FDA Briefing Document
Oncology Drugs Advisory Committee Meeting

July 24, 2007

NDA 22042

Evista® (raloxifene HCL)

Applicant: Eli Lilly

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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"

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 are healthy postmenopausal women, not patients with 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.

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 ≥ 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 is requested on whether these results are acceptable in view of the Evista adverse effects.

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. ODAC advice on this issue will be requested.

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.

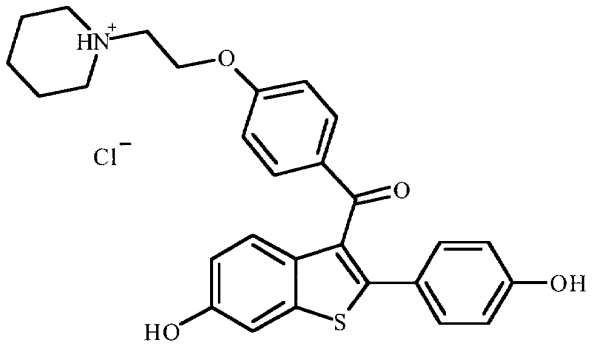
The efficacy results in the RUTH, MORE, CORE and STAR trials must be weighed against the increased risk of deep vein thrombosis, pulmonary embolism and possibly stroke death. A careful consideration of the risk/benefit ratio is especially important for these two proposed new indications in healthy post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

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.

Recommendation is deferred pending ODAC advice.

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 $C_{28}H_{27}NO_4S$•HCl, which corresponds to a molecular weight of 510.05.

Formulation: 60 mg tablets for oral administration.

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)

	RUTH		MORE		CORE		STAR	
Treatment	**Plac**	**Evista**	**Plac**	**Evista**	**Plac**	**Evista**	**Tam**	**Evista**
Number of Pts.	5057	5044	2576	5129	1018[a]	2182[a]	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

[a] 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.

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; 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.

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[a]		RR (95% CI)[b]
	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[c]	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[d]	664	741	16.83	18.66	1.11(1.00,1.23)
Cholelithiasis[e]	NA	NA	NA	NA	NA

[a]IR=incidence rate per 1000 patient-years

[b]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

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

c Hysterectomy was calculated as a risk ratio.

d Peripheral edema is not a coding term in CTC v2.0.

e 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. ODAC advice on this issue will be requested.

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[a]		RR (95% CI)
	Tamoxifen 9736	Placebo 9751	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)

[a]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 (54 deaths in raloxifene group vs. 56 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 (99) 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[a]			RR (95% CI)[b]
	Tam	Evista	Tam	Evista	Difference[c]	
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)

[a]IR=incidence rate per 1000 patient-years
[b]Relative risk for Evista compared to tamoxifen.
RR > 1 indicates higher incidence with Evista.
[c]Rate in tamoxifen group minus rate in Evista group

Table 12. STAR: Breast Cancer Stage at Diagnosis

Tumor Stage	Tamoxifen N=168			Raloxifene N=173			Total N=321		
	n (%)		IR	n (%)		IR	n (%)		IR
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;

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).

Table 13. RUTH: Breast Cancer Risk at Baseline

Characteristics	Placebo N=5,057	Raloxifene N=5,044	Total N=10,101
5-year predicted breast cancer risk (%)			
# 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
5-yr predicted breast cancer risk ≥ 1.66			
# 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)
Age (yrs.)			
# of patients (%)	5057	5044	10101
≤ 60	944 (16.69)	926 (16.38)	1670 (16.53)
> 60-≤ 65	1033 (20.43)	1029 (20.39)	2061 (20.40)
> 65-≤ 70	1213 (23.99)	1260 (24.98)	24.73 (24.48)
> 70-≤ 75	1291 (25.53)	1251 (29.90)	25.42 (25.17)
>75	676 (13.37)	679 (13.46)	1355 (13.41)
Age at menarche			
# 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
Age at first live birth			
# 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
# live births			
# 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)
≥ 3	2339 (46.26)	2260 (44.81)	4599 (45.54)

Table continues on the following page

Characteristics	Placebo N=5057	Raloxifene N=5044	Total N=10101
# 1st degree relatives with breast cancer			
# 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)
# Of prior breast biopsies			
# 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)
Prior breast biopsies with dx of invasive breast cancer			
# of patients (%)	390	345	725
Yes	1 (0.26)	0	1 (0.14)
No	379 (99.74)	345 (100)	724 (99.86)
Prior breast biopsies with dx of DCIS			
# of patients (%)	380	345	725
Yes	0	2 (0.59)	2 (0.29)
No	380 (100)	343 (99.42)	723 (99.72)
Prior breast biopsies with dx of LCIS			
# of patients (%)	380	345	725
Yes	0	0	0
No	380 (100)	345 (100)	725 (100)
Prior breast biopsies with dx of atypical hyperplasia			
# 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)
Prior breast biopsies with dx of other breast conditions			
# 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.

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 [a]	21/3900	17/3882	1.01	0.83	+0.18	1.22 (0.61, 2.46)
Ovarian Cancer [b]	17/4559	10/4606	0.70	0.41	+0.29	1.71 (0.74, 4.17)
Hysterectomy[a]	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[c]	168/4144	131/4111	7.83	6.20	+1.63	1.26 (1.00, 1.60)

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

[a] Only patients with an intact uterus were considered for the denominator (raloxifene denominator = 3900, placebo denominator = 3882).

[b] Only patients with at least one ovary were considered for the denominator (raloxifene denominator = 4559, placebo denominator = 4606).

[c] 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)			

[a] 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)
Invasive cases	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)
Non-invasive cases	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
All cases	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)

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

MORE TRIAL

MORE was a randomized, double-blind, placebo-controlled, multinational study conducted in postmenopausal women with osteoporosis. Assessment of the effect of raloxifene on incidence of all breast cancer was a secondary safety endpoint.
The **primary objectives** were to assess the effects of raloxifene treatment on the incidences of new vertebral fractures, lumbar spine *and* femoral neck bone mineral density (BMD), *and* safety. **Secondary objectives** included assessment of raloxifene on risk of CV disease and endometrial cancer. Women up to 80 years of age who were at least 2 years postmenopausal and had osteoporosis (defined as lumbar spine or femoral BMD at least 2.5 standard deviations below the mean for normal premenopausal women or at least one moderate or two mild vertebral fractures) were eligible to enroll. Patients were not enrolled based on any increased risk for developing breast cancer.

Bilateral mammograms or ultrasound (if patient refused mammogram) were required at baseline and after 2, 3, and 4 years of treatment; mammograms were optional after 1 year of treatment. Breast exams were done at baseline, but were not regularly performed during the study. The study consisted of a 36-month core treatment phase and a 12-month extension phase. Concomitant use of other osteoporosis medications, including bisphosphonates, was allowed as clinically indicated *during the 12-month extension phase*. All patients received supplemental calcium (500 mg/day) and vitamin D (400-600 IU/day) for the duration of the study. All investigator-reported cases of breast cancer were reviewed and adjudicated by a board of physicians blinded to patient treatment assignment and not employed by Lilly.

Results

A total of 7,705 patients were enrolled in the study and randomized to placebo (2,576), raloxifene 60 mg/day (2,557), or raloxifene 120 mg/day (2,572). **Median follow-up** was 47.4 months. Incidence of **all breast cancer,** a secondary safety endpoint, was statistically significantly decreased by 62% (RR 0.38, 95% CI 0.21-0.69; $p<0.001$) in the raloxifene 60-mg/day group (n = 17; IR, 1.94 per 1000 patient-years) compared with the placebo group (n = 44; IR, 5.05 per 1000 patient-years). This decrease was primarily due to a statistically significant 71% decrease (RR 0.29; 95% CI 0.13-0.58) in **invasive breast cancer** in the raloxifene 60-mg/day group (n = 11; IR, 1.26 per 1000 patient-years) compared with the placebo group (n = 38; IR, 4.36 per 1000 patient-years). For invasive **ER positive breast cancer, a** statistically significant decrease of 79% was observed: raloxifene 60-mg/day group (n = 6; IR, 0.69 per 1000 patient-years) compared with the placebo group (n = 29; IR, 3.33 per 1000 patient-years); RR 0.21, 95% CI 0.07-0.50. There were no statistically significant differences between treatment groups in the incidence of **invasive ER-negative breast cancer** (RR 1.25, 95% CI 0.27-6.28) or in the incidence of **noninvasive breast cancer** (RR 0.60, 95% CI 0.09-3.07).

MORE Efficacy and Safety Outcomes

Major outcomes of the MORE 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 raloxifene and placebo are shown.

Table 18. MORE: Efficacy and Important Safety Outcomes

Events [a]	Raloxifene 2,557	Placebo 2,576	Raloxifene IR	Placebo IR	Absolute Risk Difference	RR (95% CI)
Invasive breast cancer	11	38	1.26	4.36	-3.10	0.29 (0.13, 0.58)
Noninvasive breast cancer	3	5	0.34	0.57	-0.23	0.60 (0.09, 3.07)
Invasiveness unknown	3	1	0.34	0.11	+0.23	2.99 (0.24,156)
All breast cancers	17	44	1.94	5.05	-3.11	0.38 (0.21, 0.69)
Clinical vertebral fracture	62	107	7.08	12.27	-5.19	0.58 (0.42, 0.80)
Death	64/5129	36	3.63	4.13	-0.50	0.88 (0.58, 1.36)
Death due to Stroke	9/5129	6	0.51	0.69	-0.18	0.74 (0.23, 2.52)
Stroke	91/5129	56	5.16	6.42	-1.26	0.80 (0.57, 1.14)
Deep vein thrombosis	44/5129	8	2.50	0.92	+1.58	2.72 (1.27, 6.68)
Pulmonary embolism	22/5129	4	1.25	0.46	+0.79	2.72 (0.92, 10.85)
Endometrial and uterine cancer [b]	8/3960	5/1999	0.59	0.74	+0.15	0.80 (0.23, 3.10)
Ovarian Cancer	6/5129	6/1999	0.34	0.69	-0.35	0.49 (0.13, 1.84)
Hysterectomy[b]	40/3960	22/1999	2.93	3.24	-0.31	0.90 (0.52, 1.60)
Hot Flashes	512/5129	151	29.04	17.31	+11.73	1.68 (1.40, 2.03)
Leg Cramps	443/5129	150	25.13	17.20	+7.93	1.46 (1.21, 1.77)
Peripheral edema	340/5129	134	19.29	15.36	+3.93	1.26 (1.03, 1.55)
Cholelithiasis[c]	93/5129	45	5.28	5.16	+0.12	1.02 (0.71, 1.50

Abbreviations: IR = Incidence Rate per 1000 Patient-years; RR=Relative risk.

[a] Breast cancer and clinical vertebral fracture events are for the raloxifene 60 mg/day arm only; denominator = 2557. For the safety events of death, death due to stroke, stroke, deep vein thrombosis, pulmonary embolism, and ovarian cancer, the raloxifene 60 and 120 mg/day arms were pooled to have the greatest opportunity to detect safety signals; thus, the denominator for these events is 5129.

[b]Only patients with a uterus at baseline (pooled raloxifene n=3960, total person-years of followup=13659.16; placebo n=1999, total person-years of follow-up=6791.41). "Hysterectomy" included MedDRA Preferred Terms of "Hysterectomy," "Hysterosalpingo-oophorectomy," and "radical hysterectomy."

[c]Gallbladder status at baseline was not ascertained in the MORE trial.

Table 19. MORE: Breast Cancer Incidence by Invasiveness and ER Status

Breast Cancer Category*	Placebo N=2576 n (IR)	Raloxifene 60 mg N=2557 n (IR)	Relative Risk (95% CI)
Invasive	38 (4.36)	11 (1.26)	0.29 (0.13, 0.58)
ER Positive	29 (3.33)	6 (0.69)	0.21 (0.07, 0.50)
ER Negative	4 (0.46)	5 (0.57)	1.25 (0.27, 6.28)
ER Unknown	5 (0.57)	0	N/A
Non-invasive	5 (0.57)	3 (0.34)	0.60 (0.09, 3.07)
DCIS	5 (0.57)	3 (0.34)	0.60 (0.09, 3.07)
LCIS	0 (0.00)	0 (0.00)	NA
Invasiveness unknown	1 (0.11)	3 (0.34)	2.99 (0.24, 1.56)
All	44 (5.05)	17 (1.94)	0.38 (0.21, 0.69)

*Patients randomized in MORE to either placebo or raloxifene HCl 60 mg/day. Breast cancers reported from randomizations in MORE (48 months) are presented.

Table 20. MORE: Breast Cancer Stage at Diagnosis

Breast Cancer Stage	Placebo (N=44)		Raloxifene 60 mg (N=17)		Total (N=61)	
	n (%)	IR*	n (%)	IR*	n (%)	IR*
Stage 0	1 (2.27)	0.11	0 (0.00)	0.00	1 (1.64)	0.06
Stage I	17 (38.64)	1.95	6 (35.29)	0.69	23 (37.70)	1.32
Stage IIA	6 (13.64)	0.69	3 (17.65)	0.34	9 (14.75)	0.52
Stage IIB	0 (0.00)	0.00	0 (0.00)	0.00	0 (0.00)	0.00
Stage IIIA	1 (2.27)	0.11	1 (5.88)	0.11	2 (3.28)	0.11
Stage IIIB	0 (0.00)	0.00	0 (0.00)	0.00	0 (0.00)	0.00
Stage IV	0 (0.00)	0.00	0 (0.00)	0.00	0 (0.00)	0.00
Unknown	6 (13.64)	0.69	3 (17.65)	0.34	9 (14.75)	0.52
Staging not performed	13 (29.55)	1.49	4 (23.53)	0.46	17 (27.87)	0.97

*Incidence per 1000 patient-years. 8715 follow up patient-years in Placebo, and 8755 in Raloxifene HCl 60 mg

CORE TRIAL

CORE was a double-blind, placebo-controlled, multinational extension study that enrolled postmenopausal women with osteoporosis, previously randomized and followed up in MORE, for an additional 4 years of follow-up. The **primary objective** was to compare the long-term effect of raloxifene 60 mg/day to placebo on the reduction in incidence of invasive breast cancer in postmenopausal women with osteoporosis. The **secondary objectives** were to assess the long-term effect of raloxifene HCl 60 mg/day on the incidence of invasive ER-positive breast cancer and non-vertebral fractures in postmenopausal women with osteoporosis. Raloxifene 60 mg/day was the only active treatment dose in CORE as its efficacy was similar to raloxifene 120 mg/day in MORE in reduction in the incidence of breast cancer and new vertebral fractures

Of the 180 investigative sites that participated in MORE, 130 agreed to participate in CORE. Patients previously randomized in MORE who were at the CORE participating sites were invited to participate in CORE after their completion or discontinuation from MORE; 6,511 patients were eligible and 4,011 chose to enroll in CORE. They were not re-randomized, but the randomization assignment from MORE was carried forward into CORE. The CORE enrollees randomized to raloxifene 60 mg/day (n = 1,355) or 120 mg/day (n = 1,370 in MORE were assigned to receive raloxifene 60 mg/day in CORE (n = 2,725); those who had been assigned to receive placebo in MORE continued on placebo in CORE (n = 1,286). Thus, in CORE, approximately twice as many patients were assigned to receive raloxifene compared to those assigned to receive placebo.

Women randomized in MORE could enroll in CORE even if they were not allowed to take study medication or chose not to take it. CORE enrollees were not allowed to take study medication if they had a diagnosis of any malignancy considered to be estrogen-dependent (including malignancies of the breast or uterus), had a history of VTE, or had a safety concern during MORE that necessitated unblinding of their treatment assignment. Of the CORE enrollees, 811 (268 [20.8%] in placebo and 543 [19.9%] in raloxifene) did not take study medication, either because they met one of the criteria above or because they chose not to.

Each patient's 5-year predicted risk of invasive breast cancer was calculated at baseline using the modified Gail model. Bilateral mammograms were required at baseline and every 2 years thereafter. Clinical breast examinations were required at baseline and annually thereafter

All investigator-reported breast cancers were reviewed and adjudicated by a board of physicians specialized in breast cancer who were blinded to patient treatment assignment and who were not employed by Lilly.

Results

A total of 4,011 patients were enrolled into CORE; 2,725 assigned to receive raloxifene 60 mg/day and 1,286 to receive placebo. Because 12 CORE enrollees in the placebo

group and 9 in the raloxifene group were diagnosed with breast cancer prior to Visit 1, the analysis of the breast cancer endpoints was performed for 3,990 patients. For raloxifene, 2725 patients enrolled in CORE but 9 had been diagnosed with breast cancer prior to Visit 1, so the denominator is 2716. For placebo, 1286 patients enrolled but 12 had been diagnosed with breast cancer prior to Visit 1, so the denominator is 1274. The safety events of death, death due to stroke, stroke, deep vein thrombosis, pulmonary embolism, and ovarian cancer considered all patients who enrolled in CORE; thus, the denominators are 2725 for raloxifene and 1286 for placebo.

Breast cancer risk assessment characteristics were balanced between treatment groups at baseline. The mean **5-year predicted risk of invasive breast cancer** was 1.94% and approximately 54% of patients in each treatment group had a 5-year predicted invasive breast cancer risk of **≥1.66%.**

From CORE enrollment to the end of CORE, the incidence of **invasive breast cancer** was statistically significantly decreased by 55% (RR 0.45; 95% CI 0.23-0.89) in the raloxifene group (n = 19; IR, 2.43 per 1000 patient-years) compared with the placebo group (n = 20; IR, 5.41 per 1000 patient-years). This decrease was primarily due to a statistically significant 62% reduction (RR 0.38, 95% CI 0.16-0.87) in incidence of **invasive ER-positive breast cancer** in the raloxifene group (n = 12; IR= 1.54 per 1000 patient-years) compared with the placebo group (n = 15; IR= 4.05 per 1000 patient-years).

There were no statistically significant differences between treatment groups in the incidences of invasive ER-negative breast cancer (RR 0.95, 95% CI 0.20-5.85) or noninvasive breast cancer (RR 1.18, 95% CI 0.19-12.44).

Table 21. CORE: Breast Cancer Risk at Baseline

Variable	Placebo (N=1286)	Raloxifene 60 mg (N=2725)	Total (N=4011)
CORE Gail Score (VISIT: 1)			
No. Patients	1286	2725	4011
Mean	1.94	1.94	1.94
Median	1.70	1.70	1.70
Standard Dev.	0.93	0.98	0.96
Minimum	0.40	0.70	0.40
Maximum	11.10	13.10	13.10
Age at Menarche (VISIT: 1)			
No. Patients (%)	1286	2725	4011
6 - <12	145 (11.3)	313 (11.5)	458 (11.4)
12 - <14	575 (44.7)	1166 (42.9)	1741 (43.5)
14 - <99	565 (44.0)	1242 (45.6)	1807 (45.1)
Unspecified	1	4	5
Age at Menarche (VISIT: 1)			
No. Patients	1285	2721	4006
Mean	13.35	13.38	13.37
Median	13.00	13.00	13.00
Standard Dev.	1.56	1.63	1.61
Minimum	9.00	8.00	8.00
Maximum	19.00	19.00	19.00
Unspecified	1	4	5
Age of First Live Birth (VISIT: 1)			
No. Patients (%)	1286	2725	4011
0	31 (2.8)	59 (2.5)	90 (2.6)
>0 - <20	85 (7.6)	199 (8.3)	284 (8.1)
20 - <25	494 (44.0)	1019 (42.5)	1513 (43.0)
25 - <30	356 (31.7)	806 (33.7)	1162 (33.0)
>=30	157 (14.0)	312 (13.0)	469 (13.3)
Unspecified	163	330	493
Age of First Live Birth (VISIT: 1)			
No. Patients	1123	2395	3518
Mean	24.53	24.40	24.44
Median	24.00	24.00	24.00
Standard Dev.	8.15	7.35	7.61
Minimum	0.00	0.00	0.00
Maximum	99.00	99.00	99.00
Unspecified	163	330	493

CORE: Breast Cancer Risk at Baseline (continued)

Variable	Placebo (N=1286)	Raloxifene 60 mg (N=2725)	Total (N=4011)
CORE First Degree Relatives with BC (VISIT: 1)			
No. Patients (%)	1286	2725	4011
1 - <2	150 (90.9)	333 (89.5)	483 (89.9)
2 - <3	14 (8.5)	33 (8.9)	47 (8.8)
3 - <4	0	6 (1.6)	6 (1.1)
>=4	1 (0.6)	0	1 (0.2)
Unspecified	1121	2353	3474
Number of Breast Biopsies (VISIT: 1)			
No. Patients (%)	1286	2725	4011
1 - <2	157 (68.6)	343 (74.9)	500 (72.8)
>=2	72 (31.4)	115 (25.1)	187 (27.2)
Unspecified	1057	2267	3324
Number of Breast Biopsies (VISIT: 1)			
No. Patients	229	458	687
Mean	1.77	1.57	1.64
Median	1.00	1.00	1.00
Standard Dev.	2.95	2.17	2.46
Minimum	1.00	1.00	1.00
Maximum	40.00	35.00	40.00
Unspecified	1057	2267	3324
Any Biopsies with Atypical Hyperplasia (VISIT: 1)			
No. Patients (%)	1286	2725	4011
Yes	7 (3.1)	11 (2.4)	18 (2.6)
No	203 (88.6)	416 (90.8)	619 (90.1)
Unknown	19 (8.3)	31 (6.8)	50 (7.3)
Unspecified	1057	2267	3324

CORE Efficacy and Safety Outcomes

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

Table 22. CORE: Efficacy and Important Safety Outcomes

Events [a]	RLX 2,716	PLB 1,274	RLX IR	PLB IR	Absolute Risk Difference	Relative Risk (95% CI)
Invasive breast cancer	19	20	2.43	5.41	-2.98	0.45 (0.23, 0.89)
Noninvasive breast cancer	5	2	0.64	0.54	+0.10	1.18 (0.19, 12.44)
Invasiveness unknown	0	0	0.00	0.00	0.00	NA
All breast cancers	24	22	3.07	5.95	-2.88	0.52 (0.28, 0.96)
Clinical vertebral fracture [b]	65/2725	32/1286	8.28	8.56	-0.28	0.97 (0.62, 1.53)
Death	47/2725	29/1286	5.99	7.76	-1.77	0.77 (0.48, 1.27)
Death due to Stroke	6/2725	1/1286	0.76	0.27	+0.49	2.81 (0.34, 129)
Stroke	49/2725	14/1286	6.24	3.75	+2.49	1.65 (0.92, 2.98)
Deep vein thrombosis	17/2725	4/1286	2.17	1.07	+1.10	2.01 (0.68, 5.95)
Pulmonary embolism	9/2725	0/1286	1.15	0.00	+1.15	NA
Endometrial and uterine cancer [c]	4/2138	3/1008	0.65	1.02	-0.37	0.64 (0.11, 4.35)
Ovarian Cancer	2/2725	2/1286	0.25	0.54	-0.29	0.46 (0.03, 6.39)
Hysterectomy[c]	13/2138	10/1008	2.11	3.40	-1.29	0.62 (0.25, 1.58)
Hot Flashes	26/2725	11/1286	3.31	2.94	+0.37	1.13 (0.54, 2.52)
Leg Cramps	90/2725	36/1286	11.46	9.63	+1.83	1.19 (0.80, 1.80)
Peripheral edema	61/2725	30/1286	7.77	8.03	-0.26	0.97 (0.62, 1.55)
Cholelithiasis[d]	352725	12/1286	4.46	3.21	+1.25	1.39 (0.70, 2.94)

Abbreviations: IR = Incidence Rate per 1000 Patient-years; PLB = Placebo; RLX = Raloxifene.

[a] Breast cancer events are for the patients who enrolled in CORE and had not been diagnosed with breast cancer prior to Visit 1.

[b] Vertebral fractures were collected as adverse events.

[c] Only patients with an intact uterus were considered for denominator (raloxifene denominator = 2138, placebo denominator = 1008).

[d] Gallbladder status at baseline was not ascertained in the CORE trial.

Table 23. CORE: Breast Cancer Incidence by Invasiveness and ER Status

Breast Cancer Category	Placebo N=1,274 n (IR)	Raloxifene 60 mg N=2,716 n (IR)	Relative Risk (95% CI)
Invasive	20 (5.41)	19 (2.43)	0.45 (0.23, 0.89)
ER Positive	15 (4.05)	12 (1.54)	0.38 (0.16, 0.87)
ER negative	3 (0.81)	6 (0.77)	0.95 (0.20, 5.85)
ER unknown	2 (0.54)	1 (0.13)	NA
Non-invasive	2 (0.54)	5 (0.64)	1.18 (0.19, 12.44)
DCIS	2 (0.54)	5 (0.64)	1.18 (0.19, 12.44)
LCIS	0 (0.00)	0 (0.00)	NA
Invasive unknown	0 (0.00)	0 (0.00)	NA
All	22 (5.95)	24 (3.07)	0.52 (0.28, 0.96)

Table 24. CORE: Breast Cancer Stage at Diagnosis

Breast Cancer Stage	Placebo (N=44)		Raloxifene 60 mg (N=17)		Total (N=61)	
	n (%)	IR	n (%)	IR	n (%)	IR*
Stage 0	2 (9.09)	0.54	5 (20.83)	0.64	7 (15.22)	0.61
Stage I	12 (54.55)	3.23	12 (50.00)	1.54	24 (52.17)	2.08
Stage IIA	1 (4.55)	0.27	3 (12.50)	0.38	4 (8.70)	0.35
Stage IIB	1 (4.55)	0.27	2 (8.33)	0.26	3 (6.52)	0.26
Stage IIIA	0 (0.00)	0.00	0 (0.00)	0.00	0 (0.00)	0.00
Stage IIIB	0 (0.00)	0.00	0 (0.00)	0.00	0 (0.00)	0.00
Stage IV	0 (0.00)	0.00	0 (0.00)	0.00	0 (0.00)	0.00
Unknown	6 (27.27)	1.62	2 (8.33)	0.26	8(17.39)	0.69
Staging not performed	0 (0.00)	0.00	0 (0.00)	0.00	0 (0.00)	0.00

Abbreviations: IR= incidence per 1000 patient-years (3715 follow-up patient-years in placebo, 7810 in Raloxifene); n= number of breast cancer events in each stage; N= total number of breast cancer events.

8-Year Analysis of MORE and CORE (Sponsor's Exploratory Analysis)

The beginning of CORE did not coincide with the end of MORE. The median time between the end of participation in MORE and enrollment in CORE was 10.6 months (range 2.6 to 62 months) for both treatment groups. During this period, patients were not on study drug and may have taken other SERMs or other hormones. A time to first event analysis was performed for the subset of all MORE patients randomized to placebo or raloxifene 60 mg/day who chose to continue to participate in CORE (N = 2,641). Data for these patients were analyzed from the time of their randomization in MORE to the end of their participation in CORE, which was approximately 8 years.

Raloxifene treatment, compared with placebo, statistically significantly reduced the incidence of invasive breast cancer by 60% (Raloxifene: n = 13; IR = 1.24 per 1000 patient-years; Placebo: n = 32; IR = 3.19 per 1000 patient-years; HR 0.40, 95% CI 0.21-0.77). The statistically significant decrease in invasive breast cancer was primarily due to a statistically significant 65% reduction (HR 0.35, 95% CI 0.17-0.76) in incidence of invasive ER positive breast cancer in the raloxifene group (n = 9; IR= 0.86 per 1000 patient-years) compared with the placebo group (n = 25; IR= 2.49 per 1000 patient-years). There were no statistically significant differences between treatment groups in the incidences of invasive ER-negative breast cancer (HR 1.03, 95% CI 0.21-5.12) or noninvasive breast cancer (HR 2.05, 95% CI 0.37-11.25).