

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-042**

**MEDICAL REVIEW**

Division Director Summary Review of a Type 6 New Drug Application

NDA: 22-042

Drug: EVISTA® (raloxifene hydrochloride) Tablet

Applicant: Eli Lilly and Company

Date: September 13, 2007

EVISTA was approved for the prevention of osteoporosis in postmenopausal women in 1997 and for the treatment of postmenopausal women with osteoporosis in 1999. This Type 6 NDA was submitted on November 14, 2006 and seeks approval of the following two new indications:

**1.2 Reduction in the Risk of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis**

EVISTA is indicated for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis.

**1.3 Reduction in the Risk of Invasive Breast Cancer in Postmenopausal Women at High Risk of Invasive Breast Cancer**

EVISTA is indicated for the reduction in risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer.

The effect in the reduction in the incidence of breast cancer was shown in a study of postmenopausal women at high risk for breast cancer with a 5-year planned duration with a median follow-up of 4.3 years. Twenty-seven percent of the participants received drug for 5 years. The long-term effects and the recommended length of treatment are not known.

High risk of breast cancer is defined as at least one breast biopsy showing lobular carcinoma in situ (LCIS) or atypical hyperplasia, one or more first-degree relatives with breast cancer, or a 5-year predicted risk of breast cancer  $\geq 1.66\%$  (based on the modified Gail model). Among the factors included in the modified Gail model are the following: current age, number of first-degree relatives with breast cancer, number of breast biopsies, age at menarche, nulliparity or age of first live birth. Healthcare professionals can obtain a Gail Model Risk Assessment Tool by dialing 1-800-545-5979. Currently, no single clinical finding or test result can quantify risk of breast cancer with certainty.

After an assessment of the risk of developing breast cancer, the decision regarding therapy with EVISTA should be based upon an individual assessment of the benefits and risks.

EVISTA does not eliminate the risk of breast cancer. Patients should have breast exams and mammograms before starting EVISTA and should continue regular breast exams and mammograms in keeping with good medical practice after beginning treatment with EVISTA.

Important Limitations of Use for Breast Cancer Risk Reduction

- There are no data available regarding the effect of EVISTA on invasive breast cancer incidence in women with inherited mutations (BRCA1, BRCA2) to be able to make specific recommendations on the effectiveness of EVISTA.
- EVISTA is not indicated for the treatment of invasive breast cancer or reduction of the risk of recurrence.
- EVISTA is not indicated for the reduction in the risk of noninvasive breast cancer.

Safety and efficacy for reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis were demonstrated in three clinical trials of EVISTA 60 mg/day vs. placebo (RUTH, MORE and CORE):

The MORE trial was a randomized, placebo-controlled, double-blind, multinational osteoporosis treatment study in 5,133 postmenopausal women. The effect of EVISTA on the incidence of breast cancer was assessed as a secondary safety endpoint. After a median of 4 years on treatment, EVISTA reduced the incidence of invasive breast cancer by 71% compared with placebo (HR 0.29; 95% CI 0.15, 0.56). There were 11 invasive breast cancers in 2,557 women on the EVISTA arm compared to 38 in 2,576 women on the placebo arm.

The CORE trial was a follow-up study conducted in a subset of 4,011 postmenopausal women originally enrolled in the MORE trial. Women were not re-randomized; the treatment assignment from the osteoporosis treatment trial was carried forward to this study. After a median of 3 additional years on treatment, EVISTA reduced the incidence of invasive breast cancer by 56% compared with placebo (HR 0.44; 99% CI 0.24, 0.83). There were 19 invasive breast cancers in 2,716 women on the EVISTA arm compared to 20 in 1,274 women on the placebo arm.

The efficacy data and selected safety outcomes from the MORE and CORE studies are summarized in Table 8 from the proposed draft label:

**Table 8: EVISTA (60 mg Once Daily) vs. Placebo on Outcomes in Postmenopausal Women with Osteoporosis**

Outcomes	MORE 4 years					CORE <sup>a</sup> 4 years				
	Placebo (N=2576)		EVISTA (N=2557)		HR (95% CI) <sup>b</sup>	Placebo (N=1286)		EVISTA (N=2725)		HR (95% CI) <sup>b</sup>
	n	IR <sup>b</sup>	n	IR <sup>b</sup>		n	IR <sup>b</sup>	n	IR <sup>b</sup>	
Invasive <sup>c</sup>	38	4.36	11	1.26	0.29 (0.15, 0.56) <sup>d</sup>	20	5.41	19	2.43	0.44 (0.24, 0.83) <sup>d</sup>
ER <sup>b,c</sup> positive	29	3.33	6	0.69	0.20 (0.08, 0.49)	15	4.05	12	1.54	0.37 (0.17, 0.79)
ER <sup>b,c</sup> negative	4	0.46	5	0.57	1.23 (0.33, 4.60)	3	0.81	6	0.77	0.95 (0.24, 3.79)

ER <sup>b,c</sup> unknown	5	0.57	0	0.00	N/A <sup>b</sup>	2	0.54	1	0.13	N/A <sup>b</sup>
Noninvasive <sup>c,e</sup>	5	0.57	3	0.34	0.59 (0.14, 2.47)	2	0.54	5	0.64	1.18 (0.23, 6.07)
Clinical vertebral fractures	107	12.27	62	7.08	0.57 (0.42, 0.78)	N/A <sup>b</sup>				
Death	36	4.13	23	2.63	0.63 (0.38, 1.07)	29	7.76	47	5.99	0.77 (0.49, 1.23)
Death due to stroke	6	0.69	3	0.34	0.49 (0.12, 1.98)	1	0.27	6	0.76	2.87 (0.35, 23.80)
Stroke	56	6.42	43	4.91	0.76 (0.51, 1.14)	14	3.75	49	6.24	1.67 (0.92, 3.03)
Deep vein thrombosis	8	0.92	20	2.28	2.50 (1.10, 5.68)	4	1.07	17	2.17	2.03 (0.68, 6.03)
Pulmonary embolism	4	0.46	11	1.26	2.76 (0.88, 8.67)	0	0.00	9	1.15	N/A <sup>b</sup>
Endometrial and uterine cancer <sup>f</sup>	5	0.74	5	0.74	1.01 (0.29, 3.49)	3	1.02	4	0.65	0.64 (0.14, 2.85)
Ovarian cancer	6	0.69	3	0.34	0.49 (0.12, 1.95)	2	0.54	2	0.25	0.47 (0.07, 3.36)
Hot flashes	151	17.31	237	27.06	1.61 (1.31, 1.97)	11	2.94	26	3.31	1.12 (0.55, 2.27)
Peripheral edema	134	15.36	164	18.73	1.23 (0.98, 1.54)	30	8.03	61	7.77	0.96 (0.62, 1.49)
Cholelithiasis	45	5.16	53	6.05	1.18 (0.79, 1.75)	12	3.21	35	4.46	1.39 (0.72, 2.67)

<sup>a</sup> CORE was a follow-up study conducted in a subset of 4011 postmenopausal women who originally enrolled in the MORE. Women were not re-randomized; the treatment assignment from MORE was carried forward to this study. At CORE enrollment, the EVISTA group included 2725 total patients with 1355 patients who were originally assigned to raloxifene 60 mg once daily and 1370 patients who were originally assigned to raloxifene 120 mg at MORE randomization.

<sup>b</sup> Abbreviations: CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; IR = annual incidence rate per 1000 women; N/A = not applicable.

<sup>c</sup> Included 1274 patients in placebo and 2716 patients in EVISTA who were not diagnosed with breast cancer prior to CORE enrollment.

<sup>d</sup>  $p < 0.05$ , obtained from the log-rank test, and not adjusted for multiple comparisons in MORE.

<sup>e</sup> All cases were ductal carcinoma in situ.

<sup>f</sup> Only patients with an intact uterus were included (MORE: placebo = 1999, EVISTA = 1950; CORE: placebo = 1008, EVISTA = 2138).

The RUTH trial was a randomized, placebo-controlled, double-blind, multinational study in 10,101 postmenopausal women at increased risk of coronary events. After a median of 5 years on treatment, EVISTA reduced the incidence of invasive breast cancer by 44% compared with placebo (HR 0.56; 95% CI 0.38, 0.83). There were 40 invasive breast cancers in 5,044 women on the EVISTA arm compared to 70 in 5,057 women on the placebo arm. Efficacy and selected safety outcomes are presented in Table 9 from the proposed draft label:

**Table 9: EVISTA (60 mg Once Daily) vs. Placebo on Outcomes in Postmenopausal Women at Increased Risk for Major Coronary Events**

Outcomes	Placebo <sup>a</sup> (N=5057)		EVISTA <sup>a</sup> (N=5044)		HR (95% CI) <sup>b</sup>
	n	IR <sup>b</sup>	n	IR <sup>b</sup>	
Invasive	70	2.66	40	1.50	0.56 (0.38, 0.83) <sup>c</sup>
ER <sup>b</sup> positive	55	2.09	25	0.94	0.45 (0.28, 0.72)
ER <sup>b</sup> negative	9	0.34	13	0.49	1.44 (0.61, 3.36)
ER <sup>b</sup> unknown	6	0.23	2	0.07	0.33 (0.07, 1.63)
Noninvasive <sup>d</sup>	5	0.19	11	0.41	2.17 (0.75, 6.24)
Clinical vertebral fractures	97	3.70	64	2.40	0.65 (0.47, 0.89)
Death	595	22.45	554	20.68	0.92 (0.82, 1.03)
Death due to stroke	39	1.47	59	2.20	1.49 (1.00, 2.24)
Stroke	224	8.60	249	9.46	1.10 (0.92, 1.32)
Deep vein thrombosis	47	1.78	65	2.44	1.37 (0.94, 1.99)
Pulmonary embolism	24	0.91	36	1.35	1.49 (0.89, 2.49)
Endometrial and uterine cancer <sup>e</sup>	17	0.83	21	1.01	1.21 (0.64 - 2.30)
Ovarian cancer <sup>f</sup>	10	0.41	17	0.70	1.69 (0.78, 3.70)
Hot flashes	241	9.09	397	14.82	1.68 (1.43, 1.97)
Peripheral edema	583	22.00	706	26.36	1.22 (1.09, 1.36)
Cholelithiasis <sup>g</sup>	131	6.20	168	7.83	1.26 (1.01, 1.59)

<sup>a</sup> Note: There were a total of 76 breast cancer cases in the placebo group and 52 in the EVISTA group. For two cases, one in each treatment group, invasive status was unknown.

<sup>b</sup> Abbreviations: CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; IR = annual incidence rate per 1000 women.

<sup>c</sup>  $p < 0.05$ , obtained from the log-rank test, after adjusting for the co-primary endpoint of major coronary events.

<sup>d</sup> All cases were ductal carcinoma in situ.

<sup>e</sup> Only patients with an intact uterus were included (placebo = 3882, EVISTA = 3900).

<sup>f</sup> Only patients with at least one ovary were included (placebo = 4606, EVISTA = 4559).

<sup>g</sup> Only patients with an intact gallbladder at baseline were included (placebo = 4111, EVISTA = 4144).

In the MORE, CORE, and RUTH trials, the reduction in incidence of breast cancer was primarily due to a reduction in the incidence of ER-positive invasive breast cancers. There was no reduction in ER-negative invasive breast cancers, and there was no difference in incidence of noninvasive breast cancers between the EVISTA and placebo groups. Most invasive breast cancers were stage I or II. The number of women required to be treated for one year to prevent an invasive breast cancer in one woman ranged from 323 to 862 in the three trials.

Safety and efficacy for reduction in the risk of invasive breast cancer in postmenopausal women at high risk of breast cancer were evaluated in the STAR trial. The effects of EVISTA 60 mg/day versus tamoxifen 20 mg/day over 5 years on reducing the incidence of invasive breast cancer were assessed in 19,747 postmenopausal women in a randomized, double-blind trial. EVISTA was not superior to tamoxifen in reducing the incidence of invasive breast cancer. The observed incidence rates of invasive breast cancer were EVISTA 4.4 and tamoxifen 4.3 per 1000 women per year (risk ratio 1.02; 95% CI 0.82, 1.27). The results from a non-inferiority analysis are consistent with

EVISTA potentially losing up to 35% of the tamoxifen effect on reduction of invasive breast cancer. Fewer noninvasive breast cancers occurred in the tamoxifen group compared to the EVISTA group. EVISTA had a lower incidence of deep vein thrombosis, pulmonary embolism, cataracts, cataract surgery, endometrial hyperplasia and hysterectomy than tamoxifen, and there was a trend for a lower incidence of endometrial cancer. Efficacy and selected safety outcomes are summarized in Table 10 from the draft label:

**Table 10: EVISTA (60 mg Once Daily) vs. Tamoxifen (20 mg Once Daily) on Outcomes in Postmenopausal Women at Increased Risk for Invasive Breast Cancer**

Outcomes	EVISTA (N=9751)		Tamoxifen (N=9736)		RR (95% CI) <sup>a</sup>
	n	IR <sup>a</sup>	n	IR <sup>a</sup>	
Invasive breast cancer	173	4.40	168	4.30	1.02 (0.82, 1.27)
ER <sup>a</sup> positive	115	2.93	120	3.07	0.95 (0.73, 1.24)
ER <sup>a</sup> negative	52	1.32	46	1.18	1.12 (0.74, 1.71)
ER <sup>a</sup> unknown	6	0.15	2	0.05	2.98 (0.53, 30.21)
Noninvasive breast cancer <sup>b</sup>	83	2.12	60	1.54	1.38 (0.98, 1.95)
DCIS <sup>a</sup>	47	1.20	32	0.82	1.46 (0.91, 2.37)
LCIS <sup>a</sup>	29	0.74	23	0.59	1.26 (0.70, 2.27)
Uterine cancer <sup>c</sup>	23	1.21	37	1.99	0.61 (0.34, 1.05)
Endometrial hyperplasia <sup>c</sup>	17	0.90	100	5.42	0.17 (0.09, 0.28)
Hysterectomy <sup>c</sup>	92	4.84	246	13.25	0.37 (0.28, 0.47)
Ovarian cancer <sup>d</sup>	18	0.66	14	0.52	1.27 (0.60, 2.76)
Ischemic heart disease <sup>e</sup>	138	3.50	125	3.19	1.10 (0.86, 1.41)
Stroke	54	1.36	56	1.42	0.96 (0.65, 1.42)
Deep vein thrombosis	67	1.69	92	2.35	0.72 (0.52, 1.00)
Pulmonary embolism	38	0.96	58	1.47	0.65 (0.42, 1.00)
Clinical vertebral fractures	58	1.46	58	1.47	0.99 (0.68, 1.46)
Cataracts <sup>f</sup>	343	10.34	435	13.19	0.78 (0.68, 0.91)
Cataract surgery <sup>f</sup>	240	7.17	295	8.85	0.81 (0.68, 0.96)
Death	104	2.62	109	2.76	0.95 (0.72, 1.25)
Edema <sup>g</sup>	741	18.66	664	16.83	1.11 (1.00, 1.23)
Hot flashes	6748	169.91	7170	181.71	0.94 (0.90, 0.97)

<sup>a</sup> Abbreviations: CI = confidence interval; DCIS = ductal carcinoma in situ; ER = estrogen receptor; IR = annual incidence rate per 1000 women; LCIS = lobular carcinoma in situ; RR = risk ratio for women in the EVISTA group compared with those in the tamoxifen group.

<sup>b</sup> Of the 60 noninvasive breast cases in the tamoxifen group, 5 were mixed types. Of the 83 noninvasive breast cancers in the raloxifene group, 7 were mixed types.

<sup>c</sup> Only patients with an intact uterus at baseline were included (tamoxifen = 4739, EVISTA = 4715).

<sup>d</sup> Only patients with at least one intact ovary at baseline were included (tamoxifen = 6813, EVISTA = 6787).

<sup>e</sup> Defined as myocardial infarction, severe angina, or acute ischemic syndromes.

<sup>f</sup> Only patients who were free of cataracts at baseline were included (tamoxifen = 8342; EVISTA = 8333).

<sup>g</sup> Peripheral edema events are included in the term edema.

EVISTA is associated with an increased risk of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. An increased risk of death due to stroke was observed in the RUTH trial. Other adverse reactions (>2% and more common than with

placebo) include hot flashes, leg cramps, peripheral edema, flu syndrome, arthralgia, and sweating.

### Clinical Reviews

The MORE, CORE, and RUTH studies were reviewed by Dr. Bhupinder Mann who made the following recommendation on regulatory action:

Evista® (Raloxifene hydrochloride, 60 mg) is recommended for approval for reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis. Both the safety and efficacy of Evista® for this indication have been demonstrated adequately in the placebo-controlled trials.

Regarding risk management activity, Dr. Mann recommended a boxed warning on the increased risk of venous thromboembolism and deaths due to stroke for the following reasons:

Efficacy and safety of Evista® for reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis have been demonstrated in placebo-controlled trials; however, safe and effective use of Evista® after its marketing approval (for the above indication) will require providing clear and complete information of the risks and benefits to the patients. This can be assured by inclusion of adequate and easily accessible information in the label, and by use of a Medicine Guide. This would assure that the relevant information is easily available to the patients and they can make an informed decision.

No phase 4 commitments were recommended.

The STAR trial was reviewed by Dr. Patricia Cortazar who made the following recommendation on regulatory action:

The efficacy claims in support of this application are based on the results of four randomized controlled studies. The STAR trial supports the efficacy and safety for the reduction in the risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer. This 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 of  $\geq 1.66$  or lobular carcinoma in situ (LCIS) treated by excision only. The median Evista exposure was 3.5 years. At a median follow-up of 4.3 years, Evista treatment arm was not better than tamoxifen. In an attempt to demonstrate efficacy, a non-prespecified non-inferiority analysis was conducted using historical data from a subpopulation of women age 50 years or older from the NSABP P-1 study. The results of the non-inferiority analysis are consistent with Evista potentially losing up to 35% of the tamoxifen effect on reduction in the incidence of invasive breast cancer seen in the NSABP-P1 trial comparing tamoxifen with placebo. In addition there were fewer non-invasive breast cancers in the tamoxifen group (60) than the Evista

group (83),  $p=0.057$ . For all breast cancers the non-inferiority analysis results are consistent with Evista potentially losing up to 47% of the tamoxifen effect in the NSABP P-1 trial. In the STAR trial Evista had a lower incidence of deep vein thrombosis, pulmonary embolism, cataract surgery and hysterectomy compared to tamoxifen and there was a strong trend for a lower incidence of endometrial cancer. This must be balanced against the possibility that Evista loses up to 35% of the tamoxifen effect on reduction of invasive breast cancer.

Efficacy and safety for the reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis were demonstrated in 22,000 postmenopausal women studied in three placebo controlled trials (RUTH, MORE and CORE). Median Evista exposure in the three trials ranged from 3 to 5 years. Evista reduces the risk of invasive breast cancer. However, 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 in the three trials are Stage I or II and thus have a high cure rate. The number of women required to be treated for one year to prevent an invasive breast cancer in one woman ranges from 323 to 862 in the three trials. This is achieved at a cost of an increase in serious adverse events such as deep vein thrombosis, pulmonary embolism, and possibly stroke death.

We recommend approval of Evista for the reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer, based on the results of the four randomized trials and the ODAC recommendation from July 24, 2007. The Evista risk/benefit ratio for reduction in the risk of invasive breast cancer is narrow. Therefore, each individual postmenopausal woman's risk/benefit ratio must be carefully considered.

Dr. Cortazar made the following recommendation regarding risk management activities:

A Black Box Warning was recommended to clearly state the increased risk of venous thromboembolism and increased risk of death due to stroke.

A Medication Guide to detail the risks and benefits of treatment with Evista (in easily understandable language) must be provided to the patients taking Evista.

No phase 4 commitments were recommended.

The clinical team leader review by Dr. John Johnson made the following recommendation:

This reviewer recommends approval of Evista for both of the proposed new indications. The wording of the second new indication should be changed from "high risk for breast cancer" to "high risk for invasive breast cancer". This recommendation is conditional on revised labeling that clearly conveys the benefits and risks and a MedGuide for patients. These should warn that Evista

increases the risk for thromboembolic events. This information should also indicate that a decision whether to take Evista is important and the correct choice may differ from woman to woman. Each individual PM woman should carefully consider her own potential benefits and risks. Women must be aware that Evista does not prevent invasive breast cancer and regular mammograms and breast examinations (at least yearly) are essential. If women use Evista as an excuse for skipping or delaying screening for breast cancer, any Evista benefit is likely to be lost.

### Statistical Review and Evaluation

The statistical review by Dr. Kun He had the following conclusions and recommendations:

The applicant submitted the analyses and results of four trials, STAR, RUTH, MORE and CORE, to seek registration of raloxifene for two indications: “reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer”, and “reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis”. Raloxifene is currently approved for the treatment of osteoporosis and prevention of osteoporosis.

The data and analyses from STAR trial, which supports the indication “reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer”, failed to demonstrate the superiority of raloxifene over tamoxifen. The applicant performed a non-inferiority analysis, which was not planned in the original design, to compare raloxifene to tamoxifen. The result of the non-inferiority analysis indicated that raloxifene may lose up to 35% tamoxifen effect, but there were many problems involved in this non-inferiority analysis. Raloxifene had more events in several safety categories while had fewer events in other safety categories compared to tamoxifen.

The data and analyses from RUTH, MORE and CORE trials, which support the indication “reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis”, showed that there were fewer invasive breast cancer events in raloxifene-treated subjects than that in placebo-treated subjects. However, one should note that in RUTH trial the incidence of the invasive breast cancer was amended as a co-primary endpoint, in MORE trial the incidence of the invasive breast cancer was a secondary safety endpoint, and in CORE trial subjects were not randomized between two treatment arms. In addition, raloxifene-treated subjects had more exposure to thromboembolic adverse events than those placebo-treated subjects numerically.

This supplemental application was discussed at the Oncology Drugs Advisory Committee (ODAC) on July 24, 2007. The committee recommends approval for both indications.

The final regulatory action should be based on clinical judgment and acceptability of risk-benefit profile.

The secondary statistical review by Dr. Rajeshwari Sridhara made the following comments regarding the collective evidence supporting approval.

This application is a supplemental application for consideration of approval of raloxifen for the reduction of invasive breast cancer in postmenopausal women (1) with osteoporosis and (2) at high risk for invasive breast cancer. Raloxifen is an approved drug product and was first approved in 1997 for the prevention of osteoporosis and then approved in 1999 for the treatment of osteoporosis. Since then an estimated over 20 million women have been treated with raloxifen. Thus raloxifen has demonstrated benefit in the treatment and prevention of osteoporosis, albeit serious adverse reactions such as, deep vein thrombosis, pulmonary embolism, and possibly stroke death that have been observed and reported.

The data from the RUTH trial along with the supportive data from the MORE and CORE studies support the claim of efficacy with respect to reduction in invasive breast cancer in postmenopausal women with osteoporosis. It is to be noted that raloxifene is already an approved product for this population.

Although there appears to be raloxifene treatment effect with respect to reducing invasive breast cancer incidence in post-menopausal women at high risk for invasive breast cancer based on the results of the STAR study and supported by the three relatively large placebo controlled studies, the precise percentage of retention of tamoxifen effect is debatable as outlined above. Given that these women are healthy subjects, the benefit and risk have to be carefully considered. Whether the benefits outweigh the risks of the use of raloxifene in this population is deferred to clinical judgment.

#### Clinical Inspection Summary

The Clinical Inspection Summary by Dr. Lauren Iacono-Connors provided the following overall assessment of findings and general recommendations:

For the STAR study the data collected by Dr. Grant, Dr. Robidoux, Dr. Moroose, and Dr. Fehrenbacher appear reliable. Three of the four EIRs were available for review at the time this CIS was written. Observations noted above regarding the site of Dr. Fehrenbacher are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

For the RUTH study the data collected by Dr. Ensrud, Dr. Barrett-Connor and Dr. Cauley appear reliable. All 3 EIRs were available for review in support of the CIS. A Form FDA 483 was issued to Dr. Ensrud regarding her conduct of the RUTH

study. No other Form FDA 483s were issued. Dr. Ensrud failed to conduct the study in accordance with the investigational plan. For Dr. Ensrud's site the sample audit revealed that approximately 17% of the subjects audited (4 of 23 subjects) did not meet the protocol-specified inclusion/exclusion criteria at the time they were enrolled. Therefore, the audit suggests that approximately 17% of all randomized subjects at this site may not have met one or more inclusion/exclusion criteria at the time of enrollment. The review division may wish to evaluate the sponsor-reported protocol deviations for this site relative to that reported by other sites for the RUTH study.

The following details on the four ineligible patients at Dr Ensrud's site are provided:

Subject 5652 was participating in another clinical study at the time of randomization. The sponsor noted in a letter to the site dated June 4, 1999 (~ 2 months post subject randomization) the protocol deviation and authorized a waiver for this subject to continue in the RUTH study and cautioned the site.

Subject 5751 was randomized into the study and received drug but had taken estrogen or progesterone-containing compounds within 3 months prior to screening and within 6 months of study drug initiation. The sponsor waiver was on file.

Subject 5882 was taking a drug for hyperlipidemia at the time of the screening visit. LDL labs done at the time showed the subject had an LDL below 147. Because the subject was actively taking Zocor at that time the subject met entry criteria. Prior to the randomization visit the subject stopped taking a drug for hyperlipidemia and therefore, based on available lab screening data, no longer met enrollment criteria. The sponsor waiver was on file.

Subject 5875 was reportedly a diabetic but was managed by dietary control and no other medication. The subject was randomized into the study based on an outdated blood glucose level indicating elevation within an inclusion criteria threshold. The subject did not return to the site for study enrollment until approximately 6 months after the initial screening labs were taken. A subsequent blood glucose level was taken at that time and showed that the current blood glucose level no longer supported subject enrollment. The study monitor was contacted by the site for guidance. The monitor stated that the subject had "boarder line" values for elevated glucose and suggested the site "retest again" if the subject was willing or if not to just use the outdated blood glucose test results to support randomization. The subject was randomized at that time without retesting for blood glucose levels. A study-required follow up blood glucose level showed that the subject had elevated glucose levels. The protocol deviation was never reported to the sponsor.

*Reviewer Comment: These protocol inclusion/exclusion violations would not materially affect the study conclusions.*

### Clinical Pharmacology Review

The Clinical Pharmacology Review by Dr. Julie Bullock provided the following summary of the additional clinical pharmacology information submitted with this application:

In addition to the studies submitted to support the efficacy claim, the sponsor submitted a biomarker study (GGHW) in patients with primary breast cancer. The primary objective was to determine the short-term biologic effect of raloxifene treatment on an intermediate endpoint marker, Ki67, which is a proliferation-associated nuclear antigen. Subjects received either raloxifene 60 mg QD, raloxifene 300 mg BID or placebo for 14 days. Sparse samples for pharmacokinetics (Day 10 and 14) along with levels for Ki67, estrogen receptor and progesterone receptor measures (baseline and end of study) were taken throughout the study. No significant correlation between steady-state concentrations and change in Ki67 was observed upon analysis and no patient factors or laboratory measurements were found to influence the pharmacokinetics (PK) of raloxifene.

There was no formal PK/PD analysis done by the sponsor for the reduction in risk of breast cancer. The primary study supporting efficacy (GGIO) had sparse sampling from 250 of 10,000 patients under one dose level (60 mg QD) which made it difficult to elucidate a formal concentration/response relationship. In addition, the intrinsic and extrinsic factor results from study GGIO indicated that smoking, alcohol, age, weight or race had no effect on the steady state concentration of raloxifene. These results are identical to what was concluded for intrinsic and extrinsic factors with the original osteoporosis NDA.

The review concluded that the clinical pharmacology information is considered acceptable and did not make any labeling recommendations.

### Chemistry, Manufacturing and Controls Review

The CMC review by Dr. Sarah Pope recommended approval and granting of the categorical exclusion.

### Labeling Reviews

Labeling recommendations by Dr. Brenda Gierhart of the Division of Metabolic and Endocrine Products dated 8/13/07 were discussed and resolved during internal labeling meetings.

Labeling recommendations from Dr. Iris Masucci of the SEALD team dated 8/21/07 were discussed during internal labeling meetings.

A DSRCS review of the Medication Guide by Sharon Mills was completed on 8/30/07. The recommendations were discussed and resolved during internal labeling meetings.

Oncologic Drugs Advisory Committee

This application was discussed at the July 24, 2007 meeting of the Oncologic Drugs Advisory Committee. The committee voted on the following two questions:

***Indication: "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 of invasive breast cancer reduction in these trials must be weighed against the Evista adverse effects.

1. Is the risk/benefit ratio favorable for use of Evista to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis? VOTE.

*Vote :            Yes = 8                    No = 6            Abstain = 1*

***Indication: "Reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer"***

In the STAR trial comparing Evista with tamoxifen in post-menopausal 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% 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% of the tamoxifen effect in the NSABP P-1 trial.

2. 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? VOTE.

*Vote :            Yes = 10                    No = 4            Abstain = 1*

Conclusions

I concur with the recommendations of the medical reviewers and the medical team leader that the application should be approved, that a boxed warning should be added to the package insert, and that a Medication Guide is appropriate. Agreement has been reached

with the applicant on the contents of the package insert and the Medication Guide. The sponsor has agreed to comply with 21 CFR 208.24(d). There are no outstanding issues.

Robert L. Justice, M.D.  
Director  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Office of New Drugs  
Center for Drug Evaluation and Research

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MEDICAL OFFICER

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**Clinical Review** NDA 22042 Evista® (Raloxifene HCL)  
Patricia Cortazar, M.D.,

## **CLINICAL REVIEW**

Application Type: NDA # 22042  
Submission Number: 000  
Letter Date: November 13, 2006  
PDUFA Goal Date: September 14, 2007

Reviewers Names: Patricia Cortazar, M.D.

Team Leader: John R. Johnson, M.D.

Review Completion Date: September 6, 2007

Established Name: Evista  
Therapeutic Class: SERM  
Applicant: Lilly Research Laboratories  
Priority Designation: Standard

Indication:

“The reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer”

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## 1. EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

The efficacy claims in support of this application are based on the results of four randomized controlled studies. The STAR trial supports the efficacy and safety for the *reduction in the risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer*. This 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 of  $\geq 1.66$  or lobular carcinoma in situ (LCIS) treated by excision only. The median Evista exposure was 3.5 years. At a median follow-up of 4.3 years, Evista treatment arm was not better than tamoxifen. In an attempt to demonstrate efficacy, a non-prespecified non-inferiority analysis was conducted using historical data from a subpopulation of women age 50 years or older from the NSABP P-1 study. The results of the non-inferiority analysis are consistent with Evista potentially losing up to 35% of the tamoxifen effect on reduction in the incidence of invasive breast cancer seen in the NSABP-P1 trial comparing tamoxifen with placebo. In addition there were fewer non-invasive breast cancers in the tamoxifen group (60) than the Evista group (83),  $p=0.057$ . For all breast cancers the non-inferiority analysis results are consistent with Evista potentially losing up to 47% of the tamoxifen effect in the NSABP P-1 trial. In the STAR trial Evista had a lower incidence of deep vein thrombosis, pulmonary embolism, cataract surgery and hysterectomy compared to tamoxifen and there was a strong trend for a lower incidence of endometrial cancer. This must be balanced against the possibility that Evista loses up to 35% of the tamoxifen effect on reduction of invasive breast cancer.

Efficacy and safety for the *reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis* were demonstrated in 22,000 postmenopausal women studied in three placebo controlled trials (RUTH, MORE and CORE). Median Evista exposure in the three trials ranged from 3 to 5 years. Evista reduces the risk of invasive breast cancer. However, 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 in the three trials are Stage I or II and thus have a high cure rate. The number of women required to be treated for one year to prevent an invasive breast cancer in one woman ranges from 323 to 862 in the three trials. This is achieved at a cost of an increase in serious adverse events such as deep vein thrombosis, pulmonary embolism, and possibly stroke death.

We recommend approval of Evista for the reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer, based on the results of the four randomized trials and the ODAC recommendation from July 24, 2007. The Evista risk/benefit ratio for reduction in the risk of invasive breast cancer is narrow. Therefore, each individual postmenopausal woman's risk/benefit ratio must be carefully considered.

## **1.2 Recommendation on Postmarketing Actions**

### **1.2.1 Risk Management Activity**

A Black Box Warning was recommended to clearly state the increased risk of venous thromboembolism and increased risk of death due to stroke.

A Medication Guide to detail the risks and benefits of treatment with Evista (in easily understandable language) must be provided to the patients taking Evista.

### **1.2.2 Required Phase 4 Commitments**

None.

### **1.2.3 Other Phase 4 Requests**

None

## **1.3 Summary of Clinical Findings**

### **1.3.1 Brief Overview of Clinical Program**

Evista is marketed for the treatment (1999) and prevention (1997) of osteoporosis in postmenopausal women. Results of four double-blind randomized trials are submitted in support of two new indications: 1) "Reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis" and 2) "Reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer". Since the proposed new indications are for patients that do not have cancer, a special careful consideration of the risk/benefit ratio is required.

The RUTH, MORE and CORE trials are placebo controlled. The STAR trial has an active control (tamoxifen). The most important data supporting the proposed new indications comes from the RUTH and STAR trials. Data from the MORE and CORE trials are less important for the following reasons. The MORE trial was not a breast cancer prevention trial. The primary endpoints were clinical vertebral fracture and bone mineral density of the lumbar spine and femoral neck. Breast cancer incidence was assessed only as a safety endpoint. The CORE trial was a continuation of the MORE

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trial. Breast cancer was added as the primary endpoint. However, patients were not re-randomized and prior randomization was lost because only approximately 52% of the MORE patients participated in the CORE trial. Only about 42% of MORE patients received study drug (Evista or placebo) in the CORE trial.

### 1.3.2 Efficacy

Results of the RUTH, CORE and MORE placebo-controlled studies indicate that Evista reduces the risk of invasive breast cancer. However, 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 Stage I or II and thus have a high cure rate. This is achieved at a cost of an increase in serious adverse events such as deep vein thrombosis, pulmonary embolism, and possibly stroke death.

In the RUTH trial comparing Evista with Placebo, 5044 women were treated with Evista every day for a median of five years to prevent 30 invasive breast cancers, almost all Stage I or II. Described another way, 862 women must be treated for one year to prevent an invasive breast cancer in one woman.

The studies provide less support for the proposed new indication to reduce the risk of invasive breast cancer in postmenopausal women at high risk. 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 of  $\geq 1.66$  or lobular carcinoma in situ (LCIS) treated by excision only. Evista was not better than tamoxifen. Non-inferiority analysis results are consistent with Evista losing up to 35% of the tamoxifen effect on the incidence of invasive breast cancer seen in the NSABP-P1 trial comparing tamoxifen with placebo. In addition there were fewer non-invasive breast cancers in the tamoxifen group (60) than the Evista group (83),  $p=0.057$ . For all breast cancers the non-inferiority analysis results are consistent with Evista losing up to 47% of the tamoxifen effect in the NSABP P-1 trial. ODAC advice was requested on whether these results were acceptable in view of the Evista adverse effects.

The efficacy results in the RUTH, MORE, CORE and STAR trials must be weighed against the increased risk of deep vein thrombosis, pulmonary embolism and possibly stroke death. A careful consideration of the risk/benefit ratio is especially important for these two proposed new indications in healthy post menopausal women.

### 1.3.3 Safety

In general the protocols for the STAR, RUTH, MORE and CORE trials excluded women who were at risk for deep vein thrombosis, pulmonary embolism or stroke with exception of the RUTH trial where patients were at increased risk of coronary adverse events and presumably at increased stroke risk. Thus it is unlikely the incidence of Evista

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serious adverse events will be less in general use than in the clinical trials. We can not expect to improve the clinical trial results in general use by precautions and warnings in the Evista labeling.

In the STAR trial, when compared to tamoxifen, Evista has a decreased risk of deep vein thrombosis, pulmonary embolism, endometrial cancer, non-cancer related hysterectomy, cataracts, hot flashes and leg cramps. Women taking raloxifene had a higher number of ovarian cancer and edema.

In the three placebo controlled trials, an increase in the incidence of thromboembolic adverse events is seen in the raloxifene arm. In the RUTH trial only, the absolute risks of death due to stroke are higher in the Evista treatment arm. There is a statistically significant increase in the incidence of hot flashes, leg cramps and peripheral edema in patients treated with Evista in the RUTH and MORE trials. In RUTH trial, there is a greater incidence of cholelithiasis in Evista compared with placebo assigned patients.

### **1.3.4 Dosing Regimen and Administration**

The recommended dose of Evista for the reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis or in women at high risk of invasive breast cancer is one daily 60 mg tablet, which is the same dose recommended for the osteoporosis indication.

### **1.3.5 Drug-Drug Interactions**

#### **Cholestyramine**

Concomitant administration of cholestyramine with Evista is not recommended. Although not specifically studied, it is anticipated that other anion exchange resins would have a similar effect. Evista should not be co-administered with other anion exchange resins.

#### **Warfarin**

If Evista is given concomitantly with warfarin or other warfarin derivatives, prothrombin time should be monitored more closely when starting or stopping therapy with Evista.

#### **Other Highly Protein-Bound Drugs**

Evista should be used with caution with certain other highly protein-bound drugs such as diazepam, diazoxide, and lidocaine. Although not examined, Evista might affect the protein binding of other drugs. Raloxifene is more than 95% bound to plasma proteins.

#### **Systemic Estrogens**

The safety of concomitant use of Evista with systemic estrogens has not been established and its use is not recommended.

#### **Other Concomitant Medications**

Evista can be concomitantly administered with ampicillin, amoxicillin, antacids, corticosteroids, and digoxin. The concomitant use of Evista and lipid-lowering agents has not been studied.

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### **1.3.6 Special Populations**

Evista was studied in a postmenopausal population.

#### **Pregnancy**

Pregnancy Category X. Evista should not be used in women who are or may become pregnant. Evista may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. In rabbit studies, abortion and a low rate of fetal heart anomalies (ventricular septal defects) occurred in rabbits at doses  $\geq 0.1$  mg/kg ( $\geq 0.04$  times the human dose based on surface area,  $\text{mg}/\text{m}^2$ ), and hydrocephaly was observed in fetuses at doses  $\geq 10$  mg/kg ( $\geq 4$  times the human dose based on surface area,  $\text{mg}/\text{m}^2$ ). In rat studies, retardation of fetal development and developmental abnormalities (wavy ribs, kidney cavitation) occurred at doses  $\geq 1$  mg/kg ( $\geq 0.2$  times the human dose based on surface area,  $\text{mg}/\text{m}^2$ ). Treatment of rats at doses of 0.1 to 10 mg/kg (0.02 to 1.6 times the human dose based on surface area,  $\text{mg}/\text{m}^2$ ) during gestation and lactation produced effects that included delayed and disrupted parturition; decreased neonatal survival and altered physical development; sex- and age-specific reductions in growth and changes in pituitary hormone content; and decreased lymphoid compartment size in offspring. At 10 mg/kg, raloxifene disrupted parturition, which resulted in maternal and progeny death and morbidity. Effects in adult offspring (4 months of age) included uterine hypoplasia and reduced fertility; however, no ovarian or vaginal pathology was observed.

#### **Nursing Mothers**

Evista should not be used by lactating women. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when raloxifene is administered to a nursing woman.

#### **Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

#### **Geriatric Use**

Of the total number of patients in placebo-controlled clinical studies of Evista, 61% were 65 and over, while 15.5% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on clinical trials, there is no need for dose adjustment for geriatric patients.

#### **Renal Impairment**

Evista should be used with caution in patients with moderate or severe renal impairment. In the osteoporosis treatment and prevention trials, raloxifene concentrations in women with mild renal impairment are similar to women with normal creatinine clearance. When a single dose of 120 mg raloxifene HCl was administered to 10 renally impaired males [7 moderate impairment ( $\text{CrCl} = 31 - 50$  mL/min); 3 severe impairment ( $\text{CrCl} \leq 30$  mL/min)] and to 10 healthy males ( $\text{CrCl} > 80$  mL/min), plasma raloxifene concentrations were 122% ( $\text{AUC}_{0-\infty}$ ) higher in renally impaired patients than those of healthy volunteers. Raloxifene should be used with caution in patients with moderate or severe renal impairment.

#### **Hepatic Impairment**

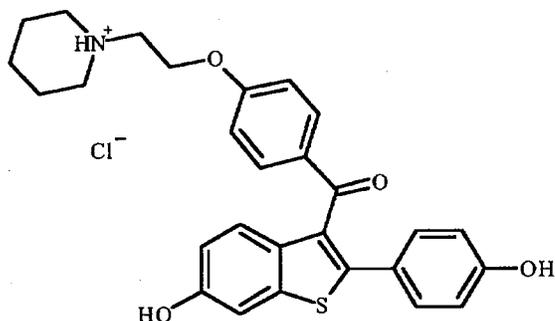
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Evista should be used with caution in patients with hepatic impairment. The disposition of raloxifene was compared in 9 patients with mild (Child-Pugh Class A) hepatic impairment (total bilirubin ranging from 0.6 to 2 mg/dL) to 8 subjects with normal hepatic function following a single dose of 60 mg raloxifene HCl. Apparent clearance of raloxifene was reduced 56% and the half-life of raloxifene was not altered in patients with mild hepatic impairment. Plasma raloxifene concentrations were approximately 150% higher than those in healthy volunteers and correlated with total bilirubin concentrations. The pharmacokinetics of raloxifene has not been studied in patients with moderate or severe hepatic impairment. Raloxifene should be used with caution in patients with hepatic impairment.

## 2. INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Evista (raloxifene hydrochloride) is an estrogen agonist/antagonist, commonly referred to as a selective estrogen receptor modulator (SERM) that belongs to the



benzothiophene class of compounds. The chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride. Raloxifene hydrochloride (HCl) has the empirical formula  $C_{28}H_{27}NO_4S \cdot HCl$ , which corresponds to a molecular weight of 510.05. Raloxifene HCl is an off-white to pale-yellow solid that is very slightly soluble in water.

Evista is supplied in a tablet dosage form for oral administration. Each Evista tablet contains 60 mg of raloxifene HCl, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include anhydrous lactose, carnauba wax, crospovidone, FD&C Blue No. 2 aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, modified pharmaceutical glaze, polyethylene glycol, polysorbate 80, povidone, propylene glycol, and titanium dioxide.

**2.2 Currently Available Treatment for Indications**

Novaldex (tamoxifen) is the only FDA approved therapy to reduce the incidence of breast cancer in women at high risk for breast cancer. “High risk” is defined as women at least 35 years of age with a 5-year predicted risk of breast cancer  $\geq$  1.67%, as calculated by the GailModel. The basis for approval for this indication was the Breast Cancer Prevention Trial (BCPT, NSABP P-1), which was a double-blind, randomized, placebo-controlled trial with a primary objective to determine whether 5 years of tamoxifen therapy (20 mg/day) would reduce the incidence of invasive breast cancer in women at high risk for the disease

The first trial that showed tamoxifen had an effect decreasing the incidence of breast cancer was on NSABP Protocol B-14, which examined tamoxifen versus placebo in patients with node-negative, estrogen-receptor-positive, invasive breast cancers. In NSABP B-14, contralateral breast cancers occurred 50% less frequently in the group receiving tamoxifen. The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) overview showed a similar reduction in the occurrence of contralateral breast cancer.

In NSABP P-1 trial, approximately 100,000 women underwent risk assessment screening, and 13,388 women were randomized into the trial. The Gail Model was used to calculate predicted breast cancer risk for women who were less than 60 years of age and did not have lobular carcinoma in situ (LCIS). The Gail Model used the following risk factors: age; number of first-degree female relatives with breast cancer; previous breast biopsies; presence or absence of atypical hyperplasia; nulliparity; age at first live birth; and age at menarche. A 5-year predicted risk of breast cancer of  $\geq$  1.67% was required for entry into the trial.

The trial results demonstrate that tamoxifen reduced the risk of invasive breast cancer by 44% (86 cases-NOLVADEX, 156 cases-placebo;  $p < 0.00001$ ; relative risk (RR)=0.56, 95% CI: 0.43-0.72). The decreased risk occurred in women of all ages entered in the trial and in women with a history of lobular carcinoma in situ (LCIS) or atypical hyperplasia. In addition, tamoxifen reduced the risk of noninvasive breast cancer by 50% ( $p < 0.002$ ). In this study, there was no impact of tamoxifen on overall or breast cancer-related mortality. See Table below for major outcomes of the NSABP P-1 Trial.

**Table 1 Major Outcomes of the NSABP P 1 Trial**

<b>TYPE OF EVENT</b>	<b># OF EVENTS</b>		<b>RATE/1000 WOMEN/YEAR</b>		<b>95% CI</b>	
	<b>PLACEBO</b>	<b>NOLVADEX</b>	<b>PLACEBO</b>	<b>NOLVADEX</b>	<b>RR</b>	<b>LIMITS</b>
Invasive Breast Cancer	156	86	6.49	3.58	0.56	0.43-0.72
Age $\leq$ 49	59	38	6.34	4.11	0.65	0.43-0.98
Age 50-59	46	25	6.31	3.53	0.56	0.35-0.91
Age $\geq$ 60	51	23	7.17	3.22	0.45	0.27-0.74
Risk Factors for Breast Cancer						
History, LCIS						
No	140	78	6.23	3.51	0.56	0.43-0.74
Yes	16	8	12.73	6.33	0.50	0.21-1.17
History, Atypical Hyperplasia						

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No	138	84	6.37	3.89	0.61	0.47-0.80
Yes	18	2	8.69	1.05	0.12	0.03-0.52
No. First Degree Relatives						
0	32	17	5.97	3.26	0.55	0.30-0.98
1	80	45	5.81	3.31	0.57	0.40-0.82
2	35	18	8.92	4.67	0.52	0.30-0.92
≥3	9	6	13.33	7.58	0.57	0.20-1.59
5-Year Predicted Breast Cancer Risk (as calculated by the Gail Model)						
≤2.00%	31	13	5.36	2.26	0.42	0.22-0.81
2.01-3.00%	39	28	5.25	3.83	0.73	0.45-1.18
3.01-5.00%	36	26	5.37	4.06	0.76	0.46-1.26
≥5.00%	50	19	13.15	4.71	0.36	0.21-0.61
DCIS	35	23	1.47	0.97	0.66	0.39-1.11
Fractures (protocol-specified sites)						
Hip	20	9	0.84	0.38	0.45	0.18-1.04
Wrist <sup>2</sup>	74	69	3.11	2.91	0.93	0.67-1.29
Total Ischemic Events						
Myocardial Infarction	59	61	2.47	2.57	1.04	0.71-1.51
Fatal	27	27	1.13	1.13	1.00	0.57-1.78
Nonfatal	8	7	0.33	0.29	0.88	0.27-2.77
Angina <sup>3</sup>	19	20	0.79	0.84	1.06	0.54-2.09
Acute Ischemic Syndrome <sup>4</sup>	12	12	0.50	0.50	1.00	0.41-2.44
Uterine Malignancies (among women with an intact uterus) <sup>10</sup>	20	22	0.84	0.92	1.11	0.58-2.13
Endometrial Adenocarcinoma <sup>10</sup>	17	57				
Uterine Sarcoma <sup>10</sup>	17	53	0.71	2.20		
	0	4	0.0	0.17		
Stroke <sup>5</sup>						
Transient Ischemic Attack	24	34	1.00	1.43	1.42	0.82-2.51
	21	18	0.88	0.75	0.86	0.43-1.70
Pulmonary Emboli <sup>6</sup>						
	6	18	0.25	0.75	3.01	1.15-9.27
Deep-Vein Thrombosis <sup>7</sup>						
	19	30	0.79	1.26	1.59	0.86-2.98
Cataracts Developing on Study <sup>8</sup>						
	483	540	22.51	25.41	1.13	1.00-1.28
Underwent Cataract Surgery <sup>8</sup>	63	101	2.83	4.57	1.62	1.18-2.22
Underwent Cataract Surgery <sup>9</sup>	129	201	5.44	8.56	1.58	1.26-1.97

<sup>1</sup>Two women had hip and wrist fractures

<sup>2</sup>Includes Colles' and other lower radius fractures

<sup>3</sup>Requiring angioplasty or CABG

<sup>4</sup>New Q-wave on ECG; no angina or elevation of serum enzymes; or angina requiring hospitalization without surgery

<sup>5</sup>Seven cases were fatal; three in the placebo group and four in the NOLVADEX group

<sup>6</sup>Three cases in the NOLVADEX group were fatal

<sup>7</sup>All but three cases in each group required hospitalization

<sup>8</sup>Based on women without cataracts at baseline (6,230-Placebo, 6,199-NOLVADEX)

<sup>9</sup>All women (6,707-Placebo, 6,681-NOLVADEX)

<sup>10</sup>Updated long-term follow-up data (median 6.9 years) from NSABP P-1 study added after cut-off for the other information in this table.

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### **2.3 Availability of Proposed Active Ingredient in the United States**

Evista was approved for the prevention of osteoporosis in postmenopausal women (NDA # 20-815) on 9 December 1997, with approval of the osteoporosis indication on 30 September 1999.

### **2.5 Presubmission Regulatory Activity**

Evista was initially developed for prevention and treatment of osteoporosis in postmenopausal women (IND 39,503). On December 9, 1997, Evista was approved for prevention of osteoporosis, based on a two-year prevention trial and a two-year interim analysis of the 3-year treatment trial (NDA 20-815) and subsequently approved for the treatment of osteoporosis on September 30, 1999.

Based on secondary data collected under secondary endpoints of the MORE (GGGK) trial, the sponsor observed there was a decrease in the incidence of breast cancer in those women taking raloxifene compared to placebo; as well as a decrease in low density lipoprotein cholesterol and other markers of atherosclerotic and coronary disease. On October 21, 1998, IND 57,137 was opened to facilitate discussions regarding breast cancer prevention as a potential indication for Evista.

On November 3, 1998 a Pre-IND meeting took place with representatives from NSABP, Lilly, Zeneca and DDOP, to discuss plans for enrollment and conduct of the P-2 (STAR) trial in women at high risk for breast cancer. NSABP filed IND 57,427 to initiate the P-2 (STAR) trial on December 3, 1998.

On January 28, 1999, FDA and the sponsor discussed a potential NDA submission for raloxifene to reduce the incidence of breast cancer. The sponsor was informed that data from study GGGK could be supportive for an NDA but did not by itself constitute adequate and well-controlled evidence of effectiveness. The CORE (Continuing Outcomes Relevant to Evista) study was started to address some of the problems identified in the MORE (GGGK) study with respect to the breast cancer endpoint, such as poorly documented baseline status, short and lack of consistent follow-up.

In a meeting on 11 May 1999 between Lilly and DDOP, DDOP encouraged Lilly to elevate the invasive breast cancer endpoint from a secondary to a primary endpoint and split the alpha ( $p < 0.05$ ) with the proposed primary coronary endpoint in the RUTH trial. Lilly revised the GGIO (RUTH) protocol to provide for breast cancer and coronary endpoints.

In November 2004, Lilly applied for Orphan Drug Status based on the failure to reasonably recover costs associated with development of raloxifene for the breast cancer risk reduction indication during the exclusivity period. Evista was granted Orphan Drug Designation on July 2005.

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A Pre-NDA meeting took place on May 25, 2005, to discuss primarily the organization and format of raloxifene sNDA submission based on data from four Phase 4- clinical studies. NSABP P-2 or STAR trial is an active comparator trial of 19,747 women treated with either raloxifene HCL or tamoxifen citrate. Study GGGK or MORE trial, a 3-year placebo-controlled study of 7705 women was reviewed by DMEDP for approval of osteoporosis in postmenopausal women (NDA 20-815). This study was extended for an additional 12 months and contains additional breast cancer data. Approximately 4000 women continued in the study extension, GGJY or CORE, for further evaluation of raloxifene's effect on risk reduction of invasive breast cancer. Finally, study GGIO or RUTH is a placebo-controlled study in 10,101 postmenopausal women at risk for coronary heart disease and has two co-primary endpoints: (1) reduction in risk of invasive breast cancer and (2) reduction in risk of major acute coronary events.

November 2005 with representatives from Lilly, NSABP, NCI and DDOP to discuss primarily the organization and content of information of data from P-2 supporting the breast cancer risk reduction indication. The following important issues were discussed:

- The trial SAP was discussed and FDA agreed that the SAP appeared to be acceptable for testing superiority of raloxifene to tamoxifen but the SAP did not include a non-inferiority hypothesis testing.
- In lieu of the clinical study report, the sponsor proposed to submit a package composed of the study protocol, STAR trial manuscript, summary tables for the adverse events, self-reported symptoms and blood test results and data files. FDA stated that the proposed package was incomplete and information that was lacking included: clinical sites information and number of patients enrolled, demographics, removal from study and protocol violations, non-allowed concomitant medications, patients characteristics including prognostic factors and data on treatment compliance, delays and modifications.

While still blinded to the results of the P-2 trial, Lilly proposed a non-inferiority analysis for P-2 and submitted this statistical plan to IND 57,137 on January 30, 2006.

Following data lock in February 2006, the sponsor informed FDA that results of study GGIO indicated a neutral effect on the coronary endpoint (e.g., no difference between raloxifene and placebo on the coronary endpoint in these women with, or at risk of, coronary events), but a positive effect on breast cancer risk reduction. Although there was no statistically significant increase in strokes, there was a statistically significant difference between raloxifene and placebo treatments with regard to stroke death ( $p=0.0499$ ). This safety signal was communicated via a press release reviewed by DMEP and subsequent discussions on proposed label language for a warning about stroke death. At this time, the sponsor also stated that the results of the P-2 trial did not show superiority of either raloxifene or tamoxifen, but did provide a safer profile, particularly endometrial cancer.

On November 30, 2006, the sponsor submitted the NDA.

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### **3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

#### **3.1 CMC**

The submission contained no new Chemistry, Manufacturing and Controls information with the exception of an updated request for a categorical exclusion. Based on the Applicant's updated request and 21 CFR 25.21, this request is granted. See Sarah Pope CMC Review for additional information.

#### **3.2 Animal Pharmacology/Toxicology**

No new animal pharmacology/toxicology data were submitted with this NDA submission. Given the available extensive clinical experience with raloxifene, animal pharmacology toxicology data is not very useful.

### **4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

#### **4.1 Sources of Clinical Data**

The sNDA consisted of an electronic submission of STAR trial, clinical study report, CRFs and datasets.

#### **4.2 Tables of Clinical Studies**

The following studies were submitted to support the Evista approval for the two indications. The STAR trial supported the approval of the prevention of invasive breast cancer in women at high risk for invasive breast cancer.

**Table 2 Studies submitted to support the Evista Application**

<b>Study Title</b>	<b>Study Name (Abbreviation)</b>	<b>Short Protocol Name</b>	<b>Study Protocol</b>
Study of Tamoxifen and Raloxifene	STAR	P-2	NSABP P-2
Raloxifene Use for The Heart	RUTH	GGIO	H3S-MC-GGIO
Multiple Outcomes of Raloxifene Evaluation	MORE	GGGK	H3S-MC-GGGK
Continuing Outcomes Relevant to Evista	CORE	GGJY	H3S-MC-GGJY

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### 4.3 Review Strategy

The applicant submitted data to support two new proposed indications. The data were reviewed by two DDOP medical officers:

The data supporting the proposed indication, reduction in the risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer were reviewed by Patricia Cortazar, MD. Data from active control trial STAR were reviewed.

The data supporting the proposed indication, reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis, were reviewed by Medical Officer Bhupinder S Mann. Data from the three placebo controlled trials, RUTH, MORE, and CORE were reviewed.

### 4.4 Data Quality and Integrity

DSI audited the following study sites for data integrity for the STAR trial. The data from each of these sites was reported as reliable.

**Table 3 Audited study sites in the STAR trial**

Inspected Entity	City, State/County	Protocol	Inspection Dates	EIR Received Date	Field Classification
Rebecca Moroosse, M.D.	Orlando, Florida	P-2 (STAR)	April 2-11, 2007	May 2, 2007 FLA-DO	NAI
Michael Grant, M.D.	Dallas, Texas	P-2 (STAR)	March 27 – April 2, 2007	April 17, 2007 DAL-DO	NAI
Louis Fehrenbacher, M.D.	Vallejo, California	P-2 (STAR)	TBD	Pending SAN-DO	Pending
Andre Robidoux, M.D.	Montreal, QC, Canada	P-2 (STAR)	April 16-20, 2007	May 22, 2007 LOS-DO	NAI

### 4.5 Compliance with Good Clinical Practices

The trials were conducted in compliance with good clinical practices:

- Informed consents were obtained as a routine
- No protocol violations were noted at the inspected sites
- The trials conformed to acceptable ethical standards

### 4.6 Financial Disclosures

Financial disclosure information submitted by the applicant Eli Lilly was reviewed. The submitted information seems to be adequate and the reviewer believes it to be in compliance with financial disclosure requirements.

## 5. CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

The disposition of raloxifene has been evaluated in more than 3000 postmenopausal women in selected raloxifene osteoporosis treatment and prevention clinical trials, using a population approach. Pharmacokinetic data also were obtained in conventional pharmacology studies in 292 postmenopausal women. Raloxifene exhibits high within-subject variability (approximately 30% coefficient of variation) of most pharmacokinetic parameters. Table 3 summarizes the pharmacokinetic parameters of raloxifene.

*Absorption*— Raloxifene is absorbed rapidly after oral administration.

Approximately 60% of an oral dose is absorbed, but presystemic glucuronide conjugation is extensive. Absolute bioavailability of raloxifene is 2%. The time to reach average maximum plasma concentration and bioavailability are functions of systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites. Administration of raloxifene HCl with a standardized, high-fat meal increases the absorption of raloxifene ( $C_{max}$  28% and AUC 16%), but does not lead to clinically meaningful changes in systemic exposure. EVISTA can be administered without regard to meals.

*Distribution*— Following oral administration of single doses ranging from 30 to 150 mg of raloxifene HCl, the apparent volume of distribution is 2348 L/kg and is not dose dependent.

Raloxifene and the monoglucuronide conjugates are highly (95%) bound to plasma proteins. Raloxifene binds to both albumin and  $\alpha$ 1-acid glycoprotein, but not to sex-steroid binding globulin.

*Metabolism*— Biotransformation and disposition of raloxifene in humans have been determined following oral administration of  $^{14}$ C-labeled raloxifene. Raloxifene undergoes extensive first-pass metabolism to the glucuronide conjugates: raloxifene-4'-glucuronide, raloxifene-6-glucuronide, and raloxifene-6, 4'-diglucuronide. No other metabolites have been detected, providing strong evidence that raloxifene is not metabolized by cytochrome P450 pathways. Unconjugated raloxifene comprises less than 1% of the total radiolabeled material in plasma. The terminal log-linear portions of the plasma concentration curves for raloxifene and the glucuronides are generally parallel. This is consistent with interconversion of raloxifene and the glucuronide metabolites.

Following intravenous administration, raloxifene is cleared at a rate approximating hepatic blood flow. Apparent oral clearance is 44.1 L/kg•hr. Raloxifene and its glucuronide conjugates are interconverted by reversible systemic metabolism and enterohepatic cycling, thereby prolonging its plasma elimination half-life to 27.7 hours after oral dosing.

Results from single oral doses of raloxifene predict multiple-dose pharmacokinetics. Following chronic dosing, clearance ranges from 40 to 60 L/kg•hr. Increasing doses of raloxifene HCl (ranging from 30 to 150 mg) result in slightly less than a proportional increase in the area under the plasma time concentration curve (AUC).

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*Excretion*— Raloxifene is primarily excreted in feces, and less than 0.2% is excreted unchanged in urine. Less than 6% of the raloxifene dose is eliminated in urine as glucuronide conjugates.

## **5.2 Pharmacodynamics**

In both the osteoporosis treatment and prevention trials, Evista therapy resulted in consistent, statistically significant suppression of bone resorption and bone formation, as reflected by changes in serum and urine markers of bone turnover (e.g., bone-specific alkaline phosphatase, osteocalcin, and collagen breakdown products). The suppression of bone turnover markers was evident by 3 months and persisted throughout the 36-month and 24-month observation periods.

In a 31-week, open-label, radiocalcium kinetics study, 33 early postmenopausal women were randomized to treatment with once-daily Evista 60 mg, cyclic estrogen/progestin (0.625 mg conjugated estrogens daily with 5 mg medroxyprogesterone acetate daily for the first 2 weeks of each month [hormone therapy]), or no treatment. Treatment with either Evista or hormone therapy was associated with reduced bone resorption and a positive shift in calcium balance (-82 mg Ca/day and +60 mg Ca/day, respectively, for Evista and -162 mg Ca/day and +91 mg Ca/day, respectively, for hormone therapy). There were small decreases in serum total calcium, inorganic phosphate, total protein, and albumin, which were generally of lesser magnitude than decreases observed during estrogen or hormone therapy. Platelet count was also decreased slightly and was not different from estrogen therapy.

## **6. INTEGRATED REVIEW OF EFFICACY**

### **6.1 Indication**

“The reduction in risk of invasive breast cancer in postmenopausal women at high risk for breast cancer”

#### **6.1.1 Detailed Review of NSABP P-2 (STAR Trial)**

**“Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer”**

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Protocol Milestones:

**Table 4 Protocol Milestones**

<b>Milestone</b>	<b>Dates</b>
Open for accrual	July 1, 1999
Protocol Original Version	March 1, 1999
Protocol Version 2 Submission	June 24, 1999
Protocol Version 3 Submission	May 2, 2003
Quality-of-life evaluation opened to accrual at selected centers	January 4, 2000
Study close to accrual	November 4, 2004
Data Cutoff	December 31, 2005
Unblinding *	April 17, 2006
NDA submission	November 13, 2006
STAR clinical study report and datasets submission	March 13, 2007

\* On April 17, 2006, the results of the analysis of data from NSABP P-2 were released. The study was unblinded, and all patients were notified of which drug they received.

**Objectives:**

**Primary:**

The primary objective of the study is to determine which of the following three statements is true:

- 1) compared to tamoxifen, raloxifene significantly reduces the incidence rate of invasive breast cancer;
- 2) compared to raloxifene, tamoxifen significantly reduces the incidence rate of invasive breast cancer; or
- 3) the statistical superiority of one of the treatments cannot be demonstrated and the choice of therapy should be based on benefit/risk considerations.

**Secondary:**

The secondary objectives of the trial are to evaluate the effect of raloxifene therapy and tamoxifen therapy on the following:

- 1) the incidence of intraductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS);
- 2) the incidence of endometrial cancer; and all other invasive cancers,
- 3) the incidence of ischemic heart disease;
- 4) the incidence of fractures of the hip, spine, or Colles' fractures of the wrist;
- 5) the toxicity and side effects of each therapy;
- 6) participants' quality of life and

7) all deaths

### 6.1.2 Study Design

The protocol design is a Phase III, multicenter, multinational, randomized, double-blind study comparing the efficacy and safety of Novaldex and Raloxifene. Nineteen thousand\* participants were to be randomized to either tamoxifen or raloxifene in a double-blind fashion. The stratification factors were age (35-49, 50-59, > 59), race (black, white, other), history of LCIS (yes, no), prior hysterectomy (yes, no), and the estimated absolute risk of invasive breast cancer within 5 years (< 2.0, 2.0-2.9, 3.0 4.9, ≥ 5.0) determined from the Gail model as developed for the P-1 trial. In order to avoid extreme inequality in treatment assignment within a clinical center, an adaptive randomization scheme using the biased-coin method of Efron<sup>42</sup> was to be employed.

This study primary endpoint was to determine if raloxifene is either more or less effective than tamoxifen in reducing the incidence of invasive breast cancer in postmenopausal women who are at increased risk for the disease. A secondary goal was to determine whether raloxifene reduces the endometrial cancer rate compared to tamoxifen.

Approximately 19,000\* postmenopausal women who are at increased risk for the development of breast cancer were to be randomly assigned to receive daily either 20 mg of tamoxifen plus a placebo or 60 mg of raloxifene plus a placebo, for a period of 5 years. Women were eligible for the trial if they were postmenopausal and their projected 5 year probability of developing invasive breast cancer was at least 1.66%, or if they were postmenopausal and they had a history of lobular carcinoma in situ (LCIS). The estimated 5 year probability of invasive breast cancer was to be determined using the breast cancer Risk Assessment Profile (RAP) generated by the NSABP Biostatistical Center. To meet these criteria, a woman's risk was to be evaluated using present age; number of first degree female relatives with breast cancer; history of previous breast biopsies; history of atypical hyperplasia of the breast; nulliparity; age at first live birth; race; and age at menarche.

Participants were to receive follow up examinations on a regular basis, including an annual mammogram and gynecologic exam. A substudy to evaluate the effect of raloxifene and tamoxifen therapy on study participants' quality of life (QOL) were to be conducted at selected centers.

The primary endpoint of the study is the occurrence of invasive breast cancer. The secondary endpoints include: DCIS or LCIS; all other invasive cancers; ischemic heart disease; fractures of the hip, spine, or Colles' fractures of the wrist; quality-of-life measures; toxicity and side effects; and all deaths.

### **Protocol Amendments:**

The protocol was amended four times.

*First amendment* dated June 24, 1999. Included changes in information resources and the

informed consent.

*Second Amendment* dated May 2, 2003: The original accrual goal for this trial was 22,000 women but, based on a planned reassessment of the sample size, the accrual goal was readjusted to 19,000 women at the time of protocol Amendment #2. Two important parameters that showed discrepancies were the accrual pattern and the breast cancer hazard rate. The actual accrual was having a slower pace than anticipated, and the current projected annual hazard rate was substantially higher than that anticipated.

*Third and Fourth amendments* dated May 18, 2006, included the following information and change of the consent form:

“ On April 17, 2006, the results of the analysis of data from NSABP P-2 were released, treatment assignments were unblinded, and all participants were notified of which drug they received. See Section 2.6 for details. Participants who have not completed their study therapy may choose to continue their assigned study drug to complete 5 years of therapy. Participants assigned to tamoxifen who have not completed 5 years of study drug at the time of local approval of Amendments #3 and #4 may choose to switch and receive raloxifene through the P-2 study to complete 5 years of study therapy. Participants who never initiated their assigned therapy may also receive raloxifene through the P-2 study through 5 years after study entry.”

Reporting of study endpoint events continues to be required after unblinding and announcement of study results.

Following unblinding investigators were to continue to follow adverse event reporting requirements. However, determination of prior experience (expectedness) and attribution will be based on either raloxifene or tamoxifen depending on which drug the participant is taking.

### **Eligibility Criteria**

#### Inclusion Criteria:

The protocol states:

The participant must be a postmenopausal woman. For the purposes of this trial, postmenopausal was defined as:

- a history of at least 12 months without spontaneous menstrual bleeding, or
- a prior documented hysterectomy and bilateral salpingo-oophorectomy, or
- age 55 years or older with a prior hysterectomy with or without oophorectomy, or age < 55 years with a prior hysterectomy without oophorectomy or in whom the status of the ovaries is unknown, with a documented FSH level demonstrating confirmatory elevation in the postmenopausal range.

The participant must be 35 years of age or older at the time of study entry, must be postmenopausal, and must have an increased risk for developing breast

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cancer. The participant must meet one of the following criteria that will be used to define increased risk for breast cancer:

- age  $\geq$  35 years with a histologic diagnosis of lobular carcinoma in situ (LCIS) treated by local excision only; or
- a minimum projected 5 year probability of invasive breast cancer of at least 1.66%.

Within 180 days prior to randomization, the participant must have a general physical examination, including a breast examination demonstrating no clinical evidence of malignancy.

Within 365 days prior to randomization, the participant must have a bilateral mammogram that shows no evidence of suspicious or malignant disease, and a gynecologic exam, including a bimanual pelvic exam and, if indicated, a pap smear.

There must be evidence of adequate bone marrow, hepatic and renal function within 180 days prior to randomization.

The participant may be receiving calcitonin or non-hormonal medications, such as vitamin D, fluoride, or bisphosphonates, to augment bone mineral density.

Exclusion Criteria:

Premenopausal status or less than 35 years of age.

Prior or suspected invasive breast cancer of any type; intraductal carcinoma in situ (DCIS); or previous lobular carcinoma in situ (LCIS) treated by mastectomy, radiation, or systemic adjuvant therapy.

Bilateral or unilateral prophylactic mastectomy.

Participation in any other cancer prevention study or osteoporosis prevention study involving pharmacologic intervention(s). (NSABP Protocol P-1 participants who received placebo are eligible.)

Existing non-malignant disease that would preclude the administration of tamoxifen or raloxifene.

Prior history of deep-vein thrombosis or pulmonary embolus. Prior history of documented cerebral vascular accident or documented transient ischemic attack.

Estrogen or progesterone replacement therapy; oral contraceptives; androgens [e.g., Danocrine® (danazol)]; luteinizing-hormone-releasing-hormone (LHRH) analogs [e.g., Zoladex® (goserelin acetate) or Lupron® (leuprolide acetate)]; prolactin inhibitors [e.g., Parlodel® (bromocriptine)]; or antiandrogens [e.g.,

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Androcur® (cyproterone acetate)]. (Women who discontinue these drugs at least 3 months prior to randomization will be eligible.) However, participants using Estring® (or a similar product) may participate in the trial.

Psychiatric condition, including history of clinical depression, or addictive disorder which would preclude obtaining informed consent or would interfere with compliance.

Tamoxifen, raloxifene, or other SERM therapy (women who, by self report, have received these therapies for less than 3 months duration and discontinue the drugs at least 3 months prior to randomization are eligible).

Current use of Coumadin or cholestyramine.

Uncontrolled hypertension. (The Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of Hypertension defines stage III hypertension as a systolic blood pressure of 180 mm Hg or a diastolic blood pressure of 110 mm Hg based on the average of two or more readings taken at each of two or more visits after an initial screening.)

Uncontrolled diabetes. (This is defined as a HbA1C test result > 9%, which roughly equates to a fasting glucose of 200 mg%.)

Atrial fibrillation.

### 6.1.3 Study Therapy

Formulation:

This double blind trial was to use both active and placebo Raloxifene and Tamoxifen tablets, in order to maintain blindness of the trial.

Dosage schedule

Patients were to be randomized to receive two tablets per day, one with active medication and the other with placebo:

- Tamoxifen (20 mg per day) plus a placebo, which contains the inert ingredients from Raloxifene tablet for a duration of 5 years or
- Raloxifene (60 mg per day) plus a placebo, which contains the inert ingredients from the tamoxifen tablet for a duration of 5 years

Dose modifications:

**Events which require discontinuing protocol therapy:**

- *Invasive breast cancer*
- *Ductal carcinoma in situ (DCIS)*
- *Lobular carcinoma in situ (LCIS)*

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- *Non-breast primary cancers*: Women with non-breast primary cancers other than basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix were to discontinue protocol therapy.
- *Pulmonary embolus*: clinical diagnosis confirmed with a V Q scan or pulmonary angiogram
- *Deep-vein thrombosis (DVT)*: clinical diagnosis confirmed with venography, venous Doppler, venous duplex imaging, or fibrinogen scan
- *Stroke*: confirmed by clinical diagnosis
- *Transient ischemic attack (TIA)*: confirmed by clinical diagnosis
- *Atrial fibrillation*: occurrence that is chronic and/or requires anticoagulant therapy, such as Coumadin.

### Dose delays:

- *Uncontrolled hypertension*
- *Uncontrolled diabetes*
- *Atrial fibrillation*
- *Hepatic toxicity*: A grade 2 (> 2.5 x upper limit of normal) or greater elevation of liver function.
  
- *Hematologic toxicity*: Should a grade 2 (WBC < 3,000, granulocyte count < 1,500, or platelet count < 75,000) or greater hematologic toxicity occur at any time during protocol therapy, the test will be repeated to ensure accuracy. If the value is confirmed, protocol therapy will be discontinued for at least 4 weeks.
- *Other toxicity*: Allergic reactions, gynecologic abnormalities, etc.). In addition to the administration of any immediate treatment, protocol therapy may be discontinued until the condition resolves.
- *Temporary delay due to immobilization*: Study medication(s) should be discontinued immediately in the event of an illness or condition leading to a prolonged period of immobilization and should not be restarted until the inciting condition or illness has resolved.

### Conditions for unblinding of protocol therapy

- *Invasive breast cancer*
- *Other conditions*: DCIS and LCIS.

## 6.1.4 Patient Evaluations

### Pre-therapy evaluations:

Women selected for entry into the study will also have the following required of them:

- History, including a specific assessment of breast cancer, cardiovascular, and osteoporosis risk factors; detailed family history of breast and cardiovascular disease; demographic information; and existing symptoms.

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- General physical examination, including a clinical breast examination, within 180 days prior to randomization, documented by a signed and dated progress note or letter.
- Gynecologic examination, including a bimanual pelvic examination and, if indicated, a pap smear. Participants with a prior hysterectomy *and* bilateral salpingo oophorectomy are exempt from this requirement. Women with a prior hysterectomy who still have their ovaries must have the gynecologic examination.
- Bilateral mammogram within 365 days prior to randomization. The report of that mammogram and any subsequent breast imaging will be submitted to the NSABP Biostatistical Center.
- CBC, differential, platelet count, alkaline phosphatase, SGOT or SGPT, total bilirubin, and serum creatinine tests within 180 days prior to randomization.
- Completion of required QOL questionnaires at centers selected to participate in the QOL substudy.

**Participants' follow-up:**

Patient monitoring is summarized in the following table.

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Table 5 Patient Monitoring STAR Trial

	Prior to Randomization		Randomization/treatment													
	Recruit-ment	Pre-entry	Pre-therapy	Months on study											Annually after 5 years	
				3	6	12	18	24	30	36	42	48	54	60		
Risk Assessment Form Signed informed consent	X															
Family history		X														
General physical exam		X <sup>a</sup>														
Health Assessment <sup>b</sup>				X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment and compliance																
Compliance Contact Report				X												
Pill counts <sup>c</sup>				X	X	X	X	X	X	X	X	X	X	X	X	X
Side effects/symptoms <sup>d</sup>		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Breast monitoring																
Bilateral mammograms		X <sup>e</sup>			X <sup>f</sup>	X <sup>f</sup>										
Clinical breast exam		X <sup>a</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X
Serum bank collection			X <sup>g</sup>													
Other monitoring <sup>h</sup>																
Gynecologic exams		X <sup>i</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology/chemistry tests <sup>j,k</sup>		X <sup>a</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X
Quality-of-life assessment <sup>l</sup>		X		X	X	X	X	X	X	X	X	X	X	X	X <sup>m</sup>	X <sup>m,n</sup>

a Within 180 days prior to randomization.  
 b Review of events, symptoms, medication use, and any hospitalizations or medical procedures since the last visit.  
 c Pill counts are not required following local approval of Amendments #3 and #4.  
 d Participants should be encouraged to report immediately any significant or persistent changes in their health that occur between follow-up visits.  
 e Within 365 days prior to randomization.  
 f All follow-up mammograms should be performed annually based on the pre-entry bilateral mammogram date.  
 g Participants must have provided consent for this sample to be collected and stored for future use prior to the sample's being drawn. The participant may restrict future use as part of the consent process (see Sample Consent Form).  
 h In addition, other events will be monitored on a regular basis (see Section 8.0).  
 i Within 365 days prior to randomization (for exceptions, see Section 6.3).  
 j CBC, differential, platelet count, SGOT or SGPT, alkaline phosphatase, total bilirubin, and serum creatinine. Differential is required only at the pre-entry visit; it is not required while the participant is on protocol therapy.  
 k Tests are no longer required if the participant permanently discontinues protocol therapy.  
 l Quality-of-life questionnaires are only to be completed at selected centers.  
 m Following unblinding on April 17, 2006, completion of QOL questionnaires is no longer required. (If a participant completed a QOL questionnaire prior to unblinding, the questionnaire must be submitted.)  
 n A final quality-of-life assessment will be obtained at 72 months.

Medical history and laboratory studies:

- A medical history was to be taken at each visit to determine whether any illness, tamoxifen- or raloxifene-related toxicity, fracture, operation, hospital admission, or alteration in protocol regimen has occurred since the previous visit.
- CBC, platelet count, alkaline phosphatase, SGOT or SGPT, total bilirubin, and serum creatinine tests are required annually, as long as the participant is receiving protocol therapy.

Compliance:

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- Participants were to be contacted at 3 months after randomization to monitor and promote compliance.

Symptoms and toxicity:

### Breast examinations

- A clinical breast examination was to be performed at each follow up visit.
- A bilateral mammogram was required annually.
- The results of all breast biopsies and cytologies (including those diagnosed as benign) were to be reported. When the report was either positive or suspicious, all mammogram reports, operative reports, and pathology reports/materials were to be submitted to NSABP Biostatistical Center for medical review.

### Gynecologic examinations

- All participants who have not had a prior hysterectomy and bilateral salpingo oophorectomy were to receive a pelvic exam and, as indicated, a pap smear on an annual basis. At each visit, participants were to be questioned about postmenopausal bleeding, bloody discharge, postcoital staining, or any vaginal bleeding.
- Participants who develop postmenopausal bleeding or staining had to undergo gynecologic evaluation, to include endometrial sampling with or without transvaginal ultrasound (TVU). If this evaluation was negative but the bleeding continues, further diagnostic procedures, such as dilatation and curettage, hysteroscopy, or saline infusion sonogram (SIS) are appropriate to rule out a specific endometrial cause of the symptoms. Participants who develop significant menstrual abnormalities and who refuse or do not comply with the recommendation for gynecological evaluation should have their protocol medication discontinued until the conditions have resolved.
- Diagnosis of any cancer or hyperplasia, as well as the results of all endometrial biopsies or cytologies, were to be reported on the event form. Copies of the operative and pathology reports and tumor blocks were to be submitted to the NSABP Biostatistical Center for review.

### Ophthalmic monitoring

- During each follow up visit, participants were to be questioned about visual changes and ophthalmic events (cataracts, retinal changes, corneal opacity, etc).

### Cardiovascular monitoring

- All cardiovascular events were to be reported. Any indication of arteriosclerotic vascular disease (ASVD), including non-fatal myocardial infarction and death due to ASVD, was to be reported.

### Fracture monitoring

- All fractures were to be reported, documenting the site, severity, and method of injury. Submission of the x ray report and any additional documentation (hospital summary, operative report, etc.) was also required.

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**Mortality**

- All deaths were to be reported to the NSABP Biostatistical Center and accompanied by a copy of the death certificate.

**6.1.5 Criteria for Efficacy Assessment**

*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 Biostatistical Center for review.

*Other breast endpoints*

- A pathologic diagnosis of non-invasive breast cancer (LCIS or DCIS) and/or atypical hyperplasia, as indicated by the pathology report from the clinical center pathologist, was required.
- Blocks of tissue were to be submitted to the NSABP Biostatistical Center for review.

*Cardiac and vascular endpoints*

*Cardiovascular death*

- *Definite vascular deaths* - any deaths due to myocardial infarction, stroke, pulmonary emboli, or other vascular events (i.e., ruptured aorta). Included sudden deaths without any other cause.
- *Presumed vascular deaths* - any deaths without any clear non-vascular cause.

*Fatal and non-fatal myocardial infarction*

- *Q wave MI* - presence of two of the following three criteria:
  - Characteristic symptoms of chest pain
  - A new, significant q wave on the standard 12 lead ECG
  - Significant elevation of serum enzymes - presence of any one of the following criteria:
    - 1) elevation of CPK MB to twice the upper limit of normal within 36 hours of onset of acute symptoms of MI;
    - 2) reversal of LDH1/LDH2 ratio within 5 days of the onset of acute symptoms of MI;
    - 3) CPK total at least twice the upper limit of normal for the laboratory that performed the test;
    - 4) SGOT, LDH, or other cardiac enzymes at least twice the upper limit of normal for the laboratory that performed the test.
- *Non Q wave MI* - presence of new and persistent ST changes on the ECG, with significant enzyme elevation in the presence or absence of chest pain;
- *Fatal MI* - defined as death within 7 days of MI, or sudden cardiac death.

*Other cardiac and vascular events*

Other cardiac and vascular events included fatal and non-fatal myocardial infarction and angina requiring percutaneous transluminal coronary angioplasty (PTCA) or coronary

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artery bypass graft (CABG); fatal and non-fatal stroke; and all vascular deaths. These conditions required a copy of the hospital discharge summary and death certificate, when applicable, for documentation of clinical endpoints.

- *Acute ischemic syndromes*: Included unstable angina and probable myocardial infarction

PROBABLE MYOCARDIAL INFARCTION - presence of a new Q wave on the ECG. Chest pain or significant elevation of serum enzymes may not be present.

UNSTABLE ANGINA - angina pectoris requiring hospitalization

- *Severe Angina* - characteristic chest pain upon exertion that requires either PTCA or CABG.

- *Stroke* - presence of neurological deficits that persist for more than 24 hours.

FATAL STROKE - death within 7 days of a stroke

- *Transient ischemic attacks (TIA)* - presence of neurological deficits that last for less than 24 hours

- *Pulmonary embolism* - clinical diagnosis confirmed with a V Q scan or pulmonary angiogram

DEFINITE - clinical diagnosis with a positive V Q scan or pulmonary angiogram

PROBABLE - clinical diagnosis with a suspicious V Q scan or pulmonary angiogram

- *Deep-vein thrombosis (DVT)* - clinical diagnosis confirmed with venography, venous Doppler, venous duplex imaging, or fibrinogen scan

DEFINITE - clinical diagnosis with positive venography, venous Doppler, venous duplex imaging, or fibrinogen scan

PROBABLE - clinical diagnosis with suspicious venography, venous Doppler, venous duplex imaging, or fibrinogen scan

NORMAL clinical diagnosis with negative venography, venous Doppler, venous duplex imaging, or fibrinogen scan

- *Peripheral vascular disease* - significant PVD requiring vascular surgery

### Osteoporosis endpoints

All fractures, regardless of site or cause, were to be reported to the NSABP Biostatistical Center.

Radiology reports of all fractures were to be submitted to the NSABP Biostatistical Center for review. Submission of x ray films for medical review were to be requested by NSABP Headquarters on a case by case basis.

### Cancers other than breast cancer

All cancers other than those of the breast were to be reported on the event form. A copy of the pathology report and blocks of the tumor were required for review.

### Mortality from any cause

A death certificate was to be submitted to the NSABP Biostatistical Center. If the participant was in the hospital at the time of death, a discharge summary was required.

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**6.1.6 Criteria for Safety Assessment**

All adverse event reporting use NCI Common Toxicity Criteria (CTC) Version 2.0 standards for adverse event (toxicity) grading. Attribution categories were as follows: unrelated, unlikely, possibly, probably, or definitely related to the study drug(s).

*Serious Adverse Event* was defined as any adverse drug experience occurring at any dose that results in any of the following outcomes: 1) death, 2) a life-threatening adverse drug experience, 3) inpatient hospitalization or prolongation of existing hospitalization, or 4) a persistent or significant disability/incapacity, or 5) a congenital anomaly/birth defect.

*Unexpected Adverse Event* was defined as any adverse drug experience that was not listed in the current product label or investigator's brochure for either tamoxifen or raloxifene. These included events that may have been symptomatically and pathophysiologically related to an event listed but that differed from the event because of greater severity or specificity.

**6.1.6 Endpoints and Statistical Considerations**

**Endpoints:**

*Primary Endpoint:*

The primary endpoint of the study was the occurrence of invasive breast cancer.

*Secondary Endpoints:*

- DCIS or LCIS
- Other invasive cancers
- Ischemic heart disease
- Fractures of the hip, spine or Colles' fractures of the wrist
- Quality of life
- Toxicity and side effects
- All deaths

**Statistical Considerations:**

*Sample Size:*

The protocol was to target a sample size of 22,000 patients. Power calculations were based on several factors including: 1) the expected hazard rate for invasive breast cancer; 2) the dropout rate for the study; 3) the rate of participant non-compliance with protocol therapy; 4) the duration of treatment effect; and 5) the anticipated pattern of participant accrual (the number of years of accrual and the number of participants accrued by year).

1) Expected annual rate of invasive breast cancer

It is assumed that the women recruited for this trial will have the same level of breast cancer risk as the postmenopausal women recruited into the P-1 trial. The

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actual observed annual incidence rate of invasive breast cancer among postmenopausal participants in the P-1 trial was 6.80 per 1000 in the placebo arm and 3.21 per 1000 in the tamoxifen arm.

2) Study dropouts

The dropout rate in the P-1 trial was about 2% per year.

3) Non-compliance

The average annual rate of non-compliance observed in the tamoxifen arm of the P-1 trial was 7.2% per year.

4) Duration of the anticipated treatment effect

The available data suggest that, for agents similar to those used in this trial, the treatment effect is not lost immediately upon cessation of therapy. Findings from the Swedish study of breast cancer patients who were randomized to treatment with tamoxifen for either 2 or 5 years support this assumption. For power computations, the sponsor assumes that the benefit of treatment (raloxifene or tamoxifen) is unchanged for the first 2 years after termination of therapy, but after that the treatment effect is lost, i.e., the participant's risk goes back to that of an individual who is not receiving treatment.

5) Accrual pattern

The sponsor estimated that 22,000\* women were to be accrued over a 5-year period at a yearly rate of 8000, 5000, 3000, 3000, and 3000, respectively. (\*This sample size was subsequently revised to to 19,000 women).

Primary analysis plan:

The protocol plan to perform the definitive analysis when 327 invasive cancers have been observed. It was anticipated that this should occur approximately 1 1/2 years after accrual was terminated. A stratified log-rank test (using the stratification variables from the randomization procedure) was to be used and conclude that one of the treatments was the more effective for reducing the incidence of breast cancer if the statistic had a two-sided p-value of less than .05.

Power of the primary analysis for several alternatives:

The sponsor calculated the probabilities, for selected scenarios of raloxifene breast cancer effect, of concluding: 1) that the superiority of one treatment for its effectiveness in reducing breast cancer incidence is sufficient to make it the preferred treatment for women eligible for this trial, or 2) that neither treatment has met this criteria and that other factors may result in each treatment being recommended for certain subsets of participants.

Table 6 Statistical Power Analysis

True (not observed) breast cancer Incident rate per 1000 person-years				Probability of concluding superiority for tamoxifen, raloxifene, or neither treatment for reducing the incidence of breast cancer		
Raloxifene	Tamoxifen	Difference in rate	Ratio of rates	Tamoxifen	Neither	Raloxifene
5.50	3.21	2.29	1.71	.99	.01	.00
5.00	3.21	1.79	1.56	.95	.05	.00
3.21	3.21	0.00	1.00	.025	.95	.025
2.14	3.21	-1.07	0.67	.00	.15	.85
1.61	3.21	-1.61	0.50	.00	.003	.997

The sponsor states:

“In computing the sample size for the trial, it was particularly important to us to assure that we would not conclude that the two treatments were equivalent if the overall increase in annual incidence rate associated with raloxifene (vs. tamoxifen) would negate half of the gain obtained from tamoxifen vs. placebo. This would occur if the incidence rate of invasive breast cancer in those receiving raloxifene increases (relative to the rate in those receiving tamoxifen) by 56%. (The overall incident rate for placebo was 112% greater than that for tamoxifen for postmenopausal P 1 participants). With the proposed sample size, we will have 95% power to detect this alternative (see the second row of Table 2).

It would also be of considerable interest if the incidence rate of breast cancer in those receiving raloxifene decreases by 1/3 (relative to the rate in those receiving tamoxifen). This would be a substantial enough reduction that we would not want to fail to identify the benefit, as such a benefit would be important to women with or without hysterectomy. The power to detect this alternative is .85 (see the fourth row of Table 2). The two other alternatives presented in Table 2 refer to extreme cases. The first row in the table represents a case in which the benefit associated with tamoxifen is such that any reduction in endometrial cancers associated with raloxifene (assuming raloxifene caused no increase risk of endometrial cancer relative to placebo) would be completely offset by a comparable increase in invasive breast cancers. The last row in the table represents a case in which the benefit for raloxifene vs. tamoxifen is essentially equivalent to the benefit associated with tamoxifen vs. placebo. We want to be virtually certain that we will not miss either of these extreme cases. The power for both alternatives exceeds 0.99. The third row of Table 2 represents the case that raloxifene and tamoxifen are equivalent for reducing breast cancer incidence. The probability that we will correctly conclude that the two treatments are equivalent is 0.95. Although we used the expected incident rate of 3.21 per thousand for this example, the probability of concluding that the two treatments are equivalent remains at 0.95, provided that the incident rates for raloxifene and tamoxifen are equal.”

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Interim analysis:

The protocol states that the objectives of interim monitoring will be to: 1) monitor toxicity, accrual, and compliance; 2) evaluate baseline assumptions used in the design of the study; and 3) monitor endpoints for early significant results. To accomplish this, summaries of data will be submitted to a committee that will function independently of the committees used to monitor NSABP treatment trials.

The primary endpoint of the trial, invasive breast cancer, will be the basis for interim analyses. The difference between treatment groups in the incidence rate of invasive cancer will be analyzed to assess if there is a higher-than-anticipated potential benefit from either treatment. This will be accomplished by using the general stopping rule proposed by Fleming et al using a two-tailed log-rank test. Six interim analyses are planned (when 47, 93, 140, 187, 234, and 280 invasive cancers have been observed). The boundaries for the interim and final analyses will be 0.00161, 0.00197, 0.00221, 0.00289, 0.00288, 0.00366 and 0.04628, respectively.

Final Analysis:

The time of final analysis will depend on the accuracy of the assumptions from Table 2. If these assumptions hold, and if the invasive breast cancer rate is 3.21/year for both tamoxifen and raloxifene, final analysis will occur approximately 6.5 years from the time that randomization is initiated.

Power for detecting a difference in endometrial cancer incidence:

A secondary study endpoint is to determine whether raloxifene reduces the endometrial cancer rate compared to tamoxifen. Two assumptions were used in the power computations:

- 1) There will be 50,000 person-years of follow-up for each arm of the study. This is the potential number of observed person-years on each arm if the accrual rate is as planned and the study is analyzed 6.5 years after the initiation of randomization.
- 2) Fifty percent of the women on P-2 will have had a hysterectomy, and thus will not be at risk for endometrial cancer. Approximately 34.4% of the women who participated in Protocol P-1 were at least 50 years of age and did not have a hysterectomy; approximately 26.3% of the women were at least 50 years of age and had a hysterectomy; and approximately 2.6% of the women were less than 50 years of age and had a hysterectomy and oophorectomy. This is the subgroup of women who would have been eligible for Protocol P-2. If the same proportions apply to the P-2 trial, approximately 46% of the women on the trial will have had a hysterectomy, which implies that approximately 54% of the P-2 participants will be at risk for endometrial cancer. To be slightly conservative, the sponsor assumed 50% of the participants will be at risk for endometrial cancer.

The power of a two-sided log-rank test to detect a benefit for raloxifene was that the rate of endometrial cancer would be 3.05 per thousand person-years for participants who receive tamoxifen, and the rate of endometrial cancer would be 0.76 per thousand person-years for participants who receive raloxifene. These were the rates observed for tamoxifen and placebo, respectively, for postmenopausal women participating in protocol

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P-1 and thus represent the expected scenario if raloxifene does not cause any increase in endometrial cancer (compared to placebo). The power for this case is nearly 1.00 (> 0.999).

A second set of alternatives is that the rate of endometrial cancer for participants receiving tamoxifen is 3.05 per thousand person-years and 1.91 for participants receiving raloxifene. This would correspond to the expected scenario if raloxifene does cause some additional cancer (compared to placebo), but at only half the increased rate associated with tamoxifen. The power for this alternative is 0.71.

Power for detecting a difference in the incidence of noninvasive breast cancers

Among postmenopausal women in Protocol P-1, the noninvasive breast cancer incidence rate was approximately 31% that of the invasive breast cancer incidence rate, and the treatment effect for noninvasive breast cancer was approximately the same as that for invasive breast cancer. For the P-2 protocol, the sponsor computed the power to test differences in noninvasive breast cancers assuming that the incidence rates for those cancers will be 31% that of invasive cancers for each of the four alternatives to equivalency that were described in Table 2. The power for detecting a difference in the noninvasive cancer rates for each of the four rate ratios 1.71, 1.56, 0.67, and 0.50 is 0.70, 0.53, 0.38, and 0.74, respectively. These are based on the assumption that a two-sided log-rank test will be computed at a significance level=0.05.

Power for quality-of-life evaluation:

Findings from Protocol P-1 indicated that it was not necessary to obtain quality-of-life information on all 22,000 participants in Protocol P-2 to have a statistically powerful assessment of quality-of-life parameters. Thus, quality-of-life monitoring was to be performed in a sample of at least 2000 participants (at least 1000 per group). The primary goal was to evaluate change from baseline between treatment groups with regard to the quality-of-life measurement scales.

The instruments planned to collect quality-of-life information contain two primary indices: a composite index for the measurement of overall physical health and one for overall mental health. There are eight subscales included in the indices which measure physical functioning, social functioning, role-physical, role-emotional, mental health, vitality, general health perception, and bodily pain. A sample size of 1670 women was to provide a statistical power of at least 0.8 (two-tailed test, alpha = 0.05) to detect a 4-unit difference between treatment groups at any particular point in time for the role-physical scale and a difference of 3 units for all the other scales. A sample size of at least 2000 women was to provide adequate power to assess quality-of-life effects and compensate for missing information that is anticipated in association with women who may become consent withdrawals, lost to follow-up, or clinic visit no-shows.

### 6.1.7 Study Results

#### 6.1.7. 1 Patient Demographics/ Disposition

##### **Patient Demographics**

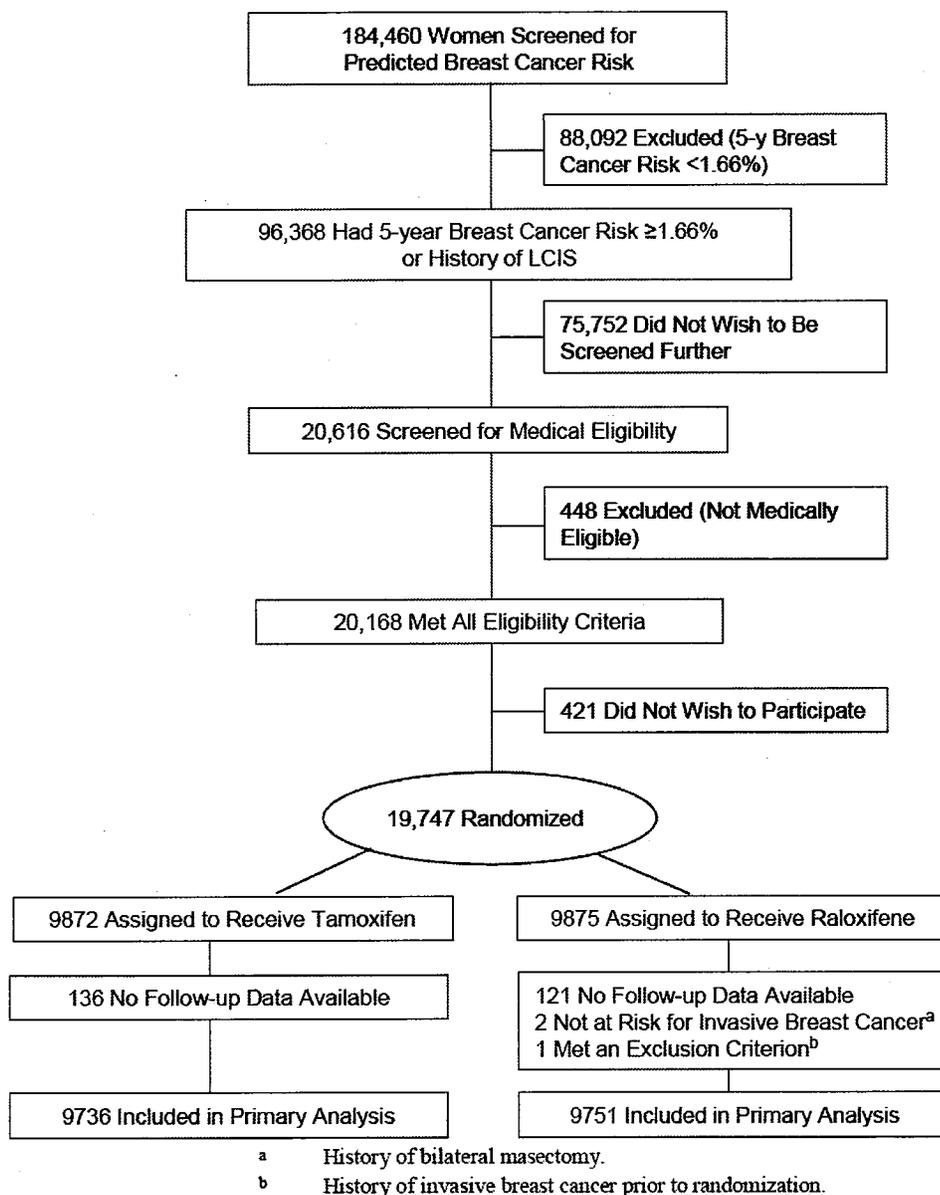
The following results are from the sponsor's analyses and tables:

##### *Enrollment:*

Nineteen thousand seven hundred forty seven women from investigational sites in Canada and US were enrolled in this study. Twenty three clinical investigators from Canada and 463 from the US participated in the STAR Trial.

A total of 184,460 women were screened to determine their risk for invasive breast cancer, using the modified Gail model (Gail and Costantino 2001). Of these, 96,368 had a predicted 5-year risk  $\geq 1.66\%$  or a history of LCIS. From this group, 20,616 were screened to determine eligibility for the trial and 20,168 were found to meet all eligibility criteria of the study. Of this group, 19,747 women were randomized to receive either tamoxifen (N=9872) or raloxifene (N=9875). Of the 9872 women randomized to tamoxifen, 136 had no follow-up data available after randomization. Of the 9875 women randomized to raloxifene, 121 had no follow-up data available after randomization, 2 patients who had a history of bilateral mastectomy were not at risk for invasive breast cancer, and 1 patient who had a history of invasive breast cancer prior to randomization met an exclusion criterion. Thus, according to the sponsor, 9736 women randomized to tamoxifen and 9751 women randomized to raloxifene were included in the primary analysis dataset. See sponsor's figure below.

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**Figure 1 STAR Trial Patient Disposition**

Of the 19,487 patients comprising the primary analysis dataset, over 92% (93.11% in the raloxifene group and 92.21% in the tamoxifen group) were continuing follow-up as of the 31 December 2005 cut-off date. Overall, 5.77% of patients withdrew consent, 1.30% of patients were lost to follow-up, and 0.27% withdrew consent and were lost to follow-up. The differences between treatment groups in the proportions of patients for each reason for study discontinuation were small and not clinically relevant.

**Table 7 STAR Trial Reasons for Study Discontinuation**

<b>Reason for Study Discontinuation</b>	<b>Tamoxifen (N=9736) n (%)</b>	<b>Raloxifene (N=9751) n (%)</b>	<b>Total (N=19,487) n (%)</b>
Continuing follow-up <sup>a</sup>	8978 (92.21)	9079 (93.11)	18,057 (92.66)
Withdrawal of consent	601 (6.17)	523 (5.36)	1124 (5.77)
Lost to follow-up	130 (1.34)	123 (1.26)	253 (1.30)
Withdrawal of consent and lost to follow-up	27 (0.28)	26 (0.27)	53 (0.27)

Abbreviations: n = number of patients; N = patients comprising the primary analysis dataset.

<sup>a</sup> Patients continuing follow-up as of 31 December 2005.

At the December 31, 2005 data cut-off, the median follow-up was 4.32 (mean 4.06) years, which was similar for the two treatment arms. See Table 2 below. The median duration of treatment was 3.43 years.

**Table 8 STAR Trial follow-up**

<b>Patient-Years</b>	<b>Tamoxifen (N=9736)</b>	<b>Raloxifene (N=9751)</b>	<b>Total (N=19,487)</b>	<b>p-Value*</b>
Mean	4.05	4.07	4.06	0.3846
Standard deviation	1.62	1.62	1.62	
Median	4.29	4.34	4.32	
Minimum	0.08	0.07	0.07	
Maximum	6.50	6.50	6.50	

Abbreviations: n = number of patients; N = patients comprising the primary analysis dataset.

\* p-Value is obtained from an F-test using Type III Sum of Squares from an ANOVA model: response=therapy.

The primary analysis of efficacy and safety included all randomized patients with follow-up data who were at risk at baseline for the diagnosis of an incident case of breast cancer. Of the 19,747 patients randomized (9872 to tamoxifen and 9875 to raloxifene), 257 (136 in the tamoxifen group and 121 in the raloxifene group) had no follow-up data after randomization. Three patients, all randomized to raloxifene, were not at risk for invasive breast cancer, as two patients had a history of bilateral mastectomy and one patient had a history of invasive breast cancer at randomization. Thus, the primary analysis dataset included 9736 patients in the tamoxifen group and 9751 patients in the raloxifene group (Table 3).

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**Table 9 Analysis Populations**

<b>Patient (n)</b>	<b>Tamoxifen Arm</b>	<b>Raloxifene Arm</b>	<b>All Patients (n)</b>
<b>ITT Population (patients randomized)</b>	<b>9,872</b>	<b>9,875</b>	<b>19,747</b>
Did not start therapy	79	85	164
No follow-up data	136	124	260
<b>Primary Analysis Population</b>	<b>9736</b>	<b>9751</b>	<b>19,487</b>

**Patient Disposition**

*Protocol violations:*

A protocol violation was defined as “related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment” per the International Conference on Harmonization (ICH) E3 Guideline. The table below summarizes the major protocol violations.

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**Table 10 STAR Trial Protocol Violations**

Nature of Violation	Tamoxifen (N=9736)	Raloxifene (N=9751)
<b>Total</b>	<b>1053</b>	<b>968</b>
<b>Baseline Entry Deviations</b>	<b>61</b>	<b>76</b>
Baseline breast exam not performed within protocol-specified time window	1	5
Baseline gynecological exam not performed within protocol-specified time window	11	7
Baseline mammogram not performed within protocol-specified time window	2	4
Baseline hematology/chemistry tests not performed within protocol-specified time window	1	2
Baseline hematology/chemistry test results abnormal	1	2
Baseline physical exam not performed within protocol- specified time window	21	21
History of DCIS	1	1
History of invasive breast cancer at entry	0	1
History of thromboembolic event (DVT, PE, TIA, or stroke)	7	7
Hormone, SERM or oral contraceptive therapy not discontinued within 90 days of entry	5	15
Polycythemia at entry	1	0
Prior malignancy which occurred less than 5 years before entry	6	1
Mastectomy	0	2
Not post-menopausal	4	7
Uncontrolled diabetes	0	1
<b>Non-Protocol Therapy</b>	<b>867</b>	<b>751</b>
Cholestyramine	15	15
Hormone or oral contraceptive therapy	679	540
Tamoxifen	59	97
Raloxifene	114	99
<b>Treatment Cessation Deviation (Did not stop treatment after protocol-specified event)</b>	<b>125</b>	<b>141</b>

Abbreviations: DCIS = ductal carcinoma in situ; DVT = deep vein thrombosis; N = number of patients in treatment group; PE = pulmonary embolism; SERM = selective estrogen receptor modulator; TIA = transient ischemic attack.

**Reviewer's Comments:**

The sponsor did not provide information on the reason for patients taking non-allowed protocol therapy and length of non-allowed treatment. Due to the size of the trial, these protocol violations might not have any impact on the study results.

*Removal from study:*

Thirty-one percent of the patients discontinue study drug (see table below). Six percent of patients in each arm discontinue study therapy due to protocol event or death. A similar percentage of patients in the Tamoxifen and Raloxifene arm discontinue study

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therapy due to adverse events and intolerable side effects.

**Table 11 STAR Trial Study Drug Discontinuation**

<b>Reason for Study Drug Discontinuation</b>	<b>Tamoxifen (N=9736) n (%)</b>	<b>Raloxifene (N=9751) n (%)</b>	<b>Total (N=19,487) n (%)</b>	<b>p- value*</b>
Took study drug	9657 (99.19)	9666 (99.13)	19,323 (99.16)	0.899
Did not discontinue (continued therapy)	6491 (66.67)	6848 (70.23)	13,339 (68.45)	<0.001
Protocol event	476 (4.89)	486 (4.98)	962 (4.94)	0.759
Death	54 (0.55)	61 (0.63)	115 (0.59)	0.518
Protocol event and death <sup>a</sup>	52 (0.53)	41 (0.42)	93 (0.48)	0.250
All other reasons <sup>b</sup>	2584 (26.54)	2230 (22.87)	4814 (24.70)	<0.001
Adverse event, medication, abnormal laboratory value	1160 (43.48)	1140 (49.69)	2300 (46.35)	
Intolerable side effect	1098 (41.15)	763 (33.26)	1861 (37.51)	
Patient decision	292 (10.94)	292 (12.73)	584 (11.77)	
Non-compliance	88 (3.30)	73 (3.18)	161 (3.24)	
Unknown reason	30 (1.12)	26 (1.13)	56 (1.13)	
Never took study drug	79 (0.81)	85 (0.87)	164 (0.84)	0.899

Abbreviations: n = number of patients; N = patients comprising the primary analysis dataset.

- <sup>a</sup> Includes patients who had a protocol event and died during the study. The death may or may not have been due to the protocol event.
- <sup>b</sup> For the subcategories listed under "all other reasons," patients may have discontinued multiple times for different reasons. Therefore, percentages for these subcategories are calculated based on the total number of records; the denominators are 4962 for the total population, 2668 for the tamoxifen group and 2294 for the raloxifene group.
- \* P-value is from a Chi-square test if total count  $\geq 10$ , or a Fisher's Exact test if  $5 \leq$  total count  $\leq 9$ . No statistical test is performed if total count  $< 5$ , or if a count in a treatment group = 0.

The sponsor reported a large variety of adverse events leading to patient withdrawal. Most of the adverse events frequencies were low except for hot flashes, vaginal bleeding and vaginal discharge that were more common in the tamoxifen arm. There was a greater incidence of discontinuations reported due to vaginal dryness and atrial fibrillation in the raloxifene group compared to the tamoxifen group.

*Demographic Characteristics:*

Of the total 19,487 patients, 27% completed 5 years of therapy. The demographic characteristics of women on the trial with follow-up data are shown in Table below. The mean 5 year risk of invasive breast cancer was 4.03%.

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**Table 12 Demographic Characteristics of Women in the NSABP P-2 STAR Trial**

Characteristic		Tamoxifen		Raloxifene	
		#	%	#	%
Age (yrs.)	≤ 49	884	9.1	878	9.0
	50-59	4856	49.9	4852	49.8
	60-69	3136	32.2	3174	32.6
	≥ 70	860	8.8	847	8.7
Race	Caucasian	9105	93.5	9112	93.4
	African American	233	2.4	243	2.5
	Hispanic	192	2.0	193	2.0
	Other	206	2.1	203	2.1
# 1st degree relatives with breast cancer	0	2838	29.1	2791	28.6
	1	5046	51.8	5132	52.6
	2	1532	15.7	1561	16.0
	≥ 3	320	3.3	267	2.7
Prior hysterectomy	No	4739	48.7	4715	48.4
	Yes	4997	51.3	5036	51.6
History of LCIS at entry	No	8845	90.8	8859	90.9
	Yes	891	9.2	892	9.1
History of atypical hyperplasia	No	7546	77.5	7512	77.0
	Yes	2190	22.5	2239	23.0
5-year predicted breast cancer risk (%)	< 2.0	1055	10.8	1101	11.3
	2.01-3.0	2993	30.7	2892	29.7
	3.01-5.00	3042	31.2	3085	31.6
	≥ 5.01	2646	27.2	2673	27.4
History of bilateral oophorectomy	Yes	2923	30.0	2964	30.4
	No	6813	70.0	6787	69.6
History of cataracts	Yes	1394	14.3	1418	14.5
	No	8342	85.7	8333	85.5

**6.1.8 Efficacy Conclusions**

Major outcomes of the STAR trial are summarized in the Tables below. Number of events, the incidence rate per 1,000 women per year and the relative risk (RR) with 95% confidence interval (CI) between raloxifene and tamoxifen are shown.

Table 13. STAR: Efficacy and Important Safety Outcomes

Type of Event	# Events (%)		IR <sup>a</sup>		RR (95% CI) <sup>b</sup>
	Tamoxifen N=9736	Raloxifene N=9751	Tamoxifen	Raloxifene	
All breast cancers	228 (2.3)	256 (2.6)	5.85	6.54	1.12(0.93,1.34)
Invasive	168 (1.7)	173 (1.8)	4.30	4.40	1.02(0.82,1.27)
Non-invasive	60 (0.6)	83 (0.9)	1.54	2.12	1.38(0.98,1.95)
Clinical vertebral fracture	58	58	1.47	1.46	0.99(0.68,1.46)
Death	109	104	2.76	2.62	0.95(0.72,1.25)
Death due to stroke	7	5	0.18	0.13	0.71(0.18,2.60)
Stroke	56	54	1.42	1.36	0.96(0.65,1.42)
Deep Vein Thrombosis	92	67	2.35	1.69	0.72(0.52,1.00)
Pulmonary Embolism	58	38	1.47	0.96	0.65(0.42,1.00)
Endometrial Cancer <sup>c</sup>	37/4739	23/4715	1.99	1.21	0.61(0.34,1.05)
Ovarian Cancer	14	18	0.52	0.66	1.27(0.60,2.76)
Cataracts	435	343	13.19	10.34	0.78(0.68,0.91)
Hysterectomy	246/4739	92/4715	13.25	4.84	0.37(0.28,0.47)
Hot Flashes	7170	6748	181.71	169.91	0.94(0.90,0.97)
Leg Cramps	5999	5373	152.03	135.29	0.89(0.86,0.92)
Edema <sup>d</sup>	664	741	16.83	18.66	1.11(1.00,1.23)
Cholelithiasis <sup>e</sup>	NA	NA	NA	NA	NA

<sup>a</sup>IR=incidence rate per 1000 patient-years

<sup>b</sup>Relative risk for raloxifene compared to tamoxifen.

Relative Risk >1 indicates higher incidence for raloxifene compared to tamoxifen

Relative Risk < 1 indicates lower incidence for raloxifene compared to tamoxifen

<sup>c</sup> Only patients with a uterus at baseline (tamoxifen n = 4739; raloxifene n = 4715)

<sup>d</sup> Hysterectomy was calculated as a risk ratio.

<sup>e</sup> Peripheral edema is not a coding term in CTC v2.0.

<sup>e</sup> Cholelithiasis is not a coding term in CTC v2.0.

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 168 cases, raloxifene 173 cases), (RR=1.02, 95% CI: 0.82-1.27). The incidence of non-invasive breast cancer was higher among women treated with raloxifene (raloxifene 83 cases, tamoxifen 60 cases; RR= 1.38, 95% CI: 0.98-1.95, p=0.057).

The STAR trial failed to achieve the primary endpoint, to demonstrate superiority of raloxifene compared to tamoxifen, in reducing the risk of invasive breast cancer. Although the STAR trial was not designed or powered as a non-inferiority study, a non-inferiority analysis was conducted in an attempt to demonstrate efficacy. Using historical trial data from a subpopulation of women age 50 years or older from the NSABP P-1

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study comparing tamoxifen to placebo (see Table 10), a hazard ratio of 0.47 for tamoxifen versus placebo was derived. Using this 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% (lost up to 35%) of the tamoxifen effect in the NSABP P1 trial (point estimate of the proportion of effect maintained was 97% ( 95% CI 65% - 128%).

Similarly, a non-inferiority analysis based on the number of all breast cancer occurrences in the STAR trial indicated that raloxifene maintained at least 53% (lost up to 47%) of the tamoxifen effect in the NSABP P 1 trial (point estimate of the proportion of effect maintained was 85% (95% CI 53% - 109%).

Eli Lilly also conducted analyses of the STAR study to compare Evista with a putative placebo. No placebo was included in the STAR study. Lilly used two methods; both make extrapolations using assumptions that are not verifiable. These approaches do not account for variability between studies, constancy assumption and have methodological problems. The focus therefore in interpreting the STAR study results should be on the actual data obtained in the STAR study and how similar or what percentage of tamoxifen effect has been retained.

In the adjuvant breast cancer setting, the FDA has required at least a 75% (equivalently to lose at most a 25%) 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.

The Table below shows the NSABP P-1 trial data supplied by Lilly. These data are different from the JAMA published article (Fisher et al. 1998) and the tamoxifen label because they are for only the subgroup of women who were 50 years of age or older in order to be comparable to the patient population in the STAR trial.

**Table 14. NSABP P-1 Trial**

Type of Event	# Events (%)		IR <sup>a</sup>		RR (95% CI)
	Tamoxifen 4010	Placebo 4008	Tamoxifen	Placebo	
Invasive breast cancer	51	107	3.21	6.80	0.47 (0.33,0.67)
Non-invasive breast cancer	25	32	1.58	2.04	0.77 (0.44,1.35)
Clinical vertebral fracture	20	28	1.25	1.76	0.71 (0.38,1.31)
Death	51	59	3.19	3.70	0.86 (0.58,1.28)
Death due to stroke	3	2	0.19	0.13	1.50 (0.17,17.91)
Stroke	35	20	2.20	1.26	1.75 (0.98,3.20)
Deep Vein Thrombosis	24	14	1.51	0.88	1.71 (0.85,3.58)
Pulmonary Embolism	16	5	1.00	0.31	3.19 (1.12,11.15)
Endometrial Cancer	27	7	3.05	0.76	4.01 (1.70,10.90)
Ovarian Cancer	8	6	0.64	0.48	1.34 (0.41,4.70)

<sup>a</sup>IR = Incidence rate per 1000 patient-years

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<sup>a</sup>IR = Incidence rate per 1000 patient-years

Table 13 presents the tumor characteristics for those patients diagnosed with invasive breast cancer. Of the invasive breast cancers diagnosed, approximately 66% of the tumors were stage I, 76% were infiltrating ductal, 68% were ER-positive, 89% were 3.0 cm or less in size, and 74% were node negative. There were no statistically significant differences between the treatment groups in regard to tumor characteristics based on histology, ER status, size, and nodal status.

**Table 15. STAR: Breast Cancer Incidence by Invasiveness and ER Status**

Breast Cancer Category	Number Events		IR <sup>a</sup>			RR (95% CI) <sup>b</sup>
	Tam	Evista	Tam	Evista	Difference <sup>c</sup>	
Invasive	168	173	4.30	4.40	-0.10	1.02 (0.82, 1.27)
ER Pos	120	115	3.07	2.93	0.14	0.95 (0.73, 1.24)
ER Neg	46	52	1.18	1.32	-0.14	1.12 (0.74, 1.71)
ER Unkn	2	6	0.05	0.15	-0.10	2.98 (0.53, 30.21)
Non-Invasive	60	83	1.54	2.12	-0.58	1.38 (0.98, 1.95)
DCIS	32	47	0.82	1.20	-0.38	1.46 (0.91, 2.37)
LCIS	23	29	0.59	0.74	-0.15	1.26 (0.70, 2.27)
Mixed	5	7	0.13	0.18	-0.05	1.39 (0.38, 5.57)

<sup>a</sup>IR=incidence rate per 1000 patient-years

<sup>b</sup>Relative risk for Evista compared to tamoxifen.

RR > 1 indicates higher incidence with Evista.

<sup>c</sup>Rate in tamoxifen group minus rate in Evista group

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**Table 16. STAR: Breast Cancer Stage at Diagnosis**

Tumor Stage	Tamoxifen N=168		IR	Raloxifene N=173		IR	Total N=321		IR
	n (%)			n (%)			n (%)		
Stage I	106 (63.10)		2.71	119 (68.79)		3.02	225 (65.98)		2.87
Stage II*	4 (2.38)		0.10	5 (2.89)		0.13	9 (2.64)		0.11
IIA	35 (20.83)		0.90	30 (17.34)		0.76	65 (19.06)		0.83
IIB	15 (8.93)		0.38	12 (6.94)		0.30	27 (7.92)		0.34
Stage III									
IIIA	3 (1.79)		0.08	4 (2.31)		0.10	7 (2.05)		0.09
IIIB	1 (0.60)		0.03	1 (0.58)		0.03	2 (0.59)		0.03
Stage IV	3 (1.79)		0.08	0		0	3 (0.88)		0.04
Unknown	1 (0.60)		0.03	2 (1.16)		0.05	3 (0.88)		0.04

IR= incidence rate per 1000 patient-years (39,000 follow-up patient-years in tamoxifen, 39,349 in Raloxifene); N= number of invasive breast cancer events. n=number invasive breast cancer events in each stage; \* indicates stage II patients lacking information to classify as IIA or IIB

The incidence of non-invasive breast cancer was higher among women treated with raloxifene (raloxifene 83 cases, tamoxifen 60 cases; RR= 1.38, 95% CI: 0.98-1.95, p=0.057). Approximately 36% of all in situ breast cancers were LCIS and 55% were DCIS, with the remainder being mixed types. Fewer cases among the tamoxifen group were evident for both LCIS and DCIS.

## 7. INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings STAR Trial

Assessment of safety was based on the reporting of toxicities (AEs collected in a nonsolicited manner at every visit and coded to CTC version 2.0) via the CRF. Additionally, 36 symptoms were specifically solicited on a questionnaire filled out by the patient. Patients reported these symptoms using a 5-point qualitative severity scale described on the questionnaire.

Fatal and nonfatal MI, severe angina, and acute ischemic syndrome were study endpoints. Vascular-related endpoints included VTE (DVT and PE), stroke, and TIA. Of note, a history of cerebrovascular accident or TIA, uncontrolled hypertension, uncontrolled diabetes mellitus, and uncontrolled atrial fibrillation (ie, chronic and/or requiring anticoagulant therapy) were exclusion criteria; therefore, the women who participated would be expected to be at a lower risk for cerebrovascular disease.

All bone fractures, including osteoporotic fractures (ie, hip, spine, and Colles' fractures of the wrist), as well as mortality and cancer, were study endpoints. Safety was also assessed with gynecological examinations, ophthalmologic monitoring, and hematology and blood chemistry assessment.

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A higher proportion of women reported vasomotor symptoms, leg cramps, vaginal discharge, and vaginal bleeding in the tamoxifen group than in the raloxifene group, whereas a higher proportion women reported vaginal dryness and dyspareunia in the raloxifene group than in the tamoxifen group.

The incidence of invasive cancer other than breast and uterine, ischemic heart disease, stroke, TIA, fracture, stroke deaths and death did not differ between treatment groups. Though not statistically significantly different, there was a clinically relevant 39% lower incidence of endometrial cancer in the raloxifene group compared with the tamoxifen group. The incidences of endometrial hyperplasia and non-cancer-related hysterectomies were lower in the raloxifene group compared with the tamoxifen group. Compared with the tamoxifen group, there was a statistically significant 31% lower incidence of VTEs (DVT or PE) in the raloxifene group. A statistically significantly lower incidence of both cataract development and cataract surgery was also observed for the raloxifene group compared with the tamoxifen group.

### **7.1.1 Deaths**

There were a total of 213 deaths (109 in the tamoxifen group and 104 in the raloxifene group). The incidence rates for death were 2.76 per 1000 patient-years for the tamoxifen group and 2.62 per 1000 patient-years for the raloxifene group (RR 0.95, 95% CI 0.72-1.25). No significant difference in stroke-related mortality was observed (5 deaths in raloxifene group vs. 7 deaths in tamoxifen group). There was no statistically significant difference in cumulative incidence between the two treatment groups in all-cause mortality (p-value=0.678).

### **7.1.2 Other Serious Adverse Events**

SAEs were defined as those adverse events graded as 3, 4, or 5, regardless of other factors, including potential relatedness to study drug or expectedness. Although many study endpoint events (eg, breast cancer, acute coronary syndrome, stroke, VTE, or death) fulfill the MedWatch definition of an SAE, they are reported as study endpoints and not as an SAE.

Of the 19,487 patients comprising the primary analysis dataset, 15.8% (tamoxifen group, 16.0%; raloxifene group, 15.6%) reported at least one SAE. There were no clinically relevant observations or treatment group differences in overall reporting of SAEs or among individual events or groupings of events. The three most commonly reported SAEs were hypertension (2.35%), mood alteration-depression (1.40%), and leg cramps (0.95%).

### **7.1.3 Dropouts and Other Significant Adverse Events**

Differences between treatment groups in the incidence of discontinuation due to an AE were consistent with adverse events (AE) and symptom findings. Except for hot

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flashes, the incidence of discontinuation due to an AE was less than 2% for total patients in the primary analysis dataset for each of these AEs. There was a greater incidence of discontinuations reported due to vaginal bleeding and vaginal discharge in the tamoxifen group than in the raloxifene group. There was a greater incidence of discontinuations reported due to vaginal dryness in the raloxifene group than in the tamoxifen group. Differences between treatment groups were small and not deemed to be clinically relevant.

### **7.1.4 Laboratory Findings**

The following hematology/chemistry blood tests were performed at baseline and annually thereafter: white blood cell, platelets, AST (SGOT), serum glutamic pyruvic transaminase, bilirubin, serum creatinine, and alkaline phosphatase . Post-baseline differences between treatment groups were not deemed to be clinically relevant. There were no findings suggestive of a change in the current raloxifene safety profile in regard to these hematology or blood chemistry parameters.

### **7.1.5 Vital Signs**

Vital sign data was not evaluated because vital sign data was not collected as a scheduled safety assessment.

### **7.1.6 Electrocardiograms (ECGs)**

Electrocardiogram data was not evaluated because electrocardiograms were not conducted as a scheduled safety assessment.

## **8. ADDITIONAL CLINICAL ISSUES**

### **8.1 Dosing Regimen and Administration**

The recommended dose is one 60 mg Evista tablet daily, which may be administered any time of day without regard to meals.

#### **Raloxifene use in patients with hepatic or renal impairment:**

Raloxifene should be used with caution in patients with hepatic or renal impairment.

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### **Renal Impairment**

In the osteoporosis treatment and prevention trials, raloxifene concentrations in women with **mild** renal impairment are similar to women with normal creatinine clearance. When raloxifene was administered to individuals with **moderate or severe** renal impairment, plasma raloxifene concentrations were 122% higher than those in healthy volunteers.

### **Hepatic Impairment**

In subjects with **mild** hepatic impairment (Child-Pugh Class A; total bilirubin 0.6 to 2 mg/dL): Clearance of raloxifene was reduced 56%; the half-life of raloxifene was not altered. Plasma raloxifene concentrations were approximately 150% higher than those in healthy volunteers and correlated with total bilirubin concentrations. The pharmacokinetics of raloxifene has not been studied in patients with **moderate or severe** hepatic impairment.

## **8.2 Drug-Drug Interactions**

### **Cholestyramine and other anion exchange resins**

Cholestyramine, an anion exchange resin, causes a 60% reduction in the absorption and enterohepatic cycling of raloxifene after a single dose.

Although not specifically studied, it is anticipated that other anion exchange resins would have a similar effect.

### **Warfarin**

In vitro, raloxifene did not interact with the binding of warfarin.

The concomitant administration of raloxifene and warfarin, a coumarin derivative, has been assessed in a single-dose study. In this study, raloxifene had no effect on the pharmacokinetics of warfarin. However, a 10% decrease in prothrombin time was observed in the single-dose study.

In the osteoporosis treatment trial, there were no clinically relevant effects of warfarin co-administration on plasma concentrations of raloxifene.

### **Other Highly Protein-Bound Drugs**

In the osteoporosis treatment trial, there were no clinically relevant effects of co-administration of other highly protein-bound drugs (e.g., **gemfibrozil**) on plasma concentrations of raloxifene.

In vitro, raloxifene did not interact with the binding of **phenytoin**, **tamoxifen**, or **warfarin**.

### **Ampicillin and Amoxicillin**

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Peak concentrations of raloxifene and the overall extent of absorption are reduced 28% and 14%, respectively, with co-administration of ampicillin. These reductions are consistent with decreased enterohepatic cycling associated with antibiotic reduction of enteric bacteria. However, the systemic exposure and the elimination rate of raloxifene were not affected.

In the osteoporosis treatment trial, co-administration of amoxicillin had no discernible differences in plasma raloxifene concentrations.

### **Antacids**

Concomitant administration of calcium carbonate or aluminum and magnesium hydroxide-containing antacids does not affect the systemic exposure of raloxifene.

### **Corticosteroids**

The chronic administration of raloxifene in postmenopausal women has no effect on the pharmacokinetics of methylprednisolone given as a single oral dose.

### **Digoxin**

Raloxifene has no effect on the pharmacokinetics of digoxin.

### **Cyclosporine**

Concomitant administration of raloxifene with cyclosporine has not been studied.

### **Lipid-Lowering Agents**

Concomitant administration of raloxifene with lipid-lowering agents has not been studied.

## **8.3 Special Populations**

### **Pregnancy**

Raloxifene is approved for use by postmenopausal women only. Raloxifene should not be used in women who are or may become pregnant.

### **Nursing Mothers**

Raloxifene is approved for use by postmenopausal women only. It should not be used by lactating women. It is not known whether this drug is excreted in human milk.

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**Geriatric Use**

Of the total number of patients in placebo-controlled clinical studies of raloxifene, 61% were 65 and over, while 15.5% were 75 and over.

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Based on clinical trials, there is no need for dose adjustment for geriatric patients.

**Renal Impairment**

Raloxifene should be used with caution in patients with moderate or severe renal impairment.

**Hepatic Impairment**

Raloxifene should be used with caution in patients with hepatic impairment.

**8.4 Pediatrics**

Raloxifene is for use in postmenopausal women only. Neither pharmacokinetics nor safety and effectiveness of raloxifene in pediatric patients have been evaluated.

**8.5 Advisory Committee Meeting**

The Oncologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 24, 2007 to discuss the Evista application. The following two questions were discussed.

Indication: "Reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer"

In the STAR trial comparing Evista with tamoxifen in post-menopausal 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% 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% of the tamoxifen effect in the NSABP P-1 trial.

1. 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?

VOTE:            Yes:10            No:4

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The ODAC Committee expressed their concern with the lack of information on the long term side effects of Evista, particularly the stroke risks in older women. The ODAC Committee also stated the importance of limiting the use of Evista on women at risk of VTEs.

### **8.7 Postmarketing Risk Management Plan**

Black Box Warning was recommended to clearly state the increased risk of venous thromboembolism and increased risk of death due to stroke.

<p><b>WARNING: INCREASED RISK OF VENOUS THROMBOEMBOLISM AND DEATH FROM STROKE</b> Serious and life-threatening events with EVISTA include deep venous thrombosis, pulmonary embolism, and death from stroke.</p>
--

A Medication Guide to detail the risks and benefits of treatment with Evista (in easily understandable language) must be provided to the patients taking Evista.

## **9. OVERALL ASSESSMENT**

### **9.1 Conclusions**

The STAR trial, which compared Evista to an active control (tamoxifen) in postmenopausal women with a high risk of developing invasive breast cancer showed that Evista was not better than tamoxifen. Non-inferiority analysis results are consistent with Evista losing up to 35% of the tamoxifen effect on the incidence of invasive breast cancer seen in the NSABP-P1 trial comparing tamoxifen with placebo. In addition there were fewer non-invasive breast cancers in the tamoxifen group (60) than the Evista group (83),  $p=0.057$ . For all breast cancers the non-inferiority analysis results are consistent with Evista losing up to 47% of the tamoxifen effect in the NSABP P-1 trial.

The efficacy results in all the Evista trials must be weighed against the increased risk of deep vein thrombosis, pulmonary embolism and possibly stroke death. Careful consideration of the risk/benefit ratio is especially important for the proposed new indications in healthy post menopausal women.

### **9.2 Recommendation on Regulatory Action**

We recommend approval of Evista for the reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer, based on the results of the four randomized trials and the ODAC recommendation from July 24, 2007. The Evista risk/benefit ratio for reduction in the risk of invasive breast cancer is narrow. Therefore, each individual postmenopausal woman's risk/benefit ratio must be carefully considered.

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### **9.3 Recommendation on Postmarketing Actions**

None

#### **9.3.1 Risk Management Activity**

Black Box Warning was recommended to clearly state the increased risk of venous thromboembolism and increased risk of death due to stroke.

A Medication Guide to detail the risks and benefits of treatment with Evista (in easily understandable language) must be provided to the patients taking Evista.

#### **9.3.2 Required Phase 4 Commitments**

None

#### **9.3.3 Other Phase 4 Requests**

None

### **9.4 Labeling Review**

Please see review of the Evista label by the Evista review team.

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/s/

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Patricia Cortazar  
9/7/2007 11:56:30 AM  
MEDICAL OFFICER

John Johnson  
9/7/2007 12:34:41 PM  
MEDICAL OFFICER  
See also my Clinical Team Leader Review.

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## CLINICAL TEAM LEADER REVIEW OF SNDA

NDA 22042

APPLICANT Eli Lilly

DRUG Evista® (raloxifene HCL)

### PROPOSED NEW INDICATIONS

1. "Reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis"
2. "Reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer"

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## EXECUTIVE SUMMARY

Evista is marketed for the treatment (1999) and prevention (1997) of osteoporosis in postmenopausal women. Results of four double-blind randomized trials are submitted in support of the two above new indications. Patients do not have cancer. Thus an especially careful consideration of the risk/benefit ratio is required.

The RUTH, MORE and CORE trials are placebo controlled. The STAR trial has an active control (tamoxifen). The most important data supporting the proposed new indications comes from the RUTH and STAR trials. Data from the MORE and CORE trials are less important for the following reasons. The MORE trial was not a breast cancer prevention trial. The primary endpoints were clinical vertebral fracture and bone mineral density of the lumbar spine and femoral neck. Breast cancer incidence was assessed only as a safety endpoint. The CORE trial was a continuation of the MORE trial. Breast cancer was added as the primary endpoint. However, patients were not re-randomized and prior randomization was lost because only approximately 52% of the MORE patients participated in the CORE trial. Only about 42% of MORE patients received study drug (Evista or placebo) in the CORE trial.

Results of the RUTH, CORE and MORE placebo-controlled studies indicate that Evista reduces the risk of invasive breast cancer. However, 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 Stage I or II and thus have a high cure rate. This is achieved at a cost of an increase in serious adverse events such as deep vein thrombosis, pulmonary embolism, and possibly stroke death.

In the RUTH trial comparing Evista with Placebo, 5057 women were treated with Evista every day for a median of five years to prevent 30 invasive breast cancers, almost all Stage I or II. Described another way, 862 women must be treated for one year to prevent an invasive breast cancer in one woman. In the MORE and CORE trials 323 and 335 women respectively must be treated for one year to prevent an invasive breast cancer in one woman.

The studies provide less support for the proposed new indication to reduce the risk of invasive breast cancer in postmenopausal women at high risk. 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 of  $\geq 1.66$  or lobular carcinoma in situ (LCIS) treated by excision only. Evista was not better than tamoxifen. Non-inferiority analysis results are consistent with Evista potentially losing up to 35% of the tamoxifen effect on the incidence of invasive breast cancer seen in the NSABP-P1 trial comparing tamoxifen with placebo. In addition there were fewer non-invasive breast cancers in the tamoxifen group (60) than the Evista group (83),  $p=0.057$ . For all breast cancers the non-inferiority analysis results are consistent with Evista potentially losing up to 47% of the tamoxifen effect in the NSABP P-1 trial.

Eli Lilly also conducted analyses of the STAR study to compare Evista with a putative placebo. No placebo was included in the STAR study. Lilly used two methods; both make extrapolations using assumptions that are not verifiable. These approaches do not account for variability between studies or the constancy assumption and have methodological problems.

In the adjuvant breast cancer setting, the FDA has required at least 75% retention (equivalently to lose at most 25%) 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. The FDA has no prior experience and thus no criteria for minimum per cent retention of an active control effect in breast cancer prevention trials.

Seeking additional support for Evista use in high risk postmenopausal women, the FDA performed exploratory subgroup analyses in normal risk women and high risk women in the RUTH trial. Evista statistically significantly reduced the risk of invasive breast cancer in the subgroup at normal risk (Gail score < 1.66), but failed to do so in the subgroup at high risk. This occurred despite the fact that there were more events in the high risk subgroup.

The reduction in the risk of invasive breast cancer in the RUTH, MORE, CORE and STAR trials must be weighed against the increased risk of deep vein thrombosis, pulmonary embolism and possibly stroke death. A careful consideration of the risk/benefit ratio is especially important for these two proposed new indications in post menopausal women who do not have cancer.

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

Assessing the Evista benefit/risk ratio is difficult because we do not know how much weight to give to each of the benefits and risks. The benefits are decreased incidence of invasive breast cancer and clinical vertebra fractures. The main risks are deep vein thrombosis, pulmonary embolus and possibly stroke death.

A crude unadjusted assessment of the benefits versus the risks in the three placebo-controlled Evista trials in PM women not selected based on invasive breast cancer risk indicates that in the RUTH trial the benefits and risks are approximately equal, in the MORE trial the benefits outweigh the risks and in the CORE trial the risks outweigh the benefits.

In the STAR trial in post menopausal women at high risk for invasive breast cancer Evista may lose up to 35% of the active control tamoxifen effect on reduction of the risk of invasive breast cancer. Evista generally has a lower incidence of serious adverse events than tamoxifen. It is questionable whether all women in the STAR trial were "high risk". The definition of "high risk" is arbitrary and its origin may be related to the need to recruit the large number of women required to conduct the STAR trial. The 1.66% risk of invasive breast cancer over the next five years in a normal 60 year old woman was designated as "high risk".

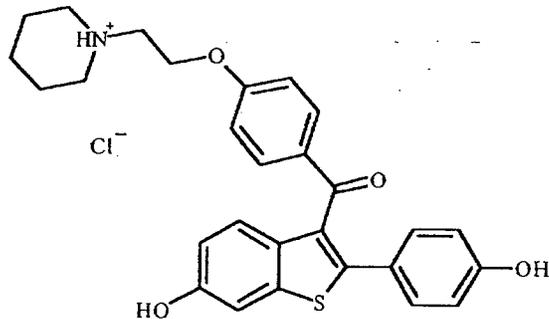
On July 24, 2007 this SNDA was presented to the FDA Oncology Drugs Advisory Committee. The Committee voted 8 to 6 with 1 abstention that the Evista benefit/risk ratio is favorable for "Reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis". The Committee voted 10 to 4 with 1 abstention that the Evista benefit/risk ratio is favorable for "Reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer".

This reviewer recommends approval of Evista for both of the proposed new indications. The wording of the second new indication should be changed from "high risk for breast cancer" to "high risk for **invasive** breast cancer". This recommendation is conditional on revised labeling that clearly conveys the benefits and risks and a MedGuide for patients. These should warn that Evista increases the risk for thromboembolic events. This information should also indicate that a decision whether to take Evista is important and the correct choice may differ from woman to woman. Each individual postmenopausal woman should carefully consider her own potential benefits and risks. Women must be aware that Evista does not prevent invasive breast cancer and regular mammograms and breast examinations (at least yearly) are essential. If women use Evista as an excuse for skipping or delaying screening for breast cancer, any Evista benefit is likely to be lost.

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## DRUG DESCRIPTION

Evista (raloxifene hydrochloride) is a selective estrogen receptor modulator (SERM) that belongs to the benzothiophene class of compounds. The chemical structure is:



The chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl) benzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl) ethoxy] phenyl]-, hydrochloride. Raloxifene hydrochloride (HCl) has the empirical formula  $C_{28}H_{27}NO_4S \cdot HCl$ , which corresponds to a molecular weight of 510.05.

Formulation: 60 mg tablets for oral administration.

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## RANDOMIZED TRIAL DESIGNS AND DESCRIPTIONS

**Table 1. Evista Randomized Trials**

Study Title	Study Name (Abbreviation)	Short Protocol Name	Study Protocol
Study of Tamoxifen and Raloxifene	STAR	P-2	NSABP P-2
Raloxifene Use for The Heart	RUTH	GGIO	H3S-MC-GGIO
Multiple Outcomes of Raloxifene Evaluation	MORE	GGGK	H3S-MC-GGGK
Continuing Outcomes Relevant to Evista	CORE	GGJY	H3S-MC-GGJY

**Table 2. Evista Trial Designs (Number of patients; Patient Population; Primary Endpoint; Age)**

Trial	N	Patient Population (Postmenopausal women)	Primary Endpoint	Median Age (Years)
STAR (Study of Tamoxifen and Raloxifene)	19,747	High risk of breast cancer*	Invasive breast cancer	58
RUTH (Raloxifene Use for The Heart)	10,101	With or at risk of adverse coronary events**	Major coronary events, Invasive breast cancer	68
MORE (Multiple Outcomes of Raloxifene Evaluation)	7,705	With osteoporosis	Clinical vertebral fracture, BMD lumbar spine & femoral neck	67
CORE (Continuing Outcomes Relevant to Evista)	4,011	With osteoporosis	Invasive breast cancer	71

\*Modified Gail score  $\geq 1.66$  or history of LCIS treated by excision only

\*\* Cardiovascular risk score  $\geq 4$

Abbreviation: BMD: bone mineral density

**Table 3. Evista Trial Designs (Study Arms; Exclusions)**

TRIAL	TREATMENT ARMS	IMPORTANT EXCLUSIONS
STAR	Tamoxifen 20 mg Raloxifene 60 mg	Hx of DVT, PE, CVA or TIA Current use of coumadin, atrial fibrillation, uncontrolled diabetes or uncontrolled hypertension
RUTH	Raloxifene 60 mg Placebo	MI, PCI, or CABG within 3 months, Hx of VTE
MORE	Raloxifene 60 mg Raloxifene 120 mg Placebo	Hx VTE, CVA within 10 yrs
CORE	Raloxifene 60 mg Placebo	Same as MORE except prior CVA not excluded

Abbreviations: Hx: History, DVT: Deep vein thrombosis, PE: Pulmonary embolism, CVA: Cerebrovascular accident, TIA: Transient ischemic attack, MI: Myocardial infarction, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass graft, VTE: Venous thromboembolic event

**Table 4. Breast Cancer Assessment (All Evista Trials)**

	RUTH	MORE	CORE	STAR
Breast cancer assessments	Mammogram q 2 yrs.  Breast exam q 2 yrs.	Mammogram 1 (optional), 2, 3, 4 yrs. + Breast exam baseline only	Mammogram q 2 year  Breast exam yearly	Mammogram yearly  Breast exam q 6 mo.

**Table 5. Pre-randomization Stratification and Statistical Tests (All Evista Trials)**

	RUTH	MORE	CORE	STAR
Pre-randomization stratification	Investigation site	None	None	Age, race, breast cancer risk, history of LCIS* treated by excision only, hysterectomy status
Statistical test For Primary endpoint	Log rank test 2-sided	Log rank test 2-sided	Log rank test 2-sided	Stratified log rank test 2-sided

\*LCIS=lobular carcinoma in situ

**Table 6. Patient Numbers by Geographical Region**

REGION	RUTH	MORE	CORE	STAR
Africa	215			
Asia Pacific	499	309	217	
Eastern Europe	2310	455	294	
Latin America	1370	492	352	
North America	1029	3616	1460	19,747
Western Europe	4679	2833	1688	

**Table 7. Study Drug Exposure (All Evista Trials)**

Treatment	RUTH		MORE		CORE		STAR	
	Plac	Evista	Plac	Evista	Plac	Evista	Tam	Evista
Number of Pts.	5057	5044	2576	5129	1018 <sup>a</sup>	2182 <sup>a</sup>	9736	9751
Median (Years)	5.05	5.06	3.94	3.95	2.98	2.99	3.31	3.53
Mean (Years)	4.31	4.32	3.24	3.30	2.68	2.66	3.1	3.2
SD	2.06	2.06	1.29	1.29	0.83	0.88	1.7	1.6

<sup>a</sup> A total of 4,011 patients from MORE continued in CORE; however, 543 of 2,725 patients enrolled in Evista arm and 268 of 1,286 patients enrolled in placebo arm in CORE did not take the study drug. Thus the number of patients with study drug exposure is 3,200.

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## STAR TRIAL

The protocol design is a Phase 3, multicenter, multinational, randomized, double-blind study in 19,747 postmenopausal women who were at increased risk for the development of breast cancer. Women were randomly assigned to receive daily either 20 mg of tamoxifen plus a placebo or 60 mg of raloxifene plus a placebo for a period of 5 years. Women were eligible for the trial if they were postmenopausal and their projected 5 year probability of developing invasive breast cancer using the Modified Gail Score was at least 1.66%, or if they were postmenopausal and they had a history of lobular carcinoma in situ (LCIS) treated by excision only. The Modified Gail Score was calculated using present age, number of first degree female relatives with breast cancer; history of previous breast biopsies, history of atypical hyperplasia of the breast, nulliparity, age at first live birth, race, and age at menarche. The protocol eligibility excluded women with prior history of invasive breast cancer, ductal carcinoma in situ (DCIS), deep-vein thrombosis, pulmonary embolus, documented cerebral vascular accident or documented transient ischemic attack, current use of coumadin, uncontrolled diabetes or uncontrolled hypertension, or atrial fibrillation. Breast exams were done every 6 months and mammograms yearly.

The **primary endpoint** of the study is the occurrence of invasive breast cancer. The **secondary endpoints** include: ductal carcinoma in situ (DCIS) or LCIS; endometrial cancer; all other invasive cancers; ischemic heart disease; fractures of the hip, spine, or Colles' fractures of the wrist; quality-of-life measures; toxicity and side effects; and all deaths.

The **primary objective** of the study is to determine which of the following three statements is true:

- 1) Compared to tamoxifen, raloxifene significantly reduces the incidence rate of invasive breast cancer;
- 2) Compared to raloxifene, tamoxifen significantly reduces the incidence rate of invasive breast cancer; or
- 3) The statistical superiority of one of the treatments cannot be demonstrated and the choice of therapy should be based on benefit/risk considerations.

The study was not designed to show non-inferiority.

## Results

The primary analysis of efficacy and safety included all randomized patients with follow-up data who were at high risk at baseline for invasive breast cancer. Of the 19,747 patients randomized (9872 to tamoxifen and 9875 to raloxifene), 257 (136 in the tamoxifen group and 121 in the raloxifene group) had no follow-up data after randomization. Three patients, all randomized to raloxifene, were not at risk for first invasive breast cancer, as two patients had a history of bilateral mastectomy and one patient had a history of invasive breast cancer at randomization. Thus, the primary

analysis dataset included 9736 patients in the tamoxifen group and 9751 patients in the raloxifene group.

The **mean 5 year risk** of invasive breast cancer was 4.03%. The **median duration of treatment** was 3.43 years. At the December 31, 2005 data cut-off, the **median follow-up** was 4.32 (mean 4.06) years, which was similar for the two treatment arms.

Of the total 19,487 patients, 27% completed 5 years of therapy. The demographic characteristics of women on the trial with follow-up data are shown in Table below.

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**Table 8. STAR: Demographic Characteristics and Breast Cancer Risk at Baseline**

Characteristic	Tamoxifen		Raloxifene	
	#	%	#	%
Age (yrs.)				
≤ 49	884	9.1	878	9.0
50-59	4856	49.9	4852	49.8
60-69	3136	32.2	3174	32.6
≥ 70	860	8.8	847	8.7
Race				
Caucasian	9105	93.5	9112	93.4
African American	233	2.4	243	2.5
Hispanic	192	2.0	193	2.0
Other	206	2.1	203	2.1
# 1st degree relatives with breast cancer				
0	2838	29.1	2791	28.6
1	5046	51.8	5132	52.6
2	1532	15.7	1561	16.0
≥ 3	320	3.3	267	2.7
Prior hysterectomy				
No	4739	48.7	4715	48.4
Yes	4997	51.3	5036	51.6
History of LCIS at entry				
No	8845	90.8	8859	90.9
Yes	891	9.2	892	9.1
History of atypical hyperplasia				
No	7546	77.5	7512	77.0
Yes	2190	22.5	2239	23.0
5-year predicted breast cancer risk (%)				
< 2.0	1055	10.8	1101	11.3
2.01-3.0	2993	30.7	2892	29.7
3.01-5.00	3042	31.2	3085	31.6
≥ 5.01	2646	27.2	2673	27.4
History of bilateral oophorectomy				
Yes	2923	30.0	2964	30.4
No	6813	70.0	6787	69.6
History of cataracts				
Yes	1394	14.3	1418	14.5
No	8342	85.7	8333	85.5

Major outcomes of the STAR trial are summarized in the Tables below. Number of events, the incidence rate per 1,000 women per year and the relative risk (RR) with 95% confidence interval (CI) between raloxifene and tamoxifen are shown.

**Table 9. STAR: Efficacy and Important Safety Outcomes**

Type of Event	# Events (%)		IR <sup>a</sup>		RR (95% CI) <sup>b</sup>
	Tamoxifen N=9736	Raloxifene N=9751	Tamoxifen	Raloxifene	
All breast cancers	228 (2.3)	256 (2.6)	5.85	6.54	1.12(0.93,1.34)
Invasive	168 (1.7)	173 (1.8)	4.30	4.40	1.02(0.82,1.27)
Non-invasive	60 (0.6)	83 (0.9)	1.54	2.12	1.38(0.98,1.95)
Clinical vertebral fracture	58	58	1.47	1.46	0.99(0.68,1.46)
Death	109	104	2.76	2.62	0.95(0.72,1.25)
Death due to stroke	7	5	0.18	0.13	0.71(0.18,2.60)
Stroke	56	54	1.42	1.36	0.96(0.65,1.42)
Deep Vein Thrombosis	92	67	2.35	1.69	0.72(0.52,1.00)
Pulmonary Embolism	58	38	1.47	0.96	0.65(0.42,1.00)
Endometrial Cancer <sup>c</sup>	37/4739	23/4715	1.99	1.21	0.61(0.34,1.05)
Ovarian Cancer	14	18	0.52	0.66	1.27(0.60,2.76)
Cataracts	435	343	13.19	10.34	0.78(0.68,0.91)
Hysterectomy	246/4739	92/4715	13.25	4.84	0.37(0.28,0.47)
Hot Flashes	7170	6748	181.71	169.91	0.94(0.90,0.97)
Leg Cramps	5999	5373	152.03	135.29	0.89(0.86,0.92)
Edema <sup>d</sup>	664	741	16.83	18.66	1.11(1.00,1.23)
Cholelithiasis <sup>e</sup>	NA	NA	NA	NA	NA

<sup>a</sup>IR=incidence rate per 1000 patient-years

<sup>b</sup>Relative risk for raloxifene compared to tamoxifen.

Relative Risk >1 indicates higher incidence for raloxifene compared to tamoxifen

Relative Risk < 1 indicates lower incidence for raloxifene compared to tamoxifen

<sup>c</sup> Only patients with a uterus at baseline (tamoxifen n = 4739; raloxifene n = 4715)

<sup>c</sup> Hysterectomy was calculated as a risk ratio.

<sup>d</sup> Peripheral edema is not a coding term in CTC v2.0.

<sup>e</sup> Cholelithiasis is not a coding term in CTC v2.0.

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 168 cases, raloxifene 172 cases), (RR=1.02, 95% CI: 0.82-1.27). The incidence of non-invasive breast cancer was higher among women treated with raloxifene (raloxifene 83 cases, tamoxifen 60 cases; RR= 1.38, 95% CI: 0.98-1.95, p=0.057).

Although the STAR trial was not designed or powered as a non-inferiority study, a non-inferiority analysis was conducted. Using historical trial data from a subpopulation of women age 50 years or older from the NSABP P-1 study comparing tamoxifen to placebo

(see Table 10), a hazard ratio of 0.47 for tamoxifen versus placebo was derived. Using this 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% (lost up to 35%) of the tamoxifen effect in the NSABP P1 trial (point estimate of the proportion of effect maintained was 97% (95% CI 65% - 128%).

Similarly, a non-inferiority analysis based on the number of all breast cancer occurrences in the STAR trial indicated that raloxifene maintained at least 53% (lost up to 47%) of the tamoxifen effect in the NSABP P 1 trial (point estimate of the proportion of effect maintained was 85% (95% CI 53% - 109%).

Eli Lilly also conducted analyses of the STAR study to compare Evista with a putative placebo. No placebo was included in the STAR study. Lilly used two methods; both make extrapolations using assumptions that are not verifiable. These approaches do not account for variability between studies, constancy assumption and have methodological problems. The focus therefore in interpreting the STAR study results should be on the actual data obtained in the STAR study and how similar or what percentage of tamoxifen effect has been retained.

In the adjuvant breast cancer setting, the FDA has required at least a 75% (equivalently to lose at most a 25%) 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. The FDA has no experience with this and thus has no criteria for it.

Table 10 below shows the NSABP P-1 trial data supplied by Lilly. These data are different from the JAMA published article (Fisher et al. 1998) and the tamoxifen label because they are for only the subgroup of women who were 50 years of age or older in order to be comparable to the patient population in the STAR trial.

**Table 10. NSABP P-1 Trial**

Type of Event	# Events (%)		IR <sup>a</sup>		RR (95% CI)
	Tamoxifen 4010	Placebo 4008	Tamoxifen	Placebo	
Invasive breast cancer	51	107	3.21	6.80	0.47 (0.33,0.67)
Non-invasive breast cancer	25	32	1.58	2.04	0.77 (0.44,1.35)
Clinical vertebral fracture	20	28	1.25	1.76	0.71 (0.38,1.31)
Death	51	59	3.19	3.70	0.86 (0.58,1.28)
Death due to stroke	3	2	0.19	0.13	1.50 (0.17,17.91)
Stroke	35	20	2.20	1.26	1.75 (0.98,3.20)
Deep Vein Thrombosis	24	14	1.51	0.88	1.71 (0.85,3.58)
Pulmonary Embolism	16	5	1.00	0.31	3.19 (1.12,11.15)
Endometrial Cancer	27	7	3.05	0.76	4.01 (1.70,10.90)
Ovarian Cancer	8	6	0.64	0.48	1.34 (0.41,4.70)

<sup>a</sup>IR = Incidence rate per 1000 patient-years

In the STAR trial no significant difference in overall mortality (104 deaths in the raloxifene group vs. 109 deaths in the tamoxifen group) was found. No significant difference in stroke-related mortality was observed (5 deaths in raloxifene group vs. 7 deaths in tamoxifen group). There was no significant difference in the number of strokes between the two groups (54-raloxifene, 56-tamoxifen; RR=0.96, 95% CI: 0.65-1.42). The number of clinical vertebral fractures was the same (58-raloxifene, 58-tamoxifen) in both treatment groups.

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, respectively (RR=0.61, 95% CI: 0.34-1.05). This difference was not statistically different. A higher number of cases (92) of deep vein thrombosis were observed in women receiving tamoxifen than in women receiving raloxifene (67) (RR=0.72, 95% CI: 0.52-1.00). Fifty-eight cases of pulmonary embolism were observed in the tamoxifen group vs. 38 cases in the raloxifene group (RR=0.65, 95% CI: 0.42-1.00). Cataract formation in women without cataracts at baseline was higher in women taking tamoxifen (435 cases) than in women taking raloxifene (343 cases) (RR=0.78, 95% CI: 0.68-0.91). There were no statistically significant differences in the incidences of ischemic heart disease between tamoxifen and raloxifene.

**Table 11. STAR: Breast Cancer Incidence by Invasiveness and ER Status**

Breast Cancer Category	Number Events		IR <sup>a</sup>			RR (95% CI) <sup>b</sup>
	Tam	Evista	Tam	Evista	Difference <sup>c</sup>	
Invasive	168	173	4.30	4.40	-0.10	1.02 (0.82, 1.27)
ER Pos	120	115	3.07	2.93	0.14	0.95 (0.73, 1.24)
ER Neg	46	52	1.18	1.32	-0.14	1.12 (0.74, 1.71)
ER Unkn	2	6	0.05	0.15	-0.10	2.98 (0.53, 30.21)
Non-Invasive	60	83	1.54	2.12	-0.58	1.38 (0.98, 1.95)
DCIS	32	47	0.82	1.20	-0.38	1.46 (0.91, 2.37)
LCIS	23	29	0.59	0.74	-0.15	1.26 (0.70, 2.27)
Mixed	5	7	0.13	0.18	-0.05	1.39 (0.38, 5.57)

<sup>a</sup>IR=incidence rate per 1000 patient-years

<sup>b</sup>Relative risk for Evista compared to tamoxifen.

RR > 1 indicates higher incidence with Evista.

<sup>c</sup>Rate in tamoxifen group minus rate in Evista group

**Table 12. STAR: Breast Cancer Stage at Diagnosis**

Tumor Stage	Tamoxifen N=168		IR	Raloxifene N=173		IR	Total N=321		IR
	n (%)			n (%)			n (%)		
Stage I	106 (63.10)		2.71	119 (68.79)		3.02	225 (65.98)		2.87
Stage II*	4 (2.38)		0.10	5 (2.89)		0.13	9 (2.64)		0.11
IIA	35 (20.83)		0.90	30 (17.34)		0.76	65 (19.06)		0.83
IIB	15 (8.93)		0.38	12 (6.94)		0.30	27 (7.92)		0.34
Stage III									
IIIA	3 (1.79)		0.08	4 (2.31)		0.10	7 (2.05)		0.09
IIIB	1 (0.60)		0.03	1 (0.58)		0.03	2 (0.59)		0.03
Stage IV	3 (1.79)		0.08	0		0	3 (0.88)		0.04
Unknown	1 (0.60)		0.03	2 (1.16)		0.05	3 (0.88)		0.04

IR= incidence rate per 1000 patient-years (39,000 follow-up patient-years in tamoxifen, 39,349 in Raloxifene); N= number of invasive breast cancer events. n=number invasive breast cancer events in each stage; \* indicates Stage II patients lacking information to classify as IIA or IIB

## RUTH TRIAL

RUTH is a randomized, double-blind, placebo-controlled, multinational study conducted in postmenopausal women with or at risk for major coronary events. The **primary objectives** were to assess whether treatment with raloxifene reduced the incidence of: 1) **Combined coronary endpoint** events of coronary death, nonfatal (including silent) myocardial infarction (MI), or hospitalized acute coronary syndrome (ACS) other than MI; or 2) **Invasive breast cancer**. Women aged 55 years or older, who were at least 1 year postmenopausal and who had established coronary heart disease (CHD) or multiple CHD risk factors were eligible to enroll. A cardiovascular (CV) **risk score** of 4 or greater was required for enrollment, using the following point system: established CHD (4 points), lower extremity arterial disease (4 points), diabetes mellitus (3 points), age 70 years or greater (2 points), current smoker (1 point), hypertension (1 point), hyperlipidemia (1 point). Each patient's 5-year predicted risk of invasive breast cancer was calculated at baseline using the modified Gail model. Bilateral mammograms were performed at baseline, every 2 years thereafter, and at the final visit. Clinical breast examination was performed at baseline and every 2 years thereafter. All investigator-reported cases of breast cancer were reviewed and adjudicated by a board of physicians who were blinded to patient treatment assignment and who were not employed by Lilly.

### Results

A total of 10,101 postmenopausal women with established CHD *or* at increased risk for CHD were randomly assigned to either placebo (N = 5,057) or raloxifene 60 mg/day (N =

5,044). The study was completed by 79% of women in the placebo group and 80% in the raloxifene group. Overall, 71% of patients in the placebo group and 70% in the raloxifene group took at least 70% of assigned medication. The **median duration of follow-up** was 5.6 years and the **median study drug exposure** was 5.1 years for both treatment groups.

Breast cancer risk assessment characteristics were balanced between treatment groups at baseline. The **mean 5-year predicted risk of invasive breast cancer** was 1.73%. Approximately **41%** of patients in each treatment group had a 5-year predicted invasive breast cancer risk of **≥1.66%**.

There were 70 cases (IR, 2.66 per 1000 patient-years) of **invasive breast cancer** in the placebo group and 40 cases (IR, 1.50 per 1000 patient-years) in the raloxifene group. The incidence of **invasive breast cancer** was statistically significantly decreased by 44% (RR 0.56, 95% CI 0.37-0.84; p=0.0032) in the raloxifene group compared with the placebo group. The statistically significant decrease in invasive breast cancer was primarily due to a statistically significant 55% reduction (RR 0.45, 95% CI 0.27-0.73; p=0.0006) in incidence of **invasive ER-positive breast cancer** in the raloxifene group compared with the placebo group. There were no statistically significant differences between treatment groups in the incidences of **invasive ER-negative breast cancer** (RR 1.43, 95% CI 0.56-3.78) or noninvasive breast cancer (RR 2.18, 95% CI 0.70-7.99). The incidence of **all breast cancer** was statistically significantly decreased by 33% (RR 0.67, 95% CI 0.46-0.97; p = 0.0270) in the raloxifene group compared with the placebo group.

Cardiovascular risk assessment characteristics were balanced between treatment groups at baseline except for a statistically significantly greater CV risk score in patients assigned to raloxifene. The **coronary primary endpoint** did not meet the prespecified significance level of 0.0423 (RR 0.95, 95% CI 0.84-1.07; p=0.4038).

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**Table 13. RUTH: Breast Cancer Risk at Baseline**

<b>Characteristics</b>	<b>Placebo N=5,057</b>	<b>Raloxifene N=5,044</b>	<b>Total N=10,101</b>
<b>5-year predicted breast cancer risk (%)</b>			
# of patients	5056	5044	10100
Mean	1.73	1.73	1.73
Standard deviation	0.77	0.76	0.76
Median	1.54	1.55	1.55
Minimum	0.52	0.50	0.50
Maximum	9.57	14.15	14.15
<b>5-yr predicted breast cancer risk <math>\geq</math> 1.66</b>			
# of patients (%)	5056	5044	10100
Yes	2091 (41.2)	2101 (41.65)	4192 (41.50)
No	2975 (58.8)	2943 (58.35)	5919 (59.50)
<b>Age (yrs.)</b>			
# of patients (%)	5057	5044	10101
$\leq 60$	944 (16.69)	926 (16.38)	1670 (16.53)
$> 60-\leq 65$	1033 (20.43)	1029 (20.39)	2061 (20.40)
$> 65-\leq 70$	1213 (23.99)	1260 (24.98)	2473 (24.48)
$> 70-\leq 75$	1291 (25.53)	1251 (29.90)	2542 (25.17)
$> 75$	676 (13.37)	679 (13.46)	1355 (13.41)
<b>Age at menarche</b>			
# of patients	5039	5025	10064
Mean	13.47	13.51	13.49
Standard deviation	1.75	1.79	1.77
Median	13.00	13.00	13.00
Minimum	8.00	6.00	6.00
Maximum	20.00	23.00	23.00
<b>Age at first live birth</b>			
# of patients	4520	4500	9020
Mean	23.34	23.43	23.38
Standard deviation	4.53	4.37	4.45
Median	23.00	23.00	23.00
Minimum	12.00	13.00	12.00
Maximum	54.00	44.00	54.00
<b># live births</b>			
# of patients (%)	5056	5043	10099
0	521 (10.30)	529 (10.49)	1050 (10.40)
1	800 (15.82)	916 (16.18)	1616 (16.00)
2	1396 (27.61)	1439 (29.51)	2934 (29.06)
$\geq 3$	2339 (46.26)	2260 (44.81)	4599 (45.54)

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Characteristics	Placebo N=5057	Raloxifene N=5044	Total N=10101
<b># 1st degree relatives with breast cancer</b>			
# of patients (%)	4584	4600	9184
0	4139 (90.29)	4149 (90.17)	8287 (90.23)
1	402 (8.77)	418 (9.09)	820 (8.93)
2	36 (0.79)	28 (0.61)	64 (0.70)
> 3	7 (0.15)	6 (0.13)	13 (0.14)
<b># Of prior breast biopsies</b>			
# of patients (%)	5041	5027	10068
0	4574 (90.74)	4611 (91.72)	9185 (91.23)
1	372 (7.38)	343 (6.82)	715 (7.10)
2	65 (1.29)	58 (1.15)	123 (1.22)
> 3	30 (0.60)	15 (0.30)	45 (0.45)
<b>Prior breast biopsies with dx of invasive breast cancer</b>			
# of patients (%)	390	345	725
Yes	1 (0.26)	0	1 (0.14)
No	379 (99.74)	345 (100)	724 (99.86)
<b>Prior breast biopsies with dx of DCIS</b>			
# of patients (%)	380	345	725
Yes	0	2 (0.59)	2 (0.29)
No	380 (100)	343 (99.42)	723 (99.72)
<b>Prior breast biopsies with dx of LCIS</b>			
# of patients (%)	380	345	725
Yes	0	0	0
No	380 (100)	345 (100)	725 (100)
<b>Prior breast biopsies with dx of atypical hyperplasia</b>			
# of patients (%)	380	345	725
Yes	8 (2.11)	4 (1.16)	12 (1.66)
No	372 (97.99)	341 (98.84)	713 (98.34)
<b>Prior breast biopsies with dx of other breast conditions</b>			
# of patients (%)	386	349	735
Yes	379 (98.19)	343 (98.28)	722 (98.23)
No	7 (1.81)	6 (1.72)	13 (1.77)

## **RUTH Efficacy and Safety Outcomes**

Major outcomes of the RUTH trial are summarized in the Tables below. Number of events and the incidence rate per 1,000 patient-years, and the relative risk (RR) with 95% confidence interval (CI) between the raloxifene and placebo groups are shown. Relative risk of less than 1.0 indicates a lower incidence with raloxifene therapy. Relative risk of greater than 1 indicates a higher incidence with raloxifene therapy.

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**Table 14. RUTH: Efficacy and Important Safety Outcomes:**

	Raloxifene 5,044	Placebo 5,057	Raloxifene IR	Placebo IR	Absolute Risk Difference	Relative Risk (95% CI)
Invasive breast cancer	40	70	1.50	2.66	-1.16	0.56 (0.37, 0.84)
Noninvasive breast cancer	11	5	0.41	0.19	+0.22	2.18 (0.70, 7.99)
Invasiveness unknown	1	1	0.04	0.04	+0.00	NA
All breast cancers	52	76	1.95	2.89	-1.04	0.67 (0.46, 0.97)
Clinical vertebral fracture	64	97	2.40	3.70	-1.30	0.65 (0.47, 0.90)
Death	554	595	20.68	22.45	-1.77	0.92 (0.82, 1.04)
Death due to Stroke	59	39	2.20	1.47	+0.73	1.50 (0.98, 2.30)
Stroke	249	224	9.46	8.60	+0.86	1.10 (0.91, 1.32)
Deep vein thrombosis	65	47	2.44	1.78	+0.66	1.37 (0.94, 1.99)
Pulmonary embolism	36	24	1.35	0.91	+0.44	1.49 (0.89, 2.49)
Endometrial cancer <sup>a</sup>	21/3900	17/3882	1.01	0.83	+0.18	1.22 (0.61, 2.46)
Ovarian Cancer <sup>b</sup>	17/4559	10/4606	0.70	0.41	+0.29	1.71 (0.74, 4.17)
Hysterectomy <sup>a</sup>	58/3900	53/3882	2.79	2.60	+0.19	1.07 (0.73, 1.59)
Hot Flashes	397	241	14.82	9.09	+5.73	1.63 (1.39, 1.92)
Leg Cramps	483	334	18.03	12.60	+5.43	1.43 (1.24, 1.65)
Peripheral edema	706	583	26.36	22.00	+4.36	1.20 (1.07, 1.34)
Cholelithiasis <sup>c</sup>	168/4144	131/4111	7.83	6.20	+1.63	1.26 (1.00, 1.60)

Abbreviations: IR = Incidence Rate per 1000 Patient-years.

<sup>a</sup> Only patients with an intact uterus were considered for the denominator (raloxifene denominator = 3900, placebo denominator = 3882).

<sup>b</sup> Only patients with at least one ovary were considered for the denominator (raloxifene denominator = 4559, placebo denominator = 4606).

<sup>c</sup> Only patients with an intact gallbladder at baseline (raloxifene n=4144, total person-years of follow-up=21467; placebo n=4111, total person-years of follow-up=21136).

**Table 15. RUTH: Exploratory Subgroup Analysis: Invasive Breast Cancer by Gail Score**

Gail Score	Invasive Breast Cancer	Raloxifene N=5,044	Placebo N=5,057	Absolute Risk Difference	Relative Risk (95% CI)	P-value
≥ 1.66	Subgroup	N=2,101	N=2,081	- 1.16	0.64 (0.36, 1.12)	.102
	No. Event (IR)	23 (2.09)	35 (3.25)			
< 1.66	Subgroup	2,943	2,975	- 1.11	-0.49 (0.26, 0.91)	.015
	No. Event (IR)	17 (1.08)	34 (2.19)			

<sup>a</sup> Patient 1220 had no Gail score and had invasive cancer.

**Table 16. RUTH: Breast Cancer Incidence by Invasiveness and ER Status**

Breast cancer category	Raloxifene 5,044	Placebo 5,057	Raloxifene IR	Placebo IR	Absolute Risk Difference	RR (95% CI)
<b>Invasive cases</b>	40	70	1.50	2.66	-1.16	0.56 (0.37, 0.84)
ER(+) cases	25	55	0.94	2.09	-1.15	0.45 (0.27, 0.73)
ER(-) cases	13	9	0.49	0.34	+0.15	1.43 (0.56, 3.78)
ER unknown	2	6	0.07	0.23	-0.16	0.33 (0.03, 1.84)
<b>Non-invasive cases</b>	11	5	0.41	0.19	+0.22	2.18(0.70,,7.99)
DCIS	11	5	0.41	0.19	+0.22	2.18(0.70, 7.99)
LCIS	0	0	0	0	0	NA
Invasiveness unknown	1	1	0.04	0.04	+0.00	NA
<b>All cases</b>	52	76	1.95	2.89	- 1.04	0.67(0.46, 0.97)

Abbreviations: ER=estrogen receptor; DCIS=ductal carcinoma in situ; LCIS=lobular carcinoma in situ; RR=Relative Risk; IR= Incidence Rate (Incidence rate is calculated as the number of patients who developed the event of interest divided by the patient-years of follow-up)

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**Table 17. RUTH: Breast Cancer Stage at Diagnosis**

Breast Cancer Stage	Placebo (N=76)		Raloxifene (N=52)		Total (N=128)	
	n (%)	IR*	n (%)	IR*	n (%)	IR*
Stage 0	5 (6.58)	0.19	11 (21.15)	0.41	16 (12.50)	0.30
Stage I	37 (48.68)	1.41	19 (36.54)	0.71	56 (43.75)	1.06
Stage IIA	19 (25.00)	0.72	9 (17.31)	0.34	28 (21.88)	0.53
Stage IIB	4 (5.26)	0.15	4 (7.69)	0.15	8 (6.25)	0.15
Stage IIIA	0 (0.00)	0.00	2 (3.85)	0.08	2 (1.56)	0.04
Stage IIIB	0 (0.00)	0.00	1 (1.92)	0.04	1 (0.78)	0.02
Stage IV	1 (1.32)	0.04	1 (1.92)	0.04	2 (1.56)	0.04
Cannot be determined	10 (13.16)	0.38	5 (9.62)	0.19	15 (11.72)	0.28

\*Incidence per 1000 patient-years: 26273 follow up patient-years in Placebo, 26666 in Raloxifene

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