR. PATRICK: Because that's what's going on in--

DR. DeROGATIS: Because we're talking about two very different distributions here. The distribution--the MCID is an optimal discriminator between distributions of change from baseline, whereas the mean scores you're referring to are a very different distribution. I don't know that there's necessarily a relationship between those distributions.

And I think the important thing is that clinical relevance here is established through--clinical relevance obvious as a hypothetical construct is established through some operational paradigms that we say we're going to do this, we're going to do that. They're logical and we agree consistently a science.

And so this particular operational paradigm, using the anchoring technique which is very traditional, well established, tied back to patient perceptions, establishes that these are, in

fact, these are differential proportions of responders which significantly favor active treatment. Now, that's a clinical relevance statement. It's an accepted one. It's by the book, so to speak.

I can't tell you what the relationship is between this traditional operational definition of clinical relevance and Dr. Davis'.

DR. PATRICK: Well, what's a little bit confusing is this "greater than or equal to 8.9," because that intimates that that's change. And it's actually a different score.

DR. DeROGATIS: That's right. It's change--

DR. PATRICK: [Simultaneous comment inaudible.]

DR. DeROGATIS: That's right.

DR. PATRICK: And I'd be very interested in the statistical comment on this.

I still think, in integrating, we are left with 50 versus 34, 44 versus 30, 51 versus 39. And then we are left with 1, 6 and 5. And somehow,

putting those two things together is a big challenge of the committee.

DR. MEYER: I have just--I have a slide--could I have slide 705, please?

[Slide.]

DR. GIUDICE: I don't want to curb the discussion, but I just want the committee to be aware that we have four other people who have questions. We have questions also for the FDA. And then we have the list of questions that we need to get done, and we have three committee members, apparently, who need to leave a little early.

So--could the sponsor please be very succinct.

DR. MEYER: Very.

Let's look at the data in a different way. Your "satisfying sexual activity," "desire" and "distress"--the key endpoints of HSDD. Here's our MCID of greater than 1--8.9 for desire, and less than 20 for distress.

Now, what did we see in the TTS patients from baseline? Because when you're out in the real

world there's no placebo group. And Dr. Shifren told us the placebo is an intervention. Women who have HSDD who are not getting treatment are not spontaneously necessarily going to increase their satisfying sexual activity by one event in four weeks.

So we have a change of almost 2 in satisfying sexual activity in the TTS-treated patients; 10.8--almost 11--in desire; minus 23 in distress.

Now let's look at the women who said they were responders. These are the ones who said they will use the patch: 4.4 per four weeks; 21 increase in desire; and almost 37 unit decrease in distress. And, just for perspective, the MCID on the Western Ontario and McMaster-Womack score for measuring pain in arthritis is 3 or 100 mm scale.

DR. PATRICK: Thank you. I simply don't think you can discount placebo in this. But we'll go on.

DR. GIUDICE: I think that's an important point that the committee, I hope, has heard.

In the queue--and if you've already had your question answered, then please let me know. Don't feel obligated to ask it.

Going through the queue--Dr. Heiman did you have something else?

DR. HEIMAN: Yes. I'll try to be brief.

It's in regards to efficacy. What I was curious about is if there's information on how quickly the treatment group got up to a clinically significant level of change. For example, did it happen at one month, or two months or three months? So that's one question.

And whether there was any diminution--even in six months. I mean, I wish we had more one-year data. But since there's older clinical information that, for example, estratase, there's an initial effect--could be some placebo in there, of course--and then it quickly diminishes. And so I'm interested in that--that question.

And related to that: any thoughts about why--do you still feel as strongly this needs to be used in chronic dosing, as opposed to intermittent

dosing.

So those things are related a little bit.

DR. MEYER: Yes--and let me take your first question first.

If I could have slide 167, please?

[Slide.]

And this sows the time course for satisfying activity, sexual desire, and distress. The blue represents placebo, the yellow represents TTS.

And we saw a difference between placebo and TTS on sexual desire and distress that was statistically significantly different from placebo as early as four weeks; also in satisfying activity.

The maximum was reached at three months--for all three endpoints. Placebo maximized and it pretty much stayed the same by about four weeks. TTS continues to go up. And on the distress it continues to go down.

DR. HEIMAN: Do you see the change in satisfying activity as being a significant decrease

from the four-week mark?

DR. MEYER: No. It's not.

DR. HEIMAN: Okay. Thanks.

And chronicity--any thoughts?

DR. MEYER: What we found in the persistence of benefit study was that if you remove the patch the effect goes away, basically.

DR. HEIMAN: Okay.

DR. GIUDICE: Dr. Emerson?

DR. EMERSON: I have two questions. The first was just hit upon a couple minutes ago--this idea of ignoring the placebo group, and assuming that the activity in the placebo group is to be an indication of placebo effect; that there's this concept that, no, that was just what was going to happen over time, and it had nothing to do with a placebo effect--as was brought out.

I notice that not only in the slide 108, where Dr. Shifren presented the effect, she gave the whole effect from baseline. And I also noticed that in the package insert the only information that's given is baseline to follow-up in the

testosterone group.

I'd like some comment about why you would disregard that placebo effect so strongly, when you don't know whether this is just a general time course. In fact, I would actually argue that that last slide, where you're starting to see a diminution of effect in both groups is actually just possibly related to the fact that you have incident cases of patients going to the doctor for HSDD, and they are actively trying, and during that period they're trying to increase the frequency of intercourse, and then after a while they give up.

DR. MEYER: I'll have Dr. Shifren comment on the clinical consequences of that. Course comparison to placebo is always appropriate in a randomized clinical trial. But then in the real world--

DR. EMERSON: And in the real world, the question is: would this have happened anyway?

DR. SHIFREN: I think none of us are saying disregard the placebo. That would be absurd.

What we found exciting about exciting

about these results is that every single aspect of HSDD that we measured improved in a statistically significant way compared to placebo. That, I think, is a very appropriate comparison to placebo.

But when you're actually looking at level of change--and I think I'm going to use hot flashes as an example--we expect a 30 percent decrease in hot flashes if a woman takes a placebo tablet. But let's say with estrogen, we expect 60 to 70 percent.

When a woman walks into my office and says, "I'm feeling better on estrogen. My hot flashes have decreased," she doesn't say, "Well, it was 70 percent, but I'm going to take away the 30 percent that would have been placebo, so I've only have a 40 percent reduction in hot flashes."

When you're actually looking at treatment effect for the patient, it is the increase from their baseline event rate.

So I think it's very important to use placebo when we're looking at the statistical significance--

DR. EMERSON: Do you not look at trade-offs between the benefit, relative to potential harm, for the toxicity, that the placebo--

DR. SHIFREN: Benefits and risks are a crucial discussion that we have with every patient.

Actually, I did want to bring out--I mean, I think actually the exciting thing about WHI is that it has informed all physicians and patients that we will never take hormone therapies lightly. I think that will actually benefit this product because I think the likelihood of off-label use has been significantly decreased, given both physicians' and patients' concerns about the long-term risks of hormone therapy.

The comments from the audience during the open session were excellent, and I really appreciate them. But I think we were sometimes undermining patients' abilities to weigh and balance risks and benefits, and to physicians' abilities to carefully read package inserts and patient information and advise their patients.

I see women in my practice every day with

debilitating hot flashes who are making very complex decisions.

DR. EMERSON: But, to that issue, don't you think it would be useful in the package insert to point out what the placebo effect was?

DR. SHIFREN: Certainly placebo effect should be in package inserts.

DR. EMERSON: Okay. I do have--

DR. SHIFREN: I completely agree.

DR. EMERSON: Okay. And I'm sorry--I'm going to be cut off in just a second, so--

Dr. DeRogatis, I have a question about this anchoring technique--two things. One is I'm a little bit bothered by this idea if we just go with where the 45 degree line intersects that ROC curve, without really thinking through--it's possible that whatever you're looking at is not even predictive.

And then the other question is: the way that this question was worded to the patients, it was post-randomization, it was just an overall question of "How was the treatment going," which meant the patient could have been considering in

these risk-to-benefit ratios.

How did this analysis proceed, in terms of the clinical benefit, if you looked at it treatment-group versus placebo?

DR. DeROGATIS: I'm not sure I understand the question, to be honest.

You're having problems with the notion of the single anchor?

DR. EMERSON: That's correct..

DR. DeROGATIS: Okay. Well--

DR. EMERSON: And basing it on an ROC curve, no matter what. Because an ROC curve could be just no better than flipping a coin.

DR. DeROGATIS: Ahh--

DR. EMERSON: You had an area under the curve of .77--which you said you felt was near excellent.

DR. DeROGATIS: Well, yes, actually it's much better. If we had put a diagonal line going the other way, which the line of no information on the ROC curve, the coefficient would have been .5. That would have been no better than flipping a

coin.

So the fact that we had .77--

DR. EMERSON: But this idea of choosing the anchor that would have intersected with that 45 degree line of no-benefit, as well. And so I'm just questioning whether there is really any scientific rationale there. And I'm also questioning whether this analysis shouldn't have been done separately for the placebo group and the treatment group--

DR. DeROGATIS: Oh, I see--I'm sorry--

DR. EMERSON: --given the generality of your questioning of patients.

DR. DeROGATIS: Yes, I see. Yes.

This is a very traditional way of doing anchoring methodology, because what you're attempting to do--and so placebo and active treatment are kept together. They're not separated out.

And the reason for this is what you're trying to do is establish a meaningful change, as opposed to looking at treatment mechanism or that

sort of thing. And so by keeping them together, you're not artificially separating and pulling out separate groups, but you're establishing in a presumably representative sample that this is the magnitude of change that represents the minimal clinically important difference.

They are often--in many, if not most anchoring techniques--kept together, placebo and treatment.

DR. RODENBERG: Can I make a quick comment, please?

In doing the analyses--I just think it might be important to know that whether we're talking about those that said they had a meaningful benefit or didn't--placebo and the active therapy groups responded very similarly, in that whether it was due to being in active therapy or placebo, if you had a large change, you considered it meaningful, and if you did not have a large change, you did not.

The difference--this is the proportion of people on active therapy that had a meaningful

benefit compared to placebo. But once a person had a meaningful benefit, they had very similar changes, regardless of the mechanism behind it.

DR. EMERSON: Using your anchoring technique, would you have come up with the exact same threshold of 1 unit for both groups?

DR. RODENBERG: I haven't done that analysis, but I can tell you that the means and the medians; the distribution for the placebo and the active group--for both the responders and non-responders--are almost identical. They're not statistically significantly different, but there is a sample size issue--you could bring that up.

But looking at them, for active therapy the mean was 4.4 on the responders, and it was 4.3 on the placebo group.

So I believe--yes, I didn't do the ROC analysis because of the low sample size. But yes, I do believe you'd actually get a very similar cut-off if you did this for just the active therapy group.

Also, the 45-degree line, it's actually

like the inverse 45-degree line. Where that intersects the ROC curve, that was the point that was used as the optimal cut-off, because it balances different types of misclassification: misclassification of true responders and misclassification of true non-responders. And so we were looking for something that basically false-positives and false-negatives were treated equally. And that's where the ROC curve intersects that, that was the optimal cut-off kind of balancing misclassification rates.

DR. EMERSON: But is there any rationale that says that where that cut-off occurs is what's truly clinically meaningful?

DR. RODENBERG: I think you can always--right. We get the patients that say, you know--when we look at the two different groups, that seems to differentiate the two, in terms of misclassification rates.

DR. DeROGATIS: Yes, you can apply different utility functions to false-positive, false-negative and true-positive, true negative.

But in a balanced equation, as Dr. Roderberg is pointing out, that's the optimum correct classification--

DR. EMERSON: That's one definition of optimum. There are many definitions of optimum.

DR. DeROGATIS: Well, it's one definition, but it minimizes misclassification of responders and non-responders.

DR. GIUDICE: I think we could go on all afternoon. But thank you.

Dr. Lockwood had a question.

DR. LOCKWOOD: A quick question, and it's for Dr. Lucas, who's thus far escaped unscathed.

[Laughter.]

And I'm sure she was relaxing there.

And it's slide 67.

I think reasonable people will debate--probably in perpetuity--whether or not there are cardioprotective or cardiotoxic effects in the younger age group of the WHI study. And some people might even still debate--I have this debate with my ex-chair in my institution all the

time--about potential for there being a causative relationship between estrogen and progesterone and breast cancer, or estrogen not playing a role.

But everyone would agree that hormone replacement therapy increases the risk of thromboembolism. And there's just no doubt and no debate and no discussion about that.

So I think if there is one single element of safety that deserves the most scrutiny it is the potential role of this patch in promoting thromboembolic disease. Now, since the prevalence is so low you would really need a very, very large study of a WHI-type to prove this.

But a reasonable surrogate is to look at coagulation indexes. And I would posit that the ones you've looked at aren't particularly useful. They're not, in fact, often affected even by oral contraceptives, if you look at the literature; and that the most sensitive single indices is probably protein-S--free protein-S and protein-S activity, which is most affected by ovarian steroids and potentially by androgens.

So my question to you is: in fact, do you have that data someplace? Were protein-S activity levels looked at? Or, in the absence of that, were any real indices of thrombin activation looked at--for example, prothrombin, fragment 1.2, thrombin, anti-thrombin complexes--something to give us a sense of whether or not TTS actually increased the generation of thrombin.

DR. LUCAS: We did look at prothrombin fragments 1 and 2 in the Phase II program. We also looked at protein-C resistance, and we looked at plasma viscosity, platelet aggregation, and we saw nothing. And then the values that you see here are what we then did in Phase III. And we've not seen anything in any of the measures.

DR. LOCKWOOD: But no protein-S.

DR. LUCAS: We did not do protein-S.

DR. GIUDICE: And a follow-up to that--not with regard to coagulation, but if you look at the data on Danazol, with regard to its being an immunosuppressant, have you looked at all at any indices of suppression of the immune system in

women on the Intrinsa?

DR. LUCAS: In what measures would that be?

DR. GIUDICE: One would have to--

DR. LUCAS: We looked at white counts.

DR. GIUDICE: No, one would have to do in vitro studies--mixed lymphocyte cultures.

VOICE: [Off mike.] Measuring TH 1 and TH 2 [inaudible.]

DR. LUCAS: No, we've not looked at that.

DR. GIUDICE: There are two other questions, and then we need to move on.

One is from Dr. Merritt, and the other from Dr. Burnett.

DR. MERRITT: n the Phase III study design you allowed patients to continue after 52 weeks into a persistence of benefit arm. Are those randomized to placebo and others were randomized to the TTS system? And you said there was loss of benefit. Is that only in the placebo arm?

DR. MEYER: No, not entirely. For the persistence of benefit study, after 52 weeks there were about--slightly over 200 women who were asked

if they wanted to participate in a 13-week study, knowing that they would get either a placebo or a testosterone patch. Now, recall, they had all been on testosterone prior to this.

Those who agreed to participate were randomly assigned to either placebo or the 300 mcg testosterone patch. And no one knew what they were getting.

Following 13 weeks on therapy they were interviewed by a trained interviewer, with an extensive script--and it was a script which we also used in the clinical relevance stud. It wasn't just a single question, it was a lot of data that we gathered.

And we asked, in these interviews, about the same sorts of questions that were covered in the instruments that they were filling out: "Did you have a decrease in desire for sexual activity," etcetera, etcetera.

And, again, interestingly enough, those randomized to placebo has a statistically significant decrease in all their sexual activity

indices relative to TTS. The only area where the two groups were the same was in a noticeable decrease in willingness for partner-initiated activity--again, consistent with what Dr. Shifren showed us.

So, again, it was about 60 percent of the placebo patents showed a decrease in these indices. And it was about a 35 to 40 percent people in the TTS group that shoed a decrease in these indices. All the p values were statistically significant.

DR. MERRITT: Thank you. So then your proposal would be that this system would need to be used chronically and long term, and at the same time the subjects would need to be on chronic and long-term estrogen?

DR. MEYER: We have no data on women not on background estrogen. So, yes, they would need to be on concomitant estrogen therapy. The patch does need to be worn continuously, and the duration needs to be discussed between the woman and her physician as to what's most appropriate for her treatment.

[Pause.]

And Dr. Shifren will tell us--

DR. SHIFREN: I do just want to add that as clinicians, since we really are using much less systemic estrogen in our menopausal patients--clearly, the major indication is bothersome hot flashes--we as a group of clinicians were very concerned about the potential for off-label use in women not on systemic estrogens, and wanted to know whether it was truly safe and effective in that group.

And so the sponsor was very responsive to our needs. Very quickly we jointly designed a trial of transdermal testosterone in surgically and naturally menopausal women on no systemic estrogen therapy. And that trial is currently ongoing at the Mass General and multiple other sites.

So, hopefully, we will have answers for that. And I think we won't know until the study is done.

DR. GIUDICE: Dr. Burnett, and then Ms. Solonche.

DR. BURNETT: Thank you. This is a safety question--safety issue question.

I guess with many things that are good you always--at least in America--want to up-size. And I just wonder what the potential for--or potential consequences may be--for somebody who may take the patch everyday, or use it perhaps in ways it's not intended to be.

And I guess the background for that concern relates to some of the data presented by Dr. Soule. I think there's a trend towards some effects here, particularly the metabolism syndrom indices.

So I'm just curious about--do you have any comments or any data with regard to that sort of concern?

DR. MEYER: For metabolic syndrome Dr. Braunstein will address that.

With respect to abuse, we are delivering 23 to over 300 times less testosterone than these women would need if they wanted to have steroid abuse.

If I could have slide 255 projected?

[Slide.]

This is what Dr. Lucas does in her spare time.

[Laughter.]

This is how many patches a woman would have to wear for about six months in order to get any significant type of abuse potential out of these patches. And there are way cheaper ways to do that now, if you go to the drugstore and get DHEA or something.

So it's not very practical or cost effective.

DR. BRAUNSTEIN: Actually, let me review a couple of safety issues, because I think there may have been some misconceptions during the FDA presentation.

If we can go to slide 337.

[Slide.]

I'll start off with some of the glucose data, and then I'm going to show one-year data in the natural menopause study, because the surgical

menopause was double-blind, placebo-controlled for six months. The natural menopause was double-blind, placebo-controlled for one year. And I think that gives a much more meaningful type of evaluation of both safety and efficacy over a longer period of time.

If we look over here, this is the glucose data. And one can see that basically, if you look at the exposure to testosterone over months--here's the double-blind period, and here's the open-label extension--that there basically is no major change in the glucose levels in these patients versus the baseline. There is, obviously, some scatter, but there's no major change.

If we go to 338--

[Slide.]

--we can look at the insulin levels. And, again, very little change over time, either in the double-blind placebo-controlled trial, or in the open-label extension.

And then if we go to 334--

[Slide.]

--the glyco-hemoglobin data is shown here. Again, no difference in glyco-hemoglobin levels in these patients.

So there's no evidence of really any metabolic deterioration. Because in the presentation that you saw, the scale of glucose changes really was quite expanded. But the changes were very, very small, and really non-significant.

If we go to slide 228--

[Slide.]

--which is the natural menopause study, there are two studies--one was a 24-week double-blind, placebo-controlled study; another was a 52-week placebo-controlled study. And if we just look at the 52 weeks--because the data is really very much the same--systolic blood pressure showed no significant change; diastolic blood pressure showed no significant change between placebo or the testosterone group.

There were no significant

differences--both lost, although the placebo group lost a little bit more weight than the testosterone group.

If we go to slide 330-

[Slide.]

--we'll show the lipid changes in the 52-week double-blind, placebo-controlled trial in naturally menopausal patients. And don't forget, these patients are also on a progestin as well as estrogen.

And so in the placebo group we can see there's baseline cluster of 210, going up a total of 2 at 52 weeks, versus testosterone group, staring off at 208, going up 6.5--again, somewhat of a regression to the mean.

HDL levels were very similar types of changes; both going up, same direction.

LDL--again, the levels--the final levels were very similar; some degree of regression of the mean; this going up, because it starts off lower; this going down.

And triglyceride levels, again, were very

similar.

If we go to 344, which shows carbohydrate levels at one year--

[Slide.]

--we can see in the placebo group the glucose levels went up 1.1 mg/dL in both the placebo and the testosterone patch group. Glyco-hemoglobin levels went down to a similar degree, and insulin levels actually went up a little bit higher in the placebo group than in the testosterone group.

And here's the six-month double-blind control group--and, again, showing very similar types of results; trying to give some degree of confidence in the longer-term safety issues.

And then if we--

DR. GIUDICE: I need to ask you how many more slides, because we need to move on. We still have the questions for the FDA.

DR. BRAUNSTEIN: I will stop. But I will summarize by saying: similarly, there are no changes in LDL, no changes in the coagulation

parameters in the natural menopause study.

And, again, protein-S was not measured.

DR. GIUDICE: Thank you.

Ms. Solonche, you had a question.

MS. SOLONCHE: Yes, first, are there any differences in your trial results related to the reason why the subject had an oophorectomy in the first place?

Second, how do you differentiate between women who are distressed about HSDD, and those who might be depressed, and therefore out of the running?

And, third, has any work been done on the possible negative psychological effects of using a medication to increase libido?

DR. MEYER: Okay. Let me start with your first one.

We did not gather any data with respect to differences in the women as to why they had the oophorectomy. They all had been oophorectomized about the same amount of time, but did not do any statistical analyses on that.

With respect to depression versus distress--everyone--an entrance criteria, because we wanted to rule out depression, all women had to take the Back Depression Inventory, and could not be depressed according to that inventory, to rule that at as a possible cause of HSDD. And then they had to score positively--or negatively, as the case may be--on the distress scale.

And then the negative psychological aspects of using hormonal therapy, we did not ask any questions about that. The fact that the women who had a positive effect remained in the trial and/or said they would continue the patch, would suggest there is a positive benefit, at least for some women. It was not listed as a withdrawal criterion. No one gave that.

DR. GIUDICE: Dr. Dorgan, the last question.

DR. DORGAN: Two very quick questions.

For the women following bilateral oophorectomy and hysterectomy, could there not be any psychological component to some of these

problems that are being attributed to decreased testosterone levels?

Dr. Shifren, would you like to address this?

And also recall that by the time the women were in this trial they were, on average, eight or nine years post-oophorectomy. I mean, they've lost their ovaries and their uterus has been removed. I would think that there could be a psychological component, but I could be wrong.

DR. SHIFREN: If you think back to the hysterectomy study--the observational study--in general what we see is that the majority of women who undergo hysterectomy actually have an improved sex-life post-operatively. And that's been shown in many large studies.

Of course, that makes a lot of sense. Women only have a hysterectomy if they have underlying pathology. So typically they have bleeding, fibroids, endometriosis. And the removal of that problem often leads to increased sexual activity and function.

What was so interesting--I thought about that Nathorst-Buhst study that I showed you earlier, is that within that group of women, you were still significantly less likely to get that increase in libido if your ovaries were removed concurrently, and significantly more likely to have lowered libido post-operatively.

DR. DORGAN: A second question--just to follow up--in your 2(b) studies, I see why you chose the 300 mcg per day dose. But you looked at a placebo, 150 mcg dose, a 300 mcg dose and a 450 mcg dose. And of all the parameters that we're looking in terms of efficacy, the greatest effect was with the 300 mcg dose.

If it's the testosterone per se--I'm not a pharmacologist--but if it's the testosterone per se that's responsible--if testosterone replacement per se would improve libido in these women, why aren't we seeing a linear effect with an increased--well, sexual increased, number of satisfying episodes of sexual intercourse, and improved personal distress when we go up to the 500 mcg dose.

I was kind of concerned that we're not seeing--we're not even maintaining the increase. It's no longer significant when we go up to 450.

Could somebody comment for me?

DR. MEYER: If you could project slide 181, please?

[Slide.]

Actually, what we found in the Phase II study is placebo and 150 were essentially the same; 450 had an effect. It was just not statistically significantly different from placebo; 300 was better.

But as you can, in some domains of the PFSF--placebo's in blue, 150 in yellow, 300 in the darker yellow, and 450 in the orange--for example, orgasm, sexual pleasure, sexual responsiveness--450 sometimes did better than 300.

But what we were interested in was the lowest effective dose. So it was sometimes but not consistently. And when we did our population PK studies, we do get dose proportionality in the doses. So you get higher blood levels of

testosterone with the 450--which, again is a bit of a conundrum. It doesn't explain the whole story unless we're at the top of the dose-response curve with 300.

But we chose 300 as the lowest effective dose.

DR. DORGAN: Okay. Thank you.

DR. GIUDICE: Thank you.

Now I'd like to ask the committee for questions to the speakers from the FDA.

Dr. Nissen.

DR. NISSEN: I had one very brief question, and that is: there were a couple of patients that had bilirubin elevations, and I want to know if any of the patients in the study--as far as the FDA can determine--met High's rule of a concomitant transaminase elevation and bilirubin elevation?

We know that testosterone has potentially hepatotoxicity, and I"m just looking for any signal there. Any of the hyperbilirubinemic patients also have elevations in liver enzymes?

DR. SOULE:: I'm unfortunately unable to

answer that question. It's possible that Procter & Gamble might be able to provide you with the answer.

DR. LUCAS: Two patients who had markedly abnormal bilirubin--could we see the box and whisker plots for bilirubin?

[Slide.]

DR. NISSEN: But what I need to see is their transaminases.

DR. LUCAS: Okay.

DR. NISSEN: You're aware of High's rule, and why it's important, I assume.

DR. LUCAS: Yes.

Could I see the bilirubin? Oh, we can't project.

We saw no difference in outliers with testosterone compared to placebo for any of the transaminases or bilirubin.

DR. NISSEN: Okay, the two patients that had elevated bilirubins, did they also have elevated transaminases?

DR. LUCAS: No, they did not. They

isolated bilirubin.

DR. NISSEN: Okay. Thank you.

DR. GIUDICE: Dr. Tobert.

DR. TOBERT: Yes, I have a question for Dr. Davis, and it refers to the FDA's first question about clinically meaningful differences.

And I thought it might illuminate the question a bit to consider other drugs, or other drug classes that the FDA considers meaningful that act on the brain, as we've heard that this product does.

For example, if you take an SSRI for depression, what kind of differences would you get? I mean, if I refer to your slides 11 and 12, you're showing that the testosterone patch sort of gets you some way back to normal, but only about a quarter of the way. And you have like a 52 percent responder rate versus 31 percent.

Now, I think that 52 versus 31 would be acceptable for something like an antidepressant. Can you--obviously you have access to a ton of data on this--could you comment on that, please?

DR. DAVIS: In our division we have not had prior drugs that really have been evaluated on a quality of life or patient-reported outcome analysis.

DR. TOBERT: But the FDA looks at this question all the time.

DR. DAVIS: Yes, but in our division we have not handled drugs of that sort, so perhaps--

DR. TOBERT: How about the PDE-5s, the newer PDE-5s? Did you have to deal with that?

DR. DAVIS: Let's have Dr. Griebel or Dr. Monroe answer that.

DR. GRIEBEL: I think each one of them is dealt with individually. And this is our first experience with female sexual dysfunction, these endpoints. And we're asking--that's why we brought it to committee. We're asking for your input on this.

DR. TOBERT: Okay. All right, I would just state that my impression is that for other drugs, this would be considered pretty good: 52 versus 31 percent. But if I'm wrong, please correct me.

DR. MACONES: This is for Dr. Soule.

Again, to go back to the post-marketing plan--which I'm having a tough time with--on your slide number 29, your second bullet-point says that recruitment goals were not previously met using this database, which seems to be a really critical point.

Could you give us a little more information about that?

DR. SOULE:: I don't know how directly I can discuss a plan that involves another product at this committee--except to say that there has been some experience with the database and goals have not been met, in terms of recruitment and timeliness.

DR. MACONES: Goals with this company?

DR. WALKER: Alexander Walker.

What we can offer and promise is a number of people. So we've got covered lives. If a product doesn't sell, if it's displaced by other products, a projection that's based on marketing will fall short.

DR. MONROE: Dr. Walker is correct. If the exposure to the drug is below their expectations, they won't be able to recruit at the rate that is predicted, so that there's two options: they'll either miss the recruitment target, or the study will have to run for a longer period of time.

And as Dr. Soule said, we were somewhat skeptical of the time-lines, based on an experience that we've had in our division. And I think we're both in agreement, Dr. Walker.

DR. GIUDICE: Dr. Patrick, and then Dr. Hager, and then Dr. Lipshultz.

DR. PATRICK: The sponsor faithfully followed the 2000 draft of the female sexual dysfunction guidance. Given the difficulties in interpreting the number of satisfactory sexual events--particularly, as DeRogatis pointed out, a fractional number is not easy to interpret--has there been a thought of trying to look at these as combined endpoints? Or what is the relationship? And why is satisfactory sexual event thought to be the primary endpoint in this area?

DR. MONROE: Well, as everyone has heard from the discussion that has ensued earlier today, this is a new area, I think, for everybody. It's an area that doesn't have clean endpoints. There's a lot of active research that's going on.

We recognize that many of the investigators in this area do have questions about this being the primary endpoint. At the time that the draft guidance was done, it reflected the best assimilation of the available data of the people that drafted the guidance, based on their interactions with various investigators in the field.

We are considering looking at this entity of hypoactive sexual desire disorder in somewhat different ways. But at the time this study was started, these were the rules, and the sponsor did follow the advice that we gave to them. And I think it's only fair, today, to evaluate their application primarily on the way the rules were set up at that time.

It doesn't mean that, as we go forward and

gain more experience in this area, we won't give greater or lesser weight to several of the secondary endpoints.

DR. GIUDICE: Dr. Hager.

DR. HAGER: Granted that this is a new area for the agency, but we do have rather long experience with a product of combined dequon-estrogen and testosterone that has been available.

Are there data regarding not reaching the primary endpoints of efficacy, but side effects, as far as breast cancer and cardiovascular risk?

DR. MONROE: Would you like to--someone is with us from our office of Drug Safety. And I think she's going to show you our experience using the adverse event reporting system--the AERS database from the agency, the spontaneous serious adverse event reports that the agency has received, perhaps over the last decade.

DR. GELPERIN: I'm Kate Gelperin. I'm a medical officer in the Office of Drug Safety. And in the interest of time, I'll just say briefly that

the type of reports that are in the AERS safety database at the FDA are generally spontaneous reports from consumers or health professionals, and so they are not clinical trial results.

With Estratest, we did run a search of the AERS safety database for serious adverse event reports--"serious" is a regulatory definition that includes death, life-threatening, requires or prolongs hospitalization, congenital anomaly, and then there's a category called "other" that's other medically important events.

And when the search was run in that way there were a total of 226 reports in the database. Of the raw counts, the most frequently reported include breast cancer, depression, headache and acne.

A review was done of the breast cancer reports with Estratest, including any report of breast cancer in which Estratest was a suspect or concomitant drug. This search showed that between the years 1992 and 2004, four unduplicated cases of breast cancer had been received, with Estratest

indicated as a suspect drug--which were not from legal sources. Patient age ranged from 31 to 56 years.

We also found a total of 69 unduplicated cases of breast cancer that were received via legal sources. The first legal case was received on October 17, 2003, and all others were received thereafter.

In each of these cases, other suspect drugs number between three and nine, and included other HRT therapies. Patient age ranges from 45 to 70 years.

There were also eight unduplicated cases of breast cancer in which Estratest was considered a concomitant drug by the reporter.

A search was done for serious events with Estratest considered suspect, which did not include the outcome called "other," since that was a way of zeroing in on perhaps some of the more serious effects that might have been required of prolonged hospitalization. And when that search was done, the most frequently reported events included CVA,

coronary artery occlusion, dizziness, headache, breast cancer, chest discomfort, depression, glaucoma, hypoesthesia, pain, and ovarian cancer.

The following category of events--cases were reviewed for cardiovascular events, including MEDRA-preferred terms, which is a way of coding spontaneous reports. We included the MEDRA Pts, cardiovascular disorder, coronary artery occlusion, coronary artery re-occlusion, myocardial infarction, chest discomfort, and chest pain.

There were a total of six cases in the data base that were serious: two myocardial infarction, three chest pain, one coronary occlusion.

In the two reports of myocardial infarction, one case occurred in a 78-year-old female who was participating in a clinical study. The even was considered by the investigator to be possibly related to Estratest.

The other report was in a 57-year-old female who was taking multiple concomitant medications, including opiates.

In the three cases of chest pain, one was attributed to cholelithiasis, and one was attributed to hypophosphatemia. And one case of coronary occlusion in a 58-year-old female was treated with a stent.

With regard to cerebrovascular effects, these included the MEDRA PT cerebrovascular disorder, cerebrovascular accident, and headache. There were a total of six unduplicated serious reports, with Estratest considered a suspect drug.

There were two reports of stroke, one in a 48-year-old female, and one in a 58-year-old female. There were three reports of serious headache, one in a 37-year-old female who was admitted to the hospital with depression, and was later diagnosed with multiple sclerosis.

The other two reports were for a 49-year-old female and a 45-year-old female. There was one report of unspecified cerebrovascular disease in a 64-year-old female.

Now, with regard to serious reports of depression, there were three unduplicated reports,

with Estratest considered a suspect drug. All three reports included other suspect drugs.

Just in summary I would say that the sense of these reports is that although spontaneous reports are important for hypothesis generation, that in this case I don't think we could regard these as in any sense confirming a hypothesis.

DR. GIUDICE: Thank you.

Dr. Lipshultz, you had a question.

DR. LIPSHULTZ: I just had a question for the FDA speakers, and that was: it seems to me that you were somewhat--at least in the briefing document--insinuating that you were not 100 percent happy with the endpoints here, in terms of change over placebo. And you've said that this is a new area, and we're looking at for the first time quality of life drug.

But that's not true. I mean, you have looked at the PD-5 inhibitors, with three instruments that are almost the exact same as the three instruments here. The names have been changed and the questions are different, but it's

the same thinking.

And what I'm asking is: is reviewing the data from the two newest PD-5 inhibitors, were those changes more robust than what we're seeing here, in terms of quality of life changes?

DR. SHAMUS: Ben Shamus. I'm the Director of Reproductive and Urologic drugs.

You know, we can look at this many different ways. One way to look at this is that it requires us to treat 100 women--expose 100 women for 15 of them to have a sort of borderline clinically meaningful effect attributable to the testosterone. I mean, there's lots of ways of looking at this, but that's basically what it boils down to.

So that is not to say there is not a clinically meaningful effect in some women, and that there is a mean statistical difference. The thing, as you know, we have to grapple with is, in a population setting, which is what we deal with here--in a population--is that benefit to the population worth the risk, whatever that may be, in

the situation.

Of course, the PD-5s or a whole different thing, in a sense, that we have a lot more experience, etcetera, in terms of the risk. And if I recall the data, actually, many of the people returned almost to normality in terms of erectile dysfunction--I don't have the figures in front of me--as opposed to here, where it's not at all the case.

But we the benefit--it is what it is, and that's what it is. And then the risk--we have to weigh those two things and make some kind of decision.

DR. GIUDICE: Thank you.

Committee Discussion

DR. GIUDICE: That's an excellent segue into question number 1, which is:"Do the efficacy data represent a clinically meaningful benefit above that of placebo for surgically menopausal women with hypoactive sexual desire disorder who are taking concomitant estrogen?"

Our task is to give our recommendations to

the FDA, with a yes or no answer.

Does the committee feel that it is ready to take a vote?

[Pause.]

Dr. Emerson?

DR. EMERSON: Just one point of clarification: you do want this question answered, basically, with that risk-benefit trade-off that you just spoke to--the concept--

VOICE: [Off mike.] That's the last one.

DR. EMERSON: Well, but the concept was saying that 15--that extra 15 responses relative to the potential risks.

So--do we want to answer the question of whether people should want to have one extra episode per month, or do we want to answer the question of is this the cost of getting this one extra episode per month is too much.

DR. GRIEBEL: The risk-benefit question, weighing in the safety, bottom-line, is at the end.

DR. EMERSON: Okay.

DR. GRIEBEL: Four.

DR. EMERSON: So just comment on efficacy. Whether the one is worth it--I mean, whether the one is something that you'd like.

DR. GRIEBEL: Mm-hmm.

DR. EMERSON: Okay.

DR. GIUDICE: We're voting on the 1, 6 and 7--essentially.

Dr. Rice?

DR. MONTGOMERY-RICE: I want to make sure I understand something.

On this "clinically meaningful benefit" was that a term that you all developed? Or is that a scientific term that I've missed in statistics?

DR. GRIEBEL: Well, there's a whole science of clinically meaningful benefit and minimal important difference that Dr. Patrick might want to comment on.

DR. PATRICK: Well, you would have learned this as clinical significance. But the term clinical is sort of odd here, because this is defined by the women. And so it's really the minimum important difference. Forget the clinical.

But you can think of it as parallel to clinical significance if you had a clinical anchor here.

DR. MONTGOMERY-RICE: But that's not the same as statistical--

DR. PATRICK: No.

DR. MONTGOMERY-RICE: --difference.

DR. PATRICK: So we're got statistical differences, and what the committee's being asked--and while I have the mike--I didn't understand this incorporating risk. The question asks about clinical benefit. It doesn't say risk in the question at all. So I'd like that clarified before we vote, because we have all these questions about risk later. And so I thought we were answering this one at a time, rather than integrating this all.

DR. MONTGOMERY-RICE: And I just want to ask one other question to the FDA.

If the event had been five more, would that have changed the question, versus it being 1.4 or whatever it was more? Would that have changed the question of being a clinically meaningful

benefit?

DR. GRIEBEL: Well, it could work both ways. If the study that was designed to define the clinically meaningful difference that you had observed was five extra events, and then the average was one for each women, then clearly it wasn't met.

DR. MONTGOMERY-RICE: But you didn't define that to begin with, did you?

DR. GRIEBEL: No.

DR. MONTGOMERY-RICE: Exactly. So you just said that it needed to be statistically different than you chose to use from baseline, and compared it to groups. So you didn't define that it had to be five more events over a four-week period of time to be clinically meaningful. Or maybe you did.

DR. MONROE: We did not, but we told the sponsor clearly that a statistical change in and of itself would not be sufficient; that they would also have to provide evidence--as they've attempted to do with this study--that the change that would be observed would be of clinical benefit to the

patients; the patients would conclude that they derived a true benefit. How they're making that decision is up to the individual that has the disorder. And that's what was attempted to be done in this case in that study.

Now, the question is--that was one of the issues we raised to the panel is there are many ways of trying to do these studies. Was that study done in an acceptable manner so that the numbers that they generated from that study, do they carry credence with you as a committee member.

In other words, we've tried to present to you the information that the sponsor has generated, and we're asking you for your independent assessment and interpretation of those data.

DR. GIUDICE: Yes, Dr. Heiman.

DR. HEIMAN: I just wanted to make a comment on this, because I do think it's tricky.

If you come from a psychotherapy side of doing interventions as opposed to a drug side, one of the things "clinical significance" can mean is you jump from the dysfunctional range into the

functional range--somewhere into the functional range. That's a way of quantifying, but it's not quite statistical--"clinical significance."

I think, in this area, that's very difficult to do, because though we have some data, as you've seen, some data on what is the normal range, I don't think we should, at this stage of the development of the field, rely 100 percent on that idea.

So what we have in this case is what they've tried to do is look for clinical relevance. And when you go there, it looks like the figure comes out somewhere around 50 percent when you try to take that table 43 apart. So that's another piece of evidence.

And, finally, if you look at one even over four weeks, I would just be careful as you consider that, to not treat that casually. That could be quite important for the women in this trial. In some ways--it just could be quite important. It may seen insignificant, and that's also, by the way--all those things actually are difficult to

judge. We don't have a lot of objective standards from which to do that.

So that's just, by the way, on the event issue. It's almost as if each of these--I'm not asking that you consider them separately, but they're very different measures, these three measures. It's hard to put them all into one, I think, and really consider what it means.

DR. GIUDICE: Thank you.

So are we ready to vote?

Okay, we're going to start on this side.

Dr. Macones.

DR. MACONES: Yes.

DR. DORGAN: No.

DR. EMERSON: I'll say yes.

DR. HAGER: In light of the significant placebo effect, and in light of apparent discontinuation of a large number of users, and the maintenance of benefit over time not increasing but staying stable--in spite of those things, I do think that there is statistically significant benefit, and so I would vote yes, with some

reservation.

DR. TULMAN: I would vote no.

DR. BURNETT: Yes.

DR. DICKEY: Yes.

DR. GIUDICE: Yes.

DR. LOCKWOOD: Yes.

DR. LEWIS: Yes.

DR. LIPSHULTZ: Yes

MS. SOLONCHE: No.

DR. PATRICK: Yes.

DR. NISSEN: Let me just qualify a little bit here--

[Laughter.]

--it's been too easy for you.

I think that the agency set a bar here for what had to be shown with regard to efficacy, and that bar was met. And so you can't change the rules--in my view.

And I think that they did--they set out to do this, they did it very carefully. They showed efficacy. Now the efficacy, I must tell you, is fairly marginal. And what didn't really come

through there--and I decided not to prolong this by questioning--but it looks to me like about 36 percent of the placebo patients would really like to continue the therapy, and about 50 percent of the treated patients would really like to continue the therapy.

And I want the sponsor to consider marketing the placebo--

[Laughter.]

--because that's a pretty good outcome.

So my answer here is yes, but it's not a very big effect, in my view.

DR. GIUDICE: Thank you.

DR. MERRITT: Yes.

DR. MONTGOMERY-RICE: Yes.

DR. GIUDICE: Thank you.

We are now onto safety. Question No. 2 is:

in the safety database, 494 surgically menopausal women were treated with TTS in combination with estrogen for 12 months. Of these 127 were treated for 18 months. There are no long-term, placebo

comparative safety data beyond six months.

The expected TTS use will be chronic in the intend population.

Is this exposure--total number of women treated and duration of treatment--adequate to demonstrate long-term safety?

Does the committee feel that it is ready to vote on this, or does it need some discussion?

Dr. Tobert.

DR. TOBERT: I had to prolong this, but I think some few--we haven't really asked any safety questions of FDA yet--or very few. And I do have one or two.

DR. GIUDICE: Well, now is the time.

[Laughter.]

DR. TOBERT: Well, firstly, I don't totally follow the logic here. The WHI studies were disappointing, but they showed what you might have expected, considering the history of oral contraception; you know thromboembolic effects were no surprise. And they were only disappointing relative to the epidemiology.

But the point is: does testosterone have any biological effects that are the same as estrogen progestin? Other than the fact, of course, that a small amount is aromatized to estradiol.

Just because the WHI studies were disappointing, I don't quite see why there's an issue with testosterone. So maybe you could explain that.

And my second question is: with regard to the randomized controlled trial that you are putting on the table, then you see I'm a big fan of randomized controlled trials. I sit on the steering committee of two of them--both of them about 10,000 patients. But I would question whether it's possible to do a study that big. And I heard the number 17,000, but I think that was not--doesn't include evaluating the risk of breast cancer, and would be in much older women.

So could you clarify those two points? What, actually, if you were to study 50-year-old women, how many you would need in a randomized

trial to answer the questions you want answered.

And the other is about the biology of testosterone versus estrogen and progestin.

Thank you.

DR. SOULE:: To take your second question first, that's really one of the questions that we have posed to you as our advisory committee. And we would like your thoughts and suggestions on what sort of trial would be optimal; what design, what duration, what sample size would be optimal.

As far as potential for risk with testosterone--as you mentioned, there is the concern about aromatization to estrogen, with the following of risks that we know to be attributable to estrogen. But I think the biggest point is that we simply don't have enough data on women taking testosterone on a chronic basis to be able to look into a crystal ball and see what we may see in a population.

DR. TOBERT: But the labels for the male products, where you're giving 20 times as much, are pretty benign. They talk about prostate cancer as

potential risk, but they're not loaded up with warnings and black boxes.

DR. SOULE:: But women are not physiologically exposed to the sorts of levels.

DR. TOBERT: Well, but this patch is providing levels that would be found in a young woman.

DR. MONROE: Well, I think you took us back to WHI in the sense that a lot of what was being target there was to bring levels back to what was in young women. And you created outcomes that were a surprise to, certainly, many people. Some of them were apparent, as we heard from the epidemiologic studies. Some were not.

And I think we feel that there may be some risk in making assumptions just because something hasn't been shown in the past in limited numbers of women treated for short periods of time relative to the anticipated clinical use.

DR. TOBERT: But that really goes to my point. Because testosterone is not thrombogenic like estrogen and progestin are. The female sex

hormones tilt the hemostatic balance towards coagulation. Testosterone does not. Men don't have to, you know--when man was evolving, women faced major hemostatic challenge every two years. That's not the case with men, so testosterone isn't procoagulant. And that, I think--you know, a lot of the findings in the WHI probably are attributable to that.

DR. GIUDICE: My interpretation of this question is that it is whether the exposure has been adequate for long-term safety evaluation, including the fact that this is a patient population that has been studied with estrogen.

So I don't think it's just the risk of testosterone. I think it's also the fact that the indication that the sponsor is going for is the use of the TTS in the setting of the surgically menopausal woman with estrogen replacement.

DR. TOBERT: Just to clarify--

DR. GIUDICE: Is the rest of the group--

DR. TOBERT: --we're not debating the safety of estrogen here. It's only--

DR. GIUDICE: I'm not so sure if we are or are not, because this is an indication for long-term testosterone therapy, potentially, in the setting of an obligate long-term estrogen therapy.

And so that is something I think that the committee needs to discuss, because this, I think, is part of the underlying issue of the long-term safety.

DR. HAGER: I fully agree. I think we are evaluating the product as presented by the sponsor; and that is in combination, in surgically menopausal females who are using estrogen.

DR. HEIMAN: Yes, and the way I also understood this question is in terms of long-term safety. And so that's very crucial, I think, in this case. Is that correct?

DR. GIUDICE: Any further discussion on this?

Yes, Dr. Lipshultz.

DR. LIPSHULTZ: As a non-gynecologist--getting back to the estrogen use over a long period of time, I mean, that's already

been discussed, decided, published and has become--it's a done deal.

So, I mean, we're not rediscovering the wheel here. I don't understand this. I mean, you know, if they're mandating these patients have to go on long-term estrogen because it's incorporated--and then use the patch, then basically aren't you back to where you were with the discussion of the safety of estrogen?

DR. LOCKWOOD: I think what Linda's saying--if I can put words in her mouth--is that we know that estrogens are thrombogenic. This drug is being used with estrogen. So the question is: does it make the estrogen more or less thrombogenic. And there's certainly some evidence, even from the WHI, that progesterone may actually make it more thrombogenic. But we don't know because, 1) there are not enough numbers and, b) I'd like to have a few more of these--

DR. LIPSHULTZ: But then you're putting a product on top of a base that already has warnings.

DR. LOCKWOOD: Right, but it would be like

using nitroglycerine and a calcium channel blocker for angina. And the question is, all right, nitroglycerine works, why not give another vasodilator? That should work even better.

But what happens when you do that is--I'm making this up. The drugs are perfectly fine.

[Laughter.]

I'm on a roll, though. But when you use them together there's some cardiotoxic effect that was not predicted, or you stop perfusing the brain and something bad happens.

And so, in fact, since you're labeling it to be used together, you have to understand the potential for synergistic or additive effects that are toxic.

DR. LEWIS: And it's not just that, but it's also that there all these warnings about "long-term"--quote-unquote--usage, because that's what's been linked to breast cancer. And we really don't have any data on that from the sponsor. And--you know, do we have concerns? Obviously, the Women's Health Initiative, if there's one thing it

taught us it's that estrogen is different than estrogen plus progestin. So what is estrogen plus androgen? We really don't know.

DR. GIUDICE: Dr. Tobert and then Dr. Dickey.

DR. TOBERT: Well, I think this discussion is actually very important. Ad maybe we can just clear it up.

My understanding--and maybe I'm completely wrong about this--is that the sponsor is recommending that if a woman is taking estrogen anyway--and I think they mean oral or transdermal estrogen. The label isn't totally clear on that. If she is taking that anyway, she can take the patch. If she stops taken systemic estrogen, she should stop taking the patch.

And the intent, at least, is not to encourage any more use of estrogen than would otherwise occur. And to that extent, it's not--the safety or otherwise of estrogen and progestin is not relevant.

DR. LEWIS: I don't think we can conclude

that. I mean, all the data we have on efficacy are from the combine usage. So, to me, looking at that data, if I'm going to prescribe the product, I would assume that there's something about having adequate estrogen on board that helps make this product work, and I would replace the patient with estrogen first--or I would consider it in somebody who's already placed on estrogen.

So--

DR. TOBERT: Would you treat the patient more or longer with estrogen? Or would you put a patient on estrogen just so you could use the patch? Because if you would, then it's a different question.

DR. LEWIS: If you're a literal, evidence-based person, you would only use it somebody who's already on estrogen. Obviously, they're studying it in patients who are not on estrogen, but we don't have those data to judge yet.

DR. TOBERT: Because if it causes more use of estrogen, that's a whole different and important

question. But it's a separate question.

DR. GIUDICE: Dr. Dickey has a comment.

DR. DICKEY: I think this alludes to the same thing we were just discussing--but this new drug application says it's only fro the surgically menopausal women, and yet when we talked about the long-term safety, it was clear that we're going to be looking at both surgically menopausal women and naturally occurring menopausal women--I presume without redoing any of the baseline data? So we'll begin to look then at some of these women may be getting three drugs: progestin, estrogen and androgen?

DR. MONROE: Well, the sponsor has parallel studies going on in women that are naturally menopausal who are presently on estrogen and progestin, and are now taking testosterone on top of that. And that's a group that I presume that they may eventually want to expand the claim for use in, depending on how the data is.

Similarly, they've indicated that they're looking at a population that's just taking

testosterone alone, or the drug might work equally well without the risk of estrogen.

So those are all things that we'll learn perhaps in the future.

DR. GIUDICE: But our charge is to look at the data that have been presented today, in the context of the indication.

DR. NISSEN: Folks, let's not make this any more complicated than it already is--you know? The question, I think, is very clearly stated. I mean, what we know is exactly what was done in these two trials. This is the database that we have. And we're being asked whether, in this population, treated in this way, whether we have an adequate safety database in order to make a decision.

I think that couldn't be more clear. And I don't think we have to dance around it.

VOICE: [Off mike.] And we can answer yes or no.

DR. GIUDICE: In fact, let's do that right now.

[Laughter.]

Now we'll start on this side of the table.

Dr. Montgomery-Rice.

DR. MONTGOMERY-RICE: No.

DR. STANFORD: No.

DR. MERRITT: No.

DR. NISSEN: And I must qualify again--

[Laughter.]

DR. GIUDICE: A simple yes or no will do.

DR. NISSEN: No, I really am--you know, first of all, I have to earn my $164 salary for coming here.

[Laughter.]

And, you know, these hormones have widespread biological effects, affecting virtually every tissue. And the heart is obviously one of the target organs, which is why you have a cardiologist sitting on the panel.

And I just have to review for a moment--just give me two minutes--to say that we have at least four or five pieces of data to suggest that there is a high probability of an excess cardiovascular risk with this product. They

include the evidence that endogenous testosterone levels are associated with coronary disease. We have the evidence from Dr. Soule's evaluation that shows that outliers are much more likely to have elevated lipids, elevated blood sugars, worse insulin resistance, increasing insulin levels; blood pressure changes of several mm/Hg, and sometimes in the range of 10 to 19 mm--which is highly associated with cardiovascular risk; elevated fibrinogen.

We also have the data on the known risks of estrogen-progesterone in the WHI study.

And so given that, the safety data base that we have of 500 patients, in my estimation, is at least an order of magnitude. I'm talking about 10-fold too small for us to assess a therapy that's likely to be used in millions of patients.

And so I think this answer is very, very clear. This is a much too small of a safety database--

VOICE: That's a no?

[Laughter.]

DR. NISSEN: --that's a no--for any reasonable assessment of cardiovascular risk.

But I do think--I want to put this on the record, because there's a very specific reason why it's too small. If we didn't know anything about these biological effects of hormones, maybe it would be okay. But we know a lot, and what we know doesn't suggest that it's a particular safe approach.

DR. GIUDICE: And your vote is?

[Laughter.]

DR. NISSEN: No.

DR. GIUDICE: Thank you.

DR. PATRICK: Simply no.

MS. SOLONCHE: No.

DR. LIPSHULTZ: No.

DR. LEWIS: No.

DR. LOCKWOOD: No.

DR. GIUDICE: No.

DR. DICKEY: No.

DR. BURNETT: No.

DR. TULMAN: No.

DR. HEIMAN: No.

DR. EMERSON: No.

DR. DORGAN: No.

DR. MACONES: No.

DR. GIUDICE: For this vote it was completely unanimous for no.

The previous question was three no's and 14 yeses.

Thank you.

The third question has three parts. The first part is: Are the safety concerns or unanswered questions associated with use of TTS in combination with estrogen that need to be studied; for example, questions about cardiovascular or breast cancer outcomes, or questions about risks and benefits in populations who are likely to use this product off-label?"

So ask the committee--I think we've actually discussed this at quite a bit of length. But I think the agency is asking us to state what these particular concerns are.

So would someone like to begin the

articulation of these?

Dr. Lockwood.

DR. LOCKWOOD: So I guess the answers would be: yes, there are safety concerns; and yes, they haven't been addressed.

And the three I'll focus on--and I'm sure other people will add--are the risk of venous thrombotic events; pregnancy exposure--obviously, given my concerns; and breast cancer.

And I think that in terms of venous thrombotic events, the follow-up that would be required--minimum follow-up--would be I'd like to protein-S activity values assessed. You probably have the data---you probably have the blood samples ready to be run. And I think it would be reasonable to follow up in the context of the actually post-approval study, the incidence of venous thrombotic events, a) because I am not overly concerned if protein-S activity levels are, in fact, normal, that there will be a strikingly elevated occurrence of venous thrombotic events, over that already anticipated with estrogen. So I

would like to see protein-S activity measure. If it were normal, then I think it would be reasonable to not change placebo versus treatment to do a post-approval follow-up in the context of the larger study proposed.

Secondly, I'm very concerned about the potential for use in pre-menopausal women, and concerned about the potential for exposing fetuses. Animal studies, particular in primates; extended virilization--levels, if possible, by labeling the testosterone; core blood; and then, obviously, some registry to follow up the fetuses that are exposed.

Lastly, breast cancer. And I think, again, the evidence is, in my mind, inconsistent toward an association. My bias is actually that androgens are protective, to be honest with you. But, again, I think follow-up in a broad post-approval study, looking specifically at the incidence of breast cancer.

DR. GIUDICE: Before we go around with additional recommendations, we need to go around just to answer a yes or a no question. That's part

a). Part b) is the actual--and I didn't make that clear--part b) is the actual delineation of what the recommendations are.

So I would like to start on this side of the table.

Dr. Macones?

DR. MACONES: Yes.

DR. DORGAN: Yes

DR. EMERSON: Yes.

DR. HAGER: Yes, there are safety concerns.

DR. TULMAN: Yes.

DR. BURNETT: Yes.

DR. DICKEY: Yes.

DR. GIUDICE: Yes.

DR. LOCKWOOD: Still yes.

DR. LEWIS: Yes.

DR. LIPSHULTZ: Yes

MS. SOLONCHE: Yes.

DR. PATRICK: Yes.

DR. NISSEN: Simple yes.

DR. MERRITT: Yes.

DR. MONTGOMERY-RICE: Yes.

DR. GIUDICE: Yes.

That was unanimous. Thank you.

Now we'll do 3-b). In addition to Dr. Lockwood's comments, are there other suggestions?

Yes, Dr. Nissen.

DR. NISSEN: It seems to me that we'd need to know about the post-menopausal patient--not the surgically menopausal patient, but the naturally menopausal patient before approval. Because the likelihood that those patients would be exposed is very, very high. And keep in mind that the naturally menopausal patient has coronary disease risks that are now approaching that of men. And so now you're talking about an entirely different risk category of patients.

And so until we've studied--until the sponsor has studied that population--you know, we're going to end up potentially exposing very large numbers of post-menopausal women to hormonal therapy for which we really don't have any evidence of whether it does or not increase cardiovascular risk.

DR. GIUDICE: Yes, Dr. Lewis.

DR. LEWIS: Yes, I'd like to see greater effort be made to enroll a larger population of African-American women. They're disproportionately affected by problems that engender hysterectomies and oophorectomies. They're at high risk for cardiovascular disease. And so I think it's going to be crucial to have a much better representation in the studies.

DR. GIUDICE: Thank you.

Dr. Hager.

DR. HAGER: Yes, and I would add Hispanics to that. Only 3 percent of the population were Hispanic. So I think minority groups need to be enrolled.

And I would just add to the comments that was previously made--and I'm dropping down a little bit, I realize--but I think that in light of the potential for off-label use of this product, we must have information from pre-menopausal women, and menopausal women. We must have information from women who are not only taking estrogen, but

are also taking with the progestin.

DR. GIUDICE: Thank you.

Yes, Dr. Dorgan.

DR. DORGAN: I'm concerned about the potential for breast cancer risk. Regrettably, in animal models--in rodents, particularly--the hormonal relationships like DHEA and breast cancer are not the same as you see in humans. And so using animal models might not suffice.

Also, we don't know the mechanism--we see observational data that women with elevated testosterone are at increased risk of breast cancer, but I agree: we don't know if it's causal, we don't even know a potential mechanism.

And so we don't have any really good intermediate markers that we could suggest to you.

I would hate to see FDA approving it and then using post-marketing drug surveillance as our only way of evaluating potential risk for breast cancer, because breast cancer doesn't occur just--you know, it's a long process. And once that process is started, stopping the testosterone is

not going to make the risk disappear like it's disappearing for acne and some of the other adverse effects. It's going to take a while before the woman's risk is lower.

I'd love to see randomized, controlled clinical trial, if people are interested in pursuing this further. I think that's the only way to really answer the question.

We'd prefer not to have any surprises like we did with the WHI.

DR. GIUDICE: Thank you.

Dr. Patrick.

DR. PATRICK: We didn't discuss this in the committee, but one of the exclusion criteria was that there could be no ongoing personal disturbances in the relationship of these couples. And I would like to see that a little bit loosened; meaning, how would this go down in normal life, where there are few disturbances in menopausal relationships--living through that.

[Laughter.]

DR. GIUDICE: Yes, Dr. Montgomery-Rice.

DR. MONTGOMERY-RICE: I do agree that many of these things need to be studied. But I also think you've got to put some of this in perspective. And putting it in perspective is that when you think about the indication for the product, and the indication of the product would be a symptomatic patient who has tried other ways to improve her libido, etcetera. And so she then does a risk-benefit analysis. And women do this every day when they come in they're having hot flushes. And they know that, based on the WHI, etcetera, that there's a potential of an increased risk of breast cancer if they take estrogen. But their symptoms are bad enough that they're willing to take that risk.

So I don't--even though there may be some increased risk--which I don't believe there probably is--with testosterone and breast cancer, I don't think that patients would do any different of an analysis than if they were coming in for estrogen for hot flushes, because this--if you were prescribing this correctly, and if we could control

how this was going to really be prescribed, then here you would have an indication of something that may actually give patients some--what are we calling it?--clinical meaningful benefit, in a patient who is actually symptomatic.

And so patients will make that same risk-benefit analysis.

However, I do agree: we don't have enough information for long-term safety.

DR. GIUDICE: Thank you. And that, then, brings us to part c) which is:"Should these concerns or questions be studied prior to approval of the product?"

So we'll go around the room again, starting with Dr. Rice.

[Pause.]

Yes or no.

DR. MONTGOMERY-RICE: I have to--I mean, everybody else has had a preference, so I have to give my little say beforehand.

I do think this drug is going to require

more study. I think that it should. However, I also say that in light of the fact that in an everyday sense, when I see patients who are coming in already using therapies that have not been tested in any type of market, etcetera, I was hopeful that we would have a product that we would be able to give patients that we know the risk and the benefits. And this product does allow that potential.

But I do, at the minimum believe that we need to look at it in the natural menopausal patient, who is going to have estrogen and progesterone on board already, to understand the concomitant hormone risk.

DR. GIUDICE: So your answer is--

DR. MONTGOMERY-RICE: Yes.

DR. GIUDICE: Thank you.

DR. STANFORD: And I will say yes, too, but I think it's an interesting issue for FDA policy, in a sense, a moving target in terms of what level of study is required for a drug.

I think the WHI has changed what probably

should be that level. So that's why I say yes.

DR. MERRITT: I would say yes.

DR. NISSEN: Yes.

DR. PATRICK: Yes

MS. SOLONCHE: Yes.

DR. LIPSHULTZ: I want to say yes, but I just want to add something here.

I mean, I understand there must be tremendous pressure about this drug. I mean, it's been expedited. It's the first drug available for the treatment of sexual dysfunction in women. And what concerns me the most--aside from what's been stated--is that there's going to be tremendous off-label use. And I just don't see how this can go to market without the data that the company is already--it looks like they're almost finished with, on natural menopausal women, because they're the ones who are going to be taking this drug, as well.

So my answer is yes, and I'd like to see that data. And I think it's to everybody's good to wait a little bit.

DR. LEWIS: I agree. I would say yes, and that's the data I want to see: the data in women who have a uterus.

Is it going to be affected by adding a progestin? Do you need a progestin? Maybe you don't. Maybe if you get an androgen effect on the uterus, maybe estrogen and androgen alone are enough. But we don't know. We just need more data.

DR. LOCKWOOD: Yes, I agree with my two colleagues, plus I'd like to see the protein-S data and the animal studies in pregnancy.

DR. GIUDICE: I vote yes.

DR. DICKEY: Yes.

DR. BURNETT: Yes.

DR. TULMAN: I vote yes. And also I don't think 20, 24, 26-week data is "long-term data.

DR. HEIMAN: The time to gain these data are before approval. So I do vote yes. I do think we need adequate long-term data that demonstrate both efficacy and safety. I do think we need it in women who are on estrogen-testosterone, as well as

estrogen-progestin-testosterone. And we need an adequately powered study.

DR. EMERSON: Yes.

DR. DORGAN: Yes.

DR. MACONES: Yes.

DR. GIUDICE: Thank you.

The first part of--oh--what were the results? Unanimous.

The first part of 3-c) is: "If yes, what studies do you recommend? And please comment on study populations, designs, endpoints, etcetera.

We have heard about increasing minority populations. Perhaps one or two people from the group could--I'm assuming you're asking for a study design, and what kinds of studies to be done before approval can be given. Is that correct?

DR. MONTGOMERY-RICE: Do we know what this natural menopause study that they're doing--do we know what the enrollment is on that? The one that's currently going on?

DR. GIUDICE: Do we know more details about it?

DR. MONTGOMERY-RICE: Do we know more details of that study?

DR. MONROE: Why don't we let the sponsor give you those details.

DR. LUCAS: We have two trials. The first trial was the one that I presented--the Natural Menopause I. We had about 550 patients that were randomized one-to-one.

The second trial, which is still ongoing but nearing completion, is a two-to-one randomization, and has just a little over 600 patients. So 400 patients will be on testosterone, and about 100 will be on placebo, and those patients have endometrial biopsies.

We are to just about 300 matched pairs. So that would be 200 in testosterone, and 100 in placebo.

DR. MONTGOMERY-RICE: Is it a year-long study?

DR. LUCAS: Yes, it is.

DR. MONTGOMERY-RICE: Okay.

DR. GIUDICE: And is that with or without--

DR. LUCAS: It is being extended, like our surgical menopause, so the patients are rolling over into an extension.

DR. GIUDICE: And is this with or without estrogen?

DR. LUCAS: It is with and progestin.

DR. MERRITT: And what dose of estrogen, please?

DR. LUCAS: Like our surgical menopause patients can use, you know, any approved estrogen does. But it is with continuous progestin.

DR. LEWIS: They both have continuous progestin?

DR. LUCAS: Both the Natural Menopause I, and the Natural Menopause II--both have continuous estrogen-progestin.

DR. GIUDICE: Yes, Dr. Nissen.

DR. NISSEN: Again, this is setting the bar very high, but I think it's important that the committee understand, and the FDA understand this issue.

Post-menopausal women, you know the

leading cause of death is cardiovascular disease. And even a hazard ratio of 1.1 or 1.2, when a million or more women are likely to be exposed, represents a huge burden of morbidity. And therefore I believe that you need a prospective, adequate sized, long-term study. I would do it in aspirin-eligible women; in other words, women who have enough risk that they would require aspirin for prophylaxis.

Now, we can discuss Framingham Risk Scores and all that, but I think you have to have a high enough risk population to simulate what could happen in the general population if this agent were used in a widespread way.

And I'd be happy to work with you, and I'll give you some thoughts from cardiovascular side about how you do that. But it's not going to be 600 patients. It's going to be 5,000 patients, or 10,000 patients.

And I recognize how high I'm setting the bar, but I must say this very clearly: the risk that was seen with Vioxx was very modest. But when

you translated that to 105 million prescriptions in 20 million Americans, it represented an enormous burden.

The potential for this agent to increase the risk of cardiovascular morbidity and mortality is substantial, and can only be answered--not the post-market surveillance. We know how badly that works. It has got to be done prospectively.

And I'm not devaluing the importance of this symptom and its treatment. But I also don't want to expose several million American women to the risk of heart attack and stroke, with their devastating consequences, in order to have one more sexual experience per month increase.

It is not an acceptable trade-off, and we cannot allow this to move forward until we have such data.

DR. GIUDICE: Dr. Tobert.

DR. TOBERT: Well, I hear what Dr. Nissen is saying. I think the committee needs to consider the practicability of doing a randomized controlled trial. I do have quite a bit of experience with

long-term, randomized trials to look at cardiovascular outcomes. And I can tell you to do a study that would rule out a 10 percent increase in the risk of major vascular events would probably require 100,000 patients--especially since the patients--I mean, really, to make it possible, you'd have to use elderly women, but elderly women, we've heard, do not use this product very much.

I think it's simply undoable. You cannot do this study. It's not practical--unfortunately.

DR. GIUDICE: I have a question for the sponsor, and that is: since the use of estrogen in post-menopausal women--and even peri-menopausal women--is decreasing, with the largest use in the peri-menopause, have you considered a trial with just testosterone alone, as opposed to adding the estrogen? Because, in reality, again, one is then committing long-term use, if one is going to be an outcomes-based type of prescriber.

DR. LUCAS: Yes, we are. We're just finishing recruiting a study that's enrolled both surgical and naturally menopausal women not on

concomitant estrogen or progestin. Vaginal estrogen is allowed.

Part of the reason is to rule out any other cause of sexual dysfunction.

DR. GIUDICE: And how large is that?

DR. LUCAS: About 750 women will be enrolled in this study, and we're looking at two doses of testosterone--the 150 mcg patch, and the 300 mcg--and placebo. And it will be one year in duration.

Double-blind.

DR. GIUDICE: Thank you.

DR. TOBERT: May I just add to my previous remarks the fact that--I mean, there is an implication that if a huge trial like this is demanded for a testosterone patch--testosterone, of course, is a natural hormone that we all have. And the implication of that is that any product--any new product--that binds to a hormone receptor--an agonist, an antagonist, not necessarily in the reproductive area--the same sort of thing could be demanded.

I don't quite see what is so hazardous, a priori, about testosterone that one should demand such huge and--as I say--in any case, impossible trials.

DR. GIUDICE: Dr. Nissen.

DR. NISSEN: Well, those of us that are male, in addition to suffering from alopecia, which I fortunately have enough testosterone to have, we have a cardiovascular risk which is substantially greater than that of women. Why? And a lot of us think that testosterone is an atherogenic substance. And there's lots of evidence to suggest that. And until proven otherwise, it must be assumed to be the case.

And so when you have a therapy here that you're going to, again, expose a lot of people to, Jonathan, you have to know this. Because on a population basis, this can involve tens of thousands of myocardial infarctions and potentially deaths.

So I just don't think we have the evidence of the safety of giving women testosterone that we

need in order to know that we're not going to make them have cardiovascular risk rates that look like those rates of men.

And until we know that, I think we've got a real problem here.

DR. TOBERT: Can I respond to that/ I mean, there is no evidence that men have higher rates of coronary disease because of their circulating androgens. All attempts to correlate circulating androgens--whether it's free or total--to the risk of coronary or cardiovascular disease have failed. I mean, there's just no correlation. It may have something to do with the testosterone surge that occurs perinatally, but certainly it doesn't have anything to do with the levels that we have as adults.

In any case, as I say, Steve--how are you going to do this trial? It's undoable.

DR. NISSEN: I don't think it's undoable, because what you're doing whenever you face a situation like this is you go to a well-defined, high-risk population, and you find out--if you can

show that the agent--what the hazard ratio is in the higher-risk individuals, then you can feel very comfortable in giving it to lower risk individuals. And so you define a group of people that are at relatively high risk: women's with lots of risk factors. And you can have an enriched population. And that's what's done in lipid-lowering trials all the time. And you know, you're involved the SEARCH trial. Those are not done in normal, low-risk people. They're done in high-risk people.

DR. TOBERT: All right. They all have an MI. And you can't do--the people who have an MI are not going to be taking this patch. There's an incompatibility.

DR. GIUDICE: Dr. Rice.

DR. MONTGOMERY-RICE: I mean, I think we need to be realistic here. People who are at high risk for cardiovascular disease are not people who are concerned about--necessarily--increasing their level of libido to the point where they would take that risk--

DR. NISSEN: That--

DR. MONTGOMERY-RICE: --let me finish, please--where they would take that risk of being enrolled in a trial. And I don't even know how realistic this is to get through the IRB.

So, while I hear what you're saying, that there is some risk--or potential risk--I don't want us to offer or suggest to the FDA that we should do some trial that's unrealistic to ever have performed.

If you think about participation in clinical trials, there are major barriers getting women to participate in clinical trials. So you're talking about not only finding women who meet this criteria of this defined sexual dysfunction, but then on top of that we want you to also be at risk for having a heart attack so we can make sure that we are not increasing your risk of having the heart attack.

I want us to be realistic here. And I don't think you're being realistic.

DR. NISSEN: Let me reassure you that patients that I see that have coronary heart

disease, that have had an angioplasty, by-pass, or myocardial infarction frequently--one of the first questions they ask when they come back in to see me is when can they resume sexual activity. So the idea that sex stops with heart disease is simply wrong.

And I think we can--I'm convinced that we could define for you a population, not of whom would be post-MI. Some of them would be multi-risk factor patients, where the risk would be high enough that you could get a signal in a reasonable size trial.

Now, where you set the hazard ratio has to be discussed. But it seems to me that that's the prudent thing to do.

DR. GIUDICE: Does the FDA feel that it has had sufficient suggestions--

[Laughter.]

--for approaches to clinical trials?

And we would assume that you would be working with the sponsor in this, as well.

DR. GRIEBEL: Yes.

DR. LEWIS: could I just bring up one more little point along those lines?

I tend to agree with Dr. Montgomery-Rice about the--you know, it's a different population. But maybe just one small thing to throw in there: women who have had a hysterectomy do tend to be at somewhat higher risk for cardiovascular disease already. So if there's any way to work within that population, perhaps you could prove the point a little bit easier.

Another surrogate that you could look at is C-reactive protein levels.

DR. GIUDICE: Yes, Dr. Heiman.

DR. HEIMAN: I would just like to speak to women's brains--and that would be since there were some significant effects with cognitive change in the WHI study, that at least some study along in here tries to track that. It hasn't been raised. There may be no risk, there may even be a benefit. But somebody should tract that because if anything that women are worried about--other than their overall life and life span--it has to do with their

cognitive functioning.

DR. LIPSHULTZ: Didn't you have some data on that? Wasn't there some data on cognitive function in one of your slides?

DR. HEIMAN: Whatever there was, there isn't enough, in my opinion.

DR. LOCKWOOD: I think it was aggression, and anxiety of something.

DR. HEIMAN: That's not what I mean. I mean in the dementia direction, as opposed to simply mood. Mood is something else which is interesting, but I'm talking about actual cognitive functioning in terms of processing information.

DR. GIUDICE: Thank you.

Yes?

DR. HAGER: Could we also suggest that DHEA be used as a marker, in addition to testosterone, total and free?

DR. GIUDICE: We can suggest that. Okay.

DR. LIPSHULTZ: [Off mike.] [Inaudible.]

DR. HAGER: Well, we have heard today that testosterone is the indicator of altered sexual

function in women. And when they have low testosterone, they have low sexual function. And that really is not true.

And I think that there's some information that DHEA may be more tightly attached to altered sexual function. And I'm just saying that we could use that as a marker.

DR. GIUDICE: Okay.

3(c) part (ii) is if we had an answer of "no" to question 3(c)--and it was unanimously "yes"--however, I think there is the issue of the claims-based cohort study, which we have discussed. And I want to bring to the attention of the committee, and ask you if we need to have any further discussion about this?

Yes, Dr. Stanford.

DR. STANFORD: Well, I'd just say that ideally a study would be done along the lines of what Dr. Nissen is suggesting. I am not totally clear on how feasible it is. And I guess that would have to be a judgment call. But if it is feasible, and you did that, I don't think you'd

need the post-marking study.

DR. GIUDICE: The claims-based study that was proposed.

DR. STANFORD: The claims-based study--yes.

DR. GIUDICE: Yes, Dr. Emerson.

DR. EMERSON: I just felt--and I think this is pretty much a moot point now--but I felt that the level of detail that was provided about how such a study would be done made it just completely impossible to judge whether that would have been adequate or not, because there would be a whole lot, in terms of how you would match patients, and whether you're getting comparable patients who were on Intrinsa versus not. And without further information I just don't think anything could be said.

DR. GIUDICE: Okay. Thank you.

So we now reach our fourth and final question, and that is: "Are the efficacy and safety data adequate to support approval of TTS?"

And I will begin on this side of the table.

Dr. Macones.

DR. MACONES: No.

DR. DORGAN: No

DR. EMERSON: No.

DR. HAGER: No.

DR. TULMAN: No.

DR. BURNETT: No.

DR. DICKEY: No.

DR. GIUDICE: No.

DR. LOCKWOOD: No.

DR. LEWIS: No.

DR. LIPSHULTZ: No

MS. SOLONCHE: No.

DR. PATRICK: No.

DR. NISSEN: No.

DR. MERRITT: No.

DR. MONTGOMERY-RICE: No.

DR. GIUDICE: It's unanimous.

I want to thank the committee for their hard work, and also our participants in the open public forum.

And this now concludes our Advisory

Committee meeting. Thank you.

[Whereupon, at 4:22 p.m., the meeting was adjourned.]

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