UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY
COMMITTEE MEETING

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TUESDAY,
OCTOBER 7, 2003

The Advisory Committee met at 8:00 a.m. in the Versailles Ballroom of the Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. Michael McClung, Acting Chairman, presiding.

PRESENT

MICHAEL McCLUNG, M.D.	Acting Chairman
HENRY BONE, M.D.	Consultant (Voting)
THOMAS O. CARPENTER, M.D.	Member
DEAN FOLLMAN, Ph.D.	Member
BARBARA LUKERT, M.D.	Consultant (Voting)
CLIFFORD ROSEN, M.D.	Consultant (Voting)
DAVID SCHADE, M.D.	Member
MORRIS SCHAMBELAN, M.D.	Member
MARTHA N. SOLONCHE	Consumer Representative (Voting)
PAUL WOOLF, M.D.	Member
ROBERT ZERBE, M.D.	Acting Industry Representative

DORNETTE SPELL-LeSANE, M.H.A., NP-C
Executive Secretary

WOMEN'S HEALTH INITIATIVE PRESENTERS

GARNET ANDERSON, Ph.D.
JANE CAULEY, D.Ph.
ROWAN T. CHLEBOWSKI, M.D., Ph.D.
JACQUES ROSSOUW, M.D.
MARCIA STEFANICK, Ph.D.

WYETH PHARMACEUTICALS TEAM

JOSEPH S. CAMARDO, MD.
CLAUS CHRISTIANSEN, M.D.
J. CHRISTOPHER GALLAGHER, M.D
ROBERT LINDSAY, M.D., Ph.D.
JAMES H. PICKAR, M.D.

FDA REPRESENTATIVES

ERIC COLMAN, M.D.
DAVID ORLOFF, M.D.
BRUCE V. STADEL, M.D., M.P.H.

PUBLIC HEARING SPEAKERS

AMY ALLINA
DAVID ARCHER, M.D.
MARIE FOEGH, M.D., D.Sc.
OMEGA L. SILVA, M.D.
JAMES A. SIMON, M.D.

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

8:07 a.m.

CHAIRMAN McCLUNG: Good morning. I'm Dr. Michael McClung, the acting Chairman of the Endocrinologic and Metabolic Drugs Advisory Committee. Let me welcome you to today's meeting. We have a very busy agenda that looks like will be an interesting and enlightening day.

Let me begin by asking the members of the Advisory Committee and our invited guests and consultants who are seated around the table to introduce ourselves to both each other and to the audience. So, sir, I'm going to have you start with your end with your mouth full. Sorry.

DR. ZERBE: Sorry. I'm Bob Zerbe, QUATRx Pharmaceuticals and I'm the Industry representative.

DR. SCHADE: I'm David Schade, Endocrinology University of New Mexico, School of Medicine.

DR. SCHAMBELAN: I'm Morrie Schambelan, Endocrinology, University of California in San Francisco ("UCSF").

DR. FOLLMAN: I'm Dean Follman, a statistician at the National Institutes of Allergy and Infectious Diseases.

DR. BONE: I'm Henry Bone. I'm an endocrinologist and the Director of the Michigan Bone and Mineral Clinic. I guess that's the main thing.

DR. LUKERT: I'm Barbara Lukert, Endocrinology, University of Kansas.

DR. CARPENTER: I'm Thomas Carpenter, Pediatric Endocrinology, Yale University in New Haven.

DR. WOOLF: I'm Paul Woolf, Adult Endocrinologist, Crozer Chester Medical Center.

SECRETARY SPELL-LeSANE: Dornette Spell-LeSane, Executive Secretary for the Committee.

MS. SOLONCHE: And just in time, Martha Solonche, New York City, the home of the New York Yankees, Patient Representative.

DR. STADEL: Bruce Stadel, Medical Officer, Metabolic and Endocrine Division (FDA).

DR. COLMAN: Eric Colman, Medical Officer from Metabolic and Endocrine (FDA).

DR. ORLOFF: David Orloff, Director,

Division of Metabolic and Endocrine Drug Products (FDA).

CHAIRMAN McCLUNG: I'm Mike McClung, an endocrinologist at the University of Oregon Health Sciences Center in the Oregon Osteoporosis Center. The next item on the agenda will be to have Ms. Spell-LeSane review the Conflict of Interest Statements regarding the Committee members.

SECRETARY SPELL-LeSANE: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the parents of impropriety at this meeting. The topics to be discussed today will not focus on any particular product or company but rather may affect all companies that make hormone therapies with estrogen-progestin that are prescribed for the prevention and treatment of postmenopausal osteoporosis.

The Conflict of Interest statute prohibits special Government employees from participating in matters that could affect their own or their employers financial interests. All participants have been

screened for interest in the products and companies that could be affected by today's discussions.

In accordance with 18 USC 208(b)(3), the Food and Drug Administration ("FDA") has granted a full waiver to Dr. Henry Bone because the need for his services outweighs the potential for a conflict of interest. A copy of the waiver statement may be obtained by submitting a written request to the Freedom of Information Office HF-135, 5600 Fisher's Lane, Rockville, Maryland 20857.

We would like to note that Dr. Jacques Rossouw, Dr. Leslie Ford, Dr. Joan McGowan and Dr. Barbara Alving were involved with the Women's Health Initiative ("WHI") Study as part of their duties as employees of the National Institutes of Health ("NIH"). We would also like to note for the record that Dr. Robert Zerbe is participating in this meeting as the Acting Industry Representative acting on behalf of regulated industry.

In the even that discussions involve products or firms not on the agenda for which an FDA participant has a financial interest, the participants

are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you.

CHAIRMAN McCLUNG: Questions or comments about that from the Committee? Let me then invite Dr. Orloff to make his opening statements to us.

DR. ORLOFF: Thank you and good morning. I'll read my statement from my seat as is my usual. Good morning. Thanks to the members of the Committee and the consultants present for their attendance and to Dr. McClung for agreeing to chair today's session. Thanks also to Drs. Stadel and Colman for their important contributions to today's proceedings.

I want to recognize in particular Dr. Stadel for a tremendous amount of work in bringing the FDA and NIH WHI group together for this conference. We are of course very grateful to the WHI investigators for their willingness to be here today

to present the trial results and to participate in discussion and particularly to Dr. Rossouw whose close contact with the FDA through Dr. Stadel has made this meeting possible. Thanks finally to Dornette Spell-LaSane for here work in managing the complex logistics and legalities and so on of this important conference.

This meeting represents the first public FDA meeting and the first joint FDA and NIH public conference on the landmark Women's Health Initiative Study of Premarin (medroxyprogesterone acetate, "MPA"), the combination therapy, in post menopausal women. As everyone present is well aware, the results of this study have dramatically affected the thinking as to the role of menopausal hormone therapy in women. The public and individual impacts of at least combination estrogen-progestin hormone therapy and of estrogen along therapy by many patients, researchers and practitioners are being reevaluated in light of the overall balance of risks and benefits in Prempro in this study that was terminated early having reached stopping criteria based on breast cancer incidence.

Since the publication of the primary WHI

trial results in July 2002, the FDA always in collaboration and/or discussion with the NIH has taken several steps. In its role in regulating the marketing of Prempro in advising physicians and patients on the safe and effective use of this and other estrogen-progestin ("E + P") combination products and of estrogen only ("E alone") products, FDA has implemented the following:

1. Approval of revised product labeling for Prempro, Premarin as well as for ultimately all U.S. marketed E + P and E along products, changes that were announced formally in early January of this year. Dr. Colman will take you through these changes in his presentation.

2. Issuance of revised guidances for industry on clinical development for post menopausal uses of new estrogen and estrogen plus progestin products and their labeling. This is with the particular goal of the development of lowest effective doses of such products.

3. Provision of information resources on the WHI and on the safe and effective use of

menopausal hormones on the FDA website.

4. Finally, most recently in early September 2003, Dr. McClellan, our Commissioner, launched a nationwide information campaign partnering with multiple organizations across the United States to raise awareness on the risks and benefits of menopausal hormone therapy in light of the results of the WHI Prempro study.

Following on the results of WHI, the basic recommendations by FDA have been consistent with those of a number of professional societies and patient advocacy groups, including the American College of Obstetricians and Gynecologists from which we'll hear a statement written today and the North American Menopause Society. Essentially the same recommendations have been applied to the use of E + P products, obviously those with the use most directly informed by WHI and in the absence of information supporting a clear difference in risk versus benefit to E alone products. They are as follows:

1. Estrogen and estrogen plus progestin products should not be used for primary or secondary

prevention of coronary or cardiovascular disease. Indeed FDA had never approved labeling recommending such use though it had become a common rationale among others for what had become known as menopausal hormone replacement therapy, a term we hold as now clearly inappropriate if not frankly misleading. Instead alternative cardio-preventive intervention should be considered.

2. Alternative therapy should be considered for the relief of menopausal symptoms particularly as a result of vulvovaginal atrophy as well as for the prevention of post menopausal osteoporosis ("PMO").

3. If estrogens and progestins are prescribed, they should be used at the lowest doses for the shortest duration to achieve treatment goals and women should regularly discuss with their healthcare providers if they need to continue treatment.

Today's meeting is intended to assess where we, the broad healthcare communities engaged in areas of patient care, research and drug development,

have come thus far, that is, since July 2002, regarding understanding of and recommendations for safe and effective use of female menopausal hormone drug products and to engage in a public discussion of where we ought to be going. The specific objective of this conference is to discuss the ramifications of the WHI Prempro results for the single chronic use, prevention directed indication for estrogen-progestin in women. That is preservation of bone mineral content after menopause.

As referred to earlier, the revised product labeling for Prempro as well as the actual or intended labels for E + P and E alone products states that if the use is solely for the prevention of PMO then alternative approval therapies should be considered. As such, these products have essentially been relegated to second line status in PMO prevention based on risk versus benefit in chronic use.

Any number of complex clinical and scientific issues remain unanswered by the WHI study or indeed are raised in its aftermath. These include but are not restricted to the risk versus benefit of

lower doses of Prempro, the risk versus benefit of other E + P combination products, the risk versus benefit of Premarin or other estrogen alone products, that is to say used in the absence of progestin, the risk versus benefit of estrogen and estrogen plus progestin products administered by alternative routes, for example, transdermally, and the impact of demographic factors as well as baseline risk factors, for example, osteoporosis, atherosclerotic cardiovascular disease, breast cancer, venous thromboembolic disease on the benefit versus risk of these products.

The agenda for today's meeting is in your package. Following the open public hearing, Dr. Eric Colman, the team leader for Osteoporosis Drugs and Metabolic and Endocrine Division at FDA will provide background on the historical and current regulatory approach to evaluation of menopausal hormones and other drug products for osteoporosis prevention and treatment. A series of presentations from the WHI group will follow with questions and discussions afterward. After lunch, Wyeth Pharmaceuticals will

present and Dr. Stadel, Medical Officer in Metabolic and Endocrine, will make a brief presentation based on his review of the WHI findings.

This is not a typical FDA Advisory Committee meeting. There is no product being considered for FDA approval today. As such, we have chosen not to ask at least at the start explicit yes or no questions but rather to attempt with our questions or with our laying out of issues to direct the deliberations and discussions on three principal topics. They are and Dr. Colman will review these as well I suspect:

1. The accuracy, appropriateness and usefulness of the revised labeling of Prempro after the WHI.

2. The implications of the WHI results for the clinical development for prevention of PMO of new estrogen plus progestin drug products, for example, vis a vis endpoints, doses studied, among others.

3. Broadly, further discussion and recommendations regarding FDA regulation of estrogen

plus progestin products for the prevention and treatment of PMO.

As you will note, the issues for discussion focus on E + P drug products as Prempro was the subject of the arm of the WHI that was terminated for safety reasons. The Premarin alone arm continues at present as you will hear from Dr. Rossouw and others. While we do not wish to exclude totally any discussion of the E alone products or of other issues not directly addressed by the WHI Prempro study, we thought it best at least for the purposes of initial discussion within the context of the results of this landmark clinical trial. We fully expect the discussion to diverge and we welcome it wholeheartedly. Again, thank you to all for your attendance and we look forward to a simulating and informative day. I'll turn it back over to Dr. McClung.

CHAIRMAN McCLUNG: Thank you, Dr. Orloff. As is the custom for these meetings, input from the community at large is invited to occur. We will have presentations by six different speakers during the

open public hearing presentation and then a read comment from one of the major clinical societies. Other comments are available in information that's on the desk outside as well. Before inviting the first speaker though, let me read this comment regarding the Declaration of a Conflict of Interest from our public hearing speakers.

"Both the FDA and the public believe in a transparent process for information gathered in decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the open public hearing speakers, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance

at this meeting. Likewise, the FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking."

With that stated, let me invite the first of our open public hearing speakers, Dr. Marie Foegh from Berlex Laboratories.

DR. FOEGH: Good morning and thank you for giving me the opportunity to give a short presentation of what I think is exciting and at least to me surprisingly positive results of a study we have conducted. Also as you can see from my first slide, I represent Berlex Laboratories and I'm an employee of Berlex Laboratories. In my short presentation, I'll give a short background and then present some of the data from the study, not all, in the short timeframe, a conclusion and some slides that brings some source that we have.

I think most of you are aware of the great

importance of preventing bone loss in post menopausal women. Certain women beyond 50 years of age have osteopenia or osteoporosis and about 14 million women have osteoporosis of the hip which results in many women in fracture. Fracture may sound simple but it may heal. But we all know in older women, this may be the beginning of the end. It's associated with a lot of disability and in many instances, death will follow.

I know we all have been used to saying hormone replacement therapy and replacement in many have been a wrong term, but if it ever were true, it may be true for osteoporosis because increased bone loss is really a lack of estrogen. What does it result in? You have osteoporosis, osteopenia and you have apoptosis of the osteocytes and so forth, but this is not a detailed scientific presentation. This is just the opening of making the statement that estrogen certainly would be a natural choice for treating osteoporosis.

We all know from the WHI study that the risks of using hormones seem bigger than we original

thought. It changed our thinking like the Chairman also said and the risk/benefit, but we also have to remember that the dose used in the WHI study may not be the lowest efficacious dose, but it is the most common used dose today. It's not unreasonably succinct that the risk may decline the lowering of dose.

What I'm showing you today will be efficacy of a dose that's 75 percent below a commonly used dose. This also actually affects the quality of life. I mean you decrease the estrogen side effects that is not life-threatening but not pleasant. It may be feasible to have your cake and eat it.

Berlex has sponsored a study on osteoporosis in women between the age of 60 to 80. UCSF was the coordinating center and you'll see some names that are familiar to the osteoporosis field and estrogen like Dr. Grady, Dr. Cummings and also on the investigator list, there are names familiar in this field.

This was a double-blind, randomized trial with 417 women that were as I said between the ages of

60 to 80 years and they all had an intact uterus. They were more than five years post menopausal and the entrance criteria was a z-score of more equal to 2.0. The estrogen dose was a weekly transdermal patch which delivers 0.014 mg of estradiol. That was tested against a placebo patch.

The goal was to increase estradiol just to 10-15 picogram per mL. This is a low level of estradiol because you may all know that women post menopausal have levels below 20 picogram per mL and nearly all men have actually levels about 20 picogram per mL which may come to a surprise to many that men have higher estradiol levels than post menopausal women.

All the women took calcium and vitamin D of reasonable doses and the study lasted for two years with follow-ups every four months. The primary endpoint was bone marrow density ("BMD") at lumbar spine. Another primary endpoint was endometrial safety. There was a series of secondary endpoints which I will show you some. The hip, of course, are bone markers and so on.

But let me focus on the lumbar spine. The blue represents the placebo group and the red represents the active arm, the estradiol group. You have the data at 12 and 24 months. As you can see, there's a 2.5 percent difference between placebo and the active arm at 24 months, a highly significant result of a P-value less than 0.001. This is very comparable to other estrogen and other compounds that SERMs use for treatment of prevention of osteoporosis.

To the hip, the results were also highly statistically significantly different both at 12 and 24 months. Again the blue is the placebo and there is as you can see an increasing bone loss and that is counteracted by the estrogen and again a highly significant difference of 1.5 percent at 24 months.

We also had a secondary endpoint of fractures. Of course we were aware that the study wasn't big enough to show any difference in fractures, but as you can see numerically at least there is a difference. There is four in the active arm and 10 fractures in the placebo arm. These are women with fractures. Some of those women had several fractures,

but this is women with fractures at any given time.

In August, most of you are aware that a study was published on what I would also call an ultra-low dose of estradiol. That was Dr. Prestwood and her collaborators. And Dr. Cummings, one of the investigators, pooled the data of these two ultra-low studies and the combined factors were that there were six fractures for the ultra-low and sixteen for placebo. This is statistically significantly different of a p-value of 0.4. This is really exciting because these are mainly osteopenic women and these are fractures that we are talking about. So it's very encouraging.

What were the adverse events? Here's adverse events we worry about namely, breast cancer, cardiovascular events. These are what they look like in this study which lasted for two years. We looked at all but what I've summarized here for you are the breast cancer and the cardiovascular. It was interesting when you glance over it. There is really no difference between the placebo and the active arm.

One interesting point is actually that we

did not have any venous thromboembolic events. If you go down to the bottomline, I thought it might be interesting also to see there were no deaths in this age group and the hospitalization was not statistically significantly different. It was 22 in one group and ten in the other.

This is the conclusion. You will notice that you haven't seen all the data. This is because I got my talk cut short yesterday. But of course I am willing to give the data if you ask. What we found is the prevention of bone loss in all the post menopausal women with this dose that is 75 percent lower than the normally used dose. It is safe for the endometrium. The study lasted for two years so for two years you do not need to use progestin. There was decrease in the bone markers and there was no difference in some of the normal estrogen related side effects like breast tenderness, headache. If you look at the bottom, there was also no difference in lipids, sex hormone binding globin ("SHBG") or C-reactive protein ("CR-P") between the two groups.

So we really think that this effect of

this ultra-low dose is kind of a paradigm shift in the risk-benefit of the hormone use. We showed that it seems that you would be able to get a fracture reduction in osteopenic patients. You can give anapost estrogen at this dose for up to two years. We do not know what happens after two years. The adverse event profile is similar to placebo. We have no increase in the vasomotor symptoms. We don't share of course bisphosphonates effects because we are transdermal products. Thank you so much for your attention.

CHAIRMAN McCLUNG: Thank you. Are there questions or comments? If not, thank you very much. The second presenter will be Susan Wysocki who is the President and CEO of National Association of Nurse Practitioners in Women's Health. If she's not here, we'll come back to that point in a moment. Next, let me invite Dr. David Archer, who will speak on behalf of the American Society for Reproductive Medicine ("ASRM"). Dr. Archer.

DR. ARCHER: Thank you very much, Dr. McClung. Good morning, ladies and gentlemen. It's a

pleasure to be with you this morning in Washington although it's a little brisk outside. I represent the American Society for Reproductive Medicine and myself at this meeting.

Both AMRM is composed of physicians and I am a physician. As such, we've been involved in medical education and clinical trials for many years. Because of this, both of us have received grants, funds, clinical research dollars from I would say every pharmaceutical company in the United States that makes a hormone preparation for menopausal women. That is my disclaimer in terms of our conflict of interest. I am expecting that ASRM will reimburse me for my expenses so I am not here as representing a pharmaceutical company.

Currently I am a professor of obstetrics and gynecology at the Eastern Virginia Medical School. I'm an obstetrician/gynecologist with advanced certification in reproduction endocrinology. The ASRM is really pleased to be a partner with the FDA in terms of its campaign for educating women as they consider hormone therapy for post menopausal symptoms.

However, we all are concerned with the fact that media publicity has resulted in symptomatic women who could benefit from hormone replacement therapy by using approved and appropriate therapy for the relief of symptoms.

We know that hormone therapy improves symptoms and the quality of life for these women. I think we're all concerned that the media has characterized hormone therapy as harmful to women, particularly in cardiovascular disease and breast cancer. I believe the scientific community and physicians realize that the relative risk numbers are often high, but the attributable risks in the community is a different issue.

Young women between the ages of 45 to 55 who are peri or post menopausal and are symptomatic are a different class of women than those reported in the WHI. These younger women are good health. They are not at apparently increased risk of cardiovascular disease with the use of hormone therapy. The current final report from the WHI in July of this year really did not find overall an increase in coronary heart

disease in women receiving hormone therapy. We do acknowledge that there was an increase in coronary heart disease in the first year of use but again point out that the average age of women in this study was 63, significantly older than the 50 year old woman that we frequently see in our practices.

As some example for this risk, if you log on to the American Heart Association website, www.americanheart.org and use the Framingham risk factor for the identification of heart disease risk in a 55 year old woman who has a mild elevation in her total cholesterol level, her actual attributable risk are her risks of developing heart disease in the next ten years is less than one percent. So we would submit that there is very low risk for these women who are younger and in good health of developing significant adverse events particularly those related to the cardiovascular system.

We feel that this underscores the fact that consumers really apply the results of what's published in the media to themselves inappropriately. Anecdotally as I've said to other people, I've had a

47 year old woman consider hormone therapy be concerned over the fact that she might develop Alzheimer's disease in the next several years. So that all of us take the sound byte from the media and apply it to our particular lifestyle.

Now we all know that breast cancer is a significant issue for women. However in the WHI, women who had never used hormone therapy and entered this trial and were randomized were not found to have a significant increase in the occurrence of breast cancer during the five years of the clinical trial. Only in those women who had previously used hormone therapy was there an apparent increase in the incidence of breast cancer.

So the average age of the woman 50 to 55 who is symptomatic and requests treatment is really not at a particularly increased incidence of breast cancer from the use of hormone therapy using the relative hazard published in the WHI. I might also point out that the most important risk factor for breast cancer from numerous publications is that of age itself.

Now as I pointed out in this anecdotal case which as I realize is inappropriate in front of an August body such as this dealing in large numbers that the issue of cognition in Alzheimer's disease really need to be clarified for the consumer. The WHI memory study showed an increase in the occurrence of cognitive decline in Alzheimer's or probable Alzheimer's disease after approximately two years of hormone therapy. However it should be pointed out which is not pointed out for many of the consumers that this study occurred in women who were over the age of 65. So the relevance of this finding to younger women is at present unknown.

I'm not cognitively impaired. I just need my helper right here in front of me. So it's obvious for the younger symptomatic woman who is complaining of hot flashes, night sweats, difficulty sleeping, mood fluctuations and vulvo-vaginal atrophy that the message that we should deliver as physicians to this group of patients is that hormone therapy can relieve these symptoms without resulting in significant mortality or morbidity in terms of its outcome.

I believe that this message is important for women who may or may not have risk factors for bone loss. Current data from the WHI and other publications indicate that standard and lower doses of estrogen with progestin or estrogen alone prevent bone loss in post menopausal women. This is based on the findings with DXA scanning and this group of individuals are duel-energy X-ray absorptiometry.

The WHI recent publication allows us to I think unequivocally conclude that estrogen plus progestin reduces the incidence of fracture of the hip, spine or vertebral body and wrist in all the subgroups of post menopausal women. We believe that these data provide a compelling reason to initiate hormone therapy for the prevention of bone loss and fractures in post menopausal women. The position of the ASRM therefore is supportive of the use of hormone therapy in post menopausal women with the understanding that this use is based on the patient's unique risk/benefit profile. I want to thank you very much for allowing me to make this presentation this morning.

CHAIRMAN McCLUNG: Thank you, Dr. Archer. Comments or questions? Thank you very much. Our next speaker is Dr. Omega Silva, the past President of the American Medical Women's Association ("AMWA").

DR. SILVA: I am Dr. Omega Silva, Endocrinologist and Past President of the American Medical Women's Association. I appreciate the opportunity to present AMWA's views on the implications of the WHI for the use of hormone therapy with estrogen and progestin as a second line drug in the prevention and treatment of post menopausal osteoporosis in women.

Founded in 1915, AMWA is an organization of 10,000 women physicians and medical students dedicated to serving as the unique voice for women's health and the advancement of women in medicine. AMWA supports the current FDA approved indications for hormone therapy. Hormone therapy is the most effective FDA approved treatment for menopausal symptoms such as hot flashes, night sweats and vulva and vaginal atrophy. Hormone therapy is also indicated for the prevention of post menopausal

osteoporosis. AMWA is proud to be a partner in FDA's menopause and hormones information campaign which provides women with important information about hormone therapy.

As physicians, our role is to review a patient's family and medical history and assess the risks and benefits of hormone therapy for that individual. We can help our patients by putting the risks into proper perspective. While hormone therapy may not be appropriate for one woman, it may be entirely appropriate for another.

With regard to osteoporosis, AMWA recognizes the enormous impact of the disease on the health of Americans, particularly women. The disease causes over 1.5 million fractures yearly at a cost of $17 billion. Following osteoporoic hip fracture, there is an excess mortality of 12 to 20 percent. Hip fracture is the second leading cause of admission to nursing homes for women.

Osteoporosis causes severe and unrelenting bone pain. It is one of the major debilitating disorders that contribute to the loss of functional

independence and quality of life in older women as noted in AMWA's position paper on osteoporosis.

To prevent osteoporosis, AMWA members recommend weight-bearing exercise, adequate calcium and vitamin D intake and the maintenance of a healthy life style. In addition, medications to prevent further bone loss may be indicated. Women who think they are at risk of developing osteoporosis should consult their physicians. Treatment plans should be initiated as early as possible because once bone is lost it's difficult to replace as noted in AMWA's osteoporosis question and answer fact sheet.

The recent study in the October 1, 2003 issue of the Journal of the American Medical Association ("JAMA") demonstrated that estrogen plus progestin increased bone mineral density and reduces the risk of all fractures in healthy post menopausal women. This decreased risk of fracture appears to be present in all subgroups of women examined. When considering effects of hormone therapy on other important disease outcomes in a global index developed by the WHI investigators, the study authors concluded

that there was net benefit of hormone therapy even in women considered to be at high risk of fracture.

On this point, AMWA notes that the global index is based on selected risks and selected benefits and not on all risks and all benefits. For example, it includes hip fractures but not for tibial fractures or menopausal symptoms, the primary reason women take hormone therapy. For some women, the risk/benefit equation might change when relief from post menopausal symptoms and prevention of tibial fractures are taken into account.

AMWA agrees with the current FDA approved labeling for hormone therapy, Prempro, which states that when prescribing solely for the prevention of post menopausal osteoporosis therapy should be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. If hormone therapy is prescribed, it should be taken at the lowest possible dose for the shortest duration of time to meet treatment goals.

The WHI results have reinforced what

physicians have known all along. Treatment decisions should be individualized. For this reason, it is extremely important for FDA to preserve physician and patient choice of therapeutic agents to prevent and treat osteoporosis. Hormone therapy remains an important option for those women at risk of osteoporosis who are unable to take non-estrogen medications.

On behalf of AMWA, I thank you for the opportunity to testify before the Committee. I have no problems with getting money from this person or that person because nobody gives me any. Now I would like to become a patient. How much time do I have? A few minutes.

Now I would like to become a patient and give you a personal scenario. I'm 66 years old and follow the textbook version of peri-menopause and menopause and post menopausal symptoms, getting those first little nasty hot flashes at age 45, becoming a post menopausal woman at 50.5. When I was 45, the data on the benefits and risks were very sparse, but became better when I was about 52 or 53. So I began

HRT and continued until May 30, 2003. At that point I said after the WHI results, "Well, maybe I can do without this HRT now." Within a week, those nasty little hot flashes returned. My husband said "For crying out loud, you're hot one minute and cold the next." Sleeping was a ritual of getting up and turning my pillow over on the cool side.

Now I was going on an Alaskan cruise in September. So I said "I'll be damned if I'm going to sweat and hot flash myself through this cruise." There was no breast cancer in my family. My aunts on my mother's side lived to be 90 plus. One just died of pneumonia at age 100. My mother did die of cerebral hemorrhage but she had no thromboembolic events. My father at age 94 just had colon cancer. Therefore, I weighed by personal risks and benefits and restarted my HRT and enjoyed my cruise and life thereafter. Many of you men may not understand and I wouldn't wish prostate cancer on any of you but if you do get it and you have to take those anti-testosterone therapies, you may feel some of these hot flashes and then you'll know what the women go through. Thank

you.

CHAIRMAN McCLUNG: Thank you, Dr. Silva. Questions or comments? Great. Thank you. Next let me invite Dr. Jim Simon who is the current President of the North American Menopause Society to deliver his remarks. Dr. Simon.

DR. SIMON: Dr. McClung, members and guests of the Committee, I would like to suggest that perhaps everyone can go home early today since today's Washington Post seems to have published a short article saying "The whole issue has already been settled." Page F-2 in today's Washington Post, it's interesting reading.

Today I need to give the following personal introduction. I'm a clinical professional of obstetrics and gynecology at George Washington University here in Washington. I am also President and CEO of a independent investigative research site that works with literally the entire pharmaceutical industry since its inception. So I potentially have conflicts as mentioned by Dr. Archer. However today and uncharacteristically of me as a person for those

of you who know me which most of the people do, I'm going to stick closely to the script provided to me by my colleagues at the North American Menopause Society and will be uncharacteristically short and non-controversial.

I would like to focus attention on the estrogen and progestin use in peri menopausal and post menopausal women position statement published by the North American Menopause Society on September 17, 2003. All the Committee members have a copy. This position statement represents a significant amount of work by a smattering of true experts on this subject from around the world including five individuals who are WHI investigators. Many of them also HERS ("Hysterectomy Educational Resources and Services") and WHIMS ("Women's Health Initiative Memory Study") investigators, and including Dr. Stefanick who is a member of this Committee. The information is available to you in this publication. For those who don't have a copy, on the web at www.menopause.org. It is an update of a former position statement from last year.

I want to focus attention only on a couple of major points and leave it to the Committee to use this learned piece of work some 14 pages with appropriate references for their own purposes. Under areas for which there was consensus on the Committee, there is definitive evidence for estrogen-progestin therapies efficacy in reducing the risk of post menopausal osteoporoic fracture. There is today no comparable evidence for estrogen therapy. Many estrogen-progestin therapies and estrogen therapy products are Government, that is FDA, approved for prevention of post menopausal osteoporosis through all term treatment.

Because of the potential risk associated with hormone therapy for women who require a drug therapy for osteoporosis risk reduction including women at high risk of fracture within the next five to ten years, alternatives to hormone therapy should also be considered weighing the risks and benefits of each. Recognition should be given to the fact that there are no published data on osteoporosis drug therapies beyond seven years.

The effects of hormone therapy on the risk of breast cancer and osteoporoic fracture in symptomatic peri-menopausal women have not been established in randomized clinical trials ("RCT"). The findings from trials in different populations, for example, the WHI, should therefore be extrapolated with caution. There is however no evidence that symptomatic women differ from asymptomatic women in either cancer or bone outcomes.

Premature menopause and premature ovarian failure are conditions associated with earlier onset of osteoporosis and cardiovascular disease, but there's no clear data as to whether estrogen therapy or estrogen-progestin therapy will reduce morbidity or mortality from these conditions. The benefits/risks ratio may be more favorable for younger women.

There were also some areas where there were no consensus that could be reached by this Committee. However there were no areas of non-consensus vis a vis osteoporosis. I would say with my personal hat on and not my North American Menopause Society hat on and they are paying for my parking

today that I would ask the Committee in their deliberations to try very hard not to further limit access to therapies this and any other so that we working in the trenches may exercise clinical judgment in the care of our patients one patient at a time. Thank you.

CHAIRMAN McCLUNG: Thank you, Dr. Simon. Questions or comments? Let me invite then Amy Allina who is the Program Director for the National Women's Health Network who will be our next speaker.

MS. ALLINA: Thank you. I am Amy Allina, the Program Director of the National Women's Health Network ("Network"). The Network is a non-profit organization that works to improve the health of all women by developing and promoting a critical analysis of health issues to influence public policy and to support consumer decision making. We accept no financial support from pharmaceutical or medical device companies. We're supported by a national membership of about 8,000 individuals and 300 organizations.

As many of you here today are aware the

Network has a long history of advocacy and consumer education on the issue of hormone therapy for women at menopause. We've spoken at numerous FDA Advisory Committee meetings on the topic over the last 15 years. We were leading advocates calling on the NIH to conduct the WHI so that women would have well founded scientific research to guide their decision making about the use of hormone therapy. We've produced extensive health education materials for women who are considering this therapy and we are also a partner with the FDA in the patient education campaign that was recently announced by Dr. McClellan.

Though we understand the perspective of the many researchers and clinicians and even some women who were disappointed with the findings of the WHI. We are really pleased that there's finally data from a large long-term RCT of hormone therapy for healthy women. Hormone therapy has been prescribed to women for decades without this data to back it up. Though the WHI results leaves some women with new questions about what's best for their health, we believe it's better to know what these questions are

than to make healthcare decisions based on unproven and false assumptions. We're also pleased to be able to speak here today and thank the FDA for the opportunity to give input on the implications of the WHI results for FDA regulation of estrogen plus progestin drug products, specifically regarding long-term use of the products for prevention and treatment of PMO.

We'd like to start by commending the Agency for acting quickly to work with sponsors on a revision of the prescribing information that accompanies Prempro and other estrogen plus progestin products that are approved for prevention of osteoporosis and for identifying it as a second line option for this purpose. Although the WHI results that were released were based only on the study of women using Prempro, FDA acted based on its recognition that other estrogen and estrogen plus progestin products work in similar ways and asked for revisions on other product labels. We agree and we believe it's important for women using those products to have information about the benefits and risks

identified by the WHI.

In thinking about the implications of the WHI results for future regulatory decisions, there are a lot of important questions about study design that the Agency is going to have to grapple with and that all of you will have to grapple with. In considering the conduct of trials or approval of an estrogen plus progestin drug product for the prevention and treatment of PMO, how many women need to be studied? How long do they have to be studied? Are there surrogate safety endpoints that the Agency can accept?

Historically approval's been based on studies of three year duration or in some cases with less, but we know that the risks of Prempro didn't emerge within that timeframe, at least with respect to breast cancer. Given the knowledge we know have about the serious health risks with estrogen plus progestin products that emerged after six years, we believe FDA cannot approve similar drugs for long-term use without requiring that they studied for that length of time. An interim exception might be made for products containing only estrogen since the arm of WHI studying

estrogen alone is on-going. Until those data are collected and analyzed, it's not known whether all the same risks will apply to those drug products.

Regarding surrogate endpoints, the WHI has shown that the surrogates that have been used in the past for cardiovascular disease were not predictive. Given what's now known about the increased risk of cardiovascular disease associated with long-term use of estrogen plus progestin drug products, surrogate safety points really aren't acceptable.

Finally, I wanted to address some of the points that were brought up in materials that Wyeth Pharmaceuticals prepared for today's meeting and that we've heard echoed in messages from a couple of other groups speaking today regarding the factors that they believe limit the interpretation or generalize ability of the WHI results. Wyeth wrote that the WHI recruited women of relatively old age in comparison to the onset of menopause and therefore that the risks associated with hormone therapy can be expected to be substantially lower than those observed in the WHI. We just wanted to emphasize - I'm sure that this point

will be brought up by the presentation from the WHI - that a third of the women in the study, the total of 5,702, were in their 50s. This is the largest RCT ever done of women in this age group.

The company also wrote that because the WHI excluded women with severe menopausal symptoms, it was examining a population that was not representative of the women for whom the product is principally indicated. In fact at the start of the trial, 12 percent of the women enrolled reported experiencing moderate to severe hot flashes or night sweats and more over, research conducted among women who were taking hormones prior to the release of the WHI result has shown that only a minority said they said taking hormones because of hot flashes.

The company also suggested that the study population wasn't representative of women for whom the product is indicated because it included a number of participants who were overweight, past or current smokers and being treated for high cholesterol, high blood pressure and diabetes. These conditions are common in the general population and like most people

who enroll in clinical trials designed to study disease prevention, the women in the WHI were probably healthier than the general population due to the healthy volunteer effect. This supposition is supported by the fact that the rates of cardiovascular disease while increased in the treatment arm were lower in both the estrogen plus progestin group and the placebo group than they are in the general population.

So in conclusion, I just want to thank the FDA again for acting promptly and responsibly when the WHI results were released and to encourage a similar approach as the Agency moves forward to consider future research and product approvals. While it is important to be clear and specific about the regimen that was studied in the WHI and the regimens for which we will have data in the future, it's also important to build on the knowledge that the trial has given us and to act based on that. Thank you.

CHAIRMAN McCLUNG: Thank you for your comments. Let me invite again Ms. Susan Wysocki if she's in the audience. If not, let me proceed and ask

Ms. Spell-LeSane if she will read into the record the comment from the American College of Obstetrics and Gynecology.

SECRETARY SPELL-LeSANE: Statement of the American College of Obstetrics and Gynecology ("ACOG") on Hormone Therapy for the Prevention and Treatment of Post Menopausal Osteoporosis for the FDA Endocrinologic and Metabolic Drugs Advisory Committee. The ACOG representing over 45,000 healthcare professionals dedicated to women's health is pleased to offer this statement to the U.S. Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee on the use of hormone therapy for the prevention and treatment of PMO in women.

Last week Cauley, et al., published an updated final analysis of fracture endpoints in WHI RCT. They found that use of conjugated equine estrogen ("CEE") 0.625 mg per day and MPA 2.5 mg per day reduced the risk of hip fracture by 33 percent, hazard ratio 0.67, nominal 95 percent confidence interval 0.47 to 0.96. Subgroup analysis showed that use of estrogen plus progestin resulted in a

statistically significant reduced risk of hip fracture in women who had experienced menopause at least 20 years previously, who had a body mass index ("BMI") of less than 25, who had at least two falls in the past year, who reported a daily calcium intake of at least 12,000 mg per day, who had no history of fracture, who had used hormone therapy for either less than five or at least ten years. Similarly hormone therapy also reduced the risk of total fractures by 24 percent, hazard ratio 0.76, confidence interval 0.69 to 0.83.

Benefits were seen in bone mineral density ("BMD") as well. The change in BMD from baseline was higher in hormone users in both hip and spine and at every interval of follow-up reported. After three years, the percentage difference was 4.5 percent for lumbar spine and 3.6 percent for total hip. This final analysis confirms that previously reported data from the WHI which demonstrates that estrogen plus progestin is protective against both fractures and loss of BMD. It is concordant as well with a wealth of other RCT and observational studies.

The evidence is strong and consistent.

Use of CEE and MPA helps prevent osteoporosis by slowing bone loss and is valuable in treating this condition as well. The WHI report however calculate a global index to quantify overall benefit versus risk of estrogen-progestin therapy. Because Cauley, et al., calculated the global index hazard ratio to range from 1.23 to 1.03 depending on a woman's risk of fracture, they concluded that there was no evidence of a net benefit and recommended that treatment with estrogen plus progestin not be used for prevention and treatment of osteoporosis in women without vasomotor symptoms.

We cannot agree with this global index approach because we believe it is to be biased. In our analysis of original WHI data on BMD and fractures, ACOG offered the following guidance:

"1. The decision about use of hormone therapy requires evaluation of the risks and benefits for each individual woman.

2. For women currently using hormone therapy, it is important to assess their reasons for using and to evaluate potential risks, benefits and

alternatives.

3. For patients with osteoporosis, other preventive therapies such as bisphosphonates and selective estrogen receptor modulators are available.

4. For women at risk of osteoporosis who have vasomotor symptoms, hormone therapy can be of benefit.

5. Periodic reassessment of the need for hormone therapy is recommended at least at every annual visit or more frequently if indicated."

We continue to support the judicious individualized use of estrogen and progestin for bone protection and believe that it is inappropriate to withhold this treatment option from those who need it and would benefit from it. While we noted that there are other agents approved for prevention and treatment of osteoporosis, each of these agents has its own contrary indications and side effects. Some actually increase hot flashes and they would not be a choice of women with vasomotor symptoms.

In offering the global index hazard ratio, the WHI investigators attempted to estimate overall

benefit versus risk. Although this concept is potentially useful from a public policy perspective, it falls short as guidance for care of individual patients. Ultimately this weighing of benefits and risks must be done by each individual physician with each individual patient.

ACOG continues to educate its fellows and their patients on the current understanding of benefits and risks of hormone therapy and participated with the FDA in its recently launched menopausal hormone therapy educational campaign. We look forward for continuing to work with the FDA on this issue. Isaac Schiff, M.D., Chair, ACOG Task Force on Hormone Therapy, Stanley Zinberg, M.D., Vice President, Practice Activities.

CHAIRMAN McCLUNG: Thank you. And I would like to thank all of the speakers for their comments and critique this morning to help set the stage for our subsequent discussion. I'm going to turn and invite Dr. Eric Colman who is the Team Leader for the Osteoporosis Drugs of the Division of the Endocrinologic and Metabolic Drugs of the FDA to

review the criteria for the effectiveness and safety in the evaluation of osteoporosis drug products and specifically as it applies to the estrogen-containing compounds. Dr. Colman.

DR. COLMAN: Thank you, Mr. McClung. What I wanted to start with is just an outline of what I'll be talking about for the next 15 minutes or so beginning with some terminology that I'll be showing you and then move into a brief regulatory history of the estrogens and the estrogen plus progestin and then show you the actual products that are currently approved for the prevention of PMO. Finally, I show you some parts of the labeling that have been changed in response to the Prempro arm of WHI.

You will see that estrogen is denoted as "E" and progestin "P". Estrogen plus progestin is "E + P". Conjugated equine estrogens is frequently abbreviated "CEE". Medroxyprogesterone acetate is "MPA". Those two compounds together comprise Prempro and Premphase. The standard post menopausal osteoporosis "PMO". Bone mineral density "BMD". And randomized control trials "RCT".

The regulatory history of estrogens dates back to 1942. This was when the Agency approved CEE or Premarin for menopausal symptoms. It was then roughly 30 years later when the labeling for estrogen said they were probably effective for selective cases of osteoporosis. This was a designation that came by way of a process called "DESI" which stands for Drug Efficacy Study Implementation. The National Academy of Sciences was contracted and they put together some experts. They looked at the available literature on estrogens and bone. The best they could come up with was a phrase saying "Estrogens are probably effective for select cases of osteoporosis." That's the way that stood for years.

In 1986, that was updated to read "Estrogens are effective therapy for osteoporosis." Throughout the 1990s, the labeling for these products used the words "management and prevention". There was a certain amount of confusion over what the word "management" meant to a lot of people. So we thought the best way to handle that was to take it out. Most recently, we have taken out the word "management" and

the labeling now simply reads "prevention of osteoporosis". I'd also mention that all of these labeling claims are based on data related to bone density and not to fracture data.

Prempro CEE/MPA was approved for the prevention of osteoporosis in 1994. It was a somewhat of an usual approval in that Premarin CEE was already approved for the prevention of PMO, the same dose 0.625. The reasoning was we have the same dose of estrogen. We're adding a progestin. At that time, some people felt that there was evidence that progestins had their own independent positive effect on bone density. The feeling was if we have a progestin that has a positive effect on bone, maybe we can lower the dose of estrogen, avoid some of the known estrogen adverse effects but still end up with a positive overall effect on bone density.

Prempro was approved in 1994 for osteoporosis. At the same time, Wyeth agreed to do a post approval study looking at lower doses of Prempro and Premarin with BMD as the primary outcome. That study has been published. It's referred to as the

"HOPE" trial. In fact, the data from that trial are the basis of the recent approval of lower doses of Prempro and Premarin, doses lower than what was used in WHI. Again those are BMD data. I will mention that again in a second.

The other thing that happened in 1994 was the Agency updated its osteoporosis guidance. The guidance had separated out estrogens from non-estrogens. As far as the estrogens were concerned, there was a statement there that said "The epidemiologic data are sufficient to conclude that estrogens reduce the risk for osteoporoic fracture." That's somewhat unusual in that the Agency took a position that epidemiologic data were sufficient to conclude a fracture benefit of estrogens. That's what was in the guidance.

Subsequently no company other than one tried to get a treatment indication which would mean a fracture indication for an estrogen or E + P. From that day on, we have been dealing primarily with prevention of PMO for estrogens. For a company to get a prevention of PMO indication, they had to do a two

year trial with lumbar spine BMD as a primary endpoint and they had to compare their drug again to placebo and show that their drug led to a statistically significant increase over placebo.

Just briefly to recap, the E and E + P products approved for the prevention of PMO, the approval came about in general through one of two mechanisms. The older products were just designated as a DESI drug or the company had to do a two-year randomized placebo controlled trial with lumbar spine as a primary endpoint. In general, the women in these trials had normal or osteopenic bone density at baseline. By and large, the trial sizes were less than 500 women.

I'd like to show you this just as a point of reference. This outlines the requirements for approval of the non-estrogens. This would be, for example, alendronate (Fosamax, Actinal (risedronate) and in fact, even SERM raloxifene. Here you will see where treatment becomes synonymous with fracture reduction and prevention, synonymous with BMD. For a non-estrogen to gain a treatment indication, the

company had to do a three year RCT demonstrating that their drug significantly reduced the risk of vertebral fracture relative to placebo.

Once that was done and the company wanted a prevention of PMO indication like with estrogens, they had to do a two year trial looking at lumbar spine BMD. That was the same as it was with the estrogens. On top of that, they had to have a large favorable preclinical profile for the drug and the clinical development program for these compounds in the last eight years have been quite large, anywhere from 5,000 to 15,000 trial subjects.

As of today, there are several E + P products approved for the prevention of PMO again based on BMD. There are no E + P products approved for the treatment of PMO, again treatment synonymous with fracture efficacy which I basically said at the bottom of this slide.

The next two slides I want to show you the actual E and E + P products that are approved for PMO. This slide shows you Prempro and Premarin. You will notice that I have shown four doses in yellow. You

recall that the 0.625 to 2.5 dose of Prempro was what was used in WHI. Fairly recently, the Agency has approved the lower doses of 0.45, 0.3, and 1.5 Prempro for the prevention of PMO. Again those come from BMD data from the study that Wyeth agreed to do back in 1994. So it's referred to as the HOPE trial.

The lower doses of Premarin were also studied in that trial. Again those data form the basis for the recent approval of two lower doses of Premarin. They are all based on BMD.

This slide shows you the other products that are approved. You will notice that there are different estrogen compounds here. There are two different progestin compounds. There are several different doses. You will also notice at the bottom there are two patches to transdermal preparations. So there are a host of different E and E + P products currently available, all limited to BMD data in fairly small trials, but they do offer some difference in the composition of the estrogen and the progestin, the doses and the delivery system through two transdermal.

To summarize, there are several E + P

products in addition to Prempro that are approved for the prevention of PMO. There are no E + P products approved for the treatment, treatment again synonymous with fracture reduction. This is somewhat ironic. WHI now provides strong evidence that E + P reduces the risk for osteoporoic fracture including the hip.

My last bullet is taken verbatim from last week's WHI Fracture paper that was published in JAMA where the authors concluded that there was "...no net benefit, even in women considered to be at high risk of fracture." Of course if you look at the global index, the women who had the highest baseline risk, their global index was getting pretty close to one. The global index does not include vertebral fractures so those components obviously will lead to I would think some discussions about "Is there possibility a subgroup who might benefit particularly with lower doses" but that's more hypothetical.

Let me move on the labeling changes at this point. I want to show you all the labeling changes. The labeling changes that I'll show you I've highlighted three sections, but the changes that have

been made to Prempro and Premarin. All manufacturers of E and E + P had been requested to make the same changes. I don't know where we stand in terms of getting the responses back but letters have been sent to those individuals saying "You need to make these changes as well even though you're a transdermal, even though you're a different preparation."

Let's go to the black box warning. This is a little tedious because I've copied a lot here. The black box warning is the first portion of the label on the Prempro label. The first thing it says is "Estrogens and progestins should not be used for the prevention of cardiovascular disease. The Women's Health Initiative study reported increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in post menopausal women during five years of treatment with CEE combined with MPA."

This gets to the other doses and other products. "Other doses of conjugated estrogens and medroxyprogesterone acetate and other combinations of estrogens and progestins were not studied in the WHI.

In the absence of comparable data, these risks should be assumed to be similar." That is the approach that the Agency has taken thus far. If you don't have data to prove you're different, you're going to be assumed to be the same.

"Because of these risks, estrogens with or without progestin should be prescribed at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman." It sounds very logical.

Now the indications and usage section, the first two indications, the first has to do with vasomotor symptoms. The second has to do with vulvovaginal atrophy. Those are two of the three continuing indications for this product. The third indication is a prevention of PMO which now reads "When prescribing solely for the prevention of post menopausal osteoporosis, therapy only should be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered." This is suggesting that this should be a second line agent or you should have real

good reason to use this over other products already out there.

Finally, the dosage and administration, some more wording that we've seen before. "Use of estrogens alone in combination with progestin should be limited to the shortest duration consistent with treatment goals and risks. Patients should be reevaluated periodically as clinically necessary." The top portion here is more about the osteoporosis. At the bottom, it says "Patients should be treated with the lowest effective dose. Generally women should be started at 0.3, 1.5 Prempro." Again this is a recently approved dose. "Dosage may be adjusted depending on the individual, clinical and bone mineral density responses. This dose should be periodically reassessed by the healthcare provider."

That concludes the basis of my presentation. I just want to leave you with some issues we hope will be the focus of today's Committee discussion. Some of these issues Dr. Orloff mentioned earlier. I just want to reiterate those. At the end of the day when all is said and done, we're going to

ask the Committee to comment on the revisions made thus far to the Prempro labeling keeping in mind that these changes have been made to the whole class of E and E + P. It's not simply Prempro. We also will ask you to discuss the implications of the WHI trial results for the future development, testing and potential approval of E + P drug products for the prevention and/or treatment of PMO.

Again I told you that currently it takes two years of BMD data to get prevention indication. You can do that with well under 500 women. We now have fairly good fracture data from WHI which if the balances were a little bit more favorable then it's possible that this Prempro would have a treatment indication now because we do have good fracture data now. There are some things to think about. How big a trial should people undertake? What should the endpoints be? Should they require to show fracture?

Finally it's just a very open-ended question for you to provide other comments or recommendations related to the WHI trial or to regulation of E + P products for the prevention and/or

treatment of PMO. Thank you.

CHAIRMAN McCLUNG: Thank you, Dr. Colman. We'll have our discussion about that during the discussion section but let me invite the Committee members if there are specific questions to address to Dr. Colman to clarify issues.

DR. FOLLMAN: Yes. I had one question. You said in the early 1990s you switched from using or thinking you should use fractures as an endpoint in your studies to using bone mineral density and the reason for this was given on the basis I assume strong epidemiologic data. When you went through that, was consideration given of the minimally effective bone mineral density difference between the two groups? I'm thinking perhaps that you could end up with a statistically significant change between placebo and a hormone replacement therapy that wouldn't really be large enough to reduce the fracture risk. So I just wanted to know when you made the change, was consideration given to that issue?

DR. COLMAN: Luckily, people were still studying doses that were what we would perhaps

consider too high now, but back then they were the standard doses. We didn't see a situation where after two years of study there was a half or a one percent difference between drug and placebo, but it was powered to the point where you could still get statistical significance. We did not put an absolute minimum on the difference.

DR. SCHADE: Just for clarification, you mentioned this approach using DESI, a term that I hadn't heard before. Is that something that's still used by the Agency or is that just historic?

DR. COLMAN: That's historic. It was done around 1962 because up to that point, drugs approved by the Agency, they only had to show some kind of rudimentary safety. People thought we have to look and see how efficacious they are. So the Agency actually contracted with the National Academy of Sciences to look at hundreds of drugs. They put together groups by discipline to review the drugs and review whatever literature out there that was on the efficacy of the drug. That's how they came up with these classifications, probably effective/ineffective.

It's an old classification scheme back in the 1960s.

DR. LUKERT: If I could just take advantage of gray hair to amplify Dr. Colman's comment about the response to the question about why estrogens were considered approvable for osteoporosis prevention or treatment on the basis of bone density whereas the drugs that were in newer classes of the time of the guidance were not, the estrogens were not at all suspected of having any effect on bone quality that would disrupt the relationship between bone mass and bone strength. Whereas concerns had arisen about, for example, fluoride. So the drugs that were unphysiologic, if you want to put it that way, were held to a higher standard when we developed those concepts, but estrogen wasn't considered to be in the same situation at all. But again, no specific magnitude could be identified.

CHAIRMAN McCLUNG: Other comments for Dr. Colman or questions? Thank you very much. We now turn to the presentation by representatives from the Women's Health Initiative and let me first thank Dr. Rossouw and the team of people he's put together to

allow this to happen. There's an integrated set of presentations that will happen, some before and others after the break. Let me propose to the Committee that we listen to the entire set of presentations and then we'll have time for questions, queries and discussion with the WHI individuals after that. Let me first introduce Dr. Jacques Rossouw to lead off the discussion from the Women's Health Initiative Investigators Group.

DR. ROSSOUW: Thank you. My job is to set the scene for my colleagues who will give us some detail. What I want to put before the panel is the reasons why NIH did this study, why this particular drug was chosen for the study, why this particular population was chosen for the study and the snapshot of the baseline characteristics of that study population to set the scene for my colleagues who will discuss the trial design, the results and some interpretation of the data.

The trial that we're going to be discussing of the WHI is part of a larger entity. There are also in that WHI trials of dietary

modification to look at whether there's reduction in certain cancers and calcium/vitamin D aimed at fracture reduction and a very large observational study. There are two trials of hormones as was here. We're going to talk about the estrogen plus progestin trial alone. The study is conducted in 40 clinical centers across the country and a coordinating center.

Now the issue of why did NIH do this study is best addressed by looking at the state of knowledge in the early 1990s when this trial was designed. I'm going to try and illustrate that with this rather complex slide, but I just want to point out a few details here. The blue line represents the prescriptions in millions of estrogens over time starting in 1960 and the black line the prescriptions of progestins over time.

As we've heard the use of estrogen to treat menopausal symptoms was approved way back in 1942, but the uptake of estrogen in the general population wasn't that big until the 1960s when there was a huge increase. It's interesting that the increase occurred in the face of rather negative news

on the scientific front. By that time, we knew that oral contraceptives were associated with cardiovascular problems and conjugate equine estrogen in men in higher doses did not prevent, in fact, increased clots and heart attacks. But overwhelming that apparently was a popular conception to which Dr. Wilson's book, Feminine Forever, appeared to contribute that hormones were generally good for womenkind.

So the cells rose dramatically and then dipped in the mid 1970s when it became known that estrogen alone caused endometrial cancer by some observational data. It increased again when it became known that progestins could prevent that increased endometrial cancer. So in the 1980s we saw a rise now concomitantly with a rise in progestin prescriptions. In the 1980s, we also learned from observation studies that the benefits appeared to outweigh the risks. Estrogen use was associated with lower CHD ("coronary heart disease") risk and with a lower fracture risk. However it was also associated with a higher breast cancer risk. Because CHD is the predominant cause of

mortality and morbidity in older women, the benefits were thought to exceed the risks. At this point, NIH became interested in doing a trial to see whether the cardiovascular benefits indeed were real.

Now in 1991, this is when specific planning for WHI trials started. In 1991 that was also the era when evidence by medicine started dominating thinking in the scientific community and the era of large randomized controlled clinical trial. From the early 1990s then, a series of trials were launched. PEPI was the forerunner of WHI. The intermediate outcomes looked and generally found favorable results. And HERS was also planned, a second prevention trial. As we now know, that didn't have positive trials for CHD and WHI was planned. So from the early 1990s on, we started getting into a higher standard of evidence and WHI is part of that higher standard of evidence. That's what we're going to be talking about.

Now at the time when this study was being planned - I must also say there was as you see an increasing use of estrogen in that period of planning

- the interest in looking at hormones for preventing heart disease were based on a substantial body of data including small trials of the biological effects looking at surrogate markers such as lipids and bone density and that all looked very positive on average on some animal model data and on a large, growing body of epidemiological evidence such including some of the best studies ever done including cohort studies. But what was deficient was a large clinical trial with disease endpoints. That was our thinking in looking at whether this should be studies.

Now part of that background, you don't have to look at the details here. I just wanted to illustrate to you how large the evidence base is for thinking that estrogen only will prevent coronary heart disease. This is a review done by Barrett Connor and colleagues in 1998. Some of the cohort studies which are the higher quality studies were known at the time when WHI was being designed. All of these were known. If you summarize the data, there was about a 40 to 50 percent apparent reduction in risk associated with estrogen only use. That was the

primary source of evidence driving the need for the trial.

At the time that we were designing this trial, there was very little known about the use of combined hormones, estrogen plus progestin, and its association with CHD. Some studies emerged during the development of the study. Except for that one, these are all in the 90s. That was a small clinical trial. So there's very little known, but when the data came out, the relative risk was very similar on average to that which was found for estrogen only. That was our assumption going in that. If there was an estrogen only effect, we would probably find the same or maybe a slightly attenuated effect based on the lipid changes for estrogen plus progestin.

However, we were aware as you are that women who used hormone may differ in several characteristics from those that don't especially those that use over an extended period of time. Hormone users are generally less obese, less likely to smoke and to consume a high-fact or high-salt diet, more physically active and more highly educated. That came

out in some of these observational studies. They are also more likely to go to doctors more regularly and have health checks done and treated and some of our treatments actually work so that may have help prevent CHD and have mammograms and other screening. So there's a surveillance bias and a healthy user bias. They are also more compliant if women who use hormones for a long time, maybe more compliant in other ways and therefore have healthy lifestyle and other attributes that are not measured typically in observational studies. Of course the long-term hormone users, we have to remember, are the successful users. These are the folks who haven't had an adverse effect. So they are going to look pretty good compared to non-users on average.

The question was whether these differences could explain why hormone users appear to have a lower CHD risk. Is the CHD risk reduction real or is part of all of it due to these various biases?

Subsequent to WHI being launched, a substantial number of second prevention trials were published. Here are six of them. We don't have to

look at the detail. I just wanted to point out that the clinical outcomes of the secondary prevention trials. None of them showed any benefit for CHD or stroke. They either showed no benefit or no benefit and early harm. The secondary prevention hormone therapy whether it's E or E + P doesn't work and maybe harmful. That emerged while we were conducting the primary prevention trial.

The actual idea that NIH needed to do a trial of hormone therapy and CHD started in the mid 1980s and panels were brought together. Expert advice was sought. The outcome of that was that the PEPI trial was done as a forerunner. Generally hormone therapy was then regarded as a promising but unproven treatment intervention to prevent CHD. Against this background of increasing use by millions of healthy older women, it was of concern that the overall benefits and risks were not known. Therefore there was this need for rigorous clinical trial. PEPI was started. HERS was started. HERS was not an NIH supported trial and WHI for prime prevention.

It's often said and we heard it today that

WHI studies the wrong population. Well, it actually studied the right population for the question it was asking which was "Whether hormone therapy is a suitable treatment in older women to prevent chronic diseases". In the mid 1995s to illustrate that point - and it was being used increasingly for those diseases - NHLBI did a survey and found that 85 percent of doctors - these were non-gynecologists - were prescribing hormone therapy. All gynecologists were prescribing hormone therapy but two percent of non-gynecologists were prescribing hormone therapy. Of those who prescribed hormone therapy, 93 percent did for so menopausal symptoms, 91 percent for osteoporosis, 41 percent for high blood cholesterol and 66 percent for CHD prevention.

At that time you will recall both the National Cholesterol Education Program, AHA, ACC, all of these bodies recommended hormone therapy as a treatment for lipid disorders and for CHD prevention. That was the climate in which we were operating. In fact, it was quite difficult to recruit for WHI in the early 1990s because many physicians advised their

patients they should not enroll because all women should have this therapy. So that was the climate. There was increasing use of hormone therapy to prevent CHD.

Now why did we choose this particular drug? Conjugate equine estrogens, Premarin, in the U.S. was and is the most commonly prescribed hormone therapy and in women with a uterus, MPA is the most commonly prescribed added progestin. Initially this was cyclic. Now it's predominantly in a continuous form in Prempro.

An important point from our point of view was that most epidemiologic data on CHD risk reduction in hormone users is based on the use of Premarin 0.625 mg. The well-known Nurses Health Study for example 66 percent of the data in those analyses are based on Premarin. Most of it is at the dose of 0.625 mg where they looked at the dose of 0.3 mg in their most recent publications. Their findings for CHD were similar. They weren't better or worse. They were similar. Now I've stated the data on combination therapy and CHD emerged later, but when they did, they looked similar

for CHD to that for estrogen only. We didn't have specific data for Prempro.

Let me move on to the study population then. Why did we choose this study population? They were post menopausal. They were a wide age range of 50 to 79. We wanted to make it as inclusive as possible and as representative as possible of the greater population of post menopausal U.S. women. So we made an effort to enroll minority women. We had this wide age range.

We had very liberal inclusion and exclusion criteria so we included women. We had no exclusion criteria for women with a high body mass index ("BMI"). Except for very extreme levels, we did not exclude those with CVD risk factors or with previous CVD provided it wasn't recent CVD. We did not exclude those with prior hormone use.

Let me turn then to some of the characteristics of the women that we did enroll. The mean BMI was 28.5. However when you look at that and break that into categories of normal weight, overweight and obese, you'll see that just over 30

percent were not overweight or obese. The results as we'll show in subsequent presentations apply to the non-obese and the obese generally speaking. To make a statement that the average BMI was 28.5 misses the point. We tried to make this enrollment as wide as possible to be as representative of the population as possible. Where feasible we do subgroup analyses. So far we haven't found any subgroups that have a moderately different experience than the overall.

Similarly for the age, this is the age distribution on the left here. 5.5 thousand (5,522) of 50 to 59. Even though the average was in the 60s we have the largest trial ever of women in their 50s. We also of course have very important information on older women. We didn't have that many women with past or current hormone use. The majority had never used hormones before, but we are able to do some analyses by prior use.

We include women with risk factors. Here are the percentages who were smokers, diabetic, hypertension, hyperlipidemia, used statins or ASA. 6.2 percent had prior CVD. I would point out however

that these numbers are all quite a bit lower than what you'll find in NHANES surveys. This population on average was indeed healthier than the average post menopausal population.

That's borne out by the fact that our CHD rates were about half of what we had predicted when we started the study. I would also point out that almost 2,000 of the women did have moderate to severe menopausal symptoms at baseline and that or the body mass index or the age or the years since menopause, any subgroup that you want to look whether they had risk factors or not, we have not been able to identify any subgroup that has a markedly or significantly different experience than the group overall.

Having set the scene, I would now like to ask my colleague Dr. Marsha Stefanick, the Chair of our Steering Committee, to show you the most important results and updates of the study. Mr. Chair, is that okay?

DR. STEFANICK: Thank you very much. It's a pleasure to be here. I'll try and be brief in this presentation. First of all, I would like to state

that the specific aims as you know were to test whether estrogen plus progestin or estrogen alone reduced the risk of CHD defined as non-fatal MI and CHD death or other CVD like stroke, increases the risk of breast cancer and reduces the risk of hip and other fractures. But also of equal importance to us was to determine the overall balance of health risks and benefits of E + P and E alone.

Women were randomly assigned based on their hysterectomy status. If they had a hysterectomy, they were assigned to either CEE at the dose 0.625 mg, essentially Premarin, or to placebo. If they still had their uterus, they were assigned to combination therapy, the same estrogen combined with medroxyprogesterone acetate or placebo. Initially there were a small group of women who were assigned to a three-way randomization. Prior to the PEPI results when the PEPI results came out, the estrogen only arm was discontinued and women were converted to the combination therapy.

The outcomes monitored by the Data Safety Monitoring Board ("DSMB") were three cardiovascular

endpoints, CHD, strokes, pulmonary emboli; three cancer endpoints, invasive breast cancer, colorectal cancer and endometrial cancer; hip fractures and deaths from other causes. In addition, the global index that you've heard about was defined as the earliest occurrence of each of those events to provide the overall balance of risks and benefits.

As you may realize, the DSMB actually requested that the investigators inform the women after most of them had completed two years of the trial that there was an unexpected finding relative to our hypothesis that there was actually an increase in the number of heart attacks, strokes and blood clots in the lungs and the legs in the women receiving active hormones compared to women taking placebo. So all the participants in the hormone trial were alerted to this information.

A year later, the DSMB required that we inform the women that now that we had completed an average of four years of the trial these excess cardiovascular events persisted in the active hormone group compared to the placebo. All of these data were

based on the combined E only and E + P trial data. The investigators were never informed, nor were the women, what was going on with the E only trial. As you all know last year, May 2002, the NHLBI accepted the DSMB recommendation to stop the E + P trial after an average of 5.2 years because the risks exceeded the benefits based on the monitoring rules which Dr. Anderson will elaborate on when she presents her presentation.

In particular, I do want to point out that we are following these women so they are still being monitored through the trial. They are just not taking their hormones at this time so that we can get information about the long term risks and benefits. Also the DSMB recommended that the E along trial continue because the risks and benefits were not yet certain and the balance was not clear. We were able to inform the women at that time that there was no increased risk of breast cancer by the 5.2 year period and we do continue to monitor these women closely. They are continuing to take their study pills.

To just focus on the E + P trial results

then, in the publication from last July, we published both the nominal confidence intervals for the hazard ratios for each of the primary events and very conservative adjustments based on the sequential monitoring and the multiple outcomes. To just point out as you see, there was a set of clear harmful events, CHD, stroke, breast cancer and pulmonary emboli and there were a series of benefits, colorectal cancer, hip fractures. Also shown here are total fractures. Death was neutral.

These were all presented in the paper last year to actually focus on the global index which was this overall balance. The main point I'd like to make by showing only one of our many Kaplan-Meier curves is that when we look at the accumulated incidence as we add these up, at no point were the E + P women better off than the placebo. The placebo were always having a lower overall risk ratio relative to the benefit. The main point is that the risk clearly exceeded the benefits in the active group.

Also presented in the paper were the annualized event rates for the primary outcomes. What

you see is that the excess risk attributed to E + P for every 10,000 women were seven more for CHD, eight more for stroke, eight more for breast cancer and eight more for pulmonary emboli. And the attributable benefits were six lower colorectal cancer, five fewer hip fractures, neutral for endometrial cancer and neutral for death.

These were the events that we published last year. This basically came out to an overall summary of 19 health problems for 10,000 women assigned to E + P versus placebo which essentially means that over five years there was a net per 100 women in the active treatment group who had a harmful outcome. Our conclusion was that treatment with E + P for up to five years is not beneficial to overall health.

Since that time, we've been publishing the more extensive data. We actually had four months more of outcomes but they had not been adjudicated and not built into the analyses when we published the data last year. Two of them I'll elaborate a bit on, the coronary heart disease risk and stroke. You'll hear

from Rowan Chlebowski the breast cancer data and Jane Cauley the fracture data when I complete my presentation.

What I'd like to do is start out first of all with the basic principle of these updated papers. We now have a mean of 5.6 years of follow-up. That's the actual length of the overall follow-up time which means that we have more cases for all of the events that were published last year. In addition, all of the major events have been centrally adjudicated. In the case of the CHD update by cardiologists, in the case of stroke by neurologists and so forth. In addition, we have additional endpoints relevant to the outcome in question and we have analyses on subgroups trying to get information about many of the questions that have come our way in terms of "Are there groups that are better off and are there groups that are worse off".

With respect to the CHD, the main point that I'd like to make from that paper, the main issue I'd like to summarize, is that when we looked at all the data, first of all, I'll point out that the hazard

ratio from the updated centrally adjudicated data is 1.24 so 24 percent increase in CHD. But the most important point that I'd like make is this was particularly elevated in the first year. The hazard ratio of 1.81 appeared in the first year.

What you see is that each year of follow-up where the first event is no longer included in each of the next years we still have an excess risk in Year 2, Year 3, Year 4, Year 5 in the E + P group. Not until Year 6 when the placebo group had essentially caught up at this point - They've been surviving all of this time. They now have their heart attacks - that's really the explanation for this reverse of the hazard ratio in the years after year five. At least that's my judgment of it.

Now I would like to point out that there had been many studies showing benefits to lipids from E + P and E only starting before the PEPI study but the PEPI study certainly emphasized that. We did see those in the subsample of women for whom lipids were measured. We did see a decrease in total cholesterol and LDL cholesterol of 12.7 percent, very similar to

data published previously. There was also an increase in HDL cholesterol of 7.0 percent which was actually a little bit better than the PEPI study. We also saw decreases in glucose, not significant, but also insulin. So the lipid benefits that we've talked about were also seen in WHI, but I think we all recognize that this is a risk factor for a disease. The disease was not benefitted. So in this case, we have to recognize that looking at lipid changes is not the appropriate approach with respect to CVD and hormones.

Also just to quickly mention in all of the analyses that are coming out, we are looking at lots of subgroup analyses. In the case of CHD, age, years since menopause, hot flashes, with and without night sweats, obesity status, race, ethnicity, education level, all of these have been examined and none of them have shown any effect in terms of the interaction. So there is no evidence that these things make a difference with respect to the overall risk associated with E + P.

Similarly we have a large list of

biomarkers and other risk factors. I will point out that one risk factor did show up as significant. LDL cholesterol, the higher the level the more likely you were to have a coronary heart attack. But I also want to point out that there were so many subgroup analyses done that we can't say this wasn't due to chance. By the time you've done 20, you have one out of 20 that could be by chance. But at any rate, we've gone to quite a bit of effort to look for subgroups that may be better off or safe. At this point, everything pretty much comes out to the same answer that the risks exceed the benefits.

I also want to point out that with respect to CHD whether women had an event in the past or whether we talked about a more comprehensive cardiovascular package or the CHD alone, we still have a net risk associated with that. So also history of heart disease did not make a difference in the risk associated with E + P.

In the stroke paper, we basically elaborated on the fact that ischemic stroke in particular was the stroke that was increased. So

where we would look at total stroke, we have a relative risk of 1.31. Ischemic strokes, it's 1.44. Hemorrhagic stroke is not significant. There weren't as many hemorrhagic strokes. As you see, the vast majority of strokes were in fact ischemic strokes.

In summary from the stroke data, we now basically continue to say that we have excess risk. Seven per 10,000 women per year are having strokes attributable to E + P in our data. The excess risk is not explained by blood pressure increase which I failed to point out that we did see. It was apparent in hypertensive and normotensives and it was apparent in all the subgroups that were examined. Also we looked at quite a few biomarkers and there was no significant interaction on the biomarkers.

Also quickly, we now published the gynecological cancers. Dr. Anderson is here today. You'll be hearing from her. Other papers have been submitted and are forthcoming but we do not yet have the data published. With respect to the gynecological cancers, invasive ovarian cancer, 32 cases; hazard ratio of 1.58; confidence interval, not significant.

Endometrial cancer, 58 cases; hazard ratio. 0.81; confidence interval, not significant. There were relatively few cases of these cancers with a suggestion of increased risk for ovarian cancer and a suggestion of decreased risk for endometrial. No appreciable differences in the distributions for tumor histology, stage or grade for either of those cancers. In the case of cervical cancer, there were 13 cases out of the 16,000 plus women and the data and the trial are really too limited to say very much more about that.

I do want to point out that we did have relatively high discontinuation rate for pill taking. That's been discussed in many settings. You see that over the course of time an increasing number of women were coming off the pills in both the placebo group shown in yellow and the active group shown in orange. But also there were an increasing percent of women going on estrogen and progestin. So that what you see below is the women who are coming off the pills here as a substantial portion of them were going on exactly the same medication but open label with their own

physician and twice as many women in the placebo group were falling into that category. When we actually look at all of the data I've talked about so far and look at the data by intention to treat, we have a 24 percent increase in CHD, 31 percent increase in stroke, 24 increase in breast cancer in the updated analyses. But when we add on to that the compliance data looking only at women who were taking at least 80 percent of their pills and censoring the event history for six months after they stopped taking pills, what you see is that in fact 50 percent higher CHD, 50 percent higher stroke and 49 percent higher breast cancer. When we actually look at the highly compliant women, the risk attributed to these hormones is even greater.

I'm not going to say anything about the quality of life data. I do want to say a few things about the WHI Memory Study ("WHIMS"). It's been pointed out and I'll point out again that this was an ancillary study restricted to women who were 65 and over at baseline and included about one-fourth of the overall study population, 4,532, with more than 90

percent of the women who were eligible to be in that trial actually participating. So it was a fairly good representative study group. Essentially the data that we have from that study shows that probable dementia happened twice as often. It was diagnosed twice as often in the E + P group relative to placebo. We actually looked at the rates per 10,000. It was 45 per 10,000 in E + P and 22 per 10,000 for the placebo which is essentially 23 excess cases per 10,000 women per year. Dementia twice as high. Mild cognitive impairment ("MCI") was actually not different between the two groups.

So come back to our new summary, we're slowly improving these risk estimates. We now can lay out that we have eight more women with breast cancer per 10,000 per year, six more with CHD, seven more with stroke. We have not yet published the updated data for pulmonary emboli or for colorectal cancer in which there were six fewer, but we have published the updated data now for hip fractures which is five fewer. So we are still in the area of over a five year period one in 100 women are having unhealthy

events related to these hormones.

We essentially stand by the same implications that we published last July. The overall risks of estrogen and progestin outweigh the benefits when taken to prevent chronic disease in post menopausal women. Estrogen and progestin should not be initiated or continued for primary prevention of coronary heart disease and the risk for CHD, stroke, pulmonary emboli and breast cancer must be weighed against the benefit for fracture in selecting from available agents to prevent osteoporosis. With that, I'm going to turn over to my colleague, Rowan Chlebowski who will present the breast cancer data.

CHAIRMAN McCLUNG: Actually, let me take the prerogative of suggesting that we actually have our break at this point because we're come back after the break and talk about specifics about breast cancer and about bone disease. Plus we're halfway through the morning. Let me propose that we have our 15 minute break, reconvene at 10:25 a.m. to continue this discussion. Thanks. Off the record.

(Whereupon, the foregoing matter went off

the record at 10:12 a.m. and went back on the record at 10:31 a.m.)

CHAIRMAN McCLUNG: On the record. Let me invite Dr. Chlebowski to the podium to continue the presentation of data from the Women's Health Initiative and to specifically address the more detailed analysis of issues related to the breast cancer risks.

DR. CHLEBOWSKI: Thank you very much. I also am delighted to be here and to give you a little bit more detail on breast cancer in the WHI. Menopausal hormone therapy in breast cancer as we've heard about CHD also has an extensive background. There were numerous observational studies suggesting that longer duration usually meaning by definition, - short duration used to be five years or less of use - would result in increased breast cancers. There were suggestions that these cancers would found at low stage and have favorable prognosis, the receptor positive predominance and more lobular in histology. In essence, the thrust was that E + P or hormones would offer an earlier diagnosis of cancers which

would otherwise anyway come forward.

When we talk about the WHI, you heard much about the characteristics of the population. I just list here a number of the things that we captured in terms of known and presumptive breast cancer risk factors. We won't go over all these data except to say that none of these characteristics differed significantly between treatment groups. So we have much breast cancer risk information.

One point that's already been made by Dr. Rossouw that I want to point back up again in this setting because one of the issues we'll be attempting to get at is the duration issue in breast cancer is how about prior hormone usage. As you've heard before three-fourths of the women had never prior hormone exposure. About six percent were current users. Those users had to wash out or stop therapy for three months before beginning their baseline evaluation.

One of the things that's different again from the WHI Randomized Perspective Trial were the issues about case ascertainment and breast safety. So baseline mammograms and clinical breast exams were

required for eligibility. Everyone was screened before entry. Annual mammograms and clinical breast exams were required when on study and importantly the dispensing procedures would not allow dispensing of the medications if safety procedures were not done. So if a woman didn't have a report of a mammogram within a window, at a time for dispensing she could not be dispensed further medication until she did get those studies.

Here's the summary of the major results which is again updated from the original publication. This data was published in JAMA of June of this year showing that on E + P there was a total of 245 versus 185 cases. Dr. Anderson who will follow me will go into more detail about the statistical analyses involved. Here we have invasive breast cancer 199 versus 150 with a hazard ratio of 1.24 and just a trend of insight to cancers. Those were the numbers of invasive cancers that we saw on E + P during a course of follow-up that ended after 5.6 years.

Here's what the Kaplan-Meier curves look like. We'll come back to some of these duration

issues. Again unweighted hazard ratio 1.24. You can see actually that the curves cross at about four years and then more E + P data. We'll look in more detail at the hazard ratios in the first two to three years where there was an apparent lower incidence of breast cancer seen on the placebo compared to the E + P arm.

Similarly to what Dr. Stefanick showed as well, we did a sensitivity analysis to perhaps allow a better comparison to some of the existing observational study data. Again what we did was participants were sensored six months after becoming nonadherent. That is not taking 80 percent of their study medications or taking non-protocol hormones. What you can see here is that our hazard ratio is now 1.49 with a earlier departure deviation of the two curves.

We looked at many subgroups, none of which really showed a different relationship of E + P to development of breast cancer. I'll just show a couple of these. This is a breakdown by age. You can see that actually this is a test for interaction. There is no interaction, 1.2 in the 50 to 59 year olds, 1.22

in 60 above. So basically it wasn't as if only the older individuals were at breast cancer risk.

Because there'll be more detail gone over in the BMI portion for fracture, we include this to look at the breakdown of hazard ratio for development of breast cancer by BMI. The trend was actually nonsignificant, but there was an appearance that maybe in the older individuals there was somewhat less of an effect on E + P to increasing breast cancer risk. Again that interaction was not statistically significant.

Dr. Anderson will go in much more detail over issues of prior menopausal hormone therapy exposure. I'll just show you this one illustration of the overall breakdown of no prior hormone therapy versus ever prior hormone therapy. You can see the P-value is 0.10 so the interaction wasn't significant. More breast cancers on E + P in both groups, a nonsignificant trend. Ever users were at somewhat lower risk. We have a question which we'll go into more detail with at a later presentations about cumulative exposure versus selection bias.

We'll point out a couple of those issues here. Here's the women with no prior menopausal hormone therapy E + P/placebo. Their hazard ratios in the first year were 0.48, 0.65. So like a 50 percent apparent reduction in the first two years for E + P compared to placebo. You don't see that in the women with prior menopausal hormone therapy. Now the other additional issue is this will provide one possible explanation for this because this prompted our look at the mammogram data subsequently.

If we look at the breast cancer characteristics by group, remember there was a suggestion from especially more recent observational studies involving E + P that lobular cancers would be largely responsible for most of the increase. Actually we saw nothing like that. We saw really that all types of cancers were the same in both groups. Again the suggestion on the predominance of the observational studies that E + P would be associated with well differentiated cancers wasn't seen. We saw the same distribution, similar histology and grade on E + P compared to that on placebo.

How about the receptor status? What we see here is that both receptor positive and negative breast cancers were greater on E + P. This number tests the interaction between E + P for receptor status. You can see more receptor positive cancers, more receptor negative cancers, more progestin receptor positive cancers, more progestin receptor negative cancers. The P-value suggests that there was a significant imbalance with respect to the number of individuals having receptor status determined. This wasn't based on size difference. We don't have an explanation for that imbalance. It appears that both receptor positive and negative breast cancers were greater on E + P.

Now this is an important data demonstration because very surprising compared again to the observational study data, we saw that actually instead of being more favorable stage, the tumors on E + P compared to placebo were larger. This difference was statistically significant. It was more likely to have node positive and more likely to be at regional stage. More advanced stage was seen on E +

P. I think the other thing I can point out that this is what you get when you have a population that has 90 percent of that population has yearly mammograms. You get an average size on the placebo of only 1.5 cm. So the cancers were larger, more likely to be node positive on the E + P arm.

This finding of similar grade, histology, and receptor status but more advanced stage where ascertainment was felt to be equivalent and that suggestion that there were apparently fewer cancers seen in the first couple of years on hormone prompted us to look at the mammograms. Basically it's our mammogram findings after one year on E + P.

As you can see, 90 percent were normal, but the abnormals were 9.4 percent versus 5.4 percent on placebo. This is a relative increase of 74 percent in abnormal mammogram frequency after one year. Most of those abnormals were in the short interval follow-up category, Category 3, but you can see that suspicious abnormalities usually leading to biopsy were also higher.

This finding persisted. This is the data

you saw before. This is the mammograms abnormal, 9.4 versus 5.4 compared to the baseline of about five percent in both groups. The cumulative after six plus years of follow-up were 30 versus 21 percent. This is the frequency of mammograms by arm. You can see that after the first year 90 percent of the women had their assigned mammograms and the cumulative goes up to 97 percent. The people that would drop off that wouldn't be required to have mammograms before dispensation. That wasn't an issue. What we have there in summary was that abnormal mammograms were associated with even one year of E + P use, a four percent absolute increase in abnormal mammograms after one year on E + P, a ten percent absolute increase in abnormal mammograms after about five years of E + P.

Now to inform some of these results especially our finding of more advanced stage, we can get some information from the recent results from the United Kingdom Million Women Study. This is based on a National Health Service Breast Cancer Screening Program trial in the United Kingdom. What their study involved was the National Health Service there invites

all women in the United Kingdom 50 to 69 years of age of have a screening mammography every three years by letters. A questionnaire regarding hormone therapy use was added to the screening invitation letter. The women showed up for their screening and then the data on their hormone therapy use was linked to National Health Service Central Registries for Breast Cancer and Death Outcomes. 1,084,110 million were identified and 9,364 invasive breast cancers were seen. I should emphasize this was a perspective cohort study. It was not randomized. It was very large.

What did they see? Now they included if women had an abnormal mammogram at baseline and were taking hormones one year before. They would be considered to be on hormones for one year and that work-up would count. So they didn't screen and eliminate cases. They included everyone. But when they did this, the relative risk of developing a fatal breast cancer by hormone therapy use at baseline had a relative risk of 1.22 which was statistically significant. They found that hormone therapy was associated with increased breast cancers and

mortality in short-term users. By short-term users, it means they were based on deaths after follow-up of 4.1 years.

How about the duration effect? Again it's really quite different than the WHI in that there's a number of differences. They included the work-ups down on baseline. Because they had mammograms done every three years and they reported the incidence data after 2.8 years, the majority of these cases would not be screening detected cancers, but would rather be clinically detected cancers without mammographic screening. By this, they get rid some of the ascertainment issues. What they saw was after one year a relative hazard ratio of 1.45 going up over time. This is the data for their E + P which was associated with increased breast cancer risk in less than one year.

How about the hormone types? Without showing all their data, they saw an increase also with E only for all types of estrogen but the risk was substantially higher for their E + P combinations. About one-third of the women had conjugated equine

estrogens, Premarin, and they had a relative risk of 1.29, conventionally significant. But other estradiol was also significant and besides medroxyprogesterone acetate, other progestins also were associated with increased breast cancer risk.

So our conclusion based on these combined findings is that combined E + P use increases breast cancers, diagnosed in more advanced stage and increases more abnormal mammograms. These results suggest that use of E + P may simulate breast cancer growth and hinder breast cancer diagnosis. Thank you. The next speaker will be Dr. Garnet Anderson who will be going over more details of the prior E + P users.

DR. ANDERSON: Good morning. It's a pleasure to be here. On behalf of colleagues, I wanted to cover the statistical methods issues, and I'll try to do that in short order because I know that's not what most of you get up early in the morning to hear. Then I will cover some of the further analyses of prior hormone therapy and breast cancer risk. These are questions that have been specifically put to us by members of the FDA.

On the statistical methods, I wanted to point out to you that the design and the primary analyses of all of our clinical endpoint data is based on a weighted log rank statistic which I've shown here. It can be written in the usual observed minus expected notation. This is trying to look at the difference in survival curves or incidence curves over time. The only thing that's unique about this is the weights which is signified here. So I wanted to describe what that means.

These weights are specified for each disease endpoint. The motivation is not to weight different diseases because that's a very difficult place to go. Rather these weights are defined by time since randomization. The motivation is actually to increase the efficiency of the study group at power. It was based on the idea which is common in prevention trials that the intervention effects will not be fully manifested right away. It will take some time for the differences in clinical endpoints to appear.

Let me show you the actual weight we used. So any differences you see in the early period are

more likely to be due to a random occurrence than to be a true treatment effect. We actually had very good observational data to say that the effect of hormones on breast cancer may take a considerable amount of time to be fully manifested.

So the weights for breast cancer were defined to be linear over a ten year period. The differences observed in the first year or so would have very little weight but increasing over time. Differences at year 10 and beyond would have full weight. That was the weighting scheme for cancer and also for mortality or global index calculations.

For CVD and fractures, the data were not so clear. In fact, the observational data tended to suggest that it was current use of hormones that was protective for CHD. Nevertheless a lot of the hypothesis came through the intermediate effects of lipids which though that might be rather immediate but its translation into a clinical impact could take some time. After quite a bit discussion, we used a three-year weighting period. By the time, we got to the three years any events occurring after that would

receive full weight.

That plays into both the analysis and it also played into the monitoring plan. Dr. Rossouw gave us a nice summary trying to understand where we were when we designed this trial. It was a prevention trial. In developing our monitoring plan which the development has been published back in 1996, we were thinking of the issue of benefits and risks with CHD being a benefit that was at that time considered so obvious that the question was "Could we really ethically continue this trial when the benefits might accrue by year three in the study when we knew the breast cancer results might take a fair amount of time to see".

The monitoring plan that we used then and continue to use now for the E only trial was based on that general idea. We would stop for evidence of CHD benefit using a standard procedure that looks like the upper tail of 0.05 level test with .025-level, one-sided test corrective for multiple looks over time, the traditional O'Brien-Fleming procedure boundary. This is exactly the same in many trials used for a

single endpoint trial.

The only catch to this is that we did develop the global index specifically for this monitoring purpose. That was to provide some measure of the risks and benefits balance at that time. Though we didn't require this to be as significant or as clear - we only looked at the .05-level, one-sided test for this - it was to be clearly weighing on the side of overall benefit to stop this trial. That was the only way that we would stop for benefit.

Stopping for harm, there were actually two alternatives. Breast cancer was our primary safety endpoint. There were prior data suggesting that this might be a problem so we defined a monitoring boundary for it alone not adjusted for multiple endpoints. Because we were interested in proving harm to the same degree of precision as you might want for benefit, the stopping level was a .05-level, one-sided test equivalent to the .10 percent type one error again adjusted with O'Brien-Fleming procedure for multiple looks over time.

If that boundary were crossed and a global

index which was supportive of harm, that's a Z-statistic less than minus one. So one standard deviation below the no-hypothesis, we would stop for harm based on breast cancer. We also defined similar stopping boundaries for all the other designated monitored endpoints of CHD, stroke, PE, hip fracture, colorectal cancer, endometrial cancer and death from other causes. Death from other causes was just to pick up anything unforeseen that was serious in terms of the health of women. These use the same .05 level tests but it was corrected with a conservative Bonferroni correction because we were looking at all those multiple endpoints and didn't want to inflate our type one error by looking at too many endpoints at once. Those are our monitoring boundaries. It was the breast cancer boundary and the global index boundary for harm that were crossed last spring.

A couple of other notes. All the analyses we present are based on intention to treatment. That means that every women randomized is analyzed and included the analysis in the arm in which she was randomized regardless of whether she stayed with that

arm. Even our sensitivity analysis looking at adherents do not cross the women over. They just sensor her data at the time she becomes non-adherent. This is the best in terms of preserving the ideal quality of a randomized trial.

We do provide unweighted hazard ratios which is a bit of awkwardness given that the trials were based on the weighted design, the weights over time. I would say that this was a compromise that we made based on the fact that we were completely wrong about our CHD findings. The assumptions underlying that design were wrong. We didn't reach the full preventive effect by year 3.

Then what do you do with the weights? Mostly when you don't have an idea of a time to effect you would do an unweighted type of statistic. We do provide unweighted hazard ratios and then associated with those, nominal and adjusted confidence intervals. The nominal 95 percent confidence intervals for those hazard ratios probably need no further comment. The adjusted however taken into account the fact that we did look at the data every six months for monitoring

purposes and we did look at multiple endpoints. We think it's only fair to bring that note of caution into the interpretation of these data.

Particularly for breast cancer, we also in some places showed the weighted P-values, P-values from the weighted analyses, because there is a discrepancy in the interpretation at points when you take the weights into account and when you don't. To be fair, the design and the analysis for these endpoints did always indicate that we would use weighted analyses.

A lot of what we're doing today and have been doing in the papers since last year has been looking subgroup analyses. These are much more difficult to interpret statistically. In the process of working through these papers, we've developed our own WHI sort of policy for how we'll interpret them. It is that our inference will be based primarily on the test of interaction.

The trial was not designed to test this specific hypothesis within each subgroup so we acknowledge that those specific subgroup tests within

themselves are low powered. That means we have a high type two error. We also have a high type one error. We've looked at many subgroup analyses. It's possible to find some that are significant by chance alone.

To minimize this as best we can, our inference is primarily based on those tests of interaction. Then we report unadjusted P-values and we say that these should be considered as hypothesis generating, not testing. Then we have asked each author of each paper to report the number of interactions they tested and to report the number that would be expected to be significant by chance alone. We feel that it is a reasonable approach to this area which is really very exploratory.

On that note, let me go to the specific subgroup analyses that I've been asked to address which is prior hormone use and breast cancer risk. I feel a little embarrassed to tell you that I'm presenting this to you without having the WHI investigators as a whole to be able to see this in advance nor our DSMB which will be reviewing some of these data for the first time in a few weeks. But

that said, this is an important meeting for all of us so I will take you through these realizing that they have not been digested by the WHI research community as they normally would.

I've been asked to look at more detailed analyses of prior hormone exposure including type, duration and recency of use, the extent of the disease by prior hormone use and a bit of mammography performance. This is an amplification of what Dr. Chlebowski already showed. I'm sorry that some of these numbers don't show up very well.

Looking by prior hormone use and invasive breast cancer, the hazard ratio is 1.09. You've seen that before. In invasive cancer, the hazard ratio is 1.86. The unweighted P-value is .04. The weighted P-value is .10 suggesting some modest evidence of an interaction with prior hormone use where women who have been exposed in the past if you looked at that by itself these Z-values of -2.7 or -3.0 are clearly statistically significant. Where you don't see that, it's just a slight trend of an increase in the women who have not been exposed previously.

But what is rather curious about this finding and I can't explain it exactly is that the rate of invasive breast cancer in women who have been exposed previously but who then were randomized to placebo is quite low. It's 0.25 here. That's the annualized incidence rate. Placebo who are not previously exposed is higher. It's 0.36. That's a little bit curious and suggests to me some sort of selection bias probably in the sense that these women are different, the prior hormone users versus the no-prior exposed group.

These are the Kaplan-Meier curves in those two groups. We should especially try to remember this one because it becomes the reference group for many other analyses. You can see that the period in which the E + P group has a lower incidence rate is at least for four and a half years, but the curves do cross. The E + P group has a slightly higher rate in the later years. Therefore the pattern is overall the same but you see a longer duration of lower rates. Whereas in the prior exposed, the separation of the curves does begin much earlier by about Year 2.

Now I want to break it down by type of prior exposure. Here I've categorized slightly differently than it was in the JAMA paper. Here prior E only exposure is only exposed to estrogen alone. These women never took progestin before. Any prior E + P, some of these women did have some episodes of E alone exposure. I wanted to keep the E alone group pure. This group is the women who had some progestin exposure. You can the hazard ratio. That's the same as before. In the prior E alone exposure, the hazard ration is 1.47. E + P is 2.19. Unweighted P-value for the interaction is 0.08. The weighted is 0.17. So again there's some kind of suggestive trends but not very strong. The suggested prior exposure particularly prior E + P seems to be associated with higher risk.

Again we note that the women with prior exposure to E + P who were randomized to placebo have a quite low rate, 0.19 percent per year versus the other two groups with about 0.36 percent per year. So women with prior exposure to E + P are clearly different.

Here are those curves. Prior E alone exposure, you can see that the crossover is about three years perhaps and then the separation doesn't seem to really show up until Year 5. Whereas, prior E + P exposure the curves differ around Year 3.

This slide shows duration of use. Here we don't see any strong trends. It looks like the no prior use as before but the prior year 2, 2 to 4 or 4 plus years was all in the same general area. Unweighted P and weighted P are basically in the same region as we've been seeing on those other slides, suggesting that maybe it is just yes-or-no prior exposure. This is one of the questions that was put to me. Is that really the case?

Here are those curves. I personally don't get a lot out of them. They all show similar pattern. There's maybe a slight difference in where the curves start to diverge.

Then the final one on this is recency of use. Here is at initial screen. So women who were using hormones at the time we first encountered them actually had to go through a three-month washout

period before they could be randomized. These are women who were using hormones before the washout period and then within the last five years but not at the baseline visit five to ten years ago or ten plus years ago. You can see all of these are generally in the same region. The P-values suggest that there's no interaction between those.

There are the curves. Hormone used at enrollment within the last five years, five to ten years ago, and more than ten years ago. Maybe the separation is coming a little bit later for older use.

One final question is the combination of prior use and BMI and I think this motivated more by the issue of osteoporosis. Here we have classified it by prior use and obese or not obese. You can see that prior use in the leaner women - I'm not sure that's exactly the way we should describe it - the hazard ratio is 1.18. No prior use and the obese women we saw no elevation there in that hazard ratio. But the prior users both of those tend to have an elevation. The P-values again are not very strong suggesting it's modest evidence for any interaction there. There are

those four curves.

In thinking about this though I was realizing that as soon as we start to make inference about prior hormone use, we've left the framework of a randomized trial. We're now starting to talk about an observational study. So we looked at the characteristics of the prior hormone users in this trial. We noticed a lot of the same things that you all know from observational work. Women who had used hormones before were younger, leaner, had a lot of characteristics that make them different. Vasomotor symptoms, parental history of fracture and had a mammogram in the last two years, a variety of things. To what extent could those issues be confounding our results?

The other thing is in terms of looking at the different hormone preparations the use of E alone or combined hormones the pattern of use is different in particular. In about 26 percent of our population, you can see that they had used hormones previously. A little bit more had been combined use. Here actually you can see overlap. The numbers don't add

up because the woman could be in either this category or that one or both. But women who had used E alone were more likely to have a shorter term exposure to estrogen than women who had used combined hormones.

A stronger contrast is in recency of use. E alone users 58 percent their exposure to E only was more than 10 years ago. Whereas combined hormone users were much more likely to be the current users. Whenever we are looking at recency of use and we don't tease a power at those two, we may be confounding that issue.

I started doing multivariate models all of these things. Controlling for multiple confounders, this is the E + P hazard ratio. I threw in just about everything on that first slide, listing the differences and characteristics plus additional breast cancer risk factors. So in that multiple variate model, the unweighted hazard ratio is 1.2. That's compared to the primary result of 1.24.

Separating it out by exposure to prior hormones, you see in women with no prior exposure the hazard ratio is now 1.02. Women with prior exposure

of any type is almost 2.0. The unweighted P-value is 0.3. The weighted P-value is highly statistically significant. Now we're getting some stronger evidence in an observational sense that there is an interaction here.

This is separating it out in the same type multi-variate model where the main effects now separate out the type of prior exposure. Women who are only exposed in the past to E alone their hazard ratio for E + P is 1.36. Now don't confuse this as the E alone hazard ratio. That's not what this is. This is the E + P hazard ratio in women who have been exposed to E alone. I know I got confused when I put it against the Million Women Study because their E alone hazard ratio is 1.3 or so. That's not what this is. And prior exposure to combined hormones is 2.46. The P-values here are not so clear. Unweighted P is 0.05. The weighted P is 0.64.

This is duration of use. Here you can see that it now looks a little bit more like an orderly trend as opposed to our unadjusted analyses. Less than five years of exposure is about 1.8. Five to ten

is 2.14. Ten plus years of exposure is 2.53. Unweighted P is 0.08. The weighted is highly statistically significant. I would say that these tests are based on a continuous variable not in these categories so it doesn't rely on us choosing the right category perfectly.

This is recency of use. You can see that at initial screen and last five years or five to ten years were all thereabout in the twofold increase range. Last hormones used ten years ago it starts to fall off. Now remember, this is any prior hormone exposure. I haven't teased apart the E + P and E alone. So this is mostly reflecting an E alone prior exposure. In fact, I couldn't fit them all where I teased both things apart like this.

This is looking at the combination of prior hormone exposure and BMI. You can see the same basic trend where it looks like women with no prior use who are obese are not at elevated risk of breast cancer. Everyone else is particularly those with prior hormone exposure and some clear evidence that this may be real.

I also want to look at effective disease by prior use and randomization assignment. You see exactly the same pattern in the size of these tumors in the women who are unexposed before the trial and those who are. They are not statistically significant because I've divided the sample size up here. But the same trend exists.

Percent positive nodes in advanced stage show the same pattern in both groups but again it's this weird thing where the placebo group in the women who had been exposed previously have a lower percent of positive nodes and lower percent of advanced stage than the placebo group with no prior exposure. So this is another very curious finding.

This is the newest data. Women received letters from us on July 8 of last year asking them to stop taking their pills but we've continued to follow them up. This is the increment of data since that time. They have not been taking our pills. Some of them have probably been taking their own pills. But you can see that we've had 21 new breast cancers in the E + P trial and 18 new ones in placebo for a

hazard ratio of 1.13. Our cumulative, combining the intervention period with the post intervention period, is 227 invasive cancers versus 170. The hazard ratio is 1.26, again especially by our weighted statistic, very highly statistically significant.

Let me try to summarize. We see a suggestion of greater E + P hazard ratios in women with prior hormone exposure. I worry when I think about this by the potential confounding of the differential characteristics of prior users. We've done a pretty good job of trying to adjust for those. There is also the issue of the potential delay in the diagnosis and how that's differential between these women with prior exposure and those who are not. We've not been able to address that. But it seems to be creeping up in the idea that these women with prior exposure randomized to placebo have these strangely lower rates. I think that's the evidence for this that there's a potential delay-in-diagnosis issue that is appearing in our data.

Our more extensive modeling does suggest that prior combined hormone use has a stronger effect

than prior E alone use. There seems to be an increasing risk of duration of prior exposure. The recency of exposure is an unclear factor. That's because in our data it's confounded with type of prior hormone use. There is modest evidence for an interaction of E + P with prior use and BMI.

As I was indicating, the data are too sparse to jointly exam type, duration and recency at least when I'm accounting for all of the confounders there. There is a difference in extent of disease by randomization status but it's consistent across the prior use groups. We note that there is some hints of differential effect by prior use, not on E + P but on the disease itself. The data on the post intervention comparisons are still quite limited suggesting maybe in the last 12 months that the hazard ratio has reduced a little bit but cumulatively we're still looking at substantial increase very similar to our own initial findings.

I want to briefly point out that we have also looked at the issue of abnormal mammograms by prior hormone use. Basically what we see is it's the

current use here. So the solid line is no-prior-use and the dotted lines are prior-use. Here's E + P and here's placebo. We really can't distinguish those with prior-use and not-prior-use. These aren't statistically significantly different, but you can see the strong E + P effect that Dr. Chlebowski already mentioned.

E + P increased the rates of abnormal mammograms. This is slightly different than the way it was presented to you before. Taking out the women who had breast cancer, any kind, advanced or invasive, among those who never had breast cancer during the study period, 32 percent of those had an abnormal mammogram and 22 percent of the placebo women had an abnormal mammogram. Those are the false positive rates. The role of prior hormone use on mammography performance is quite small. That's all I have to say on this. I would now like to introduce my colleague, Dr. Jane Cauley, who will be speaking about our trial and fracture results.

DR. CAULEY: Thank you very much. As was mentioned earlier, the fracture results were published

last week. I'm just going to go through and summarize the results that were in the paper. The objective of the analysis was to present the final results of the trial through the ending of the trial on July 7th. That adds an additional point four years of follow-up. We also similar to the other follow-up analysis wanted to test the hypothesis that the effective E + P differs by risk factors for fractures, identify a subgroup of women perhaps who are more likely to benefit from the exposure. We measured BMD in a subgroup of women. Finally we wanted to test whether the risk/benefit profile summarized in a global index differs at women at higher versus lower risk of hip fracture.

All the fracture outcomes in WHI include all fractures, including both traumatic and non-traumatic fractures except for the fractures that are listed here, fractures of the ribs, chest or sternum, skull, face, fingers and toes and cervical vertebrae were in fact excluded. All the fractures were radiographically confirmed. Hip fractures were centrally adjudicated and we had a 94 percent

agreement between central and local adjudication of hip fractures.

BMD was measured at three of the clinical centers. The three clinical centers were chosen to maximize the racial and ethnic diversity in women who would have these measurements. We measured BMD at baseline, years one and three as well as six although few of the women as yet had to have their year six measurements. So our analysis are restricted primarily to baseline, years one and three.

As mentioned, the global index was formed a priori during the design phase of the trial. This wasn't a post hoc definition of global index. It included life threatening conditions that were both primary and secondary endpoints of the trial. Again the most important thing here is that all of the analysis are intended to treat, but I just wanted to point out that hip fractures we present the adjusted confidence intervals. For all the other fractures, we present the nominal confidence intervals. Why the difference? Well hip fractures were one of eight clinical outcomes that were monitored by the DSMB.

That the only fracture outcome that we presented adjusted confidence intervals.

Now I wanted to give a little background. We tried to summarize a woman's risk factor for risk of fracture. There are various different scoring systems that have been published. Most of them have been used to identify women who may have osteoporosis. That is they are used to identify women who would benefit from having a bone density measurement. There's really only one fracture risk scoring system that's been published by Dennis Black from data from osteoporoic fractures. We followed his model and developed it within the WHI.

Initially the first step is we took the various risk factors for fractures and looked at the relative risk of the odds ratio of hip fracture in age-adjusted logistic regression models. Based on those models if the P-value is less than 0.10, they were entered into a multi-variate analysis. Those variables that were significant in the multi-variate analysis contributed to the calculation of the summary score.

The four risk factors in WHI that were significant in this multi-variate model and contributed to the scoring system are shown here. So for age, the odds ratio was statistically significant at 1.14 and a woman was assigned a zero to seven points for her age. For instance, a woman age 50 to 52 was assigned zero points for her age. Whereas a woman age 76 to 79 was assigned seven points for her age.

A history of a prior fracture after age 55 again is significant odds ratio. It was assigned two points. Current smokers were assigned two points and a low BMI was assigned one point. Essentially for each individual woman these points were then summed and we summed for the total fracture score for that individual woman. We then divided that into tertiles and looked at the various risks hazard ratios across these tertiles of the summary score. Now the area under the curve ("AUC") for the summary score of predicting hip fracture was 0.79 indicating moderate predictive strength of our summary score.

There was no difference in the summary

score by randomized groups. In this slide, we just combined the E + P and the placebo group to give you just some descriptive characteristics of women. Who were the women that we're calling at high risk of fracture? As you can see for age, the average age of women who were considered at low risk of hip fracture was 56 compared to an average ago of 72 for women who were considered at high risk of fracture.

BMI went in the opposite direction as expected. Women who were considered at high risk of hip fracture had an average BMI of 27 compared to an average BMI of 30 in women at low osteoporosis low risk of hip fracture. Percent of Caucasian increases such that 90 percent of the women who were considered at high risk were Caucasian compared to 77 percent of women at low risk of hip fracture.

The current smoking was three percent versus 16 percent. Current hormone therapy was 10 percent in the low risk group compared to three percent in the high risk group. In terms of a personal fracture history since age 55, it went from 24 percent in women who were considered at low risk of

hip fracture compared to 59 percent considered at high risk of fracture.

In terms of the subgroup of 1,000 women that we had bone density measurements on, we looked at the percent of women who had a T-score less than -2.5 using the WHO ("World Health Organization") definition of osteoporosis. There were about 12 percent of women considered at low risk who had a T-score less than -2.5 compared to 41 percent in women who were considered at high risk.

In terms of the overall prevalence of osteoporosis in the overall population, this is looking at the WHO definition based on T-scores using T-scores at the femoral neck. Overall the average T-score in the hip was about -1.0 and in the spine it was about -1.3 and did not differ by randomized group. So overall about 10 percent of women in the E + P were considered osteoporosis based on their T-score compared to 12 percent in the placebo group. This was not statistically significant. The majority of women, 53 percent, were considered to have low bone mass and about one-third of the women had normal bone density

measurements.

Now we'll get into the results. This shows the data on total fractures. On the right, there were 733 women who experienced a fracture in the E + P group which corresponds to about nine percent of women. There were 986 women who were randomized to placebo experienced a fracture. That's about 11.1 percent. Overall the annualized incidence of fracture was 1.5 percent in women on E + P versus 1.99 in women on placebo corresponding to a 24 percent reduction in total fractures that reached nominal statistical significance.

In terms of hip fracture, there were 52 hip fractures in the E + P group compared to 73 in the placebo. The overall annualized incidence of hip fracture was 0.11 percent in the E + P group compared to 0.16 percent in the placebo group. The overall hazard ratio was 0.65 so a 35 percent reduction in the risk of hip fracture associated with E + P.

In terms of wrist or lower arm fractures, 189 wrist fractures compared to 245 wrist fractures. The annualized incidence was 0.43 in women on

randomized E + P compared to 0.59 in women on placebo. The overall hazard ratio was 28 percent reduction in the risk of wrist and lower arm fractures in women randomized to E + P.

Now in WHI, we were limited to clinical vertebral fractures. There were 41 women who experienced a clinical vertebral fracture. That is a vertebral fracture that comes to medical attention. In many osteoporosis trials, they are used to looking at that data. They traditionally have used a morphometric vertebral fractures which are identified through serial radiographs. We did not have serial radiographs in the WHI. These are the clinical vertebral fractures that come to clinical attention because of pain. Overall, 0.09 annualized incident rate in E + P compared to 0.15 in the placebo group. Overall the hazard ratio was 0.66 corresponding to a significant reduction in clinical vertebral fractures.

Now we looked at various subgroups to see if the effect was different in these various subgroups. On this graph, we show the effect now because we're looking at five year age groups. This

analysis is limited to total fractures because the number other individual site specific fractures would have been too low to look at five year age groups.

There was a previous meta-analysis that was published a couple of years ago that concluded that E + P or E products may prevent fractures in younger post menopausal women but not in older post menopausal women. That analysis was based primarily on the conclusion of one study in the younger women and one study in the older women. It's the HERS study actually. So we wanted to look to see in WHI do we see a difference by age of the E + P on total fractures.

Again, the yellow dotted line is the overall hazard ratio that we observed in the overall group. The green circles here corresponds to the point estimates for each of these five-year age groups along with their 95 percent confidence intervals. The P-value for the interaction term is here. There was no evidence that the effect of E + P on fracture differed across age groups.

We also looked at various other subgroups,

years since menopause, by race, ethnicity. That was limited to the total fractures and BMD was also limited to the total fractures. All the other subgroups we looked at hip as well as wrist and clinical vertebral fractures. It didn't matter even though we looked at a number of subgroups. Dr. Anderson mentioned that we need to report the number of subgroups that we look at. If we looked at over 100, just five alone could be statistically significant by chance alone. Nevertheless in our analysis, none of the interactions were statistically significant.

The summary score data is shown here. If you focus first just on the placebo group, the annualized incidence of fractures in the placebo group in yellow was 1.33 in women who were considered at low risk of fracture and it increased to 2.74 about a doubling of the rate of fractures in women considered at high risk. But nevertheless whether a woman was low, moderate or high risk of hip fracture, you can see that there was no significant interaction between the summary fracture risk score and the effect of E +

P in reducing fractures. Therefore the E + P reduced fractures equally well in women who were considered at low risk of fracture as to women who were considered at high risk of fracture.

This just puts the WHI results in relationship of the data that were published in the Osteoporosis Research Advisory Group ("ORAG") that performed several analyses summarizing osteoporosis treatments. The pooled estimate from this meta-analysis that was published in 2002 was 0.87 with the upper confidence interval that went up to 0.08. You can see the WHI results are consistent with these previous studies and clearly show us a very strong definitive result with respect to reducing fractures.

What about the BMD results? These are the lumbar spine. We measured at the lumbar spine the hip as well as the whole body. We found consistently higher BMD measurements in women randomized to the E + P so that by the end after three years of treatment, the lumbar spine increased over 6.5 percent in the E + P group compared to about 1.2 percent in the placebo group which is overall a 4.5 difference in BMD at year

three at the lumbar spine with somewhat smaller differences at the total hip which is consistent with other osteoporosis therapy showing larger effects on lumbar spine than on the total hip.

Now we turn to the last goal which is try to identify a subgroup of women who are sufficiently at high risk of fracture that indeed the risk/benefit ratio may switch to us seeing more benefits. This is our summary score again. If you focus on the placebo group, we know that the high fracture risk women were much older. That explains somewhat why we see that most of these global index events are obviously more common in older women. But nevertheless the actual overall event rates are much greater in women considered at high risk of fracture compared to women at low risk of fracture.

Nevertheless the interaction term was not statistically significant. So the hazard ratio went from 1.2 in women at low risk of fracture, 1.23 in women at moderate risk of fracture and 1.03 in women considered at high risk of fracture. But the overall interaction term was 0.54. So essentially if you

focus on this specific point estimate, the hazard ratio, it's essentially neutral. We did not identify a net benefit in those women.

The limitations of our analysis have been pointed out by several of the other WHI speakers. We studied one E + P regiment. Our fracture risk score, the ratio of highest to the lowest risk was modest at about a twofold difference in fracture rates between women considered low versus high. We could not incorporate BMD measurements into our fracture risk score because we didn't have them measured on all of the women.

We also don't have any information on whether or not the women had a prevalent vertebral fractures and it's well known that low BMD and prevalent vertebral fractures are two of the strongest risk factors for hip fracture. It's possible, therefore, that the benefit versus risk profile could differ in women who had severe osteoporosis but we were unable or limited in our ability to identify women who had severe osteoporosis. Again we were limited to clinical vertebral fractures. I added the

global index here as a limitation but it's not really a limitation because it was designed a priori and it included life-threatening events that were basically primary and secondary endpoints of the trial. However it did not include vertebral fractures which are one of the most common osteoporoic fractures.

So in summary E + P increases BMD and reduces the risk of fracture in healthy predominantly non-osteoporoic women. The decreased risk of fracture was present in all subgroups of women examined. The effect of E + P on fracture is consistent with recent meta-analyses. Finally, the effect of E + P on the global index did not differ across tertiles of fracture risk. There was no evidence of a net benefit in women at high risk of hip fracture.

So the conclusion. Given the overall unfavorable risk/benefit ratio, the overall global index indicating more risk events than benefit events in the total population as well as the availability of other agents for the prevention and treatment of osteoporosis, we believe that estrogen plus progestin cannot be recommended for the prevention or the

treatment of osteoporosis in asymptomatic women. Before the combination of estrogen and progestin is considered for the purpose of fracture prevention, women should be fully informed about the potential adverse effects. Thank you very much. Now I'm going to turn the podium back over to Dr. Anderson who is going to address some additional questions that were posed by the Panel.

DR. ANDERSON: Okay. Following up with a few additional subgroup analyses, I was asked to look at fracture rates by prior hormone use. For this, I chose to use total fractures because in subgroup analyses you start running out of sample size pretty quickly. Total fractures obviously have the greatest numbers and the fracture data tend to line up so beautifully across the fracture site. I thought this was a reasonable way to do it.

You can see the overall results of a 24 percent reduction consistent in both women who are not exposed to hormones before the trial and those who took hormones at some point in the past. I didn't do a test for the interaction here, but I can guarantee

you that it's not statistically significant.

These are the curves. They also imply no statistically significant interactions. We did this sensitivity analysis, the per protocol thing, where when a woman became non-adherent to her study medications we stopped counting events that happened more than six months later. That actually for fractures never changed the results very much which suggests to me a certain amount of carry-over effect. The benefit doesn't stop rapidly.

Then probably more interesting is the interaction between prior hormone use and BMI. What I basically see is the same pattern. So low BMI, high BMI here in the no-prior users and the same in the prior users. It's just really the same pattern. The P-value for the interaction is 0.71. So being obese of course protects a little bit. Having prior hormone exposure protects a little bit. The interaction with E + P says that E + P is protective in all of those groups.

Those are the four curves associated with that. You can see a slightly stronger difference in

BMI it looks like. I have the scale wrong so you can't make the comparison there easily. Again unweighted P-value for the interaction is not statistically significant. I didn't do the weighted P-values because again for osteoporosis the difference between weighted and unweighted is negligible.

Several comments about the global index. I wanted to spend a little bit of time about that. This is the updated global index which is new data. It has not been published. This is data through July 7th of last year with updated endpoints, an increase of 12 percent of E + P over placebo. This is showing it by age group. It's bouncing around a little bit, but the P-value for interactions saying are these statistically different is 0.99. Truly this is the best summary when you are looking at it by age.

This is looking at it by BMI. Women with a BMI less than 25, their hazard ratio for the global index was 1.16. 1.12 for 25 to 29 and 1.08 for over 30. The P-value for interaction is 0.62. So you might think that there's a suggestion of a trend here. I didn't do it as a trend statistic. It could be that

the leaner women are slightly more at risk for one of these events. But based on this test, we don't have much evidence of that.

By some of the other fracture risk endpoints, as calculated, the P-values also suggest that the summary of the global index statistic is a valid estimate for all those subgroups.

This is the increment of data since the intervention stopped. Again this is new data so these are new events, 13 versus 17 hip fractures. So you are seeing that protection is continuing in essentially the 15 months since the trial ended. Vertebral fractures still benefit, all the fractures. Interestingly the global index also for the incremental events since the trial stopped remains elevated and it is highly statistically significant. You know the nominal Z-value, the 0.5 level test, is 1.96 or two standard deviations so this unweighted Z of -3.16 is highly statistically significant.

This is the cumulative results. Those incremental data don't change our picture of benefit for fractures very much at all. These are all

pointing in the same way they did a year ago. The statistical evidence is strong for that prevention. But so is our evidence that the overall harm is greater than the benefit with a 14 percent increase in the number of women who had one or more of those events. These are not counts of events but counts of women who had one of them. It's highly statistically significant.

I don't have a summary slide. Sorry. But I wanted to make a comment about this. When the global index was defined, it really was for the purpose of monitoring the trial because we knew we'd have risks and benefits. It was a tool to be used, but it had become more than that. We didn't really envision it playing such a role in understanding how these drugs might be used. But I think it brings to bear on the issue that prevention work is really quite difficult to do.

We didn't anticipate that the trial was going to come out this way at all. It was going to be much simpler. All we had to do was worry about whether the breast cancer was going to show up in time

for us to see it. So this global index is pristine in the sense that it was developed before we saw the data and it was based on diseases that we thought might be impacted by these interventions and that had a significant effect on the mortality of older women.

Now there's been some suggestion that it's not inclusive enough. We would certainly acknowledge that it doesn't include all the potential impacts of these medicines. It was never envisioned to. This was a prevention trial for chronic diseases. We captured the critical chronic diseases that we were looking at. We acknowledge some of the effects.

I think we need to be very cautious in the idea of expanding this global index by cherrypicking particular endpoints that we like. That's a great way to engineer something to come out the way you want it to do. But because it's been mentioned several times, I will note that the difference in vertebral fractures right here will not cancel out. If you start out in these benefits, you need to go ask for a vertebral fracture if that's a benefit. Define the criteria by which vertebral fractures make it into a new global

index and then let's start applying it to other diseases and make sure that we have captured all the risks and benefits that satisfy those criteria before we calculate it. So I think with that I will end and turn it back to my colleague, Dr. Jacques Rossouw.

DR. ROSSOUW: And don't worry, I'm not going to give my talk over again. I just wanted to summarize where WHI is going from here. Dr. Stefanick has mentioned some of the publications that are coming out in the next few months, but one that the investigators as a group feels is important is to summarize, to put everything together, all the major findings and some of the most important subgroup analyses some of which you saw today in a final comprehensive paper much like the paper last year in JAMA, but with the updated information and the informative subgroup analyses. That obviously has to wait until all of the other papers on specific disease entities have been published. That is something that we envision doing perhaps next year.

The other detailed analysis that Dr. Anderson showed you some preliminary work on is also

one I think that will be of interesting to the community. That is on breast cancer, specifically by prior use. Now as she's shown you some of the preliminary work-up of that, we haven't yet found an explanation as to why in the trial there was an apparently lesser increase in breast cancer on E + P in the women without prior use. But she also showed you that those women appeared to have baseline if you look at the placebo group to be of somewhat higher risk. So you have something strange going on here.

Then if you look at the Kaplan-Meier curves and then the year-by-year data that Dr. Chlebowski showed you, then you also get the impression that those without prior use there's something strange going on in the first three years. Why is the hazard ratio lower in the E + P group than in the placebo group in the first three years? Is that a real effect? Do you have a bimodal effect where the E + P in those without prior use initially has a dampening effect on breast cancer and then later there's an increase? I don't know what the biological explanation for that would be. Or is it an artifact

that we need to try to tease out and explain why we could not ascertain breast cancer early on in those without prior use? Those are two important publications that are coming down the pipe.

Now as my colleagues have said, the trial of Premarin alone, E alone, continues. The plan termination is 2005. Of course, it undergoes review every six months with updated data and further analyses. But the plan termination is 2005. So that tells you that the results do have some differences compared to the E + P trial.

Now in trying to explain the findings that you've seen today, the investigators have also completed and have launched a number of case-control laboratory analyses for the cardiovascular outcomes. These have By and large been completed for the major outcomes. So we're looking at whether baseline or one year lipids, coagulation, inflammation markers, other biomarkers such as homocysteine and allelic variations related to those intermediate factors whether they influence the E + P effect in the trial. Some of those have been published in the publications that

have come out over the last year, but there are others, in particular, the genomic investigations that will be published in the future.

For fractures, there is an interest in the group in looking at whether baseline estradiol and sex hormone binding globulin ("SHBG") and markers of bone turnover and allelic variations related to estrogen metabolism influence the results. Are the results different in subsets of the population more or less benefit and similarly for breast cancer again where the baseline estradiol and also testosterone SHBG and allelic variations related to hormone metabolism influenced the results or some of the more important lab investigations that are in the works?

Now for the E + P trial, we plan to continue surveillance. You saw a little bit of that data of all clinical outcomes until 2007, in other words, five years post trial follow-up. This is geared particularly to following whether the increase in breast cancer risk persists and if so for how long.

Now the E alone trial the investigators don't know the results but the Institute has agreed to

fund post-trial surveillance for two years following that study. It's basically predicated upon what we were observed in E + P. There are going to be some effects in the E alone - I don't know which - that are going to be worth following up to see whether they persist or not. They are unspecified at this point. We don't know what they will be.

Then most exciting is that the Institute has also agreed to fund a larger enterprise to ensure that the enormous amount of data and the extraordinarily valuable biological specimen repository is exploited fully to the benefit of the entire scientific community and of the population. We have a cohort of over 160,000 participants in the various trials and observational studies. We have citrated blood, EDTA plasma, serum, DNA in the form of buffy coat and in subset urine samples that we've only barely utilized a small fraction of that.

The principle here is to invite WHI and other investigators and entities including commercial entities that in some places have the best expertises particularly when you think of proteomics and genomics

to exam this dataset and to participate in the further scientific utilization of this resource. To that end, the Institute will issue a Broad Agency Announcement towards the end of 2005 with funding for 2006 to 2010 to invite the entire community to address the scientific questions that this resource can be useful for. There is some funding set aside for the Broad Agency Announcement but as part of this activity it will made clear that other sources of funding from inside NIH and outside NIH can also be applied to this resource. Now the exact structure of this and so forth has to be worked out but I thought it was important to tell all of you here that we all need to start thinking about what we can learn from WHI aside from what has been revealed so far. Thank you very much.

CHAIRMAN McCLUNG: I thank all of you for a very careful and thoughtful presentation to us that has I'm sure given us all kinds of thoughts of queries and questions to ask. We're a little behind schedule. What I propose is that we still plan to have our lunch break from noon until 1:00 p.m. We have ten minutes

for some questions that we can address to the WHI panel at the moment. Then we'll have time if we need to reopen that discussion when we come back from lunch. So are there questions that the Committee members have to direct to Dr. Rossouw and to his colleagues?

DR. CARPENTER: I was taken by the protective effect of BMI in several of the parameters that you presented. I was wondering if this could simply represent something like a dosage exposure effect or if it's even possible to look at this data with respect to dose on a per unit weight basis or something that would allow us to tell whether there's some critical exposure level that would protect you from some of the consequences.

DR. ROSSOUW: So the question is whether we can do further analyses to see whether BMI modulates the effect. I guess it gets also to the issue of what the endogenous levels are to start off with and what the response is to the treatment. It's possible, for example, that women with a higher BMI start with higher estrogen levels but also have a less

of an increment in on-treatment levels. We plan to get at some of this by looking at the baseline levels. It may also be interesting to look at the on-treatment levels in the mode and see whether that influences it. Does that answer your question or were you getting at something a little different?

DR. CARPENTER: No, I was just very simply trying to think of mechanisms by which that could happen.

DR. ROSSOUW: Right.

DR. STEFANICK: I'd just like to comment that when you say "protective effective BMI" I'm hoping you're only talking about bone and not breast because an important thing with the breast is to realize that we're comparing two groups so it may not really be protective as much as the fact that the placebo group is at a high enough risk that adding that little bit doesn't make a difference. It's like a dilution effect and I don't know if that's an appropriate thing to say. Rowan could comment on that. People have said that on other data that this BMI seems to be protecting women against the breast

cancer. It's really the case that their overall risk is higher so adding one more little risk like E + P doesn't make that big of a difference but that's my perspective.

DR. CHLEBOWSKI: As Garn points out, all these subgroups are really very tricky. One of the other things that we did not have time to present was we looked at the Gail model which is another way of looking at the tertiles of Gail model risk for five years of risk. The women who were at the absolute lowest risk again wasn't significant interaction but they had suggestion of a higher effect on breast cancer than people who had the highest risk which is a little counter intuitive to the way we think about it and that could integrate some of these things like body mass index.

So it gets back to the same question of "Are these factors such as obesity that give you a high level means that adding something on top of it doesn't matter". So the concept that we can find the low risk group is very hazardous because if anything there seems to be in some of the lower risk groups at

least for breast cancer, a suggestion that maybe E + P is a little higher relative risk, not absolute risk.

CHAIRMAN McCLUNG: And that underscores the problem in mixing or confusing absolute and relative risk. When you are taking risk defined on absolute by either the Gail model or the Black model and then looking at relative risks among groups based on absolute risk, you have to be really careful about our terminology and about how we interpret and conclude from those sorts of things. Other questions? Yes.

DR. STADEL: This is a technical question. On statistical analysis, you had outcome analyses that were both weighted and unweighted depending on people's beliefs about the nature of the disease. Were any of the interaction tests weighted based in particular on rather a known relationship of adiposity to endogenous estrogen production which could lead to a weighting of expectation with regard to the relationship of body mass to outcome? I just wondered if there was any parallel weighting of interactions testing as was done with outcome testing.

DR. ANDERSON: Yes. For the interaction test, I mostly showed you both weighted and unweighted, but I have to say that in developing the protocol and all that, we never talked about how we would do interaction tests. It's not clear to me whether the weighting that we defined for the primary endpoint comparisons is the right weight to use for interactions. I put them there out of intellectual honesty but it's not clear which is the right way to go.

DR. FOLLMAN: I had a comment for Dr. Stefanick. One thing that you looked at was the hazard ratio for the CHD over time. You showed that early on there seemed to be a harmful effect of E + P and later on it reversed. Your explanation for that was basically the patients and the women in the E + P group had already developed their breast cancer so it wasn't a fair comparison between the two groups at that point in time. But I was wondering if people had also looked at an alternative explanation where maybe the benefit of E + P takes a long time to manifest itself. I was wondering if this might explain or

relate to the epidemiological literature where you did see an beneficial effect of E + P on CVD thinking that in the epidemiologic studies women in those studies would have been followed up and would have a fair amount of prior hormone therapy as they enrolled.

DR. STEFANICK: Okay. Just to clarify, you said breast cancer but you meant CHD.

DR. FOLLMAN: Right.

DR. STEFANICK: Right. Well, the alternative hypothesis is actually the one that we tested in a HERS follow-up study because people had that same idea that there's this early harm and later benefit which they were attributing to the one-year lipid changes. We've never actually seen the four year lipid changes from either study.

But in terms of to follow up on that question, we're actually doing some very interesting analyses now within WHI on the observational study in which we have 93,000 women, many of whom are hormone users and the clinical trial. We're trying to tease that apart. Obviously I'm not going to say anything about what we're finding in that. The length of use

is an important issue. When you look at observational studies, many of the studies are looking at women who are current users and then they do a survey two years later.

So you have a very strange mixture of who is actually a user/non-user in the observational studies. I'm not really sure that we want to completely go back to the idea that there is still benefit because we see what I call the "survivor" group at the end. I'm actually going to ask Garnet to comment on this as well.

DR. ANDERSON: Yes. I want to sound a real note of caution for those year-by-year analyses. The first year comparison is a randomized comparison because everyone who is randomized goes through that first year and has an event and is counted. The second year becomes a woman who didn't have an event in the first year. That becomes the denominator. So there are survivor issues. The farther out you go on that timeline the worse it is.

In addition, we have lack of adherence that starts to feed into that in a big way and later

on. So looking at "randomized comparisons" in those later years in a year-by-year fashion is dangerous territory and I wouldn't want to make much inference about that year six data.

DR. ROSSOUW: Let me go back to the slide that prompted Dr. Follman's remark. So what Garnet was saying is that this is real result. It's actually quite a strong result, but we have to be cautious about the results after these subsequent years. Nevertheless it's interesting if you look at the rates in the E + P group over time. There's this increase here but there's no convincing evidence that it decreases over time. What's happening here, who knows? But it is striking that it's the year in which the placebo group is highest. That explains this apparent risk reduction there. This is very messy data.

I did want to point out that the observational data on this issue are very messy too. It turns out that the observational studies are most of the early events so their estimate of what happens in the first year or so after studying hormones is

very poor. But nonetheless if you look at the conventional analyses of observational data particularly the Nurses' Health Study, it suggests that the benefit is greater in the first few years and less in later years. So I don't think there's convincing evidence from the observational studies to suggest that longer duration is better. If anything, it may be the other way around.

DR. CHLEBOWSKI: Just another comment. When we're talking about duration effects and getting back to breast cancer for a second, just reminded me to really make this point again. If when we talk about the time-to-events for the breast cancer, it just reminded me that the mammograms were 74 percent more likely to be abnormal after one year, but in that first year, there was about 30 to 40 percent less cancer seen. So we ended up having almost twice as many abnormal mammograms, a significantly fewer cancers seen and more advanced cancers subsequently being delivered. Those things taken together just looking at those numbers suggest that cancers are growing during those initial years but we're not able

to see them with mammograms which are mush less effective in finding the cancers. If we're looking at those first two or three years, we really don't know what we're seeing because it appears that the E + P is making the mammographic diagnosis of those cancers much more difficult. That's why they're being seen later. So it's the same kind of question of how can we look at fairly those first two year events when we know that there's two other things that are occurring in the background.

DR. CAULEY: I just wanted to emphasize also something that Marcia said when she showed the Kaplan-Meier of the global index. At no point was the E + P curve lower showing more benefit than the placebo group. That's during the entire duration of the follow-up.

CHAIRMAN McCLUNG: All right. Now that we're warmed up with that discussion and know what the situation is going to be, let me propose that we now break for lunch. That will give all of us a chance to reflect on what we've heard and gather our questions. Let me encourage the panel members to refrain from

working on this over lunch either with each other or with others from outside our group so that we'll all come back fresh and new at 1:00 p.m. Thanks. Off the record.

(Whereupon, at 12:02 p.m., the above-entitled matter recessed to reconvene at 1:06 p.m. the same day.)

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

1:06 p.m.

CHAIRMAN McCLUNG: On the record. Okay. Let's follow up with questions and clarifications of the panel to the WHI investigators. So we'll devote 15 minutes to that and then if we need more time, we can do that later in the afternoon. Dr. Lukert, I know had a question.

DR. LUKERT: You know, there's accumulating evidence that there's a connection between vascular disease and osteoporosis, that people with osteoporosis tend to have a higher incidence of atherosclerotic change. What I was wondering is, if there's a preponderance of the people who have cardiovascular events who also were at high risk for osteoporosis. Because that would make some difference, if one of the really high risk populations were the people who had a greater tendency toward osteoporosis, you'd be more hesitant to intervene with that particular form of treatment in that group of patients.

CHAIRMAN McCLUNG: So the question is, can

they identify or did they look at --

DR. LUKERT: Yes.

CHAIRMAN McCLUNG: -- individuals based on cardiovascular risk --

DR. LUKERT: At risk for a fracture.

CHAIRMAN McCLUNG: Because they stratified on the risk of fracture and looked at it the other way around.

DR. LUKERT: Right.

CHAIRMAN McCLUNG: So you are looking at the opposite way. Dr. McCauley.

DR. CAULEY: No, we didn't really look at that. It's an excellent question. The only thing that I would point out is that the fracture risk score was based on prediction of hip fracture. So the high risk group they were much older than the low risk group. Just by their age alone, they are going to be a greater risk of CVD.

DR. LUKERT: It would be interesting however to look at that age stratified way also if you can.

DR. CAULEY: Yes, even the factors, age.

Smoking was also greater in the high risk group, but BMI went the opposite way. So some of the risk factors of CVD would be consistent with an increase of cardiovascular risk in the high fracture risk group and some not.

CHAIRMAN McCLUNG: Dr. Bone, you had a question.

DR. BONE: Yes, we've had a very nice presentation of a lot of analyses and subanalyses and subanalyses. One of the points that was made is that rather than look at the individual groups in some cases, there was a test for whether there was an interaction. We saw P-values of about 0.1 in many cases that were displayed. When we talk about a hazard ratio of 1.2 versus a hazard ratio of 1.0, was there actually testing of the power of this test of the interaction term to detect a true difference?

DR. ANDERSON: No.

DR. BONE: So that wasn't tested. Thank you.

CHAIRMAN McCLUNG: Dr. Woolf.

DR. WOOLF: Several members of the public

this morning indicated they were concerned about the potential for discontinuing Prempro or conjugated estrogens anyway for peri-menopausal women because of the symptomatology. I thought I saw a slide briefly flashed by me that seemed to indicate that the global index was equally poor for women in the lowest age group as with any. Is that a true assessment?

DR. ANDERSON: Yes. I showed you global index by five year age categories and the P-value for interaction of that was 0.99 saying that we really have no statistical evidence for a difference by age.

DR. WOOLF: Can I follow up on Dr. Bone's question? Does a failure to do a power analysis say anything about the validity of the interaction's statistics?

DR. ANDERSON: A power analysis asks "What's the probability of finding an effect if there is a true one of a certain size?" So in an interaction test, it's rather challenging to ask what the power is for something like that. We have to acknowledge that there are few women when you cut up the data so finely. To address that, we tended to do

those interactions with a continuous variable instead of dicing it up into little cells. We just did it continuously and still didn't find anything. Yes, we don't have great power in some of these. I would not want to hazard a guess of what the power would be, but this is the best data that we're going to have on that. These data pretty much stand for themselves.

DR. FOLLMAN: Just a comment on the power analysis issue, Dr. Anderson's exactly right. We don't have good power for these tests of interaction. That's just the way clinical trials are designed in a way. You design it to ask the main question and by definition, you essentially don't have good power for the interaction. So they give you some comfort if there is not interaction, but it's understood that there's not a lot of power for it. They did a lot of tests and they did some correction for the multiple tests.

I'd like to amplify on a point that Barbara made. One interesting analyses that I thought laid everything out on the line was the global index analysis particularly when you looked by tertiles of

fracture risk. But then on reflection, you realize that for this Committee we're really just interested in the women who would be getting this probably as a second line therapy for osteoporosis. So it would be interesting to look at the global index as a function of tertile risk amongst those women who would be less likely to receive hormone replacement therapy for that indication. So, for example, eliminate those who had hypertension at baseline or who had high risk for breast cancer or had dyslipidemia, maybe had prior breast cancers and so on and rerun the analysis. I was wondering if you've had thought about that or had done that kind of sensitivity analysis for the global risk index as a function of tertiles of fracture risk.

DR. CAULEY: No, we have not done that analysis. All those risk factors that you've mentioned, the dyslipidemia the prevalence was rather low. Hypertension about one-third of the women did report hypertension. For all the other risk factors, the prevalence was rather low.

DR. CHLEBOWSKI: And with respect to the breast cancer, the women self-selected against that

anyway. When we looked at the Gail risk score for the group, it was 1.5 for a 62 year old population. That's less than a 60 year old with no risk factors which is 1.7 percent five year risk. Women have to be neutral to the question and there was enough noise about breast cancer risks that those women who were higher or had more family histories just didn't enter the study.

DR. ROSSOUW: Let me just briefly respond to that. Dr. Anderson was right and you were right that you power this to look at the overall effect and if you do these subgroup analyses and the interaction tests and you don't find anything strikingly different, then you tend to believe the overall result is the one that probably applies to the subgroups as well because that is the robust result that you have. In terms of looking at clinically relevant subgroups beyond those that we've done, if someone could tell us who are the patients that are going to get this treatment for osteoporosis prevention and what are their characteristics, we could try to run such an analysis.

But I'm not sure for example that a person who has a modestly elevated blood pressure wouldn't still be a candidate for osteoporosis prevention for example. But if you could give us who are the people. Is this a targeted population? My impression in the past has been the answer is "No." Basically the gestalt was that every post menopausal woman should basically get this if she had a low BMD. Right? If there is a different kind of gestalt emerging now, then we could potentially run some analyses although again our palate will be pretty low to get informative results.

CHAIRMAN McCLUNG: Dr. Bone.

DR. BONE: Thanks. A couple of comments related to the recent discussion of Dr. Follman's question in particular and it ties into subsequent comments. The investigators did what they could with what they had as far as this risk estimate. But I think they demonstrated pretty clearly that there was some real limitations to the ability of the information available to them to classify the patients according to their risk of either developing an

osteoporoic fracture or even developing osteoporosis as we know to be defined by bone densitometry because they didn't have at their disposal the basic tools that we use for doing those things.

So a fair number of patients classified as low risk actually qualified on their basis of their bone density as having osteoporosis amongst those whom bone density were measured. We would ordinarily expect if we were going to identify a high risk group to see a much higher relative risk, say a log higher, who have a tenfold relative risk or something like that. So some of the questions that may not be possible to model but I don't know if they would be impossible to model would be to look at what the risk/benefit ratio would be in patients who actually had osteoporosis or try to imagine what would happen if we had the conventional tools that we would use to assign risk.

The understanding of what's meant by "prevention" of osteoporosis depends a lot of where you are. At the time of the U.S. guidelines were originally formulated, it just meant that your bone

density didn't go down. But I think the clinical practice probably conforms a little more closely in some cases to what the European regulatory authorities which is basically prevention of so-called "osteopenia" progressing to osteoporosis based on bone density. They actually classify early remedial post menopausal bone loss and a few years delayed which their delayed study would correspond more closely to what was done here except --

Just to take a minute. Up to five years post menopausal with osteopenia, more than five years with post menopausal to osteopenia are classified separately in the European guidance. Somebody correct me if I'm slightly off on that. It might be three years. I think it's five. So most of the patients weren't immediately post menopausal. They weren't classified on the basis of having a somewhat low bone density. But that would be the group that probably is more thought of as the prevention population by more doctors these days just to respond to the other question that Dr. Woolf so raised.

DR. WOOLF: Getting back to Dr. Rossouw's

point about who to model, I take the reverse and say "Who shouldn't be on the drug" and that's clearly the women who are hypertensive and smoke. They have a far increased risk of stroke. I think a physician who uses estrogen in that setting does so at his parol and the limited malpractice insurance. So you can exclude some of those folks, certainly risk of stroke and someone with significant hypertension and/or smokes. You should model them out because they probably wouldn't be an ideal candidate for the drug anyway.

CHAIRMAN McCLUNG: All right. Let me propose that we draw this section of the discussion to a close and move on to the next part of the program. Representatives from Wyeth Pharmaceuticals have prepared a presentation. Dr. Joseph Camardo will lead off and coordinate that.

DR. CAMARDO: Thank you very much. Good afternoon. On behalf of Wyeth, I want to thank the FDA first of all for inviting us to the Advisory Committee Meeting and for the Committee giving us the time. Our presentation today will focus on how we support the appropriate use of hormone therapy based

on the evidence available. That's evidence about the risks and the benefits, evidence from clinical studies and evidence from WHI as well.

My objective today is not to review a lot of data. I have some data but not a lot of data. My objective is really to explain to you how the medical team at Wyeth interprets the data from these studies, what data we emphasize and why although we acknowledge certain risks we continue to support estrogen/progestin as an option for osteoporosis. I also want to explain how the company responds when we receive clinical study data particularly safety data that will have an impact on the use of the product for women and practitioners.

Now I will be presenting positive data about Prempro. I want to say in advance that it's not my intention to ignore or downplay the risks observed in WHI. You will see that we take these reports very seriously. I will discuss them, but I did choose to reduce some of the effective data first. I just wanted to remind you that I'm the head of Clinical Research at Wyeth. I'm representing actually a

medical team that's been supporting our reaction to the WHI and actually our support for estrogen/progestin over the last several years.

I have four items I would like to cover today briefly. First there's an introduction. I want to explain how we come to the conclusions that E + P, the combination Prempro, should be used for osteoporosis. I also want to go over some clinical data about bone loss and estrogen therapy. This probably shouldn't be new to any of you but I did want to review it today. I also want to discuss the WHI data and it's clinical application to practice and the risk that were reserved in this trial and how we deal with them. The fourth thing is that I want to review the information in the current product label. What I mean by that is the product-prescribing information and that was I believe included in the material that was sent to the Advisory Committee.

Let me start with this one slide. These are five points that the medical team at Wyeth used to construct our recommendations about Prempro. These are really the five ideas that I want to convey to you

today.

1. The first is that prevention of osteoporosis is an important aspect of healthcare especially for women in menopause. I think we would all agree to that.

2. The second is that Prempro is effective for osteoporosis and it is one of a relatively small number of medical therapies available for osteoporosis.

3. The third point, estrogen/progestin is the only therapy that can reduce menopausal symptoms and prevent osteoporosis. I think we would agree with that too.

4. The fourth point is very important to us and I want to make sure that it's emphasized properly. Practitioners really do need to determine the use of hormone therapy for an individual based on all the evidence available and the goal of treatment. I think that should be clear from this morning's discussion and some of the questions that came up in the afternoon because there are areas about which the certainty is lacking.

5. And the final thing - and this is very important from the company's point of view as the sponsor of the product - is the Prempro label provides accurate information. The point is the point number four - practitioners need to make the decision- has to be supported by point number five which is that sponsor provides appropriate information.

Now let's go into these in a little bit of detail. I think we didn't talk about this very much today but there can be significant disability and mortality related to fractures in women. It really does demand our attention. That's why we're having a meeting today.

An interesting statistic, the National Osteoporosis Foundation advertises that every 20 seconds there's a fracture related to osteoporosis. Also I think we know this that at any given level of trauma someone with bone loss, whatever degree, is at high risk for fracture than someone without a decrease in bone density or quality. So prevention of bone loss is an important aspect of healthcare for women.

Let me summarize just the four points in

this slide.

1. First, we know bone loss accompanies menopause.

2. We know that bone loss increases the risk of hip, vertebral and other fractures.

3. We know that fracture risk increases before bone loss has progressed to the level of osteoporosis.

4. We know that hip and vertebral fractures are associated with increased mortality and also significant disability. This was alluded to earlier in the morning. One year mortality after hip fracture can be as high as 20 percent. Twenty-five percent of women need nursing home care after hip fracture. Vertebral and other osteoporoic fractures can be disabling.

Now I said I would talk about the positive data for Prempro. Prempro is effective for osteoporosis prevention and treatment of menopausal symptoms. Remember this is one of the premises that the medical team at Wyeth has based our discussion and our recommendations upon. Prempro has been shown to

reduce non-vertebral fractures especially hip fractures now even in women who do not yet have osteoporosis. You heard that this morning from WHI.

You'll also see some data from me about low dose Prempro which reduces menopausal symptoms and also increases bone density. I want to emphasize this is important because symptoms and bone loss may be concurrent medical problems. We're not really focused on symptoms today but I don't want to forget about them because that is part of the clinical presentation in some women who also have bone loss.

We also all know that because the awareness of osteoporosis has increased, this has encouraged the development of new medical therapy so that in 2003 estrogen/progestin is one of a number of agents available to protect bone health. My point here is that the availability of different therapies is an advantage. The therapies have different mechanisms. They had different side effects. This allows the women and the practitioners a reasonable array of choices because each agent has strengths and weaknesses, effectiveness, tolerability, compliance

with each therapy. They may vary with individuals. I want to emphasize this because the medical team concluded after looking our product and looking at the other products that the option to use estrogen/progestin is an advantage of women and practitioners, but it's not the only therapy available.

Let me show you something about how we think about the strengths and weaknesses. First of bisphosphonates, we know that bisphosphonates prevent fractures. There are clinical trials supporting that. But we also know that bisphosphonates may not be suitable for all women. There are limited data in non-osteoporoic women and bisphosphonates have gastro-intestinal side effects.

The selective estrogens prevent vertebral fractures, raloxifene, for example. But so far, raloxifene hasn't been shown to prevent hip fracture. Moreover, hot flashes occur in about 20 percent of women so it's not really an appropriate therapy for women with menopausal symptoms.

The fourth point here we talk about E + P

today. We know it prevents vertebral and non-vertebral fractures. We've also learned that E + P may be associated with increased risk of breast cancer and CVD in certain populations. The summary is the products have strengths and weaknesses and the variety of agents available helps to support clinical practice.

Now we also concluded - and this was the fourth point on my first slide - that the decision to use estrogen/progestin or not to use estrogen/progestin really needs to be made by the woman along with a knowledgeable practitioner. Now it's very clear to everybody that the results of the WHI study have had a major impact on the assessment of the risk/benefit for estrogen/progestin. But still a decision to use estrogen/progestin for osteoporosis and menopause and particularly in the younger women cannot be based just on the WHI study.

The overall objective of the study was not necessarily to target a therapy for every woman who may use E + P. I just remind you women with significant symptoms were discouraged from

participation in the WHI study. There were some women in the study with symptoms but that was not a major objective of the study. The study was designed to assess potential benefits of long term use. We went through those, fractures, colon cancer, CVD. We know the outcome and selected long term risks, breast cancer, DVT. We know the outcome there too. But it really wasn't designed to assess a question that physicians do face all the time which is "How to use estrogen/progestin in women closer to menopause who have bone loss and menopausal symptoms."

Now I intend to discuss the label for Prempro as the last item on the agenda. The premise here is that individual judgment requires knowledge. The label for Prempro represents again what the medical team concluded is the information to support clinical decision making. The key points about the label are shown here. You've actually seen part of this earlier today. I'll discuss them briefly at the end of my presentation, but there are four points here.

1. First the pertinent results from

numerous trials are included.

2. The safety information is updated regularly after medical review of evidence.

3. The WHI data are included in the current version of the label.

4. The information is available both to practitioners and to women. There is a product-prescribing information which is available to the prescriber. There's a patient package insert which the women will receive when a prescription is filled. There's also the recent FDA Educational Campaign which Dr. Orloff referred to in his introduction today.

Let me go back to my first five premises. Prevention of osteoporosis is important. Prempro is effective for osteoporosis. It's one of a few agents available. Hormone therapy, that's estrogen/progestin for the purpose of today is the only therapy that can reduce menopausal symptoms and prevent osteoporosis. Fourth and fifth points very important. Practitioners need to use the product, estrogen/progestin, for the individual woman after making a decision based on evidence and based on the goal of treatment. We need

to support their decision with the Prempro label providing accurate information.

I want to talk now about the clinical data for E + P. There are four points here too.

1. Rapid and progressive bone loss that occurs early in menopause can be prevented with E + P. I want to show you some of that data.

2. Most fractures occur in women who are osteopenic, not osteoporoic so early intervention may be important.

3. Prempro and I'll show this data at all doses improves bone density in osteopenic women.

4. Prempro in the WHI reduced fractures significantly even in women who were not osteoporoic.

Let me review these four points in some detail. First, this slide which I borrowed from Dr. Lindsay's Lancet article from 1976 shows that bone loss follows estrogen loss and it can be prevented with early post menopausal use of estrogen. The slide plots metacarpal bone mineral content on the Y-axis over time on the X-axis for women who were not treated after ovariectomy which is the blue line and women who

were treated immediately after surgery, the red squares, starting three years after surgery, the green and starting six years after surgery, the blue triangles.

The data from this study show that the women who started estrogen immediately after ovariectomy preserved bone mineral content at or near their baseline before ovariectomy. The women who started six years later, the blue triangles, maintained bone mineral content at about the same level it was when they started treatment but that was below their baseline from their ovariectomy. Those who started estrogen within three years actually fell in between the two extremes.

This is a biological effect and it suggests that early post menopausal use of estrogen would maintain higher bone strength. It's one of the pieces of evidence that has supported estrogen use in the early post menopausal period.

Other evidence about the incidence and the number of fractures in a large cohort study also suggests that early intervention would be useful.

This slide from Dr. Siris' paper shows that fracture incidence increases as bone density decreases. The density is only one of the factors that accounts for risk. Bone quality which is a reflection of remodeling is also very important but this does show that with lower BMD score the number of fractures per 1,000 woman years in this cohort increases several fold. It's actually highest in the women with WHO defined osteoporosis which is to the far right of the graph.

But this slide shows that in the same cohort the actual number of fractures is highest in the women with osteopenia because there are so many more women who fall into the category of mild or moderate BMD loss who are not yet osteoporoic. This is not too much different from the population in WHI. So this is not just a theoretical benefit which I showed you from the early intervention. There appears to be a practical benefit as well in that more fractures can be prevented.

Based on the biologic effect of estrogen and the consideration that prevention of further bone

loss has a clinical benefit, we evaluated Prempro at different doses specifically for osteoporosis prevention in post menopausal women, many of whom were osteopenic. These studies include the original studies of Prempro of more than ten years ago and the most recent study performed as the basis for approval of the low doses of Prempro. This recent study is the Women's HOPE study. That's the one I'll discuss briefly.

The study was designed to see if doses lower than 0.625 mg estrogen and 0.625 mg progestin, the dose that was used in WHI, would be active for symptoms and for bone loss. Two thousand, eight hundred and five women were randomized at various doses of Prempro, Premarin or placebo. The average age was 53. The average time since menopause was 4.7 years. The endpoints included among numerous things most important reduction of vasomotor symptoms and improvement in bone density and protection of the endometrium. The bone density substudy which I'll show in the next slide included 800 women who were followed for two years. Much of the data from this

study have been published.

Dr. Lindsay's publication in 2002 showed the Prempro improves bone density in all doses. On the left panel is the bone density in the spine. This declined in the placebo group which was expected. That's that blue line that's going downward. But it increased in all the time points starting at six months in the women who received 0.3 mg, the red triangles, 0.45 mg, the purple squares, or 0.625 mg. That's the dose of Prempro that was used in WHI shown by the green diamonds.

At the spine, the 0.45 dose, the purple, increased density about two percent. The 0.625 dose about three percent. All the differences reached significance compared with placebo. On the right panel are data from the hip. It's the same colors. Again bone density declined in the placebo group. In contrast, bone density was increased by all the doses of Prempro. In this case as with the spine, all the differences reached significance compared with placebo at the time points starting at about one year. By 24 months, the results for all the three doses were very

close to one another. Moreover the increase in density compares favorably with data from studies of raloxifene and bisphosphonates and I won't show you that data.

Now you've heard this in detail already today. Many epidemiology studies concluded that estrogen/progestin products were associated with a decrease in fractures in women. WHI provides evidence that fractures are indeed prevented even in osteopenic women. I took these numbers from the publication. All fractures were reduced by 24 percent. Hip fractures reduced by 33 percent. Vertebral by 35. Arm and wrist fractures by 29 percent.

But the data also indicate a very reliable and robust effect. Now I emphasize these data today because part of my job is to explain how we responded to the WHI results. Now of us on the medical team thought that we could or should ignore the highly favorable fracture results.

1. It was particularly impressive that these results were achieved even though low bone density was not a requirement for study entry. Only

about four to six percent of the women were osteoporoic. Generally we studied bone sparing agents in osteoporoic women. So this is a first study to demonstrate such a benefit in osteopenic women. It's consistent with what I told you in the last few slides about fractures in osteopenic women.

2. The fracture incidence was probably underestimated. The endpoint was clinical fractures. I think this has been explained already. Most studies we do for regulatory approval includes fine radiographs so we can detect subclinical fractures. Of the women who have a radiographically identified fracture, about 15 to 20 will develop another fracture within a year or two.

3. The reduction was observed within the first year of treatment. I'm not telling you something that you don't already probably know, but what I would emphasize is these are the data that we evaluated in making our decisions.

So there is convincing evidence that estrogen/progestin can prevent fractures. Let me just summarize these points again. There is rapid bone

loss in early menopause. Fracture incidence increases as density decreases. Most fractures occur in women who are osteopenic. Prempro improves bone density in osteopenic women close to menopause. That's what I showed you from the HOPE study. The WHI shows that Prempro reduces fractures even in women who are not screened for osteoporosis.

Now of course it's 2003. It's likely that every clinical decision includes some discussion about WHI. Practitioners need to know about it. They read about it. It's featured in numerous journals. It's a subject of CME. Women have learned about it through the media. The results are featured prominently in the Wyeth Prempro Prescribing Information. The most recent version of the label is part of that background and it's also on the website.

But as I stated in the beginning, point four if you remember, applying the results of a clinical trial really requires informed clinical judgment. There are some limitations to the evidence that are related to differences between a clinical trial and between clinical practice. The

investigators who spoke this morning actually alluded to some of these.

Again I want to point out the medical team at Wyeth reviewed and discussed the WHI data at great length, internally with the investigators, with the NIH team, with the FDA. We acted on the data last year by amending the label and supporting dissemination of the WHI data. You'll see how we did this too. But the medical team doesn't agree fully with some of the broad interpretations of the data, particularly some of the statements about the application of the data to all clinical practice especially some of the subgroup analyses.

Now we know that the subgroup analyses are supposed to be hypothesis generating. They are not supposed to be definitive. But one of the problems is that in clinical practice the women whom you actually see come from one of the subgroups or they have characteristics of one of the subgroups and some characteristics of the other. So you have to make an individual judgment.

These are the four points I want to make

about the WHI study and about how to apply the data from that study to clinical practice.

1. To remind you in general, the women who receive hormone therapy than the average age of the women in WHI. I know some younger women were studied in WHI, but in fact the most robust effects were driven mostly by the older women and they have menopausal symptoms, the women in general in practice who receive hormone therapy.

2. This one was also discussed earlier in the morning. The risk/benefit assessment in WHI didn't take into account all vertebral, that includes the clinical and morphometric fractures, and all of the nonvertebral fractures as well as some other benefits and risks. It was defined prospectively but it wasn't in fact selected.

3. Dr. Anderson referred to this one already. The global index from WHI is a clinical trial tool, but it cannot be used to assess the risk/benefit in individual women.

4. The data provide important information, being a little bit repetitious, but

clinical practice requires individual patient judgment.

Let me take these one point at a time. The first point, most women who take estrogen/progestin are younger than women in WHI. In the Women's HOPE and the other studies of estrogen/progestin in menopause, the women in the study were within five years of menopause. In general, that's because we tried to enroll women in the study in whom we can demonstrate a benefit on vasomotor symptoms, but this age group is approximately ten years younger than the average age of the WHI population. Again the robust effects were driven by the average of the population. The average age in the Women's HOPE study was about 53. The average age in the WHI study was about 63. The women in Women's HOPE were closer to menopause.

That's point number two. The women less than ten years since menopause appear to have no excess cardiac risk. Now I'm pointing that out because when you look at the paper for cardiac risk, it does look as though the women less than ten years

have no excess cardiac risk and it's consistent actually with some common sense clinical practice, some things that we know about age related risk of cardiovascular medicine. Again it's a subgroup analysis of the younger women, but the fact is that if it's hypothesis generating, one of the hypotheses could be that younger women have less cardiovascular risk.

In the absence of being able to make a clear demonstration of that fact, physicians and practitioners have to be able to make a decision for the individual woman. That's my point, not to have a discussion about the pluses and minuses of a subgroup analysis. It's to have a discussion about when you're finished with the subgroup analyses, how do the physicians use the data that you give them. It generates a hypothesis that the younger women closer to menopause may have a lower risk of using the estrogen/progestin.

The final thing is that in the younger women symptoms and osteoporosis are more likely to coexist and estrogen/progestin is the only therapy

that can concomitantly treat menopausal symptoms and prevent osteoporosis. Remember women will come to the physician partly because of a desire to treat a condition or a symptom or a problem, not just to be put into a trial for a long term prevention. So there will be a medical issue to address at the time.

I don't want to belabor this but the risk/benefit assessment did not take into account all of the osteoporoic fractures. The failure to do that when you calculate the global index may underestimate the benefit of hormone therapy for osteoporosis in general.

That's not really the point about adding up the global index. The point that I want to make and also what the medical team thinks about is that the disability from any type of fracture may have a significant impact on an individual woman. It may change the individual risk/benefit for estrogen/progestin. That's what actually has to be decided when someone wants to write a prescription.

Let me talk a little bit about the WHI global index. Dr. Anderson alluded to this. It's a

clinical trial tool. It's not really a risk management tool for individuals. It serves the purpose of a clinical trial, but it wasn't designed to serve clinical practice. I just want to point out that clinical trials evaluate the population. That's what we analyze. That's what we look at. That's what we add up. But clinical practice considers the individual risk/benefit.

I alluded to this earlier. The individual may or may not match closely. The actual population that was evaluated in the WHI trial may not match the subgroups. The age of the woman, the BMI, the time for menopause, the menopausal symptoms, the degree of osteopenia, the perceived need for osteoporosis prevention are differences that may characterize an individual and it may be very hard to characterize actually all of those differences in the population analysis that we do. So extending the results beyond the trial population really again when all of the discussion is done requires that the practitioner use judgment.

Leading to my next slide, the data provide

guidance, but clinical practice requires individual patient management. Now based on all of the data from this study and the other studies, I think the decision making process would be as follows:

1. The decision to use estrogen/progestin in menopause will be influenced by the presence, the severity of symptoms and the bone density measurement. The potential benefit of estrogen/progestin therapy on bone health should not be ignored in younger women in early post menopause, but the physician and the woman have to evaluate the benefit in light of the potential risk of vascular disease, stroke and heart attack and breast cancer. The individual risk has to be considered.

2. The use of estrogen/progestin in women with bone loss but no menopausal symptoms will have to based on the need to treatment women at high risk. We heard that the highest risk that was evaluated in WHI may not be the highest risk that will actually be seen in practice. Still those are the women who have to be treated. Also the consideration would be the unsuitability of the other handful of agents that are

available. This actually isn't too far away from the recommendation that was made by Dr. Cauley.

So let me summarize this section. How do you apply the data from WHI and a lot of other clinical studies to clinical practice and the individual woman? First, remember the women who take estrogen/progestin in general are going to be younger than the average age of the study. The risk/benefit assessment did not include all the fractures and a particular kind of fracture or a concern about a fracture may be important to a particular woman in practice. I just want to remind you again that the global index from WHI is a clinical trial tool, but it's not being advocated as some way to determine the risk/benefit for each woman. That still has to be done. The data provide guidance. Clinical practice requires individual patient management. The product information which is going to be the subject of my next section provides the information useful for practice decisions. Finally, estrogen/progestin in our estimation after evaluation by the medical team remains an important therapeutic option for

osteoporosis.

I want to talk about the product information specifically now. Let me start with one very important point about the product label. The medical team developed a label that is clear and balanced. It is the company's policy to revise the label when appropriate. Now I'm presenting the medical team's point of view which is that the current label accurately reflects the state of knowledge and the recommendations consistent with the evidence.

I want to go through these four points.

1. The product information strikes a balance so that the clinical practice is guided but its use is not appropriately expanded or limited. Those are important.

2. The label information for prescribers includes some recent results from a variety of clinical and epidemiological studies. There's a lot of data on the label.

3. The balance includes statements regarding the risks that have been reported and, with regard to safety, a conservative interpretation is

presented.

4. New data are considered for inclusion as they become available. That's exactly what happened last year when WHI became available and we worked with FDA to make changes in the label. That's exactly the process.

Now the recommendations for Prempro use are based on the evidence that we have today. For women with menopausal symptoms, Prempro can reduce symptoms and prevent bone loss. We say that and we cite the clinical trial results on bone density. For women without menopausal symptoms, Prempro is recommended only for women at significant risk for osteoporosis and for whom non-estrogen treatments have been considered. This change was made based on the results of WHI after consultation with our medical team and with the medical team of the FDA.

Let me be more specific. What does the indication actually say? Prempro or Premphase is indicated for:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.

That hasn't changed in the last year.

2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. This sentence in blue was added in the labeling as a result of the WHI. It says that "When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical products should be considered at the same time."

3. This indication about preservation of bone states "Prempro is indicated for mention of post menopausal osteoporosis." The sentence in blue was also added after consultation and review of the WHI data and it says "When prescribing solely for the prevention of post menopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medication should be carefully considered."

We also highlight certain information to promote awareness. Estrogen/progestin should not used for prevention of cardiovascular disease. That's very prominent. The risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and DVT as

reported in WHI and other studies are prominently and repeatedly noted. Specific information on breast cancer, coronary heart disease from WHI and other studies and information on dementia from the WHIMS study are also included. In fact the relevant risk of the outcomes in the global index which I discussed earlier that was published in JAMA last July is reproduced in the product information.

We also recommend therapy should be prescribed at the lowest effective dose. We also recommend that the duration of treatment should be only as long as required to meet objectives for the particular woman. As you saw this morning, a boxed warning was added and that assures that actually the prominent information is the first thing that's seen when the label is read.

Now the changes in labeling were accompanied by a communications program. The first thing was that practitioners were notified by letter of the results of the WHI and the changes in the product information. We did that last year. The data from WHI were distributed to practitioners by mail and

the Wyeth representatives were also asked to distribute a copy if necessary.

Information wasn't given just to the prescribers. There's information in the patient package insert that includes a clear assessment of the cardiovascular disease and breast cancer and other risks that we have determined are associated with the use of estrogen/progestin. So the patient gets this information as well.

The question we need to answer is "Has all this made a difference?" The data we have now on the pattern of use of Prempro is consistent with the new recommendations that have been made in the last year. I just want to address two points.

1. About 25 percent of the new prescriptions are for low dose. We're making a recommendation for low dose. The low dose was made available only around July of this year. After about four months after the low dose is available, 25 percent of the prescriptions are actually for the low dose. So prescribers are following the new recommendations which is good.

2. The second point is 94 percent of women initiate Prempro for menopausal symptom relief. It's very clear on the labeling that's where the use is directed. By and large, the substantial majority of women and prescribers are using the product now for menopausal symptom relief so younger women constitute by far the majority treated.

I want to emphasize this. The changes in labeling had the desired impact. This is very important. When the clinical research suggested a change in the use of the product, the medical team at Wyeth responded. We responded with recommendations that are consistent with the scientific data. The result as a pattern of prescribing indicates that practitioners have changed in response to the new scientific data as well.

The major conclusion I want to leave with you is that our medical team in collaboration with the FDA has been able thus far to respond to new data and to accomplish the objective I set out in the beginning which is to support the appropriate use of this particular product.

My last slide is just a summary of the key points

1. With the reminder that osteoporosis is an important medical problem, fractures cause mortality and significant disability. We don't want to forget that in our discussions.

2. There are only a handful of treatment options currently available for osteoporosis.

3. Estrogen/progestin is only one of the therapies that we know can treat both the menopausal symptoms that occur and to prevent osteoporosis.

4. We know now that Prempro prevents osteoporosis and reduces the incidence of all fractures including hip fractures.

I want to thank you for your attention. If there are any questions, I or my team will do our best to answer them. Thank you.

CHAIRMAN McCLUNG: Questions or comments? While you are gathering yours, let me make a couple. About the HOPE trial, you've emphasized that bone loss happens early in menopause and that most of the women who take estrogen now are younger. The average time

since menopause in that trial is 4.7 years.

DR. CAMARDO: Correct.

CHAIRMAN McCLUNG: The bone loss happens most rapidly in the first three to five years after menopause and then slows down. You looked at lower doses in the HOPE trial to show that it was effective in preventing bone loss. Have you actually looked at the women who were closer to menopause, those within the first three years for example when bone loss we know is faster and to know whether the lower doses of Prempro or Premarin are effective in that group of women that you are focusing our attention on?

DR. CAMARDO: The question is did we look at a subgroup of the women even closer to menopause than the average 4.7 years?

CHAIRMAN McCLUNG: Right.

DR. CAMARDO: I'm going to have to ask my team to help me out on that. Dr. Lindsay or Ginger?

DR. LINDSAY: The response to your question is that we did not look at that because we had groups of only 80 in size and it would be an inappropriate subgroup analysis.

CHAIRMAN McCLUNG: The other question I'd ask has to do with the durability of effect. One of the points that you made is that the recommendation is that estrogen be used only as long as necessary to achieve the treatment objective. Being treated forever is not a likely circumstance. Then knowing how long the protective effect of estrogen and particularly the lower doses of estrogen last becomes an important consideration. If patients are at very low risk when they're begun on therapy, treated for three years or five years and then therapy is discontinued, it could be that the benefit then last until they are old enough to be at risk. Or does the effect disappear? Have you followed the women since therapy was discontinued in the HOPE trial or in other studies?

DR. CAMARDO: Not in the HOPE study. There are actually some data that address that. I had it in one of my slides but I won't show it. I think that the conclusion that we came to is that you can assure the preservation of bone while you're using the therapy. Once this estrogen/progestin is stopped,

there is a decay period. I think that's actually been published. It's not immediate and it doesn't look like it's accelerated. What I think will happen in general and in practice is that if a practitioner and woman make a decision to use estrogen/progestin for osteoporosis after a certain period of time which is going to be hard to determine for sure, they will likely want to stop the estrogen/progestin for symptom relief if that was part of the option and continue something else for bone preservation. I think there would be no disadvantage to having used estrogen/progestin.

In fact, you might argue that there would an advantage because you would be starting from a higher baseline. I want to make sure that it's clear that I'm not advocating that if you make the decision to use the therapy that you have to continue it forever. You can continue for as long as a reasonable tolerance for the risk, clear benefit and then after that you have to use another therapy which seems to make practice sense and there wouldn't be disadvantage. Am I supposed to moderate the

questions? You're supposed to moderate the questions, aren't you?

DR. ROSEN: Rosen here. I have three questions, two specific and one general. How closely tied is bone loss to menopausal symptoms? You've tied that in several occasions, especially rapid bone loss. Can you establish for us what that connection and if you're trying to treat both at the same time, can you be sure of that as a clinician?

DR. CAMARDO: I'm going to give you part of the answer and I'm going to ask if maybe Dr. Gallagher could help me with this because he actually is a clinician in practice. What we've seen is that if we do a study, we screen several thousand women on the basis of symptoms. We manage to find a reasonable percentage of women who actually have osteopenia as well. So they are concomitant. It's a very common event in practice, but if it's okay, I'd like to ask Dr. Gallagher to respond.

DR. GALLAGHER: Dr. Gallagher, Creighton University, School of Medicine. About 50 percent of women will complain of vasomotor symptoms during the

menopause and maybe 40 percent will complain of vaginal dryness (dyspareunia). Certainly from the HOPE study, we know that the great majority of women actually develop bone loss so they are coincident conditions.

DR. ROSEN: I'm just a little concerned about the term "rapid" bone loss because as you know, Chris, this comes up all the time. How many of these people are actually losing bone rapidly and what is that definition?

DR. GALLAGHER: I think that the common figure that goes around and Claus has certainly pointed this out is that 25 percent of women have rapid bone loss after the menopause. Still there's a considerable portion who are having somewhere between average and that. So we're talking at least 50 percent. Just a point of information for the women in the HOPE study, the average number of years for menopause was 2.7, not 4.7.

CHAIRMAN McCLUNG: Not 4.7?

DR. GALLAGHER: No.

CHAIRMAN McCLUNG: Let me ask to follow

through with Cliff's question. Is there a relationship between women who are symptomatic and the rate at which bone loss occurs? Is that question that you were asking?

DR. ROSEN: That's right.

CHAIRMAN McCLUNG: So we appreciate that the bone loss happens after menopause. We appreciate that many women have symptoms. Do the women who have symptoms lose bone more quickly than those who do not symptoms? I think that's Dr. Rosen's question.

DR. GALLAGHER: I think I'd like to hand the microphone over to Dr. Christiansen.

DR. CHRISTIANSEN: There's a tight relation between rate of bone loss and estradiol concentration. There's also a tight relation between serum estradiol and the symptoms. None of that's close as to the rate of loss but those are very significant. Therefore of course, there's relation between symptoms and rate of bone loss. We have shown that many years ago.

DR. ROSEN: Okay. I just want to finish with two very quick questions. I'm not sure I

understand what you're referring to when you say "WHI did not address some non-vertebral fractures." Can you clarify for me what you're talking about "didn't report some non-vertebral fractures"?

DR. CAMARDO: Yes, what I was referring to is arm and wrist fractures. I mean included in the index calculation. I did not see.

DR. ROSEN: In the global index.

DR. CAMARDO: In the global index.

DR. ROSEN: But it's very important to appreciate that they reported all non-vertebral fractures that are standardized.

DR. CAMARDO: Yes, they did, but it wasn't included as part of the side of the benefits.

DR. ROSEN: I have one philosophical question because I am a practitioner as well. I don't quite understand why you make the distinction between what we see in clinical trials and what we do in practice. Can you tell me a little bit about that reasoning? It seems to me that we have to base what we do in clinical practice on what the evidence is. So you constantly make that distinction. This is

what's in the trial. This is what we do in practice. Can you elaborate a little bit on that?

DR. CAMARDO: I probably should have included my original slide which was a quote about how there are consensus guidelines that are developed on the basis of trials. Applying the guidelines to actual patients sometimes can be difficult.

DR. ROSEN: Oh, I'm not a fan of recommendations or guidelines but each of the practitioners has to weigh the evidence.

DR. CAMARDO: I don't disagree with you at all. I think the practitioners have to weigh the evidence. In general, when you do a trial, you have defined a population and you have taken certain steps to make sure that the population fits into the criteria that you've set up. Actually if you set up a trial and try to find the people that you want to get into it and you go into a practice, you'll find that a lot of the people may have the disease that you're trying to treat but they don't actually fit in the trial. So you have set up a situation that requires that the results be applied with care.

That's all I'm really saying.

I do not want anyone to mistake that I don't believe in the value of clinical trials. Wrong. That's absolutely not true. But I still think when you take the data you have to let the practitioners apply them. That's what I want to tie to our product information because we feel strongly that we need to provide the information balanced.

CHAIRMAN McCLUNG: Ms. Solonche.

MS. SOLONCHE: Yes. Early in your presentation, you showed a slide from a 1976 article in the Lancet. The title of it is "Bone Loss Follows Estrogen Loss and Can Be Prevented With Early Use of Estrogen." I see that all the participants in this seem to have had oophorectomies.

DR. CAMARDO: That was the study actually.

MS. SOLONCHE: My question is the studies that you've used since then and the WHI study, are these people who have had oophorectomies, surgical menopause; or are these women who have what we'll aphoristically call "natural menopause"? Do you think that makes a difference in the results?

DR. CAMARDO: The latter, natural menopause. I think it probably does make a difference in the results, but I really used the 1976 paper as a model for looking at intervention at a time point when you could determine when estrogen had disappeared rather than over time. So it was really a way of looking at a specific question about the time point of estrogen replacement when it was known when estrogen loss occurred. That was a particular situation just to test the value of estrogen. In the study participants in Women's HOPE in general are women who are going through menopause, not women who ovariectomized.

MS. SOLONCHE: Thank you.

CHAIRMAN McCLUNG: Dr. Follman.

DR. FOLLMAN: You were saying that you didn't like the idea of using the global index to help tradeoff the risks and benefits for an individual patients. The reason you gave was that really this index had been designed more for monitoring of the trial. Now it's being put to another purpose. I was wondering if you had any other reasons why you didn't

like the global index or making this individualized risk/benefit tradeoff and if you had thought about a different quantitative way of making the risk/benefit tradeoff because a large part of what we hear today is trading off risks and benefits.

DR. CAMARDO: That's a good question. I think actually the WHI investigators, not just I, pointed out some of the limitations of the global index. I found it a complicated endpoint for the trial. I think the medical team would agree with me that it didn't evaluate the benefit of the intervention the way we often evaluate the benefits of intervention which is to see what they are, define the magnitude and then have a discussion about whether the risks make it worth it. They decided really on the basis of a number which you can't just apply to a woman who walks into the office I think. That's in all cases. It's just a matter that it tends to want to homogenize the results here and it wasn't designed to be a tool. It's not like the Gail index or the Framingham. Those things assessed cardiac risk or breast cancer risk. It really isn't that. I don't

think it was designed to do that.

DR. FOLLMAN: So I guess you're saying you don't want to use that index and just look at all the data, look at the risks and benefits for the different endpoints and then make some gestalt decision based on the patient and her profile and all this information from the WHI and other studies.

DR. CAMARDO: The recommendation we are trying to make is that the data need to be available and that since there are some areas of gray there is a certain point where a physician would have to make the decision. I think that would be a fair way to say "I don't know what I would do if I were in practice." I'm not in practice right now, but I believe that there's some gray in that even when you look at the risks there are some cases where either you could evaluate that the risk is lowered because of some particular status of the individual such as low blood pressure, low cholesterol, no history of heart disease, very young and a lot of reasons that others have alluded to today and decide that maybe the risk is really low.

There are other circumstances where I think for an individual woman the risk even if you take it at face value might be worth the benefit. I don't think we want to make a judgment about that. I don't want to advocate for any particular position. I want to make it clear that our mission is to make sure that the knowledge base is adequately displayed in the labeling. I'm telling you what I think the thought process might be.

CHAIRMAN McCLUNG: We've heard that the global index was put together at the time the study was started. One of the important things to remember is that the world is different now in lots of ways than it was ten years ago. Our understanding and even the outcomes that were expected turned out to be different than were planned and predicted. Dr. Rossouw has already thrown a challenge to the clinical community that if we can come up with the justification for a different set of risk factors and benefits to be included in a different global index. My sense is that much of that data exists in some database and in your database to allow us to look at

that. So we're struggling with trying to apply in clinical practice a tool that was put together a long time ago where our understanding about each of the diseases and the effects of estrogen has moved on from that time. Please.

DR. CARPENTER: In addressing risk/benefit issues, you've shown the recent impact of your data demonstrating that lower doses of Prempro are effective in preserving bone marrow density and recent increases in prescriptions for the lower dose formulations. In that this is potentially a very useful strategy for maintaining benefit and it appears to be motivated by the potential for reducing risk, I wondered to what extent there is data being collected and what plans there are to organize or collect that data at the lower doses for these various adverse actions.

DR. CAMARDO: At the current time, we have the database from the study which is about 3,000 women followed for about a year. That's very small but we have some assessment of the cardiovascular risk in that study which is relatively small actually. That's

one thing. The only other thing at this point in time is really post marketing surveillance. We don't have at this point a study designed that would answer the particular question to the same extent that it would addressed in the larger study that we're talking about today. So as you said, we have the bone marrow density data. We have the data on vasomotor disease. We have the side effect data which we know from the HOPE study. At this point in time, the product's been out for a couple of months so we have mostly post marketing surveillance reports. That's the extent of it for right now.

CHAIRMAN McCLUNG: Dr. Woolf.

DR. WOOLF: A question and a comment. On one of your slides, you state that the duration of treatment should be only as long as required to meet objectives for the particular woman. You've talked about osteoporosis obviously not meant to be lifelong. But what about flushing? Is this something that a post menopausal woman for want of a better term outgrow or will this simply return once the estrogen preparation has been discontinued?

DR. CAMARDO: I think those are both extremes of what can happen and everything in between. I don't want to give you a flippant answer, but in fact what we've done to try to address that is to point out in the patient information that the particular objective which is flushing should be addressed on a regular basis. Our advisors are telling us that in general - these are the recommendations from ACOG and others - that a yearly reevaluation be performed and to consider to discontinue in some women. With the discontinuation, flushing will return. We know that. In others, it does apparently go away.

I could ask one of the clinicians in practice to talk about that, but the way it's been addressed is actually in the patient information. We advise that a discussion occur with the practitioner about whether you still need treatment. That generally refers to flushing because that's the most apparent one. There are others. The implication is if you don't need it anymore for flushing see if you don't. You have to try that.

CHAIRMAN McCLUNG: Dr. Schade.

DR. WOOLF: My comment about the global index really doesn't pertain specifically to Wyeth or WHI but my understanding about an index is you develop an index from a population base and then you go and test it against another population base. From what I can gather, this has not been done with the global index. It was simply meant to be a tool for deciding the severity or the risk and benefit but it really hasn't been validated in another dataset. To use it as a tool to decide risk/benefit when it hasn't been really tested in a new dataset to see its validity may in fact not be appropriate.

CHAIRMAN McCLUNG: Any other comment about that?

DR. ANDERSON: I would like to comment. I think what you were talking about in terms of developing and validating in another dataset has to do with more a risk score such as the Gail model or the fracture risk score that they were talking about where you're trying to identify risk factors of individuals and put them together to then make a simpler

stratification of individuals.

The global index is something quite different where it's trying to summarize treatment effects, not individuals. It's a summary of those benefits and it's a valid comparison of the randomized trial endpoint. It's a disease free survival statistic where the disease now is actually the whole list of diseases that we're looking for. That's what it is.

DR. WOOLF: But my point is that this distinction is liable to be lost on the public and that it is becoming in fact the Gail index or some other index of global disease. In fact from my reading of the New York Times and my local paper, the Philadelphia Inquirer, that's exactly what's happened. It's become the marker of treatment that it has become a validated instrument to decide whether to use estrogen or not. The statistical nuances are clearly lost on the public. It's hard enough for me to understand. I don't know if I do, but that information is not getting across.

DR. ANDERSON: Yes. I would say probably

none of us here want to take complete responsibility for what's in the newspapers. It's clearly limited in the sense that it was designed for this trial and never meant to go any further.

I would say that it's a very valuable tool for looking at the risk/benefit profile in a philosophical sense to have some summary index of these because we need quantitative measures of risks and benefits to help in evidence base medicine. I would say in defense of this product is that we lack that similar risk balance information for a lot of other products out there. We need to move forward to have better information like that on all these products particularly for prevention work.

Prevention work is some of the toughest. You never know with the patient that you're treating for those clinicians if you give them this medicine whether you actually prevented that disease or whether they never would have had it in the first place. The prevention is really population-based work. I'm not sure that I really agree with this individualization for prevention purposes. For treatment, it's a

different argument, but I'm going beyond my scope.

CHAIRMAN McCLUNG: Okay. Great. Dr. Schade.

DR. SCHADE: I have two short questions. You showed us data on the lowest dose of estrogens. What about a dose response curve for symptoms and the estrogen dose? You didn't show us that. You showed us with the bone mineral density. In other words, does the dose response curve look similar to the BMD response?

DR. CAMARDO: I'm going to ask for this specific question about the study Dr. Pickar to just remind me of the results for the dose response for symptoms if you could do that.

DR. PICKAR: When you look at the doses of Prempro that were studied for menopausal symptoms, they were all very similar.

DR. SCHADE: All right. I think I asked that question because obviously there is a push for the lowest dose. We're seeing reasons for that even though right now at least the prescriptions don't reflect that. That may be as you point out on your

slide that the product hasn't been available that long. The other question I have is on labeling. It's probably my ignorance. You use a term "should be seriously considered." In other words, what does that mean? I'm a practitioner and basically when you have a choice of treatments in every case you should seriously consider all the treatments and choose the optimal treatment. So it seems to me on the label unless that's a term that the FDA has utilized in many situations that I'm not aware of but as a practitioner that doesn't say very much. I just wondered about your interpretation of that "should be seriously considered" statement.

DR. CAMARDO: It is just short of requiring that an alterative agent to tried and shown to fail or be ineffective. Our medical team discussed this a lot. There's a regulatory implication to some of this which I think will be discussed later. It falls short of requiring a demonstration of failure. We thought about it and discussed it and came to the conclusion that there are some cases where it wouldn't really make sense for us to recommend that another

product be tried and fail first when you could choose among –- We thought it was sufficient to recommend choosing among the options which is not something that was ever said about the product previously and it's usually not said about products. It's usually assumed. We explicitly state that. The reason we were short of demonstrating is that we thought that there are some cases where you could predict that the products might not work anyway.

Now I should tell you there is another discussion about the older women which I would just like to mention briefly. In older women because of the incidence of dementia in WHIMS, we're actually discussing the possibility of requiring that other agents actually be used first because in the older women, there seems to be a different risk/benefit implied by the results of that study. We're discussing actually in that case maybe we should go on the other side of that recommendation and make it a little bit stronger. But it's a bit of a fine line and as said, some of the evidence suggests that you just make the recommendation to consider. Other

evidence seems to suggest that you may want to make the recommendation to try other products. Does that make sense?

DR. SCHADE: Yes. Now I understand at least what you mean.

DR. CAMARDO: Okay.

CHAIRMAN McCLUNG: Dr. Stadel.

DR. STADEL: Yes, I just have a further question on the issue of summary risk assessment. As I recall from the presentation of the fracture data in the group that was defined as being at high risk of fracture - it got pretty close to one - the global index was still slightly worse in the treated group than the placebo group, but it was getting closer. My question to you is has Wyeth proposed any further refined analyses aimed at identifying a group within the total for whom the net would be beneficial? That's what I hear you saying is that of course as a practitioner we have to say "How do the risk characteristics of this patient play against the group experience that we're using to judge?" Have there ben any specific recommendations for further analyses

using more refinements of definitions coming from Wyeth back to the WHI people?

DR. CAMARDO: Yes, the answer is that the WHI and Wyeth have actually been working on some analyses together with the understanding that the lead is always going to be taken by WHI in terms of publication and everything else. So we tend to be in line after the publication results which is appropriate I think. But we have asked to look at some of the higher risk and we've also discussed the possibility of looking at women who may be at high risk for osteoporosis and low risk for some of the other side effects.

I don't think that's an original idea. I think it's something that we discussed. I haven't discussed it. Dr. Stevenson and her epidemiology group have discussed it. The shorter answer is yes. It's a little disappointing though that high risk osteoporosis doesn't seem to be that high risk compared with the risk scale. So again you may not see in that population women who you might see in practice. That's where the limitation would be. The

answer is yes. We've actually been discussing other possible analyses. We've had some ideas. Go ahead.

DR. CAULEY: Yes, I just wanted to point out. I think we talked about the high risk women being older and this brought to my mind when you talked about this issue with regard to the risk of dementia in the older women. The high risk women that we called "high fracture risk" were actually in their 70s. That was the average age. That's the group where the dementia finding were limited to women age 65 and over. So caution also when we talk about including other aspects in the global index. It's important to include other risks and benefits. That would be something that would be needed to be included as well.

CHAIRMAN McCLUNG: Dr. Bone.

DR. BONE: It seems to me that many of us have been concerned that our major target population for treatment with hormone therapy of one kind or another would be the very early post menopausal woman within the first year after cessation of menses who has symptoms with or without low bone density at

menopause carried forward a limited number of years, probably something like three or five years during which time we would have expected most of the symptoms to resolve. Perhaps the dose could be tapered over that time. It sounds to me like one of the things that would be extremely useful would be a prospective clinical trial actually representing that group. WHI has done a commendable job but it didn't really emphasize the very early post menopausal women particularly those who are quite symptomatic. This very early phase of bone loss is also an issue that's been brought up. My question to Wyeth and it would be a question for sponsors of other products would be "Do you have any plans to look at that population specifically".

DR. CAMARDO: We have plans to continue to evaluate the low dose. We don't at the current time have plans for a study of the size and duration of the study we discussed this morning.

DR. BONE: I'm not exactly sure that it would be required to obtain quite a bit of useful information about that very specific segment.

DR. CAMARDO: It has been discussed. I don't have a specific proposal that would be ready for discussion by this Committee. I think if advice goes in that direction then it's something that we would work out with the FDA medical team to actually determine how big and how long it should be and what kind of methodologic problems we'd have to face to do it. I don't want to give an answer about anything in particular because we've really only discussed it in general terms.

DR. BONE: Having taken your point and understanding that, it's actually who we're concerned about and that's actually the treatment model that we're most focused on.

DR. CAMARDO: Okay.

CHAIRMAN McCLUNG: Other questions or comments? Yes.

DR. ZERBE: I have a question about total mortality. There's been a lot of discussion about the global index and the pros and cons of the various things that have been included. Total mortality does not appear to be different. Could you discuss a

little bit about strengths and weaknesses of the use of that as a prominent feature in the evaluation of the risk/benefit?

DR. ROSSOUW: Let me start and then Garnet can follow up and correct me if necessary. Two points about total mortality. It's an extremely insensitive index particularly when you're dealing with a drug entity that has a variety of effects, some favorable and some unfavorable. By its nature, it's going to be insensitive. Also in a relatively short period of just over five years in a healthy population, the chances of finding a significant effect on total mortality even though disease incidence may be tending in a certain direction are slimmer.

My main point is that total mortality may be an appropriate thing when you're dealing with a high risk population such as a secondary cardiovascular prevention study where most of the subsequent deaths are going to be due to that specific disease. As your treatment is effective for preventing incidence, it will also prevent mortality. We've seen that in the statin trials and hypertension

trials and so forth. For this kind of drug in a prevention study with a variety of effects in a healthy population, total mortality, you'd have to have a huge sample size and a very long follow-up to find an effect.

DR. CHLEBOWSKI: Maybe just an example from the breast cancer area where we have invasive breast cancer. We had 349 cancers which will ultimately kill 25 percent of the women even with our more effective therapies now, but that's going to take a decade. We have eight deaths now. To come back and ask that question, we'll have to come back ten years from now. I think that's true for many of these other events as well. It's a time related phenomena. It's like waiting for all of the events to occur or doing a censored analysis.

DR. ZERBE: Yes. I guess the only thing I suppose emphasizes that there really is not even the suggestion. So it isn't really an issue totally of power. There's not even a suggestion at this point that there's any increase mortality. Is that correct?

DR. CHLEBOWSKI: (Off microphone.)

CHAIRMAN McCLUNG: Dr. Camardo. Thank you very much.

DR. CAMARDO: Thank you.

CHAIRMAN McCLUNG: We are just ahead of schedule. Are there other questions that we have for the WHI group? With Dr. Rossouw's permission since we cut that short, I'm going to make sure we have our queries and information lined up before we deliberate later on. Yes. Dr. Woolf.

DR. WOOLF: Just a clarification. I recall a slide that has been shown a couple of times regarding the incidence of fractures versus the number of women who fracture in relationship to whether they are in the osteopenic or osteoporoic category. I believe one of the slides demonstrated that there are a greater number of fractures in the osteopenic group. I wondered if that holds up for both placebo and hormone treated women and if there is a discrepancy there, how one might explain it?

DR. CAULEY: That wasn't WHI data.

CHAIRMAN McCLUNG: No, that was from the NORA study so it was not a treatment study. It was

just an observational study, but a number of studies were shown that as was pointed out the total number of patients experienced hip fractures for example who have osteoporosis is less than half of the hip fracture of the population. That's because there are a lot more younger people. So while the absolute risk is higher in the group of patients with low bone density and osteoporosis, the proportion of the total fracture burden falls in younger people at lower risk. If the relative risk reduction with intervention were the same across the spectrum of risk, then the number needed to treat to prevent fractures would be a lot greater of course in the osteopenic population than in the osteoporoic population. That's just the way risk is about that.

The other facet about that is that when you look at all fractures the distribution of the types of fracture also changes substantially with age. In several epidemiologic studies in women in their 60s, hip fracture and spine fracture constitute a very small proportion of the total fractures. In the WHI, only 15 percent of the total fractures in either of

the groups were constituted by clinical spine fracture or hip fracture. So 85 percent of fractures were other fractures which to many of us at least my personal view probably have less clinical import than do hip fracture and spine fracture.

In contrast in women in their 80s, the majority of fractures that occur are hip fracture and spine fracture. So not only does the risk of fracture increase with age but the distribution of the types of fractures and the severity of the types of fractures increases with age as well. That's often not factored in or expressed in the sorts of data that we see.

DR. ROSEN: Mike, can I clarify something?

CHAIRMAN McCLUNG: Yes.

DR. ROSEN: The point is that there are many more people who are osteopenic than osteoporoic. So the number of fractures on the Y axis is going to be greater. That's just when you refer to number of fractures versus absolute risk. That's the difference. I do want to point out. Jane had a slide that she took out but the number needed to treat -- Maybe you can talk about it, Jane, the number needed

to treat because estrogen does work across prevention populations. It is important to emphasize that point from your data.

DR. CAULEY: The slide that Cliff is referring to is I just calculated the number needed to treat ("NNT") in WHI for clinical vertebral fractures and compared it to the numbers that were in the Osteoporosis Research Advisory Group ("ORAG") report. Now the problem with doing that is that other report included morphometric vertebral fractures and we only had clinical vertebral fractures. And the populations varied markedly. They define low risk in that report as BMD. They had BMD measurements on all the women. So it's difficult to compare numbers needed to treat across the different agents and across the different trials.

But it did show that in this calculation about 800 women would be needed to be treated for two years to prevent one clinical vertebral fracture in the WHI population. I say that with some limitations, no inherent and calculating NNTs and in the fact that we were limited to clinical vertebral fractures.

CHAIRMAN McCLUNG: That's a good point. Let me just come back and emphasize for the sake of what our subsequent discussion will be that NNT is not an index of therapeutical efficacy because it's driven almost entirely by the risk in the population rather than by the effectiveness of the drug. So the WHI as a very low risk population would be expected to have a high NNT as opposed to lots of other trials where patients are specifically recruited and enrolled in the study. From a cost effectiveness standpoint, that mostly reflects the population being treated rather than the therapy being considered.

DR. ROSEN: Actually I was going to make the point that if you look at the NNTs in the ORAG trial they are up over 2,000 for the bisphosphonates and only 800 for estrogen. So in a low risk group of people, actually estrogen looks like it does very well. I think it's just consistent with the data and again thinking about the caveats that we talked about already in terms of different populations.

DR. ROSSOUW: If there's a minute, I can't refrain from picking up on a discussion that panel

members had earlier and stimulated Dr. Camardo's presentation which essentially says that practitioners are back to making individual judgments based on what they think the risk profile is of the patient. We did this trial in this population to get some real evidence to help physicians make that judgment in an older population on average. I think those are very useful and you've seen how practice has changed as a result of that new evidence base.

It seems to me that if we now focus in on the younger patient who is symptomatic to fall back and say "We don't really have good data in that group and we're still back to seat-of-pants clinical judgment" is a an unsatisfactory situation. Now the data that we have in WHI is actually the best data available at this point even for that population. It is the best data.

Now for osteoporosis our data are perfectly consistent with smaller studies. That's not the issue. The issue is the non-osteoporoic outcomes, the cardiovascular and the cancer outcomes. Just to throw it back on the clinician and say "We don't have

good data on that so make your own judgment" seems unsatisfactory.

Now it does seem to me that where it's going now with most bodies and why the self recommending shortest period of the lowest possible base is a perfectly sensitive clinical thing to do. As I say, it makes a lot of sense, but can we be sure that the adverse effects are in fact less? Now they probably are less just by virtue of the fact that this is a younger population and a healthy population so one could make a very valid argument that the absolute risks are low.

So even if there is a E + P associated effect, the benefit for symptom relief and osteoporosis prevention you can assume that the benefits can outweigh the risks. As we've learned, assumptions are tricky things. So when people say, "We really need a large clinical trial to address this specifically" I must say I personally resonate to that which is not volunteering NIH to do the trial of course.

CHAIRMAN McCLUNG: All right. Before we

take our break, the final formal presentation will be the FDA review of the WHI data and comments and Dr. Stadel will lead that discussion.

DR. STADEL: As a clarification, my comments as a reviewer as a large of my job here has been to work with Dr. Rossouw in communications about the NHLBI WHI presentation here. I've been intensively enrolled in reviewing selected parts of the data. My comments now are really though intended in a little broader sense. I just reflect for a moment on the purpose of the trial which was to test the notion that there was widespread cardio-protection. It was designed to do that and did that. The purpose of this meeting is the implications with regard to the osteoporosis indication for the drugs. Those two are related but they are not identical.

So in going to that focus, let's look for a moment just as a reminder at what is currently approved by combination estrogen/progestin drug products. I merely put this up to emphasize that one drug product dose was chosen for study. I don't disagree with that. I just want to emphasize that the

class labeling and then the considerations of future testing apply to a diverse array of doses and formulations including both the medroxyprogesterone and 19-nortestosterones in the various doses of estrogen in the combination products and also in the estrogen only products, the additional consideration of transdermal versus oral administration for which there are various bits of evidence suggesting that there might be some differences. One of the questions to the Committee is their deliberations about what kinds of things should be emphasized in the development and testing of new products. I'll raise that as a global comment.

Before going ahead, the next slide I'd like to show is just the drama essentially of the historical event. This shows total prescriptions per year for Prempro 2.5 and 5.0. I combined them. It's mostly 2.5. For the Prempro low dose and for Premphase also and for the newer formulations also. Now as you can see, you have this enormous increase from 1995 on the graph and then in 1998, you have the publication of the first major paper from the HERS

trial. That's where I think you begin to see the cresting of the wave.

The acceleration slows down, tops off and then in July 3, 2000 you have the second paper from the HERS, the long term outcome paper and then on the 17th, the first paper from the WHI. So you can see on the national picture the very widespread of use of this medication. Dr. Rossouw had referred to the diverse practitioners who were prescribing at the time. In one area, we have been dealing with a public health issue having to do with the widespread use of the drug in an effort to prevent cardiovascular disease. I think the trial myself accomplished its goal in that regard and I think the prescribing data indicate an appropriate response on the part of the medical profession to learning that the observation data were not sustained in a large randomized trial.

I'd like to now comment briefly on the breast cancer data because I've been very involved in discussing this with the investigators. This is a very simple rendition of what was presented in a far more elegant and far more statistically rigorous

fashion by Dr. Anderson. I put it up this way for a particular reason and that is to emphasize my view that absolute differences are the appropriate way to communicate risk in the clinical application.

That relative risk especially when presented as percentages can easily be misunderstood by people who do not work with them on a regular basis. A change from 2:10 to 1:10 and a change from 2:1000 to 1:1000 have the same relative change but a vastly different meaning. That's a simple statement but it's one that I recurrently see a problem with in looking at editorials and the popular and the lay press information on this topic. I wanted to take this opportunity to stress it.

In the women who had prior use, the top group here there was an over the trial of 1.22 percent difference in breast cancer. I've done a very simple approach to the statistics. I thought that Dr. Anderson's modeling that used observational techniques was appropriate to a safety outcome where there are unexpected things and one has to retrofit. That did show some rigor in there being a difference between

the two groups. I think the difference is fairly apparent that in the large number of women in this trial about 74 percent of the patient population. The duration of exposure only on trial the net was two percent and not very impressive as a statistical finding.

Now this doesn't contravene that they're of the notion that it's long term use that matters. The prior use contributes. And it contributes something that we don't fully understand. Notice that the group with the lowest rate was the group that had the prior stimulus and then went on placebo. One interpretation is that the prior stimulus had stimulated cancer in susceptibles and then the remaining group when they went on placebo were at fairly low risk. That's a possibility. There are other possibilities.

The highest risk is in women who had prior use and continued on use. That is entirely consistent with the notion that very long term use of estrogen/progestin produces an increase in breast cancer. There's no disagreement with that.

However I think it's important to note that in the women with no prior use the rates are in the middle. So there's a message to a very large number of women in the country who only use this product after it was approved by the FDA and whose use would have fallen largely within the duration of use accompanied before the trial was stopped. I thought it was stopped at the appropriate time in that regard. There's a message to those individuals that if they have incurred an increase in breast cancer risk it is not a very large one and it is not a very clear one.

The next very important issue that comes to mind is what happens when women stop. This is of great practical importance to women who were taking the drug who may have revised their feelings about benefit/risk. What happens when they stop? Now this is a slide from the Million Women Study that was referred to earlier. This is not a trial. It is an observational study. I think it's a good observational study.

The graph here is one which shows the risk in the top for never users as one and for past users

by duration of use there is no increase of risk except for one little blimp at five to nine years. Current users of estrogen only there is a slight increase in risk in these data and a much more pronounced increase with the combination. So in that regard, it's quite consistent with the experience of the trial.

DR. SCHADE: Excuse me. Could you use a pointer because I can't read the slide from here.

DR. STADEL: I'm sorry. I had a lot of trouble figuring out how to make this. This is never users. This is past users whose duration was less than a year. One to four years. Five to nine years. And greater than ten years. So it's pretty flat. This is the same sort of data for women who used estrogen only. One to four years. And at ten year, there's an increase. It doesn't go up much with duration sitting around 1.3ish. 1.2 here. 1.25. I tend to round them off.

Now in contrast for the estrogen/progestin group, it went up from less than one year of 1.45 up to over 2.0 when you go up to five to nine and greater than ten sitting out here in these data. Then of

unknown HRT, I don't think is entirely relevant to this discussion.

So my main reason for showing this is twofold.

1. The current use findings are consistent with what's been reported from the randomized data.

2. The past use data are quite flat by duration of use.

I would like to also show the next slide which is from the same study. This is never users. This is all current users. This is all past users of less than five years, five to nine years time since last user. Less than five years since last use, 1.04. Within this if you look at less than one year since last year, the relevant risk is 1.15 and it's statistically significant reported in the text. Again I think these findings are consistent with what we're seeing. It provides some hope for the notion that when the stimulus is renewed the increase in risk stops. That we need very much to see more follow-up of the WHI trial data, but that's the best

interpretation I can give at the present time.

Also when this was looked at separately for past use of estrogen only and past use of estrogen/progestin, there was no increased risk. You could not isolate that by past use of less than one year duration in the way they presented the data. So my only reason in raising this is that the overall results from breast cancer are rather less frightening than one would get from reading some interpretations that I have seen.

I'd like to go on now. I only have a couple more comments. One is a well known element that needs to be considered in this whole issue. After menopause, there are many papers showing that the major source of estrogen after menopause androstenedione mostly secreted from the adrenals and and aromatized to estrone which then equilibrates with estradiol. It's in adipose tissue. I think most people believe it's in the stromal cells where aromatized enzymes are located.

It is widely believed in many papers that this accounts for the positive association between

post menopausal breast cancer and obesity. Why is this important? It's because the amount of estrogen that women make after menopause depends on their amount of adipose tissue and the functionality of their aromatizing enzymes. So if you give a specific dose of estrogen to someone who has estrogen, you could expect clinically that you might get a different response than if you give that same dose of an estrogen to someone who doesn't have estrogen.

Now I'm going to go to my last view here and this is something I very much hope that I'll hear opinion from members of this Committee from your endocrine backgrounds and others. These are just two references that I pulled out that relate to this issue. In particular, Cummings, et al. using the osteoporoic cohort study did an investigation in what's called a case cohort analysis, a technique that's not terribly important here. But what they said basically was points straightforward. They measured serum estradiol levels and the really high risk of fracture was in people who had virtually undetectable levels.

So I'd ask a question here. We're talking about "What should be done to develop new products". Should this include an effort to more highly define the indication for treatment with hormones. There are various reasons bone density may be low. One of them certainly is low estrogen but should we be working people up with hormone measures at baseline at least initially in more studies and potentially clinically?

The converse of course since this is a well existed literature and I've just cited one article which is compatible with the notion that the increase in breast cancer after menopause is very related to the increased BMI and there's a large literature relating this to the increased production of endogenous estrogen. So then one would say that giving more estrogen to someone who already has enough might not be a wise idea. Those are really my only contributions I hope to this meeting.

I will make a very brief comment about the WHIMS study, only to mention that there is some indication that endogenous estradiol estrogen in women is related to the risk of vascular dementia.

Cerebrovascular changes are recognized as contributing to Alzheimer's Disease ("AD"). This is discussed by Dr. Schumaker in the WHIMS paper and also by Dr. Katz who might comment if needed on the specific review of the WHIMS trial by the FDA. Lastly in an autopsy study, it was found that vascular changes in the absence of AD were present in patients with histories of dementia.

I put this together to say that vascular disease may be contributing more here than immediately apparent. That's important because if we tailor the doses of estrogen and the doses and types of progestin, we'll more likely be able to control any contribution of exogenous treatment to vascular disease than to other types of dementia. Thank you.

CHAIRMAN McCLUNG: All right. Thank you. Questions or comments or clarifications for Dr. Stadel from us? If not, let me suggest that we take a 15 minute break and to be back at 3:05 p.m. We will embark upon our deliberation among ourselves. Thank you. Off the record.

(Whereupon, the foregoing matter went off

the record at 2:50 p.m. and went back on the record at 3:10 p.m.)

CHAIRMAN McCLUNG: On the record. So we have completed the formal presentations by those who were invited or who asked to be a part of the presentation. The remainder of the meeting will be focused on a discussion among the Committee members to share ideas with each other and to address some of the specific issues that were posed to us by the FDA.

We're happy to have the audience stay but there won't be the opportunity for audience members to make comments or presentations unless we, the Committee, have some specific issues of clarification from either the WHI group or the group from Wyeth. To start this session, let me invite Dr. Orloff to make comments again and to provide us our charge.

DR. ORLOFF: First of all, I see that most of the WHI team has departed. I want to thank the doctors who are staying and make sure that you all thank the rest of the group for their input. I guess I should also comment that never let it be said that we "slow-pitch" our advisory committee. This is an

extremely complex issue. Also let it never be said that the FDA's job is an easy one. And with that, charge. No.

This has truly been a fascinating day and a unique one in bringing together the group of investigators of a landmark trial and obviously an extremely important and high profile public health area to present face-to-face the results, up-to-the minute and on-going plans for their study to our Advisory Committee and to have interested public as well as the particular interested pharmaceutical sponsor, the most interested perhaps be here to comment as well.

We have really two central issues that we'd like to hear more comment on. The first one relates to essentially your satisfaction, your consideration of the accuracy and appropriateness and completeness of the labeling changes that have been made to the labeling for this class of drugs after the WHI. By and large, the discussions on both sides up to this point, by the WHI group and by Wyeth, pretty much inform directly your discussion on that issue.

So we really need some more direct input. That might go fairly quickly I would anticipate.

The other one is a much more complicated issue. That has to do with the true intent of the meeting which is the implications of the WHI and its results for the future vis á vis this class of drugs particularly related to the clinical development of these drugs for use in post menopausal women. What we're asking for is some comments on everything from endpoints to inclusion criteria to duration of trials to size of trials to whatever else you may want to speculate on. I'll leave it at that. Thank you.

CHAIRMAN McCLUNG: Thank you. And I propose that we deal with those in order. So let me ask the Committee to share with me your thoughts and comments about the first issue which was your feelings about the revisions and the current prescribing information for Prempro that's been provided to us and has been presented today. Are there specific comments to make about that?

DR. SCHAMBELAN: I could continue the baseball metaphor. Unfortunately the people in the

San Francisco Bay area got used to fast pitch baseball the last weekend and so I guess I don't have to watch much more television for the next couple of weeks.

The question I had about the prescribing information really focuses on a point that was raised just before our break and actually directed to folks at Wyeth about the subtlety of the language in point three under indications and usage about the careful consideration of non-estrogen medications versus a requirement that another medication be tried. I'm not sure that I have a specific recommendation to make, but it seems to me of all the recommendations I've seen here that's the one that strikes me where we need the greatest amount of thought.

I come from the land of Grady and Cummings and Holly and Black and this has been discussed obviously since the HERS and WHI trials have come out. The focus of these individuals has been to recommend other therapies before and this is in an asymptomatic patient we're talking about now which would be presumably point number three for the prevention of post menopausal osteoporosis. From my point of view

in terms of recommendations, that's where this discussion could best go.

CHAIRMAN McCLUNG: Dr. Bone.

DR. BONE: Thank you. We certainly want to commend the investigators for managing an enormous amount of information. Their forthright recognition that the osteoporosis related questions were fairly far down the list in the considerations of the study design. We have to recognize the challenges to the FDA in calculating things like risk/benefit balance from a regulatory standpoint when we are dealing with information that wouldn't really be considered - I don't mean this with any disrespect at all for the work that was done - an adequate and well controlled trial for the indication, prevention or treatment of osteoporosis.

The patients weren't selected on the basis of their risk for those conditions. The endpoints that were measured were fracture but we don't have comprehensive bone density data. We don't have turnover markers. We don't have a lot of the information that we would want to use to relate the

risks and benefits. We have a risk scale which appears to give a relatively shallow gradient between the highest and lowest tertile. But with that gradient, it looks as though most of the disadvantage to being treated is abolished in patients who have somewhat higher risk of developing an osteoporoic fracture.

I actually think that the Agency has done a good job of incorporating this information and the company into the current labeling. It's going to be difficult to improve on this very much without having the kind of more precise estimates of effectiveness for one thing that we would drive in a purpose-built trial. We're getting to the point where we're pushing it pretty hard to try to see more than has been said with some possibility of some nuances.

The suggestion that a twofold increase in the risk of fracture is somewhere near the breakeven point which is tantalizing as something that might be incorporated into labeling but I think it's pretty soft. I'm not sure that I could make that recommendation. I really think that when we start

looking at the limitations of the way in which this enormous undertaking specifically addresses the questions that we're dealing with, I'm not sure we can add a great deal.

CHAIRMAN McCLUNG: Other comments? Dr. Follman.

DR. FOLLMAN: Yes, I have a question about the labeling. It's more my ignorance of this area. But there's this one phrase "should be prescribed at the lowest effective dose for the shortest possible period to achieve treatment goals." I wondered what "achieving treatment goals" means for osteoporosis. Does it mean that you have a target-free BMD and you try and achieve that target and so it sounds like the therapy could go on forever. I don't know what are the treatment goals for using this for osteoporosis. I think if I understood that better I'd have a better handle on what the duration might be and other points.

DR. ROSEN: Mike, can I comment?

CHAIRMAN McCLUNG: Sure.

DR. ROSEN: Yes, I think that's the problem in clinical practice. I think we don't have

good endpoints. We use bone density as a surrogate marker but I'm not so sure that it's the endpoint that we should be looking at. We have women that fracture on estrogen whose bone density goes up. That clearly can be misleading and that's a big part of the problem.

When we're talking about the indication labeling here particularly for prevention which has to be highlighted not treatment of osteoporosis where we have endpoints such as fracture, we're in a real gray zone in terms of what prevention outcomes should be. Should it just be bone density? Well, 40 percent of women taking calcium and vitamin D will maintain their BMD two or three years after menopause. This is a real gray area that we haven't established in our "osteopenic population" and that's what makes it very difficult for you as well as for us who are dealing with it on a regular basis.

DR. BONE: Could I just respond to that?

CHAIRMAN McCLUNG: Yes, Dr. Bone.

DR. BONE: One of the things here is when we're talking about prevention "Do we mean

stabilization of osteopenia or do we just mean prevention of any loss whatsoever?" We could argue that a person whose T-scores averaged plus one who took a drug and didn't drop over the next 20 years had prevention of osteoporosis. And she might have, but another way to look at this is to identify a patient with increased risk of developing osteoporosis and then modify that risk in some measurable way. Maybe that's something that we should be clarifying.

I don't think that's something that is a response of the Agency in the labeling of this particular medication in response to this particular set of information but as a general approach that bears on the next question of going forward. How we understand ourselves to be preventing osteoporosis or preventing post menopausal bone loss and how those two slightly different objectives interrelate is going to have tremendous implication especially for issue like risk/benefit analysis.

CHAIRMAN McCLUNG: My personal view about the labeling and indications is that of Dr. Bone. It's truly hard to get better than we are. The issue

of what the endpoint is for prevention is well taken. While we know that bone density is a very powerful predictor of fracture risk in untreated patients, the relationship between the magnitude of the change in bone density in response to any therapeutic intervention and the reduction of fracture risk is less well defined. So it is a hypothetical model in our head as we imagine that if we preserve bone mass and prevent the loss of bone architecture and the deterioration of bone quality that it would make things be better. But those aren't measurable endpoints or outcomes.

The issue about what to do with non-estrogen medications and whether they should be used first or recommended first is more difficult in my view for two reasons. One is the WHI has given us this huge set of information with a very large clinical trial of 16,000 women followed for five years. So we have 80,000 patient years to deal with. No other osteoporosis alternative, non-estrogen alternative, be it a SERM or bisphosphonates has that kind of information. While we are more confident

about the risks associated with longer term estrogen use, I personally am less confident about the risk profile of long term use of these other agents too. So we're not quite comparing apples and apples in that regard.

Lastly if we require that somebody be treated with another drug first and then fail, the definition of failure of therapy is an unknown issue too. Having a fracture on bisphosphonate therapy or raloxifene therapy or estrogen therapy isn't evidence of treatment failure because the drugs don't cure osteoporosis. They just reduce risk. The absence of fracture doesn't mean that the drugs are effective so we don't have a way to decide whether a patient has failed on therapy or not which would make it even more confusing from a clinical standpoint.

So from an indication standpoint, my personal view is that the changes that have been made of clarifying that the use of Prempro is for the prevention of osteoporosis, not for the treatment of osteoporosis was helpful. That it was recommended only for women at significant risk. Trying to define

that risk more specifically in the context of a label is really difficult and that's not been imposed upon any other therapy for osteoporosis. That the reminder that there are alternatives now for the prevention of bone loss is included in the statement already. That's made great progress with the changes that have been made this past year. Dr. Bone.

DR. BONE: Actually one comment that was made by Dr. Colman I think was kind of provocative. That was if we were in a better position to assess the risk/benefit relationship some of the newer data showing a reduction in hip fracture would actually support even a specific treatment indication.

But the problem as pointed out by a number of the WHI group is that we don't have the analysis at least at the moment to look at things like the effect on cognition in the same population that's at the highest risk for fracture. So we come back to the point I was making earlier about trying to go from an all-purpose trial to a very specific kind of information. This is one of the places where I'm not sure we can make that step.

CHAIRMAN McCLUNG: Other comments about the current labeling issue? Dr. Woolf.

DR. WOOLF: I personally like the wording on the third bullet point. Clearly physicians need to know what their options are. While clinical trials are meant to give us population risk, what is the appropriate treatment for a woman with significant breast family history and coronary artery disease clearly may be very different than somebody who has no family history of breast cancer and no family history of coronary artery disease and who has some vague GI problems. This gives sufficient information to physicians to take all these individual things into account and decide what treatment is best for the patient for osteoporosis.

CHAIRMAN McCLUNG: There are indications for therapy but the indications are like this. They are indications for diseases and for problems in general. They don't usually define how that diagnosis is made which gets to the point of trying to attempt to define which patient would be the candidate for in this case estrogen/progestin therapy. This is not

what's usually done in the way we're given information as clinicians about that. Is my assessment correct?

DR. ORLOFF: I think your assessment is correct. You know the hardest part about labeling a drug is to –- Put it this way. We can never expect or even hope to fully direct the practice of medicine via a drug label nor do we think that it's a good thing. As has been stated many times, the practice of medicine although we like it to be evidence-based and as Dr. Anderson has said particularly in the area of prevention that has to be based upon population studies. Nevertheless when we do take care of patients, it's one-on-one.

That said, the purpose of the label is to convey throughout the extent of the label with a particular focus within the indications and usage section that information on expected benefits and risks within the context of use in the proposed target population. We wind up hedging a lot and the way we structure these indications fall short for example of using the term "second line therapy" but logic directs that the intent here is that the only primary

indication for this use of this product at this point is for the treatment of vasomotor symptoms because as has been stated here I guess here and elsewhere that this is really the only viable therapy for that aspect of the post menopausal condition in women. We go on to say then as is clear that if you are treating because you want to direct an intervention towards the other known expected benefits of in this case estrogen plus progestin, think about what your other options are because on balance, we cannot tell you across the board that you can expect benefits that outweigh risks.

CHAIRMAN McCLUNG: Dr. Schade.

DR. SCHADE: I may be the only one who doesn't like this labeling. I'm convinced that everybody at this table who sees patients and I see patients would make the right choice. What bothers me is many physicians at least at my institution wouldn't have the background and knowledge of this whole trial and hear this type of discussion.

I actually think point number three here where we're talking about prevention of post

menopausal osteoporosis doesn't really help the physician enough. In other words, the minimum I would do is to extend the last sentence where it says "When prescribing solely for the prevention of post menopausal osteoporosis, therapy should only be considered for women at significant risk for osteoporosis and non-estrogen medications should be carefully considered." I would add something to the nature that "particularly in patients with a family history of breast cancer, with cardiovascular disease," etc. The things that we're worried about.

I would simply extend that sentence to be more helpful to the general practitioner who hasn't heard a day long discussion of the WHI. I think that this is not specific or detailed enough to be very helpful.

CHAIRMAN McCLUNG: Dr. Lukert.

DR. LUKERT: But do we really know that the people who are most likely to have these adverse effects when given estrogen were people with a family history and the other risk factors? It was my understanding that it really wasn't the case. Maybe

it wouldn't be accurate to say that we could limit this to worry about the people who had these particular risk factors. It seems to me that this insert adequately -- anyone who reads it –- If they don't read it, there's nothing that we can do about it. But a physician or patient who reads this - in my experience, the patients read them rather consistently – the dangers are going to be emphasized to them and they are going to understand that this is a drug with considerable risk as well as benefits. I think it's fairly well balanced in that regard. I'm not sure that we will be giving them accurate information if we add those risk factors. I'm not sure that increasing their susceptibility is the adverse effect in response to estrogen although we would expect it to be global.

DR. ORLOFF: I want to make a quick comment if I might of clarification.

CHAIRMAN McCLUNG: Yes.

DR. ORLOFF: Because I do agree with Dr. Lukert. Unfortunately drug labels are long and they must be read to be understood. That's a whole other discussion. But as I said the label in toto addresses

expected benefits and risks when used in the proposed target population. By and large, the indications reflect expected benefits. Elsewhere in the label you see the risks and indeed in the sections directly following indications, there are contraindications which are the strongest recommendations against the use of the drug for safety reasons. Then those are followed by warnings and by precautions.

Based upon the results of the WHI, the warnings and precautions sections of this label have been changed to add additional information about the overall risks of the product. And those risks need to be taken into account when you're sitting across or at the bedside of the individual patient and making the consideration about on the one hand whether their risk for osteoporosis which isn't something you read from this label, but whether they're at risk for any of the known potential adverse effects of this drug that your gestalt would alter your impression of the overall balance of risk and benefit.

CHAIRMAN McCLUNG: Mr. Follman.

DR. FOLLMAN: I'd like to talk about the

table on page 18 of the insert which goes into the relative and absolute risks for the various events comprising global index. I actually like this with displaying the data. I thought it laid it out in a lot of its complexity. It showed the pros and cons. The relative risk numbers are useful to the population and would be appropriate here in that we usually in clinical trials think the relative risk for the entire study is appropriate for all subgroups. That feeling has been justified by all the analyses that were done today where we show that the relative risk for the most part if not entirely were consistent across the wide variety of subgroups.

When you talk about absolute risk though, the story is a little different. The absolute risks in this table are for the entire WHI cohort. If we're thinking of osteoporosis specifically, I'm imagining this is going to be prescribed for women who are at high risk for hip fracture. If that's the case, then these absolute risks given in this table probably are too low and don't quite fully reflect the benefit you might get from hormone replacement therapy.

I did a little rough calculation based on Dr. Cauley's article where she looked at the risk of hip fracture as a function of this risk score. She showed that overall the relative risk was similar but there's a huge gradient in the risk of hip fracture as a function of this risk score. At the highest tertile, instead of expecting hip fractures in the placebo group for 10,000 person years, it would be more like 65 and for the estrogen replacement therapy, it would be more like 45 instead of 10. So instead of a difference of five, it would be something more like 20. This isn't actually an exactly correct number because I couldn't do the exact calculation based on the information in the JAMA article.

But the larger point is whether we should give more specific information regarding absolute risks in aiding the decision. We're trading off risk and benefit here. We're thinking about absolute risk for each individual decision and more precise estimates and more tailored to the individual would be helpful.

CHAIRMAN McCLUNG: My comment about that

is that there are ways that people can find out what absolute risk is. There are a variety of studies that had helped us to do and there's a move afoot among the osteoporosis and bone density community to move away from expressing bone density values in terms of T-scores and absolute values, but rather to express them in terms of absolute risk that incorporates at least three important dimensions, BMD, age and previous fractures. So determining the absolute risk in an individual is an important clinical objective. It's hard to figure out how to do that in the context in my view of a specific label that is for one particular drug. That needs to be a part of the educational process that we collectively engage in to deal with improving the understanding of osteoporosis, its risk and circumstances across the entire population. Dr. Bone.

DR. BONE: Just further to Dr. McClung and Dr. Follman's comments. If we were truly going to try to identify a group at what for those of us who make a large part of our effort in osteoporosis area we consider high risk, first of all, the risk gradient

would be a lot higher than even you're describing. Secondly, we'd be talking about an indication for the treatment of osteoporosis which is not part of the label. We go around in a circle there because once we start talking about people with a higher risk of hip fracture, we're talking about a disease for which the drug isn't actually approved at the moment. I'm not disagreeing with you. I'm just saying it takes us to a strange place.

CHAIRMAN McCLUNG: Let me attempt to summarize then what I sense is a prevailing comment. Let me see if I can do this in the right way. The current label for the combination estrogen/progestin that was studied in the WHI has been upgraded and changed substantially in two separate steps, first on the basis of results from the HERS trial and then more recently with the results from the WHI data.

The changes that have been made accurately reflect the information that was provided to the academic community from those two trials and has put the use of the medication for the prevention of bone loss and osteoporosis in a different perspective than

existed before. Changes that have been made have been very useful and positive. Collectively, we can't think of a better way to express the information than is stated in the third indication that specifically focuses on the use of Prempro for the prevention of osteoporosis.

We all recognize that none of this is perfect and this requires understanding in the background that's in the rest of the package insert that has to do specifically with the contraindications and the other risks that have been described and that are outlined in subsequent paragraphs. I personally think that it's not possible to incorporate all of that information into a succinct paragraph under the indication and usage circumstance.

With that, let me propose that we move on to the second issue which let me restate it. We're asked to discuss the implications of the WHI trial results for the future development, testing and potential approval of estrogen plus progestin drugs products for the prevention and/or treatment of post menopausal osteoporosis. We will expand the

discussion beyond what we've worked on. Who would like to open that discussion?

DR. FOLLMAN: I guess one thing that was talked about consistent with the labeling is lower dose, shorter duration. I can see that there will be movement towards doing studies like that where you have low dose and you'll look at probably a surrogate endpoint bone mineral density say and see whether that differs from placebo or not.

I worry a little bit about that. This is consistent with a point that I made earlier that you could show that there's a difference at a very low dose between placebo and the treatment in terms of bone mineral density but it might not be efficacious in terms of clinical endpoints preventing fractures of different types. If you are doing such studies you should probably be mindful of that and want to have a lowest dose that still gives you what you guess is a clinically meaningful benefit. By "guess" I guess I mean that you would use observational data correlating BMD with the probability of fracture and have some comfort that the difference in BMD would translate

into a clinical benefit. I'm just wary of going as low as you can.

CHAIRMAN McCLUNG: Dr. Lukert.

DR. LUKERT: I think that if you could have done whatever you thought would be most helpful it would be to look at transdermal estrogens as opposed to oral because of the effects of the first pass through the liver, of the effects on coagulation factors and upon the precursors of angiotensin. Those all have such vascular implications plus the effect on growth factors produced by the liver and the potential implications on those. One of our areas of investigation should be other forms of delivery.

As far as the implications are concerned, I'm just delighted when I see a patient come in with such profound vasomotor systems that she has to be treated with estrogen. I know that at the same time that this will give us some time to improve her bone metabolism while we're waiting for her get over her vasomotor symptoms. Otherwise, we're ethically on sort of shaky ground given the data we have with evidence based medicine to use estrogen as a primary

form of treatment or prevention of osteoporosis.

CHAIRMAN McCLUNG: Dr. Woolf.

DR. WOOLF: I think if we learn anything from HERS and WHI it's that we need hard endpoints and not surrogate endpoints. Any future estrogen trial have hard endpoints, fracture data, current and adverse events and we can't use surrogate endpoints because they led us astray for God knows how long. They'll make these trials very long and make them complex and make them expensive. But I don't see any alterative.

DR. BONE: Can I just respond to one point?

CHAIRMAN McCLUNG: Sure. Dr. Bone.

DR. BONE: I think if we look at the indication treatment of osteoporosis that's one point. But if we're talking about prevention of osteoporosis, we're talking about starting with a patient population at a very low risk of having a fracture in which we hope to see that the risk does not increase. It becomes a prohibitive problem to try to see a difference in fracture rate in the prevention

indication. That's the subject of a lot of discussion and writing as you know. It's the reason why the endpoints are what they are in the current guidance as to use of bone density to show prevention of post menopausal bone loss. The distinction there is between treatment of osteoporosis and prevention of post menopausal bone loss.

CHAIRMAN McCLUNG: Dr. Woolf, you're going to respond to that.

DR. WOOLF: I agree but these other endpoints are going to take some time and the adverse events. Typically the prevention trials have been two to three years and these other things are going to five or six years to develop which may give you enough time for those factors. The WHI also showed us that these are very potent drugs to prevent fractures. The question is can we leverage in future years to come up with a dose of estrogen and delivery system for estrogen that gives us the bone benefits without the cardiovascular and CNS detriments. The only way to do that is time and obviously enough patients, but some of the bisphosphonate trials were three or four

thousand patients so they are getting up there.

CHAIRMAN McCLUNG: Nine thousand patients.

DR. WOOLF: Even better.

CHAIRMAN McCLUNG: Right.

DR. CARPENTER: I can only echo the comments made by Barbara and others to pursue for future investigation both dose and delivery mechanisms. I think weighing risk and benefit in the lower doses is clearly an important strategy and one that in fact with the data coming in through post marketing would be highly encouraged to aggressively collect already at this point in time. I also would being in the role of a pediatrician having to use many drugs off-label and look at other situations in which these medications are used perhaps on but also off-label and that is the life-long effects of using these medications in women with premature ovarian failure for various reasons and that data is a smaller set but clearly everyone is applying data from studies such as WHI and others that we've heard about today extrapolating it to long term use. I think we really don't have that data. It's an important area to

pursue.

CHAIRMAN McCLUNG: Dr. Rosen.

DR. ROSEN: Thank you. One of the areas that I feel uncomfortable about in practice and also in research is predicting who is going to go on to sustain rapid bone loss. This is an area although we use bone density as a marker, we don't have the large scale trials to actually tell us what the predictive factors are. So if you knew a woman who walked in at 50 with a T-score of -1 was not likely to lose a lot of bone versus somebody who walked in and they only had a five percent bone loss as Claus has shown that some subpopulations do have those rapid rates of bone loss, those are clearly individuals that might be targeted for short-term, low dose therapy.

The truth of the matter is the markers have not done a very good job certainly not in practice of predicting that. We're getting to an era now where it's open for the NIH and other non-commercial entities to consider supporting this kind of investigation looking at proteomics, trying to predict through protein markers what are the factors

in post menopausal women that might potentially predict their subsequent rate of loss or fracture as well as genetic studies which are just starting to do in WHI.

This is an area of investigation that we still don't have a real good handle on and I'm afraid in clinical practice we have a very poor handle on it. We use bone density, T-scores of -1, but how that translates into those people five years down the road still is problematic. That's an area that we really would need tied to possibly to a prevention trial with our surrogate markers. It's going to be impossible to do a fracture study with young post menopausal women because their absolute risk of fracture is so low. But we could use another type of trial to pick up risks of rapid bone loss certainly that is a surrogate for some aspects of changes in bone quality.

CHAIRMAN McCLUNG: Right. Just to comment, there are some data about that. In the EPI trial for example with the large population, the only two things that we've been able to demonstrate predicated rates of bone loss were body size and how

close they were to menopause. The distribution of the rates of loss was actually amazingly tight. There weren't a big subset of fast losers and other who didn't lose at all. It was tightly grouped about that.

Of course, that applies not just to this drug but to any choice of therapeutic intervention for prevention. So defining who the person is to initiate pharmacologic intervention is a general question that the clinical community is still grappling with and which individual would be candidate for estrogen as opposed to an alternative is a subquestion under that big umbrella.

DR. ROSEN: Sorry, Mike. I just wanted to add that part of the problem may be that we don't have the right markers yet to predict that. That's an area of active investigation that we should consider. There are a couple of different new markers coming out or need to be explored and those are the kind of investigations we need to take up.

CHAIRMAN McCLUNG: Sure. Dr. Bone.

DR. BONE: One of the things that we

normally do as endocrinologists is try to achieve very consistent and precise control of the level of whatever hormone it is that we're administering. I'm not sure we've done as much about that in this area as we could have. Dr. Lukert's, Dr. Rosen's and Dr. Stadel's comments all make the point that first of all some of the earlier studies that were done looking at the serum estradiol levels required to stabilize bone mass might be revisited with more sensitive testing to see if much of the benefit could be achieved at somewhat lower serum estradiol levels.

Selby's paper looked like something like 45 picograms per mL or something seemed to be effective in just about everyone. There may be some individual interactions that could be in part genetically determined on that basis. Maybe there's a group that requires a lower dose where 14 picograms per mL of estradiol is just fine depending on what the SHBG is or something.

But this is what endocrinologists do. This is more challenging in the case of CEE because this is a mixture of the ingredients each of which is

going to be metabolized differently. I don't think I can add anything to the discussion that Dr. Woodcock gave last year at the NIH meeting on it where she discussed this whole topic fairly thoroughly, but the point being that it's more complicated with CEE. If we were talking about serum estradiol or could pick out what it is and we really had to be concerned with and then could thread the therapeutic needle so to speak, we might find ourselves able to be on the right place on dose response curve for a desirable effect with getting too far up the adverse effect curve.

I suspect that the dose response curve is somewhat plateau-shaped as is usually the case. And that is as often the case, the adverse event curve may not be. We may find that really understanding the endocrinology of post menopausal women better and what our targets are that we should be trying to achieve in order to mitigate this rate of loss could really put us into a more elegant, more endocrinologic approach to solving some of these problems.

CHAIRMAN McCLUNG: Other comments? Let me add a couple of my own. The question of what these

implications are for the development of other estrogen/progestin products for osteoporosis management, both prevention and treatment, really is broken down into at least three discrete categories. We met a year ago to review the guidelines again about the prevention and treatment indications in the guidance and the types of trials, the types of endpoints that were there.

Those guidance points have served us I think extremely well for the last ten years or so. The distinction of preventing bone loss in low risk populations with bone density as the primary endpoint still makes good sense until we've had some other better determinant of bone strength and bone architecture and bone quality. As we develop new imaging studies and new techniques, we may move away from simple bone density to the more sophisticated endpoints. To require fracture as an endpoint in studies where the idea is simply to prevent and stabilize the skeleton will be beyond the scope of what anyone can do.

For the treatment indication, we all agree

that surrogate endpoints aren't sufficient and that documenting fracture risk is necessary to do that. Those are already embodied and codified in the current guidelines. Whether we are talking about estrogen/progestin drugs, estrogen only drugs, different routes of administration, different doses, non-estrogens, all those still fall under that same rubric.

The major issue or another issue though that makes estrogens be unique is their risk profile and dealing with evaluating whether different doses, different preparations, different routes of administration have differences in risks is a different both investigative and certainly a different clinical question to address and may take a great deal longer time to do. It may not be practical to include in one study particularly if we're talking about prevention indications the efficacy endpoints on the one hand and the entirety of the safety endpoints that one would like to see and to demand.

There are already in the current label for this preparation and now expanded to the other

estrogen preparations the concerns and statements about risks that are extrapolated from the WHI. My thought is that for a drug to be approved for the prevention of osteoporosis it could still get there by the same route to be distinguished as being different in terms of its risk profile could be addressed in a separate question.

For an estrogen or an estrogen/progestin preparation to be assumed to be in the same category is maybe the most straightforward or the most sound place to start and require that drugs do the studies to distinguish themselves from the risks that are embodied in the WHI. That would be a different type of study that would change the contraindications and/or the risks but wouldn't change the indication.

The third piece of that is that it would be really helpful if we could work at identifying the right people, the ones at risk and whether it's estradiol levels or whether it's biochemical markers or new markers or whether it's some other combination of risk factors. It's a project probably beyond the scope of the FDA or the sponsors of studies that are

submitted to the FDA but is an NIH and/or some other global approach to things. Dr. Lukert.

DR. LUKERT: I really like the way you sorted out the issues. But I do wonder. It seems to me that the major question now though about estrogen/progestin is are there risks. We know that they do work to protect against bone loss. So I guess the thing I would question is whether we really need any other new estrogen product if we need to just assess its effect on bone. It seems to me that even the greater need is to look at the risks. That would be my only difference.

CHAIRMAN McCLUNG: Yes.

DR. ORLOFF: If I might.

CHAIRMAN McCLUNG: Yes. Dr. Orloff.

DR. ORLOFF: This is a question that can't be resolved in the abstract. Some day the data will have to be produced. What we would probably conclude from this discussion is that the burden is on the proposer and on the community involved in this field to produce a weight of evidence that supports a favorable risk/benefit profile say for example for an

estrogen or estrogen/progestin administered by an alterative route or for a lower dose of estrogen alone or estrogen plus progestin. That risk/benefit profile would thereby be distinguished from the dose and product and route of administration that was studied in the WHI. There's been a lot of speculation today based upon one or another subgroup analysis of the WHI despite cautions about inferences from those analyses that there may be reason to believe that the risk/benefit profile for Prempro for example might be different in one group versus another for example by age. Those are interesting speculations but I don't think we have any data from this trial to bring to bear on it.

I would say that we spent a lot of time today talking about the global index in the WHI. I'm not sure that there was any complete agreement on what the role of the global index was after the fact. But for a new product coming along, we would be hard pressed to from the start ask for essentially the same quality of hard data, to ask for a global index score, for a new product. We would expect sponsors to

propose a data package that would be perhaps more traditional harkening back to the usual way in which we evaluate drugs that someone referred to here earlier which is that we design trials to establish the benefit based upon our hypothesis and then we look at the safety profile and we make some judgment as to whether we think it satisfactorily safe given the benefits. We use our heads on this.

In this particular instance, we would use our heads as Dr. Bone has suggested that clearly there's every reason to believe that as you reduce the dose the risks associated or at least some of the risks associated with the use of such a product are also going to be reduced. So also are the benefits, but we have to understand that the benefits of such an intervention are monitorable.

We go into this with an assumption that particular for estrogen there is a graded and continuous relationship albeit not perfect from patient to patient but there is a graded and continuous relationship between bone mineral density and fracture risk. It comes from epidemiology. It

comes from intervention. So we believe in BMD and in practice one can monitor BMD to assess whether an individual patient has responded to the dose, route of administration and particular molecular species with which she is being treated.

That's by way of saying that ultimately we'll know when we know. I don't think that I've heard here a consensus and correct me if I'm wrong that we absolutely are looking towards a day when no estrogen or estrogen/progestin could possibly come to market for the management for post menopausal bone loss in the absence of a WHI type study.

CHAIRMAN McCLUNG: Comments about that? Dr. Bone.

DR. BONE: Yes. Broadening out a little bit from that comment from Dr. Orloff and little bit where we are, we are basically faced with class labeling based on CEE and medroxyprogesterone acetate. We faced with some uncertainty about the whole issue of generalization that's been to other compounds in these general categories that people have discussed a lot about, not so much today, but at other times.

These variations include the molecular species, the dose and the route of administration and so forth as has been mentioned.

What Dr. Orloff's comments lead us to is the question of how could a sponsor proceed or how could even an independent organization proceed to try to investigate some of these questions and have this reflected in the labeling of the drug product. It seems to me that it would be extremely difficult for the division to do away with the class labeling all together in the absence of a study of at least comparable rigor. It might not be such a big study because it could be more focused so that's a fair point. But it would have to be a very large, very well designed study to supercede with some other molecular species for example what class labeling we seem to be developing.

On the other hand, does this make this hopeless? Could it not be the case that to the extent that a treatment, a medication or a combination that was proposed within the overall umbrella of the class labeling distinguish itself in some meaningful way by

well-documented data that could be incorporated into the clinical pharmacology section of the labeling? The sponsor then would basically be able to say "Yes, we're operating within this WHI class labeling but we've been able to show that at least one element of this is somewhat different or may well be or something like that."

It seems to me that the clinical pharmacology section may be one place for this and that could result in more nuanced warnings and precautions if the data are there without disrupting everything. That's a way that a sponsor could proceed in the development of a new product to say "Okay, we're going to concentrate on what we think are two to three important things where we really think we can demonstrate an advantage. Then once we have a toehold maybe we may go for the big trial." It's just a way of thinking about that.

I have to say without wanting to open a can of worms that there's some overlap of this in the SERM area because of overlapping effects that some of these issues may arise there as well in terms of how

one distinguishes one product from another and could that be done in clinical pharmacology?

CHAIRMAN McCLUNG: Okay. Other comments?

DR. CARPENTER: Just a brief response to the issue of the global index and its future in potential other trials, it would be a mistake to entirely discard this notion - and maybe I'm speaking from the minority point of view here - but I find that particularly in the setting where an efficacy endpoint is very hard to establish where we're talking about primarily preventive efforts in whatever endpoint we're looking at. We're generally looking at continuous variable of reversing a natural phenomenon with a considerable way of other side effects of this that need to be weighed in some way against the endpoint that we're looking for.

I haven't seen anything at least to-date that can integrate this comparison better than what I've seen today in terms of the global index. So it may actually be a model by which at least other models could be amplified or modified for other comparisons. I don't think that it's something that I would

discourage as an indicator of where to go with these newer therapies.

DR. ORLOFF: I wasn't quarreling that for the purposes of producing or generating definitive information, the global index didn't have a very important role. All I was saying is that it would seem at this point a very high bar to place to ask for that standard of evidence for every new product that comes along.

CHAIRMAN McCLUNG: Dr. Follman.

DR. FOLLMAN: I'd like to comment a little about the global index also. I like it as a simple understandable way of coming up with a number that traded off risks and benefits. I would also mention that I don't see how we can come with a different global index for the WHI or try to refine it in some way. We know the results of this study so it would be like doing this study without an endpoint defined beforehand looking at all the data and all the tests and then trying to come up with the primary endpoint. It's basically impossible I think.

There's a potential refinement of the

global health index that I think could be done. It would be to somehow weight the different categories. A simple way to do this would be for each of these events, say breast cancer, hip fracture and so on, calculate the probability that you'd be dead say in the next five years if you had one or more of these, separately for each of the events and then instead of summing up, you just note whether you had one of these events or not. Then you would calculate for each woman the probability you'd be dead in the next five years based on whether you had hip fractures, a stroke and so on. That might be a way of trading off in some way what's worse, breast cancer or hip fracture or stroke.

DR. ORLOFF: I understand that the WHI investigators considered that approach and figured when all was said and done that it would just add one more level complexity to their trial, the planning and implementation that wasn't going to be worth it.

CHAIRMAN McCLUNG: Plus, it would reward events that happened late in life. They would get a higher score because the older you are the less likely

you are to be alive five years from now. There are all kind of nuances to that. I think we all agree that the global index was put together again for specific purpose of this study. We've learned a lot about the disease processes that were evaluated and the outcomes that were evaluated in the study and nothing precludes the next study if there ever is a next large study to prospectively define a modification of that index to include vertebral fractures or other endpoints that we've now learned are important as a part of these sorts of things. Dr. Woolf.

DR. WOOLF: I personally would like to keep the bar high in the next go-around because we have effective alternative therapies for osteoporosis that have their own set of baggages. We certainly know a lot about Premarin and its various forms. Why have a lesser standard of evidence and a lesser standard of commitment to the next go-around? Why pretend that we don't have this information? So I'd like to keep the bar high.

One other thing, when first I read this

material about a week or so ago, I really did not like the global index. I thought it was rather simplistic and everything was equal. In my own mind, they weren't equal and there were a whole set of things that weren't there that may not have been as devastating as breast cancer but nevertheless were pretty significant problems.

Over the course of the day, my opinion has changed because I don't know of a better alternative. I certainly haven't heard of one. We did discuss at lunch despite the Chairman's prohibition about weighting the factors of the global index. One person's weight may not be someone else's weight and you'd have a whole set of disagreements about the weighting. We can use quality-of-life years or something like that. I don't know. I got away from that. I guess I came around to the global index and liked it. Have something like that in the next go-around.

DR. ORLOFF: Mike, let me just make one more comment which is that it's important for the record for everybody to understand that this is class

labeling as Dr. Bone has said. It's class labeling because at this point we don't have sufficient not to apply in some qualitative if not direct quantitative way the results of the WHI study to this broad class of drugs. In the spirit of disclosure which is what we do in labeling, we tell people what we know either specifically or broadly about the risks and benefits.

I want to make clear that I'm not proposing that the bar shouldn't be high in order to have a drug marketed and promoted as somehow absolutely not carrying these sorts of potential risks or this overall balance of risk and benefit. That's not what I'm saying. There's a very high standard evidence and quite frankly it's a little bit difficult to imagine at this point that we're going to get there.

That being said the way we've written this label now as I said before the only true, first line use of this product is for the treatment of vasomotor symptoms. There is no reason not to encourage I believe the development of lower dose, alternative routes of administration, estrogen or

estrogen/progestin drug products that would effectively address vasomotor symptoms and then to study them in order to understand the expected effects on other aspects of the post menopausal woman's health and particularly their bone health. It doesn't mean that we would alter the way we write this label. It's just that we would have something else in the armamentarium to go to in lieu of higher dose perhaps orally administrated agents for example not to pass any judgment.

CHAIRMAN McCLUNG: Dr. Zerbe, do you have a question or comment?

DR. ZERBE: Actually all the points have been very well made and I don't have a lot to add except that the whole effort is to be applauded in terms of the data that were generated. There really does need to be caution with regard to general application. I guess that's a statement of the obvious. From an industry perspective, we need to be cautious about the bar which certainly does need to be high, but we do need to also balance that against bringing new products forward to actually replace some

of the products that do have the flaws. That would be the only thing that I would say. Thanks.

CHAIRMAN McCLUNG: Dr. Woolf.

DR. WOOLF: Speaking of bars now, there is one area where the bar is incredibly low. In fact, I think it's below ground. That's the whole notion of phytoestrogens and natural estrogens that my patients are coming in with. We don't have to worry about cancer. This is a natural product here. It will cure my bones. It will prevent osteoporosis. I understand the FDA's dilemma on this, but this has really become a problem bordering on becoming a nightmare. Somehow or other we're going to have to get a handle on this. I have no idea of what it would take, but this notion that this is natural and no data either efficacious or safe. We have to get a handle on that.

CHAIRMAN McCLUNG: I'm glad that wasn't today's issue but we'll be happy to have you volunteer to be the chair of that committee.

DR. ORLOFF: Let me get right back to you on that one.

CHAIRMAN McCLUNG: That's right. Exactly.

Other comments or issues? Let me if I can make again try to make some generality out of this. If what I say doesn't resinate with what somebody else thinks the group said, we can modify it. To address the issue that we were handed about the implications about the WHO for the future development, testing and approval for estrogen/progestin products for the prevention and treatment of osteoporosis, I have heard this. The current requirements for the approval of an estrogen/progestin product or an estrogen product for the prevention of osteoporosis is based on sound reasoning and there seems not to be a need or a big statement to change the guidelines or requirements for approval for prevention of bone loss.

With that approval however comes the class labeling of the risks that are already a part of the estrogen/progestin, estrogen labeling process. For a new product to be able to distinguish itself as being somehow unique and different in terms of the risk profile, a specific study that wouldn't necessarily have to address all of the risks simultaneously but could address a risk one at a time as Dr. Bone could

be done. Then were that data reviewed, then it could be incorporated somewhere in the package labeling to reflect that the comparison had been made and that perhaps a uniqueness for that particular product could be done. But the absence of that, the concerns about the risks that we already have before us with estrogen and progestin would not be able to be escaped. Does anybody want to work on that harder?

DR. ORLOFF: With the caveat that comparative safety claims, even implied ones, are difficult to come by.

CHAIRMAN McCLUNG: Sure.

DR. BONE: Could I just add one thing?

CHAIRMAN McCLUNG: Yes.

DR. BONE: One thing that would be extremely helpful here is if we can obtain more informative research about the possible distinctions that have been hinted at in a literature between for example different progestins and how they might interact with the risk of breast cancer and that kind of thing. This is an area not simply for large scale clinical trials but also for really intensive and

well-designed preclinical studies that could inform us in these areas.

CHAIRMAN McCLUNG: Another point that I reflect on and would just bring back that was made two or three times was that studying the population of subjects for whom either the sponsor or the clinical community thinks that a drug would be most applicable for would be helpful. We've talked about that there are different categories of risk or the different individual patients have different risk profiles and perhaps to encourage studies to be done where the clinical profiles are predefined and specific groups of patients be targeted for evaluation. This would another thing to come out of the discussions that we've had today.

The third issue was the broadest of all and was a time if there were comments beyond what we've already dealt with to make to Dr. Orloff and his team about outcomes from the WHI trial and how it relates to the issue of approval for osteoporosis indications for estrogen and progestin therapy. Any other comments? Now is the time to add that to the

discussion here.

DR. ORLOFF: Dr. Woolf already got his other comment in.

CHAIRMAN McCLUNG: Right.

DR. WOOLF: I expect a phone call.

CHAIRMAN McCLUNG: All right. With that, Dr. Orloff, we have exhausted our thoughts about this and hope that we've provided some input that you and your group can deal with over the next time here.

DR. ORLOFF: Again, thank you everybody for giving up your valuable time. We much appreciate it and we'll take it from here. Thank you. Off the record.

(Whereupon, the above-entitled matter was concluded at 4:26 p.m.)