AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGY DRUGS ADVISORY COMMITTEE

NDA 022-024, EVISTA
(raloxifine hydrochloride) Tablets
Eli Lilly and Company

Tuesday, July 24, 2007

8:00 a.m.

ACS Conference Room, Room 1066
5630 Fishers Lane
Rockville, Maryland

PAPER MILL REPORTING
Email: atoigo1@verizon.net
(301) 495-5831

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

Maha Hussain, M.D., Chair

Johanna Clifford, M.S., R.N., Designated Federal Officer

Advisory Committee Members (Voting)
- S. Gail Eckhardt, M.D.
- David Harrington, Ph.D.
- Michael Link, M.D.
- Gary Lyman, M.D.
- Joanne Mortimer, M.D.
- Michael Perry, M.D.
- Ronald Richardson, M.D.

Industry Representative (Non-Voting)
- Antonio Grillo-Lopez, M.D.

Temporary Voting Members
- Aman Buzdar, M.D.
- Otis Brawley, M.D.
- James Couch, M.D., Ph.D. (via telephone)
- Curt D. Furberg, M.D., Ph.D.
- Helen Schiff (Patient Representative)

Pamela Haylock, R.N. (Consumer Representative)
- Wyndham Wilson, M.D.

FDA (Non-Voting)
- Richard Pazdur, M.D.
- Robert Justice, M.D.
- Patricia Cortazar, M.D.
- Rajeshwari Sridhara, Ph.D.
- Bhupinder Mann, MBBS
- Kun He, Ph.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call To Order and Introduction of the Committee

DR. HUSSAIN: Good morning. I am Maha Hussain acting as the Chair this morning for the Evista hearing.

I want to begin with a statement. For the topics such as those being discussed at today's meeting. There are often a variety of opinions, some of which are quite strongly held, as you know. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair, in this case myself this morning. We look forward to a productive meeting. Thank you.

I would like to welcome you all and begin on my right with an introduction of the committee members. Dr. Pazdur?

DR. MANN: Bhupinder Mann, medical reviewer, FDA.

DR. SRIDHARA: Rajeshwari Sridhara, statistics, FDA.

DR. HE: Kun He, statistical reviewer, FDA.

DR. BRAWLEY: Otis Brawley, medical oncology and epidemiology, Emory University, Atlanta.

DR. LINK: Michael Link, pediatric oncology, Stanford.

DR. PERRY: Michael Perry, medical oncology, University of Missouri, Ellis Fischel Cancer Center. DR. RICHARDSON: Ron Richardson, medical oncology, Mayo Clinic, Rochester, Minnesota.

MS. CLIFFORD: Johanna Clifford, designated federal official to the ODAC.

DR. HUSSAIN: Maha Hussain, medical oncology, University of Michigan.

DR. ECKHARDT: Gail Eckhardt, medical oncology, University of Colorado.

DR. WILSON: Wyndham Wilson, medical oncology, NCI.

DR. LYMAN: Gary Lyman, medical oncology

and outcomes research, Duke University.

DR. HARRINGTON: David Harrington, statistician, Dana-Farber Cancer Institute.

MS. HAYLOCK: Pam Haylock, oncology nurse and consumer representative, University of Texas Medical Branch in Galveston.

MS. SCHIFF: Helen Schiff, patient advocate.

DR. BUZDAR: Aman Buzdar, from M.D. Anderson, medical oncologist, from Houston.

DR. FURBERG: Curt Furberg, Public Health Sciences, Wake Forest University.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez. I am a hematologist/oncologist and industry representative to this committee. I receive no support whatsoever from industry for my participation at this meeting.

DR. MORTIMER: Joanne Mortimer, medical oncology, City of Hope.

DR. HUSSAIN: Excellent. Welcome. Dr. Pazdur, do you want to begin for the three of you whose names were not audible?

DR. PAZDUR: Richard Pazdur, FDA.

DR. JUSTICE: Robert Justice, FDA.

DR. CORTAZAR: Patricia Cortazar, medical oncology, FDA.

DR. HUSSAIN: Before we get to the formal presentation by the sponsor, I would like to invite Dr. David Harrington, from the Dana-Farber, for designing and analyzing trials. Oh, I am sorry, Johanna will have a conflict of interest statement to discuss and then we will go to Dr. Harrington.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

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

In accordance with 21 USC 3559n)(4), a waiver has been granted to Dr. Maha Hussain for her and her spouse's stock ownership in the sponsor which is valued at less than $5,001, and stock ownership in two competing firms which is valued at between $5,001 and $25,000 per firm.

The acknowledgment and consent for disclosure document is available at the FDA's dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of the acknowledgment and consent disclosure document can be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Antonio Grillo-Lopez has been invited to participate as a non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is a retired employee of the Neoplastic Autoimmune Disease Research

Institute.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

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

DR. HUSSAIN: Dr. Pazdur?

Opening Remarks

DR. PAZDUR: Good morning. The applicant, Eli Lilly, has submitted a new drug application for Evista for two indications. The proposed indications are, number one, reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis and, two, reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer.

Evista was marketed for the treatment and prevention of osteoporosis in postmenopausal women in 1999 and 1997 respectively. Results of four double-blind, randomized trials are submitted in support of the two above new indications. Patients do not have cancer. Thus, especially careful consideration of the risk/benefit ratio is required. The RUTH, MORE AND CORE trials are placebo-controlled and are the primary trials in consideration of the first indication, that is, the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis. Dr. Bhupinder Mann, from the FDA, will present the FDA review of these trials.

The STAR trial has an active control, tamoxifen, and is the primary trial for the second indication, that is, the reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer. Dr. Patricia Cortazar will present the FDA review of the STAR trial.

Results of the RUTH, CORE and MORE placebo-controlled trials indicate that Evista

reduces the risk of invasive breast cancer in postmenopausal women with osteoporosis. Only ER positive breast cancers are reduced. There appears to be no reduction in ER negative breast cancers. Almost all of the invasive breast cancers are either stage I or stage II. This is achieved at the cost of increased and serious adverse events such as deep venous thrombosis, pulmonary embolus and possibly stroke death.

In the RUTH trial comparing Evista with placebo over 5,000 women were treated with Evista every day for a median of five years to prevent 30 invasive breast cancers, almost all stage I or stage II. Described another way, 862 women must be treated for one year to prevent an invasive breast cancer in one woman.

The STAR trial serves as the primary trial supporting the second indication, reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer. The STAR trial compared Evista to an active control, tamoxifen, in postmenopausal women with a high risk

of developing invasive breast cancer as indicated by a modified Gail score greater than or equal to 1.66 for lobular carcinoma in situ treated with excision only. The primary endpoint of the trial was to demonstrate superiority of Evista in reducing breast cancer. Evista was not better than tamoxifen.

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-1 trial comparing tamoxifen with placebo. There were fewer non-invasive breast cancers in the tamoxifen group, approximately 60, than in the Evista group which had 83. For all breast cancers the non-inferiority analysis results are consistent with Evista potentially losing up to 47 percent of the tamoxifen effect observed in the NSABP-1 trial.

The FDA has asked Dr. David Harrington to present a brief discussion on the use of the non-inferiority analysis in assessing efficacy. The efficacy results in RUTH, MORE, CORE and Star

trials must be weighed against the increased risk of deep venous thrombosis, pulmonary embolus and possibly stroke death. A careful consideration of the risk/benefit ratio is especially important for the two proposed new indications in postmenopausal women who do not have cancer. ODAC advice is requested.

In general, the protocols for the STAR, RUTH, MORE and CORE trial excluded women who were at risk for deep venous thrombosis, pulmonary embolism or stroke, with the exception of the RUTH trial where patients were at an increased risk for coronary adverse events and presumably at increased stroke death. Thus, it is unlikely that the incidence of Evista serious adverse events will be less in general use than in the clinical trials. We cannot expect to improve the clinical trial results in general use by precautions or warnings in Evista labeling.

In conclusion, the FDA will be asking ODAC members to discuss and provide their advice on the following two questions: Number one, is the

risk/benefit ratio favorable for the use of Evista to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis? And finally, the second question, is the risk/benefit ratio favorable for the use of Evista to reduce the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer? Thanks you.

DR. HUSSAIN: Thank you, Dr. Pazdur. Dr. Johnson, are you on the phone? Is he going to join us? I understand that John Johnson is going to be joining us by phone and he is also from the FDA. Dr. Harrington?

Designing and Analyzing Trials with Active Control Arms

DR. HARRINGTON: Thank you, Dr. Hussain.

[Slide]

As Dr. Pazdur mentioned, the FDA asked me to speak a bit about the use of non-inferiority analyses or non-inferiority designs in evaluating efficacy in clinical trials.

[Slide]

The usual disclaimer is here. I have no

financial support from the sponsor obviously since I sit on ODAC and my expenses will be paid by the FDA as a member to ODAC. The most important disclaimer on this slide is that I am not going to discuss the application in general. That is the role of the FDA and the sponsor. I am going to, instead, talk about some of the issues that arise in non-inferiority analyses and some of the questions that are important in evaluating this application. I will use data from the application as context.

[Slide]

As Dr. Pazdur mentioned, there are four trials that are part of the application, STAR, RUTH, MORE and CORE, and the STAR trial which was a direct comparison of raloxifene to tamoxifen has been analyzed has been analyzed with a non-inferiority analysis, and that is the one that I am going to focus on.

[Slide]

So, the main issue in the analysis of the STAR trial is a non-inferiority analysis, in other

words, an analysis in which the primary endpoint is invasive cancer. Raloxifene is the test agent. Tamoxifen is the active control.

Now, the use of active controls has actually increased dramatically in cancer as there are more and more effective therapeutics, especially in the adjuvant setting. Here we are dealing, as Dr. Pazdur said, with a presumably healthy population although one at high risk of breast cancer. There are two important features about this analysis though that are a little bit different than the usual superiority trials that use active controls, and that is, first, that we will be looking to see if there was a loss in efficacy in raloxifene versus tamoxifen and, second, one of the key features of non-inferiority designs is that they often use information outside the trial. This one does. They almost always do in order to infer the absolute effect of an agent.

There has been lots of literature about non-inferiority designs, folks at the FDA, Mark Rothman, Susan Ellenberg, Bob Temple and many

others, and there is a fair bit of controversy surrounding these designs, and as I get to the discussion of this you will see where some of those controversies arise.

So, my goal here is to point to what questions ODAC should ask or could ask in the context of a non-inferiority analysis. So, I am going to give a little bit of background here to get us there.

[Slide]

First, here is the context. This is a plot that shows the effect in the NSABP-1 trial for women greater than or equal to 50 years old, which matches roughly the postmenopausal population that is in the STAR trial. On this plot it shows that in that trial the relative risk of tamoxifen to placebo was 0.47. Numbers to the left of 1 here favor tamoxifen. Numbers to the right of 1 would have favored the placebo. The interpretation here is that tamoxifen reduces the rate of invasive breast cancers on placebo by 53 percent, or for a relative risk of 0.47 compared with a confidence

interval on the reduction scale here that ranges from 34 percent to 67 percent, obviously very strong evidence in that trial that there was a breast cancer prevention effect or breast cancer delay effect. I think the jury is still out on exactly what the long-term nature of that will be.

[Slide]

Here is the same slide in the reverse order comparing placebo, on the top, to tamoxifen only because this is the way it appears in some aspects of the application. So, everything here is the same as it was on the previous slide except it is inverted. This says that women who were on placebo were at roughly 112 percent increased risk of breast cancer compared to tamoxifen. So, the interpretation here is that the placebo increased the risk of invasive breast cancer incidence compared to tamoxifen by 112 percent, with a confidence interval that ranges from 52 percent to 303 percent.

[Slide]

Now, in the context of that trial, there

were several designs that were possible for evaluating raloxifene versus tamoxifen in an attempt to understand its absolute effect. The one that was chosen in the STAR trial, for very good reasons in context, was a direct comparison of raloxifene to tamoxifen.

Others were possible, although admittedly very, very hard to do. So, another one would have been raloxifene compared to placebo which would have given the direct head-to-head comparison of the absolute effect of raloxifene, something that we are going to try to infer in the course of today's discussion. There also could have been an even more complicated trial, raloxifene, tamoxifen and placebo which would have allowed a direct measurement of both raloxifene's comparative value to tamoxifen, raloxifene's effect to placebo, and the same population with concurrent control would have given safety information that was comparable across the three arms of this trial.

So, we have before us in the STAR trial a raloxifene versus tamoxifen comparison. That trial

was designed by NSABP-1 as a superiority trial for raloxifene versus tamoxifen. It was designed with 85 percent power to detect a relative risk, raloxifene to tamoxifen, of 0.67, in other words, designed to have high power to detect a 33 percent reduction in the rate of breast cancers favorable to raloxifene.

The NSABP was also careful to check the power calculation to make sure that if raloxifene was significantly worse than tamoxifen that would be recognized in this trial. So, there is a power specification in the design which says it has 95 percent power if the relative risk of raloxifene to tamoxifen is 1.56. Now, the 1.56 is a bit of a magic number because, remember, on the previous slide there was a 112 percent increase in the rate of breast cancers on placebo. So, here, this would have taken raloxifene half way to placebo if it had a 56 percent increase in the risk of breast cancers.

In fact, what happened was that in the STAR trial the observed relative risk was 1.02 so

the drugs declared themselves to be within the precision of the trial approximately equivalent. Precision of the trial becomes very important in that setting. So, what we have before us is a non-inferiority analysis of the STAR trial as opposed to the superiority analysis that was anticipated in the design.

[Slide]

Here is the same picture that I showed earlier that shows the effect of tamoxifen to a placebo where numbers to the right now favor the tamoxifen. This shows 112 percent increase in favor of tamoxifen, 112 percent increase on placebo. In a non-inferiority design that would replace the placebo arm by an active treatment, in this case raloxifene, the question really becomes how far along the scale to the right does the test treatment move away from 1 so that it begins to declare itself to look more and more like a placebo? And, how far along the scale are we willing to accept a loss of efficacy?

So, there are very many places where you

can put that line to accept a loss of efficacy and that is probably the single most controversial issue in non-inferiority trials, and that is where to put the non-inferiority margin.

So, here is one example put at the 1.56 spot which was implied by the NSABP design of the STAR trial, although not explicitly stated that way. In the past people have put non-inferiority margins at some absolute value of relative risk, often 1.25. The current thinking is to put non-inferiority margins at some percentage of the observed effect of the agent that has shown itself to be active. So, this is at 50 percent of the observed effect but for a statistician there is nothing magic about this number. It becomes really a clinical decision about what margin of non-inferiority someone is willing to accept.

Here is one which accepts very little non-inferiority. It moves a test agent only one-quarter of the way towards the point at which it gets to the tamoxifen-placebo comparison. This is 25 percent loss of efficacy or 75 percent

retention, and then this one would be 75 percent loss of efficacy or 25 percent retention. So, that provides the context for how non-inferiority designs are set up.

[Slide]

So, let's talk about the possible outcome of a non-inferiority trial and a non-inferiority analysis for a trial that was not necessarily designed there. Here, first, is that relative risk of 2.12 with a confidence interval about it. Here is a putative non-inferiority margin at 50 percent of the efficacy. I am just putting this down for an example so you get context here.

There are two important reasons for specifying the non-inferiority margin in the design. The first is to make sure that it is a non-inferiority trial that is sufficiently well powered. That is to say, if you start with a null hypothesis that your test agent is not as good as the active control and so you are out here some place on the right-hand side of the scale to the right of 1, you want to have a trial that is

sufficiently large; is sufficiently powered. That is, as you begin to move closer to 1 you will recognize that with high probability.

The other main reason though, that is perhaps even more important than a power calculation, is a prespecification of the non-inferiority margin which would avoid the post hoc interpretation of data, which is a possibility in any clinical trial, even a non-inferiority design where someone sees the result and then, with just a bit of thinking, convinces themselves that that is just exactly the result that they were looking for even though they hadn't specified it in the design. So, the prespecification of a non-inferiority margin is extremely important.

So, here are possible outcomes of a non-inferiority trial. For the first two here you don't need a weatherman to tell you which way the wind is blowing. In the first one, here the test treatment declares itself to be superior to an active control. Here it is inferior to an active control. The decision about these two treatments

would be clear.

The third situation is more the situation that we are in, and that is one where the test treatment declares itself to be possibly a little bit worse as a point estimate than the active control but has a confidence interval which stretches that out to the right and to the left, and so as an extreme or most conservative estimation, one might say, well, if we were to try to write down an estimate for the non-inferiority margin it might be at this left point.

In fact, that is a vast oversimplification because this inferiority margin, wherever it is put, inherits variability or uncertainty from the estimate in the previous trial. So, a proper non-inferiority analysis must account for the variability that is present in any putative non-inferiority margin.

There are two sources of variability here for a statistician. One is the within trial variability that is shown in this confidence interval, but another is the between trial

variability. If there have been other trials done comparing the test agent to a placebo or the test agent to no control they show the possible heterogeneity of the use of that agent in the population and they indicate that there may be, in fact, more variability in an estimate of a non-inferiority margin or treatment effect. So, it becomes extraordinarily important in the zone where this may be close to touching some putative non-inferiority margin that the sources of variability, the sources of uncertainty be accounted for.

The application has done that using Rothman's method for comparing a test treatment to an active control using one trial, using the NSABP-1 trial. It has elected not to assess the trial-to-trial variability and not use the other three tamoxifen-placebo trials in the literature for breast cancer and I am sure they will tell us more about why they elected to approach the analysis that way.

[Slide]

So, the goal of an active control or non-inferiority analysis is to make that leap of extrapolating from the trial at hand, which compares a test treatment to an active control, to some measure of the absolute benefit of the test treatment if a placebo had been present in the trial. So, it proceeds by estimating the effect of the test treatment compared to an active control. That is T versus C. It uses data from previous trial or trials to estimate the effect of the placebo versus the active control, along with the margin of error for that effect. That margin of error, as I said, may include within trial variability and between trial variability. Then it combines these estimates to evaluate the putative effect of the test treatment versus a placebo.

Sometimes that is done by estimating the range of retention of P versus C effect consistent with the data, and we will see that in the application for raloxifene, a range of likely values for the non-inferiority margin with the P1 trial used as the comparator here. If T, in fact,

has fewer side effects than the active control, then there are obviously very good reasons in many instances to accept some loss of efficacy in exchange for tolerability, ease of administration, perhaps increased compliance.

[Slide]

So, there are several important issues here rattling around. The most important one is the idea of extrapolation. The non-inferiority analyses are based on one or more previous trials and a current trial to use the information gained in potentially different settings. So, I am going to be a little bit fussy about the labeling here now. I am going to use the kind of labeling that causes parents to urge their children not to date statisticians, the sort of dry look at what is happening in the clinical trial.

So, in the current trial we will let T be the test treatment, C2 the active control, P a putative but not present placebo. In the previous trial or trials C1 is the same active control, P1 a placebo.

[Slide]

So, here are the assumptions that are made in conducting a non-inferiority trial. First, that the T versus C2 is well conducted so obviously one has to have a very good measureB-in this case T is not standing for tamoxifen here; it is the test treatmentB-a very good measure of the test treatment versus the active control.

Second, that we can borrow the estimate of the effect of the active control versus placebo and assume that if placebo had been present in the current trial the effect would have been the same, so that we can extrapolate to the possible T versus placebo effect. That is an assumption that the effect of the active control has not changed since prior trials or any change can be modeled.

The uncertainty in the effect or the effectiveness of P1 versus C1, the placebo versus the active control in a previous trial can be estimated so there is an assumption that we can do that. Both within and between trial variability are relevant and some active control analyses where

there is a healthy literature on the testing of the active treatment is sometimes based on a meta-analysis which provides really two pieces of important information. It provides either a sharper estimate of the precision of the estimate of the effect of the active treatment versus placebo, but it also can indicate whether there is sufficient heterogeneity in previous trials to indicate that the effect of the active control may be bounding around a little bit too much to trust its reliability in any one trial.

The clinically relevant non-inferiority margin must be specified before the analysis. I mentioned that earlier. And, all of these are used in the inference that we can take the T versus active control effect, the active control versus placebo effect and infer an active treatment versus placebo effect.

[Slide]

Here are the questions that I think are important questions to ask about a non-inferiority analysis. First, this is a question that goes

along with any clinical trial presented here and in any scientific setting, is the claim of non-inferiority supported by a biological rationale? Is there a reason to have expected the trial to turn out the way it did?

Might the effect of the active control versus placebo have been different in the current trial and in previous trials? So, over the course of time, has the administration of the active control changed since its earlier use or its earlier testing? Are the populations different than they were in the earlier trials? Is the endpoint determination being done exactly the same? Changes in any of these can mean that the active control has a different effect in the current trial had a placebo been present.

Has long-term follow-up changed the thinking of the value of the active control? So, we see trials after X many years of follow-up. We all know who work in cancer research that sometimes the long-term effects of these agents can be different. So, here I think with tamoxifen one of

the questions that was raised early is does tamoxifen prevent breast cancer, or does it simply delay the diagnosis of breast cancer, or did it in fact just help discover the subclinical breast cancers that were already present?

Does the analysis use the best available historical data on the active control to estimate both treatment effects and uncertainty? So, here we should ask about a solid justification for any trials that have been omitted from the analysis that I mentioned earlier, the three other tamoxifen, placebo-controlled trials that were done roughly concurrently with the NSABP-1 trial?

[Slide]

Is the estimated non-inferiority margin clinically relevant? Was it specified in advance? Is the reduced therapeutic effect for the test agent balanced by other benefits? Now, as a statistician, I probably get this question more often than any other and it is a question that I am always completely ill equipped to analyze. It is very, very difficult to weigh these risk/benefit

ratios if you are giving up some efficacy in exchange for reduced side effects.

Are results consistent across endpoints? As in all trials, the treatment effects measured in non-inferiority analyses are estimates of population effects, not predictions of efficacy for individuals. So, we have to be carful about not thinking that this reduces every woman's risk for breast cancer uniformly. It is a population average effect and it varies across subpopulations. So, does the application contain a clear signal to the treating clinician on when to use the active control versus the new treatment?

Now, there is one other feature that is in this application that I haven't talked about because it is also a difficult one to work with analytically, but we don't have exactly the standard situation here of a test treatment versus an active control. We have three other trials in which the test treatment was compared to placebo. So, there is a little bit of additional information although, admittedly, in slightly different

populations that ODAC will have to evaluate.

That is it. Thank you.

DR. HUSSAIN: Thank you, Dr. Harrington. I think we have a couple of minutes if any member from the committee has any questions for Dr. Harrington.

Can I begin by asking why is it acceptable to borrow data from different trials to analyze when you can never do that really in therapeutic trials yet you are applying this in, you know, thousands and potentially hundreds of thousands of people?

DR. HARRINGTON: That is almost a theological question, this business about borrowing data. You know, the wording here is fascinating so one can say that we are borrowing strength from the earlier trials or one can say that we are extrapolating, and one way of saying it sounds as if you have done something absolutely wonderful and the other way sounds like you are cheating.

So, I think in this setting the reason that statisticians have been working so hard on the

methodology to look at using information from prior trials is that there are situations where an active control has declared itself to be so effective that it is extraordinarily difficult to mount a placebo-controlled trial in the next trial. So, I think as a statistician I would certainly have preferred to see here the most complicated of those designs, raloxifene, tamoxifen, placebo. But as a working statistician I also know the difficulty of mounting such a trial in context back in the late '90s.

DR. HUSSAIN: Any other questions?

[No response]

Thank you, Dr. Harrington. We will move on to the sponsor presentation. I would like to invite Dr. Krivi.

Sponsor Presentation

Introduction

DR. KRIVI: Thank you, Dr. Hussain.

[Slide]

Good morning. I am Dr. Gwen Krivi, vice president, Lilly Research Laboratories, with

responsibility for research and development on Lilly's musculoskeletal drugs and drug candidates. I am pleased to be able to introduce today's sponsor presentation regarding raloxifene for the reduction in the risk of invasive breast cancer submission to the United States Food and Drug Administration. I want to thank the members of the Oncology Drugs Advisory Committee for their careful consideration of this topic.

[Slide]

The next slide gives an outline of Lilly's presentation. Following my introduction, Dr. Steven Cummings, principal investigator of MORE, and Dr. Larry Wickerham, project officer for the STAR trial, will present the efficacy and safety data from the clinical trials which make up this submission. Dr. George Sledge, professor of medicine and pathology, Indiana University, will present the overall conclusions regarding the benefits and risks for the use of raloxifene to reduce the risk of invasive breast cancer.

[Slide]

Additional Lilly and external experts in attendance are shown on this slide. The two additional external experts participating in this session are Drs. Joseph Constantino and Norman Wolmark of NSABP. Dr. Bruce Mitlak will moderate Lilly's portion of the question and answer session.

[Slide]

Despite advances in detection and treatment, breast cancer remains a major source of mortality and morbidity both in the United States and globally, with about 178,000 cases in the United States diagnosed annually and more than 40,000 deaths annually in the U.S. attributed to breast cancer. Women, as they age, are increasingly at risk for breast cancer. Significant research and development investment is being made to enable evaluation of the level of breast cancer risk in women, and these investments are resulting in risk evaluation tools ranging from genetic markers to risk models such as Gail to imaging techniques.

Given this focus on breast cancer risk, it

is important that women have more and better options to reduce their risk of breast cancer. Tamoxifen was approved in 1998 for reduction of risk of breast cancer in women at high risk. It is under-utilized at least in part due to concerns about its safety profile.

[Slide]

Raloxifene is a member of the class of compounds commonly known as selective estrogen receptor modulators or SERMs. Raloxifene binds to estrogen receptors in various tissues. In preclinical models raloxifene has predominantly estrogen agonist activity in some tissues, for example bone, and predominantly estrogen blocking or antagonist activity in other tissues, for example breast. Raloxifene 60 mg daily, trade name Evista, was approved for prevention of osteoporosis in 1997 and for the treatment of osteoporosis in 1999. Since approval, 22 million postmenopausal women worldwide have received raloxifene treatment.

[Slide]

Early studies of raloxifene evaluated its

effect on treating breast cancer. Raloxifene demonstrated a positive effect in one invasive breast cancer treatment study and was not effective in a second such study in a different study population. This line of research was terminated because it did not appear that raloxifene would be better than other available options for the treatment of breast cancer.

In 1992 Lilly opened the IND to test raloxifene for osteoporosis treatment. The MORE Phase 3 clinical trial for osteoporosis included evaluation of the effect of raloxifene on breast cancer as a secondary endpoint.

In 1998 analysis of the three-year breast cancer data from MORE led Lilly to open an IND and begin discussion with the Oncology Division on raloxifene as a risk reduction therapy for invasive breast cancer. Furthermore, based on the three-year MORE breast cancer data and the 1998 approval of tamoxifen, NSABP opened the IND for STAR.

In 1998 Lilly also opened the IND and

initiated the RUTH study, investigating the effect of raloxifene on cardiovascular events in women at high risk for coronary heart disease.

In 1999 the CORE study was initiated to follow-up patients from MORE. The primary endpoint of the CORE study was invasive breast cancer.

During the period from 1999 to 2001 the Oncology Division and Lilly engaged in a series of communications regarding the necessity for confirmatory evidence to support the beneficial effect of raloxifene on reducing the risk of invasive breast cancer seen in MORE. In the course of these discussions, the Oncology Division encouraged Lilly to elevate the invasive breast cancer endpoint in the RUTH trial from a secondary to a primary endpoint. Further, the Oncology Division at that time suggested that data on breast cancer risk reduction from the revised RUTH trial and from STAR, if positive, would serve as confirmatory data for MORE.

Lilly followed the Oncology Division's recommendations and the totality of the data on

raloxifene's effect to reduce the risk of invasive breast cancer will be presented today. The NDA under consideration this morning was submitted in November of 2006.

[Slide]

Through this NDA submission we are requesting the addition of two indication statements to the current indication language in the U.S. Evista label. I will discuss the request in two parts, starting with the statement describing the demonstration of reduction of risk of invasive breast cancer in postmenopausal women with osteoporosis. For reference, the current indication will be shown on this and the next slide.

We are requesting the additional indication language shown on this slide to clearly communicate this newly confirmed benefit of raloxifene therapy to postmenopausal women taking or considering taking raloxifene for osteoporosis. The current product label reflects the already established favorable benefit/risk profile in this

population, and includes all efficacy and safety information from clinical trials for osteoporosis plus cardiovascular safety information including stroke death from the RUTH trial. Regarding breast cancer, the current product label states, and I quote, the effectiveness of raloxifene in reducing the risk of breast cancer has not been established, unquote.

We believe the collective data from MORE, CORE, RUTH and STAR provide substantial evidence of consistent, clinically important breast cancer risk reduction in a broad population of postmenopausal women. The current indication language should be updated to reflect this additional benefit of raloxifene.

[Slide]

The second additional indication statement we are requesting reflects the efficacy of raloxifene in reducing the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer. The STAR trial, supported by data from MORE, CORE and RUTH, establishes that

raloxifene has similar efficacy to tamoxifen in reducing the risk of invasive breast cancer in postmenopausal women at high risk of breast cancer. Furthermore, raloxifene has a favorable safety profile when compared with tamoxifen.

Therefore, we believe the totality of the data establishes a benefit/risk profile for raloxifene in postmenopausal women at high risk of breast cancer that is favorable when compared with the already approved tamoxifen. We further believe that for postmenopausal women at high risk of breast cancer raloxifene should be available as an alternative therapeutic option to tamoxifen.

[Slide]

The four studies making up this submission are shown on this slide. The data from these studies will be presented this morning. In total, more than 37,000 women participated in the STAR, RUTH, MORE and CORE trials resulting in over 76,000 patient years of exposure to raloxifene in these trials.

These studies establish the efficacy of

raloxifene in reducing the risk of invasive breast cancer in a broad population of postmenopausal women, and support the favorable benefit/risk profiles in postmenopausal women at high risk for breast cancer and postmenopausal women with osteoporosis.

I am now pleased to introduce Dr. Steven Cummings, of the San Francisco Coordinating Center, CPMC Research Institute and the University of California San Francisco, who was the principal investigator for MORE. Dr. Cummings will discuss the results of the MORE, CORE and RUTH trials.

Benefits and Risks of Evista - MORE/CORE/RUTH Trials

DR. CUMMINGS: Thank you.

[Slide]

I will describe the results from the MORE, CORE and RUTH trials.

[Slide]

MORE was the first large clinical trial of raloxifene. It was a multicenter, double-blind, placebo-controlled trial and included 7,705

postmenopausal women who had osteoporosis. Women with a history of breast cancer were excluded. Women were randomized to one of three groups, either 60 mg, 120 mg of raloxifene or placebo for three years, with a planned one-year extension. The primary objectives were to determine the effects of raloxifene on x-ray detected vertebral fractures and bone density.

[Slide]

Breast cancer was a secondary endpoint included among other outcomes that were thought to be influenced by estrogen. Specifically, the MORE protocol stated that the occurrence of breast and endometrial cancer will be assessed since the estrogen antagonist action of raloxifene on reproductive tissue is expected to have a protective effect with respect to these diseases. Therefore, in MORE we systematically assessed breast cancer cases and specifically before enrollment women were required to have mammograms and ultrasound exams with no evidence suggesting cancer. Mammograms were then done at two, three

and four years and any cases reported by clinical sites were adjudicated by a board of experts. Those experts were blinded to treatment and none were Lilly employees.

[Slide]

Since 120 mg and 60 mg of raloxifene had very similar effects, I will show data from the 60 mg group because that became the registered dose. In the MORE trial the mean age was 67 years old. Almost all of the participants were Caucasian; 12.5 percent reported a first degree family history of breast cancer; 23 percent had hysterectomies; about 29 percent had previously taken estrogen therapy.

[Slide]

Raloxifene reduced the risk of vertebral fractures by about 40 percent and it was on the basis of these results that raloxifene was then approved for the treatment of osteoporosis. I think it may be useful to know that vertebral fractures are important because they cause about six months of acute pain and disability, and some go on to cause chronic pain and impaired function.

[Slide]

During four years raloxifene reduced the risk of breast cancer by 71 percent. This translates into about three fewer cases of invasive breast cancer per 1,000 women years.

[Slide]

By the way, the results were essentially identical for the 120 mg group, as represented by the dotted line.

[Slide]

There were very few non-invasive breast cancers in MORE but no differences between the groups.

[Slide]

The reduction in risk of breast cancer was due to an 80 percent reduction in the risk of ER positive breast cancer, with no apparent effect on the much smaller number of ER negative cancers.

[Slide]

Now, at the end of MORE we extended the trial for four more years to determine whether the reduction in risk seen in the four years of MORE

continued for an additional four years. Therefore, the primary endpoint was invasive breast cancer and about 4,000 women in MORE continued into CORE.

[Slide]

The next set of slides illustrate the transition from MORE into CORE. There were three randomized groups in MORE and after a short period of screening and enrollment for CORE, those in the placebo and 60 mg groups were carried forward in their original blinded at randomized groups.

[Slide]

Since 60 mg was the registered dose at that time, those taking 120 mg were blindly reassigned to 60 mg a day.

[Slide]

CORE continued for four more years, bringing the total of those two trials to eight years of treatment.

[Slide]

In CORE at baseline we collected data to calculate the five-year risk of breast cancer using the Gail model. The Gail model is a validated

instrument for estimating a woman's risk of breast cancer for risk factors such as age and family history of breast cancer.

At baseline women in CORE had annual breast examinations. Mammograms were required at years two and four. As in the MORE trial, reports of breast cancer were adjudicated by three specialists blinded to treatment and not employed by Lilly.

[Slide]

Women with a Gail risk greater than 1.66 percent have been considered at high risk. The average five-year risk of breast cancer from the Gail model was 1.9 percent in the placebo and the raloxifene group. Just over half of women in CORE had a predicted risk of breast cancer that exceeded 1.66 percent.

[Slide]

For the CORE period there was a 56 percent significant reduction in the incidence of breast cancer. This decrease translates into three fewer cases of invasive breast cancer per 1,000 women per

year, similar to the absolute risk reduction ever seen in MORE.

[Slide]

Now, when the results were stratified by the Gail risk score, those with a risk below 1.66 percent had a 35 percent reduction in risk of breast cancer, and those above 1.66 percent had about twice the incidence of breast cancer and 65 percent reduction in that risk.

[Slide]

There was no statistically significant interaction between a woman's risk and the effect of raloxifene on risk of breast cancer. This means that the reduction in risk in these subgroups is similar to the overall reduction in risk.

[Slide]

In the subgroup assigned to 60 mg of raloxifene or placebo, in both MORE and CORE raloxifene reduced the risk of breast cancer by 60 percent.

[Slide]

Now to the RUTH trial.

[Slide]

When the RUTH trial started in 1998 it was widely believed that estrogen therapy reduced the risk of heart disease by improving lipoprotein levels and vascular function. Raloxifene had been shown to improve lipoprotein levels and also decrease levels of fibrinogen concentrations. Therefore, RUTH was designed to test the hypothesis that treatment with raloxifene would reduce the incidence of CHD or coronary heart disease.

[Slide]

So, RUTH was a randomized, placebo-controlled, double-blinded trial that enrolled over 10,000 postmenopausal women who had a high risk of coronary heart disease based on a set of risk factors. The RUTH trial was designed with the primary endpoint of the composite of heart disease events.

[Slide]

Based on discussions with the FDA, about two years into the RUTH trial while recruitment was continuing breast cancer was added as a second

primary outcome.

[Slide]

There were no statistically significant differences between groups in baseline characteristics that included a mean age of 67.5 years; 84 percent were Caucasian. The mean body mass index was 28.8; 12 percent smoked. About 14 percent had taken estrogen therapy and 6 percent had taken a combination of estrogen and progestin in the past.

[Slide]

Based on the Gail model, the average five-year risk of breast cancer was just over 1.7 percent. Forty-one percent of the participants had a high risk Gail score. Family history of cancer was found in about 10 percent; 9 percent had a history of breast biopsy; 1.7 percent had a past history of atypical hyperplasia.

[Slide]

Raloxifene had no effect on the risk of heart disease.

[Slide]

Over a median of 5.6 years of follow-up women assigned to raloxifene had a statistically significant 44 percent reduction in the risk of invasive breast cancer.

[Slide]

When these results were stratified by Gail score, those with a risk below 1.66 percent had a 51 percent reduction and those in the high risk group a 35 percent reduction in risk.

[Slide]

There was no statistically significant interaction. This means that the reduction risk in these subgroups was similar to the overall reduction in risk.

[Slide]

So, in summary, raloxifene reduced the risk of breast cancer in all three trials with a spectrum of incidence of breast cancer, 44 percent in RUTH, 71 percent in MORE and 56 percent in CORE.

[Slide]

Now I will turn to the safety of raloxifene observed in these trials.

[Slide]

In MORE raloxifene was associated with an increased risk of thromboembolic disease, including DVT and pulmonary embolus, but there was no overall difference in mortality rates. This profile was similar to that found in CORE.

[Slide]

As will be pertinent to the STAR trial, there were no significant differences in vaginal bleeding, endometrial hyperplasia, endometrial cancer or cataracts. There were, however, more hot flushes, leg cramps and peripheral edema noted in the raloxifene group.

[Slide]

Here is a summary of the of outcomes in the raloxifene or placebo group, and the difference of those number of events per 1,000 women years without invasive breast cancer, the balance of benefits and risks if one is considering osteoporosis alone.

[Slide]

If one adds invasive breast cancer

reduction this is the overall profile.

[Slide]

Note that there was no significant difference in the incidence of endometrial and uterine cancer between the raloxifene and the placebo groups in any of the trials.

[Slide]

Among women with a high risk of heart disease in the RUTH trial raloxifene increased the risk of venous thromboembolic events, had no significant effect on overall mortality, no effect on the overall risk of stroke, but there was an increased incidence of risk from death from stroke. Women in the raloxifene group had a reduced risk of clinical vertebral fractures. The details of these adverse experiences are in the briefing document.

[Slide]

Now, the current label for prevention and treatment of osteoporosis notes the increased risk of VTE, hot flushes, leg cramps and peripheral edema. Based on the RUTH trial, the label also

states Evista should not be used for the primary or secondary prevention of cardiovascular disease. Increased risk of death due to stroke occurred in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. No increased risk of stroke was seen. Consider the risk/benefit balance in women at increased risk for stroke.

[Slide]

So, the overall benefits and potential harms are more neutral for women at high risk for cardiovascular disease.

[Slide]

Raloxifene is indicated for osteoporosis. I believe that postmenopausal women who are considering raloxifene for osteoporosis should be informed about its effects on risk of breast cancer.

Thank you, and now I would like to introduce Dr. Larry Wickerham who is the project officer for STAR. Larry?

Benefits and Risks for Evista - STAR

DR. WICKERHAM: Thank you, Dr. Cummings.

[Slide]

Good morning. It is pleasure, on behalf of the NSABP investigators, to review the results of the STAR trial.

[Slide]

As you have heard, the STAR trial is actually the second NSABP breast cancer chemoprevention trial. The first study, our P1 trial, compared tamoxifen to placebo in 13,000 women at increased risk for breast cancer and the results at four years had demonstrated a 49 percent reduction in invasive breast cancer and a 50 percent reduction in non-invasive disease.

On this slide are the P1 results through seven years, demonstrating the durable nature of the benefits. Based on these P1 results and the MORE trial results that you just saw from Dr. Cummings, the NSABP designed our P2 study, a study of tamoxifen and raloxifene.

[Slide]

The STAR trial included postmenopausal

women at increased risk for future development of breast cancer. They were stratified based on their age, their Gail model scores, race, whether or not they had had a history of lobular carcinoma in situ of the breast, and whether or not they had had prior hysterectomy. They were then assigned to receive either tamoxifen or raloxifene, in a double-blinded fashion, daily for a five-year period.

[Slide]

The inclusion and exclusion criteria you see here. To be eligible for the trial women had to be postmenopausal and at least 35 years of age. Breast cancer risk eligibility was determined by history of LCIS treated by local excision or a Gail score of at least 1.66 percent or greater, that is, a risk of developing invasive breast cancer over the next five years of at least 1.66 percent.

We excluded women with a prior history of invasive breast cancer or ductal carcinoma in situ, and in order to reduce the risk of possible toxicity we also excluded women with a prior

history of deep vein thrombosis, pulmonary emboli, cerebral vascular accident, transient ischemic attack, uncontrolled atrial fibrillation, uncontrolled hypertension or uncontrolled diabetes.

[Slide]

The primary aim of the study was to determine which of the following three statements is true: Compared to tamoxifen, raloxifene significantly reduces the incidence of invasive breast cancer; compared to raloxifene, tamoxifen significantly reduces the incidence of invasive breast cancer; or, the statistical superiority of one of the treatments cannot be demonstrated and the choice of therapy should be based on benefit/risk considerations.

The trial was not designed or powered as a non-inferiority study. To have done so would have required a sample size of at least 60,000 women which was simply impractical. The study was sufficiently powered to detect clinically relevant differences and evaluate the relative benefits and risks of tamoxifen and raloxifene.

[Slide]

The primary objective of the study was, indeed, to evaluate the effects of raloxifene compared to tamoxifen in reducing the incidence of invasive breast cancer in this population of postmenopausal women.

[Slide]

Secondary objectives included evaluation of the effect on non-invasive breast cancers, endometrial cancers, ischemic heart disease, fractures of the hip, spine or wrist, toxicity and other side effects.

[Slide]

The trial began in July of 1999. We screened over 180,000 women for risk eligibility, of whom 96,000 proved to be risk eligible and in a little over five years we randomized 19,747 women. This analysis has slightly over 79,000 women years of follow-up and just over four years of average follow-up.

[Slide]

The baseline characteristics of the women

in the trial are balanced the two treatment groups and show a mean age of 58.5 years. Ninety-three percent are Caucasian; 51 percent had hysterectomy prior to entry in the study. This was not by chance alone. We gave potential participants not only their Gail score but an estimate of the risks and benefits coming into the trial. Clearly, women who had had a hysterectomy had no risk of endometrial cancer associated with tamoxifen therapy and, as a result, a higher benefit/risk ratio. Seventy-one percent of the women had at least one first degree relative with breast cancer; 9 percent had LCIS; 23 percent a history of atypical hyperplasia. And, their mean Gail scores were just over 4 percent. This translates into a lifetime risk of just over 19 percent.

[Slide]

There were 168 women in the tamoxifen group and 173 women in raloxifene who developed an invasive breast cancer during the study follow-up. The p value from the log rank test is 0.99. This slide shows the cumulative incidence curve for

invasive breast cancers over six years, with tamoxifen in blue and raloxifene in yellow. The two curves are clearly overlapping, and with close to 20,000 women in the trial there was a difference of five invasive breast cancers, with a risk ratio of 1.02.

[Slide]

The trial does not, indeed, include the placebo alone group. This was a conscious decision on the part of the NSABP when we designed the trial. As I mentioned, the results from P1 had demonstrated that tamoxifen could reduce the risk of invasive cancer by 50 percent and, as a result, we thought it inappropriate to offer a placebo alone option in the STAR trial. The Gail model allows us, however, to project that there would have been just over eight breast cancers per 1,000 women per year and that both tamoxifen and raloxifene reduced that risk to a little over four breast cancers per 1,000 women per year.

[Slide]

If we look at the various categories of

Gail scores, that is less than three percent, three to five percent, or greater than five percent, raloxifene and tamoxifen were equally effective in each of these categories.

[Slide]

The tumor characteristics of the breast cancers that did occur in both the tamoxifen and raloxifene groups were comparable when we look at receptor status, tumor size and nodal status. The women were carefully followed at regular physical exams and mammograms and as a consequence the majority of the cancers are early stage tumors.

[Slide]

Women with a history of LCIS or atypical hyperplasia clearly have a substantially increased risk for subsequent development of invasive breast cancer. In P1 this was the group of individuals who had the greatest benefit from tamoxifen and in the STAR trial tamoxifen and raloxifene were equally effective in reducing invasive breast cancer in these women with a prior history of LCIS or atypical hyperplasia.

[Slide]

Raloxifene does not appear to be as effective as tamoxifen in reducing the incidence of non-invasive breast cancer, that is, LCIS and DCIS combined. In the P1 trial tamoxifen reduced this by about 50 percent.

[Slide]

If we break out the cases into DCIS, LCIS or a mixture, the numbers become quite small and, as in the overall effect, there was no statistically significant difference.

Why would a SERM be able to prevent invasive disease but not be able to reduce non-invasive disease? Well, we are not certain why that would occur. I think the first step is to make certain that is actually accurate. The finding is not statistically significant and we plan to continue to follow these STAR ladies for as long as they are willing to be followed.

[Slide]

There were fewer uterine malignancies in the treated group. This too did not quite reach

statistical significance, in part because 51 percent of the women had a hysterectomy prior to entry into this trial and, as a result, had no risk of uterine malignancy.

[Slide]

Further diminishing the power to identify a difference was the fact that during the course of the trial there were over twice as many hysterectomies performed in the tamoxifen-treated women for benign disease. Hyperplasia, a well-known risk factor for endometrial cancer, was far more common in the tamoxifen-treated women as well.

[Slide]

There was no difference in ischemic heart disease overall between the tamoxifen and the raloxifene groups, nor were there significant differences in the individual components of myocardial infarction, severe angina, or acute ischemic syndrome.

[Slide]

Both of these drugs have been shown to

have positive effects on bone in postmenopausal women, and there was no difference in fractures overall or in the selected sites of hip, spine or wrist.

[Slide]

There were no differences in overall mortality. There was no difference in the individual categories of cancer death which includes breast cancer deaths, circulatory or vascular related deaths, or deaths from other causes.

[Slide]

Both of these agents are SERMs. Both are known to increase the risk of venous thrombolic events. However, there were far fewer DVTs and pulmonary emboli in the raloxifene-treated group. This represents a significant 30 percent reduction.

In P1, the tamoxifen versus placebo trial, there was a significant increase in the numbers of cataracts and cataract surgery in the tamoxifen-treated women. In the STAR trial raloxifene does not appear to increase the risk of

cataracts, although the normal age-related cataracts remain common in both groups of women.

[Slide]

In summary, compared to tamoxifen, raloxifene was similar in decreasing the risk of invasive breast cancer; not as effective at decreasing the risk of non-invasive disease. But raloxifene was associated with fewer adverse events related to the uterus, fewer thromboembolic events, fewer cataracts, and fewer cataract surgeries.

The results demonstrate that raloxifene is an effective agent in the prevention of invasive breast cancer and an attractive one because it has fewer serious side effects compared to tamoxifen.

Thank you. Let me stop there and I will turn the podium over to Dr. George Sledge.

Benefits and Risks of Evista - Conclusions

DR. SLEDGE: Thank you, Dr. Wickerham.

[Slide]

Colleagues and friends, it is now my pleasure to summarize the risk/benefit profile for raloxifene. Let me start by asking a fairly simple

question. Do we need a new chemoprevention agent for breast cancer?

[Slide]

Several years ago I sat on this committee during its deliberations on tamoxifen as a chemoprevention agent and, indeed, served as primary reviewer. That ODAC meeting was a contentious one and the controversy surrounding tamoxifen chemoprevention continues to this day. Despite recent improvements in diagnosis and therapy, breast cancer remains a major cause of cancer mortality. And, despite evidence that tamoxifen reduces the incidence of invasive breast cancer, few women actually use it for this purpose.

Why is this? First, I think because real toxicities limit its use. Secondly, because it is perceived both by doctors, especially the non-oncologists who prescribe the agent and high risk women, to be a cancer drug with a poor risk/benefit ratio.

[Slide]

So, what is the risk/benefit ratio like

for raloxifene? Raloxifene consistently reduced invasive breast cancers in postmenopausal women across a spectrum of risk in four large, placebo-controlled and active-controlled studies.

[Slide]

As presented by Dr. Wickerham, the primary analysis of STAR shows that the relative risk of raloxifene compared to tamoxifen is 1.02, with a confidence interval ranging from 0.82 to 1.27. Now, in the absence of a placebo group an important question is how much of tamoxifen's effect is retained?

A non-inferiority analysis was provided by Lilly to shed light on this question. The effect of tamoxifen versus placebo from the P1 study in women 50 years or older was used as a reference. This analysis showed that in STAR raloxifene retained 97 percent of tamoxifen's effect. The confidence boundaries in this analysis imply that raloxifene could retain at least 65 percent to at most 128 percent of tamoxifen's effect respectively.

[Slide]

These STAR data in my opinion suggest that raloxifene and tamoxifen are equally effective with regard to preventing invasive breast cancer. Raloxifene may be less effective in preventing non-invasive cancers, a finding that I and most of my colleagues find perplexing and lacking a plausible biologic rationale. It is inarguable, however, that invasive cancers are far more hazardous than non-invasive cancers, and I would suggest that a chemoprevention agent should be judged primarily for its ability to prevent potentially lethal cancers.

[Slide]

With regard to non-invasive cancers, the placebo-controlled trials do not deliver a consistent message, though in all three of these trials the incidence rates in both study arms are less than what might have been predicted based upon the SEER database.

[Slide]

With regard to risk, I find the picture

fairly straightforward. Raloxifene is a safer drug than tamoxifen, with significantly fewer venous thromboembolic effects, uterine side effects and cataracts.

[Slide]

Looked at in absolute terms, a woman taking raloxifene is four percent less likely to undergo a hysterectomy, 0.6 percent less likely to have a blood clot, and one percent less likely to have cataracts as a result of her treatment during five years of therapy.

[Slide]

With regard to time, expense and arguably hazard, the lower rate of serious events outweighs the slightly and, I would add, non-statistically significant higher rate of non-invasive cancers. With regard to the number needed to treat, a standard measure of therapeutic efficacy and prevention strategies, raloxifene, like tamoxifen, compares favorably with other prevention strategies. I personally take a statin for essentially the same number needed to treat the

benefit achieved with raloxifene.

[Slide]

Based upon a reasonable review of risk and benefit, postmenopausal women at high risk for the development of invasive breast cancer I think now should have a choice.

[Slide]

In addition to high risk women, women receiving raloxifene for osteoporosis also appear to benefit with regard to breast cancer risk reduction. Raloxifene is a well-established, FDA-approved agent for the treatment of osteoporosis as demonstrated by more than a decade's experience. The reduced risk of invasive breast cancer observed in MORE has been confirmed in RUTH and STAR. This is an important benefit for these women.

[Slide]

Shown here is the incidence of clinically apparent vertebral fracture on the X axis and invasive breast cancer on the Y axis in placebo assigned women from the MORE trial and, for

reference, for the women over the age of 50 from the P1 tamoxifen trial.

Though we often think of women at high risk for osteoporosis as having a lower risk of breast cancer, the data from the placebo-controlled MORE trial suggest that the risk is substantial and that the reduction in risk seen with treatment is in the same range with that seen in the P1 trial.

[Slide]

Now, the overall health benefit may, indeed, be greater if one considers the reduction in breast cancer events together with the reduction in clinical vertebral fracture events.

[Slide]

Based on this data, it is reasonable to suggest that postmenopausal women considering raloxifene for the treatment of osteoporosis should be informed about the potential additional benefit on their risk of invasive breast cancer.

[Slide]

In conclusion, since 1998 an estimated 22 million women who are postmenopausal have received

raloxifene to prevent or treat osteoporosis. Clinical trials involving more than 37,000 postmenopausal women now provide information on the benefits and risks of the use of raloxifene to prevent or reduce the risk of invasive breast cancer. The benefit/risk ratio is favorable in postmenopausal women at high risk for breast cancer and in women taking raloxifene for osteoporosis. Raloxifene, therefore, represents a reasonable alternative to tamoxifen for the prevention of invasive breast cancer.

I thank the committee for the chance to present these data.

DR. HUSSAIN: Thank you. I would like to invite Bhupinder Mann to begin the discussion for the FDA.

FDA Presentation

Medical Review

DR. MANN: Good morning.

[Slide]

I am Bhupinder Mann, one of the two medical officers who are reviewing the new drug

application 22042, and I will be presenting part of the FDA review of this application. The applicant is Eli Lilly and the drug is Evista or raloxifene hydrochloride.

[Slide]

This is the FDA Evista review team for the two new indications that we are discussing today.

[Slide]

Evista, henceforth referred to as raloxifene, is an approved drug. It is indicated for the treatment and prevention of osteoporosis in postmenopausal women. The applicant is seeking approval for raloxifene for two new indications. The first proposed new indication is the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis. The data to support this indication come from three placebo-controlled trials of raloxifene, the RUTH, the MORE and the CORE trials. I will be summarizing the FDA review of the data from these three trials.

[Slide]

The second proposed new indication is the

reduction in risk of invasive breast cancer in postmenopausal women at high risk for breast cancer. Currently, tamoxifen is approved for a similar indication in women 35 years of age or older and either pre- or postmenopausal. The data to support raloxifene for the proposed new indication shown there come from the NSABP study of tamoxifen and raloxifene, widely known as the STAR trial. The FDA review of these data will be presented by Dr. Cortazar.

[Slide]

Prior to approving raloxifene for the proposed new indications, the FDA must address the issues related to its safety and efficacy adequately. The clinical benefit of raloxifene, a reduction in the incidence of invasive breast cancer, needs to be weighed against the increased risk associated with raloxifene exposure such as an increase in the incidence of thromboembolic adverse events listed here.

[Slide]

The currently approved drug for reducing

breast cancer incidence is tamoxifen. It was approved after an Oncology Drugs Advisory Committee meeting in September of '98. Tamoxifen is indicated to reduce the incidence of breast cancer in women at high risk for breast cancer. Note here that the tamoxifen approved indication is not limited to reducing the incidence of invasive breast cancer or to the menopausal status. The supporting data for tamoxifen came from the NSABP breast cancer prevention trial P1. Women at high risk of invasive breast cancer were eligible for the trial. To be eligible, women had to be 60 years old or to have a projected five-year risk of invasive breast cancer that was equal to or greater than that of an average 60-year old woman, that is, 1.66 percent.

The risk was calculated using a modified Gail model. Women with previous breast cancer or ductal carcinoma in situ were excluded. Women with lobular carcinoma in situ treated with lumpectomy and radiation were eligible.

[Slide]

The three raloxifene placebo-controlled trials are listed here. All women who participated in these trials were postmenopausal. High breast cancer risk was not required for entry into any of these trials and the other eligibility criteria differed among them.

The first trial in this list, the RUTH trial, is the largest of the placebo-controlled trials. It enrolled women who were at high risk of coronary heart disease. Its primary endpoints are incidence of major coronary events and incidence of invasive breast cancer.

The second trial, the MORE trial, enrolled women with osteoporosis. Its primary endpoints were effect of raloxifene on the rate of new vertebral fractures and lumbar spine and femoral neck bone mineral density. Breast cancer incidence was a secondary safety endpoint in the MORE trial.

The third trial on this list, the CORE trial, was conducted after a remarkable reduction in the breast cancer incidence was observed in the MORE trial. The CORE trial was an extension of the

MORE trial. All of the eligible patients came from the MORE trial and the incidence of invasive breast cancer was the primary endpoint.

Entry of eligible patients into the CORE trial was not based on re-randomization. Approximately 62 percent of the women who were eligible elected to participate in the CORE trial.

[Slide]

The treatment arms and the exclusion criteria of the three raloxifene placebo-controlled trials are listed here. Looking at the last column, titled "exclusion criteria," one can note that the patients who were at increased risk of thromboembolic adverse events due to any prior history were excluded from these trials.

[Slide]

The efficacy results from the RUTH trial relevant to the proposed indication are shown here. Forty women in the raloxifene arm and 70 in the placebo arm developed invasive breast cancer. The respective incidence rates are 1.50 and 2.66 per 1,000 person-years. This is an absolute risk

difference of 1.16 per 1,000 person-years and it favors raloxifene. The risk of invasive breast cancer was, thus, decreased by 44 percent in the raloxifene arm compared with the placebo arm and this is statistically significant. Stage information was not available for all of the cancers diagnosed during the study. When the stage information was available, most of the cancers were early stage. Ninety-two percent of the cancers in the placebo arm and 83 percent of the cancers in the raloxifene arm were diagnosed at stage IIA or lower.

A few words here about the denominator term "person-years." This term combines the number of persons in the study and the time at risk for each person so the quantity, 1,000 person-years, can be obtained by following 1,000 persons for a year or by following 100 persons for ten years. Person-time analysis assumes that the two components, the number of persons and the time at risk, contribute equally to the event rate. This is an important drawback of the person-time

analysis and needs to be taken into account when comparing or extrapolating the results between studies with different follow-up durations.

[Slide]

This table, based on the data from the RUTH trial, is an attempt to show the safety and efficacy of raloxifene together for comparison. The first column is a list of several safety and efficacy variables. Invasive breast cancer and clinical vertebral fractures relate to evaluation of raloxifene efficacy. The other events relate to evaluation of raloxifene safety. The last but one column in this table shows the absolute risk differences between the two study arms for the incidence rates of the events shown in the first column. All of the differences are per 1,000 person-years. Absolute risks of invasive breast cancer and clinical vertebral fractures are 1.16 and 1.30 lower in the raloxifene arm. However, the absolute risks for death due to stroke, stroke, deep venous thrombosis and pulmonary embolism, all of these are higher in the raloxifene arm.

If the listed benefits are considered together and compared with the listed adverse events considered together, the overall efficacy and overall safety appear about equal. However, such a lumping together and comparison are crude at best and are inconclusive. One is making the assumption that avoiding any one outcome has the same importance to a patient as avoiding any of the other outcomes. The impact of a DVT on an individual is quite different than that of invasive breast cancer. Different individuals are likely to weigh the risks and benefits differently. This is a fairly complex issue and requires further discussion by this committee.

[Slide]

The results from the MORE trial are shown here. Breast cancer incidence was the safety endpoint in this trial. Eleven women in the raloxifene arm and 38 in the placebo arm developed invasive breast cancers. The respective incidence for it were 1.26 and 4.36 per 1,000 person-years, an absolute risk difference of 3.10 in favor of

raloxifene. Thus, the risk of invasive breast cancer was decreased by a very remarkable 71 percent in the raloxifene arm compared with the placebo arm. Stage information was not available for all the cancers diagnosed during the study. However, just as was seen in the RUTH trial, when the stage information was available most of the cancers were early stage. Ninety-six percent of the cancers in the placebo arm and 90 percent of the cancers in the raloxifene arm were diagnosed at stage IIA or lower.

[Slide]

This table is similar to the one shown for the RUTH trial and the last but one column shows the absolute risk differences for selected efficacy and safety endpoints. All of the differences are per 1,000 person-years. The absolute risk of invasive breast cancer and clinical vertebral fractures are lower in the raloxifene arm, 3.10 and 5.19 per 1,000 person-years respectively. Also, the absolute risks of death due to stroke and stroke are lower. All of these risk reductions

favor raloxifene. However, the absolute risks of deep venous thrombosis and pulmonary embolism are higher in the raloxifene arm. Based on the magnitude of reductions in the incidence of invasive breast cancer and clinical vertebral fractures, the overall benefit from raloxifene appears to outweigh the overall risk.

[Slide]

The results from the CORE trial are shown here. Recall that the CORE trial was an extension of the MORE trial. Study entry was not based on re-randomization, and approximately 62 percent of the eligible women from the MORE trial elected to participate in the CORE trial. Nineteen of 2,716 women in the raloxifene arm and 20 of 1,274 women in the placebo arm developed invasive breast cancers. The respective incidence rates are 2.43 and 5.41 per 1,000 person-years with an absolute risk difference of 2.98 and that favors raloxifene. The risk of invasive breast cancer was decreased by 55 percent in the raloxifene arm compared with the placebo arm. As was seen in the RUTH and the

MORE trials, when the breast cancer stage at diagnosis was known most cancers were early stage. Ninety-four percent of the cancers in the placebo arm and 90 percent of the cancers in the raloxifene arm were diagnosed at stage IIA or lower.

[Slide]

This table is for the CORE trial. Once again, the last but one column shows the absolute risk differences per 1,000 person-years for the efficacy and safety events listed in the first column. The absolute risks for invasive breast cancer and clinical vertebral fractures are lower in the raloxifene arm, 2.98 and 0.28 per 1,000 person-years respectively. These risk reductions favor raloxifene. However, the absolute risks of death due to stroke, stroke, deep venous thrombosis and pulmonary embolism, all of these are higher in the raloxifene arm. Based on these data, the overall safety concerns appear to outweigh the benefits.

[Slide]

This is our attempt to summarize the

benefits and the risks observed in the three raloxifene placebo-controlled trials. Wide variation is seen across the three comparisons. The absolute risk reductions in the incidence of invasive breast cancer in the RUTH, MORE and CORE trials are 1.16, 3.10, 2.98 per 1,000 person-years respectively.

As raloxifene is currently approved for prevention and treatment of osteoporosis, invasive breast cancer reduction can be considered an additional benefit. However, the effect size of this benefit is hard to quantify with any precision. In each of the three trials when the raloxifene and placebo arms are compared an increase in the incidence of thromboembolic adverse events is seen in the raloxifene arm.

In the RUTH trial the increased incidence of thromboembolic adverse events appears to be of the same magnitude as the reduced incidence of invasive breast cancers and clinical vertebral fractures.

In the MORE trial the benefits seem to

outweigh the risks easily. However, in the CORE trial the increased risk of thromboembolic adverse events seems much larger when compared to the benefit. Based on these data, it is difficult to determine if the overall benefit clearly outweighs the overall risk.

[Slide]

Finally to summarize these data in terms of raloxifene efficacy, raloxifene reduced the incidence of invasive breast cancers in three placebo-controlled trials. However, wide variation in the effect size was observed. Based on the absolute risk reduction in the RUTH trial, the number of women needed to treat for one year to prevent one invasive breast cancer is 862. But the number needed to treat is 323 when based on the risk reduction seen in the MORE trial, and it is 335 when based on the risk reduction seen in the CORE trial.

It should be noted here that it would be incorrect to compare the number needed to treat from the placebo-controlled raloxifene trials with

the number needed to treat obtained from the NSABP breast cancer prevention trial P1. In that trial all the women were at high risk of developing breast cancer and reductions in the incidence of both invasive and non-invasive breast cancers were observed.

To summarize these data in terms of raloxifene safety, an excess of thromboembolic adverse events was seen in the raloxifene arms in each of the three placebo-controlled trials. So, to conclude, the benefits of raloxifene are a variable reduction in the risk of invasive breast cancers and prevention and treatment of osteoporosis. These benefits need to be weighed against the increased risk of thromboembolic adverse events seen in each of the three placebo-controlled trials. These comparisons are complex and they require clinical judgment. Accordingly, we are seeking the advice of the Oncology Drugs Advisory Committee.

Thank you very much for your attention. Next, Dr. Cortazar will present part of the FDA

review.

Medical Review

DR. CORTAZAR: Good morning.

[Slide]

I am going to present the FDA review of the STAR trial submitted to support the marketing approval of raloxifene for the reduction in risk of invasive breast cancer in postmenopausal women at high risk for breast cancer.

[Slide]

First, I want to point out that tamoxifen is the only drug currently approved to reduce the incidence of breast cancer in women at high risk for the disease. The NSABP P1 was a trial that supported the approval of tamoxifen for the reduction of breast cancer incidence. This slide shows the P1 trial data supplied by Lilly. These data are different from the published article and the tamoxifen label because it shows only the group of women who were 50 years of age or older in order to be comparable to the postmenopausal patient population in the STAR trial.

The data showed that tamoxifen had a decreased incidence of invasive breast cancer and a non-significant decrease in the incidence of non-invasive breast cancer. There was also a non-significant reduction in the number of clinical vertebral fractures. There was no overall difference in mortality or death due to stroke. Women treated with tamoxifen had an increased risk of stroke, deep vein thrombosis, pulmonary embolism and endometrial cancer. The risk of endometrial cancer almost approaches the benefit of breast cancer reduction. The rate of cataract and cataract surgery was slightly higher in the tamoxifen group. That is not shown on this slide.

[Slide]

The STAR trial is a randomized, Phase 3 multicenter, double-blind study in 19,747 postmenopausal women who were at increased risk for the development of breast cancer. The study was conducted mainly in the U.S. and a few centers in Canada. Women were randomly assigned to receive either 20 mg of tamoxifen plus a placebo or 60 mg

of raloxifene plus a placebo daily for a period of five years. Stratification factors included age, race, history of LCIS, prior hysterectomy and absolute risk of invasive breast cancer within five years. The study was not generally designed to show non-inferiority.

[Slide]

Women were eligible for the trial if they were postmenopausal and their projected five-year probability of developing breast cancer using the modified Gail score was at least 1.66 percent, or if they were postmenopausal and they had a history of lobular carcinoma in situ treated by excision only.

[Slide]

The protocol eligibility excluded women with prior history of invasive breast cancer, ductal carcinoma in situ or previous lobular carcinoma in situ treated by mastectomy, radiation or systemic adjuvant therapy. The STAR trial also excluded women at risk for blood clots and strokes, namely, those with a history of vascular events,

uncontrolled hypertension or diabetes and uncontrolled atrial fibrillation. As you can see, this was a highly selected group. Not only were the participants at high risk for breast cancer, but they were also selected to minimize the risks of adverse events.

[Slide]

The primary endpoint of the STAR study is the occurrence of invasive breast cancer. A pathologic diagnosis of invasive breast cancer as indicated by the pathology report from the clinical center pathologist was required. Blocks of tumor tissue were to be submitted to the NSABP for central review.

[Slide]

The breast cancer incidence in the STAR trial is summarized in this slide. Number of events, the incidence rate per 1,000 women per year and the relative risk with 95 percent confidence interval between raloxifene and tamoxifen are shown. IR is the incidence per 1,000 women years or the annual incidence per 1,000 women. There are

relatively few events in the study. Therefore, it is necessary to express the results as incidence per 1,000 women. Relative risk higher than 1 indicates higher incidence of events with raloxifene compared to tamoxifen.

After a median follow-up of 4.32 years, the incidence of invasive breast cancer was not reduced among women assigned to raloxifene compared to tamoxifen. Tamoxifen is 168 cases, raloxifene 173 cases. The incidence of non-invasive breast cancer was also higher among women treated with raloxifene, raloxifene 83 cases and tamoxifen 60 cases.

[Slide]

The major outcomes of the STAR trial are summarized in this table. ARD means the absolute risk difference. We need to consider not only relative risk but ARD to understand the size of the change in risk. Risk reduction may be large but if the initial risk is small the absolute benefit is small. A negative ARD means fewer events are associated with raloxifene compared with tamoxifen.

A positive ARD means a higher number of events is also seen with raloxifene compared with tamoxifen. The limits of the confidence intervals can be used to assess the statistical significance of the benefits or risks of raloxifene therapy.

In general, if the upper limit of the confidence interval is less than 1, then a statistically significant benefit or risk exists. Again, the number of breast cancer events were higher in the raloxifene treatment arm. There are no significant differences in overall mortality, stroke related mortality, strokes or clinical vertebral fractures. A higher number of cases of deep vein thrombosis and pulmonary embolism were seen in women receiving tamoxifen compared to women receiving raloxifene.

[Slide]

In the STAR trial a higher number of endometrial cancers were observed in the tamoxifen group compared to the raloxifene group, 37 cases versus 23 cases. This difference was not statistically different. This was calculated in

patients with a uterus at baseline. Cataract formation in women without cataracts at baseline was higher in women taking tamoxifen. During the study follow-up period the number of known cancer-related hysterectomies was also higher in the tamoxifen group. Hot flushes and leg cramps were also more frequent in the women taking tamoxifen. Edema was more frequent in women taking raloxifene.

[Slide]

To summarize the safety events, women taking tamoxifen had a higher incidence of deep vein thrombosis, pulmonary embolism, endometrial cancer, cataracts, known cancer-related hysterectomy, hot flushes and leg cramps. Women taking raloxifene had a higher number of ovarian cancer and edema.

[Slide]

The STAR trial failed to achieve the primary endpoint which was to demonstrate superiority of raloxifene compared to tamoxifen in reducing the risk of invasive breast cancer.

Therefore, a non-prespecified non-inferiority analysis was conducted in an attempt to demonstrate efficacy. Using historical data from a subpopulation of women aged 50 years or older from the P1 study a relative risk of 0.47 for tamoxifen versus placebo was derived.

[Slide]

The following are the requirements to demonstrate non-inferiority. First, it is necessary to have an active control. In this case tamoxifen, which is the only approved drug for this indication, is the active control.

Second, an active control effect size should be estimated. This should be done based on a meta-analysis of historical randomized studies to estimate the tamoxifen effect. In this case, a subpopulation from a single P1 study was used to estimate the tamoxifen effect size.

Lastly, it is necessary to have a prespecified percent of active control effect size to be retained. In this case, retention was not prespecified at the science stage of the trial.

Also, this is the first non-inferiority analysis in a breast cancer prevention study and no standard has been set. ODAC advice will be requested.

[Slide]

This slide shows the results of the P1 study in the subgroup of patients 50 years or older. In this group there was a 53 percent reduction in the risk of invasive breast cancer with tamoxifen.

[Slide]

Again, using the P1 data as the tamoxifen effect size, a non-inferiority analysis based on the number of invasive breast cancer occurrences in the STAR trial indicated that raloxifene maintained at least 65 percent of the effect estimated in the NSABP-1 trial. The 95 percent confidence interval was very wide, 65 percent to 128 percent.

In a non-inferiority trial we want to rule out a prespecified percent retention which is dependent on the disease setting and available therapy. Here we can say that based on the STAR trial results raloxifene may lose up to 35 percent

of the tamoxifen effect with 95 percent confidence. This is the primary regulatory concern. However, since a percent of retention was not prespecified and we have not considered a non-inferiority claim in a prevention setting whether 65 percent retention is adequate is unknown.

[Slide]

In the adjuvant breast cancer setting, the FDA requires at least a 75 percent retention of an active control effect for an efficacy claim based on non-inferiority. In a prevention trial it is not clear what the minimum percent retention of an active control effect should be for an efficacy claim based on non-inferiority.

[Slide]

Also, for the sake of comparison, a non-inferiority analysis based on the number of all breast cancer occurrences in the STAR trial indicated that raloxifene maintained at least 53 percent of the tamoxifen effect estimated in the P1 trial. Again, the 95 percent confidence intervals were wide, 53 percent to 109 percent.

[Slide]

This slide summarizes the important issues in the STAR trial. The STAR trial did not show superiority of raloxifene compared to tamoxifen for reducing the risk of invasive breast cancer. A non-inferiority analysis shows that raloxifene could lose up to 35 percent of the tamoxifen effect in reducing the risk of invasive breast cancer. A non-inferiority analysis shows that raloxifene could lose up to 47 percent of the tamoxifen effect in reducing the risk of all breast cancer. There were fewer non-invasive breast cancers in the tamoxifen group compared to the raloxifene group.

[Slide]

When compared to raloxifene, tamoxifen has increased risk of deep vein thrombosis, pulmonary embolism, endometrial cancer, non-related hysterectomy, cataracts, hot flushes and leg cramps.

[Slide]

Does the benefit or raloxifene, invasive breast cancer reduction of at least 65 percent of