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	6/2576	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=22)		Raloxifene 60 mg (N=24)		Total (N=46)	
	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).

ONCOLOGY DRUGS ADVISORY COMMITTEE

On July 24, 2007 the Evista SNDA was presented to the FDA Oncology Drugs Advisory Committee. The Committee expressed concern whether invasive breast cancer was being prevented or just delayed. There was concern whether the Evista benefit would persist over the long term and that adverse events may increase in incidence or new adverse events appear over the long term. There was also concern regarding what duration of Evsita administration should be recommended. There was concern that non-invasive breast cancer was not decreased. The Committee found it difficult to assess the benefit/risk ratio with any precision. These concerns were reflected in the Committee vote. The vote was 8 to 6 with 1 abstention that the Evista benefit/risk ratio is favorable for PM women with osteoporosis and 10 to 4 with 1 abstention that the Evista benefit ratio is favorable for PM women at increased risk. Labeling should warn that Evista increases the risk of thromboembolic events. A MedGuide was also suggested.

DISCUSSION

For the new indication of reducing the risk of invasive breast cancer in PM women with osteoporosis the benefit/risk ratio appears favorable, but the decision to use Evista should be individualized for each woman. This is especially true if the woman is not already on Evista for osteoporosis and is making a decision between Evista and other drugs for osteoporosis treatment.

For the new indication of reducing the risk of invasive breast cancer in PM women at high risk of invasive breast cancer the benefit/risk ratio appears favorable, but is more difficult to assess. Because of the necessity of a non-inferiority analysis of the STAR trial the amount of invasive breast cancer reduction can not be precisely quantitated. Evista may lose up to 35% of the tamoxifen benefit. Evista generally has fewer serious adverse effects than tamoxifen. The choice is not just between Evista and tamoxifen. A very acceptable choice is just to have regularly scheduled (at least yearly) mammograms and breast examinations.

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 clinical 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". The incidence of osteoporosis in PM women is about 20% and the incidence of osteopenia is about 35%. Fifty percent of PM women will have an osteoporotic fracture at some time in their life. It appears that 80-90% of PM women could fit one or both of the proposed two new indications.

The Evista benefit/risk ratio will differ among women. Each woman's potential benefit and risk should be individually assessed. For example, women with atypical hyperplasia, lobular carcinoma in situ or a risk of invasive breast cancer during the next five years of 5% or greater would have more Evista benefit than other women, but their risk of serious adverse events would not be impacted by their higher risk for invasive breast cancer.

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 thrombembolic 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.

John R. Johnson, M.D.
Clinical Team Leader Oncology Drugs
September 6, 2007

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/s/

John Johnson
9/6/2007 02:36:00 PM
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Evista® (Raloxifene hydrochloride, 60 mg) for Reduction in the Risk of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis

CLINICAL REVIEW

Application Type	NDA
Number	22042
Submission Code	SE 1
Letter Date	Nov 13 2006
Stamp Date	Nov 14 2006
PDUFA Goal Date	Sep 14 2007
Reviewer Name	Bhupinder S Mann MO John R Johnson TL
Review Completion Date	Sep 07 2007
Established Name	Raloxifene
Trade Name	Evista
Therapeutic Class	Estrogen Receptor Agonist-Antagonist or Selective Estrogen Receptor Modulator (SERM)
Applicant	Eli Lilly
Priority Designation	S
Formulation	Tablets for oral administration
Dosing Regimen	60 mg/day
Indication	Reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis
Intended Population	Postmenopausal women with osteoporosis

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1 EXECUTIVE SUMMARY

1.1 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.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Black Box Warning on the increased risk of venous thromboembolism and increased risk of deaths due to stroke:

- 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.

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® (Raloxifene hydrochloride, 60 mg) is available as tablets for oral administration and it is marketed for the treatment (1999) and prevention (1997) of osteoporosis in postmenopausal women. In the reviewed NDA, results of four double-blind randomized trials in postmenopausal women were submitted in support of the two new indications:

- Reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis
- Reduction in the risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer

- There were three placebo-controlled trials of raloxifene: Multiple Outcomes of Raloxifene Evaluation (MORE), its continuation Continuing Outcomes Relevant to Evista (CORE), and raloxifene Use for the Heart (RUTH).
    - RUTH, MORE, and CORE enrolled 10,101, 7,705, and 4.011 postmenopausal women, respectively
    - Patients in the placebo-controlled raloxifene trials have been followed for 3 to 8 years.
- Active control raloxifene trial Study of Tamoxifen and Raloxifene (STAR) enrolled 19,747 patients and followed them for approximately 4 years (see Dr. Cortazar's review for details).

1.3.2 Efficacy

Data from three placebo-controlled trials, the RUTH, MORE and CORE trials were submitted to support the first new proposed indication. The most important data supporting the proposed indication comes from the RUTH trial. Data from the MORE and CORE trials are less important for several 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, MORE and CORE indicate that Evista reduces the risk of invasive breast cancer: relative risks favoring raloxifene over the placebo were 0.56, 0.29, and 0.45, respectively.

- 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.

Reviewer Comments: *Benefit of raloxifene is modest, eg, in the RUTH trial, 5,057 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 were treated for one year to prevent an invasive breast cancer in one woman. This was achieved at a cost of an increase in serious adverse events such as deep vein thrombosis, pulmonary embolism, and possibly stroke death. The efficacy results in the RUTH, MORE, CORE and STAR trials needed careful weighing against the increased risk of deep vein thrombosis, pulmonary embolism and possibly stroke death. A careful consideration of the risk/benefit ratio was especially important and therefore the Oncology Drugs Advisory Committee (ODAC) advice was requested.*

1.3.3 Safety

Data on safety of raloxifene is available from the three placebo-controlled trials of raloxifene: MORE, its continuation CORE, and the RUTH trial.

- RUTH, MORE, and CORE enrolled 10,101, 7,705, and 4.011 postmenopausal women, respectively
- Median durations of patient-exposure to raloxifene in RUTH, MORE, and CORE were approximately 5, 4, and 3 years, respectively.
- Patients in these trials have been followed for 3 to 8 years.

The following adverse events (AEs) are clinically important and are likely treatment related. (For further details, please see 7.1).

Venous thromboembolic event (VTE)

- A *statistically significant* increase in deep vein thrombosis (DVT), pulmonary embolism (PE), and other VTEs was observed in the raloxifene arms in RUTH (44% increase) and MORE (89% increase) trials.
- *Numerical increases* in the incidence of DVT and the incidence of PE, i.e. DVT and PE events counted separately rather than under single VTE events category, were observed in raloxifene assigned patients in RUTH, MORE, and CORE trials.
  - This increase was statistically significant for DVT in MORE.

Hot flushes, leg cramps, and peripheral edema

- There were statistically significant increases in the incidences of *hot flushes*, *leg cramps* (*muscle spasms*), and *peripheral edema* in raloxifene assigned patients in RUTH and MORE.

- There was a numerically higher incidence of hot flashes and leg cramps in CORE.

Death due to stroke

- This important safety observation was noted in RUTH only:
  - A statistically significant (p=0.0499) 49% increase in the incidence of the *death due to stroke* was observed in raloxifene (compared with placebo) assigned patients.

- No such increase was observed in MORE.
- An increase was observed in CORE but it was not statistically significant.

Cholelithiasis

- In RUTH, there was a *statistically significantly* greater incidence of *cholelithiasis* in raloxifene- compared with placebo-assigned patients (3.3% versus 2.6%).
- This increase was not statistically significant in MORE or CORE.

Conclusions and Important Limitations of the Data

The primary endpoints for the 3 placebo-controlled clinical trials were efficacy endpoints—accordingly, the sample size in each trial was determined based on the expected rates of efficacy events in the experimental and the control arms. Therefore:

- The risk of both type 1 and type 2 errors is high, i.e., due to small sample size relative to the difference in incidence rates of events between the study arms, the risks can be under or over estimated.
- Statistical significance testing of the safety events is neither reliable nor conclusive.

Safety conclusions were made considering the above limitations of the analyses. The applicant agreed to include the information on VTE, death due to stroke, and cholelithiasis risk in the label.

1.3.4 Dosing Regimen and Administration

Recommended Dose:

- The recommended dose of raloxifene for reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis is one 60 mg EVISTA® tablet daily, which may be administered any time of day without regard to meals.

- The same dose of raloxifene is recommended for prevention and treatment of osteoporosis.
  - Additional supplementation with calcium and vitamin D are recommended for osteoporosis prevention or treatment

- Elemental calcium: 1500 mg/day
- Vitamin D: 400-800 IU/day

- Raloxifene at a dose of 60 mg/day has been studied in both placebo and active control trials.
  - In one of the placebo-controlled trials, a dose of 120 mg/day was studied in over 2,500 postmenopausal women; however, no significant differences in safety or efficacy were found compared to the 60 mg/day dose.

- There were three placebo-controlled trials of raloxifene: Multiple Outcomes of Raloxifene Evaluation (MORE), its continuation Continuing Outcomes Relevant to Evista (CORE), and raloxifene Use for the Heart (RUTH). These trials enrolled over 17,000 patients from diverse populations and followed them over 3 to 8 years.
- Active control raloxifene trial Study of Tamoxifen and Raloxifene (STAR) enrolled 19,747 patients.
  - The data from the STAR trial was submitted to support a second indication for raloxifene: reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer (These data were reviewed by Dr. Patricia Cortazar.)

1.3.5 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

- 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.

1.3.6 Special Populations

- Raloxifene has been studied adequately in the population for which it will be approved: postmenopausal women.

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.

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.
- See 8.1.

Hepatic Impairment

- Raloxifene should be used with caution in patients with hepatic impairment.
- See 8.1.

Children

- Raloxifene is for use by postmenopausal women only. Neither safety nor efficacy has been studied in children.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Evista (raloxifene hydrochloride) is a selective estrogen receptor modulator (SERM), i.e. it is an estrogen receptor agonist-antagonist. Raloxifene belongs to the benzothiophene class of

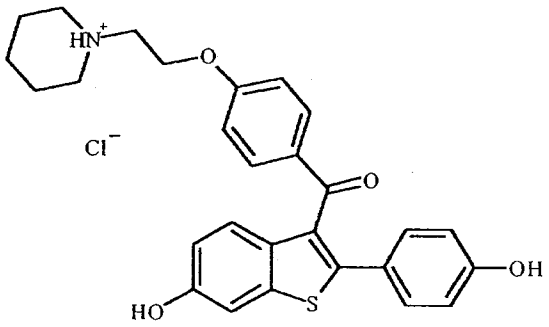


Figure 1 Raloxifene hydrochloride: chemical structure.

compounds. The chemical structure is shown above. 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.

Evista is currently marketed for the treatment (1999) and prevention (1997) of osteoporosis in postmenopausal women.

The applicant submitted the results of four double-blind randomized trials in postmenopausal women in support of the two new indications:

- Reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis
- Reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer

2.2 Currently Available Treatment for Indications

- No drug is currently approved for the first proposed new indication (reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis).

- Tamoxifen is approved for the second proposed new indication (reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer).

2.3 Availability of Proposed Active Ingredient in the United States

Evista® (Raloxifene hydrochloride, 60 mg) is available as tablets for oral administration and it is marketed for the treatment (1999) and prevention (1997) of osteoporosis in postmenopausal women.

- It is manufactured by the applicant Eli Lilly and has been marketed worldwide since its approval in 1997 for prevention of osteoporosis. It has been used by several million women worldwide.
- The most recent labeling changes occurred in July 2007 after the results of the RUTH trial were available.
  - Increased risk of venous thromboembolism (VTE) and the risk of death due to stroke were included in the label.
  - Lack of benefit from raloxifene in reducing the risk of cardiovascular events was also included.

2.4 Important Issues With Pharmacologically Related Products

- Increased risks of thromboembolism, uterine endometrial cancer, and vasomotor symptoms are known to be associated with the use of SERMs like tamoxifen and raloxifene.
- Effects on bones and serum lipids (and possibly cardiovascular events) are known to be favorable for tamoxifen.

2.5 Presubmission Regulatory Activity

- Please see Dr. Cortazar's review.

2.6 Other Relevant Background Information

- None for this part of the review.
- Please also see Dr. Cortazar's review.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

CMC reviewer noted the following:

"Reference is made to the Applicant's Type 6 NDA submission dated 13-NOV-2006. 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.
"The current Type 6 NDA will utilize the previously-approved (60 mg) tablet formulation.
"Internal discussion with the Medical Officer (Dr. B. Mann) confirmed that there are no proposed revisions in dosing that necessitate re-examination of the corresponding drug substance impurity profiles.
"All previously-approved CMC information remains satisfactory. The Applicant's request for a categorical exclusion is granted, and there are no outstanding CMC issues with this Type 6 NDA.
"From a CMC standpoint, this Type 6 NDA is recommended for approval."

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

Sources of data for this part of the review are the three placebo-controlled raloxifene trials. Clinical study reports and data tables of the following studies were reviewed in depth:

- Multiple Outcomes of Raloxifene Evaluation (MORE)
- Continuing Outcomes Relevant to Evista (CORE)
- Raloxifene Use for the Heart (RUTH)

4.2 Tables of Clinical Studies

- The following tables show the salient features of raloxifene studies that were submitted to support the two proposed indications in this NDA submission. Names of the trials, patient populations, primary endpoints, median ages of the enrolled patient populations, designs of the trials, treatment arms, and important exclusions are shown.

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 trials designs (patient population, primary endpoint, and median 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 trials designs (treatment arms and exclusions)

TRIAL	TREATMENT ARMS	IMPORTANT EXCLUSIONS
STAR	o Tamoxifen 20 mg o Raloxifene 60 mg	o Hx of DVT, PE, CVA or TIA o Current use of coumadin, atrial fibrillation, uncontrolled diabetes or uncontrolled hypertension
RUTH	o Raloxifene 60 mg o Placebo	o MI, PCI, or CABG within 3 months, o Hx of VTE
MORE	o Raloxifene 60 mg o Raloxifene 120 mg o Placebo	o Hx VTE, CVA within 10 yrs
CORE	o Raloxifene 60 mg o Placebo	o 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

4.3 Review Strategy

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

- The data supporting the first proposed new 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.
- The data supporting the second proposed new indication (reduction in the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer) were reviewed by Medical Officer Patricia Cortazar.
  - Data from active control trial STAR were reveiwed.

4.4 Data Quality and Integrity

DSI audited the following study sites for data integrity for the placebo controlled trial RUTH. This trial was selected as it had breast cancer incidence as a primary study endpoint. The data from each of these sites was reported as reliable.

Kristine Ensrud, M.D., M.P.H. (Principal Investigator)
University of Minneapolis
Epidemiology Clinical Research Center
1100 Washington Avenue South, Suite 201,
Minneapolis, MN, 55415

Protocol	H3S-MC-GGIO (RUTH)
Subjects Randomized	105
Subjects Audited	23

Elizabeth Barrett-Connor, M.D. (Principal Investigator)
University of California, San Diego School of Medicine
9500 Gilman Drive, Mail Code 0607
LaJolla, CA 92093-0607

Protocol	H3S-MC-GGIO (RUTH)
Subjects Randomized	74
Subjects Audited	20

Jane A. Cauley, Dr.PH (Principal Investigator)
Univ Of Pittsburgh School Of Medicine,
130 DeSoto St., A524,
Pittsburgh, PA, 15261

Protocol	H3S-MC-GGIO (RUTH)
Subjects Randomized	112
Subjects Audited	21

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 reveiwed.
- This reviewer did not find any issues relevant to the integrity of the data submitted to support this NDA: the trials were double-blind placebo-controlled trials and breast cancer cases were adjudicated by an independent panel in each trial.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Raloxifene pharmacokinetics were extensively described in the human pharmacokinetics, pharmacodynamics, and bioavailability section of the initial and subsequent regulatory submissions for the indication of prevention and treatment of osteoporosis in postmenopausal women. In brief, approximately 60% of an oral dose of raloxifene is absorbed. Metabolism is extensive and the majority is excreted in the feces. The terminal half-life is approximately 28 hours due to enterohepatic cycling.

Since the prevention (NDA 20-815/000; June 8, 1997) and treatment (NDA 20-815/SE1; March 30, 1999) of osteoporosis applications, the sponsor has conducted additional trials in which the population pharmacokinetics and pharmacodynamics of raloxifene in patients with primary breast cancer (GGHW) and the steady-state raloxifene concentration data (GGIO) in postmenopausal women were evaluated. No patient factors or laboratory measurements were found to influence the PK of raloxifene. The results of the population PK and safety analysis from prior review indicated that age, weight, ethnicity, body weight, race, renal function, alcohol use and smoking status did not effect raloxifene pharmacokinetics. In addition there was no statistically significant effect of plasma raloxifene concentrations related to adverse events, treatment emergent side effects, or death.

5.2 Pharmacodynamics

In study GGHW, a phase 3 study of raloxifene in patients with primary breast cancer, the short-term biologic effect of raloxifene on an intermediate endpoint marker, Ki67, which is a proliferation associated nuclear antigen, were studied.

- Patients received raloxifene 60 mg QD, raloxifene 300 mg BID or placebo for 14 days. Sparse samples for PK (Day 10 and 14) along with levels for Ki67, estrogen receptor and progesterone receptor measures (baseline and end of study) were taken during the study. A one compartment model with first-order absorption (Ka) and first-order elimination was selected to describe the pharmacokinetics of raloxifene following oral administration. Each covariate was tested for a relationship with clearance or volume of distribution using both linear and nonlinear models.
- No significant correlation between steady-state concentrations and change in Ki67 was observed and no further pharmacokinetic/pharmacodynamic model was developed.

5.3 Exposure-Response Relationships

There was no formal PK/PD analysis done by the sponsor for the reduction in risk of breast cancer.

- The primary study supporting efficacy (RUTH/GGIO) had sparse sampling from 250 of 10,000 patients at one dose level (60 mg QD) which made it difficult to elucidate a formal concentration/response relationship.
- 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.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The applicant has proposed two new indications for raloxifene. Bhupinder S Mann, Medical Officer, is the clinical reviewer for the first indication (this review), and Patricia Cortazar, Medical Officer, is the clinical reviewer for the second indication:

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"

6.1.1 Methods

Data from the trials shown in the following table were used to evaluate evidence supporting the first proposed new indication.

Table 4 Clinical trials supporting the first proposed new indication.

Study Title	Study Name (Abbreviation)	Protocol Name (Abbreviation)	Study Protocol
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

- RUTH, MORE and CORE trials are placebo-controlled trials.
- The most important data supporting the proposed new indications comes from the RUTH trial.
- Data from the MORE and CORE trials are less important:
  - 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 a secondary objective and was assessed as a safety endpoint.
  - The CORE trial was a continuation of the MORE trial. Breast cancer was added as the primary endpoint. However, the patients were not re-randomized and prior randomization was lost because only approximately 52% of all

MORE patients participated in the CORE trial and approximately 42% of MORE patients received study drug (Evista or placebo) in the CORE trial.

6.1.2 General Discussion of Endpoints

Endpoint: Invasive breast cancer incidence

Invasive breast cancer incidence is the endpoint of interest for the proposed new indication of reducing the risk of invasive breast cancer in the postmenopausal women with osteoporosis. Incidence of breast cancer was a primary endpoint in the RUTH and the CORE trials; it was a secondary objective and a safety endpoint in the MORE trial.

Breast cancer incidence (invasive and non-invasive) was the endpoint used for approval of tamoxifen for the indication of reducing the risk of breast cancer in women at high risk for breast cancer.

Usefulness of the endpoint (invasive breast cancer incidence): invasive breast cancers cause significant morbidity due to metastases and can be life-threatening—thus their incidence is clinically relevant. Reducing the incidence of invasive breast cancer provides a direct clinical benefit to the patient.

Limitation of the endpoint (invasive breast cancer incidence): New breast cancers, both invasive and non-invasive, in a mammogram screened population show up as mammographic abnormalities. While some radiological features may be associated with invasive vs. non-invasive breast cancers, these are not diagnostic. Adequate evaluation of mammographic abnormalities is required—this requires similar surgical procedures and adequate pathology evaluation. Moreover, non-invasive breast cancers do require adequate surgical treatment (which might include mastectomy), and radiation therapy if breast conserving surgery was performed. A vast majority of the patients are given adjuvant tamoxifen for five years. Moreover, about half of the ductal carcinoma in situ (DCIS) are invasive when recurrent. Thus the narrowly defined endpoint, invasive breast cancer incidence, is useful to evaluate a limited clinical benefit.

Detection of breast cancers in the studies occurred by bilateral mammograms and physical exam. **Mammography** is widely used to screen healthy women for breast cancer and is an acceptable technique for detection of early breast cancers in the studies reviewed under this sNDA.. The diagnosis of invasive breast cancer was confirmed by biopsy and histologic examination

In the **RUTH trial** 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.

In the **MORE trial** bilateral mammograms or ultrasound (if patient refused mammogram) were required at baseline and after 2, 3, and 4 years of treatment. Mammograms were optional at 1 year of treatment. Breast exams were done at baseline, but were not regularly performed during 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.

In the **CORE trial** 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.

6.1.3 Study Design

The treatment arms and the important exclusion criteria of the three raloxifene-placebo controlled trials are shown in the table. All three trials were randomized, double-blind and placebo-controlled.

- For the efficacy analysis of MORE trial, the data form raloxifene 60 mg arm only were used. For the safety analysis in MORE trial the data from both 60 and 120 mg were used.

Table 5 Treatment arms and important exclusion criteria in raloxifene placebo-controlled trials.

TRIAL	TREATMENT ARMS	IMPORTANT EXCLUSIONS
RUTH	o Raloxifene 60 mg o Placebo	o MI, PCI, or CABG within 3 months, o History of VTE
MORE	o Raloxifene 60 mg o Raloxifene 120 mg o Placebo	o History of VTE, CVA within 10 yrs
CORE	o Raloxifene 60 mg o Placebo	o Same as MORE except prior CVA not excluded

Abbreviations: 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

Design and Analyses of the Raloxifene Placebo-controlled Study Conducted in Postmenopausal Women at High Risk for Coronary events: RUTH/GGIO trial

The RUTH trial was a randomized, double-blind, placebo-controlled, multinational study conducted in postmenopausal women at risk for major coronary events. A total of 10,101 postmenopausal women with established CHD (Coronary Heart Disease) or at increased risk for CHD were randomly assigned to either placebo (N = 5,057) or raloxifene 60 mg/day (N = 5,044). The active treatment phase ended after the last randomized patient had been followed for at least 5 years.

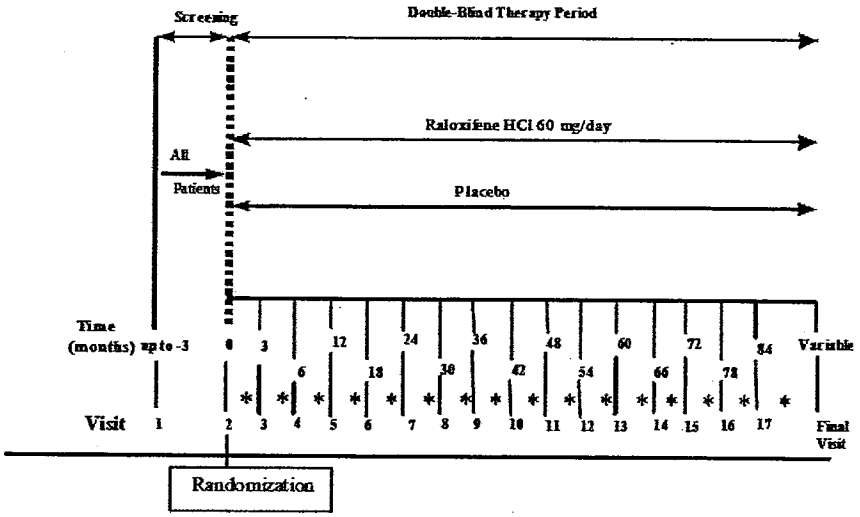
The **primary objectives** were to assess whether treatment with raloxifene, compared with placebo, reduced the incidence of:

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**

Secondary endpoints included the following:

- Cardiovascular (CV) death, nonfatal (including silent) MI, hospitalized ACS other than MI, myocardial revascularization, and stroke, assessed separately and as a combined endpoint
- Coronary death
- All-cause mortality
- Hospitalized ACS
- All-cause hospitalization
- Non-coronary arterial revascularization or non-traumatic lower extremity amputation
- All breast cancer
- Fractures
- Venous thromboembolic events (VTEs)

Figure 2 RUTH/GGIO Study design.



*Retention-related telephone contacts may occur between scheduled visits.

Source: GGIO CSR Figure GGIO.9.1.

Eligibility: postmenopausal women at high risk for CHD.

Inclusion criteria:

Women aged 55 years or older, who were at least 1 year postmenopausal and had established CHD or multiple CHD risk factors, were eligible to enroll.

A **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)

Exclusion criteria:

- An MI, a coronary artery bypass graft (CABG), or a percutaneous coronary intervention (PCI) within 6 months of randomization
- Being investigated for suspected breast carcinoma or with a known history of breast carcinoma

- A history of cancer or VTE
- Unexplained uterine bleeding within 6 months of randomization
- Class III or IV heart failure
- Chronic liver or renal disease
- Use of oral or transdermal estrogens within 6 months of randomization
- Concurrent use of other sex hormones or selective estrogen receptor modulators (SERMs)

Level of breast cancer risk did not determine the eligibility of women for the RUTH trial: women at a high or a general population breast cancer risk were eligible. However, each patient's **5-year predicted risk of invasive breast cancer** was calculated at baseline using the **modified Gail model**. The breast cancer risk factors in the model include:

- Current age
- Age at menarche
- Nulliparity or age at first live birth
- Number of female first degree relatives diagnosed with breast cancer
- Number of breast biopsies
- Presence of atypical hyperplasia in a biopsy sample
- Race

- **Study drug** was permanently discontinued when a participant was unblinded or diagnosed with breast cancer or venous thromboembolism.
- The use of **CV medications** to treat CHD or CHD risk factors was encouraged.

- **Bilateral mammograms** were performed at baseline (within 12 months before randomization), every 2 years thereafter, and at the final visit
- **Clinical breast examinations** were performed at baseline (within 3 months before randomization) 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. The adjudicators determined:

1) Whether the patient had a primary breast cancer, and whether it was invasive or noninvasive
2) What the ER status was
3) Whether the cancer may have been pre-existing (ie, evident on the baseline mammogram), or was new (ie, identified on a post baseline mammogram)

The **diagnosis of a breast cancer** was based on the findings reported in the **local pathology report** (or equivalent document describing the pathology findings). The following items were used to determine whether or not a breast cancer may have been preexisting:

- Mammogram films from baseline through diagnosis
- Related radiology reports

- Any reports provided for additional studies performed, such as magnification views or an ultrasound

Estrogen receptor status of the tumor was ascertained from the **pathology report** (ie, immunocytochemical assay).

Statistical analysis of breast cancer events

- Analysis of the primary endpoint of invasive breast cancer was performed for all randomized patients using time to first event methods.
- The final analysis significance level (2-sided) for invasive breast cancer was 0.008.

Design and Analyses of the Raloxifene Placebo-controlled Studies Conducted in Postmenopausal Women with Osteoporosis

The effect of raloxifene on the incidence of invasive breast cancer was determined in two studies conducted in postmenopausal women with osteoporosis, the MORE and the CORE studies/clinical trials.

Because CORE was a follow-up trial to MORE, an analysis of the data from time of randomization in MORE to the end of CORE (hereafter referred to as the 8-year MORE/CORE or GGGK/GGJY analysis) was performed. The study designs of MORE and CORE and the design of the 8-year MORE/CORE analysis are discussed below.

Study Design for MORE/GGGK

The MORE trial was a randomized, double-blind, placebo-controlled, multinational study conducted in postmenopausal women with osteoporosis. The 7,705 patients enrolled in the study were randomized to one of three treatment groups:

- Placebo (N=2576)
- Raloxifene HCl 60 mg/day (N=2557)
- Raloxifene HCl 120 mg/day (N=2572)

The **primary objectives of MORE** were to assess the effects of raloxifene treatment, compared with placebo, on the **incidences of new vertebral fractures, lumbar spine** *and* **femoral neck bone mineral density (BMD),** *and* **safety.**

Secondary objectives included assessment of raloxifene treatment on the **risk of CV disease, breast cancer,** and **endometrial cancer.**

Assessment of the effect of raloxifene on the **incidence of all breast cancer** was a **secondary safety endpoint.**

Eligibility: Women up to **80 years of age,** and who were **at least 2 years postmenopausal** and had **osteoporosis** were eligible to enroll. *Osteoporosis was defined as lumbar spine or femoral BMD at least 2.5 standard deviations (SDs) below the mean for normal premenopausal women or at least one moderate or two mild vertebral fractures.*

Patient enrollment was not on the basis of any increased risk for developing breast cancer. However, assessment of the **effect of raloxifene on the incidence of all breast cancer** was a **secondary safety endpoint.** Patients were **required** to have a baseline and follow-up mammograms. A baseline breast exam was done, but there were no regularly scheduled breast exams during the trial.

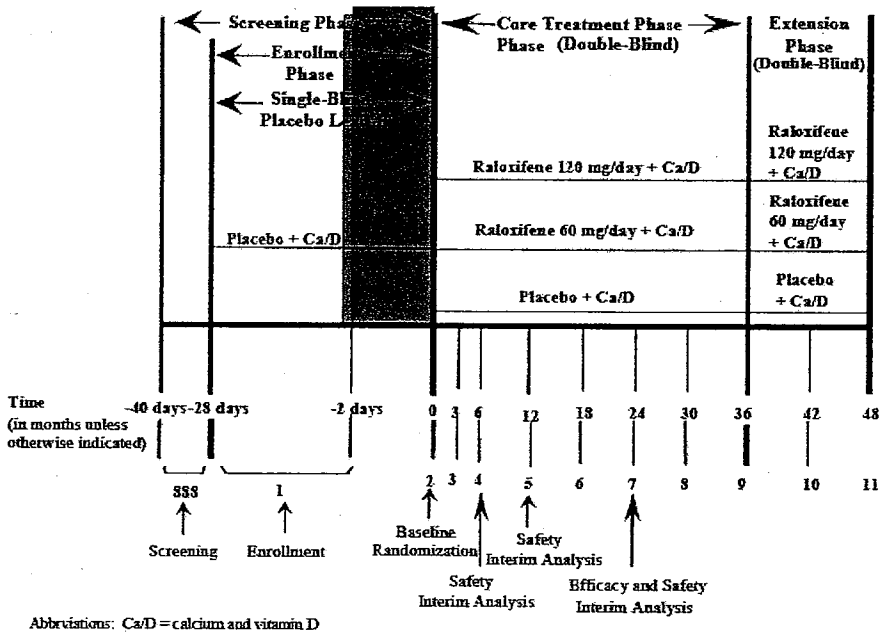
Exclusion criteria included:

- A known history of breast cancer
- History of deep vein thrombosis (DVT), thromboembolic disorders, or cerebrovascular accident within the past 10 years
- Abnormal uterine bleeding
- Chronic liver disease

The study consisted of a 36-month core treatment phase and a 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
- Concomitant use of other osteoporosis medications, including **bisphosphonates**, was allowed as clinically indicated *during the 12-month extension phase*.
- Study drug was permanently discontinued when a participant was unblinded or diagnosed with breast cancer or VTE.

Figure 3 MORE/GGGK Study design.



Source: GGGK CSR Figure GGGK.9.1.

Bilateral mammograms or ultrasound (if patient refused mammogram) were required at the baseline (within 3 months before randomization) and after 2, 3, and 4 years of treatment; mammograms were optional at 1 year of treatment.

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

For each reported case of breast cancer, the adjudicators were presented with as much of the following information as was available to the sponsor:

- Mammographic and other relevant radiologic reports
- Mammographic films (originals or copies)
- ER status
- Pathologic reports from biopsy and/or surgical specimens

For each investigator-reported breast cancer, the adjudicators determined:

1) Whether the case was invasive primary breast cancer
2) What the ER status was
3) Whether the cancer may have been preexisting (ie, present on the baseline mammogram) or new (occurring after the baseline visit)

Statistical analysis of breast cancer

Statistical analyses of the adjudicated breast cancer data were not prospectively defined as an efficacy endpoint in the protocol. However, safety analyses of breast cancer data was a predefined secondary objective and these analyses showed a reduction in the incidence of breast cancer in raloxifene-assigned patients compared with the patients assigned to placebo. Thus, further analyses to determine the effect of raloxifene on the breast were conducted. The final analysis significance level (2-sided) was 0.05.

The only raloxifene doses examined for efficacy in reducing incidence of breast cancer have been 60 mg/day and 120 mg/day, and MORE is the only study providing comparative data for both doses. The following table presents the incidence rates of *all* breast cancer and *invasive* breast cancer in patients assigned to each of these doses. **The effects of raloxifene 60 mg/day or 120 mg/day to reduce the incidence of *all* breast cancer (p = 0.810) or *invasive* breast cancer (p = 0.622) were similar.** Because the incidence rates of *all* breast cancer and *invasive* breast cancer were similar for these two raloxifene doses, the proposed indication being sought is for the 60 mg/day dose, which is the approved dose for prevention and treatment of osteoporosis. Therefore, for MORE results for raloxifene HCl 60 mg/day only will be presented in this efficacy review.

Table 6 Annual Incidence Rates and Hazard Ratios (*All* Breast Cancer and *Invasive* Breast Cancer; All Randomized Patients; MORE 48-Month Data)

Breast Cancer Category	Treatment	N	n	Patient-years of Follow-up	IR	HR vs. Placebo (95% CI) p-value	HR vs. Rlx HCl 60 mg/day (95% CI) p-value
All Breast Cancer	Placebo	2576	44	8716	5.05	-	-
	Rlx HCl 60 mg	2557	17	8756	1.94	0.38 (0.22, 0.67) p-value < 0.001	-
	Rlx HCl 120 mg	2572	16	8868	1.80	0.35 (0.20, 0.63) p-value < 0.001	0.92 (0.46, 1.82) p-value = 0.810
	Pooled Rlx[a]	5129	33	17624	1.87	0.37 (0.23, 0.58) p-value < 0.001	-
Invasive Breast Cancer	Placebo	2576	38	8718	4.36	-	-
	Rlx HCl 60 mg/day	2557	11	8756	1.26	0.29 (0.15, 0.56) p-value < 0.001	-
	Rlx HCl 120 mg/day	2572	9	8869	1.01	0.23 (0.11, 0.48) p-value < 0.001	0.80 (0.33, 1.93) p-value = 0.622
	Pooled Rlx	5129	20	17625	1.13	0.26 (0.15, 0.44) p-value < 0.001	-

Abbreviations: CI = confidence interval; HR = hazard ratio; IR = incidence rate per 1000 patients per year, calculated as the number of patients who developed the event of interest divided by the event-specific patient-years of follow-up; N = number of patients analyzed; n = number of patients with breast cancer event; ; No.= number; N/A = not applicable; Rlx = raloxifene.

[a] Pooled Rlx refers to the Rlx HCl 60 mg/day and Rlx HCl 120 mg/day data pooled.

CORE/GGJY Study Design

The CORE study was a double-blind, placebo-controlled, multinational study that enrolled postmenopausal women from the MORE study *for an additional 4 years of follow-up*. All of these women had osteoporosis and had been randomized to raloxifene or placebo in the MORE study.

The **primary objective of CORE** was to compare the long-term effect of raloxifene HCl 60 mg/day versus 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 **nonvertebral fractures** in postmenopausal women with osteoporosis.

The selection of raloxifene HCl 60 mg/day as the only active treatment dose in CORE was based on the following:

- Raloxifene 60 mg/day had similar efficacy to raloxifene 20 mg/day in MORE in terms of reduction in the incidence of breast cancer; and
- Raloxifene 60 mg/day had similar efficacy to raloxifene 120 mg/day in MORE in terms of reduction in the incidence of new vertebral fractures

The **observation period** for the primary analysis of the breast cancer endpoints was defined by relationship to the patients' enrollment in MORE:

- The observation period began on 01 January 1999, during the fourth year of MORE, and continued through the 4 years of CORE.
  - The date of 01 January 1999 was chosen because that was the date of the last breast cancer data analysis to support the osteoporosis treatment indication.
- The start of the observation period (01 January 1999) was also the date at which the primary study endpoint changed from incidence of vertebral fractures (MORE) to incidence of invasive breast cancer (CORE). Thus, the CORE observation period began at least 3 years after the randomization of patients into the MORE and continued for approximately 8 years after the randomization of patients into MORE.

The following figure shows the study design of CORE and its relationship to MORE.

Of the **180 investigative sites** that **participated in MORE**, only **130 sites** agreed to **participate in CORE**. Patients who were randomized in MORE and who were at the 130 investigative sites choosing to participate in CORE were invited to participate in CORE after their completion or discontinuation from MORE. All patients randomized in MORE at these 130 sites (N=6,511) were eligible for CORE, and 4,011 chose to enroll in CORE, comprising a population hereafter referred to as **CORE enrollees**.

As per the CORE protocol, **CORE enrollees were not re-randomized**; instead, the **randomization assignment from MORE was carried forward into CORE.**

CORE enrollees randomized to raloxifene (60 mg/day, n = 1,355; 120 mg/day, n = 1,370) in MORE were assigned to receive **raloxifene 60 mg/day (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 the patients were assigned to receive raloxifene as compared to placebo.

Women randomized in MORE could enroll in CORE even if they were not allowed to take study medication or chose not to take study medication.

- 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 patients (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.

Study drug was permanently discontinued when a participant was diagnosed with breast cancer or venous thromboembolism.

Concomitant use of other osteoporosis medications, including bisphosphonates, calcitonin, or fluorides, was allowed during CORE.

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 (within 12 months before 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. For each investigator-reported case of breast cancer, the adjudicators were provided with as much of the following information as was available to the sponsor:

- Reports of all mammograms considered abnormal
- Other relevant radiologic reports
- ER status
- Pathologic reports from biopsy and/or surgical specimens

Mammograms were defined as abnormal if the written report suggested that follow-up imaging procedures were required, if a lesion that required sampling was identified, or if the investigator deemed the mammogram to be clinically significant for other reasons.

Breast cancer analyses for CORE were performed using time to first event methods. As the start of the CORE observation period (01 January 1999) overlapped with the fourth year of MORE, there was a risk that breast cancers reported from 01 January 1999 to the end of the fourth year of MORE might be counted twice: i.e., be included in the MORE analysis and in the CORE primary analysis.

- To avoid this double-counting of breast cancers (in the CORE and MORE overlapping period from 01 January 1999 to the end of MORE) the Clinical Summary of Efficacy presents the results from CORE enrollment (Visit 1) to the end of CORE (Visit 5) under the CORE study only.
- Of the 4,011 CORE enrollees, 21 (12 in placebo and 9 in raloxifene) had developed breast cancer prior to Visit 1 and, therefore, they were excluded from the analysis of the breast cancer endpoints.

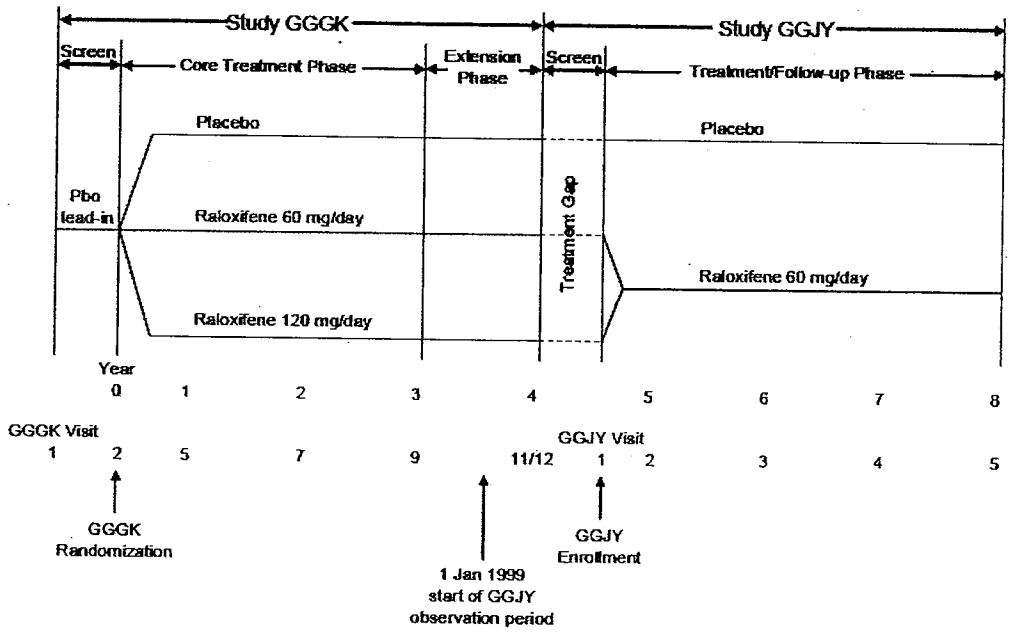
Limitations in interpreting the results of the CORE analysis relate to the issues of bias and population heterogeneity. The subset of patients who chose to participate in CORE is not a random sample of all the MORE randomized patients and, therefore, the benefits of randomization in MORE may not apply in the analysis of the subset.

- Patients who died during MORE could not participate in CORE
- Patients who were less healthy may not have chosen to participate in CORE, and consequently the CORE cohort may have been healthier than the rest of MORE.
- Compared to MORE-only patients, CORE enrollees were younger. Fewer reported having a family history of breast cancer or history of hormone therapy use at baseline of MORE.
- During MORE, among patients assigned to placebo, there was a statistically significantly greater incidence of invasive breast cancer in MORE-only patients compared to the CORE enrollees.
- Of the 180 investigators participating in MORE, 50 chose not to participate in CORE. Of the 130 MORE investigators who chose to participate in CORE, not all of the MORE randomized patients chose to enroll in CORE. This selection bias may have impacted the CORE cohort in that patients who did participate in CORE were not randomly chosen.
    - Patients randomized at MORE sites which chose not to participate in CORE would not have had the option to participate in CORE.
    - At the MORE sites which chose to participate in CORE, patients decided to participate or not participate in CORE.
- Follow-up clinical information for patients who did not continue into CORE was not collected after the end of their participation in MORE.

Time between the MORE and the CORE trials

The beginning of CORE did not coincide exactly with the end of MORE (ie, there could have been a period of time between a patient's end of participation in MORE and the beginning of her participation in CORE):

- 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 but could have taken marketed Evista, tamoxifen, other SERMS, or a hormone.



Abbreviation: Pbo = placebo.
The dotted line during the GGJY screening period denotes time between the conclusion of GGGK and the start of GGJY, during which time patients were not receiving study therapy (patients were allowed to take marketed raloxifene or hormone therapy during the "treatment gap").
Source: GGJY CSR Figure GGJY.9.1.

Figure 4 Study design for MORE and its continuation study CORE.

Design of 8-Year Analysis of MORE and CORE

- A time to first event analysis was performed for the subset of those MORE patients who were randomized to placebo or raloxifene 60 mg/day and who chose to continue to participate in CORE (N = 2,641).
- Data for these patients was analyzed from the time of their randomization in MORE to the end of their participation in CORE, which was approximately 8 years.

Table 7 Analysis Data Sets for MORE (GGGK), CORE (GGJY), and 8-year MORE/CORE (GGGK/GGJY)

Analysis Data Set	Duration	Treatment Groups	Breast Cancer Endpoint
GGGK: All GGGK patients randomized to Raloxifene HCl 60 mg/day or placebo N=5133	4 years from GGGK randomization to end of GGGK	Placebo (N=2576); Raloxifene HCl 60 mg/day (N=2557)	All breast cancer, including invasive breast cancer, was a secondary endpoint
GGJY: GGJY enrollees who had not developed breast cancer at GGJY enrollment (Visit 1) N=3990[a]	4 years from GGJY enrollment (Visit 1) to end of GGJY (Visit 5)	Placebo (N=1274); Raloxifene HCl 60 mg/day (N=2716)	Invasive breast cancer was a primary endpoint
8-year GGGK/GGJY Analysis: All GGGK patients randomized to raloxifene HCl 60 mg/day or placebo and who chose to continue in GGJY N=2641	8 years from GGGK randomization to end of GGJY	Placebo (N=1286); Raloxifene HCl 60 mg/day (N=1355)	Analysis of invasive breast cancer incidence

Abbreviation: N = number of patients included in the analysis.

[a] Of the 4011 GGJY enrollees, 21 (12 in placebo and 9 in raloxifene) were excluded from the breast cancer analyses because they had been diagnosed with breast cancer before GGJY enrollment (Visit 1).

Adequate and well-controlled studies

- The RUTH trial can be considered as adequate and well-controlled: both form a regulatory and a clinical perspective
- The MORE trial was adequate and well-controlled to address its primary objective. Breast cancer incidence was a secondary endpoint and it was carefully evaluated; however, the trial size was not based on expected breast cancer events in the control and the treatment arms, and the results are not definitive. MORE patients were not re-randomized prior to entry into CORE and approximately 50% of patients in MORE did not enter into CORE. Randomization was lost and CORE results are not definitive.

- Placebo-controlled design of these trials helps to dissect an assessment of the treatment effect; however, the reliability of the measurement of the effect-size is curtailed as noted above
- Blinding, randomization, and adjudication of breast cancers by a board of physicians who specialized in breast cancer and were not employed by the applicant minimized bias

6.1.4 Efficacy Findings

RUTH

N = 10,101 postmenopausal women with established CHD or at increased risk for CHD

Assigned to placebo	= 5,057
Assigned to raloxifene	= 5,044
Median age	= 67.6 years
Median duration of follow-up	= 5.6 years
Median study drug exposure	= 5.1 years

Treatment Compliance

- 71% of patients in the placebo group and 70% in the raloxifene group took at least 70% of assigned medication and were classified as adherent to treatment (p=0.62).
- The study was completed by 79% of women in the placebo group and 80% in the raloxifene group (p=0.02).

Breast cancer risk assessment

Breast cancer risk using the modified Gail Model was calculated at the baseline. Breast cancer risk assessment characteristics were balanced between treatment groups at baseline.

- The **median 5-year predicted risk of invasive breast cancer** was 1.55%.
- Approximately **41%** of patients in each treatment group had a 5-year predicted invasive **breast cancer risk of ≥1.66%.**

The following table shows the breast cancer risk factors and breast cancer risk assessment of the patients enrolled in the RUTH trial

Table 8 RUTH: Breast cancer risk factors and breast cancer risk assessment of the enrolled patients

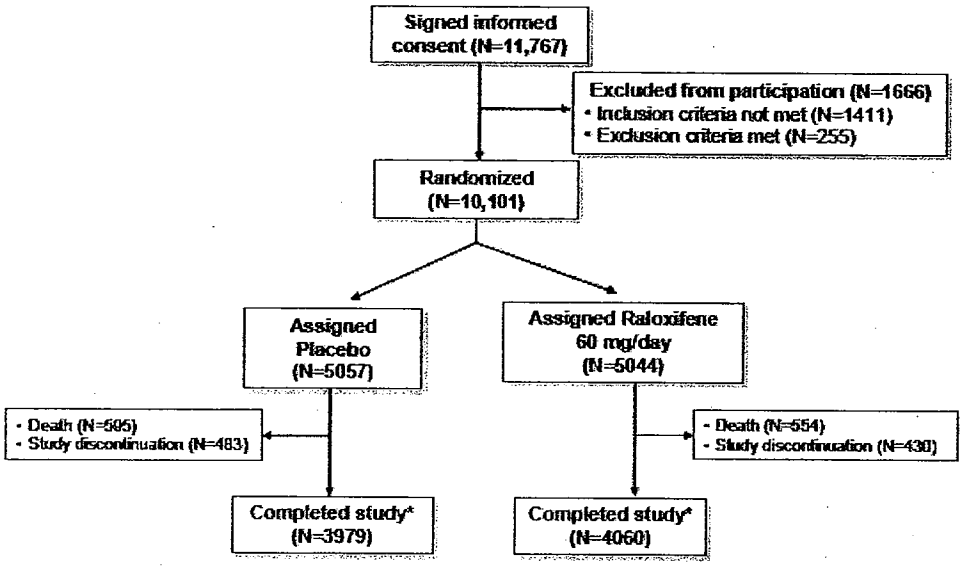
Characteristics	Placebo N=5,057	Raloxifene N=5,044	Total N=10,101
5-year predicted breast cancer risk (%)			
# of patients	5056	5044	10100
Mean	1.73	1.73	1.73
Standard deviation	0.77	0.76	0.76
Median	1.54	1.55	1.55
Minimum	0.52	0.50	0.50
Maximum	9.57	14.15	14.15
5-yr predicted breast cancer risk ≥ 1.66			
# 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)

Patients Disposition

Figure 5 RUTH/GGIO: Patient disposition.



*Final visit on or after March 1, 2005

Source: GGIO CSR Figure GGIO.10.1.

Breast cancer events

A total of 132 **breast cancer** (invasive, non-invasive, unknown invasive) events, reported in 129 patients (76 in placebo, 53 in raloxifene) during the study period, were sent for adjudication.

- 128 patients (76 in placebo, 52 in raloxifene) had at least one adjudicated breast cancer.
- Breast cancer analyses were based on the 128 patients who had at least one adjudicated breast cancer.

Table 9 RUTH: breast cancer events, incidence rates, absolute risk difference, and relative risk.

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)

Invasive breast cancer

Placebo group = 70 cases (IR, 2.66 per 1000 patient-years)
Raloxifene group = 40 cases (IR, 1.50 per 1000 patient-years)

- The incidence of **invasive breast cancer** was statistically significantly decreased by 44% (HR 0.56, 95% CI 0.38-0.83; p=0.0032) in the raloxifene group compared with the placebo group. Thus, the breast cancer primary endpoint (incidence of invasive breast cancer) was achieved in accordance with the protocol-specified significance level of 0.008.
- The statistically significant decrease in invasive breast cancer was primarily due to a statistically significant 55% reduction (HR 0.45, 95% CI 0.28-0.72; 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** (HR 1.44, 95% CI 0.61-3.36) or noninvasive breast cancer (HR 2.17, 95% CI 0.75-6.24).
- The incidence of **all breast cancer** was statistically significantly decreased by 33% (HR
- 0.67, 95% CI 0.47-0.96; p = 0.0270) in the raloxifene group compared with the placebo group.

Table 10 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

Exploratory subgroup analysis of invasive breast cancer by Gail Score ≥ 1.66 or < 1.66

Table 11 RUTH: Exploratory subgroup analysis of invasive breast cancers 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.

Outcome of the coronary primary endpoint

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 compared with patients assigned to placebo. This difference was driven by a statistically significant larger proportion of patients in the raloxifene group with a reported history of CABG.

- The coronary primary endpoint did not meet the prespecified significance level of 0.0423 (HR 0.95, 95% CI 0.84-1.07; p=0.4038).

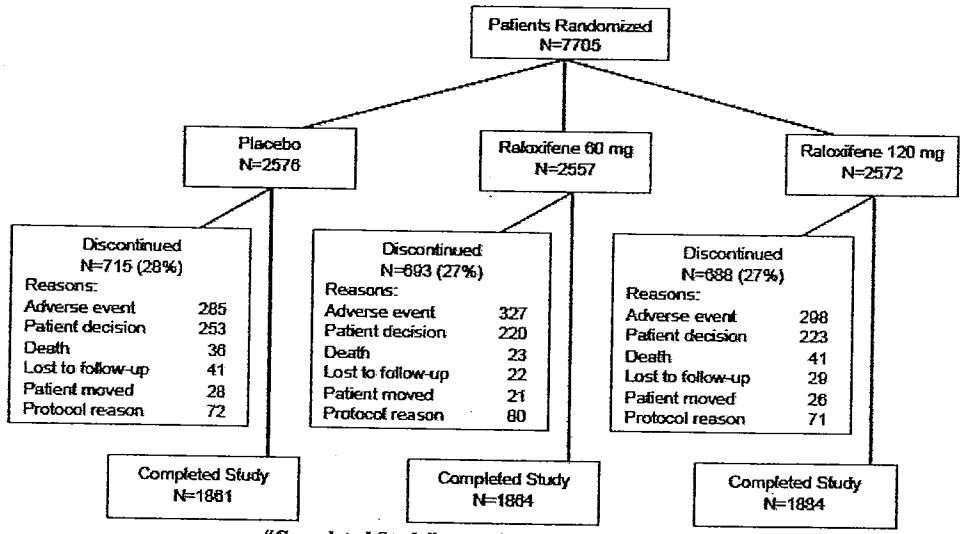
MORE

N = 7,705 postmenopausal women with osteoporosis

Assigned to placebo	= 2,576
Assigned to raloxifene 60 mg/day	= 2,557
Assigned to raloxifene 120 mg/day	= 2,572
Median age	= 66.9 years
Median follow-up	= 47.4 months.

Patient disposition

- The figure below shows the patient disposition. 72.2% of the patients in the placebo group and 72.9% in the raloxifene group were followed to study conclusion.



"Completed Study" comprises patients who ended the trial with a designation of "regular completed," "early completed," or "completed protocol, but had an adverse event."
"Protocol reason" comprises patients who ended the trial because of "protocol variance" or "protocol entry criteria not met."
Source: GGGK CSR Table GGGK.10.1.

Figure 6 MORE: Patient disposition.

Breast cancer events

- Incidence of **all breast cancer** was a secondary safety endpoint of the MORE trial.

Table 12 MORE: Breast cancer events, incidence rates, and relative risk.

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.

During the 4 years of MORE, the incidence of **all breast cancer** was statistically significantly decreased by 62% (HR 0.38, 95% CI 0.22-0.67; p<0.001):

- Raloxifene group = 17; IR, 1.94 per 1000 patient-years
- Placebo group = 44; IR, 5.05 per 1000 patient-years

- This statistically significant decrease in **all breast cancer** was primarily due to a statistically significant 71% decrease (HR 0.29; 95% CI 0.15-0.56) in **invasive breast cancer** in the raloxifene HCl 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).

- The statistically significant decrease in **invasive breast cancer** was primarily due to a statistically significant 80% reduction (HR 0.20, 95% CI 0.08-0.49) in incidence of **invasive ER positive breast cancer** in the 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).
- There were no statistically significant differences between treatment groups in the incidence of **invasive ER-negative** breast cancer (HR 1.23, 95% CI 0.33-4.60) or in the incidence of **noninvasive breast cancer** (HR 0.59, 95% CI 0.14-2.47).

Breast cancer stage at diagnosis

Table 13 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

Analysis of the **primary study objective** showed that at 48 months of study follow-up, the **incidence of new vertebral fractures** was statistically significantly reduced and **femoral neck and lumbar spine BMDs** were statistically significantly increased in the raloxifene HCl 60-mg/day group compared with the placebo group. These results were consistent with the 3-year MORE/GGGK results (ie, those at the end of the core treatment period before concomitant bone active agents were allowed) which were previously submitted to the FDA (NDA 20-815) in support of the osteoporosis treatment indication.

CORE

CORE was a continuation of MORE: postmenopausal women with osteoporosis who had been randomized in MORE participated in CORE.

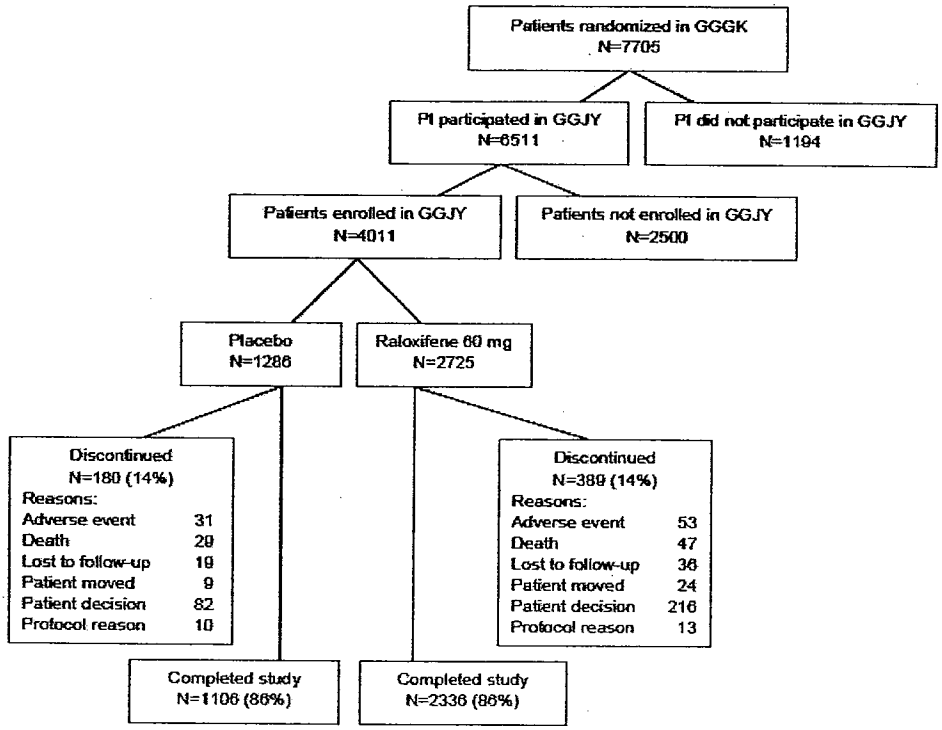
N = 4,011

- Raloxifene group = 2,725
  - MORE treatment assignment raloxifene 60 mg = 1,355
  - MORE treatment assignment raloxifene 120 mg = 1,370
- Placebo group = 1,286

Median age = 71.0 years

Patient disposition in CORE is shown below

Approximately 86% of patients in each of the treatment groups were followed to study conclusion.



Abbreviation: PI = primary investigator.
"Completed Study" comprises patients who ended the trial with a designation of "protocol completed" or as "completed the protocol, but had an adverse event." Patients who discontinued because of "protocol reason" ended their participation in the trial because of "protocol variance" or "protocol entry criteria not met."
Sources: GGJY CSR Figure GGJY.10.1, GGJY CSR Figure GGJY.10.2, GGJY CSR Table GGJY.10.1.

Figure 7 CORE: Patient disposition.

Breast cancer risk assessment

- Breast cancer risk assessment characteristics were balanced between treatment groups at baseline.
- The median **5-year predicted risk of invasive breast cancer** was 1.70% and approximately 54% of patients in each treatment group had a 5-year predicted invasive breast cancer risk of **≥1.66%.**

Table 14 CORE: Breast Cancer risk at the 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

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

Assessment of breast cancer events in CORE

- Incidence of invasive breast cancer was assessed from enrollment in CORE (Visit 1) to the end of CORE (Visit 5).
- Of the 4,011 CORE enrollees, 12 in the placebo group and 9 in the raloxifene group were diagnosed with breast cancer prior to Visit 1 and were not included in the analysis; thus, the analysis of the breast cancer endpoints was performed for 3,990 patients.

Breast cancer events in CORE

The incidence of **invasive breast cancer** was statistically significantly decreased by 56% (HR 0.44; 95% CI 0.24-0.83) in the raloxifene arm compared to the placebo arm:

- Raloxifene = 19; IR, 2.43 per 1000 patient-years (denominator = 2,716)
- Placebo = 20; IR, 5.41 per 1000 patient-years (denominator = 1,274)

- The statistically significant decrease in invasive breast cancer was primarily due to a statistically significant 63% reduction (HR 0.37, 95% CI 0.17-0.79) 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 (HR 0.95, 95% CI 0.24-3.79) or **noninvasive** breast cancer (HR 1.18, 95% CI 0.23-6.07).

Table 15 CORE: Breast cancer events by invasiveness, ER status, incidence rates, and relative risk.

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)

Note: Of the 4,011 CORE enrollees, 12 in the placebo group and 9 in the raloxifene group were diagnosed with breast cancer prior to Visit 1 and were not included in the analysis; thus, the analysis of the breast cancer endpoints was performed for 3,990 (1,274 + 2,716) patients.

Breast cancer stage at diagnosis

Table 16 CORE: Breast Cancer Stage at Diagnosis (including non-invasive breast cancers).

Breast Cancer Stage	Placebo (N=22)		Raloxifene 60 mg (N=24)		Total (N=46)	
	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.

Results of 8-year MORE-CORE Analysis

In the 8-year MORE-CORE analysis, raloxifene (n = 1,355) statistically significantly reduced the incidence of invasive breast cancer by 60% (HR 0.40; 95% CI 0.21-0.77) compared to placebo (n = 1,286):

- Raloxifene = 13 cases; IR, 1.24 per 1000 patient-years
- Placebo = 32 cases; IR, 3.19 per 1000 patient-years

- 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).

Comparison and Analyses of Results across Studies

The four studies providing data to support the 2 new proposed indications enrolled postmenopausal women with different risk profiles:

- RUTH: postmenopausal women at increased risk for major coronary events
- MORE and CORE: postmenopausal women with osteoporosis
- STAR: postmenopausal women at increased risk for invasive breast cancer

The four studies also differed in terms of study design and objectives. Only the RUTH, MORE, and CORE trials are discussed in detail in this review.

Study Populations

The three studies targeted three different populations of postmenopausal women as reflected in the **inclusion criteria**:

- **RUTH** enrolled postmenopausal women at risk for major coronary events, defined as either having established CHD or multiple risk factors for CHD.
  - Participants were required to have a CV risk score of 4 or greater.
- **MORE** enrolled postmenopausal women with osteoporosis defined as a femoral neck or lumbar spine BMD measurement 2.5 or more SDs below normal peak bone mass for healthy premenopausal women (T-score ≤-2.5) or radiographic documentation of prior vertebral fracture.
- **CORE** enrollees were postmenopausal women with osteoporosis defined by the inclusion criteria for MORE; women randomized in MORE were eligible to enroll in **CORE.**

- Exclusion criteria related to breast cancer which were common to all studies included a prior or suspected history of breast cancer and a history of cancer within the previous 5 years, except for excised basal or squamous cell carcinoma.
- Systemic estrogen therapy was not allowed concurrently with study medications, or within 6 months of randomization in RUTH or MORE.

- All of the women who participated in these four studies were postmenopausal, and most were White (>83% in either treatment arm of each study).
- The populations enrolled differed with respect to some breast cancer risk factors and geographic regions.

The following table summarizes the baseline characteristics of the patients included in the analyses performed for the four studies. In general, the baseline characteristics of the patients enrolled in STAR differed from those of the RUTH and MORE patients.

Table 17 Summary of Baseline Characteristics (Studies RUTH/GGIO, MORE/GGGK, CORE/GGJY, and STAR/P2 and the MORE/GGGK Subset Randomized to Raloxifene HCl 60 mg/day who continued in CORE/GGJY)

Characteristic	GGIO (N=10,101)	GGGK (N=5133)	GGJY Enrollees[a] (N=4011)	GGGK subset Randomized to Rlx 60 mg/day Continuing in GGJY[b] (N=2641)	P-2 (N=19,471)
Age, yrs (median)	67.6	66.9	71.0	66.1	58.0
White, %	83.96	95.85	96.20	96.29	93.50
BMI, kg/m^2 (mean± SD)[c]	28.77 ± 5.14	25.24 ± 4.01	25.63 ± 4.06	25.25 ± 3.84	N/A
Years postmenopausal (mean ± SD)[d]	19.40 ± 8.81	18.82 ± 8.49	N/A	17.96 ± 8.10	N/A
Previous HT, % Yes[e]	6.11	29.31	N/A	25.31	N/A
Female family history of breast cancer , % Yes[f]	9.77	12.47	13.43	11.47	71.4
Prior hysterectomy, % Yes[g]	23.01	23.07	21.60	20.56	51.50
5-yr predicted risk of invasive breast cancer ≥1.66% , % Yes[h]	41.41	N/A	54.00	N/A	100

Abbreviations: BMI = body mass index; HT = hormone therapy (includes estrogen alone or estrogen/progestin); N/A = not available; N = number of patients assessed; pts = patients; yrs = years.
a At CORE/GGJY baseline.
b Characteristics for MORE/GGGK subset randomized to raloxifene HCl 60 mg/day or to placebo at MORE/GGGK baseline who continued into CORE/GGJY.
c Data relating to BMI was available for 10,071 randomized patients in RUTH/GGIO, 5132 randomized patients in MORE/GGGK, 3975 enrollees in CORE/GGJY, and 2640 randomized patients in the MORE/GGGK subset continuing into CORE/GGJY.
d In RUTH/GGIO, data relating to years postmenopausal was available for 10,099 randomized patients.
e Data relating to prior HT use was available for 9904 randomized patients in RUTH/GGIO, 5118 randomized patients in MORE/GGGK, 2635 randomized patients in the MORE/GGGK subset continuing into CORE/GGJY.
f Data relating to the number of first-degree female relatives with breast cancer was available for 9184 randomized patients in MORE/GGIO, 5011 randomized patients in MORE/GGGK, 2590 randomized patients in the MORE/GGGK subset continuing into CORE/GGJY.
g In RUTH/GGIO, data relating to prior hysterectomy was available for 10,086 randomized patients.
h In RUTH/GGIO, the 5-year predicted invasive breast cancer risk was available for 10,100 patients.

- On average, patients in the STAR trial were 10 years younger (median age, 58.0 years) than the RUTH and MORE patients.
- A greater proportion of STAR patients reported a family history of breast cancer (approximately 71%) than did those in RUTH (approximately 10%) and MORE (approximately 12%).
- Women at increased risk for invasive breast cancer, defined as either a histology diagnosis of LCIS treated by local excision only or a minimum projected 5-year probability of invasive breast cancer ≥1.66%, were eligible to enroll in STAR; all patients had a 5-year predicted probability of invasive breast cancer ≥1.66%.

- Although risk of invasive breast cancer was not an inclusion criterion for RUTH, 41% had a 5-year predicted risk ≥1.66%.
- For MORE, the information required to calculate a 5-year predicted risk for invasive breast cancer was not collected at baseline.
- However, this data was collected for the CORE enrollees at baseline of CORE and 54% of the CORE enrollees had a 5-year predicted risk of invasive breast cancer ≥1.66%.
- In the STAR trial, approximately half of the patients (51%) reported having had a prior hysterectomy whereas prior hysterectomy was reported by only 23% of the patients randomized in RUTH and 23% of those randomized in MORE.
- Even though RUTH enrolled postmenopausal women with or at risk for CHD, and MORE enrolled postmenopausal women with osteoporosis, the baseline characteristics of the two populations were similar with respect to median age (approximately 67 years); years post menopause (approximately 19); proportion reporting having had a prior hysterectomy (approximately 23%); and proportion reporting a history of breast cancer in a first-degree female relative (approximately 10%).
- Patients in RUTH and MORE differed with respect to their prior hormone therapy use, ie, nearly 30% of women in MORE reported having taken hormone therapy prior to study enrollment, compared to only 6% in RUTH. Patients in RUTH had a greater body mass index (BMI) (approximately 29 kg/m2) than did those in MORE (approximately 25 kg/m2).

- CORE enrollees were on average 4 years older at CORE baseline than those randomized in MORE; this is expected as CORE enrolled a subset of patients randomized in MORE and enrollment (Visit 1) of CORE occurred approximately 4 years after MORE randomization.
- At baseline of MORE, the characteristics of the MORE subset randomized to placebo and raloxifene HCl 60 mg/day who continued into CORE (N=2641) were similar to those of the entire MORE cohort randomized to placebo and raloxifene HCl 60 mg/day (N=5133).

Invasive breast cancer risk characteristics

- A high risk of invasive breast cancer was not an inclusion criterion for any of the placebo-controlled studies. Information was collected at baseline in RUTH and CORE to calculate the 5-year predicted risk for invasive breast using the modified Gail model.
- In RUTH, breast cancer risk assessment characteristics were balanced between treatment groups at baseline. The median 5-year predicted invasive breast cancer risk was 1.55%, and approximately 41% of patients in each treatment group had a 5-year predicted invasive breast cancer risk of ≥1.66% based on the modified Gail model.
- In CORE, breast cancer risk assessment characteristics were balanced between treatment groups at enrollment (Visit 1). The median 5-year predicted risk of breast cancer was 1.70% and approximately 54% of patients in each treatment group had a 5-year predicted invasive breast cancer risk of ≥1.66% based on the modified Gail model.

Comparison of Efficacy Results of All Studies

- For all studies, diagnosis of invasive breast cancer was based on the local pathology report or equivalent document.
- For the three placebo-controlled studies (RUTH, MORE, and CORE), all investigator-reported breast cancers were reviewed and adjudicated by a board of physicians who were blinded to patient treatment assignment and who were not employed by Lilly.
- For the STAR trial, investigators provided information related to the pathologic diagnosis (invasive or noninvasive), ER status, and stage of tumor and copies of all supporting documentation for review and confirmation by the NSABP medical personnel blinded to treatment assignment.

Results of the Placebo-Controlled Studies

RUTH

- RUTH enrolled postmenopausal women at risk for major coronary events and the effect of raloxifene on the incidence of invasive breast cancer was a primary endpoint.
- Raloxifene treatment statistically significantly decreased the incidence of invasive breast cancer by 44% (HR 0.56, 95% CI 0.38-0.83; p=0.0032), primarily because of a statistically significant reduction in the incidence of ER-positive invasive breast cancer compared with placebo.
- The absolute risk reduction per 1000 patients treated with raloxifene for 1 year was 1.16 cases of invasive breast cancer.

MORE

- MORE enrolled postmenopausal women with osteoporosis and the effect of raloxifene on the incidence of all breast cancer, including invasive breast cancer, was a secondary safety endpoint.
- Raloxifene treatment statistically significantly decreased the incidence of invasive breast cancer by 71% (HR 0.29; 95% CI 0.15-0.56; p<0.001), primarily because of a statistically significant reduction in the incidence of ER-positive invasive breast cancer compared with placebo.
- The absolute risk reduction per 1000 patients treated with raloxifene for 1 year was 3.10 cases of invasive breast cancer.

CORE

- CORE enrolled a subset of postmenopausal women with osteoporosis who were randomized in MORE. The effect of raloxifene on the incidence of invasive breast cancer was the primary endpoint.

- From CORE enrollment (Visit 1) to the end of CORE (Visit 5), raloxifene treatment statistically significantly decreased the incidence of invasive breast cancer by 56% (HR 0.44; 95% CI 0.24-0.83; p=0.009), primarily because of a statistically significant reduction in the incidence of ER-positive invasive breast cancer compared with placebo.
- The absolute risk reduction per 1000 patients treated with raloxifene for 1 year was 2.98 cases of invasive breast cancer.

MORE-CORE 8 year cohort

- The effect of raloxifene on the incidence of invasive breast cancer over 8 years was examined in a subset of postmenopausal women with osteoporosis who were randomized to raloxifene HCl 60 mg/day or placebo in MORE and who continued in CORE.
- In this analysis, raloxifene treatment statistically significantly decreased the incidence of invasive breast cancer by 60% (HR 0.40; 95% CI 0.21-0.77; p=0.004), primarily because of a statistically significant reduction in the incidence of ER-positive invasive breast cancer compared with placebo.
- The absolute risk reduction per 1000 patients treated with raloxifene for 1 year was 1.95 cases of invasive breast cancer.

The MORE data demonstrates a statistically significant risk reduction in the risk of invasive breast cancer over 4 years of treatment with raloxifene in postmenopausal women with osteoporosis. CORE was designed to permit continued follow-up of patients who had been randomized to treatment in MORE: approximately 62% of the eligible MORE patients (approximately 52% of all MORE patients) chose to enroll. The CORE patients were not re-randomized, remained blinded to study medication, and continued on their original treatment assignment in MORE.

CORE demonstrated that over additional 4 years of follow-up, there was a statistically significant decrease in the incidence of invasive breast cancer in the raloxifene group compared with the placebo group. Therefore, when considered together with results from MORE, CORE provides support that the treatment effect of raloxifene on invasive breast cancer persists beyond 4 years. This is also supported by an analysis where the patients who participated in both MORE and CORE were followed over a total of up to 8 years.

While the results from these analyses are supportive, they need to be considered with the limitations that the constancy assumption between the MORE and CORE cohorts can not be assumed and that there was a period of time between the two studies when no study medication was given.

Results of the Active-Control Study

(For details, please see review by Dr. Patricia Cortazar)

The P-2 study (NSABP STAR trial) enrolled postmenopausal women at high risk for invasive breast cancer. High risk was determined using a modified Gail Model. The trial was primarily designed to show superiority of raloxifene over tamoxifen in reducing the incidence of invasive breast cancer in postmenopausal women. Results of the primary analysis, based on 19,471 randomized patients, showed no statistically significant difference between the effect of tamoxifen and the effect of raloxifene on the incidence of invasive breast cancer. The trial failed to show superiority of raloxifene over tamoxifen. A non-inferiority analysis (with the limitations of a superiority trial analysis for non-inferiority) showed that raloxifene may lose up to 35% of tamoxifen effect.

- There were 163 cases of invasive breast cancer in the tamoxifen group and 168 in the raloxifene group.
- The incidence rate was 4.30 per 1000 patient-years in the tamoxifen group and 4.41 per 1000 patient-years in the raloxifene group (RR, 1.02; 95% CI 0.82-1.28).
- The majority of invasive breast cancers (72.3% in the tamoxifen group and 68.1% in the raloxifene group) were ER positive.
- There were fewer cases of noninvasive breast cancer in the tamoxifen group (57 cases) than in the raloxifene group (80 cases) (incidence, 1.51 versus 2.11 per 1000; RR 1.40; 95% CI 0.98-2.00).

Summary of Efficacy Results across Studies

Invasive Breast Cancer

Across the placebo-controlled studies, a statistically significant reduction in the incidence of invasive breast cancer in women assigned to raloxifene is noted.

- This reduction in incidence of invasive breast cancer ranged from 44% in the RUTH trial, which had breast cancer incidence as a primary endpoint, to 71% in the MORE trial, in which the incidence of breast cancer was a safety endpoint.
- In each of the placebo controlled trials, the reduction in incidence of invasive breast cancer in the raloxifene group was primarily due to a statistically significant reduction in the incidence of ER-positive invasive breast cancers.
- There was no reduction in the incidence of ER-negative invasive breast cancer in patients assigned to raloxifene compared with those assigned to placebo.

In the STAR trial (women at high risk of invasive breast cancer), more cancers were seen in the raloxifene arm, but the difference was not statistically significant: RR, 1.02; 95% CI 0.82-1.28; the results of a non-inferiority analysis showed that raloxifene could lose up to 35% of tamoxifen effect (maintain 65%) in reducing the incidence of invasive breast cancer.

Noninvasive Breast Cancer

Compared to placebo, raloxifene did not show a statistically significant difference in the incidence of noninvasive breast cancer. The placebo-controlled studies were not designed to evaluate the effect of raloxifene on noninvasive breast cancers no definite conclusions can be drawn. Compared to the total number of all breast cancers, only a few cases of noninvasive breast cancers were reported (RUTH: 16 of 128; MORE: 8 of 61; and CORE: 7 of 46).

In the STAR trial, 468 breast cancers were reported, and 137 were noninvasive. Numerically more noninvasive breast cancers were reported in patients assigned to raloxifene (n = 80) than those assigned to tamoxifen (n = 57); however, this difference was not statistically significant (p=0.052). However, once again, the trial was not designed to detect a difference in the incidence of non-invasive breast cancer.

Reviewer Comments: *The sponsor concluded that in the placebo-controlled studies, raloxifene did not increase or decrease the incidence of noninvasive breast cancer, and in the STAR trial, the patients assigned to tamoxifen had numerically fewer noninvasive breast cancers than the patients assigned to raloxifene, but this difference was not statistically significant. This reviewer is of the opinion that no such conclusions can be drawn: the trials were not to powered to detect differences in the incidence of non-invasive breast cancer.*

Comparison of Results in Subpopulations in the placebo-controlled trials

- In the RUTH trial, raloxifene reduced the incidence of invasive breast cancer whether the patient had a 5-year predicted invasive breast cancer risk of <1.66% or ≥1.66%, as determined by the modified Gail model, although the reduction in the risk for the subgroup of women with risk ≥ 1.66% was not statistically significant. Benefit was seen whether women were ≤65 years old or >65 years old, or had family history of breast cancer (yes/no).
- Such subgroup analysis was not possible for the MORE and the CORE trials as the relevant information for modified Gail model calculations was not collected in the MORE trial, and number of patients in CORE is further reduced.
- Few non-white patients were enrolled; therefore, the effect of raloxifene among subgroups by race could not be adequately assessed.

Compliance with Mammograms and Clinical Breast Examinations

RUTH

Mammograms and clinical breast examinations were scheduled at randomization and every 2 years thereafter.

- At baseline, almost all patients were compliant with mammograms and clinical breast examinations (99.96% and 99.17%, respectively).
- At 4 years, approximately 88% of eligible patients were compliant with the scheduled mammogram and clinical breast examination.
- At 6 years, approximately 80% and 85% of the eligible patients were compliant with the scheduled mammogram and clinical breast examination, respectively.
- Compliance with post-baseline mammograms and clinical breast examinations was consistent between treatment groups at all scheduled time points.

MORE

Bilateral mammograms or ultrasound (if patient refused mammogram) were required at baseline (within 3 months before randomization) and after 2, 3, and 4 years of follow-up; mammograms were optional after 1 year of follow-up.

- At baseline, almost all patients (99.97%) were compliant with breast imaging (ie, mammogram or ultrasound) and 48% elected to have the optional breast imaging procedure at Year 1.
- Compliance with post baseline mammograms was consistent between treatment groups at all scheduled time points, with over 90% of the eligible patients being compliant with the 4-year scheduled mammogram.

CORE

Bilateral mammograms were required at (or within 12 months prior to) baseline (ie, enrollment or Visit 1) and every 2 years thereafter; clinical breast examinations were required at baseline and annually thereafter.

- At baseline, almost all patients were compliant with mammograms and clinical breast examinations (99.25% and 99.23%, respectively).
- Compliance with post baseline mammograms and clinical breast examinations was consistent between treatment groups at all scheduled time points, with approximately 95% of the eligible patients being compliant with the 4-year mammogram and clinical breast examination.

In summary, in the placebo-controlled studies, the majority of patients were compliant with scheduled breast imaging procedures and clinical breast examinations. Therefore, it is unlikely that any missed procedure directly impacted the breast cancer analyses.

Analyses of benign breast diseases in the placebo-controlled studies

RUTH

- There were no statistically significant differences between treatment groups in the incidences of benign breast changes or diseases and breast conditions, except for breast hypertrophy.
- The proportion of patients who reported breast hypertrophy was statistically significantly higher among patients in the placebo group compared with the raloxifene group but the clinical relevance of this finding is unclear.
- Atypical hyperplasia was reported in 6 patients (5 in the placebo group and 1 in the raloxifene group).

MORE

- Raloxifene was not associated with the adverse events of breast pain, breast enlargement, or breast engorgement.
- Breast-related serious adverse events reported after baseline were breast carcinoma (1.7% in placebo group versus 0.6% in raloxifene HCl 60-mg/day group; $p<0.01$), breast neoplasm (0.3% in placebo group versus 0.1% in raloxifene HCl 60-mg/day group), and fibrocystic breast disease (0.0% in placebo vs. 0.1% in raloxifene).
- In terms of treatment-emergent adverse events related to the breast, fewer patients in the raloxifene group (n=217, 8.5%) than in the placebo group (255, 9.9%) reported any breast-related adverse event.
- A number of various types of breast discharge were assigned to the COSTART term "female lactation". Female lactation was reported more frequently in the raloxifene group than in the placebo group (0.2% and 0.0%, respectively; $p<0.05$). The clinical relevance of this observation is not clear, as only 4 cases were reported.

CORE

- From CORE enrollment (Visit 1) to the end of CORE (Visit 5), there was no statistically significant difference between the placebo and raloxifene treatment groups in reported incidence of benign breast disease (2.1% in placebo group vs. 1.5% in raloxifene group; $p=0.173$). One case of atypical hyperplasia was reported, that being in the raloxifene group.
- In the 8-year MORE/CORE analysis, the incidence rates for benign breast changes or diseases and breast conditions were numerically similar between the raloxifene group and the placebo group. One case of atypical hyperplasia was reported in the placebo group.

In summary, raloxifene has not been associated with an increase or decrease in reported benign breast diseases or conditions and few cases of atypical hyperplasia have been reported in patients assigned to raloxifene.

Analysis of Clinical Information Relevant to Dosing Recommendations

The approved, marketed dose of raloxifene HCl for the prevention and treatment of osteoporosis in postmenopausal women is 60 mg/day. This daily dose of raloxifene was used in the pivotal trials RUTH and STAR, and in the supportive studies MORE and CORE.

- In MORE, the patients were randomized to placebo, raloxifene 60 mg/day, and raloxifene 120 mg/day.
- The demographic and other baseline characteristics of the patients did not differ among the three treatment groups at baseline. In particular, the three groups were similar with respect to baseline factors related to breast cancer risk (age, family history of breast cancer, previous use of hormone therapy).
- The effect of raloxifene in reducing the incidence of invasive breast cancer was not different between raloxifene HCl 60-mg/day and 120-mg/day assigned patients.

Based on the available clinical information, the recommended dose is raloxifene HCl 60 mg/day.

Persistence of Efficacy and/or Tolerance Effects

RUTH assessed the effects of raloxifene compared with placebo for a median of 5.6 years of study follow-up. The study concluded after the last randomized patient had been followed for at least 5 years.

- Of the 10,101 patients randomized, 84% (n = 8523) were followed for at least 5 years, 45% (n = 4517) were followed for at least 6 years and 0.9% (n = 86) were followed for at least 7 years. During the study, there was a total of 51,010 patient-years of study drug exposure with the median being 5.05 years.
- Reduction of invasive breast cancer risk is seen through 6 and 7 years of treatment with raloxifene.

The 8-year analysis of MORE/CORE provides data supporting persistent efficacy of raloxifene therapy for up to 8 years of follow-up.

- Of the 2641 patients who comprised the MORE subset randomized to raloxifene HCl 60 mg/day or placebo and who continued in CORE, 95% (n = 2505) were followed for at least 7 years and 90% (n = 2377) were followed for at least 8 years. The median time between the end of MORE and the beginning of CORE was 10.6 months during which time patients were not assigned to study medication but could have taken raloxifene or another SERM.
- Persistence in the reduction of invasive breast cancer in the raloxifene group is seen through Years 7 and 8 of follow-up.

In summary, these data indicate that the efficacy of raloxifene, compared with placebo, in reducing invasive breast cancer persists for over 5 years of follow-up in postmenopausal women having a median 5-year risk of developing breast cancer of 1.55% (RUTH) and for up to 8 years of follow-up in postmenopausal women with osteoporosis (MORE/CORE).

6.1.5 Clinical Microbiology

- Not applicable

6.1.6 Efficacy Conclusions

Conclusions:

- The efficacy of raloxifene in reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis is demonstrated by the three placebo-controlled raloxifene trials.
- Benefit of raloxifene persists as long as a woman is taking raloxifene. Whether the benefit would persist after a woman has stopped taking raloxifene, as is seen with tamoxifen, is not known.
    - Data on women off raloxifene is not available form these trials.
    - Follow-up durations in RUTH, MORE, and CORE trials are 5.6, 4.0 and 3.9 years. A subset of MORE patients that continued in CORE trial has been followed up for nearly 8 years. These durations of follow-up assure that the benefit of raloxifene persists while the patients are taking raloxifene.
    - Whether the benefit would persist (as seen with tamoxifen) off raloxifene is not known at present.
- A wide variation in the breast cancer risk reduction is seen across the studies.
    - The absolute risk reductions seen in the RUTH, the MORE, and the CORE trials are 1.16, 3.10, and 2.98 per 1,000 person-years. Accordingly the number of women needed to treat (NNT) for 1 year to prevent one case of invasive breast cancer is 862, 323, and 335, respectively.
    - Some variation among the studies can be expected due to the differences in the risk factors for breast cancer development in different study-populations. Unfortunately, breast cancer risk factors information was not collected in the MORE trial—the trial was not designed to evaluate the effect of raloxifene on breast cancer. It is quite likely that this is a random variation. The results of the MORE and the CORE trial are similar, as the CORE trial is only a continuation of the former.
- Raloxifene did not reduce the risk of non-invasive breast cancers in the STAR trial; the total number of cases is too small in the placebo-controlled trials to draw any conclusions.
- Raloxifene did not reduce the risk of ER negative breast cancers.
- Breast cancer stage at diagnosis. Notably the vast majority of the breast cancers in the three trials were stage IIA or less, both in the raloxifene and the placebo arms.

- As breast cancer incidence is only reduced and the risk is not eliminated by using raloxifene, the need for women taking raloxifene to continue with every one to two years screening mammograms remains
- Patients who were at risk of thromboembolic adverse events were excluded from all three trials; accordingly, patients at risk of thromboembolism should not be offered raloxifene treatment.
    - Despite the exclusion of patients at risk of thromboembolic AEs, a higher relative risk for these AEs was seen in all three placebo controlled trials
- The dose of raloxifene to be used for the proposed indications of breast cancer risk reductions is the same as that used and approved for prevention and treatment of osteoporosis and has been adequately studied in the supporting trials