the tamoxifen effect, with a potential loss of up to 35 percent of tamoxifen effect without a reduction in risk of non-invasive breast cancer outweigh the risk of adverse events?

[Slide]

I would like to summarize the application taking into account the four randomized, controlled trials.

[Slide]

For the first indication, reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis, in addition to the known benefit of raloxifene treatment for prevention of osteoporosis, there is a reduced risk of ER positive invasive breast cancer compared with placebo. However, the benefit comes with an increased risk of deep vein thrombosis, pulmonary embolism and possibly stroke deaths compared to placebo.

[Slide]

For the second indication, the reduction in risk of invasive breast cancer in postmenopausal

women at high risk for breast cancer, the magnitude of the raloxifene benefit when compared to tamoxifen benefit is uncertain. The evidence for reduction in risk of invasive breast cancer by raloxifene is less compelling than the evidence for tamoxifen. In general, raloxifene appears to have less risk compared to tamoxifen in this highly selected population. Possible losses of tamoxifen effect are important, especially when raloxifene also has risk of side effects. It is uncertain if the balance of benefits and risk factors for women at high risk is favorable because the magnitude of the benefit is unknown. Thank you.

Questions from the Committee

DR. HUSSAIN: Thank you. We will go now to questions from the members of the committee. The way this would work is you, please, raise your hand or alert Johanna or myself that you have a question and then we will call on you. Please make your questions brief, and I am going to request from the FDA and the sponsor to make your answers also brief and to the point. We will begin with Dr. Brawley.

I think he raised his hand first.

DR. BRAWLEY: Can we go to Eli Lilly slide 63? This is I think a question for Dr. Wickerham. Dr. Wickerham, the question is did the NSABP P1 verify or validate the Gail model such that it is fair to say that if there had been a placebo arm in this STAR trial one would have expected the 325 breast cancers?

DR. CONSTANTINO: Actually, I am Joe Constantino, the statistician for the P1 and for the STAR trial. Indeed, the placebo arm of the P1 data was used to validate the Gail model. It was published in the peer review literature in 1999 and actually the model was shown to be very accurate in predicting the incidence of breast cancer. In that placebo arm there were approximately 170 breast cancer cases and the model I think was off by four events. So, the model is very accurate. It gives a very good population-based estimate of the incidence of breast cancer and, in fact, that is what we used to design the P1 trial for the expected rates for P1 and for P2.

DR. HUSSAIN: Dr. Perry?

DR. PERRY: This is for the two FDA reviewers. A number of the comments you made regarding the disadvantage of raloxifene compared to tamoxifen looked at relative risk where the confidence interval crossed 1, for instance for the risk of ovarian cancer where the risk is 0.060 to 2.76, and you make something of that. To me, that is inconsequential. I can't make any conclusion from that but you actually listed that as a relative disadvantage of raloxifene. Is that appropriate?

DR. MANN: I will leave it to Dr. Cortazar to comment regarding the ovarian cancer. But the thromboembolic adverse events are seen across all three studies.

DR. PERRY: I understand that, but when you are talking about the data you used here we are talking about a confidence interval across 1.

DR. MANN: Yes.

DR. PERRY: My limited statistical knowledge says that when a confidence interval

crosses 1 it is no longer valid and you can't draw conclusions from that. You have apparently drawn conclusions from that.

DR. MANN: Yes, and I will explain why. The reason for that is that the primary endpoint in these trials is not trying to look at the adverse events so the trials do not have, to begin with, the power to differentiate that. So, as a result, yes, the risk of both type 1 and type 2 errors is high. But that is true of adverse events with all drugs and you have to look across the studies.

DR. PERRY: But my point is still if the confidence interval crosses 1 the statistically significance of the observation is muted and we can't conclude necessarily that things are worse between tamoxifen and raloxifene based on that particular statistical event.

DR. MANN: I will let Dr. Cortazar respond to this.

DR. CORTAZAR: You know, regarding the STAR trial, my slide was to summarize the safety events; it was not like the conclusion that it was

statistically significant. That was not mentioned.

DR. PERRY: Well, if it was not statistically significant then we shouldn't be mentioning it.

DR. CORTAZAR: You know, I just mentioned that the number of women taking raloxifene had a higher number of ovarian cancers.

DR. SRIDHARA: Can I?

DR. HUSSAIN: Yes.

DR. SRIDHARA: To be fair, we also said that with respect to tamoxifen as well none of them were statistically significant and it is just to say, okay, here are events which were greater in the tamoxifen arm and here are events where raloxifene event were more. So, in both of them there was no statistical significance and we are putting both of them there.

DR. HUSSAIN: Dr. Harrington?

DR. HARRINGTON: Thank you. I have three questions for the sponsor. First, this may be for Dr. Wickerham or someone from NSABP. You mentioned that when you designed the STAR trial rough

calculations showed that you would need 60,000 participants for a non-inferiority design. That implies that there must have been some non-inferiority margin that you had behind that calculation that you wanted to use to exclude raloxifene. So, what was the non-inferiority margin that you were thinking about prior to doing STAR?

DR. CONSTANTINO: Actually, I think Dr. Wickerham actually said at least 60,000 and that is because we actually assumed a variety in percent retention, and the 60,000 would have been for 65 percent retention. For 75 percent retention it would have been 98,000 women. Both of those would have been a 20-year study or more; 20 years just for accrual to be achieved, and we realized that that was just not possible to do.

So, we sat down with our clinical investigators at NSABP with the NCI and we asked them to tell us, well, what is a clinically meaningful amount of retention that you think would make sense. Assuming that tamoxifen had already

been demonstrated to show a reduction of about 50 percent and that, as Dr. Cortazar had pointed out, the excess risk of endometrial cancer was very close to the gain in reduction of breast cancer, the clinicians decided that, if we could eliminate the risk of endometrial cancer, an acceptable retention would be 50 percent retention. As you pointed out very eloquently in your presentation earlier on, that was exactly why we designed the trial to have the power to rule that out, to make sure that we were keeping at least 50 percent of the retention.

DR. HARRINGTON: Second question, and this one may be for the sponsor that provided the analysis. So, there were three other randomized, placebo-controlled studies of tamoxifen that ran roughly concurrently to the P1 trial that were enlarged in the IBIS trial and the Italian trial, and they showed I think some heterogeneity and they showed I think reduced risks which were not quite as large as the P1 trial. So, I would like to hear a little bit about why those trials are not

formally included in the analysis, along with the point that the FDA made that the analyses sometimes use meta-analyses of existing results.

DR. ROTELLI: I am Matt Rotelli, statistician for Eli Lilly & Company. That is correct, there were three other studies in addition to the P1 study historically.

[Slide]

These studies had a different population of women, different evaluation of the endpoints, different concomitant medications. So, our intention was, without the placebo being included in the STAR study, to provide an estimate in the context of historical data of raloxifene's efficacy. So, we felt that it was important to use data that was most applicable to the population being studied. Based on this overview of those four studies, the P1 study and the subgroups of women greater than 50 from that study most closely approximated the population of interest for STAR.

DR. HARRINGTON: Did you do a sensitivity analysis to see what would happen if you included

in your non-inferiority analysis some of these other trials?

DR. ROTELLI: Yes, we did and, as expected, there is increased variability as you start looking at broader populations of women. Here we see the results from four different analyses. At the top confidence bounds show the analysis we provided based on women over 50 from the P1 study as a historical reference. The second line demonstrates all women from the P1 study, premenopausal as well as postmenopausal and, as expected, there is some increased variability. Then, if you use the meta-analysis of those four studies, published by Kusik, if you go against the subset of women greater than 50 to approximate the postmenopausal population, again, quite a wide confidence interval, and if you go for all women in that analysis we may be gaining somewhat in the precision but it is still a quite wide confidence interval. It is also reassuring that all point estimates line up very close to 1.

DR. HARRINGTON: So, if I interpret that

third line correctly then, if you use the Kusik meta-analysis raloxifene could have lost up to 60 percent of the tamoxifen effect. Is that right?

DR. ROTELLI: That is right. It is extremely wide. It is equally likely it could have gained 142 percent but those are the bounds.

DR. HARRINGTON: Okay. Then, one last question about the transition from MORE to CORE. There was a little bit about that in the talk but I know that in the CORE population there are twice as many women on raloxifene as there are on the placebo arm. That suggests to me that there was some sort of self-selection ongoing in the transition between MORE and CORE, that women on raloxifene were maybe more likely to elect to be in the continuation. Could you give me a little bit of an explanation there?

DR. CUMNMINGS: I think the difference between the two groups numerically in CORE is small. Yes, there probably was some selection on the basis of past history of fractures. Again, that was a very high risk group for osteoporosis

and those who continued on into CORE perhaps were slightly more likely to self-select on that basis. But the difference is small.

DR. HARRINGTON: So, I think the answer to that, that someone just reminded me of, is that since MORE had two different doses of raloxifene you continued the 60--

DR. CUMMINGS: Yes, because there were two doses.

DR. MITLAK: And patients were not aware of their treatment assignment when they entered CORE. They were blinded.

DR. HARRINGTON: Did you ask if they knew what they were getting when they moved from one to the other?

DR. CUMMINGS: It was blinded.

DR. HARRINGTON: I know it was blinded.

DR. HUSSAIN: Dr. Cortazar, you had a comment to make?

DR. CORTAZAR: He already addressed it.

DR. HUSSAIN: He already addressed it? I have a couple of questions. I have actually three

questions, one to the sponsor, one to the statisticians and one to the FDA.

Dr. Wickerham, in his presentation, indicated that when the STAR trial was designed when, they looked at the objectives as being compared to one or the other that one significantly reduced the incidence, and that they used clinically relevant reductions in incidence as part of their desire to do so because a non-inferiority would have been a huge trial. What is the clinically relevant difference that you would say something would trump the other one that was proposed in the trial and the assumptions in the trial?

DR. WICKERHAM: As Dr. Constantino reviewed briefly, the hope was that we would eliminate the excess risk of endometrial cancers associated with tamoxifen and balance that with no more than a 50 percent loss in the tamoxifen effect on invasive breast cancer.

DR. HUSSAIN: And was it your conclusion from completing the STAR trial that raloxifene is

as good as tamoxifen?

DR. WICKERHAM: Indeed, based on invasive breast cancers and the reduction in endometrial cancers, yes, that is our conclusion. And, we had planned to move it forward in the control arm of a subsequent prevention trial.

DR. HUSSAIN: Forgive my ignorance with regard to breast cancer prevention, but did raloxifene, based on that trial, get denied approval for an indication in prevention? Was it denied approval or is raloxifene now used at all? I mean, I don't see an indication for it in prevention.

DR. WICKERHAM: I think that is what we are talking about today.

DR. HUSSAIN: No, no, I understand. I don't mean to sound like I am confused, but if your original argument was very strongly based on a randomizedB-not borrowed data, not anythingB-just a head-to-head comparison, what was the reason that it was denied approval? Was it because you did not show it to be non-inferior?

DR. WICKERHAM: It has not been denied approval.

DR. HUSSAIN: So, it was never put forward for prevention even though you did a large randomized trial?

DR. MITLAK: Until now.

DR. HUSSAIN: Until now. And what has taken it that long?

DR. WICKERHAM: Well, the results were just presented and published last year. The sponsor submitted this for this discussion today in November of last year, and it took until now--

DR. HUSSAIN: So, this is the first time that this drug comes in to be looked at?

DR. WICKERHAM: That is my understanding, for prevention.

DR. HUSSAIN: I would like to move now to a questionB-and thank you for the clarification because that was my understanding; I just wanted to clarify it-Bto the statisticians. If it is okay to borrow from one or the other, you know, you have multiple trials and you can look at it, and if you

used the data from the STAR trial-Band I ask this question because a lot of the discussion, as I see it, or the argument from the FDA is driven by benefit/risk but it has to do with the retention of effect. So, if you looked at tamoxifen in the STAR trial and you did an exercise in statistics and compared it to the original placebo-controlled trial, how much tamoxifen effect would be retained compared to the original trial? The reason I am asking is could there be population changes and, therefore, based on what you look at you could do that? So, that is one question.

The second question, can you do the opposite? Take tamoxifen from the STAR trial and look at how good does it look or how bad does it look compared to raloxifene in the RUTH, MORE and CORE trials?

DR. HARRINGTON: Let me take a crack at the first question and perhaps the FDA would like to add something, with the statisticians from the sponsor.

So, the lack of a placebo arm in the STAR

trial prevents one from knowing what the tamoxifen effect would have been in this trial. It is simply not possible to do that, except through a putative placebo using the Gail model. So, we don't have that information. That is why any active control trial that uses information from prior trials has to be analyzed very, very carefully because you are making a leap across trials and so you need to have your parachute on when you make that leap in order to make sure that you have looked at all the possible sources of bias that might cloud the picture.

On your second question, Dr. Hussain, you could conceivably look now at whether you might not market tamoxifen compared to raloxifene based on the raloxifene placebo-controlled trials. But, as was pointed out by the FDA and the sponsor, they are not in exactly the same populations so we don't have a direct look at the tamoxifen-raloxifene effect in the same population in which tamoxifen was approved.

DR. HUSSAIN: It doesn't answer my

question. Can someone else answer it or is it not answerable? If the retention of effect is all driven by extrapolating from one study to the other, if you were to do the same exercise for tamoxifen in the STAR trial and look, just for the fun of itB-call it something different, not tamoxifen--and look at it in the original placebo-controlled trial to see how much of its effect it actually retained, why can that exercise not be done?

DR. BRAWLEY: Let me help.

DR. HUSSAIN: Because a lot of the argument has to do with retention of effect and it is okay to compare raloxifene with a placebo from a previous trial but we are not doing the same for tamoxifen.

DR. BRAWLEY: Dr. Hussain, let me help you. Joe Constantino, did tamoxifen in the STAR trial have the same effect as tamoxifen in the P1 trial on women over the age of 50?

DR. HUSSAIN: Thank you.

DR. CONSTANTINO: The answer to that

question is the point estimate says yes. The relative risk was 97 percent for comparing tamoxifen to raloxifene and, therefore, the assumption is that the effect was very similar. If you use the Rothman methodology and put the confidence limits on it goes down to 65 percent. That would say that instead of a 50 percent reduction as tamoxifen was giving, it would be about a 33 percent reduction in risk of breast cancer with raloxifene. That could be as high as about a 64 percent reduction if you include the upper arms because it is just as possible that the upper arm is true as the lower arm. I think that is answering your question. So, the range would be between a 33 percent and a 64 percent reduction in the risk compared to the placebo population.

DR. HUSSAIN: And that is for tamoxifen?

DR. CONSTANTINO: No, that would be for raloxifene.

DR. HUSSAIN: And what would it be again for tamoxifen?

DR. CONSTANTINO: For tamoxifen, yes, it

would essentially be that same kind of boundary because the rates were very close.

DR. HUSSAIN: Okay. And, the final question to the FDAB-I am sorry, go ahead.

DR. SRIDHARA: I think you will get some idea if you look at the presentation of the P1 data that was in the second slide. The incidence rate for invasive breast cancer on tamoxifen was 3.2 in that case and in the STAR study that was 4.3. So, there were some differences but it could be just due to chance. The number of events is so small in each of these, it is hard to say whether there was a difference. However, as pointed out, certainly the patient population was different and even the P1 data that we are presenting here is only greater than 50 year-old women whereas the STAR study did include women who were less than 50 as well when we were doing all the efficacy analyses. So, it was not in the STAR study only greater than 50 years of age. This was kind of artificially picked out to represent postmenopausal women so we don't know that actually they were all postmenopausal, but

this was the best that we could get from P1.

DR. HUSSAIN: And the final question has to do with the side effect issue. Is it not reasonable to argue that if the FDA approved raloxifene in a wider patient population and accepted the risk/benefit--understanding that people don't have to take raloxifene; they can take Fosamax and may not have the same cardiovascular risks and all of the rest of it, yet it was felt that the risk/benefit ratio was in favor. And, when you add to that argument that the comparison, in my opinion, ought not to be based on a control of nothing or a placebo but, rather, what is the alternative in that case, tamoxifen, and when you look at the STAR trial you could argue either way but it seems to me that raloxifene may be even safer in some aspects. Why are you looking at the risk as compared to placebo as opposed to tamoxifen because, certainly, it is for a specific indication, not just take it for the heck of it?

DR. MANN: The application is for approval in two different populations. The first indication

is for reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis. In those trials the women who were participating were not selected on the basis of high risk, whereas the second indication is for women who are at high risk of breast cancer. I mean, the risk/benefits in both populations are different because the benefits are different.

DR. CORTAZAR: Correct, and regarding the STAR trial, what we are saying is that, you know, you see less benefit.

DR. HUSSAIN: Miss Schiff?

MS. SCHIFF: I have three questions. I don't know who should answer them. One, I am wondering if you looked at any other side effects that are important to women, cognition, libido, depression and weight gain? Because we have seen these in women with breast cancer on tamoxifen so I am just wondering if it was looked at in raloxifene.

Secondly, I have a question about the dose. My understanding is that for osteoporosis

you don't just give it for five years, and I think we all know that the longer you are on a SERM the more likely you are to have a bad side effect so that is why it is limited to five years and we can see in the CORE trial that actually that is what happened. The side effects got worse. So, how do you intend to handle that contradiction? And, what is the dose you are asking for, for the women with osteoporosis?

Also, I just wanted to know what the differences were in the different trials between an HRT and, also in terms of side effects, why gallbladder? There seemed to be a showing that there were problems with gallbladder, and why that was not included in the risks and benefits that were made. It was just kind of left out, but there seemed to be a higher risk for women on raloxifene.

I also was wondering what number of women in the P1 trial were on tamoxifen for five years versus those on raloxifene in the STAR trial, because only 27 percent were on for five years in the STAR trial and I was wondering what that number

is in the P1 trial.

The final thing is I was wondering--

DR. HUSSAIN: Could I ask the sponsor to perhaps take the first two questions and then afterwards you can ask a third question?

MS. SCHIFF: All right.

DR. MITLAK: Good morning. I am Bruce Mitlak. I am a physician at Lilly. Thank you for your questions. I believe the first question that you asked about was, was cognitive function assessed in patients who received raloxifene? As you may recall from the slide that Dr. Cummings provided, cognitive function was one of the secondary objectives that was of interest in the MORE trial and it was formally evaluated. Patients were evaluated at baseline to assess for dementia and were followed-up with a battery of cognitive tests. Patients who performed in the lowest ten percent had formal workups.

The publication by Christine Yaffe summarizes the results from that analysis. The bottom line was that overall there was no

difference in cognitive function. She found that by looking at patients who had developed dementia or patients who had some change in cognitive function there appeared to be a small benefit in the 120 mg group but not the 60 mg group compared to placebo.

The second question you asked about was quality of life, and quality of life instruments were also used in the MORE trial and there were really no significant differences in the quality of life instruments. There were several instruments that were used. The ones that were appropriate for the geographic region based on language were applied and there were no significant differences picked up with respect to this issue of cognitive function or depression.

The third question you asked was on the issue of duration of treatment.

MS. SCHIFF: I also asked about libido and weight gain.

DR. MITLAK: I don't believe there was an increase in weight gain in our placebo-controlled

trials. With respect to libido, in the placebo-controlled trials I don't believe there was a difference also. So, if that addresses those questions for you, on duration of treatment perhaps Dr. Cummings can also help answer the issue with respect to duration of treatment and the way it is currently indicated and the way it is currently used in practice for management of patients with osteoporosis. From the standpoint of breast cancer risk reduction what we are providing for you today is data from the STAR trial which shows that it was studied, or it is being studied for up to five years in women with breast cancer compared to tamoxifen, and over those five years the effect between raloxifene and tamoxifen is quite similar, as you have seen.

We also provided data from the MORE and CORE trial that provided support that the effect of treatment would last for up to eight years, and we believe that the labeling should clearly communicate that information so that physicians have that available in making decisions about

treatment duration.

DR. CUMMINGS: I would just repeat that the CORE trial was designed to study the effect on invasive breast cancer over the course of eight years. In fact, it was not designed to study fractures as an endpoint so that clinical vertebral fractures were only, for example, reported as an adverse experience. I think in a patient who has osteoporosis in general, yes, you would expect that that treatment may continue for longer than five years and it is for that additional comparison for benefits and risks that invasive breast cancer was studied as the primary for eight years.

MS. SCHIFF: I have my next question.

DR. HUSSAIN: Just a second. What did you say? I am sorry.

DR. PERRY: I asked if I could pick up on that duration question. Is my understanding then that Lilly's recommendation is that women with osteoporosis who are at risk of breast cancer take Evista for life?

DR. CUMMINGS: No. I think in patients who

are being treated for osteoporosis you need to reevaluate patients every several years. That is often done, for example, with repeat testing of bone density. There are risks and benefits because their histories of fractures or changes with age will differ. I think clinically I would recommend, as would others, that you reassess periodically.

DR. PERRY: That didn't quite answer the question. What is the recommended duration of treatment for Evista in the prevention of breast cancer? Five years? Eight years? Life?

DR. CUMMINGS: There is no endpoint for that recommendation.

DR. PERRY: So, the question is it could be indefinite?

DR. CUMMINGS: It could, yes.

DR. BRAWLEY: May I follow-up on Dr. Perry's question? In the package insert for treating osteoporosis or treating prevention of osteoporosis, two different questions really, is there a duration for treatment with Evista?

DR. MITLAK: Evista, like the

disphosphonates are indicated for prevention and treatment of osteoporosis. The results of the trials that support them are described and there is no specific limitation to duration of treatment.

DR. HUSSAIN: Miss Schiff, you had one more question?

MS. SCHIFF: Yes. I just wanted to ask the sponsor whether they were aware of the fact that after tamoxifen was approved for prevention there was a risk/benefit analysis done and tamoxifen was shown not to beB-the risks were not worth the benefits for most women over 60 with a uterus. If you had known that or if you knew that wouldn't you have put a placebo into that trial since we are treating only womenB-you are proposing raloxifene just be for postmenopausal women and, yet, the risk/benefits of tamoxifen in postmenopausal women were not beneficial for most women?

DR. HUSSAIN: Sponsor?

DR. MITLAK: Yes, to answer that, raloxifene was included in the STAR trial and I think the placebo-control data supports that it

does not have an effect on stimulating the endometrium or causing endometrial or uterine cancer. So, I think that is one of the factors that is considered in making a benefit/risk. We have worked with the results from our Phase 3 trials to try and identify patients for whom the benefits most clearly outweigh the risks, and have focused our indications on those patient populations.

While we agree that the trials taken broadly show an effect of breast cancer risk reduction across a broad population of women, we have tried to focus the indications in the women for whom the benefits most clearly outweigh the risks and, as Dr. Sledge highlighted, he gave, at the level of a group of patients being treated for a period of time the balance of benefits, favorable effects versus risks.

DR. HUSSAIN: Dr. Mortimer?

DR. MORTIMER: I think this question is probably to Dr. Cummings. As Dr. Sledge previously pointed out, the risk of breast cancer is lower in

women who are osteoporotic. That is pretty convincing from the Framingham data. Further, there is data that women who have the highest estrogen levels, the highest quartile of estrogen levels, are the women who benefit from chemoprevention.

So, my question and concern as we extrapolate data from an osteoporosis trial to the general population is what do we know about the natural history of breast cancer in osteoporotic women? I presume it is different. And, is it just, you know, elderly women with breast cancer or is there something unique about these individuals and the natural history?

DR. CUMMINGS: Let's go back to the two points you raised. Yes, there are a couple of studies that show a relationship between bone density or osteoporosis and risk of breast cancer. But, in fact, that data is quite heterogeneous. We have recently shown, for example, no relationship between bone density and risk of breast cancer in a large study. So, whether that

is true is now a little less clear. There is no evidence, to my knowledge, that the prognosis or the natural history of breast cancer differs according to one's bone density.

DR. MORTIMER: Is there actually data for that?

DR. CUMMINGS: No, to my knowledge there isn't any data. I don't know of any such data. I think there was a second question that you asked about estrogen concentrations.

DR. MORTIMER: Yes.

DR. CUMMINGS: The study that I published about estrogen and reduction of risk was also contradicted by a study we did several years later using Pg1 data where we didn't see that association. So, whether estrogen is useful for identifying women who benefit is right now unclear.

DR. HUSSAIN: Dr. Furberg?

DR. FURBERG: I had a couple of questions regarding safety for the sponsor. First, there is a two-fold higher absolute risk of thromboembolic events in the MORE trial compared to the RUTH

trial. In fact, in the MORE trial it is an 80 to 160 percent higher risk of these events compared to placebo. So, the question is what is the explanation? Did you use different exclusion criteria? That is question one.

The other one is what are your proposed contraindications in the labeling? I think it is critical for us to know. For example, I assume you are going to use the exclusion criteria from the trials so your contraindications would be women with a history of thromboembolic events, atrial fibrillation, and there may be other things we need to know about.

DR. MITLAK: Certainly. We don't have a simple explanation for the first question that you asked. There is a subtle difference in the exclusion criteria. The MORE trial excluded women who had a past history of DVT within the past ten years; for the RUTH trial it was any past history. It is subtle. There are geographic differences. Also, you need to realize that the RUTH cohort was a cohort of patients who had either established

coronary disease or a high risk for coronary disease and were receiving multiple medications already.

To answer your second question, we have current labeling that provides guidance around the findings that we have seen in the STAR trial. Let me show you two slides.

[Slide]

The first was the slide that Dr. Cummings presented. The wording on the bottom part of the slide is currently in the Evista label. The Evista label is one of the first labels to have been translated into the new labeling format, which is a more easily understood format for presenting the data on the product. The front page of that is a highlighted section and these two statements are currently included in the highlight section: Evista should not be used for the primary or secondary prevention of cardiovascular disease, and describes the increased risk of death due to stroke that was seen in the trial of postmenopausal women with documented heart disease.

Now, if I can also ask for the slide that focuses on the actual warnings and precautions section of the label to get at your question about what guidance is being provided--

DR. HUSSAIN: Can I ask, please, to make it brief because we have a few more questions?

DR. MITLAK: Let me just tell you. What the warning section says is that patients who are at significant risk for stroke should consider the benefit/risk, and the factors that are listed are stroke, TIA, atrial fibrillation, hypertension and smoking. Those are listed as factors for stroke that need to be considered. This is the statement.

[Slide]

Let me show this quickly. This is currently in the label. This is the warning that is in place.

DR. FURBERG: And history of thromboembolic events?

DR. MITLAK: Yes, that was in the label before the RUTH study and that continues in the label.

DR. FURBERG: Thank you.

DR. HUSSAIN: Dr. Link?

DR. LINK: I just have two questions I guess to the FDA, based on some of the concerns that they have raised. So, one relates to non-inferiority and one relates to the fact that the breast cancers that were prevented actually presented at low stage.

So, the first of these is about the non-inferiority. This is philosophical. Let's say you have a drug that is known--I mean, it is accepted that it is not as good as a drug that is already indicated but has a much better toxicity profile. The likelihood is that, you know, people are going to take it as opposed to a drug with a bad toxicity profile which they don't like. Is there any reason that that wouldn't be approved on that basis just because it has a better risk/benefit profile even though everybody accepts up front not that it is possible that it is not inferior but that it is well-accepted that it is inferior? That is my first question.

DR. PAZDUR: We do not have comparative efficacy standards. Okay? Obviously, the drug should be safe and effective for the prescribed indication. So, there is not an indication that the drug has to be safer or better than. We do not have a comparative efficacy standard.

DR. LINK: But what if it is as good as.

DR. PAZDUR: Well, when you start getting into decrements of efficacy, then one has to raise the question whether one should have the drug out there. Then that becomes a safety issue. For example, if were talking about a curative regimen and one had a response rate but no data on survival, etc., that would be an unsafe drug. Yes, it is potentially effective but the proof is not there. So, there is not a comparative efficacy issue.

The reason why we are doing a non-inferiority analysis here is that basically we are trying to demonstrate efficacy. Okay? That is the issue here and we have a failed superiority trial here and, therefore, we need a way to

demonstrate efficacy. And, you could do that in several ways. You could be superior to a drug in a randomized trial, which they did not show, or you could show non-inferiority and that is the reason why we are doing this non-inferiority analysis.

DR. LINK: But aren't there studies that show efficacy compared to placebo although that wasn't the primary design of the study? In other words, the drug works. It may not work as well.

DR. PAZDUR: In a different population, yes. Then we are asking you, obviously, since it is done in a different population obviously this osteoporotic population, could you infer those results? Obviously, we want you to take a look at the totality of data here. But for the second indication--and that is why we carefully broke it out into two indications--for the non-osteoporotic population, basically women at high risk, we have the one trial here, the STAR trial, which did not meet its primary endpoint. We are trying to take a look at that to establish efficacy by doing a non-inferiority analysis.

DR. LINK: What I was trying to do is sort of get an idea overall philosophically, not particularly here. So, there are some times when a drug that is less efficacious but has a much better toxicity profile would be--

DR. PAZDUR: Could be. For example, there are many triptans out there for migraine headaches, three, four, five or six. Okay? They did do randomized, and the first one was obviously Imitrex. They didn't go out and do multiple head-to-head comparisons--

DR. LINK: Good pun!

DR. PAZDUR: I didn't even mean it. They did basically placebo-controlled trials and demonstrated efficacy. Okay? Here again, in oncology, because we are dealing with life-threatening diseases for the most part or, in this case, a comparator drug that had been available we do active controls. But it is to demonstrate efficacy, not comparative efficacy.

DR. HUSSAIN: But, Rick, just to clarify, we are required, however, to look at the totality

of the data--

DR. PAZDUR: Correct, for both safety and efficacy.

DR. HUSSAIN: B-for the purposes of the questions. Because it is 10:30 right nowB-I am sorry, you will get the chance to ask, but what I am going to suggest we do is break now and then when we come back to resume the discussions of the committee. Those of you who are on the list to ask questions will get a chance to ask the questions. I hope that will be okay. Dr. Couch, we will get to your questions and I will put you on the list.

[Brief recess]

Open Public Hearing

DR. HUSSAIN: We are in the second part of the morning session. This will be the open public hearing. I would like to read a statement before inviting the public presenters to make their statements:

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To

ensure such transparency at the open public hearing session of the advisory committee 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 speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance of 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 your speaking.

The FDA and this committee takes great importance in the open public hearing, and we really respect and appreciate your willingness and

your efforts in coming here and sharing with us your sentiments. The insight and comments provided can help the agency and this committee in their consideration of the issues before us.

That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the Chair. That is myself. Thank you for your cooperation. Thank you.

MS. CLIFFORD: Our first speaker is Connie Rufenberger. Here you are, right here, ma'am.

MS. RUFENBERGER: Oh, good. I like this better than up there. I thought I was going to have to walk up there and I was going to say it is just observational but it looked like walking the plank at "Pirates of the Caribbean." I would much rather be back here.

I did want to start by saying that to me

as a consumer I thinkB-and it is observational, not like the data you have been watchingB-the American public would be so gratified to see the care and the consideration, and I can't even imagine the years of education and thought that are in this room, looking at this topic. I think sometimes, as in everything that is public in government, there is a lot of controversy but they would be impressed. It is an impressive group. I also think just from observation that with the care and the detail in the slides that you could pool about four of those slides and, as a consumer, create an exquisite piece about risk and benefit for the education of the consumer when they are allowed to make the decision about their choice on this matter.

As far as financial, I have been doing this for 25 years as a survivor and an advocate so I have been on both sides of the table with a lot of people in this room. I am glad to see we have all survived and aged and, hopefully, we are all a lot smarter about breast cancer. Let's see, I want

to be very clear that my past relations with Eli Lilly have included participation in their advocacy and professional relations advisory board and this is how I became aware of the opportunity to speak today. I am the director of project development for the Catherine Peachey Fund, and in 2001 the Catherine Peachey Fund asked Lilly to do a matching program for the Catherine Peachey Fund in order to fund an endowment for breast cancer prevention at the Indiana University Simon Cancer Center. This program is now called the Catherine Peachey Breast Cancer Prevention Program. But those of you who know me know that I have very strong opinions and they are very seldom influenced by that type of thing, and I have not received any money for my travel or to give my testimony today. And it is really unique because when I started at 34 with this we didn't have a seat at the table. We couldn't get in the room. Now we get badges. So, that is nice.

As a breast cancer survivor, consumer advocate and activist, I appreciate this

opportunity to give my opinion regarding the FDA approval of Evista and an option for postmenopausal women for the prevention of breast cancer.

I first had invasive breast cancer at the age of 34. I made the decision that a mastectomy and eventual reconstruction were the best options for me. I was offered lumpectomy and radiation but I felt the potential risk for that course of treatment, along with the follow-up that it entailed, was not the best for me. I made an informed decision.

Over the last 25 years I have devoted my attention full time as a volunteer and fund raiser in the breast cancer field. I have participated on grant reading panels for the Department of Defense, the National Alliance of Breast Cancer Organizations, and participated as a consumer representative on the NCI Progress Review Panel in 1997B-and here goes the voice; I am not nervous or anythingB-and the Mammography Panel for the NCI on mammography screening for women between the ages of 40 and 50. As I have watched breast cancer

research evolve, I have become most interested in the science of breast cancer prevention.

At 34, with a very young daughter, I was sure that by the time she was my age we would have progressed significantly and that breast cancer would no longer be a major threat to her and the women of her generation. This has not happened. As my daughter turned 34 this year, the age of my first diagnosis, the only real addition to her breast cancer health surveillance is the inclusion of the MRI, and this is still controversial and not a form of prevention.

I was diagnosed with a second invasive breast cancer in the contra lateral breast at the age of 52. Because my initial breast cancer was diagnosed and treated 25 years ago, I did not have the opportunity to have tamoxifen offered for the possible prevention of the second breast cancer. I did begin tamoxifen after the treatment for my second breast cancer. Had Evista been available I might have been able to switch to Evista and possibly have avoided the three endometrial

biopsies required due to the thickening of my endometrium.

Waiting for our daughters to develop breast cancer in hopes of early detection so that they can have the treatments which we now know may not be cures is not acceptable.

In 2001 the Catherine Peachey Fund made a commitment to create an endowment for the Catherine Peachey Breast Cancer Prevention Program at the IU Simon Cancer Center. When I approached Dr. Steven Williams, the director of the IU Simon Cancer Center, with the concept he showed great foresight and courage, and I think it did take courage, in taking on the development of this program, as did Dr. Anna Maria Storniolo who agreed to become the director of the program.

In the past prevention was a concept that was not an option in the breast cancer arena. I remember reading grants where, if it said anything about prevention, the grants went on the floor; it was not for us to consider. Now, however, women with a real or perceived high risk for breast

cancer have a place to seek information and the opportunity to develop a plan to utilize whatever mechanisms are available for the prevention of breast cancer. Breast cancer prevention programs are being implemented in many centers across the country, driven by consumer demand and the emerging medical options for breast cancer prevention-Bnot a dirty word.

Women make important life-altering decisions every day. As the primary healthcare decision makers in most families, women are called upon to do their research and make decisions. It is a right and a responsibility. Women are capable of understanding the risks and benefits of medications and treatments offered to them and to the people that they care for.

When a woman goes to a fertility clinic great care is taken to insure that the risks and benefits of the treatment are carefully outlined. There is no guarantee of a pregnancy at a fertility clinic. Breast cancer prevention is exactly the same thing. If a woman decides to seek a program

and treatments which she hopes will prevent breast cancer, there are no guarantees but there is a right to have access to whatever means are available to safely achieve the goal of preventing breast cancer. We all know that none of these institutions, the government, research institutions or hospitals will become the producers of pharmaceuticals. Medical science without the option of the commercialization of treatment options will stagnate. Progress will be made only when the scientists, pharmaceutical companies and the consumers work together. This relationship is not a negative or something that should cause us to be overly suspicious. With the FDA as the watchdog and the integrity of the pharmaceuticals and the scientists under close scrutiny, this is the best partnership in the world. And, I really do suggest that given what we see coming in from other countries now where they don't have the type of scrutiny that we have, even though it is not perfect as I suppose none of us are, this is still an exquisite system.

And, as a consumer, I want the best and the brightest clinician researchers--such as Denis Slamon, Anna Maria Storniolo, Susan Clare and George Sledge, and the list goes on and on--working closely with the FDA and the pharmaceutical companies. Only with these close interactions can we speed good targeted preventatives to market and, thus, into the clinic.

At 55, I decided to take an aromatase inhibitor after three years of tamoxifen. With the guidance and scrutiny of the FDA, this choice was made available to me. Even knowing the unknowns such as the long-term side effects and how long the drug should be taken, I made the decision to take an AI. I applaud the FDA for making this choice available to me and to those of us who are at high risk for breast cancer and progression of the disease.

We have only taken baby steps in the design of prevention drugs. These drugs are primarily for the postmenopausal population, and not for my daughter or the daughters of my fellow

survivors.

Approving Evista for breast cancer prevention, knowing its risk profile from its osteoporosis application, is yet another step forward. Women will have access to the vast amount of information that has come from the STAR trial for the process of making their personal decision. What we learn from the increased use of Evista, added to the information from the long-term follow-up of the STAR trial, will lead us, we hope, to the development or utilization of existing drugs for chemoprevention in the younger population. And when you work in breast cancer, and this is anecdotal, in recent years I find myself working with 36-year olds, 32-year olds, 28-year olds and 24-year olds and that is where we have to look and we have to keep moving forward for these women.

Our only road to success in the war against breast cancer and all cancers is based upon embracing the science of the cause and prevention of cancer, strengthening the working relationship between the pharmaceutical companies, the consumers

and the agencies like the FDA and the NCI. Our system works and we need to utilize our opportunities, such as evaluation of Evista for breast cancer prevention, to drive the science of prevention and empower the consumer to make educated decisions about participating in the future. The future must be a world where prevention is the norm and treatment for breast cancer and all cancers is historical.

And I really appreciate the time and energy that all of you are taking in looking at this drug, and I think the consumers would be pleased.

MS. CLIFFORD: Thank you. Our next speaker is Jane Zones, with Breast Cancer Action.

DR. ZONES: Hello. My name is Jane Zones and I am on the board of Breast Cancer Action. I paid my own way to this meeting and Breast Cancer Action has had a long-standing policy of not accepting contributions from any entity, and in particular pharmaceutical companies that present a conflict of interest for our organization.

When we were established in 1990, our founders believed that women affected by the disease would show the way in pushing for answers that would lead to the end of the scourge of breast cancer. That work has taken the form of providing information, policy advocacy and community organizing. We believe that access to information is vital and we recognize that structural changes in society are needed ultimately to prevent breast cancer.

Since our founding in 1990, BCA has emphasized the need to find the root causes of breast cancer so that we can truly prevent the disease. There is abundant evidence that the genesis of many cases of breast cancer lies with our toxic environment. Yet the focus of national resources devoted to breast cancer prevention has been on the development of drugs to lower the incidence of breast cancer rather than finding environmental triggers of the disease.

BCA opposed the 1998 FDA approval of tamoxifen for use in high risk health women to

lower the risk of breast cancer. Despite years of direct-to-consumer advertising by AstraZeneca, tamoxifen's manufacturer, utilization of tamoxifen by healthy women to reduce breast cancer risk has remained quite low.

Raloxifene's manufacturer, Eli Lilly, hopes that its product will prove more popular as a so-called prevention pill than tamoxifen. Many postmenopausal women are already taking it for its approved use to increase bone density even though it is ineffective in reducing hip fracture.

Raloxifene has been widely prescribed off-label to healthy women to lower breast cancer risk for many years now. In December, 2005 Eli Lilly paid fines totaling 36 million dollars for illegally promoting the drug to doctors as a breast cancer preventative.

Results from the STAR trial show that raloxifene and tamoxifen are equivalent in reducing invasive breast cancer risk. Raloxifene has been portrayed, in particular by the NCI, as safer than tamoxifen but published results show that the

differences between most of their side effects are not statistically significant. Exceptions are that raloxifene users had fewer deep vein blood clots and cataracts than tamoxifen users. One of our members who participated in the STAR trial told us that subjects were told to suspend taking their assigned medication several days before airplane travel which could possibly have affected blood clot outcomes. Women have taken the treatments for an average of only three years at the time the study was ended.

Subsequent publication of the RUTH trial results showed a 49 percent increased risk of fatal stroke, and a significantly increased risk of venous thromboembolic events in those given raloxifene compared to a placebo control group. In RUTH there was a 35 percent reduction in the risk of clinical vertebral fractures but no significant reduction in the hip or other fractures in the raloxifene group.

Research on drug products that lower the risk of breast cancer has been problematic in three

major areas: lack of long-term follow-up for safety, comparative studies that do not include a placebo group, and misleading reporting of findings. These studies and their promotion by drug manufacturers, including Eli Lilly, appear to be designed to promote sales of products to large populations of women without clear evidence of long-term safety.

Studies of so-called breast cancer prevention medications have focused on the specific goal of achieving lowered breast cancer incidence. Originally, overall survival was the primary endpoint for the tamoxifen prevention trial P1 but this was changed subsequently to lower the breast cancer incidence. Ending trials early for benefit is becoming common and increasingly problematic. While the breast cancer benefit may be clear in terms of the numbers of new cases diagnosed, at least in the short term, the clinical benefit, particularly for healthy women, is compromised because of the extent of harmful side effects being unknown.

Follow-up of participants in the tamoxifen-placebo trial after seven years, published in 2005, showed no survival benefit for tamoxifen and, in fact, more women died in the tamoxifen group than in the placebo group, although it was not statistically significant.

More breast cancer develops over a period of a decade or longer. When a trial is stopped after several years we cannot determine the persistence of the early protective benefit. Does the medication actually prevent cancer or just delay its development? Study sizes are too small and follow-up too short to reveal rarely occurring adverse outcomes and long-term safety, or to assess the possibility that risks continue to develop after cessation of treatment. In addition, we have no way of knowing overall survival in these study groups. Yet, in order to make informed decisions about medical treatments, women need sound data to consider risks and benefits together, information that is not available about raloxifene.

The STAR trial compared raloxifene

directly to tamoxifen without benefit of a placebo group. The decision to not include a placebo control group was heavily criticized at the beginning of the trial and eliminated the possibility of knowing how taking either drug compares to taking no drug at all. BCA agrees with FDA staff that Eli Lilly's use of a theoretical placebo in re-analyzing STAR data is unacceptable.

The practice of running studies that compare one drug against another, without providing a control group to determine whether no treatment is as good as the treatment being evaluated, assumes that one of the drugs is a highly regarded treatment and that denying that treatment would be unethical. BCA believes that tamoxifen's benefits have not been shown to outweigh the drug's risks in most healthy women. Since the results of the tamoxifen trial are the basis of the decision not to conduct placebo-controlled trials, BCA believes that a placebo control group should be included in all drug trials designed to examine reduction in risk of developing breast cancer.

A third major problem with the risk reducing medication studies for breast cancer has been misleading reporting of results. It has become the practice to make public announcements of results prior to peer reviewed publication. Such announcements, and even journal articles, often couch statistical findings in the most positive manner and create a media outpouring that is almost always exaggerated and misleading.

Because breast cancer is a relatively rare occurrence in women, even those at high risk, differences in incidence portrayed using relative risk tend to appear much larger than absolute risk differences. An example of this comes from findings of the STAR trial, which found both raloxifene and tamoxifen reduced breast cancer by 50 percent. Maryann Napoli, of the Center for Medical Consumers, explains what this means:

Of the 9,700-plus women in each drug group, about 167 got breast cancer. This translates to 1.7 percent, whereas, 3.4 percent would be expected to develop breast cancer had they

not taken a drug, hence, the 50 percent reduction in breast cancer incidence. Another way of saying the same thing is 98.3 percent of women will not get cancer if they take raloxifene or tamoxifen, whereas, if they take no drug 96.6 percent of women will not get cancer, an absolute difference of 1.7 percent. Obviously, much more research is needed to determine who is at high risk for breast cancer.

On the other hand, risks are portrayed in terms of absolute risk, making them appear relatively negligible. Furthermore, average lengths of treatments are expressed as medians rather than means to make them appear longer.

Women deserve to be fully informed about the benefits and risks of drugs to lower breast cancer risk prior to making the decision about whether or not to take them. At present, individuals are making decisions under conditions of uncertainty.

Breast Cancer Action, while clearly understanding the large numbers of women at risk for developing breast cancer, does not advocate

using drugs to treat risk. We, therefore, oppose the applicant's request before the committee today. It is difficult to imagine a drug powerful enough to actually reduce the incidence of breast cancer that will not have serious side effects. The FDA should hold treatments for healthy people to a higher standard than medications for people who are sick. Thank you very much.

MS. CLIFFORD: Thank you. Our next speaker is Carolina Hinestrosa.

MS. HINESTROSA: Good morning. I don't have any personal conflicts. My organization, the National Breast Cancer Coalition, has a board-approved policy that limits the amount of funding we can receive from pharmaceutical companies. We do receive some funding from Eli Lilly that supports some of our programs.

Again, my name is Carolina Hinestrosa. I a am twice breast cancer survivor and the mother of a 16-year old girl. I am the executive vice president of the National Breast Cancer Coalition Fund. NBCCF welcomes the opportunity to testify

before ODAC about the expectations of our community for breast cancer prevention and our concerns regarding current approaches in chemoprevention.

As in any health setting, FDA has the responsibility to make sure patients receive treatments with proven efficacy, that the safety profile of those treatments is well understood in order to determine the balance of benefit and harm, and ultimately to help ensure that patients and healthy individuals don't receive costly treatments and interventions that are unlikely to help them.

Since its inception in 1991, the National Brest Cancer Coalition has been fighting for improvements in breast cancer research and care as key pieces of our mission to end breast cancer. NBCCF and its hundreds of member organizations and thousands of individual members also embrace the philosophy of evidence-based healthcare. While much of research efforts focus on the treatment of existing breast cancers, we strongly believe that if we are to make meaningful progress in our mission we must uncover the causes of breast

cancer, understand who truly is at risk, and develop safe and effective interventions to stop the disease from developing in the first place.

Unfortunately, little meaningful progress has been made in this important area. We still don't know what causes breast cancer or whether the environment plays a role. Known risk factors explain far fewer than 50 percent of new cases. As a consequence, screening and more recently risk reduction recommendations are based on limited and rudimentary tools of risk assessment.

While the burden of breast cancer is real and unacceptably high, we must strive for screening and prevention interventions that truly target those at risk on the basis of clinically relevant biological markers, as opposed to settling for the current imprecise and decades old approach of population-based risk factors. Our goal must be to spare our daughters and granddaughters the horrendous consequences of a breast cancer diagnosis.

At the same time, we want to ensure that

prevention is for real, effective, sustained and safe. After more than a decade and a half of chemoprevention research in breast cancer, the consumer community expects much more precise understanding of who might benefit from chemopreventive drugs and whether the benefit is worth the human and financial cost of the intervention.

NBCCF has expressed concerns for many years about the breast cancer chemoprevention clinical trials program. Our concerns have focused on the lack of specificity in identifying a population of women at truly high risk for breast cancer which results in the potential exposure of thousands of women who will never develop breast cancer to potent drugs, some with well-known and serious side effects, but also those with potentially unknown side effects. We expressed disapproval of the early stopping of the P1 trial and subsequent crossover of patients to the tamoxifen arm which undermined the prospects for long-term determination of risk and benefits.

The Coalition also expressed serious reservations about the STAR trial's design. First, the study did not include a placebo group. Second, it studied a different population to that in the P1 trial and did not include a high risk premenopausal group of women, even though the results from the P1 trial showed that more women younger than 50 years of age at high risk for breast cancer benefitted more and had fewer adverse effects from tamoxifen than women older than 50 or than premenopausal women.

The results of the STAR trial were presented earlier this year, along with the results of other trials. There was no statistical difference in the incidence rate of breast cancer between the raloxifene and tamoxifen groups. The use of raloxifene resulted in significantly fewer blood clots and cataracts compared to tamoxifen. Both drugs had similar safety profiles in terms of occurrence of uterine cancer and stroke. However, when compared to placebo, the effect of raloxifene on thromboembolic events remains a concern.

We must remember that neither raloxifene nor tamoxifen has been shown to prevent breast cancer. All we know is about a reduction in the risk of developing breast cancer. There are a number of questions that need to be answered before women begin taking any drug for risk reduction in breast cancer.

First, whether these drugs will reduce a woman's long-term risk of developing or dying from breast cancer, and whether they extend a woman's life. Second, when to begin, and for how long a woman should be on these drugs. Third, what long-term side effects do these drugs have, particularly raloxifene. Fourth, how women's treatment options will be impacted if they develop breast cancer while under these drugs.

For today's ODAC meeting, FDA points to the observed loss of tamoxifen effect in the raloxifene arm, up to 37 percent for invasive breast cancer and up to 47 percent for all breast cancers, and asks ODAC's guidance on what is acceptable in view of raloxifene's adverse effects.

FDA also points to its own exploratory subgroup analysis in postmenopausal women at normal risk and at high risk. The results are disconcerting. Raloxifene significantly reduced the risk in the subgroup at normal risk, but failed to do so in the subgroup at high risk.

As consumers, we urge the ODAC and the FDA to apply the highest level of rigor to the evaluation of all interventions in breast cancer, even more so in the prevention and risk reduction settings where healthy women, potentially millions of them, could be exposed. It is not enough to conclude equivalency between raloxifene and tamoxifen if it doesn't tell us the full story and there is reasonable doubt about non-inferiority of raloxifene.

Considering that most women will not develop breast cancer in their lifetime, including those considered to be at high risk by this STAR trial's parameters, taking tamoxifen or raloxifene as a risk reduction measure will be unnecessary for most. Unfortunately, we don't yet fully understand

the risk factors of breast cancer and don't have the precise risk assessment methods with which to figure out which women would benefit the most from these drugs. Until we do, we won't be able to properly target either of these interventions.

Lessons from P1 tell us that women understand this gap and are unwilling to take the risk for an uncertain benefit. We must change the paradigm and pursue research to uncover the causes of breast cancer hand-in-hand with research on clinically relevant markers of risk that are meaningful for risk reduction at the individual level. Thank you.

MS. CLIFFORD: Thank you. We have one additional speaker, Desiree Godard, with the National Women's Health Network.

MS. GODARD: Hi. My name is Desiree Godard, and I am speaking today on behalf of the National Women's Health Network. The Network is a member-supported non-profit organization that works to improve the health of all women by influencing policy and supporting informed consumer

decision-making. We accept no financial contributions from pharmaceutical companies or medical device manufacturers. The Network has supported my being here today.

In the late 19780s, the women's movement began to urge scientists to shift focus from treating breast cancer to preventing it. The National Cancer Institute responded by launching a study of tamoxifen, then the most common drug for breast cancer treatment for use by healthy women as a possible preventative measure.

The National Women's Health Network opposed the proposed study, recommending that the NCI pursue a different kind of prevention research that would investigate the causes of breast cancer and identify ways to protect women from the disease by limiting their exposure to identified causes.

In 1992, a former Network board member, Adrianne Fugh-Berman, co-authored an editorial in the Lancet, titled "Tamoxifen: Disease Prevention or Disease Substitution." The article predicted that the use of a treatment drug in healthy women

would end up causing as many other diseases and complications as it would prevent. But the NCI study continued despite the Network's reservation and recommendation.

The study results were as the Network predicted. Tamoxifen was effective in preventing breast cancer in healthy women, but not without great cost. Tamoxifen increased the risk of endometrial cancer and caused serious blood clots and strokes, all potentially fatal conditions. When compared to traditionally effective public health prevention techniques, such as vaccinations and clean water, tamoxifen seemed a very dangerous approach. The FDA approved tamoxifen in 1998 for reducing the risk of developing breast cancer but few healthy women chose to use it.

Despite the initial results showing significant harm, NCI continued with the second study, STAR, comparing tamoxifen with raloxifene, also a selective estrogen receptor modulator. Last year, when NCI announced the results of STAR prior to publication, they intimated that raloxifene was

safer than tamoxifen while just as effective in lowering breast cancer risk. When the STAR results were published two months later, they showed almost no significant differences in effects of the two drugs.

Using the numbers released by NCI, we calculate that of the nearly 10,000 women who took raloxifene for up to five years, only 30 benefitted once the serious risks are taken into account. While some women may appreciate this marginal benefit, the National Women's Health Network questions whether it should be viewed as a major advance in preventing breast cancer.

Furthermore, we don't know whether or not raloxifene, or tamoxifen for that matter, truly prevents breast cancer or just delays it. NCI's earlier trial of tamoxifen compared to a placebo only followed women for two years after they stopped taking their pills, not nearly long enough to know whether tamoxifen's benefit is lasting. This trial can't answer that question either.

Early results of this trial also suggest

that raloxifene may affect the development of breast cancer in a different manner than tamoxifen. Tamoxifen reduces the likelihood of developing ductal carcinoma in situ, also called DCIS, and lobular carcinoma in situ, LCIS. The majority of women who developed these conditions will never develop invasive breast cancer, but some women with DCIS can progress to invasive breast cancer. In the STAR trial raloxifene had no effect on the number of women who developed DCIS or LCIS. It is unclear what this means and whether or not it is important.

The published results of the STAR trial seem to indicate that the risks of raloxifene aren't quite as bad as those of tamoxifen, but it is still not safe enough for most women to use. And, we learned from painful experience that when it comes to prevention there is good reason to wait until enough information is available for women to truly make informed choices.

In June the NCI halted a new breast cancer prevention trial comparing raloxifene with two

aromatase inhibitors, 15 years and millions of dollars too late. The National Women's Health Network is glad that the NCI leadership finally recognized the problems inherent in promoting disease substitution as disease prevention. While the drugs have real value for preventing disease and recurrence for women who have already had breast cancer, most healthy women don't want to trade one disease for another.

The Network urges the Food and Drug Administration to recognize that the risks of raloxifene are as important as the benefits it could provide for healthy women. Please do not approve an approach that will expose healthy women to increased risks for one disease in order to protect them from another. Thank you.

DR. HUSSAIN: Thank you. On behalf of the committee, I would like to thank all the public hearing presenters for their comments today. This will end the public hearing section of the meeting today. We will no longer take comments from the audience, and I would like to go back to questions

and discussions among the committee.

We have technically about 45 minutes unless we are allowed to go slightly over, and I have several individuals who still had questions that needed to be addressed. I will not take any more questions beyond what we have on the list, and then we can go to the discussion of the questions from the FDA. Since I promised Dr. Link, he will be first. You will be first, sir.

Questions to the ODAC and ODAC Discussion

DR. LINK: Thank you very much. This one is an easier one, and that is that one of the concerns that was raised in the FDA briefing was the concern that the cancers that were actually prevented were largely early stage. The question is whether this really is relevant here because these were patients that were followed very closely. They were getting mammography frequently. So, the question is whether that really is a legitimate concern in this when we are talking about a broad use of the drug, and whether the early stage at diagnosis really just reflects

closeness of monitoring of this particular patient group on the trial.

DR. MANN: That, as you know, is true of both the placebo as well as the raloxifene. The fact that most of the cancers were detected at early stage, that is true both for the placebo as well as for the raloxifene.

DR. LINK: Both groups were monitored very carefully, the same.

DR. MANN: Yes.

DR. CORTAZAR: That is true. I agree with your comment, however, we are looking at these applications in terms of benefit versus risk so we had to question that.

DR. PAZDUR: But one would expect in clinical practice that these people would be followed also with mammograms and such. That needs to be discussed.

DR. LINK: [Off microphone].

DR. HUSSAIN: Dr. Wilson?

DR. PAZDUR: Perhaps the sponsor could answer that question because that might come up in

the labeling of this. What would you consider as some type of follow-up on these women? Obviously, they are getting this medication. What would be the routine follow-up on these women? Identical to the trial?

DR. MITLAK: If I could ask Dr. Sledge to help address this, but I think we would refer to the professional practice guidelines that are available.

DR. SLEDGE: I think, Dr. Pazdur, that is a very important question. Certainly, in clinical practice a woman who is receiving this agent for osteoporosis will be seeing a physician regularly for a variety of evaluations, including bone marrow density and gynecologic examinations. That patient certainly also, one would hope, would follow the established guidelines for screening mammography and physician's breast examination. Now, the reality is, as we all know, that mammography is not used as widely as has been recommended. So, as one goes from clinical trials to clinical practice, as you mentioned in your opening comments, the reality

is we never do quite as well in clinical practice as we do in clinical trials.

If I could comment on stage I and stage II breast cancers in these trials, the vast majority of breast cancers diagnosed in the United States are stage I and stage II breast cancers and, indeed, the vast majority of women who die of breast cancer initially had stage I and stage II breast cancer. So, to write these off as readily curable and non-dangerous is, frankly, not something that most breast cancer physicians would subscribe to.

DR. WILSON: My question is for the sponsor. I am trying to get a handle on what some of the practical implications would be for the first proposed indication. In thinking about that, the whole question seems to surround the bouncing risk/benefit. If one goes to the CORE and the RUTH studies and looks at the subset analysis where you divide relative risk as a function of the Gail model, it looks like, in those groups, the absolute benefit is relatively small. We are talking about

1.2 prevented cases per 1,000 patient-years. If we look at the CORE study, most of the benefit was in patients that had higher risk disease by the Gail model. Many of those patients, I would presume, would be considered to be in a high risk group that might fit a standard paradigm for receiving prevention.

Hence, I would like the sponsor to comment on that because it seems to me that, in fact, the patients who would most benefit from this might otherwise be included under the second indication, or fall under the use of tamoxifen. How do you balance the risk/benefit for these low risk patients where their relative benefit appears to be very, very small?

DR. MITLAK: Thank you for the question. The numbers I believe, as Dr. Cummings reviewed during the studies, are as you reflect. In the MORE study the average benefit, the actual number of cases prevented per 1,000 women treated for a year was approximately 3. The number in the CORE study was about 3 and the number in the RUTH study

was about 1.2. As you highlight and I think as we have noted, for reasons that are not completely clear, the women with high risk of heart disease had a lower background risk of breast cancer and, while there was a statistically significant reduction, the absolute risk difference was lower in that population and, hence, the number needed to treat was higher in that population.

The question about how we balance this, I think what we are suggesting is that women would receive this for osteoporosis based on their risk of fracture. The additional information about the average effect on the risk of breast cancer should be one of the benefits that they should consider in making a decision on whether to take treatment.

As I highlighted a few moments ago, we think that the overall balance of benefits and risks in the women who were recruited into the RUTH study because they were at high risk for heart disease was far more neutral. We are not suggesting that this is a group in whom the benefits clearly outweigh the risks. We think

there is more of a balance there. So, I think that it is likely, as you are suggesting, that there is a significant effect in both of the osteoporosis studies, MORE and the follow-up study CORE, and that individuals' benefit will likely in part reflect their underlying risk of breast cancer.

DR. WILSON: Right, but I think one of the concerns, one of the practical implications of this is that a patient trying to weigh those risk/benefits may not understand that the relative benefit of preventing breast cancer if they in fact have low risk disease by the Gail model is extremely small, and I think raises the question of whether or not it even reaches a point that it should be part of those low risk patients equations for deciding to go on to this drug to prevent osteoporosis. Patients may decide not to go on this drug to prevent osteoporosis because they are concerned about long-term risks that I don't think have been defined. I just think that one has to consider that these nuances may escape patients when they are just blanketly told that it helps

prevent breast cancer.

DR. MITLAK: Dr. Cummings, would you help address this?

DR. CUMMINGS: I think in clinical practice the balance or risks and benefits for a patient with osteoporosis would not include simply a blanket statement that you are at decreased risk of breast cancer by taking this medication. The counseling of women who have osteoporosis is about potential benefits and risks for breast cancer and the other risks I think would include an assessment of their risk of breast cancer as well. The situation with a patient with osteoporosis is a little different because they have a known benefit in terms of reducing their risk for vertebral fractures. That may change the threshold at which you would recommend the drug because of its breast cancer benefit as well.

DR. HUSSAIN: Dr. Buzdar?

DR. BUZDAR: Yes, the question which I wanted to raise is that there is no question that when we look at the efficacy of two drugs,

tamoxifen and raloxifene, raloxifene looks slightly maybe less effective, but then we look at the safety point of view, and also it has fewer side effects. But I did not see from the FDA or from the sponsor when we look at these both risks and the benefits in a balanced way what the total therapeutic index is. If the drug is less effective and has slightly fewer side effects, does it balance out compared to the tamoxifen? Because when we look at the tamoxifen therapeutic index in postmenopausal patients, why did the drug not become so popular, because the therapeutic index of the drug is very narrow and the drug is not utilized, and most of the patients are not willing to accept the risks. I think that is an important issue which is lacking and I want to see if the sponsor or the FDA wants to address that.

DR. CORTAZAR: With the STAR trial our conclusion is that it is very difficult to balance the risk and the benefit because we really do not know what is the magnitude of the benefit. It was very difficult to measure it. So, if you don't

know how much you are benefitting and you know what the risks are, you know, it is really difficult to know where the balance goes.

DR. BUZDAR: Yes, but the thing is that if you develop a stroke your life is changed forever.

DR. CORTAZAR: Exactly.

DR. BUZDAR: And if you develop a breast cancer, still you may have a chance to be cured. So, I think these things can be adjusted and some kind of appropriate modeling has to be done to answer this question.

DR. HUSSAIN: Dr. Couch, are you on the phone? No? Because I understand he is one of the consultants that is supposed to be here. Can you find him? I am going to go to Dr. Richardson.

DR. COUCH: Could I make a couple of comments about the stroke situation, please?

DR. HUSSAIN: Yes, please.

DR. COUCH: If we just backup a moment-Bcan you all hear me? Am I talking too loud? Not loud enough?

DR. HUSSAIN: No, you are just fine.

DR. COUCH: If we look at the stroke situation in general, the risk factors for stroke are well-known. Going back to the old Framingham study, age is the most potent risk factor for stroke. Blood pressure is number two. Heart disease is number three; cholesterol number four; diabetes number five. It took a while to establish smoking as a risk for stroke but it appears to be a much more potent factor in younger women, especially those that are taking birth control pills.

The heart disease, I will make a comment there, in the Framingham study heart disease dealt mainly with hypertensive heart disease and the measure that was used that was most effective was the presence of ventricular hypertrophy based on EKG readings. Now, if we go to the RUTH trial, which is probably the one that is the most pertinent to the cardiovascular and stroke risk here, age was balanced fairly evenly. I did not see any information about blood pressure, cholesterol, diabetes or smoking. Atrial

fibrillation was mentioned. It was not really noted very well whether it was treated, untreated; how long it had been; whether the patients were on coumadin, etc.

So, it is very difficult to try to make sense of some of these numbers. If we just take the gross numbers for a moment, again taking the RUTH trial primarily, the stroke death on raloxifene was 1.5 times the placebo group for stroke death, and that was close to being significant, with the hazard ratio of 0.98 to 2.3. All stroke was almost even, but for raloxifene it was 1.1 times the placebo, again 0.91 to 1.32.

The problem here, of course, as has been pointed out in many ways in the discussion, is this is a long-term process. The issue of stroke risk is not one that you measure over one year or five years. It is really a risk that you measure over longer periods of ten to maybe 30 years. I don't know that we have adequate evaluation to really make much of a statement. Clearly, the changes were not statistically significant in the trials

that were given. Nevertheless, the long-term risk is something that must be taken into consideration and the stroke death in the RUTH trial of 1.5 times the placebo group does give me some concern. If you multiply this over a number of years--even though the numbers were fairly low to begin with, if you multiply this over a number of years, over ten years this could get to be a very significant number. You know, as was pointed out before, stroke, when it does occur, modifies life significantly and, of course, stroke death modifies it even more.

I would like to see if some subanalysis could be done to look at the blood pressure, cholesterol, diabetes and smoking ratios between the two groups, and see if any of these factors could account for the differences between the raloxifene and placebo groups. Also, is there a difference in atrial fibrillation which, of course, is a very potent risk factor for stroke if untreated.

Is there any further comment or area that

I can comment on? That is the end of my preliminary comments.

DR. HUSSAIN: Perhaps I have a question for you, doctor, and maybe the sponsor can address it. So, if the drug is on the market for osteoporosis and some massive amount of women are taking it worldwide, is there no data on the risk of stroke and a. fib. and the rest of it in that population, recognizing that the bulk of osteoporotic women are going to be the older women? Are you aware of any data, or perhaps the sponsor can address that?

DR. COUCH: I am not aware of any data at this point, but that is certainly postmarketing data that perhaps could be collected and looked at. I don't know how good the data would be as a postmarketing study because those are always difficult to look at. I would suggest that if one goes back and looks at the studies that were done for osteoporosis and did the same kind of analysis I suggested that might help to answer the question. I am not aware of the data.

DR. MITLAK: Could I have slide 609, please?

[Slide]

What I would like to do is just to present again the data that we have been talking about. What this slide shows is the incidence of stroke in the RUTH trial, the MORE trial, the STAR trial and also for comparison the incidence of stroke in women in the P1 trial aged over 50.

As we have highlighted, the RUTH trial included women at high risk for heart disease. At the time the trial was designed there was a belief that raloxifene might actually be protective on stroke and, therefore, women with a past history of stroke and women with atrial fibrillation were included in the study. As you can see, there is no difference in the incidence of stroke for five years in the RUTH trial.

You can see the information for the MORE trial and STAR trial. I think it is important also to note that in the MORE trial stroke itself was not an endpoint and the way that the safety terms were grouped probably overestimates in this plot the incidence of stroke.

You can see in comparison the incidence of stroke in the STAR trial and in the P1 trial where women were younger and, indeed, the younger age might have a substantial explanatory effect on the difference in risk of stroke across these studies.

DR. MORTIMER: And can I see the duration of drug, the mean duration? Is there a difference in the time that people were on a SERM?

DR. MALIK: In the RUTH the median was about 5.6 years. In the MORE trial the treatment was up to four years. In STAR the median observation was about four years.

DR. COUCH: Can I make a suggestion though that a four-year timeline is not a very good timeline to be able to take a look at the process?

Another aspect of this, you mentioned that the patients were younger. We certainly see if you have a group under age 60 and you have increased the stroke risk, you have really made a significant change in the overall situation because the risk of stroke under age 50 is really fairly low and then begins to rise significantly after age 50. In the

60s the overall risk of stroke is about 685 per 100,000. In the 70s it is around 1,700 per 100,000; in the 80s 2,500 per 100,000. This is incidence per year. Below age 50 it drops down to about 22 to maybe 35 per 100,000. It is quite low. So, if you have increased the stroke risk in the group under age 50 or perhaps even under age 60, that could be very significant.

DR. HUSSAIN: Thank you. Dr. Richardson?

DR. RICHARDSON: I would like to just touch on a couple of things that Dr. Couch mentioned and Joanne also mentioned relating to duration of therapy. I would like to know if there are changes in occurrence of these adverse events, such as deep venous thromboses or strokes, over time in the studies that have been reported.

Putting it another way, I assume that people who had DVT came off study. Did they come off study at the same rate in the second, third and fourth year of the trial as they did in the first year?

DR. MITLAK: Can I answer that question in

a flip order for you with respect to the incidence of stroke over time in the RUTH study?

[Slide]

This slide shows the cumulative hazard ratio for stroke in patients in RUTH. So, this was the high risk cardiovascular population. The hazard ratio at one year becomes progressive. As you see, the numbers increase over time. So, the hazard ratio for strokes as we interpret these data remains constant for over the seven years during which we have data.

With respect to venous thrombotic events, I think what has been described based on the MORE study, and which is included in labeling, is advice that the risk of venous thrombotic events is highest during the first four months of treatment that was observed in the osteoporosis study, and gives guidance about having patients discontinue treatment if immobilization, travel, etc. is anticipated because immobilization increases the risk of thrombotic events regardless of therapy.

DR. RICHARDSON: One other question, and

that is I am curious how many women the sponsor believes may be candidates for raloxifene. Is this to be everybody over the age of 60? And, how long should they take it?

DR. MITLAK: As I have mentioned before, we have tried to create proposed labeling to focus in on the patients in whom we believe the benefits most clearly outweigh the risks and for whom clinical trial data provides guidance for physicians on how to interpret the benefits and risks for the patients. It is not all postmenopausal women. It is women at high risk for breast cancer. And, also to inform women who are considering this for osteoporosis about treatment.

The duration of treatment, as we mentioned, we have five years of information from STAR and if you consider MORE and CORE together we have information out to eight years, and we think that should be very clearly laid out to physicians in making decisions about duration of treatment.

DR. RICHARDSON: But there must be a number that you have come up with, with respect to what

you think that market is.

DR. MITLAK: To answer you in the same way that Dr. Cummings talked about, I mean, if we are still talking about duration of treatment, I think that each patient-physician interaction has to review benefits and risks and make decisions about whether to start treatment and whether to stop treatment, and we are hoping to be able to provide information on that.

DR. RICHARDSON: Well, you already cited the information in the brochure about the numbers of folks that you thought would be benefitted or have been proposed to have a benefit, potential benefit from tamoxifen. It was something on the order of 25 percent of the women between age 35 and 79 with a breast cancer risk of 1.67 percent. So, you got a number there.

DR. MITLAK: Could I ask either Dr. Wickerham or Dr. Constantino if they would like to comment specifically on the analyses that have been done on tamoxifen?

DR. CONSTANTINO: I believe the analysis

you are referring to is one that was done by Dr. Friedman and the National Cancer Institute where he took the risk/benefit data from the P1 study, determined how many women in the U.S. population would be eligible based on the criteria of having a Gail score of at least 1.66 percent and then, understanding the relationships between the risk of disease and age and race, extrapolated to determine that in terms of tamoxifen about 2.5 million women in the United States would be at high enough risk to take tamoxifen and would benefit from tamoxifen.

In terms of raloxifene, the information used to re-extrapolate those relative risks and take into account the fact that raloxifene has fewer side effects, Dr. Friedman is actually working on that paper at the moment. It has not been submitted or finalized yet. I believe that is what you are talking about.

But, surely, if you look at the number of postmenopausal women in that study, the number who would have been eligible for tamoxifen and would benefit would be about 1.2 million women who were

over age 50 essentially if we are using that as a marker for postmenopausal and, because of the improved risk/benefit ratio and fewer side effects with raloxifene, that number would probably be higher with raloxifene.

DR. HUSSAIN: Can I follow-up on Dr. Richardson's question? I think leaving this upper end open forever is very problematic. So, a person, let's say myself who is in their 50s and supposedly has high risk, then if I am destined to die at 80 I am supposed to take this drug for 30 years. That seems like a lot to ask. And, it would seem to me that if you had information so far from all your trials, understanding that they are not complete in terms of follow-up, survival and such, why can't you use the median of what you have done so far in terms of exposure as your guide, as opposed to deferring it to the primary care physician and saying, well, it is up to you, between you and your patient to discuss, without any specific guidance or information?

DR. MITLAK: I think at the end of the day

we are open to discussing whether the labeling has to provide this sort of guidance.

DR. HUSSAIN: But don't you feel that this is your obligation?

DR. MITLAK: Again, I think for use in osteoporosis and for medicines to be used for a range of indications, I think to set a precise timeline doesn't take into account that individual patient needs may be different. I think if there is a compelling reason to have an absolute duration of treatment, we are open to discuss that.

DR. HUSSAIN: Dr. Lyman?

DR. LYMAN: I won't rehash the methodologic issues that Dr. Harrington and others have addressed, but just one question which perplexes me and I think it does you folks as well, and that is the apparent efficacy here in terms of invasive breast cancer but apparent lack of effect in non-invasive disease. My question is whether you are aware of any preclinical or early clinical data that would suggest a rationale, particularly in the context of this issue we are talking about of

limited duration of follow-up in these trials, that might suggest that what we are doing here is more delaying the development of invasive disease from pre-invasive disease, rather than necessarily preventing invasive disease over the long haul.

DR. WICKERHAM: Yes, as I mentioned, we are continuing to follow-up these individuals to see if this, at the moment non-significant, difference in non-invasive disease goes one way or the other with additional follow-up. We have begun to look at other mechanistic plausible issues. We are looking at a variety of standard markers, ER, PR, HER2 and KI67 to see if there are differences both in invasive and non-invasive, I might add. Dr. Paik is looking at molecular profiles of these tumors as well, using an affymetrix trip, interestingly, funded by the Pennsylvania State tobacco fund dollars. Pennsylvania is one of the few states that use their funds for cancer research.

There is also some suggestion that raloxifene may have more of an impact on mammographic density than tamoxifen, which could

lead to an unmasking bias. If that were to be true, you would expect there to be a catchup phenomenon over time so follow-up remains an important issue.

We have the capability, as we have done in P1, to assess the benign biopsies that have occurred over time in this trial. That is tedious process but one we are considering to see if we can see the impact not just on DCIS but biopsy findings of hyperplasia and earlier findings that did occur in P1, and gave us insight to suggest that the SERM tamoxifen at least had an impact on true prevention.

DR. HUSSAIN: Thank you. The final comment is from Miss Schiff and then I am going to have to stop the questions and we are going to have to go to the FDA questions. Miss Schiff?

MS. SCHIFF: Yes, I just wanted to say that I agree really wholeheartedly with the testimony of the last three advocates, but I wanted to point out two important things for consideration that I think the panel should know about.

One is that, you know, tamoxifen was looked at for more than five years and it was found to be not as good. In other words, using it for a longer period of time causedB-and I think it was breast cancerB-a trend towards more breast cancer and statistically significantly more endometrial cancer, I think. But, anyway, it was stopped at five years. So, I think that the length of time raloxifene is given is a very important question.

The other thing that I think people should know is that tamoxifen was stopped being given to ER negative women to protect the contra lateral breast. And, that is why I think survival is really a key point to be looked at even if it takes, you know, ten years, and it is such a shame that the tamoxifen trial wasB-you know, that there was crossover to the STAR trial because we really need to see, you know, what this drug is doing in the long run for prevention because we are giving it to so many women who are not going to get breast cancer.

I just think really that, you know, from a

woman's point of view I think it is really unconscionable not to look at survival. I know it would take a long time but if we had left the tamoxifen trial goB-I know there is some data on eight years now but it is basically not randomized data if people crossed over to the STAR trial.

So, I just think, you know, there are always side effects, long-term side effects that we don't know and those are the ones that I am very concerned about, the unknown side effects in long, long-term data.

DR. BRAWLEY: Dr. Hussain?

DR. HUSSAIN: Yes, but, Otis, you had better make it extremely brief.

DR. BRAWLEY: Okay. I have heard from the advocates a couple of things that are just out and out wrong. Misappropriation of the science in terms of epidemiology; reduction of period relevance, that is, reduction of risk over the period in which the individual is taking the drug is accepted by epidemiologists as being prevention for example. I also heard that the P1 trial was

initially designed as a survival trial and that it was changed to an incidence-based trial. As far as I know, that is totally wrong and I am getting head shaking from the people at NSABP.

I just want to say we need to slow down. One of the advocates said we need to stop exaggerating. I think we need to stop exaggerating and we need to look at the facts, and I will stop at that point.

DR. HUSSAIN: Thank you. Dr. Justice?

DR. JUSTICE: We will be using a somewhat different procedure today for voting. First I will read the questions and answer any questions that the committee might have regarding need for clarification. Next, prior to the vote on each of the questions, we would like to go around the table and have each committee member give a brief discussion of the question. Then, finally, we would like the committee to vote on each question by a show of hands.

So, now I will read the questions which are on page three of the handout. For the first

indication, which is reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis, the RUTH, MORE and CORE Evista trials were placebo-controlled. The demonstrated Evista benefit on invasive breast cancer reduction in these trials must be weighed against the Evista adverse effects.

The question is, is the risk/benefit ratio favorable for the use of Evista to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis?

The second indication is reduction of invasive breast cancer in postmenopausal women at high risk for breast cancer. In the STAR trial comparing Evista with tamoxifen in postmenopausal women at high risk of invasive breast cancer, Evista was not superior to tamoxifen in reduction of risk. Non-inferiority analysis results are consistent with Evista potentially losing up to 35 percent of the tamoxifen effect on the incidence of invasive breast cancer seen in the NSABP-P1 trial. There were fewer non-invasive breast cancers in

the tamoxifen group, 60, than the Evista group, 83. For all breast cancers the non-inferiority analysis results are consistent with Evista potentially losing up to 47 percent of the tamoxifen effect in the NSABP-P1 trial.

The question is, is the risk/benefit ratio favorable for use of Evista to reduce the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer?

DR. HUSSAIN: Can I ask you a question?

DR. JUSTICE: Sure.

DR. HUSSAIN: Is it possible to propose a middle ground question or no?

DR. JUSTICE: I think so.

DR. HUSSAIN: So, could the question actually combine one and two and say reducing the risk in women who are postmenopausal, have osteoporosis, and at high risk of breast cancer?

DR. JUSTICE: Yes, that is a third question.

DR. HUSSAIN: That would be a third question. Can we add that?

DR. PAZDUR: We could but, remember, these questions are based on what the sponsor is asking. We could include that in your comments.

DR. HUSSAIN: So, it could be done that way. Thank you.

DR. PAZDUR: For the sake of time perhaps we could do this, as we go around the room perhaps people could discuss both of these indications so we don't have to go round the room twice, and then vote on them separately, for the sake of time.

Does everybody understand the questions as outlined? We don't want to get half way through the voting and have somebody say how do you define this. So, everybody understands the questions here. Are we objectively stating what we want here? Okay? Risk/benefit ratio in the two indications that the sponsor is asking for. If you have further comments, those should be comments regarding the new population. So, let's go around the room, both questions, if you could discussB-you don't have to give your vote. If you want to give your vote, that is fine but at the end we will be

doing hand votes. We will record for the record who is raising their hands so it is reflected in the record who is offering opinions, but it speeds things up somewhat. But we want to hear people's opinions first. Remember, we are more interested in what you have to say than the actual vote here.

DR. HUSSAIN: So, to make it clear can I ask that we do the discussion first and then do a vote? And I am going to ask the committee members, who wish to leave here on time for lunch, to not be too verbose and just stick to the point. Dr. Brawley, you get to have the honor of beginning.

DR. BRAWLEY: I am on the far right, eh? Is the risk/benefit ratio favorable for use of Evista to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis? I think with three very well controlled trials, yes. They were well-controlled, placebo-controlled trials.

In terms of the reduction in the STAR trial, despite the fact that STAR compares tamoxifen and raloxifene, I think that in one's interpretation one has to be cautious in comparing

the two. And, that slide that I asked Dr. Constantino to show where the Gail model is put up against tamoxifen and raloxifene, that, to me, is overwhelming evidence that raloxifene reduces versus placebo. I am moved by the fact that I did hear that a 60,000 person trial would have been required for a true non-inferiority trial. So, I do believe raloxifene is effective in reducing risk of breast cancer. I believe it reduces the period prevalence. By the way, that is, the time in which the drug is being used to treat it. I do not believe we should be rigorous in our comparing tamoxifen versus raloxifene.

DR. HUSSAIN: Thank you. Next?

DR. LINK: So, I share Dr. Brawley's opinion. I am a little worried about the number needed to treat so in terms of just an indication, but overall I think that since tamoxifen has been approved for this indication, I think I am swayed by the need to have something with a better therapeutic ratio, if you will, admitting the possibility that this will have less prevention

effect but more likely to be tolerated by women. So, those are the concerns that sort of swayed me to agree with yes for these.

I don't understand really what is to be gained by the first indication. In other words, you know, if you have osteoporosis and you are taking this drug anyway, you know, oh yes, by the way, you are going to, you knowB-it is like you will get to die so don't order now because you will also get some [off microphone].

DR. PAZDUR: The world is a very competitive environment.

DR. LINK: So, admitting that I don't understand the benefit, but I am [off microphone].

DR. HUSSAIN: Dr. Perry?

DR. PERRY: Well, I am going to vote yes on both these. I think that raloxifene clearly has benefit and I think the side effects are I think somewhat exaggerated. The confidence intervals that look at some of these side effects I think cross the 1 boundaries so I don't think they are statistically significant. I think that they are

watching. I think that a lot of people get deep venous thromboses and I think if you pick your patients carefully you can reduce the risk of these particular side effects.

I also will take this opportunity to say that I think the reason a lot of women are not on tamoxifen who might be on tamoxifen is that tamoxifen is off patent and there is no manufacturer pushing the drug to say take tamoxifen for breast cancer because no drug company is going to benefit from it. There is no more nolvodex; there is only tamoxifen. AstraZeneca has given it up and so there is no competitive advantage in that market for tamoxifen. If a company were to pick it up for that indication, then that might be something different. But I think the benefit is not as great as we would like. The side effects are more than we would like. But overall on bases I think it is justified.

DR. HUSSAIN: Dr. Richardson?

DR. RICHARDSON: Well, I have to confess that I am troubled by all of this. I think

tamoxifen and Evista, in reality both have minimal activity for either of these indications. They have toxicities that are significant. The long-term side effects aren't fully known but certainly seem to persist over time, and I am particularly troubled by some of Dr. Couch's remarks with respect to stroke risk in older women. I find the number of patients needed to treat for some benefit is astounding. And, I will vote when the time comes.

DR. HUSSAIN: Hussain, for the record. I would begin fundamentally by making a disclaimer which is that in general I have problems with prevention trials that don't look at actually how many lives we are saving. So, this is a different philosophical issue.

Putting my comments in the context of the questions here, I think that the trials--considering that it is going to be impossible to do the most perfect trial in terms of numbers and suchB-that the trials have accomplished what they started to prove. On both accounts, I

believe the risk/benefit ratio, within the context of what I will say just in a moment from now, is a yes. I do think that some restrictions ought to be put on duration. I don't think it ought to be left to the primary care physicians. Absolutely, it is not a good thing. I also think that clear exclusion criteria have to be included and potentially consideration for contraindications altogether.

I do believe that even though in the discussions there was a lot about the non-invasive cancers, even though I am not in breast cancer, I would argue that the non-invasive, the EIS cancers may not be the cancers we wish to prevent. I think the invasive cancers is the real issue. So, yes on both accounts.

DR. ECKHARDT: Eckhardt. So, I think the discussion that revolves around the first question is a little bit easier in that I sort of envision this as a bit of a value added in a patient who is being treated for osteoporosis. I think what I didn't hear a lot of comment on was, you know, I

think normally you would discuss the risk/benefits in relationship to other drugs being used for osteoporosis presumably and we didn't really talk a lot about that. But I think, again, this is probably a little bit of an easier question here because you have patients that would be receiving therapy and that you would clearly need to carve out the higher risk population.

I think the second question is tougher for me. You know, I think what we are seeing is that these trials are often flawed for many reasons and the drugs that we have that are being used have flaws but, on the other hand, they can have true benefit in focused patient populations. So, where my concerns really lie with this is in the further narrowing and focus on what is the patient population that can truly benefit in this setting and, clearly, duration of therapy. So, I think that those are two hurdles because as we are comparing this to tamoxifen, as we have heard, this for many people is considered to be a somewhat flawed drug so, at best, raloxifene is exactly the

same or, at worse, it is worse than a drug that we consider to have some flaws.

DR. WILSON: I too am struck by the large number of patients that need to be treated in order to see benefit with both tamoxifen as well as this agent. Also, with the lack of long-term toxicity data, long-term efficacy data and the absence of a survival benefit for tamoxifen, and from a biological point I continue to be concerned that we are delaying or modifying the natural history of breast cancer but we may not ultimately be stopping it overall.

I do think that the STAR trial does show, in my view, that raloxifene does have some prevention benefit. Whether or not it is equivalent to tamoxifen or slightly less I think is still an open question. It does appear to be somewhat less toxic. So, I would say that if one felt that the short-term benefit of tamoxifen was worth approving, based on that alone, that there probably would be some merit in approving raloxifene.

I have a larger problem with the first indication because if one looks at the absolute benefit it would appear that benefit is, both in one of the studies as well as I think from first principle, mostly going to be in high risk patients, those with Gail scores over 1.67. That is the group that would fall into the second indication. Therefore, they could be getting that drug as part of that second indication that, therefore, leaves the patients at very low risk of disease where the benefit is very, very small. Because this agent is going to be given mostly by general medical doctors or by OB/GYN, I don't think that the relative risk of the Gail model is really going to be well explained, and I would hate to see this question of breast cancer obscuring other balances of risk/benefit when patients are trying to decide, number one, should they get anything for osteoporosis or, number two, whether or not another osteoporotic drug may have a better profile.

DR. MORTIMER: Mortimer. In answer to the first question, I think three very-well designed

placebo-controlled trials did show that raloxifene does decrease the incidence of breast cancer. Whether the risk/benefit ratio actually favors its use as a preventive agent I think is really a hard one to answer with the data that we have at hand.

I think the recent data from the Women's Health Initiative that suggests that early hormone replacement therapy in the younger women has a protective effect and the opposite effect in the older women makes me worry, especially listening to Dr. Couch, that as we use these SERMs in older women, the osteoporotic group, they really may have a risk/benefit ratio that is adverse. But, nonetheless, I think the sponsor did demonstrate a decreased incidence of breast cancer.

I have more difficulty extending this to the population at large of high risk women on the basis that I think, whether the data is conflicting or not, I am worried that if the bone is an end organ and the breast is an end organ of hormone effect, probably the natural history of this disease is not the same in osteoporotic women as

other women and, in the absence of data that says that they are, I am concerned about extrapolating the data to the high risk women without osteoporosis.

Secondly, I am consistently troubled by the lack of decrease in ductal carcinoma in situ. If DCIS is a precursor for invasive cancer, why in the MORE study, why in the RUTH study and in the STAR was there not a benefit for decrease in DCIS? For those reasons, I have a hard time extending it to the larger population.

DR. LYMAN: I will start off by saying that I think the sponsor has worked with NSABP, of course, with the NCI and with the FDA to design their studies and monitor their studies of this as a chemopreventative and I think they are to be commended for the work they have done with that.

I do think, however, we all as clinical trialists need to listen to what all of us are saying to one another and even the advocacy community is saying, and that is, we need to think about longer-term follow-up in our controlled

clinical trials. Nowhere is that more in need than in the prevention setting where the event rates are low and the potential toxicity benefit profile could possibly be unfavorable.

I think we might want to discuss the possibility, if we approve it, of mandating or upgrading the post-approval monitoring that needs to be done in the purported populations, osteoporosis patients or high risk patients, because I think both sustained efficacy and the toxicity issues have been eloquently discussed and I think we want more data and we want longer-term follow-up.

Having said all that, as a breast cancer oncologist, I do think the use of raloxifene to reduce the risk of breast cancer in women, many of whom are already taking the drug for osteoporosis prevention or treatment, seems reasonable. And, the data from the randomized, placebo-controlled trials seems to offer, to my opinion, a reasonably favorable benefit/risk profile as far as the data goes. I am also somewhat reassured by the survival

data, although limited and not powered for survival outcomes and not necessarily significant but, if anything, trending towards favorable survival outcome. That is reassuring after considering all these other issues.

For the high risk population, I think compared to tamoxifen, as I read the data and hear the data, raloxifene seems to be similar in efficacy and similar or somewhat better in terms of the safety profile. I am not at all comfortable with the non-inferiority analysis that we have been forced to consider given the lack of a placebo group in the STAR trial. I think that data weighs very little in my decision to vote for these two indications.

DR. HARRINGTON: I am going to vote no on the first question because I think that the population there is too broad. Even though those were the populations in the trial, they include postmenopausal women at low risk for breast cancer and I didn't see clear evidence for the benefit of continued use of raloxifene in postmenopausal women

with osteoporosis who progress on their osteoporosis and from whom you would then remove raloxifene as an osteoporosis treatment, and whether the risks there are worth continuing in order to prevent putative breast cancer in the future.

Question two is a tough one because of the non-inferiority analysis here in a trial that is not properly controlled. I think I am going to vote yes on that one because we have a drug out there, tamoxifen, with its advantages and its possible flaws and I think that is a setting where women at high risk for breast cancer and their physicians have an option where it would be very nice to have a second option because there I think the risk/benefit ratio, for me, comes in much sharper focus because the potential comparisons there are the side effects of raloxifene versus the side effects of tamoxifen. Whereas, in question one it is really the side effects of raloxifene versus no treatment at all in women who perhaps do not need this for their osteoporosis any longer.

MS. HAYLOCK: Haylock. I think on question one the value of the drug has been shown, but I am very concerned about the issue of the candidates for taking the drug, especially people who are maybe unknown at risk for stroke at this point in time, and incidence of stroke seems to go up while the age of stroke survivors goes down. I think that there was a real lack of defining properties of that population in the study.

I also think it is a big concern when this drug is available in clinical practice, again, for the issues of thromboembolic events and particularly stroke in these populations because so many people are not being monitored for their risk of stroke or they have an unknown risk of stroke. So, I think that that is a real danger.

And, in the second question, I think that the risk of invasive breast cancer in these women is high so I would probably be more in favor of a yes vote for that one.

MS. SCHIFF: I agree with what Dr. Richardson said, and I am going to vote no on both

of these because I really think we don't know the long-range effects in terms of survival, and I really think that that is an important question when you can't decide individually who is at high risk of breast cancer but you are looking at such big populations.

In addition to that, I think we know about the healthy women effect, that the women in these trials are going to be healthier than women who get this drug out of the trial. I would also like to add that with the FDA not having the power it needs to pull a drug off the market or to regulate direct-to-consumer advertising, I think although this is not the typical consideration for ODAC, it is a consideration for an advocate. I spent a year getting the tamoxifen ad pulled for prevention and they had put in the relative risk reduction for breast cancer and the absolute risks of the side effects.

So, within that whole context, I am voting no on both of these. I think our money can be spent finding out really who is at high risk before

we start giving people dangerous drugs.

DR. HUSSAIN: Dr. Couch, are you there?

DR. COUCH: Yes, I am here. Thank you. Obviously, I am not an oncologist and will not vote here. I would advocate that a long-term surveillance program must be put in place and the individual risk factors for stroke, as I went through, be considered. There may be subgroups here under hypertension, hypercholesterolemia, diabetics, smoking that may influence the stroke risk to a greater or a lesser extent. So, it may well be possible to identify a subgroup that would have either a greater or a lesser risk, and perhaps you can identify a subgroup that you could really minimize any stroke risk and utilize the drug in that situation.

As I think has been pointed out, there is not going to be one drug that will fit every situation here, and in medicine we always have to try to tailor whatever drug we are using to the particular situation. So, I think that we might be able to identify a subgroup that would be at lower

risk for stroke or a subgroup that would be at higher risk for stroke for which we certainly would not want to use this medication.

I think the major issue is going to be to look at 10- and 20-year follow-up. Perhaps some of this could be done by going back and looking at the raloxifene and osteoporosis data, and looking to see if there is a significant increase in risk in women that may have been taking the raloxifene for a longer period of time, or may have taken it ten years ago or so and what is their stroke risk at this point even though they may have discontinued the medication. So, from that standpoint, I think we need to be careful.

Finally, I think from the standpoint of cardiac risk, if someone already has cardiac risk is this going to advance or multiply the risk for further either cardiac or stroke events in patients, and should this group be taken out of consideration as far as being users of raloxifene. I believe that is the end of my comments. Thank you.

DR. HUSSAIN: And just for the record, you said you are not planning on voting?

DR. COUCH: I don't think I have the expertise. I would vote to abstain--

DR. HUSSAIN: So, we will record you--

DR. COUCH: I don't think I have the expertise in the oncologic aspect of this drug to really make much of a difference. By the way, I do want to apologize to the committee for not being there. We had two different planes that I tried to get on and both of them had mechanical difficulties and there was just no way I could get there.

DR. HUSSAIN: Okay. Are you in a fun place, I hope? The beach, hopefully?

DR. COUCH: I am sorry.

DR. HUSSAIN: Thank you.

DR. BUZDAR: Yes, I think that looking at the data the question is, is the risk/benefit ratio favorable for use of Evista. I think the data from the RUTH and MORE and CORE trial clearly demonstrates that, yes, you can reduce the risk of breast cancer. The question is that there is no

way the data was presented whether this risk/benefit ratioB-because we also saw that it substantially increases the risk of stroke and other thromboembolic complications which are associated with the drug which has estrogenic properties.

So, I would say that benefit/risk thereB-but the question is, is the risk/benefit ratio favorable? I think the answer is that it is not very clear from the data which was presented, the way it was presented.

And the same question is that if you look at question number two, is the risk/benefit ratio favorable for Evista, Evista is somewhat less effective in reducing non-invasive breast cancer and even slightly invasive breast cancer. Again, the risks versus benefit ratio is not clearly defined. So, I think these questions still remain very grey on both sides.

DR. FURBERG: I am basically supportive but only with some safeguards and there are two things. One, I think there should be strong efforts to

limit potential harm and that should be done both at the time of initiation of they so we clearly layout the contraindications and so on, and also during follow-up. People change their status and their risk of complications may change. So, there should be fairly strict monitoring of what is going on.

The other safeguard is to somehow restrict overuse. I worry about direct-to-consumer advertising and that every other woman in the U.S. is going to be on the drug unless we clearly try to restrict use to the women where the drug is shown to be effective.

So, there are three solutions that I propose. One, in the labeling possibly--I am not suggesting thatB-a black box just to bring people's attention that there are risks involved and so on. And, I would focus on the thromboembolic events and other contraindications.

The other one, the one that is mentioned is for the sponsor to commit to a medication guide, a document to be given to every woman getting the

drug, laying out the rationale for treatment and what they should pay attention to and when they should contact their doctor.

Then, I agree with a couple of the earlier people who suggested postmarketing surveillance. I think that is critical. It should clearly go beyond five years, and to set up a patient registry with specific prespecified hypotheses. And, I wish we, in the U.S., had the European model so a re-review of the drug would occur automatically after a certain number of years. I would like to see a re-review in, say, about five years to see what the experience has been and whether the drug should stay on the market with no restrictions. Thank you.

DR. GRILLO-LOPEZ: Thank you, Dr. Hussain. I have three comments. First, I think that the data are clear and I would be willing, based on the data as presented and discussed today, to make a decision and make a recommendation. Secondly, we have to, of course, accept that tamoxifen is approved and on the market and that raloxifene

shows at least similar efficacy and perhaps a better safety profile.

Thirdly, given the comments of my colleagues on the committee, I would like to provide a word of caution and that is that although some of the concerns are very real and valid, the data are what they are and we cannot ask for these studies to show what they cannot show, what they were not designed to show, the questions that were not asked at the design stage of the studies.

It would be nice to have had twice as many patients on these studies, but they are large enough as it is and these studies are very costly. It is very difficult to enroll patients. It takes a long time to enroll patients and you have to stop somewhere. Also, the observation time is what it is. We cannot expect to have data on 20, 30 years observation times when the studies haven't been ongoing for that long.

So, we have to put aside some of those concerns, real and valid as they are, and the committee today has to vote based on the

information that is available and not expect something different from the data.

DR. HUSSAIN: Thank you, Dr. Grillo-Lopez. You want to say something?

DR. PAZDUR: Yes, let us have a hand vote then on each of the questions with yes, no and abstain, and if the exec. sec. could read for the record who is voting for each of the votes. So, the first question then is yes, followed by no and abstain.

DR. HUSSAIN: So, only those who are eligible to vote, please, raise your hand on the first question. The yes voters on the first question, hands up and keep them up until Johanna tells you to bring them down.

DR. PAZDUR: She could name them for the record, Johanna. And, the question is, is the risk/benefit ratio favorable for use of Evista to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis? Yes?

MS. CLIFFORD: Diane, I will go around the room, if you could record for me. Thank you. Dr.

Brawley yes; Dr. Perry yes; Dr. Maha Hussain yes; Dr. Link yes; Dr. Mortimer yes; Dr. Lyman yes; Dr. Gail Eckhardt yes; and Dr. Furberg yes.

DR. PAZDUR: Did she get everybody's name that voted yes? So, the next question is no to that question, a vote for no. Please raise your hand.

MS. CLIFFORD: Dr. Buzdar no; Miss Schiff no; Miss Haylock no; Dr. Harrington no; Dr. Wilson no; Dr. Richardson no.

DR. PAZDUR: And the next, abstaining.

MS. CLIFFORD: Are there any that abstain, other than Dr. Couch? We did note for the record that Dr. Couch had abstained.

DR. PAZDUR: Let's go to the second question then. Is the risk/benefit ratio favorable for use of Evista to reduce the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer? Those voting yes, please raise your hand and, Johanna, would you please?

MS. CLIFFORD: The vote to question number one was 10 to 6 yesB-I am sorry, 8 to 6.

Those voting yes to question number two, Dr. Otis Brawley; Dr. Michael Perry; Dr. Richardson; Dr. Link down there; Dr. Hussain; Dr. Wilson; Dr. Lyman; Dr. Harrington; Pam Haylock; and Dr. Furberg.

DR. PAZDUR: No to that question?

MS. CLIFFORD: No to question number two, Dr. Buzdar; Miss Schiff; Dr. Mortimer; Dr. Gail Eckhardt.

DR. PAZDUR: Abstaining?

MS. CLIFFORD: Abstaining, Dr. Couch. That is 10 to 4 yes to question number two.

DR. PAZDUR: Thank you. I would just like to emphasize for the audience since there is another drug that will be discussed and we are trying to control access to the room since it is somewhat limited, if you will take any personal itemsB-we cannot guarantee that the same individuals will be coming in to their seats; you cannot save your seat. Okay?

DR. HUSSAIN: Please come back at one o'clock. Thank you.

[Whereupon, at 12:30 p.m., the proceedings were recessed, to reconvene at 1:00 p.m.]