FOOD AND DRUG ADMINISTRATION

ADVISORY COMMITTEE FOR

REPRODUCTIVE HEALTH DRUGS

Rockville, Maryland

Monday, September 8, 2008

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CINDY PEARSON

DIANA ZUCHERMAN

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P R O C E E D I N G S

(8:03 a.m.)

DR. CARSON: Welcome. This is the Advisory Committee for Reproductive Health Drugs to the FDA. So hopefully, you're in the right place at the right time.

My name is Sandee Carson. I'm the chair of this Committee. And we have some interesting presentations in store for you today by both the sponsor and the FDA. But before we begin the meeting, I'd like to go around the Committee and have us all introduce ourselves.

Let me begin by saying that I'm Sandee Carson. I'm a reproductive endocrinologist and professor of obstetrics and gynecology at the Warren Alpert Medical School of Brown University, director of the Division at Women and Infants Hospital of Rhode Island.

MS. BHATT: Good morning. My name is Kalyani Bhatt. I'm the designated federal

official.

DR. GARDNER: My name is Jacqueline Gardner. I'm a professor from the University of Washington, Department of Pharmacy.

DR. LIU: I'm Jim Liu. I'm a reproductive endocrinologist, and I'm chairman of the Department of OB/GYN at the Case Medical Center, Case Western Reserve in Cleveland, Ohio.

MS. PORTIS: I'm Natalie Compagni Portis, and I'm the patient representative.

DR. COLLINS: I'm Mike Collins. I'm from the National Institutes of Health. I'm an endocrinologist with expertise in bone and mineral metabolism. I'm the chief of the Skeletal Clinical Studies Unit.

DR. ADASHI: Good morning. I'm Eli Adashi. I'm also a reproductive endocrinologist and a professor at Brown University.

DR. ROTHSTEIN: I'm Adrienne Rothstein. I'm a clinical analyst in the Division of Reproductive and Urologic Products.

DR. WILLETT: Jerry Willett, medical

officer, Division of Reproductive and Urologic Products, FDA.

DR. MONROE: I'm Scott Monroe. I'm the director of the Division of Reproductive and Urologic Products.

DR. SHAMES: I'm Dan Shames. I'm the deputy director of the Office of Drug Evaluation III at FDA.

DR. GUT: Good morning. I'm Robert Gut. I'm a senior medical director at Novo Nordisk. I'm the industrial representative here.

DR. ROSEN: Hi, I'm Cliff Rosen. I'm the medical director of Translation on Clinical Medicine at Maine Medical Center.

DR. CARSON: Brad, I think we're going to need a new screen.

DR. MERRITT: Good morning. Diane Merritt, professor of Obstetrics and Gynecology, Washington University, St. Louis.

DR. JOHNSON: Julia Johnson, vice chair of Gynecology at the University of

Vermont.

DR. NELSON: Larry Nelson. I'm an investigator at the Intramural Research Program of the National Institutes of Health. I'm a reproductive endocrinologist.

DR. STADEL: Bruce Stadel. I'm a retired medical officer with the Division of Metabolic Endocrine Products at the FDA.

DR. GOOZNER: I'm Merrill Goozner with the Center for Science in the Public Interest, and I'm a consumer representative on this Committee today.

DR. GILLEN: My name is Daniel Gillen. I'm an associate professor of statistics at the University of California, Irvine.

DR. CARSON: Thank you. In your packet, you'll see the agenda, and also, you have slides from the sponsor's presentation. For topics such as those being discussed at today's meeting, there are a variety of opinions, some of which are quite strongly held. Our goal at today's meeting is to hold a fair

and open forum for discussion of these issues. And those individuals who have strong views can express their views without interruption.

So as a gentle reminder, individuals will be allowed to speak into the record only if recognized by this chair. And we look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of this meeting.

We are aware that members of the media are anxious to speak with FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with media until after the conclusion of the meeting.

Also, the Committee is reminded to please refrain from discussing meeting topics during breaks and during lunch.

Thank you.

Let me also suggest that in your packet to the Committee are the listed questions that we'll be voting on later today. I have always personally found it helpful to look at those questions prior to the open forum and to the presentations so you have an idea of what especially to ask when we'll be voting later.

Let me turn it over to Ms. Bhatt, for the discussion of the Conflict of Interest.

MS. BHATT: Thank you, Dr. Carson. Good morning. I first would like to remind everyone present to please silence your cell phones if you haven't already done so. I would also like to identify the FDA press contact, Rita Chappelle. If you're here, please stand. Okay, she's not here.

I will be reading the Conflict of Interest. The FDA is convening today's meeting of the Advisory Committee of

Reproductive Health Drugs under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representatives, all members and temporary voting members are Special Government Employees, SGEs, or Regional Federal Employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the Committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those at 18 U.S.C. Section 208 and Section 712 of the federal Food, Drug, and Cosmetic Act, FD&C Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this Committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to

grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of this Committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of U.S.C. Section 208, their employers.

These interests may include investments; consulting; expert witness

testimony; contracts/grants/CRADAs; teaching/speaking/writing; patients and royalties; and primary employment.

Today's agenda involves discussions of New Drug Application (NDA) 22-242, proposed trade name Fablyn, lasofoxifene tartrate -- tablets -- originally developed by Ligand Pharmaceuticals, Inc., in the collaboration agreement with Pfizer, for the proposed indication of the treatment of osteoporosis in postmenopausal women at the increased risk of fracture. This is a particular matters meeting during which specific matters related to Fablyn will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the Committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

With respect to FDA's invited industry representative, we would like to

disclose that Dr. Robert Gut is participating in this meeting as a non-voting industry representative, acting on behalf of regulatory industry. Dr. Gut's role at this meeting is to represent industry in general and not any particular company. Dr. Gut is employed by Novo Nordisk, Incorporated.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all participants to advise the Committee of any financial relationship that they may have with any firms at issue.

Thank you.

DR. CARSON: Just in time. Our first speaker is Dr. Scott Monroe, who as you've heard

is the director of the Division of Reproductive and Urologic Products at FDA.

This will give Committee members a couple of moments to go ahead and read those questions while we're waiting.

DR. MONROE: Can you put on my first slide or do I do that? How do we get my first slide up? Thank you.

I'll reintroduce myself. I'm Scott Monroe, the director of the Division of Reproductive and Urologic Products at the FDA. And I also welcome you to this meeting of the Advisory Committee for Reproductive Health Drugs.

I'd like to thank Dr. Carson and the other members of the Advisory Committee for their participation in this meeting, because I know the preparation and actual participation requires a considerable commitment of time.

The focus of today's meeting is NDA 22-242, which has been submitted by Pfizer

for lasofoxifene tartrate. Lasofoxifene is a Selective Estrogen Receptor Modulator, or SERM, that Pfizer has been investigating for the proposed indication of treatment of osteoporosis in postmenopausal women at increased risk of fracture. The Division is asking the Committee members to evaluate the information that has been provided in the Pfizer and FDA background documents -- information that will be discussed further today.

More specifically, we are asking the Committee, via a series of questions, to provide guidance to the Division regarding, first, several safety issues that are of concern; and second, the overall risk/benefit profile for lasofoxifene for the treatment of postmenopausal osteoporosis.

Some of the Committee members and audience may be wondering why this Advisory Committee, instead of the Advisory Committee for Endocrine and Metabolic Drugs, is being

asked to review a potential new therapy for the treatment of postmenopausal osteoporosis. Amongst the reasons is that responsibility for the review of new products for the treatment of osteoporosis is being transferred from the Division of Metabolic and Endocrine Products to the Division of Reproductive and Urologic Products.

In addition, some of the safety issues that are of concern in this NDA are gynecologic-related issues, which this Advisory Committee is very well-suited to address. As you will also note, several experts in the area of osteoporosis therapy, who are not regular members of this Committee, are participating in today's meeting.

Osteoporosis, as most of you know, is a disorder characterized by low bone mass, and structural deterioration of bone tissue, leading to fragile bones and increased risk of fractures. Osteoporosis is a serious

public health concern, both because of the number of women that are affected and the morbidity that is often associated with the disorder.

Estimates made by the National Osteoporosis Foundation include the following: Approximately 10 million Americans have osteoporosis, of which 80 percent are women; up to 50 percent of women 50 years of age or older will have an osteoporosis-related fracture in their lifetime; and in the year 2005, there were estimated to have been approximately 2 million osteoporosis-related fractures in the U.S., resulting in a health care cost of approximately $17 billion.

This slide lists approved therapies in the United States for the treatment and/or prevention of postmenopausal osteoporosis. Bisphosphonates are frequently prescribed for the treatment of osteoporosis, and include alendronate, ibandronate, risedronate, and

zoledronic acid. Other anti-resorptives include calcitonin and estrogen products. Teriparatide, an analogue of parathyroid hormone, is considered to be an anabolic bone agent because of its pharmacological effect of stimulating the formulation of new bone. Among the class of Selective Estrogen Receptor Modulators, only raloxifene is approved for the treatment of postmenopausal osteoporosis.

The Division does not have any specific efficacy-related questions for the Committee. The Division believes that the applicant's pivotal Phase 3 study, known as the PEARL study, has demonstrated that treatment with lasofoxifene for up to three years significantly reduced the risk of a new or worsening radiographic vertebral fracture.

The Division's questions for the Committee focus on safety issues of concern, and the overall assessment of the benefit/risk profile for lasofoxifene for

treatment of postmenopausal osteoporosis.

The next several slides will list the safety issues of greatest concern to the Division, and the specific questions that we are asking the Committee to address. We request that the Committee focus particular attention on those areas of the applicant's and the Division's presentation that pertain to these safety issues.

The safety issue of greatest concern to the Division is that of all-cause mortality. The hazard ratios for all-cause mortality in lasofoxifene-treated subjects compared to subjects receiving placebo were increased in the PEARL study and in the applicant's overall Phase 2/3 development program for lasofoxifene.

Unexpectedly, the increase in all-cause mortality was greater in the 0.25 milligram dose group, the lower dose group.

As seen in the table, the lower limit of the 95 percent confidence limit for

the hazard ratios in the 0.25 milligram dose groups either just reached 0, as is seen for the PEARL study, or did not -- I'm sorry, just reached one, as is seen in the PEARL study, or did not cross one, as is seen in the Phase 2/3 overall program.

We are asking the Committee two questions related to all-cause mortality. The first is, do you believe that these data regarding all-cause mortality reflect a true increase in mortality in lasofoxifene-treated subjects?

The follow-up question is, if you believe there is a true increase in mortality, do you believe that the applicant's regional analysis of the distribution of the deaths, which shows the imbalance to be largely in Region 2, namely Mexico, Central and South America, is reassuring regarding the safety profile of lasofoxifene for use by women in the United States?

The second issue of concern regards venous thromboembolic events. The data provided in the NDA demonstrated a significant increase in the risk of overall venous thromboembolic events, deep venous thromboembolic events, and pulmonary emboli in lasofoxifene-treated subjects.

The specific question that we are posing to the Committee regarding this issue is, are the safety findings for venous thromboembolic events in lasofoxifene-treated women of greater concern than those associated with the use of approved hormonal products for postmenopausal osteoporosis therapy or menopausal symptom therapy?

The third safety issue concerns the significant increase in the proportion of lasofoxifene-treated subjects who developed gynecologic-related adverse events. These events were endometrial polyps, endometrial thickening or hypertrophy, and vaginal bleeding.

These adverse events led to a significant increase in the proportion of lasofoxifene-treated subjects who underwent uterine-related medical procedures to evaluate or treat these events.

We are addressing two questions related to gynecological adverse events to the Committee. The first is, do the gynecologic adverse events associated with lasofoxifene treatment entail a significant management problem for general health care providers and/or burden for patients?

The second question is, should endometrial biopsies be performed in women taking lasofoxifene who are not having vaginal bleeding, but are found incidentally to have endometrial thickening on an imaging procedure?

The final questions to the Committee concern the risk/benefit profile of lasofoxifene in the specific population of women with osteoporosis for whom treatment

with lasofoxifene might be indicated. We're asking the Committee members to discuss and vote, first, upon the following question: Is there a population of postmenopausal women with osteoporosis in which the benefit of treatment with lasofoxifene is likely to outweigh the risks?

Our final two questions for the Committee concern the population of postmenopausal women with osteoporosis for whom lasofoxifene might be indicated. The first of these final two questions relates to the previous question, and is -- if there is a population in which the benefit/risk profile would be favorable, would this population be all women with postmenopausal osteoporosis -- limited to a subgroup at higher risk for fracture than the general population of women with osteoporosis -- or limited to women who do not tolerate other osteoporosis therapies or in whom other osteoporosis therapies are not appropriate?

Our final question is, if you believe that treatment should be limited to a higher risk for fracture population, how would you define this population? In responding to this latter question, we'd like the Committee's thoughts regarding the use of an algorithm such as the fracture risk assessment, or FRAX tool, which includes both bone mineral density and other risk factors that might better identify women at higher risk for fracture than the use of bone mineral density alone.

The agenda for the remainder of this meeting is as follows. In a moment, Pfizer will make its presentation. After a short break, the FDA will make its presentation. The Committee will then have the opportunity to pose questions to both Pfizer and the Division. After lunch, there will be an open public hearing, followed first by Committee discussion regarding the FDA's issues and questions, and later by

Committee voting.

I'll now turn the meeting back to Dr. Carson.

Thank you.

DR. CARSON: Thank you. Let me just remind the Committee that if you could write down your questions and also to whom you want those questions addressed, we'll address them all at 11:00 to both sponsor and FDA.

So at this point in time, let me ask the sponsor, Pfizer, Incorporated, to come forward. And Mr. Brian Green, who is the director of Worldwide Regulatory Strategy for Pfizer Global Research and Development, will begin.

MR. GREEN: Thank you, Dr. Carson.

Good morning, ladies and gentlemen. My name is Brian Green, lasofoxifene regulatory lead. On behalf of Pfizer, I would like to thank you for the opportunity to review our lasofoxifene data. The proposed trade name for lasofoxifene is

Fablyn.

The indication for which we are currently seeking approval is the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

The following presentation will show that lasofoxifene, at a proposed dose of 0.5 milligrams per day, is safe and efficacious for the proposed indication.

Our presentation this morning will be as follows: Dr. Steven Cummings, director of the Coordinating Center, and professor emeritus of Epidemiology and Biostatistics and Medicine at the University of California at San Francisco, will set the stage by providing an overview for the unmet medical need in the treatment of osteoporosis.

Dr. Cummings will be followed by Dr. David Thompson, lasofoxifene development team leader, who will provide an overview of the development program, and discuss the lasofoxifene efficacy results.

Dr. Roisin Armstrong, clinical lead, will then present the safety results for lasofoxifene.

Next, Dr. Claudia Turner, from our safety and risk management organization, will discuss how our proposed risk management plan will address the identified and potential risks of lasofoxifene use.

Finally, Dr. Steven Goldstein, professor of Obstetrics and Gynecology at New York University Medical Center, will discuss the benefit/risk profile of lasofoxifene, and provide his clinical perspective on the findings.

In addition to my colleagues from Pfizer, the consultants listed on this slide will also be available to respond to your questions.

At this point, I would now like to introduce Dr. Steven Cummings.

DR. CUMMINGS: Thank you very much. It's my pleasure this morning to give you a

brief overview of the definition, the prevalence, and the consequences of osteoporosis; the risks and consequences of several common conditions in postmenopausal women; and the efficacy and safety of current treatments for osteoporosis.

I'd like to start off by thanking Scott Monroe for giving the first part of my presentation.

Thank you, Scott.

But I get to show visuals to tell you that above represents normal bone and below represents osteoporotic bone. And visually, you can see that osteoporosis is characterized by low bone mass. And you can see structural deterioration that's associated with osteoporosis. And that's why the bone is more fragile and leads to a substantially increased risk of fractures.

Osteoporosis is diagnosed using bone density. The T-score are numbered standard deviations minus 2.5 below the

average for young adults, or is defined as a vertebral fracture. As Scott indicated, about 10 million women in the United States are said to have osteoporosis according to the National Osteoporosis Foundation, which means that a 50-year old -- as Scott has said, a 50-year-old has about a half chance during her lifetime of suffering a fracture.

And of the 2 million fractures that you were told that are attributable to osteoporosis, a half a million of them are vertebral fractures, but 3 times as many are nonvertebral fractures.

And this problem, as society ages, will continue to grow to 3 million fractures it's estimated attributable to osteoporosis by 2025, representing around a $25 billion health care expenditure per year.

Fractures impair the quality of life. I'll go through clinical, vertebral, and then nonvertebral fractures. We've done studies in which women keep diaries after a

fracture occurs. And from those, we have found that in the short term, a woman who suffered a clinical vertebral fracture has about three weeks of bed rest and six months of limitations in their daily activities.

And studies by Greendale and colleagues that surveyed women's functional status about seven years on average after these fractures showed that over that long term, women who had suffered clinical vertebral fractures had an increased risk of difficulty with bending, with lifting, with dressing, and shopping.

Now, nonvertebral fractures, over the short term, are a more heterogeneous group, but are associated with about a two to six month limitation of activity of daily living. And again, over the longer term, still are associated with difficulties dressing, shopping, and doing housework.

Now, let me turn to several other diseases for postmenopausal women. Here are

the lifetime risks of disease events in white postmenopausal women looking forward from the age 50. So a 50-year-old woman looking forward has about one chance in three of suffering a nonvertebral fracture, and about one in six women will develop a vertebral fracture. About one-third will develop diagnosis of coronary heart disease, and one in five will suffer a stroke. About one out of eight postmenopausal women will eventually develop breast cancer.

These conditions are associated with decrements in quality of life. On a scale where death represents a 100 percent in decrease in quality of life, in the first year after a clinical vertebral fracture, studies of women indicate that this is equivalent to about a 37 percent decrease in quality of life. Nonvertebral fractures, on average, about a 14 percent loss of quality of life in the first year. The diagnosis of coronary heart disease associated with about

a 10 percent loss. And stroke, over a 50 percent loss of quality of life; whereas early breast cancer associated with about a 23 percent decrease in quality of life.

And so therefore, I think that the ideal treatment for postmenopausal women would decrease both vertebral fractures and nonvertebral fractures, decrease the risk of coronary heart disease, as well as decreasing the risk of stroke, decrease breast cancer risk, and also relieve menopausal symptoms that include hot flashes and vaginal atrophy. And do all of that without increasing the risk of endometrial cancer or venous thromboembolic disease.

Now, let's turn to the treatments we have for osteoporosis. Again, Scott outlined them nicely, and I'm not going to talk about parathyroid hormone, which is limited to more severe osteoporosis.

Bisphosphonates decrease the risk of vertebral fractures by about 50 to

70 percent. Most of them also decrease the risk of nonvertebral fractures on the order of to 20 to 35 percent.

Bisphosphonates also have adverse events -- adverse affects -- and alendronate, which is taken as a pill, has been associated occasionally with gastrointestinal discomforts. And alendronate and zoledronate, in some studies, not all, have been associated with an increase in serious adverse events of atrial fibrillation.

Zoledronate is given as an intravenous infusion once yearly. And with the first infusion, about 15 percent of women suffer acute phase reactions, meaning fever and myalgia. Now, very rarely, osteonecrosis of the jaw, which is bone that's exposed in the jaw, has been associated with the long-term use of bisphosphonates for the treatment of osteoporosis. And recently, two case series suggest that the long-term use of alendronate, and perhaps other

bisphosphonates, might increase the risk of femoral shaft fractures.

Now, as a consequence largely of the concerns about osteonecrosis of the jaw, use of bisphosphonates has decreased about 20 percent during the last year.

Turning to estrogen therapy, in the Women's Health Initiative, we found that estrogen therapy decreased the risk of vertebral fractures by about 35 to 40 percent, and nonvertebral fractures by about a third. But in the WHI, we also found that hormone therapy was associated with an increased risk of breast cancer, coronary heart disease, stroke, venous thromboembolic disease, and in a substudy increased the risk of dementia among those age 65 or older.

The profile differed somewhat for estrogen therapy alone, as indicated by the asterisks. Raloxifene, the other approved SERM, decreases the risk of vertebral fractures by about 35 to 40 percent, but does

not decrease the risk of nonvertebral fractures. It also has been shown to decrease the risk of invasive breast cancer by 50 to 70 percent, with no effect on the risk of coronary heart disease or stroke.

Raloxifene has adverse effects. Venous thromboembolic disease increased by a factor of two or three. It does not increase the risk of vaginal bleeding, but in trials with ultrasound surveillance, there is an increase in the occurrence of endometrial polyps that's about twofold, and about a twofold increase in the incidence of endometrial biopsies.

So this leads me to a simple summary of current treatments for osteoporosis. You can see bisphosphonates reduce the risk of fractures, and that's it. Raloxifene decreases the risk only of vertebral, but not nonvertebral fractures, and decreases the risk of breast cancer, not other diseases. Hormone therapy decreases

the risk of fractures of both types, but because of its other effects on other postmenopausal diseases, it's no longer recommended by experts for the treatment of osteoporosis first line.

Let's return to the ideal treatment for postmenopausal women. It would decrease both vertebral and nonvertebral fractures; it would decrease the risk of coronary heart disease, and stroke, and breast cancer, while relieving menopausal symptoms of hot flashes and vaginal atrophy; and would do all that without increasing the risk of endometrial cancer or venous thromboembolic disease. And of course, no current treatment that we have meets all of those needs.

And with that, I'd like to turn over the podium to Dr. David Thompson.

DR. D. THOMPSON: Good morning. I'm David Thompson, team leader for lasofoxifene. I've been involved with the program since its inception, having led the program that

discovered lasofoxifene, and now as the development team leader.

The extensive development program has characterized the benefits and risks of lasofoxifene across multiple studies. Lasofoxifene offers a unique constellation of benefits as a new therapeutic option for the treatment of osteoporosis. We will define each of those benefits.

Additionally, we've characterized the risks associated with lasofoxifene. We will define each of those risks. Further, we have developed a risk management plan that is designed to minimize those identified risks.

Our focus today is to define the benefits and risks of lasofoxifene for the 0.5 milligram dose in the treatment of osteoporosis in postmenopausal women. The data support a favorable benefit/risk profile of lasofoxifene 0.5 milligrams.

Lasofoxifene is a Selective Estrogen Receptor Modulator, or SERM, and is

in the same chemical class as raloxifene. Lasofoxifene binds selectively and with high affinity to the estrogen receptors, and initiates gene transcription in target tissues. Lasofoxifene acts as an estrogen agonist in the bone and as an antagonist in the breast.

Throughout the preclinical and clinical program, lasofoxifene has shown consistent efficacy and safety. The lasofoxifene clinical development program has been extensive. The clinical program included more than 15,000 patients in 40 clinical trials. There were 23 Phase 1 studies and 11 Phase 2 studies. These studies established doses that achieved efficacy and safety across multiple indications in multiple populations.

The Phase 3 program consisted of six studies that evaluated three different indications -- osteoporosis prevention, vaginal and vulva atrophy, or VVA, and

osteoporosis treatment. The blue bars in the slide represent the trials conducted in the treatment of osteoporosis in postmenopausal women, and reflect the largest number of patients in the program.

Since the submission of the two NDAs for osteoporosis prevention and VVA in 2004, the patient exposure to lasofoxifene has increased approximately nine-fold, and now totals about 28,000 patient-years of exposure. Importantly, these additional patient-years of exposure build a solid foundation for understanding the safety of lasofoxifene. The PEARL trial specifically addresses the safety and efficacy of lasofoxifene in the treatment of osteoporosis in postmenopausal women.

PEARL, postmenopausal evaluation and risk reduction with lasofoxifene, is a perspective double-blind randomized placebo-controlled multicenter global study conducted with an ITT design and analysis.

An important element of this study was the inclusion of patients in the study who were randomized, began treatment, but opted to go off treatment; i.e., ODIS, off drug in study. Patients who opted to discontinue treatment were encouraged to remain in the trial, thus providing more extensive safety information about patients beyond the 30 day cutoff used for reporting safety events in most clinical trials. These ODIS patients were included in analyses.

Women were enrolled in PEARL who were between the ages of 60 and 80 years of age, and at least five years postmenopause. To be included in the trial, each patient must have been at increased risk for skeletal fractures, as reflected by a low bone mineral content in the spine or hip. Also, patients could be enrolled if they had less than four vertebral fractures at baseline.

PEARL was designed as a three-year study. During the eight-week run in and

prior to randomization, all patients received Vitamin D and calcium supplementation. Vitamin D and calcium supplementation was continued throughout the trial for all patients.

8,556 patients were randomized to one of three groups -- placebo, 0.25 milligrams lasofoxifene, or 0.5 milligrams lasofoxifene QD dosing. Each group contained 2,852 patients. The three-year trial design was consistent with the regulatory guidance for the evaluation of new treatments for osteoporosis.

The primary endpoint in the three-year PEARL trial was the reduction of risk in radiographic vertebral fractures. Also, two key secondary endpoints were designated -- multiple vertebral fractures and clinical vertebral fractures. Additional secondary endpoints included nonvertebral fractures, bone mineral density, ER positive breast cancer, major coronary events, and

vaginal PH. Prior to the completion of the three-year time point and before the unblinding of the three-year data, PEARL was extended to five years to obtain long-term safety and efficacy data.

At the completion of three years, all subjects were required to consent to continue in the trial, either continuing on their randomized treatment or remaining in the trial for observation, but off treatment. Approximately 92 percent of the 8,556 patients who were randomized into PEARL completed the three years of the trial, and approximately 74 percent of the patients completed five years of study.

Primary endpoints in PEARL at five years were reductions in nonvertebral fractures and ER positive breast cancer. Key secondary endpoints at five years included clinical fractures and hip fractures. Other secondary endpoints at five years included clinical fractures, invasive breast cancer,

and major coronary events.

External blinded independent endpoint committees adjudicated key endpoints throughout the conduct of the PEARL trial. The breast cancer endpoint committee adjudicated breast cancer cases.

The cardiovascular committee adjudicated coronary events, venous thromboembolic events, stroke, and cause of death for all subjects. The gynecology committee adjudicated endometrial cancer, endometrial hyperplasia and surgery due to prolapse, and urinary incontinence.

Also, PEARL utilized expert external central imaging readers to adjudicate radiologic findings, including all fractures, breast density, and endometrial thickness. A central group of expert pathologists read endometrial biopsies.

Baseline characteristics were well-balanced across each of the three groups. Mean age at randomization for the

three groups was about 67 years of age. Also, patients were about 19 years postmenopause. Each of the groups had a baseline lumbar BMD T-score of -3.0 at baseline that indicated increased risk of fractures. About 28 percent of the subjects in each of the groups had a baseline vertebral fracture at randomization. The population in PEARL is reflective of the general population of postmenopausal women with osteoporosis.

Lasofoxifene demonstrated consistent efficacy in postmenopausal women across multiple endpoints both at three years and at five years. The efficacy of lasofoxifene will first be described for bone and then or vaginal atrophy. As recommended by the FDA, we will present three-year data for efficacy results, with the exception of major nonvertebral fractures, for which we will show results at five years, as these results differed from those at three years.

Safety results presented next by Dr. Armstrong will be based on five-year data. The results from PEARL support the efficacy of 0.5 milligram lasofoxifene in the treatment of osteoporosis in postmenopausal women. In bone, lasofoxifene reduces bone reabsorption, as reflected in reduced bone turnover and increased bone mass. Lasofoxifene at 0.25 and 0.5 milligrams significantly reduced bone turnover as early as one month, as revealed by the reduction of C-telopeptide on the left panel -- one of the four biochemical markers of bone turnover evaluated in PEARL -- this reduction in bone turnover wasn't accompanied by an increase in bone mineral density of the lumbar spine observed with lasofoxifene 0.25 and 0.5 milligrams as early as three months, and maintained over the three years of the study as shown on the right panel.

Increases in bone mineral density of the hip and bone mineral content of the

whole body were also observed with lasofoxifene, but are not shown here. This effect on bone mineral density with lasofoxifene was also associated with a reduction of radiographic vertebral fractures. At three years, lasofoxifene reduced radiographic vertebral fractures, the primary endpoint in PEARL.

The incidence of vertebral fractures in the lasofoxifene 0.5 milligram group was reduced by 42 percent compared to placebo. The incidence of vertebral fractures was reduced from 6.4 percent in the placebo to 3.8 percent with lasofoxifene 0.5 milligrams. The 0.25 milligram dose reduced the rate by 31 percent relative to placebo.

These reductions in vertebral fractures were statistically significant. Importantly, this reduction in fractures was also observed in patients who entered the trial with a prevalent fracture at baseline, and thus were at greater risk of fracture.

In women with a prevalent fracture at baseline in the left panel, lasofoxifene 0.5 milligrams reduced subsequent vertebral fractures by 48 percent, consistent with the reductions in the overall PEARL population. Placebo patients showed a fracture incidence of 11.3 percent, while the lasofoxifene 0.5 milligram patients had a rate of 6.0 percent. In the lasofoxifene 0.25 milligram group, the vertebral fracture rate in this group as reduced by 30 percent. These reductions were statistically significant.

In women who entered the trial without a prevalent fracture in the right panel, the placebo rate at three years was 4.6 percent, while the lasofoxifene 0.5 milligram group had an incidence of 2.9 percent, a 37 percent reduction.

Lasofoxifene 0.25 milligram reduced the vertebral fracture incidence in the subgroup by 32 percent. These reductions were statistically significant.

Lasofoxifene also showed a significant reduction in nonvertebral fractures. Nonvertebral fractures excluded those of the feet, hands, face, and skull. At three years, lasofoxifene 0.5 milligrams significantly reduced the incidence of nonvertebral fractures. Nonvertebral fractures are associated with significant morbidity. These fractures are reduced with bisphosphonates, but not raloxifene. The incidence of nonvertebral fractures in the placebo group was 7.2 percent at three years and was reduced to 5.9 percent in the lasofoxifene 0.5 milligram group; a statistically significant 22 percent reduction. The 0.25 milligram group showed a nonsignificant reduction of 14 percent.

Major nonvertebral fractures, a subgroup of nonvertebral fractures, were not significantly reduced at three years, but were reduced at five years with lasofoxifene 0.5 milligrams. The major nonvertebral

fractures included sites in the skeleton that are impacted by osteoporosis, and include hip, pelvis, femur, lower leg, humerus, forearm, wrist, and rib. At five years, the placebo group had an incidence of major nonvertebral fractures of 6.7 percent. Lasofoxifene 0.5 milligrams reduced the incidence to 5.1 percent, a 25 percent reduction. This reduction was statistically significant.

A nonsignificant 11 percent reduction was observed with lasofoxifene 0.25 milligrams. Hip fractures, one of the fractures that comprise nonvertebral fractures was not significantly reduced at three or five years. At three years, lasofoxifene showed a numerical reduction in hip fractures. The placebo group had 23 hip fractures, the lasofoxifene 0.25 milligrams had 20 hip fractures, and the lasofoxifene 0.5 milligrams had 18 hip fractures.

Overall, when evaluating the effect

of lasofoxifene on bone fractures in postmenopausal women with osteoporosis, efficacy was observed across a number of different skeletal sites. Lasofoxifene 0.5 milligrams showed consistent and significant reductions in radiographic vertebral fractures in patients with and without prevalent fractures at baseline. A reduction in clinical vertebral fractures and hip fractures was not significant.

An effect that differentiates lasofoxifene from other SERMs is a significant reduction in nonvertebral fractures. Also, at five years, a significant reduction in major nonvertebral fractures was observed with lasofoxifene 0.5 milligrams, but not 0.25 milligrams. Thus, lasofoxifene 0.5 milligrams demonstrated efficacy across both vertebral and nonvertebral fractures in postmenopausal women with osteoporosis.

Besides efficacy and fracture

reduction, lasofoxifene has demonstrated other benefits in postmenopausal women, including improvement in signs and symptoms of vaginal atrophy. In postmenopausal women who reported bothersome symptoms of VVA, lasofoxifene was effective in alleviating these symptoms. The most bothersome symptoms reported by women at baseline in the Phase 3 VVA trial included dyspareunia, dryness, burning, or itching, or dysuria, and must have been moderate or severe at baseline.

Lasofoxifene at 0.25 and 0.5 was effective at reducing bothersome symptoms of VVA seen in the upper left panel. In addition, lasofoxifene was also effective at reducing clinical signs of VVA, including reducing vaginal pH in the upper right panel; reducing the proportion of parabasal cells, the lower left panel; and increasing the number of superficial cells, lower right panel, in the vaginal mucosa. These findings provide evidence that lasofoxifene has

beneficial effects in the treatment of VVA in postmenopausal women.

Consistent with the results in the VVA trial, lasofoxifene also demonstrated improvements and clinical signs of VVA in the PEARL trial. Lasofoxifene 0.5 milligrams, the proposed dose for the treatment of osteoporosis, demonstrated beneficial effects on clinical signs of VVA. A significant reduction of vaginal pH was observed with lasofoxifene in postmenopausal women with osteoporosis, but without symptoms of VVA in the left panel. Lasofoxifene also showed a significant improvement in the vaginal maturation index on the right panel, demonstrating an increase in the superficial cells, the brown bar, and concomitant reduction of parabasal cells in the green bar.

These findings with lasofoxifene in postmenopausal women with osteoporosis confirm earlier findings of the efficacy in

the earlier VVA studies with lasofoxifene in postmenopausal symptoms with bothersome symptoms of vaginal atrophy. The results from PEARL further demonstrate that the benefits of lasofoxifene in treating VVA persisted through three years of treatment.

The mechanism of efficacy in alleviating the symptoms of VVA, and thus providing benefit to postmenopausal women, is understood. The benefits of lasofoxifene in women with VVA are the result of differentiation of parabasal cells into intermediate and superficial cell types.

Intermediate and superficial cells, unlike parabasal cells, contain glycogen. Glycogen acts as a substrate for the lack of bacillus, which in turn produces lactic acid and lowers the vaginal pH with lasofoxifene. These changes lead to the recorded improvements in vaginal health.

In summary, lasofoxifene 0.5 milligrams reduced the rate of vertebral and

nonvertebral fractures. In addition, lasofoxifene has also demonstrated benefit in the treatment of VVA. These data indicate that lasofoxifene 0.5 milligrams of efficacious in the treatment of osteoporosis in postmenopausal women. The data indicate that lasofoxifene is a new efficacious option for the treatment of osteoporosis that also delivers additional benefits in postmenopausal women.

Dr. Armstrong will now present a review of the safety data with lasofoxifene in postmenopausal women.

DR. ARMSTRONG: Good morning, ladies and gentlemen. My name is Roisin Armstrong, and I'm the clinical lead for the lasofoxifene development program.

The safety of lasofoxifene has been well-characterized. The data will show it is generally safe and well-tolerated. There are two safety findings of note, both of which are known effects with this class of drug: an

increase in venous thromboembolic events, and an increased incidence of diagnostic uterine procedures. And these shall be discussed together with other important events of interest for SERM.

With respect to mortality, there were no significant differences for lasofoxifene overall or in PEARL when pooled across the entire Phase 2/3 clinical program. Likewise, there were no significant differences for the lasofoxifene 0.5 milligram dose, either in PEARL, or across the entire Phase 2/3 clinical program.

There were, however, statistically significant increases for lasofoxifene 0.25 milligrams both in PEARL and the entire Phase 2/3 clinical program. Each of these issues will be reviewed in detail.

First, I will review the general safety profile for lasofoxifene from the Phase 2/3 clinical program, in which the five-year PEARL data contributes over

80 percent of the patient-years of follow-up. The overall program contributes important and relevant information for adverse events, treatment discontinuations, and serious adverse events. These will be discussed based on integrated data from across the entire Phase 2/3 clinical program as of the cutoff date for the four-month safety update.

The update, which is submitted to FDA four months from the date of the initial NDA, provides updated clinical safety information during the regulatory review process. Mortality will be presented first for the PEARL study, which contributes 96 percent of the total deaths, and then for the rest of the clinical program. The presentation of safety events of special interest for SERMs will also focus on five-year data from the PEARL trial. Lastly, there will be a separate examination of the gynecological safety data.

Overall, the adverse events seen on

lasofoxifene are typical of those expected with a SERM. The most common adverse events were muscle spasms, hot flashes, and vaginal discharge. And these events were mild to moderate in severity. The rates of these events were consistent across doses, as reflected in the columns for the 0.25 milligram and 0.5 milligram doses, along with the pooled dose group.

The pooled group on this slide, which will also be shown on subsequent slides, reflects a 600-fold dose range that has been studied in the Phase 2/3 clinical studies, ranging from 17 micrograms per day to 10 milligrams per day. Discontinuations attributed to adverse events were comparable across the four groups at approximately 9 to 11 percent.

Events contributing to discontinuation occurred at low rates. Hot flash was the most common at approximately 2 percent, with an absolute difference

compared to placebo of 1 percent. Treatment discontinuations due to muscle spasms and deep vein thrombosis also occurred more commonly in lasofoxifene patients, but differed from placebo by 0.3 to 0.6 percentage points. Treatment discontinuations for any reason occurred at similar frequency across the four groups.

Similarly, the incidence of serious adverse events was generally low across groups. The most common serious adverse events on lasofoxifene were in two categories -- those that were venous thromboembolic, such as deep vein thrombosis and pulmonary embolism, and those events that would contribute to an increase in diagnostic uterine procedures, such as uterine polyps and the event of endometrial hypertrophy, which represents the finding of endometrial thickness on ultrasound.

There was also an increased incidence of the preferred term uterine

polyps. The venous thromboembolic events and the gynecologic events will be covered in more detail after examination of the mortality results. The mortality data will be presented first for the PEARL study, which contributed 96 percent of the deaths in the clinical program.

In PEARL, after five years, there were 228 deaths among 8,556 patients, comprising 38,551 patient-years of observation. The death rate was 5.1 events per 1,000 patient-years on placebo, and 6.3 events per 1,00 patient-years for those assigned at random to lasofoxifene. This difference of 1.2 deaths per 1,000 patient-years was not statistically significant, as indicated by the 95 percent confidence interval minus 0.4 to 2.9.

Likewise, there was no significant difference in mortality for lasofoxifene 0.5 milligrams compared to placebo through five years in PEARL. Specifically, there were 73

deaths in the lasofoxifene 0.5 milligram group, and 65 deaths in the placebo group, giving a hazard ratio of 1.12, with a corresponding 95 percent confidence interval of 0.80 to 1.56, and a P-value of 0.511.

In the lasofoxifene 0.25 milligram dose group, there were 90 deaths, giving a hazard ratio of 1.38, with a 95 percent confidence interval from 1.00 to 1.89, and a p-value of 0.049. It is noted that any possible difference between the 0.25 milligram dose and placebo is most apparent only during the final year of follow-up.

We conducted a number of exploratory analyses in PEARL to discover potential reasons for the apparent difference for lasofoxifene 0.25 milligrams compared to placebo. With respect to person, we did not observe any significant differences in baseline characteristics. As regards place, there was a significant association for only one of the five pre-specified regions, and

this is described in detail in the briefing document.

As noted, the difference for the 0.25 milligram dose group compared to placebo has a p-value of 0.049. In a post-talk exploratory subgroup analysis, Region 2 comprises 21 percent of the sample size, but 56 percent of the possible excess in the 0.25 milligram group. This is due primarily to a lower mortality rate in the placebo group. As expected, exclusion of Region 2 data would render the 0.25 milligram dose comparison not significant.

All such subgroup analysis of the 0.25 milligram dose are useful to formulate, not test, hypotheses. More importantly, all the overall analyses of the 0.5 milligram, as well as the pooled data, are always, and reassuringly, not statistically significant.

Finally, with respect to time, there were no significant differences in follow-up rates. According to its charter,

the PEARL cardiovascular endpoint committee reviewed every death, and assigned each a single cause based on predefined categories.

Coronary deaths occurred in 21 patients on placebo, 18 on lasofoxifene 0.25 milligram, and 18 on lasofoxifene 0.5 milligram. For stroke deaths, there were 5 on placebo, 12 on lasofoxifene 0.25 milligrams, and 7 on lasofoxifene 0.5 milligrams.

Other vascular deaths were 2, 6, 2, respectively, and these included 5 fatal events associated with pulmonary embolism -- 3 on lasofoxifene 0.25 milligrams, and 2 on lasofoxifene 0.5 milligrams.

Cancer deaths occurred in 20 patients on placebo, 34 on lasofoxifene 0.25 milligrams, and 25 on lasofoxifene 0.5 milligrams. The individual causes of death in the other category were diverse, and no single cause was predominant. The numbers

were 13, 18, 17, respectively, and for trauma-related deaths, these occurred in four patients on placebo, two on lasofoxifene 0.25 milligrams, and four on lasofoxifene 0.5 milligrams.

To further explore the possible not significant increases in fatal events of stroke and cancer for the lasofoxifene 0.25 milligram dose group, we also evaluated total incident cases by treatment group. For total stroke, there were 61 on placebo, 50 on lasofoxifene 0.25 milligrams, and 46 on lasofoxifene 0.5 milligrams. For total cancer, there were 148 on placebo, 15four on lasofoxifene 0.25 milligrams, and 146 on lasofoxifene 0.5 milligrams.

We also examined adjudicated cancer deaths by anatomical site. The only anatomic site which showed an excess of more than one cancer death on lasofoxifene 0.5 milligrams compared to placebo was lung, where there were seven on lasofoxifene 0.5 milligrams

compared to two on placebo. Of these seven, two were diagnosed in the first four months of randomization, and six deaths occurred in the first three years of the study.

In the lasofoxifene 0.25 milligram group, the numbers by anatomical site were small. The largest numerical increase relative to placebo for any cancer type was three events. This occurred for fatal cancers of the brain, one versus four; colorectum, two versus five; esophagus, zero versus three; and stomach, one versus four. Of these, one of the brain cancers, one of the esophageal cancers, and one of the colorectum cancers occurred in patients who received lasofoxifene for less than three months.

In the other 16 Phase 2/3 clinical trials of shorter duration, lasofoxifene was evaluated in doses ranging from 17 micrograms per day to 10 milligrams per day. There were nine deaths in 4,923 patient-years on

lasofoxifene: one death on lasofoxifene 0.025 milligrams; four deaths on lasofoxifene 0.25 milligrams; three on 0.5 milligrams; and one on 2.5 milligrams. The causes of death for these nine cases include one suicide, a drowning accident, two motor vehicle accidents, and deaths attributed to other illnesses.

When these deaths are pooled with PEARL, the difference in death rates remains 1.2 per 1,000 patient-years, and the 95 percent confidence interval includes no difference. In all Phase 2/3 clinical trials including PEARL, there were 237 deaths among 14,960 patients, comprising 45,396 patient-years of observation. The death rate was 4.4 events per 1,000 patient-years on placebo, and 5.6 events per 1,000 patient-years for those assigned at random to lasofoxifene.

This difference of 1.2 events per 1,000 patient-years was not statistically

significant, as indicated by the 95 percent confidence interval from -0.2 to 2.6.

We have presented these data visually, as we believe them to be more conservative than those for the lasofoxifene 0.5 milligram dose, even though this is the dose for which we are seeking approval and for which the evidence in all Phase 2/3 clinical trials, including PEARL, provide even greater reassurance. Specifically, the death rate was 4.4 events per 1,000 patient-years on placebo, and 5.3 events per 1,000 patient-years for those assigned at random to lasofoxifene 0.5 milligrams.

The difference of 0.9 events per 1,000 patient-years was not statistically significant, as indicated by the 95 percent confidence interval from -0.7 to 2.5.

Based on the totality of evidence, there is no statistically significant increase on mortality for lasofoxifene over all or on lasofoxifene 0.5 milligrams, the

proposed treatment dose. The 95 percent confidence intervals include no difference overall or for lasofoxifene 0.5 milligrams. Chance appears to be a likely alternative explanation for the observed findings in the 0.25 milligram dose.

Even if the finding for lasofoxifene 0.25 milligrams represents a valid statistical association, causality is unlikely, as there is no consistent pattern of mortality. The increases in stroke or cancer mortality are not reflected in the overall incidence of events. There is no biologically plausible mechanism, and there is no biologically plausible dose response relationship.

To provide greater certainty on this issue, a post-approval independently and externally monitored prospective long-term safety cohort study is proposed that will provide important information on any potential effect on mortality and other

safety events that are known to occur with other SERMs. These are breast cancer, venous thromboembolic events, stroke, and coronary events.

PEARL was the only lasofoxifene study to prospectively define a reduction in risk of breast cancer as an efficacy endpoint. By agreement with the FDA, the breast cancer results from PEARL are presented as part of the safety presentation. The prospectively defined co-primary endpoint at five years was ER positive breast cancer. Through five years, lasofoxifene 0.5 milligrams significant reduced the risk of ER positive breast cancer by 81 percent. The possible 48 percent reduction on the 0.25 milligram dose was not statistically significant.

Lasofoxifene 0.5 milligrams also significantly reduced the risk of other breast cancer categories. The significant reductions were 79 percent for all breast

cancer; 83 percent for ER positive invasive breast cancer; and 85 percent for invasive breast cancer. Of note, in the lasofoxifene 0.5 milligram dose group, there were no breast cancer events between three and five years.

Consistent with data reported for other SERMs, lasofoxifene was associated with an approximate twofold increased risk for venous thromboembolic events, VTEs. VTEs, which included events of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis, were also adjudicated by the cardiovascular endpoint committee. The majority of VTEs were deep vein thrombosis, DVT.

There was an approximately twofold increased risk for DVT in lasofoxifene patients as seen with other SERMS, accounting for the majority of the difference seen in VTEs. For pulmonary embolism there were two events on placebo; 12 on lasofoxifene 0.25

milligrams; and nine on lasofoxifene 0.5 milligrams. The differences compared to placebo for pulmonary embolism were statistically significant. A review of the literature indicates that the incidence of pulmonary embolism on lasofoxifene in the PEARL trial is consistent with that reported for other SERMs.

An increased risk of stroke has been seen with other SERMs. In the PEARL study, strokes and transient ischemic attacks were adjudicated by the cardiovascular endpoint committee. Lasofoxifene was not associated with an increased risk of stroke. In an analysis that excluded transient ischemic attacks, TIAs, there was a significant reduction in the incidence of stroke in both lasofoxifene dose groups compared to placebo.

In an analysis that included TIAs, there were observed reductions in both lasofoxifene groups compared to placebo that

did not reach statistical significance.

There were improvements in some markers of cardiovascular risk, as assessed through three years of treatment in a subgroup of patients in the PEARL trial. In a substudy of markers of cardiovascular risk at three years in PEARL, we examined both arthrogenic and inflammatory markers. As expected for this class of drugs, there were significant benefits for lasofoxifene on total and LDL cholesterol. In addition, and unlike other SERMs, lasofoxifene significantly reduced high sensitivity C-reactive protein, a sensitive marker of inflammation and a predictor of both coronary and cerebral vascular events.

There was a reduction in the cumulative incidence of major coronary events through five years in PEARL. The composite endpoint of major coronary events included coronary death, non-fatal myocardial infarction, new ischemic heart disease,

coronary revascularization procedures, and hospitalizations for unstable angina. Lasofoxifene 0.5 milligrams, which is represented by the blue line on this figure, was associated with a significant 32 percent reduction in major coronary events through five years with a corresponding p-value of 0.016. There was no significant difference for lasofoxifene 0.25 milligrams, illustrated by the gold line at a p-value of 0.077.

The most common adverse events associated with lasofoxifene were hot flash, muscle spasm, and vaginal discharge -- events that have been seen with other SERMs. The most common serious adverse events were venous thromboembolic events and gynecological events that contribute to an increase in diagnostic uterine procedures.

An increase in the term of uterine polyps was observed, and polyps will be reviewed in the summary of gynecological safety data to follow.

Mortality risk was not significantly different compared to placebo. Lasofoxifene decreased breast cancer risk. In addition, lasofoxifene decreased stroke risk and decreased the risk of major coronary events consistent with the observed significant decrease in total and LDL cholesterol levels, and also high sensitivity C-reactive protein. Lasofoxifene 0.5 milligrams has a favorable general safety profile and its adverse events resemble those of other SERMs.

Lasofoxifene has demonstrated unique safety advantages, and in addition, has a favorable gynecological safety profile, both in terms of endometrial safety and other gynecological outcomes.

Of the 8,556 patients in the PEARL study, approximately 20 percent did not have a uterus at baseline. The remaining patients have been characterized according to whether or not they had surveillance by transvaginal

ultrasound, TVU, during the course of the study.

Patients could be designated as having TVU surveillance if they participated in one of the two protocol TVU substudies. TVU-I or TVU-P are based on local requirements. In other patients, TVUs would have been performed only as required for patient management. For example, as investigative follow-up triggered by vaginal bleeding. These patients have been categorized as real world patients. Since their follow-up would be in response to clinical concern, hence, they are expected to better approximate what would be anticipated to occur with lasofoxifene in clinical practice.

Important gynecological events of interest will be reported across the different patient subsets that are shown on this figure. Central pathology review was performed on biopsies from the two protocol

TVU substudies, as well as in patients with a local pathology report of a malignant or premalignant finding. A central pathology review was performed in a sequential manner by up to three expert gynecological pathologists who were blinded to study treatment, prior pathology assessment, and colleague assessment.

Gynecological outcomes that will be presented include endometrial cancer and endometrial hyperplasia. We will also describe the benign endometrial effects observed with lasofoxifene, including sonographic findings and endometrial polyps. Additionally, we will describe vaginal bleeding and the incidence and nature of diagnostic uterine procedures. And finally, we will present data for pelvic organ prolapse.

Endometrial cancer was adjudicated by the PEARL gynecological endpoint committee, a blinded expert and independent

committee. There was no evidence of an increased risk of endometrial cancer in women taking lasofoxifene. Through five years in the PEARL trial, there were three events on placebo, and two events on each lasofoxifene arm. Looking across the entire Phase 2/3 clinical program, which resulted in four additional events of endometrial cancer, the hazard ratio also was less than one.

There was no increase in the precursor to endometrial cancer, endometrial hyperplasia. A total of five cases were confirmed by the gynecological endpoint committee in adjudication. Two of the five cases had tissue samples that underwent central pathology review. In the remaining three cases, no tissue was available for the central pathology review process. The absolute incidence rate of endometrial hyperplasia on lasofoxifene through five years was 0.24 events per 1,000 patient-years. This is below the threshold

of regulatory guidance for detecting endometrial hyperplasia should an increased risk actually exist.

Further, although there was one additional confirmed case of endometrial hyperplasia on lasofoxifene outside of the PEARL study, this does not change the conclusion that the absolute incidence rate is low and does not indicate an increased risk associated with lasofoxifene treatment. The results from PEARL do illustrate the importance of using centrally read results to obtain accurate histological diagnoses.

Of more than 1,400 locally read endometrial samples collected throughout the development program, the pattern of cystic change observed with lasofoxifene may have resulted in the incorrect diagnosis of endometrial hyperplasia in less than 3 percent of cases. There were 40 that were read as hyperplasia locally, but found to be benign cystic changes by the central

laboratory. FDA review of the cases had confirmed the finding of cystic atrophy, as reported in their briefing document. Risk management efforts will be directed at minimizing this incongruence, in part by providing insight into the histology of cystic change.

In the left hand panel is a low power magnification of endometrial tissue in a lasofoxifene-treated patient, highlighting areas of cystic dilatation of glands separated by stroma. On the right is the high power magnification where the cuboidal epithelium with monotonous nuclei is clearly visible.

The findings observed in biopsy in lasofoxifene patients are consistent with benign cystic atrophy, endometrial histology that may be confused as simple hyperplasia. These changes are distinct from dosing with estrogen.

Estrogen activates proliferative

pathways, increasing the incidence of endometrial cancer and endometrial hyperplasia. In contrast, lasofoxifene does not activate estrogen mediated proliferative pathways and does not show evidence of increased endometrial cancer risk.

The specific findings with lasofoxifene represent a characteristic profile in the endometrium. Biopsy reveals a benign cystic atrophy, a variant of the most common postmenopausal endometrial finding, atrophic in active endometrium, as well as increased cystic echotexture and increased endometrial thickness on ultrasound as demonstrated in the TVU-I substudy.

The incidence of sonographic endometrial cystic change was approximately 21 percent after three years' exposure to lasofoxifene compared to about 2 percent on placebo. There was no evidence of a dose response effect or an effect of treatment duration.

The effect was variable and appeared to be reversible, either spontaneously while remaining on treatment in some patients, or upon discontinuation of treatment in others.

Endometrial thickness was also characterized over three years in the same subset of TVU-I patients. Lasofoxifene was associated with a mean of approximately 1.5 millimeter increase in the thickness of the endometrial lining, which was observed by one year and was sustained thereafter.

This effect was also demonstrated to be reversible, either spontaneously on treatment in some patients, or upon discontinuation of treatment in others. The findings of both echotexture and endometrial thickness are the result of histological effects of benign cystic atrophy.

Preclinical data suggests a mechanism for benign cystic atrophy. Gene transcription studies in the ovariectomized

rat uterus show that lasofoxifene activates multiple gene pathways associated with increased vascular permeability and uterine hydration in the endometrium. Supporting these data, there was a small increase in rat uterine wet weight, but not dry weight, consistent with hydration, but not proliferation.

In the primate model, there was an increase in cystic luminal volume, but not an increase in epithelial volume. Again, consistent with increases in hydration, but not proliferation.

The data suggests that lasofoxifene increases vascular permeability which results in transudation of fluid which accumulates in the glandular lumen and results in cyst formation and a thickening of the endometrial lining. This results in cystic echotexture and increased endometrial thickness on ultrasound on the left which are manifestations of benign cystic atrophy on

biopsy which is demonstrated on the right. Importantly, these effects occur in the absence of proliferation.

Lasofoxifene was also associated with an increased incidence of benign endometrial polyps, a finding that has been observed with other SERMs. Endometrial polyps were analyzed in the subset of patients who participated in the TVU-P substudy and whom a transvaginal ultrasound was performed at month 36, only to determine the prevalence of asymptomatic histological findings. In this patient subset, lasofoxifene was associated with an approximate 2.24 increased odds of an endometrial polyp. All endometrial polyps in lasofoxifene-treated patients were atrophic/inactive.

Along with the benign cystic changes, the benign polyps may have contributed to some additional reports of vaginal bleeding. The absolute incidence of

vaginal bleeding was 2.6 percent in lasofoxifene 0.5 milligram patients, compared to 1.3 percent on placebo. This translates into three additional patients with vaginal bleeding on lasofoxifene per thousand patient-years who will require further evaluation to rule out endometrial cancer.

The episodes of vaginal bleeding themselves were well-tolerated. The majority of patients who reported bleeding reported a single episode during the five years of treatment. Since uterine sonographic surveillance has been reported to increase the incidence of diagnostic uterine procedures with other SERMs, this endpoint was analyzed in the subset of PEARL patients with no planned sonographic surveillance.

The incidence of patients with one or more diagnostic procedures was approximately 7 percent and 3 percent for lasofoxifene- and placebo-treated patients, respectively. This translates into 10

additional patients with at least one diagnostic uterine procedure on lasofoxifene per thousand patient-years. The most common of these was endometrial biopsy.

Based on clinical review of the diagnostic uterine procedures on lasofoxifene, these can be attributed to the 1.3 percent excess in vaginal bleeding seen on lasofoxifene and follow-up of asymptomatic benign findings in patients with an unscheduled TVU.

Importantly, national and international guidelines recommend diagnostic follow-up in postmenopausal women when the woman presents with vaginal bleeding. Diagnostic follow-up is not recommended where there is no vaginal bleeding.

A comprehensive assessment of endpoints associated with pelvic organ prolapse and urinary incontinence was a central component also of the PEARL trial. This included use of a validated anatomical

assessment using the modified halfway measure, an assessment of urinary incontinence in the TVU-I substudy using the validated King's Health questionnaire, as well as analysis of surgical events for prolapse that were adjudicated by the gynecological endpoint committee. Representative results for anatomical uterine prolapse scores at year three are reflective of the lack of change in this endpoint.

At baseline, there was a balanced distribution across the three treatment groups for anatomical uterine prolapse score. At month 36, the final time point for anatomical prolapse assessment, there was a similar balance distribution of uterine prolapse scores across the three treatment groups.

The King's Health questionnaire was administered to all patients in the TVU-I substudy at baseline and at years one, two, and three. Incontinence symptoms scores were

comparable across the treatment groups at baseline and through the three years of follow-up. Despite the lack of signal for prolapse scores and incontinence, there was an increase in the rate of surgery for prolapse or incontinence.

Through five years, surgery for pelvic organ prolapse or urinary incontinence occurred in 1.9 percent patients on lasofoxifene 0.25 milligrams, 1.6 percent on 0.5 milligrams, and 1.2 percent on placebo. The 0.7 percent difference on the lasofoxifene 0.25 milligram dose group was statistically significant.

The gynecological safety findings for lasofoxifene 0.5 milligrams are summarized. There is no evidence to suggest that lasofoxifene increases the risk of endometrial cancer or hyperplasia. Lasofoxifene is associated with benign effects on the endometrium, which are visualized as cystic echotexture and

increased endometrial thickness on ultrasound, and which reflect benign cystic atrophy and biopsy. Importantly, these effects occur in the absence of proliferation.

There is an increased incidence of vaginal bleeding which translates to an excess of three patients per thousand patient-years. The increase in vaginal bleeding and the benign endometrial effects observed on ultrasound contribute to an excess in diagnostic uterine procedures of 10 patients per thousand patient-years. The magnitude of this effect is anticipated to be smaller post-approval as a result of risk minimization activities to be outlined next by Dr. Turner.

No consistent pattern was observed with pelvic organ prolapse. There was a significant increase in surgery for this event on lasofoxifene 0.25 milligrams, while the difference with lasofoxifene 0.5

milligrams was not statistically significant. In contrast, anatomical prolapse scores and urinary incontinence symptoms scores did not indicate worsening of the endpoint.

These favorable safety results will be supported by an enhanced post-approval pharmacovigilance program, which will include an independently monitored prospective cohort study that will collect further information and any potential effect on mortality, as well as other safety events that are known to occur with other SERMs.

I will now turn over to Dr. Claudia Turner, who will present our proposed risk management strategy for lasofoxifene.

Thank you.

DR. TURNER: Thank you, Dr. Armstrong, and good morning, everyone. My name is Claudia Turner, and I represent Pfizer's Safety and Risk Management organization. The proposed risk management program is designed to detect and mitigate the identified and potential risks of

0.5 milligram lasofoxifene. To address the identified risk of venous thromboembolism and increased diagnostic uterine procedures, as well as potential risks of lasofoxifene, the proposed risk management program consists of four major components. First, beyond the proposed label and patient information leaflet, the targeted educational and outreach program will address the risks associated with lasofoxifene.

We're also committed to risk communication. The patient, to regulatory agencies, and health care providers, including physicians, pharmacists, nurses, nurse practitioners, and physician's assistants, using a variety of means to disseminate information.

In addition to routine pharmacovigilance, safety monitoring will be enhanced by conducting an independently and externally monitored post-approval long-term safety respective cohort study.

Lastly, the effectiveness of the

risk management plan will be assessed on a regular basis.

These components will be used to mitigate the risk of venous thromboembolism and increased diagnostic uterine procedures.

Venous thromboembolism occurred in an excess of 0.07 percent in patients treated with lasofoxifene. Deep vein thrombosis accounted for three-quarters of venous thromboembolic events.

Pulmonary embolism occurred in nine lasofoxifene subjects versus two placebo subjects. Together, these events contributed to an approximate twofold increase in venous thromboembolism, which is comparable for what has been reported for raloxifene by Grady et al.

This risk will be managed in the following ways. Health care providers are already familiar with this class of terms. And the proposed label wording will reinforce their awareness of VTE risk and the

contraindication in women with a history of VTE. Importantly, patients will also be informed about this risk via the patient information leaflet and the Internet.

Content will include a description of predisposing factors, the symptoms of VTEs, and how to reduce this risk. Patients will be instructed to contact their physicians immediately if they're experiencing the symptoms of VTE.

The goal of this communication will be to prompt patients to actively engage in managing their own health. The independent, externally monitored, long-term safety perspective cohort study will allow further characterization of the risk of VTE in a real-world patient population, and comparison to the incidence of this event and raloxifene treated subjects as well.

With respect to increased diagnostic uterine procedures, lasofoxifene was associated with an excess of 10 women

undergoing diagnostic uterine procedures per thousand patient-years of exposure. The most common of these were endometrial biopsies.

As reported by Martino et al., raloxifene similarly increases the incidence of diagnostic uterine procedures. Following approval, it is anticipated that the three excess events of vaginal bleeding on lasofoxifene will result in three excess procedures, consistent with established guidelines. These guidelines recommend that diagnostic uterine procedures should be performed only upon the occurrence of vaginal bleeding, and recommend against routine uterine surveillance.

Risk management efforts will focus on reducing the number of unnecessary procedures by increasing an awareness of and adherence to these guidelines. This approach has been successfully applied to tamoxifen use, despite it's known risk for increasing endometrial cancer.

This risk will be communicated to health care providers in the proposed label wording. Education efforts to reduce the risk of unnecessary uterine diagnostic procedures target two audiences: Health care providers, so that they're aware of established guidelines for uterine surveillance; and pathologists, so they can correctly differentiate between benign cystic atrophic endometrium and endometrial hyperplasia.

Educational materials will be developed with the input and review of gynecologists and pathologists, and with the approval of regulatory agencies.

Of course, content may be delivered through educational sessions, both with the international scientific conferences and in local community-based forums. Peer review publications could be an additional means to communicate information. A web-based education program will include prerecorded

lectures or panel sessions by key thought leaders in the field. The effectiveness of our education program will be accessed by web-based comprehension testing, and by monitoring the incidence of uterine procedures and women treated with lasofoxifene, lasoxifene or neither therapy, as part of the prospective cohort study.

A draft proposal for this cohort study was included in the NDA submission, but the study design will be modified based on consultation for both regulators and external experts. Appropriate health care databases are being evaluated to achieve a minimum of 400,000 patient-years of exposure, which is 10 times the exposure of the PEARL study.

This will provide adequate power to detect plausible differences in serious adverse events, including rare events such as endometrial cancer. Analogous to independent data and safety monitoring boards and clinical trials, we will propose an

independent special advisory committee, or SAC, for this prospective cohort study. SAC will meet regularly to review the progress of the study and the safety data. An independent statistical and data analysis center will provide SAC with regular safety analysis. The SAC will meet regularly and make recommendations simultaneously to the FDA and Pfizer regarding drug safety.

The identified and potential risk of known SERM class effects listed here are proposed as endpoints for this study. These will be discussed and agreed upon by the regulators, the SAC, and Pfizer. This study will also include the collection of data on other medical events. Should any additional risks emerge during approval, these will be communicated by the SAC to Pfizer, the FDA, and other regulatory agencies.

Pfizer will work with the FDA to determine appropriate actions and means of communicating any emergent risk. We are

committed to conducting a thorough, ongoing evaluation of lasofoxifene in a sufficient number of women to allow meaningful conclusions regarding its safe and effective use in a real-world setting.

In conclusion, the two identified risks associated with lasofoxifene are well-characterized and are known to occur with raloxifene, a therapy that's been used for more than 10 years, and continues to have a positive benefit-to-risk ratio.

The proposed risk management plan will enhance the benefit/risk profile of lasofoxifene and optimize its safe and effective use in appropriate patients. An independent and externally monitored prospective cohort study is proposed right after the long-term safety of lasofoxifene.

We are committed to working closely with FDA and other regulatory agencies to ensure the suitability of the various components of this plan so that it

effectively mitigates risk in patients and optimizes the benefit/risk profile of lasofoxifene.

Now, Dr. Steven Goldstein will place the risk of increased diagnostic uterine procedures into the context of clinical practice, and will access the overall benefit/risk profile of lasofoxifene.

Thank you.

DR. GOLDSTEIN: Good morning. My name is Steve Goldstein, and I'm a professor of obstetrics and gynecology at the New York University School of Medicine. I really come here today wearing two hats. First, I've spent more than 15 years in much of my academic career trying to understand what the effects of various SERMs are on the uterus. And so I'm here today to help explore what lasofoxifene does do and what it does not do to the endometrium.

The other hat that I wear is that of a clinician. In my gynecologic practice at New York University, I see 80 to 90 women

a week, almost all peri- and postmenopausal women. And I'm also the co-director of the bone density unit at NYU. And as we've heard, osteoporosis and prevention of fracture is a major health concern, and will only get more and more important as our population ages.

As a clinician, there are many issues that can go into choosing the optimal agent for treating a patient with osteoporosis. Some of these are data-driven. Some of these take into account co-existing needs, and even the fears and perceptions sometimes that the patient brings to the table. And I will try to discuss these issues as well.

This is an overview of what I want to cover. We're going to talk about some of the risks and benefits and try to put this into clinical perspective. But let me move right into uterine safety, my main personal interest.

As you've already heard, more than 2,400 women with uteri were treated with lasofoxifene for five years. There was no signal of endometrial cancer. There was no signal of endometrial hyperplasia.

Clearly, this drug is not like estrogen in the uterus, and this drug is not like tamoxifen. It does produce some well-characterized benign endometrial effects, which we will talk about, including the benign cystic atrophy and the benign polyps.

These are published data. The tamoxifen risk here of 4.01 comes from the breast cancer prevention trial in the women over 50, because it's one of the few instances where tamoxifen patients who didn't already have breast cancer were being treated with that drug.

Estrogen being an increased risk for endometrial cancer is well-known, and this comes from Deb Grady's work with a

2.8-fold increase. We've already heard raloxifene has about a 10 percent non-statistically significant decrease in endometrial cancer. And if we put all of the lasofoxifene-treated patients into this graph, we see a 16 percent non-statistically significant reduction in endometrial cancer with lasofoxifene.

What about hyperplasia, the marker that we look for in the concerns about endometrial cancer? Estrogen -- and this is per 1,000 patient-years results, when used unopposed, which we don't do -- in 145 cases of hyperplasia. Tamoxifen, almost 18 cases per thousand patient-year. Raloxifene published data, .23 cases lasofoxifene, virtually identical to raloxifene, .24.

This is a video clip, and I apologize for the lights not really being down. But this is a uterus in long axis. For those of you who are not gynecologists, this thin, central, linear white line is the

endometrial echo showing an atrophic endometrium.

What does this represent? It represents the interface between the two sides of a single layer of low cuboid epithelium. And this thin white line is the interface between them. And this is what we would like to see on a patient who is displaying atrophic endometrium.

This is the transvaginal ultrasound image of benign cystic atrophy. You can see that the investigator here has put these cursors at 18 millimeters apart. Clearly, this is not a thin white line. Clearly, this does not prove an inactive atrophic endometrium. And it's not hard to understand why if you saw this in a drug that could cause cancer and hyperplasia, you would be somewhat concerned.

When you put some saline into the uterine cavity, a procedure called sonar historiography, this black area in the center

is the fluid that we have instilled. The endometrial layer surrounding the fluid is thin and we've measured it at less than 3 millimeters. And these black or sonar lucent areas here, here, here, and here, as well as here, here, here, and here, represent this benign cystic atrophic change.

And if we look at this through a hysteroscope, we can see that the surface epithelium is pale and atrophic. We see these coarse vessels that are typical of atrophy in general. And when these vessels break, it causes the bleeding that's associated with atrophic bleeding in all postmenopausal women.

And these little blebs underneath this pale surface represent these dilated cystic glands which were just shown so nicely. Here's the surface epithelium with a low cuboidal layer of basalis, and these are dilated cystic glands lined with inactive epithelium that become fluid-filled that are

so easily seen on ultrasound and are mistaken for endometrial pathology.

What about polyps? You heard quite nicely from Dr. Armstrong that there is about a 2.2-fold increase if we pull all of the lasofoxifene data in the 0.5 milligram dose. You see here a 1.68 odds ratio, which is not statistically significant. This is virtually identical to the published incidence of raloxifene causing endometrial polyps published by Silvana Martino, with an odds ratio of 1.7 for raloxifene.

But what's most important about this slide was that every single lasofoxifene polyp that was identified and removed in this study was inactive atrophic on histopathology.

What about bleeding? We've already heard that there's a low incidence of bleeding, in excess of about three per thousand patient-years, over the placebo group. This is about a twofold increase that

was statistically significant. And yes, in spite of the fact that this was virtually always associated with endometrial atrophy, in clinical practice, women who are postmenopausal who present with bleeding will need to have some procedure done to exclude cancer, even though this drug doesn't cause cancer.

We talk about the increase in diagnostic uterine procedures in PEARL, and you've already heard that there were approximately 10 patients per thousand patient-years who had a diagnostic procedure. We've just discussed that 3 in 10 that were due to bleeding, the other 7 were due to investigators perhaps having imaging for other reasons, who saw pictures like the one I just showed, who then went on to perform a procedure. And I will discuss this in more detail.

We also know that raloxifene causes an increase in uterine procedures, as also

published by Silvana Martino.

So what do we conclude in terms of risk? Well, the gynecologic effects of lasofoxifene are benign. No increase in cancer. No increase in hyperplasia. We do see this increase in benign cystic atrophy, and the micro-cystic changes on transvaginal ultrasound have been interpreted as endometrial thickness. We do see a small increase in benign endometrial polyps, a small increase in vaginal bleeding, and a small increase in diagnostic uterine procedures.

And I think you've also heard that the venous thromboembolic events are similar to raloxifene. So I think the take-home message is that to me as a clinician, the safety profile of this compound is very similar to raloxifene.

Moving on to the benefits. As a clinician, when I think about an agent like lasofoxifene and how that would fit into my

day to day practice, it offers excellent bone efficacy, certainly the best of the SERM class. We heard so nicely from Dr. Cummings about the adverse impact on women of vertebral fracture. Lasofoxifene decreases that by 42 percent with a highly significant p-value.

But perhaps more importantly to me as a clinician, this is the first SERM that decreases non-vertebral fractures 22 percent, and also highly statistically significant.

Vulvovaginal atrophy, a huge issue for my postmenopausal patients. Current treatments for osteoporosis do nothing to improve vulvovaginal atrophy. We heard quite nicely that lasofoxifene improves symptoms in women who are complaining, and improves objective parameters of maturation index and vaginal pH.

Lasofoxifene reduces the risk of major coronary events. Not a small issue for patients who -- remembering the Women's

Health Initiative, come in with concerns about will an agent that you're going to treat them with increase their risk of heart disease? It also reduces their risk of stroke. Not an unimportant point in a clinician's mind.

And like other SERMs, lasofoxifene decreases the risk of invasive breast cancer. And at a point where any woman about to embark on therapy for osteoporosis, I believe we must take into account what is her potential risk for breast cancer.

Coming back to the uterus once again, no increase in cancer hyperplasia. We talked about the association with glandular cystic atrophy, which is a benign change and does not require intervention. We've talked about the three per thousand excess of vaginal bleeding, overwhelmingly associated with endometrial atrophy, which will require intervention. But I want you to focus on this last bullet.

This bullet says: Does result in a small excess. Really, what this bullet should say is: Did result in a small excess of 10 per 1,000 patient-years of diagnostic uterine procedures. Because when you set out to study a molecule like this and you don't know if it's tamoxifen-like and you don't know if it's safe, if you see funny-looking ultrasounds found incidentally, you are obligated to do those extra diagnostic procedures.

But now, with all of this data, understanding that there is no cancer, there is no hyperplasia going forward, those procedures would not need to be done. And yet in the context of a clinical trial, certainly, it was necessary.

What other options are available to me? Well, certainly bisphosphonate is an excellent choice. We treat low bone density with it, we avoid it in patients who have esophageal problems. But there are now

factors out there. And I say here, "real or perceived," because increasingly patients come to me and want to stop taking their bisphosphonate, or do not want to go on it because of media tension for over-suppression of bone, media tension on long bone fractures with continued use, and osteonecrosis of the jaw. And so rightly or wrongly, many patients are refusing to continue or embark on bisphosphonate therapy.

In summary, these are the attributable benefits and risks of lasofoxifene 0.5 milligrams. We see here the number of cases prevented in terms of vertebral fracture, and this is per 10,000 patient-years: 93 cases of vertebral fracture prevented, 58 cases of non-vertebral fracture prevented, 16 cases of breast cancer prevented, 24 major coronary events prevented, 14 cases of stroke prevented, 1,005 cases of vulvovaginal atrophy prevented.

And, yes, there will be 12 additional deep vein thrombosis, 5 pulmonary emboli.

And if you look at PEARL, 98 diagnostic uterine procedures. But I hope I've convinced you that the proper number for diagnostic uterine procedures is closer to the range of 30 and not 98, because those women who are not bleeding do not need to be invaded.

So we come back to where we started. The ideal treatment for postmenopausal women with osteoporosis would do a number of things. It would decrease vertebral fracture. Lasofoxifene does that. It would decrease non-vertebral fracture. Lasofoxifene does that. It would decrease coronary heart disease. Lasofoxifene does that. It would decrease stroke. It does that. Decrease breast cancer. Lasofoxifene does that. It would decrease or improve vulvovaginal atrophy, and that is something

that lasofoxifene does. And it would not cause an increase in endometrial cancer or hyperplasia, and lasofoxifene fits that bill, too.

And perhaps someday we'll find a SERM that will also decrease hot flashes and not increase VTE, but right now, it seems that all SERMs do that.

So I want to leave you with this notion. Based on its proven efficacy and clearly favorable benefit/risk profile, lasofoxifene is an excellent agent for appropriately selected postmenopausal women with osteoporosis.

Thank you very much.

DR. CARSON: Thank you very much to all of you who presented today. The slides were succinct and clear, readable. The presentation was on time, and I thought all of you did a really terrific job in informing us.

We very much appreciate that.

Now we'll have a break. And again,

the panel, write down your questions. We'll have questions after FDA's presentation. The Committee members are asked to remember that there should be no discussion of the committee -- of the meeting topics, either amongst yourselves or with members of the audience.

Restrooms are out to the right and then around to the left. And we should resume at 10:15.

(Recess)

DR. CARSON: The FDA presentation will be by Dr. Jerry Willett, who's the medical officer of the Division of Reproductive and Neurological Products.

DR. WILLETT: Good morning. My name is Jerry Willett. I'm a medical officer in the Division of Reproductive and Neurologic Products at the Food and Drug Administration.

I would like to welcome and thank the members of the Advisory Committee for volunteering their time and participating in

the meeting this morning.

My talk will focus on what our division has identified as the key efficacy and safety components for lasofoxifene in the treatment of postmenopausal osteoporosis.

Lasofoxifene has been submitted by Pfizer under NDA 22-242. The dose proposed for marketing is a 0.5 milligram oral tablet taken daily. The proposed indication is the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

In the efficacy section of this presentation, I will provide a brief description of the overall lasofoxifene clinical development program for osteoporosis, and then I will discuss the pivotal Phase 3 study. For the pivotal study, there will be a discussion of the overall study design, the study objectives and endpoints, information regarding fracture assessment, and finally, the primary and principal secondary efficacy results.

The clinical development program for the treatment of osteoporosis included a single large, randomized, placebo-controlled, Phase 3 trial. This pivotal trial will be discussed in greater detail in subsequent slides.

Nine additional osteoporosis-related Phase 2/3 studies were submitted in support of the pivotal study. Six osteoporosis-related Phase 2 studies were completed. These studies provided dose finding analyses, some comparative information against an active comparator, bone mineral density data, and bone reabsorption data.

The other three Phase 3 clinical trials included two large placebo-controlled trials for osteoporosis prevention and one other osteoporosis prevention trial that included both an active comparator and placebo.

The pivotal Phase 3 study was Study

2181002. The study was also referred to as the PEARL study, which is an acronym for postmenopausal evaluation and risk reduction with lasofoxifene. I will refer to this study as the PEARL study in the remainder of my presentation.

The PEARL study was initially planned as a three-year study. Three years is the recommended study duration sought by the agency for approval of osteoporosis treatment drugs. Before the three-year study was completed, the applicant extended the study to five years. Additional primary efficacy endpoints and principal secondary endpoints were added, and additional safety data was obtained with this two-year extension.

The PEARL study was randomized in an equal distribution among three treatment arms each enrolling 2,852 postmenopausal osteoporotic women.

The treatment arms included two

lasofoxifene doses of 0.25 milligram and 0.5 milligram daily in addition to placebo. All subjects in the study received vitamin D and calcium supplementation.

The primary objective that was assessed during the initial three years of the PEARL study was the risk of new or worsening radiographic vertebral fractures. The two principal secondary objectives were also vertebral in nature and defined radiographically. These secondary endpoints were clinical vertebral fractures and multiple vertebral fractures.

Clinical vertebral fractures were defined as those radiographic spinal fractures associated with symptoms of pain or discomfort expressed by the subject.

The two co-primary objectives for the five-year PEARL study were non-vertebral fractures and estrogen receptor-positive breast cancer. The principal secondary objectives were all clinical fractures and

hip fractures.

The division will not be presenting data on the five-year efficacy objectives. We have not received a final report on the five-year PEARL study, and an analysis of these secondary efficacy objectives is not critical in our review of the three-year efficacy results.

However, as noted later in this presentation, we have included five-year safety results that we feel are pertinent for discussion at this meeting, and important in our assessment of the risk-benefit analysis of lasofoxifene.

Osteoporotic postmenopausal women were accepted into the PEARL study if their femoral neck or lumbar spine T-score fell in a range between -2.5 to -4.5. Additionally, the entry criteria required that there be no clinical diagnosis of a new vertebral fracture within the past 12 months and no more than three vertebral fractures on X-ray.

These types of criteria can help preclude very seriously affected individuals from being enrolled in placebo-controlled trials.

Lateral X-rays that covered the area from T-4 through L-4, were obtained at four scheduled time points during the first three years of the PEARL study. These time points included screening one, two, and three years. X-rays were also obtained at the time a subject experienced any symptoms suggestive of a fracture.

New or worsening vertebral fractures were identified in the PEARL study by utilizing two central reading sites in Hamburg, Germany, and San Francisco.

Semi-quantitative scoring of zero for no fracture, one for a mild fracture, two for a moderate fracture, and three for a severe fracture, was used to initially identify subjects with vertebral fractures. Confirmation of the fracture required at least one additional reading, either a

concurrence of the semi-quantitative analysis, or confirmation utilizing a quantitative measurement of the anterior mid and posterior vertebral height.

Measurements of the vertebrae that showed a decrease of 20 percent and at least 4 ml were considered significant of a fracture.

In this table, the primary efficacy endpoints of the three-year PEARL study are presented. Statistical significance is shown for both doses of lasofoxifene compared to placebo in the reduction of new or worsening radiographic vertebral fractures. The hazard ratio for the lower dose is 0.69, and the hazard ratio for the higher dose is 0.58.

Attention should also be paid to the absolute reduction in new or worsening fractures, in addition to the relative reduction. The percentage of fractures in the placebo arm of the PEARL study was 6.4 percent. With fracture percentages of

4.7 percent in the lower lasofoxifene dose and 3.8 percent in the higher lasofoxifene dose, the absolute reduction in fractures is 1.7 percent and 2.6 percent respectively.

Other osteoporosis treatment trials have used a relative risk analysis rather than a time-to-event hazard ratio analysis. As can be seen in this table, the p-values in the relative risk analysis compared to placebo are also statistically significant, so with either analysis, the efficacy of lasofoxifene for reduction of new or worsening radiographic vertebral fractures has been confirmed.

Approximately one-third of the subjects with new or worsening fractures in the PEARL study had clinical vertebral fractures. Again, clinical vertebral fractures were defined as those radiographic spinal fractures associated with symptoms of pain or discomfort expressed by the subject.

This table shows the results for

this principal secondary endpoint. Although there appears to be a trend for the 0.5 milligram lasofoxifene dose, the findings are not statistically significant.

This table shows the results of the applicant's other principal secondary endpoint in the three-year PEARL study, that of multiple new or worsening vertebral fractures.

Statistical significance was demonstrated in this analysis. It is noteworthy in this slide, however, in the top row, to see that the majority of subjects had no fractures.

In conclusion, for efficacy, the applicant has achieved their primary objective in the pivotal Phase 3 PEARL study, namely that treatment with lasofoxifene for up to three years reduced the risk of new or worsening radiographic vertebral fractures.

The safety section of this presentation has been divided into the

following components. There will be a brief description of the safety data base and then a discussion of the adverse events of particular interest. These adverse events include: Deaths, venous thromboembolic events, stroke, major coronary events, gynecologic related events, and breast cancer.

For this NDA, the Division has received three major submissions of safety data. The first occurred with the original submission. This submission had a cutoff date of May 22, 2007. The second submission was the four-month safety update that had a cutoff date of December 3, 2007, and then the third major submission included a preliminary five-year report for the PEARL study along with the PEARL study datasets. This submission included all safety data through April 16, 2008.

Some of the upcoming slides describing safety findings will be composed

of three-year data from the original submission since three years was the length of some of the substudies that focused on gynecologic safety.

A few slides containing integrated safety results will show the results from the four-month safety update, which is the last complete integrated summary received, and then the remainder of the slides that will be presented will be derived from the full five years of the PEARL study.

The overall safety database for lasofoxifene is quite large, with over 30,000 lasofoxifene subject years of data and over 14,000 placebo subject years. When looking at the 0.25 milligram and the 0.5 milligram doses in this table, slightly over half of these patients were in the PEARL study.

The PEARL study subjects make up even a larger percentage of the subject years due to the long duration of exposure in the PEARL study.

The safety issues of particular concern in lasofoxifene treated subjects include the following: first, a numeric increase in all-cause mortality, particular attention will focus on fatal cancer and fatal stroke; second, an increase in venous thromboembolic events with a specific focus on increased pulmonary emboli; and third, an increase in gynecologic adverse events with attention focused on increased endometrial thickening, increased vaginal bleeding, and increased uterine related procedures.

I'll begin first with the first issue of concern, that of all-cause mortality. As can be seen in this table, the PEARL study reported the majority of the deaths in the lasofoxifene clinical program with 90 deaths in the 0.25 milligram treatment arm, 73 deaths in the 0.5 milligram treatment arm, and 65 deaths in the placebo one.

The nine deaths that occurred in

other lasofoxifene studies are shown in the column to the right. All nine deaths occurred in subjects in the lasofoxifene treatment arms, with none reported in the placebo arms.

This table provides the all-cause mortality hazard ratios for the treatment arms in the PEARL study. For the 0.25 milligram dose, the hazard ratio is 1.38, with a confidence interval extending from 1.0 to 1.89. For the 0.5 milligram dose, the hazard ratio is 1.12, with a confidence interval extending from 0.8 to 1.56.

Seven of the nine deaths in the non-PEARL studies occurred in the 0.25 milligram and the 0.5 milligram doses. Adding these seven deaths results in hazard ratios slightly greater than those seen in the preceding slide. The hazard ratio now for the 0.25 milligram dose is 1.44, with a 96 percent confidence interval lower bound above one. The hazard ratio for the 0.5

milligram dose is 1.16, with a 95 percent confidence interval lower bound below 1.0.

In the PEARL study, an independent committee adjudicated the cause of death to a single cause. Each event was assigned to one of 11 defined categories which are shown here. They include: Sudden death, fatal myocardial infarction, fatal ischemic heart disease, deaths associated with revascularization procedures, stroke, other vascular causes, cancer, suicide, homicide, other traumatic death, and then finally an "other" category, which includes those cases which could not be assigned to the first 10.

This table highlights two of the adjudicated categories where deaths in the lasofoxifene-treated subjects were numerically increased over that of placebo. Deaths attributed to cancer occurred in 34 of the subjects taking the lower dose, 25 of the subjects taking the higher dose, and 20 of the subjects taking placebo.

Fatal strokes occurred in 12 of the subjects taking the lower dose, 7 of the subjects taking the higher dose, and 5 of the subjects taking placebo.

Fatal cancers were increased to a degree in both doses of lasofoxifene compared to placebo, as shown in this table. The hazard ratios were 1.69 and 1.24 respectively for the lower and higher doses of lasofoxifene, the lower bound of the 95 percent confidence interval for the 0.25 milligram dose slightly less than 1.0.

This table further subdivides the subjects in the cancer death groups into body site locations where the lasofoxifene-treated subjects exceeded those found in the placebo group. Increases in the number of cases were seen in malignancies in the brain, lung, and GI tract, which included esophageal, gastric, and colorectal.

This table provides the hazard ratios for fatal stroke in the PEARL study.

The hazard ratios were 2.39 and 1.40, respectively, for the lower and higher doses of lasofoxifene, with confidence intervals both overlapping one.

Overall stroke hazard ratios that include both fatal and non-fatal stroke will be presented in a subsequent slide.

This table highlights two other adjudicated categories where deaths in the lasofoxifene-treated subjects were numerically increased over that of placebo. The other vascular category included such events as pulmonary embolism and ruptured aneurism. Deaths in the other vascular category occurred in six of the subjects taking the low dose, two of the subjects taking the high dose, and two of the subjects taking placebo.

Amongst this other vascular category, pulmonary embolism was listed as a cause for death in three of the subjects taking the lower dose, two subjects taking

the higher dose, and none in subjects taking placebo.

The other category listed at the bottom included such causes as chronic lung disease, pneumonia, and sepsis.

Death in the other category occurred in 18 of the subjects taking the lower dose, 17 of the subjects taking the higher dose, and 13 of the subjects taking placebo.

As would be anticipated with the Selective Estrogen Receptor Modulator (SERM), lasofoxifene is associated with venous thromboembolic events. Our issues for concern relate to an increase in overall VTEs in the lasofoxifene-treated subjects compared to placebo, a significant increase also in deep venous thromboses in the lasofoxifene-treated subjects, and also a significant increase in pulmonary emboli.

This table shows the hazard ratios for lasofoxifene compared to placebo for any

VTE. The hazard ratio for the lower dose is 2.67, with a 95 percent confidence interval lower bound greater than 1.0. The hazard ratio for the higher dose is 2.06, with a 95 percent confidence interval lower bound also over 1.0.

In this Kaplan-Meier graph, all VTEs are represented in a cumulative analysis over time. The upper curve is a 0.25 milligram dose. The middle curve is a 0.5 milligram dose, and the lower curve represents subjects taking placebo. As can be seen from the graph, venous thromboembolic events occur early in the course of treatment and continue to rise compared to placebo throughout the five-year course.

This table shows the hazard ratios for lasofoxifene compared to placebo for deep venous thromboses. The hazard ratio for both doses are both above 2.0, similar to that seen with the analysis of any VTEs.

The hazard ratios for pulmonary

emboli are presented in this slide. The hazard ratios are higher than that found for DVT, nearly 6.0 in the 0.25 milligram dose, and over 4.0 in the 0.5 milligram dose. The number of events is smaller overall and the confidence intervals are wider compared to DVTs.

In comparison to fatal strokes in the PEARL study where the number of subjects in the lasofoxifene treatment groups was slightly greater than placebo, the number of lasofoxifene-treated subjects in the overall stroke assessment, which also includes transient ischemic attacks was less than that seen in placebo, there does not appear to be a safety signal for lasofoxifene when analyzing all stroke events.

Major coronary events included five separate adjudicated categories: Coronary death, non-fatal myocardial infarction, coronary revascularization, documented new ischemic heart disease, and hospitalization

for unstable angina. The cardiovascular endpoint classification committee adjudicated these categories.

The number of events was less in each of the lasofoxifene treated dose groups compared to placebo and there is no evidence of a safety signal based on these hazard ratios.

A number of gynecologic issues will be discussed in this presentation. These issues include endometrial cancer, uterine sarcoma, endometrial hyperplasia, endometrial polyps, endometrial thickening, vaginal bleeding, and uterine procedures.

As shown in this table, the percentage of lasofoxifene-treated subjects developing endometrial cancer in the overall clinical development program was similar to that of placebo. The percentages were all close to 0.1 percent.

Uterine sarcoma is mentioned in this presentation primarily because it has

been associated with another selected estrogen receptor modulator, mainly tamoxifen, and warnings concerning sarcoma are found in the tamoxifen label.

Two cases of uterine sarcoma were reported in the lasofoxifene clinical program. One was a case of carcinosarcoma and the other was an endometrial stromal sarcoma. Both of these cases were identified fairly early in the treatment course and could possibly have been preexisting.

The number of endometrial hyperplasia cases identified in the lasofoxifene treatment arms was very small with two cases each for the 0.25 milligram and the 0.5 milligram groups.

An increase in endometrial polyps was identified in a substudy of the PEARL study. In this substudy, all subjects underwent transvaginal sonography at the end of three years. Endometrial polyps were histologically confirmed in 8.8 percent of

the subjects taking the lower dose, 5.5 percent of the subjects taking the higher dose, and 3.3 percent of the subjects taking placebo. A similar increase in polyps was also identified in a larger, full analysis set of women with a uterus in the PEARL study.

Although some polyps are expected to remain small and asymptomatic, and we agree also with atrophic changes seen in a number of these polyps, it is anticipated that an increase in endometrial polyps will lead to increased uterine procedures.

Uterine issues of concern include: An increased percentage of lasofoxifene-treated subjects who developed an endometrial thickness of 8 millimeters or greater and an increased percentage of subjects taking lasofoxifene who developed vaginal bleeding.

This study shows the number of subjects in a special substudy of the PEARL

study who developed endometrial thickness greater or equal to 8 millimeters. This is of important clinical concern, since many clinicians today will thoroughly evaluate postmenopausal patients who had been identified with endometrial thickness greater than 4 to 5 millimeters.

Yearly uterine sonographic assessments were performed in this PEARL substudy.

As can be seen in this table, the cumulative percentage of subjects with endometrial thickness of 8 millimeters or greater, approaches nearly 20 percent by three years in lasofoxifene-treated subjects.

This table describes endometrial thickening of 8 millimeters or greater in other lasofoxifene studies in addition to the PEARL study.

A cumulative percentage increase appears to correlate with duration of therapy.

This table shows the increase in vaginal bleeding with lasofoxifene use compared to placebo. The hazard ratios were 1.68 and 2.01, respectively, in the low and high doses of lasofoxifene with both 95 percent confidence interval lower bounds above 1.0. It is anticipated that this doubling in vaginal bleeding in conjunction with endometrial thickening will lead to increased uterine procedures.

The last issue of concern is the increased number of uterine procedures in the lasofoxifene-treated subjects compared to placebo.

The number of subjects with one or more uterine procedures for cause in the five-year PEARL study was 115 subjects, or 8.5 percent in the group taking the lower dose, 103 subjects, or 7.6 percent in the group taking the higher dose of lasofoxifene, and 46 subjects, or 3.4 percent in the group taking placebo. So again, approximately

doubling.

This table shows the number and incidence for different uterine procedures in the PEARL study. Subjects could be counted more than once in this table. Endometrial biopsy procedures were approximately twice that of placebo, and there was also an increase in procedures in the lasofoxifene-treated subjects compared to placebo that are not office based and would require anesthesia.

Although the applicant has presented data this morning showing less breast cancer in lasofoxifene-treated subjects than in placebo treated subjects, DUP and the Division of Drug Oncology Products, do not concur with the applicant's conclusion that the PEARL study has demonstrated that treatment with lasofoxifene reduces the risk of developing breast cancer.

The reasons for our non-concurrence include the following: Breast cancer was not

a primary objective at the very onset of the PEARL study. The study lacked a very detailed breast cancer risk assessment of subjects; the study was not prospectively powered to demonstrate a reduction in breast cancer; and the total number of breast cancer events was low.

However, there is certainly, from a safety standpoint, from their presentation, we can certainly say that there is no safety signal for breast cancer.

In summary, the principal safety concerns that we have identified include a numerical increase in all-cause mortality, which has been identified more prominently in the 0.25 milligram dose of lasofoxifene, an increase in venous thromboembolic events, and an increase in distinct uterine changes which will lead to more uterine procedures being performed, some of which may require anesthesia.

And in conclusion, treatment with

lasofoxifene reduced the risk of new or worsening radiographic vertebral fractures, however several safety issues have been identified that impact the risk-benefit profile. The Committee will be asked to consider these safety concerns and consider how they impact the overall risk-benefit assessment.

Thank you very much.

DR. CARSON: Thank you. We're a bit early, so why don't we go ahead and proceed with questions to the sponsor, and if you have separate questions for Dr. Willett, he'll also answer those, I'm sure. I'd ask that you raise your hand and then ask the question.

Yes?

DR. GARDNER: Jacqueline Gardner from the University of Washington. I have a question related to subgroup analyses. When we're thinking about risk management, risk communication, I wonder if the sponsor could tell us what work they've done in looking at

subgroups of women that we might define as at higher risk, specifically of venous thromboembolic events.

I'm particularly interested in whether you've done analyses by age, younger women, than those women who were less long postmenopause, and also within the Hispanic groups that appear to be at higher risk of all-cause mortality, can you shed any light for us on why we would think of those women in those clinical trials in Central and South America differently than we might for U.S. Hispanic women? What about lifestyle for example? Smokers? Can you enlighten us a little more on who might be -- as to who might be at higher risk that we might look at going forward in defining risk?

MR. THOMPSON: To answer your question on the VTE subgroup analyses, Dr. Margaret Johnson will address that question.

DR. JOHNSON: Good morning. Dr. Margaret Johnson. We have assessed risk, I

believe is your question for VTEs -- across the groups, the treatment arms, the risks for VTE appear to be balanced across the treatment groups for issues such as BMI and smoking. We did look more closely at patients who developed venous thromboembolic events for some of these risk factors, and found that the majority of the risk factors were clinical, such as the ones where patients were mobilized following surgery of a fracture, and that was the main risk that we saw for VTEs.

MR. THOMPSON: You were asking -- and if can clarify the question you were asking with respect to Hispanics, was that in relation to mortality? Was it in relation to VTEs? If you could --

MS. JOHNSON: We have a question put to the Committee today relative to how we feel about the clinical trial results from the Mexican and Central American, and whether we think that it's important for U.S. women, and I'd like to know whether you think it is.

MR. THOMPSON: Thank you. Dr. Roisin Armstrong will address that question further on Region 2.

DR. ARMSTRONG: Sorry. Roisin Armstrong. So yes, what I would like to share with you is the region analysis that we have undertaken in the PEARL trial. This is in accord with the five prospectively defined regions that were in accordance with the protocol, although the analysis in and of itself was an exploratory post hoc analysis.

And just by way of setting up what will follow, I'm going to share a series of three slides that will show the cumulative incidence of mortality, first in Regions 1, 3, 4, and 5, and I can elaborate on the countries that contribute to those regions, then Region 2 by itself, and then I'd like to bring it all together to summarize the information.

So if I can please project S-32. What we're showing on the screen is the

cumulative incidents of mortality for the regions combined: Region 1, which represents North America including the United States, Western Europe, Australia, and South Africa; Region 3, which represents India; Region 4, which represents Asia; and Region 5, which represents Central and Eastern Europe, Egypt, and Turkey.

Together, these regions contribute 79 percent of the PEARL patient population. When we look at the cumulative incidence of mortality for this population, this subset, there's no difference across three treatment groups.

In the next slide, I will share for Region 2, please project S-33. Region 2 constitutes Mexico, Central and South America, 21 percent of the total patient population, where there are a total of 44 events. And you can see what's illustrated on the Kaplan-Meier, the gold line is the lasofoxifene 0.25 milligram dose group and

the blue line is the 0.5 milligram dose group, and the red line is placebo.

There is a difference of 14 events between the lasofoxifene .25 milligram dose group and placebo in Region 2 which was 56 percent of the difference that was observed across the full analysis set. There was an observed difference there of eight events on the 0.5 milligram dose group relative to placebo, and in placebo in this region, there were a total of seven deaths for the five years of the PEARL study.

When we bring this all together in the next slide, and please project S-34 -- my apologies, this slide starts to get a little bit busy as all the six slides collapse together -- but we retain the dotted lines indicating Region 2, and what you can see is the lasofoxifene 0.25 and 0.5 milligram dose groups are very comparable with the remaining -- I beg your pardon -- with the three other treatment groups in all other

regions combined and really what is on the lower part of the Kaplan-Meier curve is those seven deaths for Region 2, which occurred through the five years of the follow-up of the PEARL trial.

MR. THOMPSON: As far as any additional analyses that we've done -- we did do a significant number of others to try to understand the difference, and I would ask Dr. Thompson to come up to describe further analyses that were done to further address this.

DR. THOMPSON: Good morning. I'm John Thompson. I'm the project statistician for lasofoxifene. When we saw these results, we undertook a large variety of analyses. We looked at age, we looked at BMI, we looked at years postmenopausal, and we could not find a treatment by mortality interaction for any of those endpoints.

DR. CARSON: Dr. Gillen?

DR. GILLEN: This is somewhat of a follow-up question to Dr. Gardner's question and

what we were just looking at. So a lot of what we've been presented with are hazard ratios and though exploratory, when we look at the full data, what we see is somewhat of a late occurring treatment effect.

I think the Woman's Health Initiative was mentioned earlier, and that's kind of a classic example, where this was designed under a proportional hazards framework, but when we look at things over time, we see differences that might occur. I wonder if -- I saw arrow bars that were sitting up, can you report to us both pooled across regions and stratified by Region 2 versus others, the five-year cumulative mortality rate along with confidence intervals so that we can have those to compare. I'm particularly concerned with long-term survival.

MR. THOMPSON: Dr. Armstrong?

DR. ARMSTRONG: I will be asking my colleagues to project a slide from the main

deck. I believe it's to address the incidence rate of mortality and the confidence intervals are on that. So what we will look to share with you is the five-year data from the PEARL trial.

So while my colleagues are pulling up the main deck, just to recap, through the five years of the PEARL trial, please project M-35 -- actually, sorry, I think that's the incorrect slide. I think it's the slide with the confidence intervals and the incidence rates. What we have in our backup slides in the safety presentation, we do have cumulative incidents rates for mortality for the individual doses for the PEARL study.

And just, again, by recapping, there were a total of 65 deaths on the placebo group. There were a total of 90 deaths on the 0.25 milligram dose group, and there were 73 on the lasofoxifene 0.5 milligram dose groups.

Please project M-34. This is for the lasofoxifene dose pooled from the five

years of the PEARL trial, so this is combining the 0.25 and the 0.5 milligram dose group, and the difference here is absolute difference in incidence rate of 1.2 events per 1,000 patient-years with a confidence interval it spans -0.4 to 2.9.

If that's the information you were looking for.

DR. GILLEN: Actually, stratified by the treatment groups, and I was hoping to see minus the Region 2 group as well if we have that.

DR. ARMSTRONG: We have that, and I can share that with you. If you could please project the slide for the mortality in PEARL that shows the incidence rates for the two individual dose groups.

Please project S-17. What we show here is for the individual dose groups in comparison to the placebo and the incidents rate on the 0.25 milligram, 7 events per 1,000 patient-years, and for the 0.5

milligram dose group, 5.7 events per 1,000 patient-years in comparison to placebo for 5.1 events per 1,000 patient-years.

DR. GILLEN: We don't have the inference available for the contrast between and the two arms at five years. So you've given us the individual confidence intervals, I'm wondering about the difference in mortality rates.

DR. ARMSTRONG: We will have to get that information for you.

DR. JOHNSON: Yes, I had some concerns in regards to uterine procedures. I wanted to ask regarding that. Am I to understand that that was not continued from three to five years? And what do we know, when we looked at the numbers, it appeared that there was an increase in thickness of the endometrium over time and whether or not that was further assessed in any manner from the three- to five-year time period.

And then my second question would be, how will we advise clinicians to monitor

these patients with bleeding, with ultrasound, that will minimize procedures?

MR. THOMPSON: Dr. Jim Proulx will address your question.

DR. PROULX: Good morning. Jim Proulx, Pfizer gynecologist. With regard to the questions, just to clarify again, first, you asked about the number of subjects that had thicknesses of greater than a certain number of procedures?

DR. JOHNSON: Yes. There was a substudy looking at the thickness. Was that extended beyond three years?

DR. PROULX: No, that was not. It was a three-year substudy looking at transvaginal sonography at baseline, years one, two, and three, and that's where much of our data on thickness comes from.

DR. JOHNSON: Do we have any data beyond three years?

DR. PROULX: What we have beyond that is the fact that all these patients did continue

in the study, so we have their endpoint data with regard to hyperplasia and cancer and procedures in the other substudy, which was really what we called the real world population, those without any surveillance being performed per protocol.

DR. JOHNSON: So we don't have ultrasounds after three years on those individuals?

DR. PROULX: That's correct.

DR. JOHNSON: And then my concern was, this increased thickening, how is this going to be successfully monitored by clinicians in patients on this medication, because I presume they'll be on it for extended periods of time.

DR. PROULX: What I'd like to do is discuss briefly the monitoring that we did in our study and what type of morbidity incurred thereafter and then bring up Dr. Steven Goldstein, who can talk about the type of management paradigm which we would pose post-approval.

With regard to the endometrial thickness, this was again studied in that 300 approximately subjects, in that substudy over three years, and what we observed is that the majority of people did not demonstrate any increases in endometrial thickness, and amongst those that did, the histology findings were all benign in those women.

In fact, the majority of women did not have any increase that stayed -- progressively increased. It actually went down on serial measurements and it appears to us that serial surveillance is what leads to increased incidents of these findings. If we looked twice as often, we'd actually see perhaps more of these findings as they appear to be somewhat transient, and this appears consistent with this hydration theory that was put forth where these things are spontaneous events that can resolve over time and thus finally, over the 20,000 patient-years of observation of lasofoxifene

alone, there was no excess of hyperplasia and cancer, and we would not expect to employ any additional surveillance as a result.

I'd like to bring up Dr. Goldstein to speak further about our management paradigm we would recommend.

DR. GOLDSTEIN: Steve Goldstein again, from New York University. Absent any bleeding, the recommendation would be that these patients do not need to be invaded. There needs to be an education process, not just for this drug, there needs to be an education process for incidentally discovered thick endometrium in all postmenopausal patients. It appears that as many as 10 to 17 percent of patients who have not bled, if interrogated with ultrasound, will have thick endometrial echoes.

And the thick endometrial echo today is where the simple cyst of the ovary was many years ago when those patients were routinely subjected to surgery, until we finally realized that that was a benign

finding. And for one, I think that the education program that this sponsor has outlined is something that I really welcome. Because I think it would not only help the lasofoxifene-treated patient, but I think it would help move the needle for all patients who have incidental findings of thickened endometrial echo, because there has never been any validation that this, absent bleeding, absent any high-risk factors, needs any kind of invasion.

All that was ever studied was that in postmenopausal women who were bleeding, the presence of a thin, distinct echo excludes pathology, and as the FDA -- the Agency has pointed out, many clinicians have misappropriately turned this around to believe that incidental finding of thickening needs to be invaded regardless of drug or no drug, and so I think that this program would be helpful.

But in specific answer to your

question, I do believe that any postmenopausal patient who bleeds, whether they're on this drug or any other drug, needs to have endometrial cancer ruled out. You and I as gynecologists know that that's one of the first things we learn, and that will be necessary.

Realize, however, this hydration effect is not usually, in my experience, associated with the cervical stenosis that you can see with certain other agents where there is central endometrial fluid collections and those can be very difficult services to dilate into a simple biopsy on these patients don't fit that kind of picture.

DR. CARSON: Along those lines, let me just ask, I think there were six or seven patients with endometrial cancer in the -- six, I guess, in the PEARL study that were on the drug, and four in the placebo -- of the patients on the drug, how many of those with endometrial

cancer had vaginal bleeding?

MR. THOMPSON: Dr. Proulx will address that.

DR. PROULX: Good morning. Jim Proulx again. Please project GY-10. This is a listing of the subjects within the PEARL study that had endometrial cancer listing those that had bleeding, and the majority of the subjects did in fact have bleeding presented with early stage disease and with generally endometrial tumors.

DR. CARSON: So then there are two patients there without vaginal bleeding, how can you, if you don't do a biopsy on a patient who doesn't have a thickened endometrium and those two patients don't have vaginal bleeding, how would the diagnosis have been made?

DR. PROULX: Again, I can call up Dr. Goldstein to speak further about the basis for the surveillance guidelines, but in short, I would suggest that they will ultimately bleed and that's the basis for choosing the guidelines.

DR. GOLDSTEIN: Can you put that slide back? Yeah, but you need to put it here because I can't see that far. Sorry about that. Ophthalmology was never my strong point.

Notice that both patients who did not bleed were on placebo and there will be perhaps a small incidents of people who don't bleed initially, but as gynecologists we know that endometrial cancer usually presents early and with bleeding, but in every case of lasofoxifene-treated patients with an adenocarcinoma of the endometrium, all of those presented with bleeding.

DR. CARSON: Dr. Portis?

DR. PORTIS: I have a question going back to the endometrial thickness. I notice that you used a measurement of greater than 8 millimeters, but it's my understanding that the usual measure is greater than 4 millimeters and so I wonder if you can explain why you chose 8 millimeters. That's not typical.

MR. THOMPSON: Dr. Proulx?

DR. PROULX: At the time this study was developed, what constituted someone with an abnormal thickness was a subject of some debate and we've actually looked at a number of various measurements of endometrial thickness over the course of time, in fact studying any amount of endometrial thickness, perhaps, but we have another way of measuring endometrial thickness that I could project for you.

If you could please show GY-102. This is the same dataset from which Dr. Willett presented. Again, this is depicting women that have a thickness greater than 5, and instead of the 19 and 17 subjects on lasofoxifene, what you saw for that measurement, this shows women with 4 in placebo cohort, 42 and 35. The majority of women did not develop this degree of abnormality, but some did. And again, asymptomatic findings with also normal histology, also identified in this definition of a subset.

DR. LIU: This is a question for Steve Goldstein. When you do look at the cystic changes on ultrasound, is there a difference in any like Doppler assessed blood flow versus someone who's not exposed to lasofoxifene? You discriminate based on that?

DR. GOLDSTEIN: What I'd be giving you is anecdotal. Clearly, Doppler blood flow was not carried out in this particular study. And as you saw very nicely on the H and E histopathology, these are fluid-filled cystic spaces. There's no increased vascularity. You don't see this -- does not light up if you interrogate it with color flow Doppler, and I don't know what the uterine vessel resistive indices, might be that study hasn't been done, but I don't think there's a need to interrogate such patients with color flow Doppler.

Both you and I know it would be a very interesting academic study to carry out, but there's no suspicion that there's any vascularity here whatsoever.

DR. CARSON: Dr. Collins?

DR. COLLINS: Hi. Mike Collins. So if I understand it correctly, across multiple endpoints, there are concerns more with a lower dose than with a higher dose including deaths, VTEs, polyps, procedures, et cetera. So one of the questions is really to try and figure out if any of these things are real or by chance as suggested.

Now, is there anything from the preclinical data that can help us with this in terms of a dose response affect? In other words, in some women, in some tissues, in some models, do we see an estrogen effect or an anti-estrogen effect to help us try and figure out whether any of these changes are real or chance?

MR. THOMPSON: We've looked comprehensively across the preclinical studies that have been done to investigate relationships between the various doses and the signals that were recorded and organ by organ we looked at

this. For example, when we look in the breast, we see a very nice dose response with respect to the effect of lasofoxifene, as in the bone, we see a dose response effect that we see with lasofoxifene. And to further expand on this in terms of the preclinical studies that looked at tox findings, et cetera, that may shed light on this, I'll ask Dr. Beierschmitt, the toxicologist, to come up to review these data.

DR. BEIERSCHMITT: Good morning. I'm Bill Beierschmitt, the preclinical toxicologist. We looked extensively at the results of our data all the way back from a single dose all the way up through our two-year oncogenicity studies, and overall, we saw no indication of hormesis in any type of effect that we saw, toxicological effect, or any kind of an effect that demonstrated -- or hormetic effect that could possibly be a mechanism for anything that could explain the deaths in this particular case.

Overall, our dose responses were as we would have expected them.

DR. COLLINS: So you never saw as you went from a lower dose to a higher dose or vice versa even, that an estrogen effect, whether it was converted or changed to an anti-estrogen effect, so to speak?

DR. BEIERSCHMITT: No, we didn't see anything like that, that where it looked like at a lower dose it had an estrogenic, antagonist effect and then it switched to the higher dose. No, we didn't see any results such as that.

DR. COLLINS: And related to this, too, so in terms of the VTEs, what I understood was said earlier, that there is no association with smoking?

MR. THOMPSON: Dr. Johnson, would you address that?

DR. JOHNSON: Just to clarify -- there is an association between smoking and VTE. What I meant to say was that the incidents of smoking was balanced across baseline. When we looked at individuals who had VTEs, there was an increase in smokers -- however, the predominant factor we

saw was related to immobilization related to surgery.

DR. CARSON: Dr. Gardner?

DR. GARDNER: I have a question for Dr. Turner about the projected post-marketing surveillance suggestions and specifically regarding the patient information leaflet. Can you tell us what risks you plan to communicate in that for patients, or things that they can do to help themselves to avoid risk and also will this be -- is this plan to be distributed with the packaging or are you intending that pharmacists or physicians or someone else will hand that out? I appreciate that you also have a web-based plan, but what about what you're calling PIL?

MR. THOMPSON: Dr. Turner?

DR. TURNER: The Patient Information Leaflet will include the risks of VTEs and potential for increased diagnostic procedures. As far as VTEs, we're going to be telling them about the signs and symptoms of VTEs, especially

deep vein thrombosis, you know, swelling in the legs, redness, things like that. We'll be telling them ways to mitigate this risk, in other words, if they know they're going to have surgery, they should discontinue the lasofoxifene three weeks beforehand.

If they're going to be gone on an extended period of travel which would require immobilization periods, you know, to make sure they're getting up and walking around, things like that. We'll also be telling them to -- in the label and information leaflet -- that their physician should be considering the risk/benefit ratio if they have superficial thrombophlebitis, active malignancy, and so forth, so these kinds of things will be in the Patient Information Leaflet. They will also be on the internet website.

They will also be -- they will be handed out with the packaging, but we will be providing materials to any health care

provider program to distribute, kind of the principle of many times, many ways of communicating, and then we will have several ways to evaluate the effectiveness of these programs and one will be, as we mentioned in the cohort study, we'll be looking at the incidence of these events relative to raloxifene and women not treated with the SERMs. I will also be doing self-testing on the Internet, so people who do avail themselves of that will be able to test their own comprehension.

Recently at the ESPY meeting, there were a couple of abstracts where they demonstrated success of these approaches to educational programs.

DR. GARDNER: Sorry, what about smoking as a risk factor, communicating?

DR. TURNER: Definitely.

DR. GARDNER: And then when you say handed out with the packaging, is it going to be incorporated in the packaging or are you

expecting that the pharmacist will hand them?

DR. TURNER: It will be in the actual packaging, but we would like the pharmacist to also have that so that they can inform as well.

DR. GARDNER: Reinforce. Thanks.

DR. CARSON: Dr. Merritt?

DR. MERRITT: I appreciate that the data as it's being collected, is being submitted, so we have three-year data, data from December, and data from April of this year. Of the 8,556 patients who are enrolled in this study, how much is fully completed data that we're looking at? It seems at the five-year mark, we're seeing some of the increase in morbidity and mortality. So how many more patients are yet to be reported? Has everyone completed the trial now and you're just finishing up? Please tell me where we are.

MR. THOMPSON: All patients in the trial have completed therapy. All patients have been reported through the preliminary study report of the five-year data. So the trial is

finished and the final report has not been issued for the trial, but the preliminary report has been done, but which contains all of the patients for all of the data.

DR. CARSON: Dr. Gillen?

DR. GILLEN: This is following up on Dr. Collins' question, actually, about the differences in mortality rates between the dose groups and kind of counterintuitive to me, at least, dose response. You said that there was no preclinical evidence. Has exploratory analysis been done to look at, for example, is there differences in duration on study drug between those two arms? To talk about total dose and things of that nature, that maybe could explain some of this?

MR. THOMPSON: As you noted, we have done an extensive analysis of the mortality and the various components of that, and Dr. Armstrong can explain that.

DR. ARMSTRONG: We have looked at the follow-up and exposure in the patients across

the three treatment groups, and indeed, they are balanced in the PEARL trial.

DR. CARSON: Dr. Portis?

DR. PORTIS: I noticed that in the presentation, you mentioned the negative effects of lasofoxifene are similar to other SERMs, you said. So I wonder, do you know if lasofoxifene presents -- does it have a unique advantage over the other SERMs that are currently available?

MR. THOMPSON: As was noted in the presentation, one of the advantages that lasofoxifene has over the currently available SERM, raloxifene, is a beneficial effect in non-vertebral fractures. This is a clear differentiating factor in that the PEARL data did show a reduction in non-vertebral fractures very consistent, in the PEARL trial and this does differentiate it from SERMs.

Also, the effect that is observed in the coronary events is differentiated from raloxifene. The significant reduction in stroke, if you exclude TIA, is a

differentiating factor from raloxifene, as that's the only one currently indicated for that. Also, the improvements in VVA would be another consideration to put into that equation as far as the differentiating features of lasofoxifene compared to available SERMs.

DR. CARSON: Dr. Liu.

DR. LIU: To follow up on Dr. Willett's point of an increase in fatal cancers with no specific organ system, has there been anything similarly reported for raloxifene in the RUTH trial or any of the other SERM trials with raloxifene that would show the same pattern?

MR. THOMPSON: In terms of the mortality and the incidents, Dr. Armstrong can discuss the incidences.

DR. ARMSTRONG: The totality of data available with raloxifene today does not show an increase in mortality, and is based again on public information, is not associated with any

increase in fatal cancer or cancer.

DR. LIU: A follow-up question to the benefits. You didn't present a lot of the information on vulvovaginal atrophy, specifically symptoms other than saying that the symptoms were decreased. What specific aspects were significantly better than the placebo group and could you elaborate more on the vulvovaginal symptoms?

MR. THOMPSON: Dr. Johnson?

DR. JOHNSON: The design of the study -- there's a pivotal Phase 3 study which looked at symptoms of vulvovaginal atrophy, and the women who entered into the trial had to have at least one symptom that was moderate or severe, and the full symptoms were burning, itching, dysuria, and dysparnia. So those were the four symptoms that they were asked about.

And then we looked on a four-point scale to see change in those symptoms over a 12-week period, which was the regulatory requirement to look at this particular

symptom.

DR. CARSON: Dr. Adashi?

DR. ADASHI: Going back to safety for a moment, if we were to take 100 eligible women who wanted to be treated by the drug, relative to DVTs and taking into account the background incidents, how many actual women -- or what's the excess burden that we will see above and beyond the background and to reduce it to simple terms, just 100 women, for example?

MR. THOMPSON: In terms of the DVTs, you're asking?

DR. ADASHI: DVT and then we can perhaps cover the PE and if time permits, I'd like to ask some of the same about the benefits.

MR. THOMPSON: Dr. Johnson?

DR. JOHNSON: As far as the benefit/risk is concerned, with respect to deep venous thrombosis, we would expect a net of approximately 12 extra events on the lasofoxifene 0.5 milligram treatment, and for pulmonary embolism, approximately five events.

MR. THOMPSON: Per --

DR. JOHNSON: I'm sorry, per 10,000 patients. Sorry. Would you please project No. 26? Thank you.

DR. ADASHI: In terms of the benefits. If we were to treat 100 or 10,000 women, how many would actually accrue a benefit in terms of the primary endpoint of vertebral fracture, again relative to background or placebo?

MR. THOMPSON: Again, I could please project slide 26. In this evaluation, again, looking at the cases prevented, the number of actual cases that would be prevented with 0.5 milligram, 93 per 10,000 patients would be prevented with vertebral fracture, and add on to that approximately 58 non-vertebral fractures would be prevented with lasofoxifene 0.5 treatment.

DR. CARSON: Dr. Johnson?

DR. JOHNSON: Yes, I'm going to continue some concerns in regards to comparing discussion to other SERMs. Looking at the

pulmonary emboli risk, how does this compare to other SERMs that are out on the market? Because, you can see that indeed there is between a four- and a six-fold increase of PE risk with this agent.

MR. THOMPSON: Dr. Johnson?

DR. JOHNSON: When trying to assess risk with other SERMs, the most appropriate one would be to compare an osteoporosis treatment population, and that would be the equivalent of the MORE trial for raloxifene. Please project S-111. And when we look to the three-year time point in PEARL, and compare it with the three-year time point for raloxifene, we can see that the absolute number of pulmonary embolism events is lower on lasofoxifene compared with raloxifene, and the hazard ratio, because of the very small numbers, one in placebo and four in the 0.5 milligram dose, is slightly higher, but the confidence intervals overlap and they are certainly very comparable.

DR. CARSON: Dr. Merritt?

DR. MERRITT: Dr. Willett's slide number nine, it speaks about the blinded central reading of fractures, and I'm not a radiologist. So there's readings of zero, one, two, and three, that were semi-quantitative as well as semi-quantitative yes or no, and then a quantitative millimeter measurement. And could someone explain to me how objective or subjective these types of readings are because they're very key to your dataset?

MR. THOMPSON: Dr. Fuerst, would you please address that question?

DR. FUERST: Tom Fuerst, scientific director for osteoporosis services at Synarc. Synarc was the central radiology laboratory that assessed vertebral fracturing in this study. The technique for evaluating vertebral fracture for PEARL was modeled after the MORE trial, with a slight modification, but both studies began with a semi-quantitative reading which is a radiologist subjective assessment of the presence or absence of vertebral fracture.

It's semi-quantitative in the sense that the severity of the fracture, the degree of height loss or height reduction, is estimated visually, not by measurement, but visually, into those categories of mild, moderate, and severe.

Any time a patient in this trial was identified to have an incident of vertebral fracture by the semi-quantitative technique, that patient went on to have those films read by two additional methods. One of those was the quantitative morphometry technique, and in that method, a specific measurement of the vertebral body height at baseline and each follow-up visit is made, and that height change over time is evaluated using a criteria of a 20 percent reduction in vertebral body height.

It's also a 4 millimeters absolute change in vertebral body height as a threshold for defining the presence of the incident vertebral fracture.

So all incident fractures by SQ had that assessment, and in addition, they had a second visual assessment and that was a binary semi-quantitative assessment which was simply a yes/no decision rather than evaluating the severity of the fracture, so the three grades of mild, moderate, and severe, were collapsed into one grade of yes, there's a fracture present, or no, there is no fracture present.

The final answer about whether a fracture was present or not was based on agreement of two out of three of those techniques, at least two out of three of the techniques.

DR. CARSON: Let me -- before you sit down, let me just clarify something. Were only those that were initially identified as having a fracture reread or was everything reread?

DR. FUERST: No, that's correct. All patients in the trial had the semi-quantitative reading and because the majority of patients did

not have an incident vertebral fracture, that was the only assessment that they -- patients that were identified with an incident fracture by SQ had that confirmed by these independent techniques.

DR. CARSON: So the patients who were absent of fractures never had their reading blindly read?

DR. FUERST: No, they were always blinded --

DR. CARSON: So everybody did?

DR. FUERST: Everybody was blinded and then only those that were -- blinded and centrally read, and then those with instant fractures went on to have additional assessments.

DR. CARSON: So did -- again, everybody had two readings?

DR. FUERST: Everybody had one reading which was the semi-quantitative reading and a positive result of the semi-quantitative reading, those patients went on to have the two

additional readings for a total of three.

DR. CARSON: So there may have been a significant false normal reading?

DR. FUERST: Yeah. That's an excellent point. The sensitivity of the semi-quantitative reading, at least in our hands, is in the range of 92 to 93 percent. So it's unlikely to have missed a fracture. Fractures don't disappear so if it was missed at one year, it was very likely identified at the two year or three year visit. So we think the false negative rate is low.

DR. CARSON: Thanks.

MR. THOMPSON: Also, all patients did get an X-ray on a yearly event and those were submitted for this quantification.

DR. CARSON: Thank you. Dr. Nelson?

DR. NELSON: My question is about the increased overall case mortality in the low dose, whereas it wasn't found in the higher dose. My question is, do you know what the power you had was to detect a similar increase

in mortality in the higher dose as to what you found in the lower dose? In other words, this might just be a type 2 error in not detecting the mortality in the higher dose. Can you tell us what the power was?

MR. THOMPSON: Dr. Koch, can you address that question?

DR. KOCH: The nominal p-value for the low dose was about .05 with the sample size that was there. I have not done a formal calculation of power for the high dose or for the low dose as well, but typically, when the nominal p-value is about .05, if you were to use the same sample size in a new study, the power would be about .50.

DR. NELSON: So am in interpreting this right? There's a 50 percent chance you wouldn't detect the same degree of mortality in the higher dose if you analyzed it?

DR. KOCH: Well, probably the interpretation that is a more reasonable interpretation is to actually recognize that the

high dose and the low dose actually were not significantly different from one another and that was why the sponsor used the combined doses to obtain an assessment and that was what they actually showed in their main presentation and in that presentation, they got the confidence interval that went from something like -.4 per 1,000 to about 3 per 1,000. So when you actually improve the power and consider both of the doses together because the two doses really were not different from one another, then you still end up getting an overall result that indicates no difference.

So that was a way in which one brought more power to the assessment, because as I said, when you compared the two doses with one another, there was no suggestion of a significant difference between them even though there was a directional trend that suggested the lower dose had a higher rate than the higher dose, that trend being somewhat counter-intuitive.

DR. CARSON: Dr. Adashi?

DR. ADASHI: I wanted to explore a tad more the risk/benefit ratio and I found the slide that you actually projected, I don't know what number you have it, but it's 25 in our handout titled "attributable benefits and risks." Tell me if this is a fair characterization. Subject to 10,000 patient-years of treatment, we can expect about 150 women to experience prevention of either vertebral or non-vertebral fractures while at the same time experience a somewhat lower number, about 130 or so, events that we characterize as serious adverse events.

Is that a fair characterization of the balance?

MR. THOMPSON: Based on the benefit/risk, and I don't have that table before me -- can we get the table --

DR. ADASHI: It's a wonderful bar graph, in a sense, but the --

MR. THOMPSON: So please project slide

25.

DR. ADASHI: Yeah, that's the one.

MR. THOMPSON: So you're computing the addition between the two fracture types to get the hundred and --

DR. ADASHI: Yes, about 150.

MR. THOMPSON: And can you please clarify the question, 150 --

DR. ADASHI: So I am making the assumption that if we subject -- if we extend the therapy to 10,000 patient-years, we can expect at the end of the treatment with a .5 milligram dose, about 150 women to accrue a benefit in terms of vertebral and non-vertebral fractures, actually having been spared that outcome.

MR. THOMPSON: That's right.

DR. ADASHI: But at the same time, some other women we assume, are going to be experiencing a number of adverse side effects, and I just added up the three that are listed here, those I believe are the serious ones, and

they are about 130 combined or 120 combined. I was just trying to be sure that I am reading this correctly and/or ascribing this correctly.

MR. THOMPSON: What you have computed is the vertebral fracture protection against the net risks associated that we've described and that would include the diagnostic uterine procedures as a component in that index. And I would like to please ask Dr. Susan Johnson and then Dr. Goldstein to please expand on that, to give it an overall assessment of the two relative to each other in terms of the fractures prevented versus a uterine procedure.

Dr. Johnson?

DR. JOHNSON: Sure. So I'm Susan Johnson. I'm a professor of obstetrics and gynecology at the University of Iowa, and during this trial was the chair of the Data Monitoring Board, but I also am here addressing the question as a clinician who has focused my practice on menopausal patients for the past 15 years.

So I think, Dr. Adashi, the issue for me in looking at this data is the inclusion of diagnostic uterine procedures on the risk side just to someone sort of walking in off the street seems inappropriate. So the vast majority of those procedures done in the United States are going to be outpatient endometrial biopsies which those of you who are gynecologists know are procedures done every day, take typically less than five minutes, are very safe, so I don't want to diminish the burden to a woman who has to undergo one of those procedures.

But when you contrast that experience, which is a single event, very short, against a vertebral fracture or a non-vertebral fracture, there's just no comparison between the two.

And then I think it's also important to remember that there are -- even if we ignore the probable benefit for breast cancer and coronary events, the benefit for

vulvovaginal atrophy is actually -- sounds as if it might not be too significant, but it actually is. A lot of those women who have that condition, who experience painful intercourse and the other serious symptoms that were mentioned earlier, will, in addition to whatever osteoporosis drug they're taking, they're going to -- some of them have to take estrogen which they really don't want to do, and so there's 1,000 women who might avoid having to take a second drug.

So I guess my bottom line is, I think including that list as an equivalent to a DVT or a pulmonary embolus -- they're just different magnitudes of risk.

DR. ADASHI: I have just one last follow-up question. Again, just for edification, is it correct to assume that we would accrue the benefit of 150 prevented fractures after subjecting -- after maintaining the therapy for 10,000 patient-years. So is it correct to state that maybe 1 percent or less of

the target therapeutic pool is actually a beneficiary? Is that a correct or incorrect statement?

MR. THOMPSON: Dr. Cummings, can you address that question?

DR. CUMMINGS: To make sure I understand it, would you mind repeating what you asked?

DR. ADASHI: So in other words, to accrue the benefit of 150 prevented fractures for the 10,000 patients in question --

DR. CUMMINGS: Yes.

DR. ADASHI: Does that mean we have to treat this many to accrue this few?

DR. CUMMINGS: For the prevention of fractures, with the numbers 150 out of 10,000 per year -- it's like 1.5 percent per year prevented -- you look at this in a longer term perspective too. It's not just one, it's two, three, four, five years during which these events began to accrue. Prevention of fractures is -- the prevention of fractures is a longer

term undertaking in patients. It's not just this year, it's year after year after year. Risk also increases with age, and so the longer one takes it, theoretically, not just theoretically, the greater the benefit will be in reduction of fracture risk.

Does that clarify your question?

DR. ADASHI: It does. But it does seem as if it would inevitably take treating about 10,000 patients to see the benefit for about 150 of them.

DR. CUMMINGS: Or 100 patients, 1.5 per 100 per year. Yes. Prevention generally does involve treating a number of more patients, many more patients, than will get a benefit from any preventive undertaking, be it hypertension or cholesterol, and that's also true for the prevention of osteoporosis.

DR. ADASHI: I guess that's another plug for personalized medicine.

DR. CUMMINGS: What's that?

DR. CARSON: Dr. Adashi, I think on

the sponsors advisory -- that briefing document, I think on page 20 is a chart where they list the number needed to treat. I think you may find the answer to your question.

DR. ADASHI: Okay.

DR. CARSON: Dr. Gillen?

DR. GILLEN: Going back to the comparison with raloxifene and the safety profile, both Dr. Goldstein's presentation and in our briefing document, you mentioned that raloxifene also increases uterine procedures, but I didn't see actually -- at least I didn't catch anywhere in either of those two documents, a quantification of the vaginal bleeding rate. I wonder if someone can quantify that for us.

MR. THOMPSON: Dr. Proulx?

DR. PROULX: Hi. Good morning. Jim Proulx again. You're after the quantification of the vaginal bleeding rates with lasofoxifene or raloxifene?

DR. GILLEN: Raloxifene. Yes.

DR. PROULX: The methodology used to

measure vaginal bleeding in the MORE trial was a slightly different methodology than that employed in the lasofoxifene program. In our study, any woman presenting with vaginal bleeding was evaluated and treated as if she was potentially at risk for endometrial cancer, and a different methodology was utilized in MORE where there was a clinical assessment of whether or not that bleeding was likely to be uterine in origin, and if you cold -- this is data I'll project to you which is based on piecing together things from the medical review for that trial, so GY-179 project, please?

This is the data on that basis, and on the top of the stacked bars are the rates for placebo, raloxifene, and the high dose of raloxifene that was felt to be, or deemed by the investigator, at least, to be non-uterine in origin, and not further investigated. And the lower stacked bar, which represents the majority for each treatment group, that shows rates of what was deemed to be uterine

bleeding.

DR. CARSON: Dr. Goozner?

DR. GOOZNER: I always have to say I'm not a doctor. I'm the Consumer Rep here.

I'm having a hard time. We have so many different categories that we're looking at and we're not talking about the cancer or the overall mortality, both of which showed a strong signal. So is there any attempt at all to try to do a combined serious events ratios and to compare that to a benefit?

MR. THOMPSON: A number of different things could be looked at, for example, to try to distill this down. What we have tried to provide you in the basically, overall picture of the number prevented versus number treated was sort of a global look at this including the different adverse events that were reported and, for example, the number of procedures as well as the pulmonary emboli in VTE. There are other ways to look at it. There are other indices that can be used to consider to get global

indexes for example and we have done the women's WHI global index in looking at the overall benefit of lasofoxifene and it is positive when we do that global health index according to what the WHI has conducted.

That's one method of doing that.

DR. CARSON: Dr. Nelson?

DR. GOOZNER: Do we have that data?

MR. THOMPSON: We will get those data for you shortly.

DR. NELSON: Can you tell us what percentage of the vertebral fractures were symptomatic?

MR. THOMPSON: Approximately 29 to 31 percent of the fractures were clinical vertebral fractures, which is consistent with the clinical fracture -- the total vertebral fracture.

DR. NELSON: So about 70 percent of them were asymptomatic?

MR. THOMPSON: That's correct, and they were identified on X-ray.

DR. NELSON: I had another question about -- I'm impressed with the stromal growth and I wonder, do you have any -- what's your pathologic opinion about the increase in the amount of stroma in the endometrium? And also, is there any evidence that your agent stimulates stromal proliferation in vitro?

MR. THOMPSON: We can answer this in two ways. First I would ask Dr. Beierschmitt to come up and describe the stromal changes that have been recorded in non-clinical, and then I would like to ask Dr. Kurman to come up to address the questions around stromal changes with lasofoxifene. Dr. Beierschmitt?

DR. BEIERSCHMITT: Good morning. Bill Beierschmitt again. Preclinical toxicologist. With regard to stromal effects that we have seen in our preclinical studies, in our two year oncogenicity study in mice, we actually saw a decrease on stromal polyps in those particular animals. We also did a two-year study in ovariectomized monkeys to simulate the

menopausal condition. In that particular situation there was a mild increase in stromal fibrosis but this was something that was also seen in the ovariectomized monkeys compared to the non- ovariectomized monkeys.

MR. THOMPSON: Dr. Kurman?

DR. KURMAN: Robert Kurman, professor of pathology, gynecology, and obstetrics in oncology Johns Hopkins and chief of the division of gynecologic pathology.

In looking at the endometrium, specifically I think maybe the issue with polyps -- what we were struck by was the distinct absence of proliferation in terms of mitotic activity and more an appearance of edema which I think goes along with the postulate that this is due to hydration vascular permeability with leakage of fluid in creating the thickening of the endometrium and in some instances, localized into the form of a polyp.

DR. CARSON: Dr. Johnson?

DR. JOHNSON: Yes, I was curious if you were planning to market this for vaginal symptoms and if so, how are you going to do that, and if not, are you planning to do further studies in that area?

MR. THOMPSON: Under consideration today is lasofoxifene for the treatment of osteoporosis in postmenopausal women, and we do not intend at this point to market the drug for the treatment of VVA at this point. That is a consideration in the future should we pursue that, but at this point, there is not the intention that we're simply looking at these data for the treatment of osteoporosis in postmenopausal women and what we have cited here is these additional benefits in the treatment of postmenopausal women, but not for the indication of treatment of VVA itself.

DR. JOHNSON: Yes, I guess I would just ask you to be cautious in that regard since the studies are somewhat limited.

DR. CARSON: Dr. Portis.

DR. PORTIS: I want to just piggyback on what you said, Dr. Johnson, because that is a concern, because there's also the mention about breast cancer which FDA seems to not agree with what you've said but with other SERMs we've gone down that route, that things are being diagnosed -- or being prescribed for prevention of breast cancer when we don't really have the data to support that, but prior to -- there was an answer to Dr. Adashi's question about the issue of prevention in general and I'm concerned then about giving relatively healthy women a drug with some very serious side effects and I hope somebody can speak to that. And we've run into problems with that before especially when we don't have long term safety data yet.

MR. THOMPSON: The program with lasofoxifene does have a significant patient-year exposure -- five years have been collected with lasofoxifene to this point in time and the fractures that it does prevent, and I might also add that some of the women that

were treated in lasofoxifene, 28 percent did have prevalent fractures, so it did have the disease. And I'd also like Dr. Cummings to please come up and further expand on that.

DR. CUMMINGS: I would agree with you that this is not -- the drug should not be used in healthy women. We're considering this for patients with osteoporosis. That's a disease. That's a substantial increase in the risk of fractures and I think in that circumstance, there is consensus among experts and those who make guidelines that women with osteoporosis would overall benefit from treatment to prevent those fractures, so it's not for normal women, it's for women with osteoporosis.

DR. CARSON: Let me just remind the panel that this time is really now for questions from the sponsor. We'll have discussion time and be able to voice our opinions later when we discuss the questions. Dr. Gut?

DR. GUT: Robert Gut, Novo Nordisk. We had quite an intensive discussion about

venous thromboembolic events. And that's no surprise because this is one of the main FDA concerns, but it's also not surprising to see a small increase of VTEs with lasofoxifene, because we had the same increase with raloxifene. And my question is, did you look at the hemostatic parameters changes in your very impressive development program? You conducted almost 40 clinical trials: 26 Phase 1, 11 Phase 2, 6 Phase 3. Did you look at fibrinogen changes? Factor 7? Factor 5? Anti-thrombin 3, pertain C or S in any of your -- if yes, did you find any changes?

MR. THOMPSON: Dr. Johnson will address it.

DR. JOHNSON: The only one of those factors that we did look at was fibrinogen and we saw significant reduction in fibrinogen in women treated with lasofoxifene. The other factors were not routinely connected and have not been found to be good predictors. The most reliable predictor of VTE is clinical

circumstance, such as immobilization and fractures.

DR. GUT: Thank you.

DR. CARSON: Dr. Gardner?

DR. GARDNER: I'm looking at the proposed indication and Dr. Cummings just reiterated that we're talking only about women with osteoporosis. The proposed indication says more specifically "postmenopausal women with osteoporosis who are at increased risk of fractures." Could you talk a little more about how you intend to characterize osteoporotic women who are at increased risk so that we can be sure what we're talking about here?

MR. THOMPSON: The submission of lasofoxifene to the FDA was about simultaneous with a submission to the EMEA. The current labeling indication for the EMEA for this is the treatment of osteoporosis in women at increased risk for fracture, and so to be consistent with the labeling language globally, this was the language that was used.

However, recognizing that this does differ from perhaps other labeled drugs for this, this could be discussions going forward to make this more consistent with the language that's currently used in other medications in the U.S. This was done to make this a consistent language between the two regulatory agencies, however, this would be potential discussion going forward.

DR. GARDNER: Then, excuse me, could you give us a little more enlightenment about how the EMEA defines -- we saw their guidelines, but in terms of the labeling, or in comparison with other products, how do you characterize increased risk?

MR. THOMPSON: Looking -- if I can try to present the EMEA perspective, the EMEA does not recognize the prevention of osteoporosis going forward. What the EMEA recognizes is the treatment of osteoporosis and this category now has been slightly modified to include perhaps those women who have been declared at high risk.

For example, due to their bone marrow density scores, due to fracture assessment categories with respect to -- and so, therefore, there are categories that can sort of put women at the highest risk for fracture. And that was part of the attempt by the EMEA in order to provide that single indication, but get proper language for those where prevention isn't an indication as to how that might be addressed.

DR. CARSON: Since we only have about six more minutes left in this session, I wonder if you'd had -- Mr. Goozner had asked for some data earlier you said -- do you have that?

MR. THOMPSON: Yes. Please preview -- please project RM-31. In looking at a global index, the WHI is one index that could be considered. This would include the first occurrence of CHD, stroke, pulmonary emboli, et cetera, and lasofoxifene 0.55 compared incidents of designated events per 100 patient-years of 1.66 compared to a placebo of about 2.03, so that when you look at this overall

categorization based on this particular index, there would be a suggestion of an improvement with lasofoxifene.

DR. CARSON: Go ahead.

DR. GOOZNER: Follow up on that, it appears that there's very limited cancer data in that index. It just looks at colorectal cancer, not all the cancers that were found in your clinical trial?

MR. THOMPSON: There are limitations to these indices and this was the one that was used by the Women's Health Initiative, so that is a fair comment.

DR. CARSON: Dr. Stadel? Did you have a question, Dr. Stadel?

DR. STADEL: Did you compare the cause of death profile for the Region 2 placebo group to the cause of death profiles for the other placebo groups? I'm interested because of the apparent low rate in the Region 2 data as to whether a comparison of the causes of death would shed any light on what seems to be

missing.

Dr. Armstrong will share those data with you.

DR. ARMSTRONG: Thank you. Yes, we have looked at adjudicated death causality broken down by region, specifically by Region 2 and we can share that data with you and then compare it, if that would be helpful, to the adjudicated death causality for the four remaining regions combined.

So if I could ask for S-35, please to be projected. And here we have the death causality for the 43 deaths that occurred in Region 2 across the three treatment arms of the study. Now recognizing that this represents 21 percent of the patient population, so about a fifth, and hence a much larger dataset than what I will share with you in a moment for the four remaining regions combined. But looking through, most events were really into quite small numbers in terms of the coronary, stroke, other

vascular, cancer -- no trauma-related events, and then events adjudicated as other.

And on the next slide, which I will show you, and again, it contributes the 79 percent of the patient population -- please project S-36. So here, we have then a total of 185 deaths, obviously a much larger denominator where we see a pattern that is perhaps consistent with the full analysis set. And so by that I mean the coronary events are in direction at least, consistent with what we're seeing with the full analyses set.

We did observe a difference in the 0.25 milligram dose group compared to placebo for fatal stroke, and these regions combined, the absolute difference is four events.

And then we have the other vascular events, and then cancer again, where we're seeing that difference on the 0.25 milligram dose group with the 0.5 comparable to placebo. Basically the same.

DR. CARSON: Dr. Rosen?

DR. ROSEN: One of the parts of the presentation that we've heard is the meeting of the approval for the fracture indication and I just wanted to get a sense from Dr. Thompson or Dr. Cummings about the contrast between your SERM and bisphosphonates because you need 200 plus subjects to prevent one non-vertebral fracture and you have non-statistical significance for hip fracture reduction and only 22 percent reduction for non-vertebral fractures.

So how is this going to be pitched to patients who you want to treat for osteoporosis since head-to-head with a bisphosphonate, it's somewhat different?

MR. THOMPSON: As you know, a bisphosphonate does provide somewhat of a different characteristic profile than would a SERM. Lasofoxifene, for example, with the effects that it's seen in vertebral fractures as well as non-vertebral fractures as well as

clinical fractures -- clinical fractures were also observed with lasofoxifene comparable to bisphosphonate, and the primary distinction is hip fractures that some bisphosphonates have relative to lasofoxifene.

For example, even though lasofoxifene showed a numerical reduction, it wasn't powered adequately to derive that statistical benefit. And so, therefore, the primary difference is in hip fractures. And comparison of non-vertebral fractures is quite comparable in that the non-vertebral fractures, for example, are in the 20-plus percent range, which is consistent with lasofoxifene. And the vertebral fractures do show some comparability as well in terms of their reduction overall. But as you note, hip fractures is one of the big differences. So I would put bisphosphonates somewhat on the same level in terms of non-vertebral and vertebral fractures, but not for hip fractures. And then the other benefits that

do accrue, for example, with lasofoxifene that we've reported, that would also add to the benefit profile compared to bisphosphonate.

But I'd ask Dr. Cummings to further expand on that.

DR. CUMMINGS: Dr. Rosen, that's a good question, the comparison to bisphosphonates.

There have been a -- there have been several meta analyses done by the Cochrane Collaboration to estimate the reduction in non-vertebral fractures with risedronate and with alendronate. And in both those cases the estimates have been around a 20 percent reduction in non-vertebral fractures, which is similar to what's seen here. And the big difference, for me, is the hip fracture, proof that there is a reduction with bisphosphonates. And that would lead me towards recommending a bisphosphonate for the elderly woman that's

say 60 to 65 who has a particularly increased risk of hip fracture.

But for other patients with osteoporosis -- I mean, as you know, from balancing this clinically, when you talk to a patient you talk not just about fractures. In this case, you talk about the other profile of benefits and risks so I don't end up telling a patient exactly what they should do. We talk about the benefits and risks and we make an informed choice, and in this case, I think the other parts of the profile may lead the doctor and the patient to choose this instead of the bisphosphonate.

But the -- Cliff, does that answer your question?

DR. CARSON: We have three more questions in the queue and then we'll break for lunch. Dr. Merritt?

DR. MERRITT: With five years of safety data, are you proposing that this product would be given to women long term or shorter

term, and what sort of monitoring for safety are you planning going forward beyond five years?

MR. THOMPSON: Osteoporosis is a chronic condition, and we have in PEARL demonstrated the benefit safety of lasofoxifene through five years, and therefore, this -- there should be, therefore, consideration for chronic therapy with lasofoxifene. Also from the point of view of monitoring, there would be no recommendation from the sponsor that would recommend long term monitoring, but simply following the normal guidelines for vaginal bleeding would be -- as all SERMs would be indicated in their labeling, that any vaginal bleeding should be followed up. That would be the consideration for lasofoxifene as well.

DR. CARSON: Dr. Nelson?

DR. NELSON: Yeah, I wanted to follow up on Dr. Adashi's line where it seems to take treating a large number of patients to find a benefit in a few. And I'm wondering if that might in part be due to the fact that all the

patients were given vitamin D and calcium. And I wondered if they had any evidence about what percentage of their patients were vitamin D deficient at baseline, what percent of their patients had inadequate calcium at baseline?

MR. THOMPSON: We assess vitamin D at baseline, 25 D at baseline. And there was -- it was in the normal range, the overall, and it was well-balanced across groups.

This, however, was done after the baseline, as I indicated in my introduction where we had a running period, where calcium and vitamin D was provided in eight-week run-in period -- six- to eight-week run-in period in order to equilibrate people before the initiation of therapy. And so that baseline reading of vitamin D would reflect that six to eight weeks of run-in with calcium and vitamin D, so it wouldn't completely reflect their situation prior to the initiation of the run-in period.

However, in that particular case,

they did show a balanced -- and they were normal between the groups in terms of their vitamin D-2 levels.

DR. CARSON: And finally, Mr. Goozner.

DR. GOOZNER: I believe you propose doing a 40,000 woman study -- cohort study moving forward if the drug is approved. Did I get the number right?

MR. THOMPSON: A cohort study would be proposed going forward that Dr. Turner can explain further details on.

DR. GOOZNER: My question would be, would you agree to -- it seems like there's very large data gaps -- for instance in raloxifene and also in the bisphonates -- would you consider doing a study that included large cohorts of women on other drugs as well?

MR. THOMPSON: Dr. Turner, can you address that question?

DR. TURNER: I want to first emphasize that the particular details of this study have not been worked out because we do want to work

this out in conjunction with FDA so all concerns are addressed, but the study in broad strokes as planned will include a lasofoxifene arm, a raloxifene arm, and an arm with women on neither. We will be collecting information that will allow us to stratify that so-called control group for bisphosphonates as well. And at this point we're anticipating 50,000 patients for 8 years, which would give us 400,000 patient-years of exposure.

DR. CARSON: Terrific. Well, thank you so much and we have no more questions and it's time for lunch. Thank you to Pfizer and your team. Very well-prepared answers, and panel, very thorough questions. Let's break for lunch. And again, committee members, please remember that there should be no discussion of the meeting during lunch among yourselves, with the press, or any other member of the audience.

There is a table, I'm told, reserved for us downstairs in the restaurant.

And we should meet back here at

five to 1:00 to begin the meeting at 1:00.

Thank you.

(Whereupon, at approximately 12:07 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:07 p.m.)

DR. CARSON: I apologize for the delay in starting. There was a problem with lunch downstairs.

This is the Open Public Session. Both the Food and Drug Administration 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, 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 such financial relationship.

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

The FDA and this Committee place great importance in the open public hearing process. The insights and comments provided can help the Agency and this Committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this Open Public Hearing to be conducted in a fair and open way, where every participant is

listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by this Chair. Thank you for your cooperation.

The first speaker at the Open Public Hearing will be Ms. Cindy Pearson from the National Women's Health --

MS. PEARSON: Thank you.

DR. CARSON: Network.

MS. PEARSON: Sorry.

DR. CARSON: Please, go ahead.

MS. PEARSON: I'm the executive director of the National Women's Health Network, which is an independent, not-for-profit women's health consumer advocacy organization. We are supported primarily by the contributions of our members, who comprise thousands of individuals nationwide, and partially by foundation grants. We accept no funding from any part of the medical industry. And I've received no help with my expenses in getting here today.

I also wanted to share with you

what I've done to prepare my remarks for today. I've had a chance to review the briefing documents that became available on Friday on FDA's website, and I listened to all the presentations this morning.

And I want to start with a couple of thank yous. The first thank you is to the FDA in its insistence on placebo-controlled trials. Thanks to the FDA's insistence on placebo-controlled trials, post-menopausal women and women with some menopausal symptoms now know placebo pills are effective against hot flashes, placebo patches are effective in increasing sexual desire, and as of this morning, we now know that at least one placebo pill is fairly effective on vaginal atrophy. This is very interesting news. So thank you, FDA, for insisting on the kinds of trials that got us this information.

I have another partial thank you for the sponsor. This is to thank them for responding to a concern that women often ask

us, and I'm sure clinicians get this question, as well, which is what do we know about women of color and osteoporosis. And the sponsor really deserves thanks from women for having made quite an effort to get some women of color in their trials. Why I say it's a partial thank you is still very few African-American women are represented.

The sponsor is very open about those numbers. And it seems like you had to go far beyond the U.S. borders to get a good percentage of women of color in the trial. But at least it is an advance on what we've known heretofore.

Now I want to go on and comment about this application. As I said in my introduction, the National Women's Health Network is a nonprofit, independent women's health consumer watchdog group.

We exist to raise the concerns of women in the regulatory and health care process. And we think the concerns of women

should be important to clinicians, to researchers, and to regulators. And to put it very simply, women's concerns, when talking about any particular health condition, can be stated as: If I take this treatment, will I feel better? If I don't feel bad now, will this treatment prevent me from feeling bad or experiencing something bad? And will this treatment I'm taking cause problems for me or make me feel worse?

Having read both the briefing documents and listened to all the presentations this morning, I think at this point it's very difficult for a woman to find an answer to those simple questions from the information about this drug. We've been presented with information that was developed through multiple NDAs. We've been presented with information from the same trial, but multiple endpoints of the same trail. And as I've read and sat and listened, I have the distinct impression that the data are being

plucked from these various places, different endpoints and different NDAs, and presented in a selective way.

Now, if the narrow risk/benefit were to be considered, if a woman came and said, what's the chance that I'll shrink by more than 4 millimeters in the next three years -- i.e., what's the chance that I'll have an asymptomatic vertebral fracture that can be diagnosed on X-ray versus what's the chance that I'll experience something troublesome in trade for reducing that chance that I'll shrink?

We could answer that question. Those data are there. The woman would get a response of: Your chance of shrinking, with no other signs of problems, is reduced by X percent. And your chance of having something awful, like a serious or fatal clot or something troubling, and maybe kind of a little bit risky, and maybe even, in a rare case, fatal. We know in other trials of

fatalities that came about as a result of a hysterectomy that came about as a result of the study drug. A woman could make a good decision based on that information. How important it would be to women to avoid the chance of shrinking or to come up with a slightly lesser chance that she'll prevent the chance of shrinking and having pain and discomfort, which is obviously, in most women's opinion, a lot more important. If a woman were presented with those numbers, she could make a good decision.

But almost nothing of what we've seen today gives us any hope that that would be what a woman was presented with, if this drug were to be approved based on the request today. Most of the presentations, and most of the Committee's questions to the sponsor during the question period, were about a much, much broader constellation of benefits and the risks that have come up. As a seasoned consumer watchdog, I really felt

like I was seeing the beginning of a marketing campaign today. Why are we talking about vaginal atrophy, for example, when it was supposedly proven as a benefit in an NDA that was not approved by the FDA? And that the company has said they do not plan to market for that indication.

Why do those numbers get to be up there on the benefit side of a bar graph? Why are we talking about a non-vertebral fracture benefit and a clinical fracture benefit when those data are from a five-year endpoint and have not yet been fully reviewed by the FDA?

I want to make the point that women rely on the FDA as a point at which new drugs and new procedures have to pass when their risks and benefits, and the appropriate group to whom they could be -- the new thing could be used, are weighed in an objective fashion. And what I believe we heard this morning would leave me to recommend to the Committee

that they advise the FDA not to approve based on three-year data, not because the three-year data don't meet the narrow definition that's in the FDA Guidelines for treatment of osteoporosis, but because it's so blatantly clear that that won't be the way in which this drug is considered, and used, and has an effect on American women.

So our recommendation this morning to the Committee is that they advise the FDA to wait until those five-year data, which the trial is done, the women have completed. It's just a matter of the company taking the time to go through the next steps for full review, cleaning the dataset, all those things, get them into the FDA, and let the FDA do the kind of careful review that it has been able to do on the three-year data. If that's the conversation that's going to be happening, that's what the women of America need, are those data to be grappled with.

And similarly, this alleged benefit

on vaginal atrophy. If that is going to be described by the company as a benefit, then why not require the company to resubmit that original NDA. And the FDA may have some rules limiting what they can ask companies to do, but from the consumer world, we get to ask for what we want. And I think on behalf of women who have logical, sensible, and kind of simple questions, those are the questions that they really need answered, and that's the role that the Advisory Committee could play today.

Thank you.

DR. CARSON: Thank you. The next speaker is Ms. Diana Zucherman from the National Research Center for Women and Families.

DR. ZUCHERMAN: Thank you. I am Dr. Diana Zucherman, and I'm pleased to have the opportunity to testify today as president of the National Research Center for Women and Families. Our nonprofit research and education center does not accept contributions from companies that

make medical products that we evaluate, or competing companies, and so I have no conflicts of interest and nobody paid my way here except our organization.

Our center is dedicated to improving the health and safety of adults and children, and we do that by scrutinizing medical and scientific information and research to determine what is known and not known about specific treatments and prevention strategies, and to compare their safety and effectiveness.

In addition, I am fellow at the University of Pennsylvania Center for Bioethics, and a board member of two non-profit organizations that work to improve resources at the FDA: The Alliance for a Stronger FDA and the Reagan-Udall Foundation. I was trained in epidemiology at Yale Medical School, did research at Yale and at Harvard, and have worked on federal health policy issues for Congress, the Institute of

Medicine, and for non-profit organizations for 25 years. And I've studied FDA decision-making on numerous safety issues for almost 20 years. We all know that osteoporosis is a serious disease. And fortunately, there are other, several different treatments available. And those options should help you and help the FDA determine whether the risks of this drug, Fablyn, outweigh the benefits.

I've examined the data that were made public and listened to the presentations this morning. And as we all agree, the data indicate that Fablyn at .5 milligrams significantly decreases the risk of new or worsening radiographic vertebral fractures by about 50 percent at first. But that's only from 2 percent to 1 percent during the first year and approximately 4.5 to 2.2 percent during the first 2 years.

And then over three years, something strange happens to those numbers.

The change decreases and the benefit is then from about 6.5 percent to almost 4 percent at three years. And the five-year data are only preliminary, so I won't be talking about those.

But even at those levels, even at those significant levels, that is only for asymptomatic fractures. And as has been mentioned by one of the Panel members, the difference, the improvement on symptomatic fractures was not statistically significant. And only was it not statistically significant, it was not particularly meaningful. At three years, it was only half of 1 percent difference, so from about 1.7 percent to 1.2 percent of symptomatic fractures.

And since the benefits of reducing these vertebral fractures seem to decrease over time when you look at it through X-rays, and are not significant when you look at it clinically, it's very unfortunate that the

five-year data are not complete and that they were only preliminarily analyzed, and I think it's absolutely necessary that those be analyzed more carefully and analyzed by the FDA.

So one of the surprises was that at three years, the death rate was similar for the dose whether it was .5 milligrams or .25 milligrams. But at five years, the death rate was higher for women taking the lower dosage. But even so, the death rate was higher for women taking Fablyn than for placebo, and those findings are obviously worrisome.

The increased risk of death was primarily from cancer, stroke, and other non-coronary vascular causes, and that's consistent with mortality data from other SERMs.

In addition, a number of serious adverse reactions other than death was also higher among women taking Fablyn, especially

for those who were -- those adverse reactions classified as treatment related, such as pulmonary emboli, uterine polyps, and deep vein thrombosis.

So the question really is what does this mean for women? Clearly, the benefits of this drug are really very small. A hundred women have to take this drug for a year -- I'm sorry, for three years in order for half of a woman to benefit in terms of symptomatic, either pain or discomfort, coming from a vertebral fracture. In contrast, the women taking the drugs, whether they benefit or not, are more likely to die, and slightly more likely to have serious adverse reactions.

So as you consider what this would mean for women in the United States, which is the role of the FDA, for real women, not women in a research study, keep in mind that there were very rigorous exclusion criteria for the major study of Fablyn. If you look

at page 18 of the FDA's memo, you will see a very long list of exclusion criteria, such as atrial fib, history of breast cancer or DCIS, history of various types of hip or vertebral fractures, or stroke or MI during the last six months. And in addition, to be in this study, women had to have a certain level of osteoporosis, not too high and not too low.

As I think we can all agree, in the real world, if this product is approved and made available, the people -- the women taking it will not fit these exclusion criteria; it will be a much broader range of women. And we don't really have any data on what the safety or risks would be for those women.

Now, in the ideal world, we could tell patients what the risks and benefits seem to be for this product compared to other products on the market, and let them decide, with the help of their doctor, whether they are willing to take the risks in order to get

the potential benefits. But in the real world, we all know that that isn't exactly what's going to happen for several reasons.

In our experience, many doctors will not know all the exclusion criteria for these studies and they will not know all the caveats, no matter what the labels say. And even those doctors who do know, and there are certainly doctors who are very careful about looking at all of the risks of a drug, but even they may not be so terrific at conveying those risks to patients. And if even the FDA and the sponsors can't agree on exactly whether the death rate is higher or not, and exactly what adverse reactions are higher and lower, it will be even more difficult for doctors to make that decision and convey it to patients.

I also want to mention that just under 1 percent of the women in this study are black. The other women of color are primarily from other countries. And I think

it's really very unfortunate that when you're talking about osteoporosis which affects all women in this country, that they haven't really been studied in a way that's helpful for them in knowing whether this product is safe or effective.

Also, just want to mention that because the other countries, for example, India and Croatia, have women, perhaps, with quite different diets and different levels of exercise, we don't really know how that could affect osteoporosis and this drug for them.

Finally, the data from these studies are short term. We don't know the long-term risks. Even three years or five years, which is, you know, not bad for these kind of clinical trials, still doesn't really tell us very much. Remember that the average longevity for women in this country is 80 years old. Women who make it to be post-menopausal are likely to live even past 80. So these are women who are going to live

for 20 or 30 more years, and yet we have three to five years of data on a type of drug that we know from tamoxifen and other studies tend to have a differential effect after five years. So we really need more information about both the risks and the benefits past five years because as has been said by the sponsor, if women are going to take this drug, most likely they will be taking it for the rest of their lives, not just for a few years.

So in conclusion, I would say the data are incomplete to draw any conclusions about whether the benefits outweigh the risks. But looking at the data so far, it seems like the benefits do not outweigh the risks. And in our opinion, the FDA should not be approving a drug based on wishful thinking, such as, oh, it probably will reduce the risk of breast cancer, even though we don't know for sure whether it does. Or it probably will continue to help reduce

fractures, even though we don't have data to actually support that.

So I think it's really important for you, as the Advisory Committee making recommendations to the FDA, to make sure that the criteria are really looked at. And the criteria are supposed to be proof, not assumptions, but proof of whether this drug is safe, and proof of whether it's effective, and proof of whether the benefits outweigh the risks.

Thanks very much, and I'd be happy to answer any questions.

DR. CARSON: Thank you very much.

DR. GOOZNER: Thank you very much for your presentation, Ms. Zucherman. I have a question. At the very beginning, you said that you were thankful that there were other drugs that were available. Do you have any estimation that you could give, because I haven't -- I haven't heard it this morning, of what the relative risks are of other drugs that are

available for osteoporosis compared to this one?

DR. ZUCHERMAN: Well, that's a wonderful question. And, of course, it's the key question. And the problem is we don't have those kind of research comparisons to make the answers. We do know that SERMs have particular risks associated with them that are different from other kinds of osteoporosis drugs, and that's exactly why, I believe, that the FDA wanted more studies of longer-term cancer risks. And one of the things I didn't mention is that, of course, the short-term benefits and risks can be very, very different. Normally, cancer takes, as everyone knows, it takes a lot longer to develop, and you're unlikely to see much of a cancer risk for a drug in three years or even five years.

But if these women are in fact start taking it when they're in their 50s and live to be 80, or at least have the potential to live to be 80, they could easily get cancer in 20 years, and we wouldn't know that

from these data.

So I guess the short answer is no, we don't know. But we do know that SERMs, in general, do have particular risks, cancer being one of them, pulmonary emboli being another, and so there are some real concerns about this particular drug, particularly in light of the very low benefit in terms of symptomatic fractures.

DR. CARSON: Thank you. The Open Public Hearing portion of this meeting has now concluded, and we will no longer take comments from the audience.

The Committee will now turn its attention to address the task at hand, and that is the careful consideration of the data before the Committee, as well as the comments of the public made today.

There is one -- the sponsor does have some data regarding a question answered this morning that they retrieved for us. And so let me -- Brian, are you presenting?

DR. THOMPSON: Could I please have Dr. Goldstein stand up, please, first of all, to reaffirm a point.

DR. GOLDSTEIN: Yes, I was asked to put this back into some clinical perspective. I think we have heard today, both from the Agency and from the sponsor, and even from some of our speakers, and that we can all agree that osteoporosis is a significant health care issue. These are not healthy women. This is a serious disease. It is a silent disease until fracture occurs. And as a clinician, I certainly have a shrinking list of choices with which to treat people. Women do not want to take estrogen.

Increasingly, they don't want to take bisphosphonate. I have many women on bisphosphonate, but I have many women who have chosen to come off or will not go on because of recent media attention. And what that really does is leaves me with SERMs. And right now SERMs means raloxifene, and I have many women on raloxifene. And it's a

good agent. But this agent, I hope you realize, offers some significant advantages over raloxifene. The non-vertebral fracture benefit is huge. The decrease in coronary heart disease, the decrease in stroke, and the improvement in vulvovaginal atrophy are all things that I must take into account when I am treating my patients.

I needed to clarify the breast cancer issue. Clearly, this is not an agent for preventing breast cancer. We have other agents for that. But in factoring in choosing an agent for an osteoporotic patient, taking into account her risk of breast cancer, and the data that has been generated here, I think, is absolutely essential and cannot be ignored.

So as a clinician and a researcher, I view this drug as a valuable addition to my armamentarium in trying to care for my patients with osteoporosis.

DR. THOMPSON: We were awaiting data.

We do not have the data at this time to present.

DR. CARSON: Okay. Thanks. That was not my understanding when Brian came up.

Okay, let me open the discussion to the Panel on any -- we're -- any discussion that -- let me just say -- that you wanted to make prior to actually going to Question No. 1. Dr. Rosen?

DR. ROSEN: Just a point of clarification. Has there been a head-to-head trial between raloxifene and lasofoxifene for fracture or for bone density?

DR. CARSON: I do not believe there is. Was there a head-to-head trial between raloxifene and -- one, right? Yes. Small --

DR. THOMPSON: There were two trials that were conducted head-to-head with raloxifene for bone mineral density. And lasofoxifene was evaluated against raloxifene. Raloxifene at 60 milligrams; lasofoxifene at .25 milligrams. And the effect that was -- that lasofoxifene showed a significant improvement in BMD compared to

raloxifene.

DR. ROSEN: No fracture data --

DR. THOMPSON: There were no fracture data. These were short phase II studies.

DR. ROSEN: And this was .25.

DR. THOMPSON: This was .25, that's correct. It was significantly different than -- for BMD compared to raloxifene for the lumbar spine.

DR. ROSEN: So some statements have been made that your -- that this drug is better than raloxifene for fractures, but we're not sure of that. We're only -- based on what we can compare across populations; is that correct?

DR. THOMPSON: That's correct. If I could project these 178 these data are showing for the one study for two years duration where -- E178. The data is comparing the placebo value with the raloxifene change of 1.31 compared to 2.21 with lasofoxifene being .25.

DR. CARSON: Dr. Johnson.

DR. JULIA JOHNSON: Yes, could I ask

you, for a second time, thinking about risk/benefit, tell me again: did the MORE Trial show a significant increase in the risk of pulmonary embolus for raloxifene, and how does that risk compare to the risk found with your trials.

DR. THOMPSON: For pulmonary embolism?

DR. JULIA JOHNSON: Yes.

DR. THOMPSON: Dr. Johnson, could you please show that?

DR. MARGOT JOHNSON: This is a comparison of the PEARL and MORE trials. MORE was the raloxifene trial, and this is a comparison at the three-year time point for which we had equivalent data. As you can see, the number of events on lasofoxifene for pulmonary embolus was 1 in placebo group and four on the .5-milligram group. For raloxifene, there were 3 in the placebo-treated group and 10 in the 60-milligram group. And the hazard ratios, you'll see on the bottom of that, are comparable with overlapping confidence

intervals.

DR. JULIA JOHNSON: But it was not significant in this trial. Am I correct?

DR. MARGOT JOHNSON: That's correct.

DR. CARSON: Dr. Merritt.

DR. MERRITT: Thank you for answering my question earlier about the five years of data that you've collected, and you have given preliminary information. Could you please tell me, do we have all the information or do we have preliminary information? I'm confused now.

DR. THOMPSON: We do have all of the information for five years.

DR. MERRITT: Is we you or the FDA?

DR. THOMPSON: We have shared the five-year data with the FDA. And as agreed upon, we agreed to show the three-year data with respect to the bone fracture endpoints, and not the five-year data.

DR. MONROE: We did get five-year data very recently, which we haven't completed our review of, nor have we gotten a final report.

So it's been data, but not in the way we usually get final data.

So that's why we're considered preliminary, and the document that was submitted to us was called a preliminary five-year report. So I just want to clarify that.

DR. THOMPSON: Correct.

DR. CARSON: Dr. Nelson, did you have a question? Oh, okay. Dr. Gardner.

DR. GARDNER: When we're thinking about risk and benefit, we always try to consider what alternatives are available to people. And we've heard how some of the clinicians associated with the sponsor feel about this. I'm wondering if I could ask my clinician colleagues on the Panel whether they feel that we -- they really need -- I don't have the exact term that was just used, but an additional arrow in your armamentarium, here. Are you feeling the same kind of loss of alternatives for your patients that we've heard

about? Do you feel like we have to consider the absence of good alternatives in thinking about how we judge risk and benefit?

DR. CARSON: Dr. Liu.

DR. LIU: Well, I must submit that I don't see the severe osteoporotic patients in my practice.

The menopausal patients I see are primarily only about up to 10 years out. So they would probably not fall into the realm of being either given a SERM. And the majority of the ones that don't want to go on hormone therapy, that have a low bone density, I tend to use a bisphosphonate at the present time.

DR. CARSON: Dr. Rosen.

DR. ROSEN: Yes, I think the decreasing use of bisphosphonate and the over treatment of some individuals with bisphosphonate, sort of, led to reporting of some unusual side effects, raises questions about using an alternative medication that is

not a bisphosphonate. So I think that in the clinical scenario, there is room for discussion about a SERM that has non-vertebral fracture efficacy.

I'm not sure it's the first line drug for severe osteoporosis. And that's all I see, is severe osteoporosis. But virtually every one of my patients has a question about bisphosphonate use. And I think this provides an alternative for those individuals who have already suffered a fracture and are considered osteoporotic, in the true sense of the word, and high risk, and this may provide an alternative option for them.

DR. CARSON: Dr. Collins.

DR. COLLINS: Yes, I've been wrestling with this question, trying to think what my answer and what my response would be. And I think, first of all, patients come with a lot of misinformation about the risks of bisphosphonates. And one of my first jobs is not to accept their misinformation, but to put

it in perspective and re-educate them. So. So that's one of the first jobs.

And then -- so, then, in terms of the severe osteoporotic patient, there hasn't been any discussion of the use of Forteo, which is the most potent drug we have. And I think in that sort of patient, that's what I would go with first.

So I'm trying to put together in my own mind what would be the niche of this drug that wouldn't be occupied by raloxifene. And I'm not quite sure where that is yet. But that's where I stand at the moment.

DR. CARSON: Dr. Portis.

DR. PORTIS: I just wanted to make a comment about your question because I'm always concerned about a lack of options being a reason to approve something when we have limited or incomplete information. I understand the challenge. I'm not a clinician, but a patient. I understand the challenge as a clinician when you don't have good options. But I just get

concerned about: then we have to have something; well, even if it's not a good something.

DR. CARSON: Dr. Johnson.

DR. JULIA JOHNSON: Yes, I'm pondering the answer to your question. But there -- I would say there is a limited number of patients who would benefit. Patients who cannot tolerate bisphosphonates, which is a population that are sent to me fairly often. And then offering them a SERM is always a potential option. The biggest concern they always have is in regards to the risk of DVT. And so, you know, this offers no advantage in regards to that.

It does have other long-term potential options, but those are not yet fully examined to be able to say that yes, it will be beneficial in the long term in terms of other benefits. It's really just comparing it to what's currently available.

DR. CARSON: Any other Panel discussion before we move on to the questions?

Let's go to Question 1. Now,

before we do this let me remind you that we are using new FDA voting procedures which will be simultaneous voting. So with this question after we discuss, I will call for you to answer yes by raising your right hand. And then we'll have to go around and have those with raised hands read your name into the record. And then to save some tired arms, we'll go back around and you can explain your answers if you so choose. And then we'll do the same thing for the answer no and for abstentions.

So let's begin. Do you believe that these data regarding all-cause mortality reflect a true increase in mortality in lasofoxifene-treated subjects? Please answer with yes, or no, or unable to determine. But let's be -- first, let's talk about -- let's make sure we understand the question before we vote and have any discussion necessary before actually taking the vote.

Do you believe that these data

regarding all-cause mortality reflect a true increase in mortality in lasofoxifene-treated subjects?

Dr. Adashi?

DR. ADASHI: Just to be sure, you know, I and everybody else has the facts right, as I recall there was only a trend for the all-cause mortality.

And then it was really the 0.25 dose that I think had the significant difference of a placebo.

Is that a fair statement?

DR. CARSON: Yes. And when that was further looked at, I believe that was especially found in the fifth year in Region 2 when trying to look at, which was Central and South America and Mexico.

Dr. Gillen?

DR. GILLEN: To me, it's phrased somewhat vaguely, to be totally honest. I want to know if I'm interpreting this correctly because I'm interpreting it as saying do I

believe that there is sufficient evidence to conclude that there's an increase in mortality in lasofoxifene-treated patients. Is that the way I should be interpreting this? Because that to me is slightly different than believe that there is a true increase and that this is supporting that.

DR. CARSON: The answer is yes.

DR. GILLEN: So I'm looking for sufficient evidence to conclude that there is a mortality difference.

DR. CARSON: Are we ready to vote?

DR. GOOZNER: Is it time for comment or later?

DR. CARSON: Discussions before we vote, yes.

DR. GOOZNER: I suppose I just have one last question on the mortality data which has to go to the Region 2 question. I mean, we're told that one section had different results, and if you take those out we get a different result. And I'm sure if it was a

different question people would not ask to take out that result. So if somebody could clarify for me what is the real basis for claiming that this data should not be looked at that came from Mexico or Latin America? I heard it a number of times, but I just don't quite get the point. I mean, the data is the data, and now we're being asked to sort of discount some data.

DR. CARSON: Dr. Monroe?

DR. MONROE: Well, Question 1 is a two-part question. One was do you believe -- I think the way Dr. Gillen has presented it -- that there is sufficient data to conclude or that there is likely a true increase in mortality, or you could say no, or you could say you just can't determine it based on what data there are available.

And then Part B of Question 1 said that if you believe there is an increase, do you believe that there was justification in removing the data of Region 2 from the overall data set. And if you did believe

that there was justification, what would the implications of that be for use in the United States.

So you have the questions because 1(a) and 1(b) are linked, and you really have to look at them as a unit, because what you're just raising now is exactly the way we have put this scenario together.

Now, you're saying what's the justification or what isn't the justification. That's one of the dilemmas we're also addressing here, and that's why we're asking for your thoughts about this because I think there are people in this room that would say it's perhaps justified, and there are other people that would say it's not justified. And we'd like the thoughts of those of you that are here to give us some guidance today as to what you think about it.

DR. CARSON: Dr. Merritt.

DR. MERRITT: Are we to consider all doses of lasofoxifene or just the 0.5 data?

DR. CARSON: All doses. Is that right?

DR. MONROE: You should consider all the data, but the company is only seeking marketing approval for the 0.5. But you have data that was obtained with the 0.25, and you have to determine what bearing those data have on your assessment of the 0.5 dose.

DR. CARSON: Dr. Monroe, would you like this question rephrased? Or do you want it asked as is? Do you want us to vote as is or would you like to rephrase that rephrasing Dr. Gillen's comments?

DR. MONROE: I'm not entirely sure how much your rewording has changed our question. How in your mind does your rewording affect the way that question is written?

DR. GILLEN: It affects my answer. Because the way it's written right now, if you ask me if there is a true increase in mortality -- I don't know if I can say my answer because we're voting -- it would reflect my

answer. Unable to determine as determining truth one way or the other in order to be able to discriminate between hypotheses. If you ask me if I've been given sufficient evidence I can give you a yes or a no with respect to that.

DR. SHAMES: Well, this is the data that confronts us at the moment. And we have to decide if this reflects reality based on the data that we're given. It is easier for us to answer the question that you're posing also. But this is, you know, as in many cases we are given information which may not be all the information we desire or that's possible.

So in this case I think we are going to have to ask ourselves does this information -- do we think it reflects -- how strongly do we feel it reflects an increase in mortality?

DR. GILLEN: So let me get clarification then. You do not want me to interpret it as is there sufficient evidence to conclude that there's a difference in mortality?

DR. MONROE: I think that's why we left the unable to determine part and gave you three options.

DR. SHAMES: Right.

DR. MONROE: Because we felt there might be people, such as yourself, that would look at it differently.

DR. SHAMES: Yes.

DR. MONROE: It might imply a higher or lesser standard. And so that's why we didn't have just yes or no. We left it as unable to determine.

And then once again I would think that those of you who might have a yes or unable to determine should really consider 1(b). So let's do it that way.

DR. CARSON: We'll leave the question then as is. And let's vote on that. Do you believe that this data regarding all-cause mortality reflect a true increase in mortality in lasofoxifene-treated subjects? All those voting yes, please raise your hand.

Okay, and could we have -- keep your hand -- no, there isn't a button for that, so could you just say yes with your name into the record?

DR. NELSON: Yes, Nelson.

DR. GOOZNER: Yes, Goozner.

DR. CARSON: And now would you like to explain your answers? You can opt to explain your vote or not opt to explain -- or not explain.

DR. NELSON: My assessment is there's sufficient evidence to say there's increased mortality in the 0.25 dose. And then we get to the question, is this a Type 1 or Type 2 error in which dose? The lower dose or the higher dose? And it could well be it's a Type 2 error in the higher dose that didn't show up. And when I put this in the context of the whole picture, I believe it's sufficient evidence.

DR. GOOZNER: My answer is sort of the same. It's in the numbers. At least on the 0.25 dose. And there's certainly a signal on

the 0.5 dose. And we're being asked to discount the signal for extraneous reasons. And I didn't find those to be -- I wasn't given any reason to discount it. Not to say that the reason was invalid.

DR. CARSON: Those voting no, please raise your hand. And please read that into the record.

DR. JOHNSON: No, Julia Johnson.

DR. STADEL: No, Bruce Stadel.

DR. CARSON: No, Carson.

DR. ADASHI: No, Adashi.

DR. CARSON: Explanations?

DR. JOHNSON: Yes, although I see the excellent point made by the other members of the team. I do think that looking at this data in detail, it does not appear that there is any focused area in terms of increased risk. The increased causes of death were not ones that would typically be associated with this type of medication, and I think there is enough to be explained with the difference in the groups from

different parts of the world.

DR. STADEL: Mine is an uncomfortable answer, but nevertheless it is my answer. And the reasons are the absence of a dose response relationship and the lack of focus that I could see in the organ systems affected. So I just feel that without any evidence along those two lines, that's my vote.

DR. CARSON: I've no other comments. Dr. Adashi?

DR. ADASHI: Oh, I would say ditto to Dr. Stadel. Those are the main reasons.

DR. CARSON: And those who vote unable to determine? Would you go around and read your answer into the record please?

DR. ROSEN: Rosen, unable to determine.

DR. MERRITT: Merritt, unable to determine.

DR. GILLEN: Gillen, unable to determine.

DR. GARDNER: Gardner, unable to

determine.

DR. LIU: Liu, unable to determine.

MS. PORTIS: Portis, unable to determine.

DR. COLLINS: Collins, unable to determine.

DR. CARSON: And explanations?

DR. ROSEN: So I'm bothered by the lack of dose response data, but I hate subgroup analyses.

So I'm really troubled by going in and look at which subgroups and then taking them out. So I don't think we have sufficient information. And I think this is a very common scenario in these kind of hearings where we get to a certain point, we have a cutoff, and we have to make a decision. And very often it's not the appropriate time to do that.

DR. MERRITT: Similar. The failure of a dose response. And also, I think there may be more data that we need to very carefully weigh.

DR. GILLEN: So to give my rationale, the sponsors are asking for approval for the 0.5 mg dose. So that leaves me with two options. One is to either consider the 0.25 dose and the 0.5 dose to be different beasts, which I am unwilling to do. If that were my stance, then I would only be talking about the 0.5 mg mortality data that we're seeing there.

That leaves me with the option -- because I think it's a somewhat unintuitive dose response that we're seeing there to pull those data, in which case, if I'm going to take as the 95 percent confidence interval, which I think would still be somewhat conservative in this case as what's going to rule out hypotheses here, it's still including one on the lower end. And it could be up as high as 65 percent. Therefore, I have insufficient evidence to conclude that there is an increased risk in this mortality.

DR. GARDNER: Gardner. I'm troubled

by the disparity between the Region 2 data and the other data. Given the demographic makeup of the United States, I can't answer -- consider a question that says since we only saw this in Mexico, Central and Latin America, do you feel good about introducing it into the United States? So I need to know more about that before I can vote like this.

DR. LIU: I agree with Clifford. I hate subanalyses. I think they're -- in this case it's probably not warranted.

MS. PORTIS: I guess I just want to echo Dr. Gardner that considering the diversity in the United States, I don't think we can just piece this part out and then be comfortable to go forward.

DR. COLLINS: My discomfort is related to Dr. Gardner's of the subgroup and the high number of Latinos in our country. And in the dose response in the counterintuitive, but not unprecedented response with agonist-antagonist drugs, I think still there's something there

that needs to be sorted out, especially given that those affects were seen on multiple endpoints death from thromboembolic events and polyps.

DR. CARSON: Thank you. Okay, there were no abstentions, and there were two votes for yes, four for no, and seven for unable to determine.

Question B is for discussion only. And if you believe that there is a true increase in mortality, do you believe that the applicants' regional analysis of the distribution of the deaths, which shows the imbalance to be largely in Region 2, is reassuring regarding the safe use of lasofoxifene by women in the United States?

So it's really you two whose comments we'd like. You thought there was an increase.

DR. NELSON: Nelson. I don't find it reassuring.

DR. CARSON: Okay.

DR. GOOZNER: No, I think I addressed this in my earlier comments. I can't remember -- I wish I had the whole time to read the whole document again that the company submitted. I did read it and I found -- all I can say at this time is that I found the arguments just very confusing even there by trying to explain away that particular piece of data -- about the nature of the patients that were enrolled in Latin America. And as I thought about it more and more, I almost got kind of angry about it because we see all of these clinical trials run offshore and they're clearly in many countries where clinical trials go. Very different patient populations than the patient populations that are going to be using these drugs.

But we're being asked more and more to approve drugs based on that kind of data, and then people don't want to live with the implications of that. And I don't find that to be acceptable.

DR. CARSON: Okay. Let's move onto Question 2, venous thromboembolic events. Are the safety findings for venous thromboembolic events in lasofoxifene-treated women of greater concern than those associated with the use of approved hormonal products for post-menopausal osteoporosis or menopausal symptom therapy?

Let me just ask if the question is clear or there are any particular problems with the question as read?

Dr. Gardner?

DR. GARDNER: Can I just ask, do you mean of greater concern than the VTE events associated with use of approved hormonal products or a more general characterization?

DR. CARSON: Dr. Monroe?

DR. MONROE: Yes. Well, as far as hormonal products for post-menopausal osteoporosis, we have another SERM. We have estrogen products, as Dr. Johnson has mentioned as well. And then also, many members of this panel use estrogen products for basal motor

symptom therapy as well, which is also associated with thromboembolic risks, as we know from the WHI. So we wanted to get a sense from those folks who -- both those that perhaps use SERMs more that do a lot of osteoporosis therapies, as well as those of you who perhaps see less osteoporosis but are comfortable using estrogen-type products for other menopausal symptoms -- as to how you see the risks of thromboembolic events with this in relation to that and the types of patients you're presently using those products for.

DR. CARSON: Okay, ready to vote? Any discussion first? Discussion about this? Mr. Goozner?

DR. GOOZNER: No, no, no.

DR. CARSON: Dr. Adashi?

DR. ADASHI: I'm just wondering how well informed are we with respect to head-to-head studies, you know, in terms of this application versus existing products? I think in the absence of such information, you know, it

would be a fairly obvious answer. Is this a good time to ask the applicant to maybe say something about the ability of such information or the lack thereof?

DR. CARSON: Can you ask a specific question that you can address to the sponsor?

DR. ADASHI: Well, has this particular application, this particular drug, been compared with existing options out there as described here? Other forms of hormonal therapies in terms of VTEs?

DR. D. THOMPSON: To clarify the question, so comparative data with respect to lasofoxifene with a hormonal agent, or in this case, again, we have the comparison with raloxifene.

DR. ADASHI: I would say raloxifene and if you have anything about hormone replacement therapy.

DR. D. THOMPSON: We have -- I can project a slide. It's project S350, if possible. We have done the trial that I

explained earlier. There was a trial that we called CORAL where we compared 0.25 lasofoxifene with raloxifene.

And here you can see that there was a single VTE in this trial.

DR. CARSON: Any data even on overall risks of that hormone therapy? Estrogen therapy?

DR. D. THOMPSON: No, we do not have that.

DR. CARSON: Dr. Nelson?

DR. NELSON: I have a question to clarify. Is there -- is estrogen approved for use of therapy of post-menopausal osteoporosis now an approved indication?

DR. CARSON: Yes. Prevention.

DR. NELSON: Yeah, I'm talking specific therapy though.

DR. CARSON: Oh.

DR. NELSON: Because this is what we're asked here about. This is an indication for therapy for osteoporosis, correct?

DR. MONROE: Well, we wrote it to be even more general than that because we have a large number of gynecologists that use estrogen products to treat menopausal symptoms -- hot flashes, vulva or vaginal atrophy as well. Now, it's not the same indication, but we know from the WHI study that use of these products for those indications as those studies were conducted are associated with thromboembolic events similar to thromboembolic events we saw here.

Now, are there any direct comparative data against a non-SERM? I suspect there are not. And this is the situation we are almost always faced with in that we don't have comparisons against everything we would like to compare against. And so, again, you've seen the same data that we have seen in regard to thromboembolic risk associated with lasofoxifene. And I do believe that's pretty close to truly reflective of the five year data. That's my

guess. I think in terms of serious types of adverse events, I believe the company has focused on them, and I'm assuming they provided us with all those data so that the rates you see for pulmonary emboli, and DVT, and so forth, I think, are what you would see with five year use of lasofoxifene.

And most of you at this table that are gynecologists are very familiar with the WHI data. And so what we're asking really again is to just put this in a broad perspective as to whether you think the risks are in the same ballpark, much worse. You know, you have to make that kind of a judgment yourself here. You're treating a different disease, but again, we're trying to get a sense for how all of you folks that have had experience with hormone products in menopausal women feel about the data that you just saw today.

DR. CARSON: Okay. Are we ready to vote? Any other comments? Okay. So those

voting yes that you feel there are safety findings for venous thromboembolic events in lasofoxifene-treated women that are of greater concern than those treated with approved hormonal products, please raise your hand.

Would you read your answer into the record, please?

DR. NELSON: Nelson. I think there is increased risk with regard to the fact that this is something that's going to be used for years, whereas the standard for hormonal therapy in menopausal women is to give the lowest dose for the shortest period of time to treat symptoms. So in that regard I think this is more significant.

DR. CARSON: Okay. Would you read your answer into the record?

MS. PORTIS: Yes. Portis, yes. And similar -- I think again, my concern is about that we don't have as much long-term data to compare it to the other products.

DR. CARSON: Are there any more yeses?

Okay, could we vote no? May I see your hands if you're voting no to that question? Okay, would you just, again, read your name into the record so -- and then we'll go back around.

DR. ROSEN: No, Rosen.

DR. MERRITT: No, Merritt.

DR. JOHNSON: No, Johnson.

DR. CARSON: Read your name into the record with your vote, please.

DR. STADEL: No, Bruce Stadel.

DR. GILLEN: No, Gillen.

DR. CARSON: No, Carson.

DR. GARDNER: No, Gardner.

DR. LIU: No, Liu.

DR. COLLINS: No, Collins.

DR. CARSON: If you'd like to comment on that, Dr. Rosen?

DR. ROSEN: I voted no because I think the data looked very similar to estrogen and raloxifene.

I would like to have seen some more sponsor data on potential etiologic

factors -- protein levels that might contribute to risks. So screening those individuals that could be at higher risk, are they different than the ones that have been treated with raloxifene, for example?

DR. CARSON: Any comments?

DR. JOHNSON: Yes, I had significant concerns because of the evidence that there is an increased risk of pulmonary emboli. Having said this, overall the risk appears to be very similar to that seen with other -- with the other SERM, with estrogen use, but I would ask the company to continue to follow this very closely.

DR. CARSON: Comments?

DR. STADEL: For similar reasons, I think the data look similar to the data that we've seen about raloxifene. And my recall from a number of years of data on estrogen replacement therapy, that the results are very similar. I think more data from follow up is always a good idea, and since they're planning a

large EPI study, they might be able to get more information. It would help to come up with practical suggestions for reducing the risk for sort of things, like move around in the airplane cabin. Practical kind of information may emerge.

DR. GILLEN: I'm basing my answer on the comparison of raloxifene and the data that's coming from the MORE study, or I don't see sufficient evidence to conclude that there is an increased risk in VTEs on the new drug. The thing I want to express here, I think the way these questions are written are somewhat specific, but they're tailoring a certain way, but at the end of the day -- I do feel that there's late occurring trends that we may be missing here, you know, that have been kind of popping up through the data. And so by me saying no here, that means I don't believe that there's evidence that I had to conclude that there is a total difference here. But I do think that the proper way to do this is to do a

head-to-head comparison on these things and look at the SAEs that are coming up across the two groups, and long term follow up. So I wanted to state that.

DR. CARSON: I have nothing to add from what's been said.

Dr. Gardner?

DR. GARDNER: Nothing to add.

DR. LIU: The lesson here is that it's very similar to raloxifene and to estrogen on the low pressure side, but in contrast with estrogen, you also have strokes, et cetera, on the high pressure side -- the arterial side, which is different. So SERMs are a little bit different animal than estrogens in terms of the high pressure, high flow side, as opposed to the lower pressure, low flow side, which is the venous side.

DR. COLLINS: Nothing to add.

DR. CARSON: And do we have any abstentions? That wasn't a choice this time. We fooled you. Any abstentions?

So can we assume -- we need to have everybody's vote, so would you like to vote or would you -- would you like to join one of the other groups or would you like to abstain?

DR. ADASHI: I will abstain in this case, but I do want to make a plea for evidence rather than judgment. I want us all to heed some comments we heard from Dr. Zucherman earlier, as well as from the gentleman to your left who I can't see without my glasses. And so in the absence of head-to-head comparison, and in the absence of a compelling study, the one we were shown with about 500 subjects if I'm not mistaken, and so forth, I just don't know that we should make recommendations in the absence of the evidence.

DR. CARSON: And would you read your abstention into the --

DR. GOOZNER: Goozner, I abstain. My focus on this question was on the word greater. We certainly had no evidence to answer yes, and

so therefore, the implication of no was that we had some evidence to say that. And I didn't have evidence of that either.

DR. CARSON: There were two votes for yes in favor of the question. In regard to the question, nine for no, and two abstentions.

Let's move on to Question No. 3, gynecologic issues. This is -- these two questions are for discussion only.

Question 3 is do the gynecologic adverse events associated with lasofoxifene treatment -- for example, endometrial thickening and vaginal bleeding -- entail a significant management problem for general health care providers and/or burden for patients?

Dr. Liu?

DR. LIU: Generally, most practitioners will not routinely scan the uterus for endometrial thickness unless there is a specific reason, such as vaginal bleeding or some other gynecological complaint. And so

assuming that the package insert and there's education, that probably isn't going to result in a significant increase in the number of procedures for just endometrial thickening alone.

As with any menopausal woman who is having vaginal bleeding, I think the gold standard is endometrial sampling, and so that will not decrease because there is an increase in incidence of vaginal bleeding in patients on lasofoxifene.

DR. CARSON: So you really also answered Question 3(b), which we can probably discuss simultaneously. That endometrial biopsies, you're saying, should not be performed for endometrial thickening, just found incidentally, right?

Dr. Johnson?

DR. JOHNSON: Although a good point is made for the nine cystic changes, this does raise some concerns because I think increasingly we are doing ultrasounds as screenings. They're

being done as part of GOG protocols. There's going to be intermittent findings of endometrial thickening. And if you look at the percent of women at the five-year point, 19 percent of them had endometrium greater than 8 millimeters. And even though we would say that those women should not have a biopsy if they did not have bleeding, I think that would be a tough persuasive argument to make to clinicians. So I have significant concerns that this will lead to increased procedures.

And if you looked at the number of procedures crossing out the endometrial biopsies, looking at only the surgical procedures that were done, it still was two to one for the group on the SERM as compared to the placebo, 103 to 45. So I really do think that this is going to put women at increased risk for gynecologic procedures. If this does go forward, I do think that significant effort to both gynecologists, primary care providers, and pathologists is

going to be critical. Otherwise, we will see a marked increase in procedures done to women.

DR. CARSON: Would you go ahead and answer Question 3(b)? Do you think that endometrial biopsies should be done incidentally for endometrial thickening or just for vaginal bleeding? Weigh in on that.

DR. JOHNSON: That is a very good question. I mean, I -- if I had someone who I knew was on this medication and I knew that this was a side effect of this medication, could I just watch it and no biopsy it? Yes. But I would still probably watch it in some manner, which means another ultrasound. So I would still want to know that the thickness did not change over time. But suggesting perhaps that with this medication it may change over time so they would end up with a biopsy.

So that's kind of a mixed answer. But no, would I immediately biopsy? No, I think that is reasonable, but I think some

form of monitoring of these patients needs to be considered.

DR. CARSON: Dr. Collins?

DR. COLLINS: Yeah, I think it makes a difference as to who's prescribing the medication. So if it's prescribed by me, an endocrinologist, and I see bleeding, I don't have the option of, you know, sort of quick and dirty endometrial sampling.

It requires a referral to a gynecologist. And a referral to someone is seen by that person, I think, with a sort of heightened level of urgency. And more might be done rather than less. So I think there's a difference given who is prescribing it.

DR. CARSON: Any other discussion from panel on these gynecologic issues? Yes, Dr. Portis?

MS. PORTIS: I guess I'll just say that, of course, more procedures does mean more stress on the patient, even though someone said an endometrial biopsy isn't a major procedure.

It still is significant and is stressful on the patient. And I go back to this issue, too, of the eight millimeters versus the four. So at four millimeters, which was pointed out in the materials, I'm assuming, not being a doctor -- a medical doctor -- that even more people will be being screened and will have thickening at four when we're only talking about eight. So that number is even bigger.

DR. CARSON: Dr. Johnson?

DR. JOHNSON: Just one other small statement. The study only went up to three years. It really would be important, I believe, that if the argument is that this is a normal, benign change that you see with this medication, which may well be true, I think they need to prove that to us with ongoing study.

DR. CARSON: Okay. I also had one comment that we saw how the diagnosis on pathology was made with cystic hyperplasia in the endometrium and then when read centrally by the pathologist these were discarded. But

again, out in the real world, and we've heard so much of that today, that's what the physicians are going to see. They're going to have the pathologist out there who reads cystic hyperplasia reading this. And so it is something to keep in mind about that.

Okay, let's move on to the benefit/risk profile. This is a vote. Again, yes, no, and abstention as the three possible answers.

Is there a population of post-menopausal women with osteoporosis in which the benefit of treatment with lasofoxifene is likely to outweigh the risks? And does everyone understand the question first? Do we need any clarifications of the question?

Dr. Collins?

DR. COLLINS: I understand the question, and maybe this isn't the time to ask this, but so when I first saw this question, and I'm trying to think of that person who this is

good for, and it would be that person whom I want to have some impact on their breast cancer risk and their coronary disease risk, but now I'm not clear. What's the final word on that? Do we take those data into account in deciding here now -- that is the breast cancer risk and the coronary disease risk -- or are the data not in on that? I'm not clear on those two points.

DR. CARSON: Do you want -- I have to ask, do you want us to just answer this question regarding the three-year data or to also take into consideration the entire preliminary set of data?

DR. SHAMES: Well, I think we're interested in your opinion, and you have to decide what you're going to incorporate into your opinion.

That's -- you know, and how important these factors are. We're not going to make it that easy on you. Go ahead.

DR. MONROE: You raise a different dimension to our question because there's sort

of a second part. Before you even get to B it says, if so -- we gave you some examples of different populations that might be, again -- and our thought process in giving these others was -- obviously, with Number 3, it limits it to a population that doesn't have many other options. And so that could be potential population. If you look under 4, it says, if so, could this population be the general population? A woman -- a population that's higher risk for fracture or population that might not tolerate, let's say, bisphosphonates.

And the second option there was just to consider, because as Dr. Adashi and others raised before, in any therapy for osteoporosis -- even though we're not calling this prevention, we're calling it treatment -- we're still not -- we're treating -- at least if we're just using bone density, we're treating low bone density. We're not necessarily sure what the risk of that person having a fracture would be.

And again, if you go down to 4(b), if you just think about the whole series of questions we have here, there are some other tools that are now being offered for consideration, such as the fracture risk assessment tool that perhaps Dr. Rosen might want to chat about. We didn't really put that in our background, but there are some algorithms that do a better job of predicting a woman's likelihood of getting a fracture within a defined period of time.

So where we are going with this question is at what point might you feel, if you have reservations about using this therapy in any woman who just happens to have a bone density of, let's say, less than 2.5, which is the official definition of osteoporosis, would you want to perhaps recommend that it be used in somebody who has a higher probability of a fracture so you don't have to treat as many people before you get a benefit? Or do you want to consider a

different population?

Now, you raised a whole new dimension of potential options. And many of those that you heard about, such as the reduction in, I guess, in coronary events -- those are not primary endpoints.

They were secondary endpoints. The study wasn't really -- as far as I know, and the company is free to correct me -- designed to look at those. So if they had failed, we just wouldn't be hearing about them today.

And as we know, if you look at enough endpoints, some are going to win; some aren't going to win. And so we've heard about a lot of them that have won today. And I'm talking about efficacy endpoints, not safety. I think there's been a good disclosure of safety.

So again, if you talk to Dr. Gillen, and perhaps he'd like to address this with all these multiplicity of options of winning, normally one would ask that an

adjustment be made to allow for this, or that someone would have declared a priori and ordered an analysis so you wouldn't have to perhaps take as large a penalty. So what you are going to walk away with in terms of feeling that those other advantages have been proven to the level that you believe they are true advantages, you'll have to make your own decision. But I think we, as an agency, would be certainly not likely to be granting indications for those. And whether they would get into a label is something that would have to be discussed further.

Would you like to discuss --

DR. CARSON: Dr. Gillen.

DR. MONROE: Perhaps for your colleagues about when you have a large number of secondary endpoints or -- and so forth? And then perhaps Dr. Kammerman, if you want to add something at the end as well.

DR. GILLEN: Yeah. Just to follow up on what Dr. Monroe said. You know, the study

was designed to look at a primary endpoint, which is a radiographic vertebral fractures. And that's exactly what I'm going to be basing my opinion on.

The other secondary endpoints the study was not powered for. The inference that's been made has not been adjusted for it to look at the multiple comparisons and multiple endpoints. And so I think the study had a very clear focus when it started out with the primary endpoint that they were intending to do. I personally am interpreting this as analyzing the risk to benefit ratio. You have to take into account everything that comes into play -- all risks and benefits that may come into practice, but the idea being that you would prescribe this under the primary indicated indication.

DR. CARSON: Dr. Cummings, did you have something?

DR. D. THOMPSON: David Thompson.

DR. CARSON: Oh, sorry.

DR. D. THOMPSON: I'd just like to address the question if these were five year data that we were prescribing in terms of the multiple coronary events, as well as the breast cancer events. And the breast cancer -- the ER positive breast cancer -- was a primary endpoint at five years, and there was approximately 90 percent power to assume a 70 percent difference. And so when it was a prespecified endpoint -- secondary endpoint from the beginning -- that then was put into as a primary endpoint at five years.

Also, the major coronary events were indeed a secondary endpoint, but again, they were prespecified at the beginning, and they were adjudicated and so forth through an external adjudication committee. So these were five-year data that we did present as far as those two endpoints.

DR. CARSON: You two look so much alike.

(Laughter)

DR. GILLEN: So exactly when was the amendment made, and at what time had you seen breast cancer data prior to amending the protocol to make it a primary endpoint in the five-year?

DR. D. THOMPSON: All of the -- the amendment to continue the study to extend it to five years was before there was any data on blinding of the three-year trial. So this was not done with any advance -- without any information coming from the three-year trial. So it was done prior to any unblinding of three-year data.

DR. LIU: Was the secondary endpoint adjusted or are you talking about just as a secondary endpoint for the coronary?

DR. D. THOMPSON: For the major coronary events it was not adjusted.

DR. LIU: What would it be if it was adjusted? I'm sure you've looked at it.

DR. D. THOMPSON: Dr. Thompson, can you address that?

DR. J. THOMPSON: Good afternoon. John Thompson again. How we would have approached that -- somehow we would have had to set up a process a priori if we were looking at the process you speak about. It was a secondary endpoint. It was supportive of our indication. And we handled it in that manner. I don't know if Gary Koch would have any additional comments that would help.

DR. D. THOMPSON: Again, just in supporting information around the major coronary events, the lipid changes were apparent. This was a prespecified endpoint in the secondary analysis. So this was giving it further information.

DR. KOCH: Gary Koch, University of North Carolina. For the three-year analysis, the primary was specified as the vertebral fracture. There were also two key secondary analyses or two key secondary endpoints. Maybe you could bring up ST-6 for the three-year analysis. So bring up ST-6.

In any event, those were multiple vertebral fractures and clinical vertebral fractures. And there was a prespecified method for how the Type I error was going to be controlled by moving from the primary endpoint to the secondary endpoints.

At five years there were two co-primary endpoints, and those were specified as they are. And there was a multiplicity method to manage those two co-primary endpoints. And there were two key secondary endpoints. There was success on the primary endpoint at three years. There was success within the prespecified method for multiple vertebral fractures as a secondary at three years. There was success on both of the co-primaries at five years. The two secondaries at five years, there was not necessarily a process to getting to those. The cardiac events was a prespecified secondary, meaning it was something that was going to get scrutiny. It was not something

that was part of a Type 1 error control procedure.

DR. CARSON: Dr. Nelson?

DR. NELSON: Since we still have questions about whether there's an increase in the all-cause mortality with this agent, for me to answer this question I'd like to know is there any evidence about how much reduction in mortality there would be if this agent is approved. Do we have any evidence or speculation even about that?

DR. D. THOMPSON: Dr. Hennekens, can you address that question?

DR. HENNEKENS: You know, I guess I was asked to look at these mortality data because I was an independent scientist chairing the data and safety monitoring board for Illuminate, a Pfizer drug that was stopped early because of its increased mortality hazard. And in randomized trials of prevention and treatment of cardiovascular disease and cancer, one typically sees increases or decreases in

non-fatal events first, then fatal events second, and only later, much later, any increase in total mortality.

So any increase in total mortality in the absence of increases -- a consistent pattern of increases in non-fatal and fatal events really is not the way one sees the accumulation of data in these large scale trials.

And therefore, if one accepts that regardless of whether there are prespecified endpoints of breast cancer, of coronary disease, and of stroke, and that these are real, then one would predict that over the long-term of treatment and follow-up, they would translate into importantly relevant reductions in cause specific mortality from breast cancer, from coronary heart disease, and stroke. But that, of course, is speculation, and it's based on what you see emerging from clinical trials that are used to treat or prevent cardiovascular disease

and cancer.

DR. NELSON: Well, could you give us an estimate? How many patients would you need to treat to save one life with this drug?

DR. HENNEKENS: Well, first of all, I am not a person who believes that there's any increase in mortality. I think not the subgroup data, which are really very, as some of you have said, not very reliable. The overall data and the 0.5 milligram data show no increases in total mortality.

So on the downside, I don't think there's a totality of evidence, in my view as an independent scientist, that suggests there's an increased mortality hazard either due to exposure to the drug overall or to the 0.25 milligram dose.

With regard to coronary heart disease and stroke, if you have a 20 percent reduction in mortality or more, which is what you see here, this will translate into important reductions in vascular deaths. But

that kind of a model of number needed to treat is really a function, not of the benefit of the drug but the risk of the patients and the studies in which you're doing the randomized trials.

So I don't feel that it's a very useful estimate here because I think the useful thing is what I heard from Dr. Goldstein. That is, that as a clinician I have to weigh, you know, women with osteoporosis, the potential benefits on all the things that are putative benefits against the potential hazards. And it looked like, from what I heard from him, that this was in the direction of net benefit.

DR. CARSON: Thank you. Let me again bring the discussion back to the focus again. The discussion is by the panel on the question of is there any particular subgroup that would benefit particularly by the drug. Yes?

MS. KAMMERMAN: Lisa Kammerman, statistical reviewer. There's one twist to this

five-year study. The study -- in order to extend for two years, the participants up to three years had to be reconsented. And not everybody reconsented. So the population being followed between three and five years isn't necessarily the same population that was followed up through three years. So the effect of those who did not reconsent hasn't been discussed.

DR. CARSON: Dr. Gillen?

DR. GILLEN: Can you quantify the percentage of individuals that did not reconsent?

MS. KAMMERMAN: There's probably around 300 per treatment group. So around 800, 900 people.

DR. COLLINS: Were they balanced among all groups, the non-reconsenters?

MS. KAMMERMAN: Yes.

DR. CARSON: Any other panel issues or questions?

DR. GILLEN: Were those individuals

that did not reconsent followed up for any safety data?

DR. D. THOMPSON: No.

DR. CARSON: Dr. Portis?

MS. PORTIS: I am just thinking back to Ms. Pearson's comments about -- I'm starting to see the marketing campaign that comes when people start talking about things like breast cancer risk and prevention, and all those things that we really don't have the data about. And I think, you know, breast cancer risk or vaginal changes or hot flashes -- so I feel like we get into murky territory if in our thinking we throw that into our response to that question because we don't have the information to look at that yet or make decisions based on those things yet.

DR. CARSON: Okay. Any other comments? Dr. Collins?

DR. COLLINS: I'm still confused. So the breast cancer was a primary endpoint appropriately tested and this drug was found to be protective. Is that correct?

DR. CARSON: Dr. Monroe?

DR. MONROE: I don't think the Agency would agree with that interpretation. We don't do breast cancer in our division, per se. We consulted this to the Division of Drug Oncology Products. And for somebody to get a claim that their drug prevents breast cancer or reduces it, there's a number of additional criteria that they would like to see. The company perhaps would like to expand upon that because I think at one time they did perhaps consider actually looking for a formal breast cancer prevention claim.

DR. D. THOMPSON: Again, to reemphasize the fact that we are not seeking an indication for breast cancer prevention here. We are simply not seeking that. As Dr. Monroe said, there were discussions a number of years back where it was considered with the oncology division. What would it take to develop a drug like this for breast cancer and breast cancer prevention? At that time we opted not to do the

development for the prevention indication, so therefore, it was a safety endpoint in this study. And what we did show was a significant reduction in breast cancer.

All breast cancer -- ER positive breast cancer, invasive breast cancer -- with 0.5 milligram lasofoxifene compared to placebo at five years.

DR. CARSON: Thank you. Okay, let's -- Dr. Collins?

DR. COLLINS: Not to keep beating this. So then when this -- if this drug comes to market and the package insert is put together, will the package insert be able to say that it was associated with a decreased risk of breast cancer? I'm the clinician, you know, writing the script. I'm trying to think who's the one that's the right group to get this. Are these the data that I'm going to have to work with?

DR. MONROE: At this point I can't tell you whether the package insert would

include those data or not. It would require further review of those data. As we made clear to you and the company's made clear, the five-year data came in late in the review cycle, and except for the fact that it had significant bearing in terms of the things that we were worried about, we normally would not have felt that it had undergone complete reviews. So in terms of the breast cancer data and the strength of the findings, you saw what the company presented. I believe the numbers are correct, but it's more complicated than just having correct numbers.

There's a lot of other issues, again, in terms of design, and the way it was put together, and whether those people who are best able to really -- and have had a lot of experience to ensure that.

If one is going to make a statement like that -- and I think this is where we get into these gray areas that we heard from the folks that presented earlier -- that the

difference between having an indication and then getting it labeled as sort of descriptive, and then how one interprets it, sometimes that differentiation gets very gray. So we're obviously cautious in what we would even allow in there in terms of descriptive material. And at this point I can't tell you what -- should this drug get approved -- what the labeling would say vis-a-vis the findings from this particular study. Clearly, we would not want whatever is in labeling to over represent what one could interpret.

DR. CARSON: Okay. So then -- oh, sorry, Dr. Stadel?

DR. STADEL: I wonder if I'm on.

DR. CARSON: It's not on. Your mic isn't on.

DR. STADEL: Now it's on? I hope I'm not missing something about stroke, but in the papers that I read as background of stroke section and Dr. Willet's memo, there's no

significant effect. And I'm hearing it talked about that there is. And I'm somewhat confused about what it is that's going on.

DR. WILLETT: We saw a very small increase in fatal strokes. But if you look at all the strokes combined and then you add in the TIAs, there isn't a statistical significance there. There's just a slight increase in fatal strokes when you looked at that. But that wasn't statistically significant, though.

DR. STADEL: Decrease in total strokes?

DR. WILLETT: Pardon?

DR. CARSON: Your microphone.

COURT REPORTER: Your mic is off.

DR. STADEL: There's not a decrease in strokes?

DR. WILLETT: There is -- there wasn't -- when you include TIAs, there's not a statistical decrease. There's lesser numbers when you look at it.

DR. STADEL: I see. Thank you.

DR. CARSON: Dr. Portis? Okay, so let's vote on Question 4. Do you think there's a population of postmenopausal women who have osteoporosis that would benefit -- have a higher benefit than risk ratio by being treated with lasofoxifene? And those voting yes, please raise your hand. Would you just read your answer into the record?

DR. ROSEN: Rosen, yes.

DR. MERRITT: Merritt, yes.

DR. JOHNSON: Johnson, yes.

DR. STADEL: Bruce Stadel.

DR. GILLEN: Gillen, yes.

DR. CARSON: Carson, yes.

DR. GARDNER: Gardner, yes.

DR. LIU: Liu, yes.

DR. COLLINS: Collins, yes.

DR. CARSON: And would you like to justify your answer or comment on your answer?

DR. ROSEN: I think the data speak for themselves. Primary and secondary endpoints have been met.

DR. MERRITT: In the real world there won't be subgroups treated, but I think there are categories of women who would benefit from the additional options here.

DR. JOHNSON: Yes, certainly there is only one other medication available for -- currently for women who cannot take bisphosphonates and cannot take estrogen. So this offers another option for those women.

DR. GILLEN: You missed Forteo, too.

DR. CARSON: Dr. Stadel?

DR. STADEL: I think that's very well-put about another option. And I also note that there's a reasonably large sized group of women who have had hysterectomies and for whom some of the concerns that were discussed about polyps, and vaginal bleeding, and cystic endometrial changes really wouldn't apply. And another option for them is, I think, a no loser.

DR. GILLEN: Yeah, I believe that for women not able to tolerate bisphosphonates, then this represents an alternative. So I would

restrict my answer. So the second part of this question is what would the population be? I would say it's three. Those women that are unable to tolerate other medications. I would emphasize again though that I think it's important that even if it's going to be used in this particular subpopulation that extended follow up be done on long-term survival and long-term DVT risk.

DR. CARSON: I have nothing to add.

DR. GARDNER: I concur with Dr. Gillen about option number three. And although I've heard Forteo twice today, Forteo is not a user-friendly alternative for a lot of women. And so while it may be a clinical option from the standpoint of the clinician for women, it's less than idea. And so having something that would be easier to take that still would fit within that profile would be my vote.

DR. LIU: It's already been said.

DR. COLLINS: I think one of the questions, though, here and the one, two, three,

limited to a subgroup of higher risk for fracture, I mean, I think that's the place where you are willing to tolerate the inconvenience of the injection or the high risk. I don't see this as a drug for that.

I do see this as a drug for a specific subgroup. A specific niche.

DR. CARSON: May I ask those voting no to raise their hands? And would you read this into the record?

DR. NELSON: Nelson, no.

DR. GOOZNER: Goozner, no.

MS. PORTIS: Portis, no.

DR. CARSON: And explanation of your answer?

DR. NELSON: Well, from my perspective with the open question about all-cause mortality, and without any evidence about how this might avoid mortality, I'd find a hard time identifying a group I could give this to.

DR. GOOZNER: As I raised the question earlier, this is not just one or the other risk.

There's a composite of risks here, and there's a measure of benefit. And so we're being asked to measure the benefits of this drug against the risks of this drug. And I can't really figure out what the risks are based on the data that we've been given.

And then when it comes to just the question that people raise about it having another agent, there is another agent in this class, and it seems to me that when another agent in the class comes along -- I don't know if it's fair or not, but it is held -- could be held to a higher standard in order to answer some of those very specific questions that were raised by the first drug in the class. And we didn't get those answers.

MS. PORTIS: I have nothing to add. I agree with both comments.

DR. CARSON: And may I see those who abstained from voting? And explain your abstention.

DR. ADASHI: I'm probably abusing this option and replacing it for the unable to determine option. But there are three issues in my mind. One is I am generally concerned about the risk/benefit ratio. Secondly, if the drug were to be approved, I think it would be a good idea to focus it on a subgroup of women, as opposed to a broader population. But I wouldn't really know what that would be at this time. And even if I did, I think in the absence of a study that's specifically directed to that end, I would be at a loss to really comment. So to the extent that the Chair can tolerate this abuse, I've taken that prerogative.

DR. CARSON: Lucky I don't pay your salary.

DR. ADASHI: Good. It's the other way around after all.

DR. CARSON: Yeah. Dr. Adashi was my dean. There were nine yeses, and three nos, and one abstention to that question.

Let's talk a little bit

about -- some of you mentioned as we went around -- those of you who voted yes about the particular population that you would say in particular those women might benefit, why don't we just comment on a particular subpopulation that you think would be likely to receive this drug.

Dr. Rosen?

DR. ROSEN: So I just want to clarify some issues about Forteo. And I would tend to agree that it's a fallback position for a lot of individuals with severe osteoporosis. But it isn't user friendly, and it's running over $9,500 a year. And it's a very difficult drug to use by primary care physicians because trying to get reimbursement from insurers is extremely hard.

So there is the potential to use this agent in individuals who can't take bisphosphonates or who may be otherwise noninclined to take some risks if there are perceived risks by the individual.

In terms of who's at greatest risk, I think it's worth remembering that the nonvertebral fracture risk that was demonstrated here is comparable -- although I didn't believe it until I saw the metanalysis at lunchtime -- is really comparable to what is seen with other therapies. And I will remind you that ibandronate, which was approved by the FDA, has nonvertebral fracture risk and non hip fracture risk that's very similar, as well as raloxifene.

So I think this drug really comes in at a very similar place to a lot of the other agents. And my one concern would be to label this drug as very restricted to only individuals who fail other therapies because I think that worked with parathyroid hormone, but it did so for a number of reasons. And I think, again, it's a judgment that has to be made when you weigh all the factors in a given individual who present to your office with multiple different concerns ranging from

OMJ or subtrochanteric fractures.

On the negative side, I'm really dismayed that we don't have a head-to-head trial. And I think, again -- and I think this comes back to Dr. Adashi's point -- is that without head-to-head trials, we really can't make absolute definitions about what drugs work and don't work. And I think that's one of the lessons that we continue to go back to Pharma about.

As somebody mentioned, trying to hold this drug to the same standard as the first drug that was approved in this category does require head-to-head therapy.

So I'm against restricting it to a specific population, but in my own mind I would use bisphosphonates first. And I would use the FRAX dataset from Sheffield that's easily accessible -- the 10 year fracture risk -- to identify those individuals who might benefit from this drug because they're at higher risk and are unable to take the

bisphosphonates.

DR. CARSON: Dr. Monroe?

DR. MONROE: Before we let you escape from us here, in terms of the three choices we had put forth, would you -- I think you were saying number one, leave it just for osteoporosis, or were you saying number two? I wasn't clear. I know you didn't want to just limit it to number three.

DR. ROSEN: I didn't. And that's why I didn't answer for A when you asked me because I was afraid to commit myself to one of the three categories. And the reason is, I think, because we -- because I think this drug is in the category of all the other agents that we've approved for osteoporosis. And it requires a judgment on the -- both the patient and the provider to make a decision.

And I think we now have the tools. I mean, in the past we treated many, many more people than we needed to with low bone density. But now we have the FRAX dataset.

We have cutoffs of 20 percent 10-year fracture risk or 10 percent for hip fracture. And I think those can be utilized at the bedside to identify individuals. So my scenario would be I think this woman has a 22 percent 10-year fracture risk. You need to be treated. Here's the pluses and minuses of bisphosphonates. Here's the pluses and minuses of the SERMs. And I think those options cannot be restricted by a label but have to be discussed openly.

So that's my response. I think we have the tools now to be able to assess overall fracture risk. The instrument is quite accurate.

DR. CARSON: So you're limiting it to the postmenopausal patient who is at high risk for fracture?

DR. ROSEN: That's right. I mean, I'm not -- I don't believe in osteopenia. I've never believed in it. I think we should never have approved drugs based on prevention alone,

particularly bisphosphonates. So I look at overall fracture risk and make that determination.

DR. MONROE: And do you have sort of a number if you were using, let's say, the FRAX tool?

DR. ROSEN: Well, 20 percent for --

DR. MONROE: Twenty percent over 10 years?

DR. ROSEN: 10-year fracture risk for nonvertebral -- or vertebral fractures and 10 percent 10-year fracture risk for hip fractures.

DR. MONROE: Thank you.

DR. CARSON: Any other comments on the particular group of women who might benefit most by this drug? Or the target group?

Okay, let's move on to Question 4(b), which is also for discussion only. If you believe that treatment should be limited to a higher risk for fracture population, how would you define this population? And we've

already heard Dr. Rosen suggest a 20 percent risk for nonvertebral fractures. And did you say 10 percent for hip fracture?

DR. ROSEN: Ten percent.

DR. CARSON: Sounds good to me. Any other comments? Dr. Monroe?

DR. MONROE: Before you sort of explore 4(b) further, it wasn't clear to me what most of those individuals who thought that there was a place for this drug amongst the three options we had sort of put forth felt. A few of the individuals over here made some comments, but could we do that in perhaps a little bit more transparent way so we could hear and learn from everybody that we've assembled here? Thank you.

DR. CARSON: Sure. Why don't actually we go ahead --

DR. MONROE: You can do that with 4(b) if you wish and do it, but I'd like a little bit more transparency or clarity as to -- we know how Dr. Rosen feels very clearly right now but

I'm not sure about everyone else. And there may be many, many people that just don't feel that they're in a position to be as detailed because of the types of patients they manage.

DR. CARSON: Those people -- those individuals obviously who voted yes to Question 4(a), maybe we can just go around the room and solicit your opinion regarding should the treatment be limited to just a higher risk population group, or what population group per se as mentioned in 4(a).

Did Dr. Merritt vote yes?

Dr. Merritt, I don't remember your vote.

DR. MERRITT: I voted yes.

DR. CARSON: So do you want to answer?

DR. MERRITT: I voted yes. It will be very important for the practicing clinician, practicing primary care physician, gynecologist, not the bone specialist, to understand the limits of the study and also to understand the material that's available so they can appropriately counsel the patient. So I didn't

want to say no because I thought that meant there would be no use for this drug. So I said yes because I thought there is a use. But one would have to weigh counseling their patient and their needs.

DR. JOHNSON: Yes, I think the primary use for this medication may be for those who do not tolerate bisphosphonates. I think I stated this earlier. If I can persuade the company to do further studies, there may also be a use for women who have vaginal atrophy.

DR. CARSON: So it would be all women with osteoporosis, regardless of their fracture risk?

DR. JOHNSON: No, actually, I've been educated today. I would look at women who are at significant risk for fracture because you have to look at the risks of using this medication and who do not tolerate bisphosphonates.

DR. CARSON: Dr. Stadel? Dr. Stadel, do you have an opinion on this? Can you weigh

in? A group in particular who might benefit by this drug?

Who this drug would be used for?

DR. STADEL: No, I don't.

DR. CARSON: Okay. Dr. Gillen?

DR. GILLEN: Yeah. As I stated before, I think that we're dealing with a drug that absolutely medits efficacy endpoint on vertebral fractures, but also has a risk profile that I think we need to be cautious with. And therefore, my recommendation is that it should be high risk women who are not able to tolerate bisphosphonates, you know, after you've exhausted first voter therapies.

DR. CARSON: And I personally think it would be all women with -- all postmenopausal women with osteoporosis. And the risk/benefit discussed with the woman and a clinician-patient decision made.

DR. GARDNER: I have nothing to add. I had said number three before. I'm not a clinician, and so it may be we move between two

and three, which is significant risk. Whether the clinicians need to be able to decide about whether bisphosphonates have worked or not worked, or need more education to dispel rumors, I don't know. But something in there.

DR. LIU: I would add that not only the women with severe osteoporosis and at higher risk for fracture, but those individuals that can tolerate the hot flashes, because that will be a significant side effect and drop out for women that don't tolerate it.

DR. COLLINS: So yeah, I think it's a subgroup. Those who don't tolerate bisphosphonates.

And I just have the comment, you know, with the availability of intravenous bisphosphonates, the nontolerant -- true nontolerability of bisphosphonates is a relatively small group, I think. But anyway, those who don't tolerate it, don't want it, and those at high risk. And I don't know, is it 10 and 5 on the FRAX data or is it 10 and

3?

DR. ROSEN: Yeah, if --

DR. COLLINS: Yeah, please. But I like the FRAX data, too. And I think those numbers are evidence-based numbers and they're important.

DR. CUMMINGS: If you don't mind my clarifying. The National Osteoporosis Foundation has recently issued guidelines. And the numbers that are within that are for women with osteopenia.

That is with bone densities higher than this -2.5. Within that group, there is considered to be a higher risk group. The numbers that have been used based on cost effectiveness analyses are 20 percent 10-year risk of major osteoporotic fractures, and 3 percent 10-year risk for hip fractures. And that's the current guidelines.

But that's a bigger group than the group of osteoporosis. That extends it beyond into osteopenia. Osteoporosis is the

more severe --

DR. ROSEN: I should add that they're an advocacy group, so one has to be cautious about interpretation.

DR. CARSON: Any other comments from the panel to weigh in? FDA?

Well, thank all of you. Thanks to the public for your interest, the sponsor, and most importantly, thanks to the panel for all of your hard work in getting to this point, and you're truly energetic, enlightening discussion today.

Bye.

(Whereupon, at approximately 3:02 p.m., the MEETING was adjourned.)

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