Oncologic Drugs
Advisory Committee Briefing Document

Evista® (raloxifene HCl)

Invasive Breast Cancer Risk Reduction

Meeting Date: 24 July 2007

Division of Drug Oncology Products

Answers That Matter.

Eli Lilly and Company

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Executive Summary

Introduction

The Oncologic Drugs Advisory Committee (ODAC) has been asked to participate in the Food and Drug Administration's (FDA) evaluation of the New Drug Application (NDA) 22-042 for Evista® (raloxifene hydrochloride [HCl], hereafter referred to as raloxifene) for the reduction in risk of invasive breast cancer in postmenopausal women at high risk for breast cancer and the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis.

Raloxifene received FDA approvals in the United States on 09 December 1997 and 30 September 1999 for the prevention and treatment of osteoporosis in postmenopausal women, respectively. The approved raloxifene label stated then, as it does now, that "(t)he effectiveness of raloxifene in reducing the risk of breast cancer has not been established." A recently completed clinical program now provides extensive evidence of the effect of raloxifene in reducing the risk of invasive breast cancer in postmenopausal women. The totality of the data supports the appropriate use of raloxifene to reduce the risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer and in postmenopausal women with osteoporosis.

The registration study for the treatment of osteoporosis (Multiple Outcomes of Raloxifene Evaluation [MORE]) established a positive benefit/risk profile of raloxifene for the treatment of osteoporosis in postmenopausal women with osteoporosis. MORE also showed that raloxifene decreased the incidence of invasive breast cancer by a statistically and clinically significant 71%, compared with placebo. However, because breast cancer risk reduction was a secondary endpoint, the evidence was not sufficient for the approval of an additional indication for this population.

Based on the MORE findings and discussions with the Division of Drug Oncology Products (DDOP), Eli Lilly and Company (Lilly) developed a 4-year continuation (Continuing Outcomes Relevant to Evista [CORE]) of the MORE study to further explore the initial breast cancer risk reduction findings in postmenopausal women with osteoporosis. At that time, the FDA indicated that independent confirmation of these early results would be necessary and that analyses demonstrating long-term clinically and statistically significant differences in the incidence of invasive breast cancer between patients treated with raloxifene and placebo would provide supportive evidence of efficacy.

Thus, in 1999, based on DDOP recommendations on how to substantiate the effect of raloxifene on invasive breast cancer, Lilly added invasive breast cancer as a primary endpoint in the Raloxifene Use for The Heart (RUTH) study in women at risk for major coronary events. About the same time, the National Surgical Adjuvant Breast and Bowel Project (NSABP) implemented the Study of Tamoxifen and Raloxifene (STAR). The FDA stated that "(d)ata from a prospective randomized study of raloxifene in which the

reduction in the incidence of breast cancer is the primary endpoint will be needed, such as data from the STAR study. If positive, evidence from both studies [MORE and STAR] (or from 3 studies, with RUTH) will allow extension of your indication."

Data from these three randomized clinical studies have been analyzed and form the basis of NDA 22-042 filed in November 2006. Taken together, these studies enrolled more than 37,000 postmenopausal women and represent more than 76,000 patient-years of exposure to raloxifene. Lilly believes that NDA 22-042 provides substantial evidence demonstrating a positive benefit/risk profile of raloxifene in reducing the risk of invasive breast cancer in postmenopausal women at high risk of breast cancer and in postmenopausal women with osteoporosis.

Unmet Clinical Need

Breast cancer is a major public health issue worldwide. After skin, the breast is the most common site of cancer in women, and breast cancer is second only to lung cancer as a cause of death from cancer among women. It accounts for 26% of all female cancers and is responsible for 15% of cancer-related deaths in women (Cancer Facts and Figures 2007). It is estimated that more than 178,000 women will be diagnosed with invasive breast cancer in the United States in 2007, and more than 40,000 of those women will die from the disease this year (Cancer Facts and Figures 2007).

Tamoxifen is the only agent approved to reduce the risk of breast cancer in women at high risk for developing breast cancer. However, the use of tamoxifen for reducing the risk of breast cancer has been limited (Gradishar and Cella 2006). Among the reasons for the limited use of tamoxifen is the risk profile, which includes an increased risk of endometrial cancer (Gradishar and Cella 2006).

Unapproved therapies are currently being investigated (Kelloff et al. 2006) for their efficacy in reducing breast cancer risk but definitive evidence of their clinical profile will not be known for at least several years. This includes the class of aromatase inhibitors (AIs) that have been evaluated in breast cancer adjuvant studies and are being evaluated for their efficacy in reducing the risk of breast cancer in women at increased risk of breast cancer (Kelloff et al. 2006).

Thus, the need exists now for an agent that can reduce the incidence of invasive breast cancer with a favorable benefit/risk profile.

Clinical Efficacy

Efficacy of Raloxifene in Reducing the Risk of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis

MORE was a double-blind, randomized, placebo-controlled multinational study consisting of a 3-year treatment phase and a 1-year extension phase designed to primarily examine the effect of raloxifene on the risk of fracture in postmenopausal women with osteoporosis. MORE randomized 7705 postmenopausal women with osteoporosis

(median age, 66.9 years) to treatment with placebo (N=2576), raloxifene HCl 60 mg/day (N=2557), or raloxifene HCl 120 mg/day (N=2572). MORE treatment groups had comparable baseline demographic characteristics. Median study follow-up was 3.95 years.

Breast cancer was one of the secondary endpoints evaluated in the study. Breast cancer efficacy results are presented for only the 60 mg/day dose because it is the approved dose for prevention and treatment of osteoporosis. It should be noted that the incidence rates (IRs) per 1000 patient-years for all breast cancer and for invasive breast cancer were not significantly different (p-value=0.810 and p-value=0.622, respectively) between the MORE raloxifene 60 and 120 mg/day dose groups. The IRs for all breast cancer and invasive breast cancer were 1.94 and 1.26 for the raloxifene 60 mg/day dose group and 1.80 and 1.01, respectively, for the 120 mg/day dose group.

Raloxifene showed a statistically significant 71% decrease in the incidence of invasive breast cancers (Table ES.1), compared with placebo, in postmenopausal women with osteoporosis.

Table ES.1. Invasive Breast Cancer Results in MORE

MORE (N=5133)[a]						
	Number of Events		IR			
	PBO N=2576	RLX60 N=2557	PBO N=2576	RLX60 N=2557	ARD	HR (95% CI)
Invasive breast cancer	38	11	4.36	1.26	-3.10	0.29 (0.15-0.56)

Abbreviations: ARD = absolute risk difference between raloxifene and placebo; CI = confidence interval; HR = hazard ratio; IR = incidence rate per 1000 patient-years; N = number of patients analyzed; PBO = placebo; RLX60 = raloxifene HCl 60 mg/day.

[a] Patients randomized in MORE to either placebo or raloxifene HCl 60 mg/day. Breast cancers reported from randomization in MORE to end of MORE (48 months) are presented.

In MORE, 8 cases of noninvasive breast cancer occurred (all were ductal carcinoma in situ [DCIS]), 5 among 2576 placebo-assigned patients and 3 among 2557 raloxifene-assigned patients.

These results suggested a possible beneficial effect of raloxifene on the incidence of invasive breast cancer. Exploration of the persistence of this possible benefit was undertaken by following a subset of MORE patients on their respective randomized therapy for an additional 4 years. This follow-up study is CORE.

CORE enrolled 4011 postmenopausal women with osteoporosis (median age, 71.0 years) who had been randomized in MORE. The primary objective of CORE was to evaluate the effect of raloxifene HCl 60 mg/day versus placebo on the incidence of invasive breast cancer in postmenopausal women with osteoporosis.

For all CORE patients, a treatment gap occurred between the end of their participation in MORE and the start of their participation in CORE (the median time off therapy was approximately 10.6 months). Treatment continued to be blinded in CORE. Women assigned to placebo in MORE were assigned to placebo in CORE and women taking raloxifene HCl 60 mg/day or 120 mg/day in MORE were assigned to receive raloxifene HCl 60 mg/day in CORE. Consequently, approximately twice as many women in CORE were taking raloxifene HCl 60 mg/day compared with placebo. Of the CORE enrollees, 21 women, who had developed breast cancer during MORE and who had been included in the MORE breast cancer analysis, were excluded from the CORE breast-cancer endpoint analysis.

CORE treatment groups were balanced with regard to breast cancer risk factors; at enrollment both treatment groups had a mean Gail model-based 5-year predicted risk of invasive breast cancer of 1.94%.

During the 4 years of CORE, raloxifene showed a statistically significant 56% decrease in the incidence of invasive breast cancer (Table ES.2), compared with placebo, in postmenopausal women with osteoporosis.

Table ES.2. Invasive Breast Cancer Results in CORE

CORE (N=3990)[a]						
	Number of Events		IR			
	PBO N=1274	RLX60 N=2716	PBO (N=1274)	RLX60 (N=2716)	ARD	HR (95% CI)
Invasive breast cancer	20	19	5.41	2.43	-2.98	0.44 (0.24-0.83)

Abbreviations: ARD = absolute risk difference between raloxifene and placebo; CI = confidence interval; HR = hazard ratio; IR = incidence rate per 1000 patient-years; N = number of patients analyzed; PBO = placebo; RLX60 = raloxifene HCl 60 mg/day.

[a] This analysis includes only those patients enrolled in CORE who had not been diagnosed with breast cancer prior to enrollment (N=3990 of 4011 enrolled patients). Breast cancers reported from CORE enrollment (Visit 1) to the end of CORE are presented.

In CORE, 7 cases of noninvasive breast cancer occurred (all were DCIS), 2 among 1274 placebo-assigned patients and 5 among 2716 raloxifene-assigned patients.

Efficacy of Raloxifene in Postmenopausal Women at Risk for Major Coronary Events

The positive effect of raloxifene on lipids and other markers of cardiovascular risk observed in MORE and other raloxifene studies, and the encouraging data from observational studies with estrogens suggested a hypothesis that raloxifene could have a beneficial effect on coronary heart disease (Mosca et al. 2001). As a result, RUTH was initially developed to test that hypothesis. Following discussions with the DDOP (11 May 1999) on how to substantiate the effect of raloxifene on invasive breast cancer that had been observed in MORE, Lilly was advised by DDOP to add invasive breast

cancer risk reduction as a primary endpoint to the existent primary coronary endpoint in RUTH and to split the trial significance level of 0.05 between the two primary endpoints. All breast cancer was and continued to be a secondary endpoint in RUTH.

RUTH was a double-blind, multinational, randomized, placebo-controlled study of postmenopausal women at risk for major coronary events evaluating two primary endpoints: (1) reduction in risk of major acute coronary events and (2) reduction in risk of invasive breast cancer. The appropriate statistical adjustments for two primary endpoints were established a priori.

RUTH randomized 10,101 women (median age 67.6 years) to treatment with placebo (N=5057) or raloxifene HCl 60 mg/day (N=5044). The median study drug exposure was 5.1 years for both treatment groups. The median duration of follow-up for both treatment groups was 5.6 years.

RUTH treatment groups had similar baseline characteristics. Both treatment groups had a mean Gail model-based 5-year predicted risk of invasive breast cancer of 1.73%.

Raloxifene showed a statistically significant 44% decrease in the incidence of invasive breast cancer (Table ES.3), compared with placebo, in postmenopausal women at risk for major coronary events.

Table ES.3. Invasive Breast Cancer Results for RUTH

RUTH (N=10,101)						
	Number of Events		IR			
	PBO N=5057	RLX60 N=5044	PBO N=5057	RLX60 N=5044	ARD	HR (95% CI)
Invasive breast cancer	70	40	2.66	1.50	-1.16	0.56 (0.38-0.83)

Abbreviations: ARD = absolute risk difference between raloxifene and placebo; CI = confidence interval; HR = hazard ratio; IR = incidence rate per 1000 patient-years; N = number of patients analyzed; PBO = placebo; RLX60 = raloxifene HCl 60 mg/day.

In RUTH, 16 cases of noninvasive breast cancer occurred (all were DCIS), 5 among 5057 placebo-assigned patients and 11 among 5044 raloxifene-assigned patients.

Efficacy Summary of the Placebo-Controlled Studies

The placebo-controlled studies provide substantial evidence that raloxifene, compared with placebo, demonstrates a clinically meaningful reduction in invasive breast cancer in postmenopausal women with osteoporosis or at risk for major coronary events.

The CORE follow-up study of MORE patients provides evidence that the effects of raloxifene in decreasing the risk of invasive breast cancer persist during an additional 4 years of treatment.

A small number of cases of noninvasive breast cancer were observed in the randomized placebo-controlled studies, MORE and RUTH, and in the placebo-controlled follow-up study of MORE participants, CORE (all of which were DCIS); the incidences for raloxifene and placebo groups were not significantly different in any of these studies.

Efficacy of Raloxifene in Postmenopausal Women at Increased Risk of Invasive Breast Cancer

STAR was a randomized active-comparator study that examined the effect of raloxifene and tamoxifen in reducing the incidence of invasive breast cancer. The foundation for the STAR study was the earlier NSABP P-1 study (Fisher et al. 1998) that evaluated the efficacy of tamoxifen versus placebo in reducing the incidence of invasive breast cancer in women at increased risk for the disease.

STAR randomized 19,747 women with a Gail model-based 5-year predicted breast cancer risk greater than or equal to 1.66% or a history of lobular carcinoma in situ (LCIS) to treatment with tamoxifen 20 mg/day or raloxifene HCl 60 mg/day. The mean age of the population was 58.5 years and their mean 5-year predicted risk was 4.03%. No clinically relevant differences were observed in patient demographics and baseline characteristics between treatment groups. The mean duration of treatment was 3.1 and 3.2 years for tamoxifen and raloxifene, respectively. The mean duration of study follow-up was 4.1 years.

Raloxifene reduced the incidence of invasive breast cancer to a comparable extent as tamoxifen (Table ES.4) in postmenopausal women at increased risk of invasive breast cancer.

Table ES.4. Invasive Breast Cancer Results in STAR

STAR (N=19,487)						
	Number of Events		IR		ARD	RR (95% CI)
	TMX N=9736	RLX60 N=9751	TMX N=9736	RLX60 N=9751		
Invasive breast cancer	168	173	4.30	4.40	+0.10	1.02 (0.82-1.27)

Abbreviations: ARD = absolute risk difference between raloxifene and tamoxifen; CI = confidence interval; IR =incidence rate per 1000 patient-years; N = number of patients analyzed; RR = risk ratio for patients in the raloxifene group compared to patients in the tamoxifen group; RLX60 = raloxifene HCl 60 mg/day; TMX = tamoxifen.

Two methods, a Gail model-based calculation of the expected invasive breast cancer incidence rate for an untreated group and Rothmann's method (Rothmann et al. 2003), were used to assess the estimated effect of raloxifene relative to a putative placebo, as described briefly in the following two paragraphs.

Based on a mean predicted 5-year breast cancer risk of 4.03% for the STAR population, the expected incidence rate for an untreated group, had one been included in the study,

was estimated to be 8.2 per 1000 patient-years. Tamoxifen and raloxifene reduced the estimated incidence rate by nearly half (tamoxifen; IR 4.30 per 1000 patient-years and raloxifene; IR 4.40 per 1000 patient-years).

A pre-specified analysis based on Rothmann's method (Rothmann et al. 2003) showed that raloxifene maintained at least 65% of the effect of tamoxifen on invasive breast cancer (point estimate of the proportion of effect maintained is 97%, 95% confidence interval [CI] 65%-128%). The relative risk of raloxifene versus putative placebo was estimated to be 52%, had a placebo group been included in STAR.

Raloxifene and tamoxifen demonstrated comparable efficacy among women with different baseline characteristics (age, history of LCIS, history of atypical hyperplasia, 5-year predicted breast cancer risk, or family history of breast cancer). There were no significant differences between treatment groups in breast cancer characteristics, including clinical stage at diagnosis. Raloxifene and tamoxifen had comparable effects on the yearly incidence rate of invasive breast cancer through 6 or more years of study follow-up.

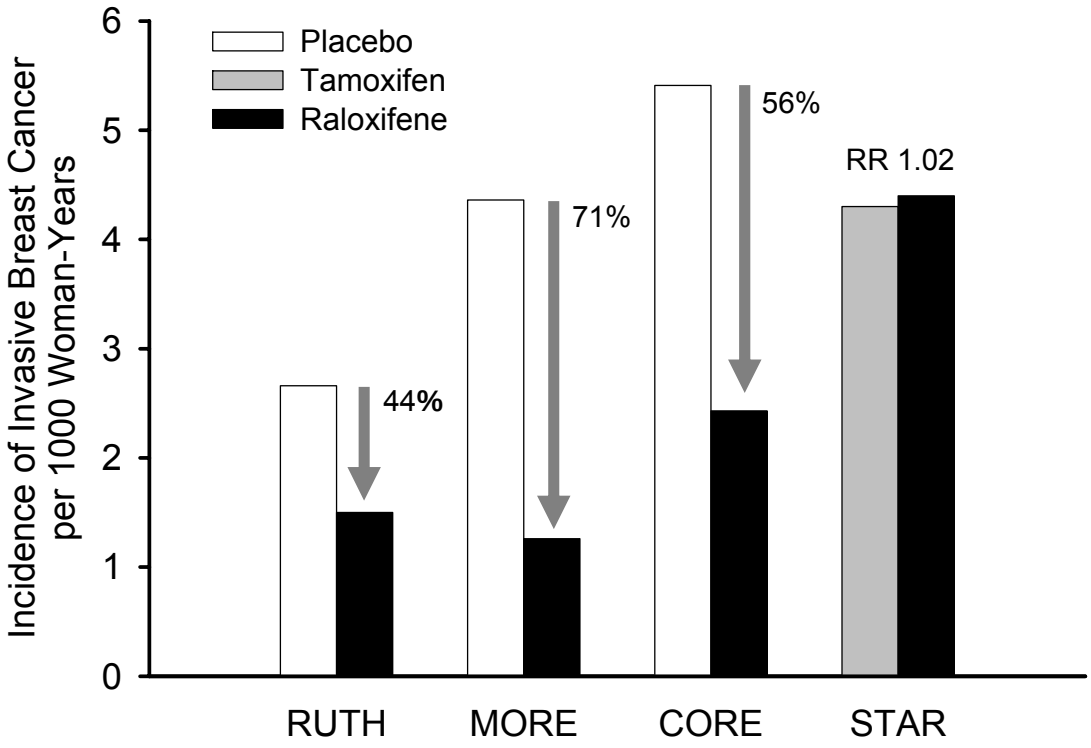
Though not statistically significant, women in the tamoxifen group had fewer noninvasive breast cancers (60) than women in the raloxifene group (83) (risk ratio [RR] 1.38, 95% CI 0.98-1.95). For reference, the incidence of noninvasive breast cancer in the STAR raloxifene group was comparable to that observed in the placebo-assigned women 50 years of age or older in the NSABP P-1 study of tamoxifen (2.12 [STAR] to 2.04 [P-1] per 1000 patient-years) (Fisher et al. 1998). Based on this comparison, tamoxifen reduced the risk of noninvasive breast cancer, while raloxifene appeared to have no effect.

Efficacy Summary of the Active-Comparator Controlled Study

STAR showed that raloxifene is comparable to tamoxifen in reducing the risk of invasive breast cancer in postmenopausal women at increased risk of breast cancer.

Overall Efficacy Summary

As evidenced in Figure ES.1, raloxifene demonstrated significant efficacy in reducing the incidence of invasive breast cancer in postmenopausal women in MORE, CORE, RUTH, and STAR, regardless of their baseline invasive breast cancer risk.



Abbreviation: RR = risk ratio for raloxifene:tamoxifen.
Note: Invasive breast cancer was a secondary endpoint in MORE.

Figure ES.1 **Evidence of invasive breast cancer risk reduction regardless of baseline breast cancer risk.**

Clinical Safety

Safety of Raloxifene in Postmenopausal Women with Osteoporosis

Table ES.5 summarizes important safety outcomes in MORE. The raloxifene HCl 60 mg/day and 120 mg/day groups were combined for these analyses so as to provide the greatest opportunity to detect safety signals.

Table ES.5. Important Safety Outcomes in MORE (Incidence Rates per 1000 Patient-Years)

Events [a]	PBO N=2576 n	RLX N=5129 n	PBO N=2576 IR	RLX N=5129 IR	p-value*
Death	36	64	4.13	3.63	0.522
Death due to stroke	6	9	0.69	0.51	0.552
Stroke	56	91	6.42	5.16	0.191
Pulmonary embolism	4	22	0.46	1.25	0.053
Deep vein thrombosis	8	44	0.92	2.50	0.006
Endometrial and uterine [b] cancer	5	8	0.74	0.59	0.528
Ovarian cancer	6	6	0.69	0.34	0.201

Abbreviations: IR = incidence rate per 1000 patient-years; n=number of events; N = number of patients analyzed; PBO = placebo; RLX = raloxifene.

[a] For the safety events of death, death due to stroke, stroke, deep vein thrombosis, pulmonary embolism, and ovarian cancer, the raloxifene HCl 60 mg/day and 120 mg/day groups were pooled for analyses so as to provide the greatest opportunity to detect safety signals; thus, the denominator for these events is 5129.

[b] Only patients with an intact uterus were considered for the denominator (raloxifene denominator = 3960, placebo denominator = 1999).

* Obtained from log–rank test.

Raloxifene, compared with placebo, statistically significantly decreased the incidence of clinical vertebral fractures (refer to Table 17) and was associated with a statistically significantly increased incidence of deep-vein thromboses (DVTs).

With the exception of statistically significant reductions in all breast cancers and invasive breast cancer in MORE, raloxifene versus placebo showed no statistically significant difference in the incidences of all cancers or any specific type of cancer.

For postmenopausal women with osteoporosis, MORE established the safety profile for raloxifene HCl 60 mg/day. The current US package insert includes the MORE safety data, and these data are supported by the approximately 12 million patient-years (estimated 22 million patients) of worldwide clinical experience with marketed raloxifene.

Safety of Raloxifene in Postmenopausal Women at Risk for Major Coronary Events

Table ES.6 summarizes important safety outcomes in RUTH. Per protocol, the RUTH population was at risk for major coronary events.

Table ES.6. Important Safety Outcomes in RUTH (Incidence Rates per 1000 Patient-Years)

	PBO N=5057 n	RLX60 N=5044 n	PBO N=5057 IR	RLX60 N=5044 IR	p-value*
Death	595	554	22.45	20.68	0.160
Death due to stroke	39	59	1.47	2.20	0.0499
Stroke	224	249	8.60	9.46	0.303
Clinical vertebral fracture	97	64	3.70	2.40	0.007
Pulmonary embolism	24	36	0.91	1.35	0.129
Deep vein thrombosis	47	65	1.78	2.44	0.100
Endometrial and uterine cancer [a]	17	21	0.83	1.01	0.556
Ovarian cancer [b]	10	17	0.41	0.70	0.181

Abbreviations: IR = incidence rate per 1000 patient-years; n=number of events; N = number of patients analyzed; PBO = placebo; RLX 60 = raloxifene HCl 60 mg/day.

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

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

* Obtained from log-rank test.

In RUTH, compared with placebo, raloxifene showed no effect on the risk of major coronary events, the incidence of death, or the incidence of stroke. Raloxifene was associated with a statistically significant (p=0.0499) increase, compared with placebo, in the incidence of death due to stroke (Table ES.6). As in MORE, raloxifene versus placebo showed a statistically significant decrease in clinical vertebral fractures and an increased incidence of PEs and DVTs (Table ES.6).

With the exception of statistically significant reductions in invasive breast cancer in RUTH, raloxifene versus placebo showed no statistically significant difference in the incidences of all cancers or any specific type of cancer.

Safety of Raloxifene in Postmenopausal Women at Increased Risk of Invasive Breast Cancer

Table ES.7 summarizes important safety outcomes in STAR.

Table ES.7. Important Safety Outcomes in STAR (Incidence Rates per 1000 Patient-Years)

	TMX N=9736 n	RLX60 N=9751 n	TMX N=9736 IR	RLX60 N=9751 IR	p-value*
Death	109	104	2.76	2.62	0.678
Death due to stroke	7	5	0.18	0.13	0.552
Stroke	56	54	1.42	1.36	0.819
Clinical vertebral fracture[a]	58	58	1.47	1.46	0.968
Pulmonary embolism	58	38	1.47	0.96	0.037
Deep vein thrombosis	92	67	2.35	1.69	0.041
Endometrial cancer	37	23	1.99	1.21	0.055
Endometrial hyperplasia	100	17	5.42	0.90	--
Hysterectomy [b]	246	92	13.25	4.84	--
Ovarian cancer	14	18	0.52	0.66	0.508
Cataracts	435	343	13.19	10.34	<0.001
Cataract surgery[c]	295	240	8.85	7.17	0.014

Abbreviations: CI = confidence interval; IR = incidence rate per 1000 patient-years; N = number of patients analyzed; n=number of events; RLX60 = raloxifene HCl 60 mg/day; RR = risk ratio; TMX = tamoxifen.

[a] Reported as osteoporotic fracture of the spine in the STAR clinical study report.

[b] Only patients with an intact uterus at baseline were considered for the denominator (tamoxifen denominator, 4739; raloxifene denominator, 4715).

[c] Only patients who were cataract free at baseline were considered for the denominator (tamoxifen denominator, 8342; raloxifene denominator, 8333).

* Obtained from log-rank test.

Overall, for postmenopausal women at increased risk for invasive breast cancer, STAR data support a more favorable safety profile for raloxifene compared with tamoxifen.

Overall Safety Summary

For postmenopausal women at increased risk of osteoporotic fractures, the raloxifene safety profile was established in osteoporosis prevention and treatment clinical studies, and is supported by the approximately 12 million patient-years (estimated 22 million patients) of worldwide clinical experience with marketed raloxifene.

For postmenopausal women at increased risk for invasive breast cancer, STAR data show that raloxifene has a more favorable safety profile than that of tamoxifen.

Conclusion

The FDA approved raloxifene more than 9 years ago for the prevention, and 7 years ago for the treatment, of osteoporosis in postmenopausal women. Based on the results of the studies included in NDA 22-042, and presented in this document, it is now established that if a postmenopausal woman with osteoporosis takes raloxifene to decrease her risk of osteoporotic fractures, she will also decrease her risk of developing invasive breast cancer.

Postmenopausal women at increased risk for invasive breast cancer need options to reduce their risk. Lilly believes that raloxifene, like tamoxifen, should now be considered an option for invasive breast cancer risk reduction in postmenopausal women at high risk for the disease. In this population, raloxifene demonstrates efficacy comparable to tamoxifen to reduce the risk of invasive breast cancer with a more favorable safety profile than tamoxifen.

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1. Introduction

1.1. Background

Evista® (raloxifene hydrochloride [HCl], hereafter referred to as raloxifene) received Food and Drug Administration (FDA) approvals in the United States on 09 December 1997 and 30 September 1999 for the prevention and treatment of osteoporosis in postmenopausal women, respectively. Since first approval through 30 November 2006, an estimated 22 million patients in 88 countries worldwide have received raloxifene, representing approximately 12 million patient-years of treatment.

The current raloxifene label (Evista package insert 2003) includes very limited breast cancer data under the heading of "Effects on Breast," which concludes with the following sentence: "The effectiveness of raloxifene in reducing the risk of breast cancer has not been established."

Lilly believes that data from the recently completed STAR and RUTH studies, combined with data from MORE and its follow-up study, CORE, now provide substantial evidence that raloxifene reduces the risk of invasive breast cancer in postmenopausal women at increased risk for the disease or with osteoporosis.

The focus of this application is on the use of raloxifene for the reduction in risk of invasive breast cancer in postmenopausal women. To this end, Eli Lilly and Company (Lilly) submitted New Drug Application (NDA) 22-042 to the FDA in November 2006, seeking approval for the following indication statements for raloxifene:

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

The reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis.

1.2. Targeted Indication: Invasive Breast Cancer Risk Reduction

Breast cancer is a major public health issue worldwide. After skin, the breast is the most common site of cancer in women, and breast cancer is second only to lung cancer as a cause of death from cancer among women. It accounts for 26% of all female cancers and is responsible for 15% of cancer-related deaths in women (Cancer Facts and Figures 2007). It is estimated that more than 178,000 women will be diagnosed with invasive breast cancer in the United States in 2007, and more than 40,000 of those women will die from the disease this year (Cancer Facts and Figures 2007). Recent information indicating a decrease in the annual age-adjusted US incidence rate of breast cancer (Ravdin et al. 2007) does not diminish the importance of breast cancer as a major public health issue.

1.3. Development of Raloxifene for Reduction of Invasive Breast Cancer Risk

Raloxifene is a member of a benzothiophene series of compounds previously described as antiestrogens for their ability to inhibit estrogen-responsive breast epithelial cell growth (Jones et al. 1984). Raloxifene is classified as a selective estrogen receptor modulator (SERM) based on its ability to elicit prototypical estrogen-like effects on the bone and on certain aspects of lipid metabolism while acting as an estrogen antagonist in reproductive tissues such as the breast and uterus (Kauffman and Bryant 1995; Bryant et al. 1996). The basis for the pharmacology of the tissue-selective estrogen agonist and antagonist effects of raloxifene resides with the high affinity interaction of raloxifene for estrogen receptors (ERs). The ability of raloxifene to compete with estrogen for ER binding is believed to account for the estrogen-antagonist effects in breast and uterus tissue, whereas the high affinity interaction of raloxifene with ER in bone, vascular, and hepatic tissue is believed to produce estrogen-like effects of reduced resorption of bone, vasorelaxation, and lowered serum cholesterol. Additional mechanisms that have been proposed to account for tissue selectivity include the presence, quantity, and type of nuclear protein co-activators and co-repressors (Montano et al. 1999) in each cell type and the distinct response of cells to SERMs depending on the subtype of ER (α or β) expressed (Jones et al. 1999).

At the cellular level, results of extensive work have shown that raloxifene antagonizes estrogen-stimulated proliferation of breast cancer cells (reviewed in Sporn et al. 2004). This effect has been studied most thoroughly in the MCF-7 tumor cell line, a human mammary adenocarcinoma-derived cell line with a robust proliferative response to estrogen. In MCF-7 cells, raloxifene is a potent inhibitor of estrogen-induced proliferation. In cell culture, these antiproliferative effects of raloxifene are specific for estrogen-driven responses, as raloxifene fails to demonstrate antiproliferative activity in estrogen-independent mammary carcinoma cell lines, including the androgen-sensitive Shionogi cell line.

As shown in the early 1980s (Clemens et al. 1983), anti-mammary tumor effects of raloxifene also have been observed in a variety of in vivo breast cancer models. There are reports that tumors induced by such chemical carcinogens as nitrosomethylurea (NMU) and dimethylbenzanthracene (DMBA) are prevented when raloxifene is commenced at the time of, or before, administration of the carcinogen (Sporn et al. 2004). In the NMU model, raloxifene resulted in a decreased incidence and weight of breast tumors.

Drugs that block the action of estrogen on tumor cells are used for treatment of breast cancer either in advanced disease or the adjuvant setting. In the adjuvant setting, the SERM tamoxifen citrate (hereafter referred to as tamoxifen), at present the only marketed therapy for risk reduction of breast cancer, is efficacious in reducing the risk of breast cancer recurrence (Fisher et al. 1989). The finding of a decrease in contralateral breast cancer incidence in women with unilateral breast cancer following adjuvant tamoxifen

therapy led to the concept that tamoxifen might play a role in breast cancer prevention in otherwise healthy women. Consequently, the National Surgical Adjuvant Breast and Bowel Project (NSABP) implemented a breast cancer prevention study (P-1) to evaluate the efficacy and safety of tamoxifen in reducing the risk of breast cancer in generally healthy women at increased risk for the disease (Fisher et al. 1998).

P-1, a double-blind, randomized, placebo-controlled clinical study conducted in North America, demonstrated that tamoxifen statistically significantly reduced the risk of invasive breast cancer in women at high risk for breast cancer (Fisher et al. 1998). However, safety concerns were noted with the use of tamoxifen. Specifically, tamoxifen was associated with an increased risk of endometrial cancer, venous thromboembolism (VTE), stroke, and cataract compared with placebo. For many women at high risk for breast cancer, the risk of these undesirable side effects outweighs the benefits of treatment (Freedman et al. 2003).

Nearly coincident with the completion of P-1, a 2-year interim analysis of the Lilly sponsored osteoporosis treatment study H3S-MC-GGGK, also known as Multiple Outcomes of Raloxifene Evaluation (MORE), hereafter referred to as MORE, revealed that raloxifene was associated with a decreased incidence of breast cancer. Lilly designed MORE with a 3-year treatment and 1-year extension phase to evaluate the effect of raloxifene on vertebral fractures and bone mineral density (BMD) in women with osteoporosis. Breast cancer incidence was a protocol-specified secondary endpoint. The study screened for baseline preexisting breast cancers by physical examination and mammography within 12 months of randomization. Breast cancers were prospectively ascertained through protocol-mandated mammography conducted at study years 2, 3, and 4. The MORE 4-year data demonstrated that raloxifene statistically significantly reduced the risk of invasive breast cancer in women with osteoporosis.

Prior to and in parallel with the study of raloxifene for the prevention and treatment of osteoporosis, Lilly evaluated the efficacy of raloxifene for the treatment of breast cancer in the Phase 1/2 Study B5U-MC-JEAA, the Phase 2 Study H3S-MC-JOAA, and the Phase 3 Study H3S-MC-GGHW. Overall, the efficacy results from these early studies were modest and Lilly did not pursue further studies of raloxifene for the treatment of breast cancer.

Study H3S-MC-GGJY, also known as Continuing Outcomes Relevant to Evista (CORE), hereafter referred to as CORE, was designed to collect long-term breast cancer and nonvertebral fracture data from the MORE cohort. CORE enrolled women who had been randomized to treatment in MORE and who chose to enroll in CORE. CORE showed that raloxifene statistically significantly reduced the risk of invasive breast cancer in the women from MORE who continued in CORE.

Based on the results of the P-1 and MORE studies, the NSABP implemented the P-2 study (also known as Study of Tamoxifen and Raloxifene [STAR], hereafter referred to as STAR) in 1998. The purpose of STAR was to directly compare raloxifene with

tamoxifen for their relative effects on the risk of invasive breast cancer in generally healthy postmenopausal women at increased risk of breast cancer.

Finally, raloxifene was studied for its effect on clinical coronary events in postmenopausal women at risk for major coronary events in Study H3S-MC-GGIO (also known as Raloxifene Use for The Heart [RUTH] hereafter referred to as RUTH). Following discussions with the DDOP (11 May 1999) on how to substantiate the effect of raloxifene on invasive breast cancer that had been observed in MORE, Lilly was advised by DDOP to add invasive breast cancer risk reduction as a primary endpoint to the existent primary coronary endpoint in RUTH and to split the trial significance level of 0.05 between the two primary endpoints.

1.4. Current Therapies

Tamoxifen is the only agent approved to reduce the risk of breast cancer in women at high risk for developing breast cancer. Tamoxifen was approved for the reduction in risk of breast cancer based on the results of P-1 (Fisher et al. 1998). Tamoxifen efficacy for reduction of risk of breast cancer in women at high risk for developing breast cancer has been tested and supported in other studies (Cuzick et al. 2003).

1.5. Unmet Clinical Needs

The use of tamoxifen for risk reduction of breast cancer in women at high risk for breast cancer has been limited. In fact, based on a 5-year predicted risk for developing breast cancer of at least 1.67%, 10 million women in the United States, aged 35 to 79 years, were projected to be eligible to take tamoxifen for breast cancer chemoprevention (Freedman et al. 2003). Using a model that weighed both the benefits and risks of tamoxifen, approximately 2.5 million (25%) of these women were projected to have a net benefit from tamoxifen therapy (Freedman et al. 2003). Despite having the option to use tamoxifen prophylactically to reduce the risk of breast cancer, relatively few eligible women do so for disease prevention (Gradishar and Cella 2006). Among the reasons for the substantial under use of tamoxifen for breast cancer risk reduction may be its perceived benefit/risk profile, including an increased risk of endometrial cancer.

Aromatase inhibitors (AIs) have been evaluated in breast cancer adjuvant studies and are being evaluated for their efficacy in reducing the risk of breast cancer in women at increased risk of breast cancer (Kelloff et al. 2006) but are not currently approved as a breast cancer risk reduction therapy. In the breast cancer adjuvant studies, AIs have shown a decrease in contralateral breast cancer and a reduction in breast cancer recurrence (Kelloff et al. 2006). However, the AIs are associated with a statistically significant increase in the risk of fracture (Eastell et al. 2006). Definitive data on the clinical profile of AIs with regard to the reduction of risk of breast cancer will not be available for at least several years.

Thus, the need exists now for agents that can reduce the incidence of invasive breast cancer with a favorable benefit/risk profile.

1.6. Regulatory and Registration History of Raloxifene

Raloxifene was initially developed as a therapeutic agent for prevention and treatment of osteoporosis in postmenopausal women (Investigational New Drug Application [IND] 39,503). Raloxifene was approved for prevention of osteoporosis on 09 December 1997 based on a 2-year prevention study and a 2-year interim analysis of the 3-year treatment study, MORE (NDA 20-815). Raloxifene was subsequently approved for the treatment of osteoporosis on 30 September 1999. In the MORE treatment study, raloxifene showed a decreased incidence of breast cancer, compared with placebo. However, these data were not sufficient to establish an indication. Consequently, the approved label under the heading of "Effects on Breast" states that: "The effectiveness of raloxifene in reducing the risk of breast cancer has not been established."

Lilly opened IND 57,137 on 21 October 1998 to facilitate discussions regarding breast cancer prevention as a potential indication for raloxifene. Representatives from the NSABP, Lilly, and Zeneca met with the DDOP in a Pre-IND meeting on 03 November 1998 to discuss plans for enrollment and conduct of the STAR study in women at high risk for breast cancer. On 03 December 1998, the NSABP filed IND 57,427 to initiate the STAR study.

On 11 May 1999 (IND 57,137 Meeting Minutes [11 May 1999]), the DDOP informed Lilly that data from STAR, if positive, could be used in conjunction with the results from MORE/CORE and/or RUTH to obtain an indication for reduction in incidence of invasive breast cancer in postmenopausal women. Specifically, Lilly was informed that, "The STAR study (randomized double-blind trial where reduction in the incidence of breast cancer is the primary endpoint) will provide important comparative data to tamoxifen and will support an indication in high-risk women." DDOP also "strongly recommended proceeding with MORE/CORE and RUTH." DDOP stated further that, "Submission of data from MORE/CORE and from RUTH could extend the populations included in the indication and would provide 8-year follow-up, longer than that obtained in the NSABP P-1 trial. These data may influence the wording of the indication." At this same meeting, in further discussion about the RUTH protocol relative to the proposed indication, Lilly was advised to add invasive breast cancer risk reduction as a primary endpoint to the existent primary coronary endpoint and to split the trial significance level of 0.05 between the two primary endpoints. Subsequent to this discussion, RUTH was amended to examine the long-term effect of raloxifene on the incidences of two primary endpoints: (1) a combined coronary primary endpoint and (2) invasive breast cancer. To adjust for the multiplicity of these primary endpoints and to maintain the overall alpha at 0.05, the coronary primary endpoint was tested at a 0.0423 significance level and the breast cancer endpoint at a 0.0080 significance level. All breast cancer was and continued to be a secondary endpoint in RUTH.

On 25 May 2005, Lilly met with DDOP in a Pre-NDA meeting to discuss the organization and format of the NDA submission in support of the breast cancer risk reduction indication. Subsequent to this meeting, on 15 November 2005, representatives from Lilly and NSABP met with DDOP in a second Pre-NDA meeting to discuss the STAR data with respect to the organization and content of the NDA submission in support of the breast cancer risk reduction indication. STAR was designed and powered to detect a clinically relevant improvement in the invasive breast cancer risk reduction of one treatment over the other. The protocol stated that, in the event that superiority was not established by either therapy, choice of therapy should be based on benefit/risk considerations. To facilitate determination of this objective and, while still blinded to STAR results, Lilly proposed an analysis (Rothmann et al. 2003) (1) to further quantify the relative efficacy of raloxifene compared with tamoxifen and (2) to estimate the putative hazard ratio for raloxifene versus placebo, had such a group been enrolled in STAR, in the historical context of the tamoxifen effect as demonstrated in P-1, for women age 50 years or older. Lilly submitted this statistical plan to IND 57,137 in January 2006.

In November 2006, Lilly submitted the present NDA 22-042 to the FDA.

In March 2007, Lilly submitted the 4-Month Safety Update comprised of STAR data collected through 30 September 2006.

2. Overview of Clinical Studies

2.1. Phase 3 Controlled Clinical Studies of Efficacy and Safety

The efficacy of raloxifene for the reduction in incidence of invasive breast cancer in postmenopausal women has been demonstrated in three randomized clinical studies, consisting of two randomized placebo-controlled studies (conducted by Lilly) and one randomized active-comparator controlled study (conducted by the NSABP under the auspices of the National Cancer Institute [NCI]). These are:

- Multiple Outcomes of Raloxifene Evaluation (MORE)
- Raloxifene Use for the Heart (RUTH)
- Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer.

The Continuing Outcomes Relevant to Evista (CORE), a follow-up study of MORE participants, provides additional data in support of the long-term efficacy of raloxifene for the reduction in incidence of invasive breast cancer in postmenopausal women.

The key features of each study are summarized below and in Table APP.1 (Appendix 1).

2.1.1. Placebo-Controlled Studies in Postmenopausal Women

2.1.1.1. Studies of Postmenopausal Women with Osteoporosis

The effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis was evaluated in MORE and its follow-up study, CORE. The study designs of MORE and CORE are described below. The primary and secondary analyses for these studies used the intention-to-treat principle.

2.1.1.1.1. MORE

MORE was a double-blind, randomized, placebo-controlled multinational study that examined the use of raloxifene in postmenopausal women with osteoporosis. The study consisted of a 3-year treatment phase and a 1-year extension phase (Figure 1). The MORE data presented in this document are for the entire 4-year study period. The 7705 women enrolled in the study were randomized to treatment with placebo (N=2576), raloxifene HCl 60 mg/day (N=2557), or raloxifene HCl 120 mg/day (N=2572).

To be eligible for participation in MORE, a woman had to have been age 80 years or younger, at least 2 years postmenopausal, and diagnosed with osteoporosis, defined as lumbar spine or femoral BMD more than 2.5 standard deviations (SD) below the mean for normal premenopausal women or at least one moderate or two mild vertebral fractures. Women with a history of breast cancer were not eligible to enroll.

The primary objectives of MORE were to assess the effect of raloxifene treatment, compared with placebo, on the incidence of new vertebral fractures, lumbar spine and

femoral neck BMD, and safety. A secondary safety objective was to assess the effect of raloxifene on the incidence of breast cancer, regardless of invasiveness status.

Sections 3 and 4 provide MORE efficacy and safety data, respectively.

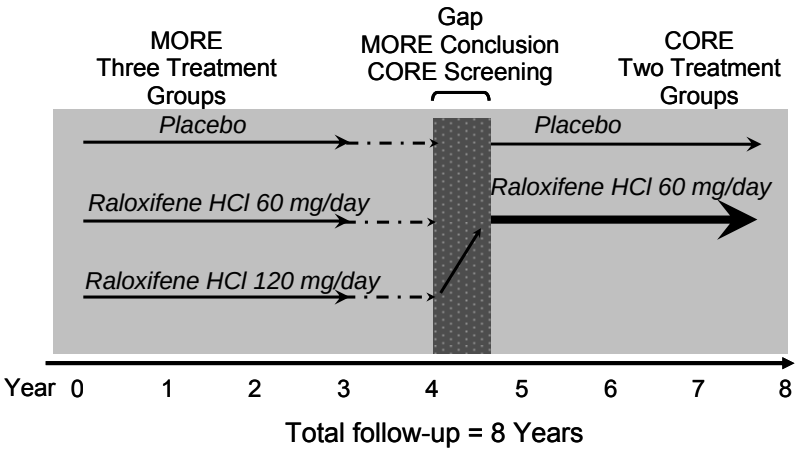


Figure 1. MORE and CORE study design.

2.1.1.1.2. CORE

CORE was a double-blind, placebo-controlled, multinational study designed to collect long-term breast cancer and nonvertebral fracture data from the MORE cohort. CORE enrolled women who had been randomized to treatment in MORE (Figure 1) and who chose to enroll in CORE.

As per the CORE protocol, CORE enrollees received the same therapy they had received in MORE. Specifically, patients randomized to raloxifene HCl 60 mg/day (N=1355) or 120 mg/day (N=1370) in MORE were assigned to receive raloxifene HCl 60 mg/day in CORE (N=2725); those randomized to placebo in MORE were assigned to receive placebo in CORE (N=1286). Consequently, approximately twice as many women in CORE were assigned to receive raloxifene HCl 60 mg/day compared with placebo. For all CORE patients, a treatment gap occurred between the end of their participation in MORE and the start of their participation in CORE (the median time off therapy was approximately 10.6 months). During this gap, patients did not receive study drug but could have taken marketed raloxifene, tamoxifen, other SERMS, or a hormone.

CORE was a follow-up study of MORE participants but with different primary and secondary objectives. 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. A secondary objective was to assess the long-term effect of raloxifene on the incidence of invasive, ER-positive breast cancer.

Sections 3 and 4 provide CORE efficacy and safety data, respectively.

2.1.1.1.3. 8-Year Analysis of MORE and CORE

As noted above, MORE had two raloxifene HCl treatment groups (60 mg/day and 120 mg/day). Women who were assigned to the raloxifene HCl 60 mg/day dose (N=1355) or placebo (N=1286) in both MORE and its follow-up, CORE, allowed for continuous follow-up at the 60 mg/day dose (except during the previously described treatment gap between the end of MORE and the start of CORE), compared with placebo, for up to 8 years. Post hoc analysis of breast cancer event data for these women, from the time of their randomization in MORE to the end of their participation in CORE, provides long term efficacy information at the 60 mg/day dose, the dose for which the proposed indication is being sought.

2.1.1.2. Study of Postmenopausal Women at Risk for Major Coronary Events

2.1.1.2.1. RUTH

RUTH was a double-blind, randomized, placebo-controlled, multinational study examining the long-term effect of raloxifene HCl 60 mg/day versus placebo (Figure 2) on the incidences of two primary endpoints: (1) a combined coronary primary endpoint (defined as coronary death, nonfatal [including silent] myocardial infarction [MI], or hospitalized acute coronary syndrome [ACS] other than MI) and (2) invasive breast cancer in postmenopausal women at risk for major coronary events. To adjust for the multiplicity of these primary endpoints, the coronary primary endpoint was tested at 0.0423 significance level and the breast cancer endpoint at 0.0080 significance level. All breast cancer was and continued to be a secondary endpoint in RUTH.

To be eligible for participation in RUTH, women had to have been age 55 years or older, at least 1 year postmenopausal, and have established CHD or multiple CHD risk factors. Participants had to have a CV risk score ≥4 according to a point system that took into account established CHD (4 points), lower extremity arterial disease (4 points), age 70 years or older (2 points), cigarette smoking (1 point), hypertension (1 point), or hyperlipidemia (1 point). Women with a suspected breast carcinoma or with a known history of breast carcinoma were not eligible to enroll. The 10,101 women enrolled in the study were randomized to treatment with placebo (N=5057) or raloxifene HCl 60 mg/day (N=5044). The active treatment phase ended after the last randomized patient had been followed for at least 5 years.

Sections 3 and 4 provide RUTH efficacy and safety data, respectively.

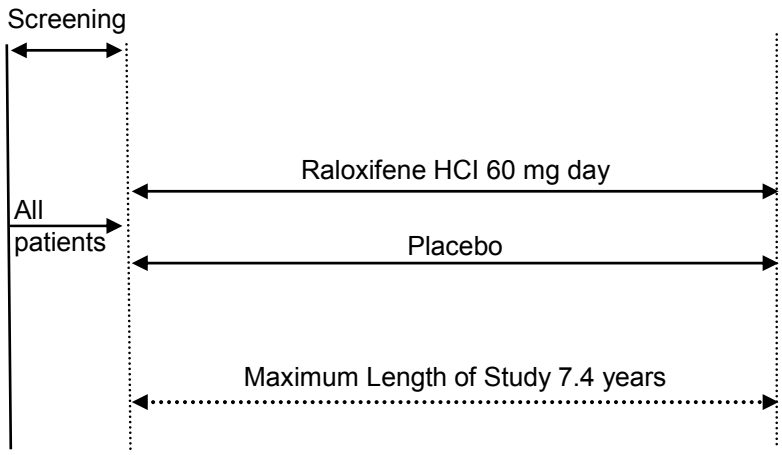


Figure 2. RUTH study design.

2.1.2. Active-Comparator Controlled Study in Postmenopausal Women at Increased Risk of Invasive Breast Cancer

The NSABP implemented the STAR study to directly compare raloxifene and tamoxifen in a population of postmenopausal women at increased risk for invasive breast cancer. The foundation for the STAR study was the earlier NSABP P-1 study (Fisher et al. 1998), described briefly here for context.

P-1 evaluated whether 5 years of tamoxifen 20 mg/day versus placebo reduced the incidence of invasive breast cancer in women at increased risk for the disease. P-1 also assessed the effect of tamoxifen on ischemic heart disease and fractures. P-1 enrolled 13,388 pre- and postmenopausal women, who were at least 35 years old and who had a Gail model-based (Costantino et al. 1999) 5-year predicted risk of breast cancer of at least 1.66% or a history of lobular carcinoma in situ (LCIS). The majority (57.6%) of women enrolled in P-1 had a 5-year predicted risk between 2.01% and 5.00%.

P-1 demonstrated that tamoxifen, compared with placebo, reduced the risk of invasive breast cancer by 49% (risk ratio [RR] 0.51, 95% confidence interval [CI] 0.39-0.66) and the risk of noninvasive breast cancer by approximately 50% (RR 0.50, 95% CI 0.33-0.77) (Fisher et al. 1998). Regarding the endpoints of ischemic heart disease and bone fractures, P-1 showed that tamoxifen, compared with placebo, did not have an effect on the incidence of ischemic heart disease and that it was associated with fewer fractures of the hip, spine, and wrist though not statistically significantly so. With regard to safety, tamoxifen was associated with the adverse events (AEs) of uterine cancer, stroke, VTE, and cataracts.

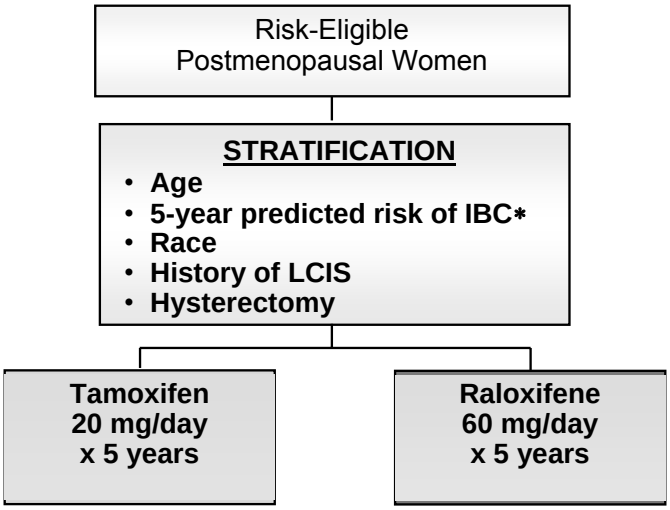
P-1 enrolled both pre- and postmenopausal women whereas STAR enrolled only postmenopausal women. Because menopausal status was not recorded in P-1, those women age 50 years or older (WHO 1996) in P-1 are considered representative of a postmenopausal population and, consequently, used as the reference group for the postmenopausal population of STAR. In this population of P-1 patients, tamoxifen

versus placebo decreased the incidences of invasive and noninvasive breast cancer by 53% (RR 0.47, 95% CI 0.33-0.66) and 23% (RR 0.77, 95% CI 0.44-1.35), respectively.

Subsequent to P-1, the NSABP designed the randomized, double-blind, active-controlled STAR study to evaluate the effect of raloxifene versus tamoxifen in reducing the incidence of invasive breast cancer in postmenopausal women at increased risk of invasive breast cancer. The study, like P-1, was conducted in North America.

To be eligible for participation in STAR, a woman had to be at least 35 years of age, postmenopausal, and have either a Gail model-based (Costantino et al. 1999) 5-year predicted risk of invasive breast cancer of at least 1.66% or a history of LCIS treated by local excision alone. The study excluded patients with a history of invasive breast cancer, ductal carcinoma in situ (DCIS), deep vein thrombosis (DVT), pulmonary embolus (PE), stroke, transient ischemic attack (TIA), current use of coumadin, uncontrolled diabetes or hypertension, or atrial fibrillation.

STAR randomized 19,747 postmenopausal women to receive either tamoxifen 20 mg/day (N=9872) or raloxifene HCl 60 mg/day (N=9875) for a maximum of 5 years of treatment. Randomization was stratified by age, 5-year predicted invasive breast cancer risk based on the Gail model, race, history of LCIS, and hysterectomy status (Figure 3). Analyses were performed using all randomized patients who had at least one postbaseline visit (primary analysis dataset [N=19,487]). Per protocol, the final intention-to-treat analysis was performed once a prespecified number of breast cancers (at least 327) were observed. As of 31 December 2005, approximately 25% of the study population had completed 5 years of treatment. For the remainder of the patients, the planned 5-year treatment period is ongoing.



Abbreviations: IBC = invasive breast cancer; LCIS = lobular carcinoma in situ.

* Based on Gail model.

Figure 3. STAR study design.

The primary objective of STAR was to determine if:

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

The secondary objectives of STAR were to evaluate the effect of raloxifene therapy and tamoxifen therapy on the incidences of:

1) DCIS or LCIS;
2) endometrial cancer;
3) ischemic heart disease;
4) fractures of the hip, spine, or Colles' fractures of the wrist; and
5) patients' quality of life (Land et al. 2006).

The protocol also called for the evaluation of the toxicity and side effects of each therapy.

Sections 3 and 4 provide STAR efficacy and safety data, respectively.

STAR analyses presented in this document are based on follow-up data reported as occurring on or before 31 December 2005. To date, Lilly has provided DDOP with STAR data in the format of a publication (Vogel et al. 2006) submitted with NDA 22-042, a clinical study report (CSR) submitted on 13 March 2007, and a 4-month Safety Update submitted on 14 March 2007. Two data locks were used to prepare these documents.

Although the manuscript and the CSR analyses both incorporated patient follow-up occurring on or before 31 December 2005, the publication is based upon a data lock on 31 December 2005 for which only the summary datasets used for the manuscript were preserved by the NSABP. As the DDOP requires a complete set of all raw data files not just summary data files, a new data lock for which all raw data files were preserved was implemented on 30 September 2006. The Lilly-authored CSR used the 30 September 2006 dataset, but censored follow-up at 31 December 2005 in order to provide an analysis that would be as comparable as possible to the timing of follow-up used for the manuscript. Consequently, minor numerical differences in reported data exist between the two documents. These differences do not affect the overall interpretation of the data. The 4-month Safety Update incorporated all data collected as of 30 September 2006. To prevent confusion and to enable comparison, Lilly has included Table APP.7 (Appendix 1.2), which provides the key efficacy and safety data from the manuscript, the CSR, and the Safety Update.

3. Efficacy of Raloxifene in Reduction of Risk of Invasive Breast Cancer

3.1. Individual Studies Supporting Efficacy

Despite differences in study population, three randomized clinical studies of raloxifene (two placebo-controlled studies [MORE and RUTH] and one active-comparator controlled study [STAR]) have consistently shown the efficacy of raloxifene for reduction in the incidence of invasive breast cancer in postmenopausal women. CORE, the follow-up study of MORE participants, further supports the long-term efficacy of raloxifene in reducing the incidence of invasive breast cancer in postmenopausal women. Section 2 provided an overview of these studies. Table APP.1 (Appendix 1) summarizes their key features.

In all of these studies, a local pathology report or equivalent document verified the diagnosis of invasive breast cancer. For the placebo-controlled studies, a committee of non-Lilly breast cancer specialists blinded to patients' treatment reviewed and adjudicated all investigator-reported cases of invasive breast cancer. For the active-comparator controlled STAR study, an NSABP physician blinded to patients' treatment reviewed and confirmed all investigator-reported cases of invasive breast cancer.

All analyses were based on adjudicated breast cancer cases and followed intention-to-treat principles.

Because the three randomized clinical studies differed in terms of study design and evaluated three distinct study populations, the study data were not pooled for the analyses of breast cancer endpoints. Together, the randomized studies enrolled more than 37,000 postmenopausal women, each enrolled more than 7000 postmenopausal women, and each provided a follow-up duration of 4 or more years.

Efficacy data and conclusions are presented by study population and study as follows:

- Postmenopausal women with osteoporosis (MORE and CORE).
- Postmenopausal women at risk for major coronary events (RUTH).
- Postmenopausal women at increased risk for invasive breast cancer (STAR).

3.2. Efficacy of Raloxifene in Postmenopausal Women with Osteoporosis (MORE and CORE)

Note that efficacy results provided in this section for the MORE, CORE, and the combined MORE/CORE analyses are for the raloxifene HCl 60 mg/day dose versus placebo, because raloxifene HCl 60 mg/day is the approved dose for the prevention and treatment of osteoporosis. Moreover, incidence rates for all breast cancer and for invasive breast cancer were not significantly different (p=0.810 and p=0.622,

respectively) between the raloxifene HCl 60 mg/day and 120 mg/day doses in MORE. Further, CORE studied only the raloxifene HCl 60 mg/day dose as MORE had demonstrated no significant benefit for raloxifene HCl 120 mg/day over 60 mg/day.

3.2.1. The MORE Study

The MORE study randomized a total of 7705 postmenopausal women with osteoporosis (median age, 66.9 years) to treatment with placebo (N=2576), raloxifene HCl 60 mg/day (N=2557), or raloxifene HCl 120 mg/day (N=2572). MORE treatment groups were balanced with respect to baseline demographic characteristics. In MORE, 96.4% of patients were treatment compliant (defined as ≥70% of study drug taken). Median follow-up was 47.4 months.

Compared with placebo, raloxifene showed a statistically significant 62% decrease (hazard ratio [HR] 0.38, 95% CI 0.22-0.67) in the incidence of all breast cancer.

Compared with placebo, raloxifene showed a statistically significant 71% decrease in the incidence of invasive breast cancers (Figure 4 and Table 1) and a statistically significant 80% decrease in the incidence of ER-positive breast cancer (Table 1). No significant difference in the incidence of ER-negative breast cancer was observed between treatment groups (Table 1).

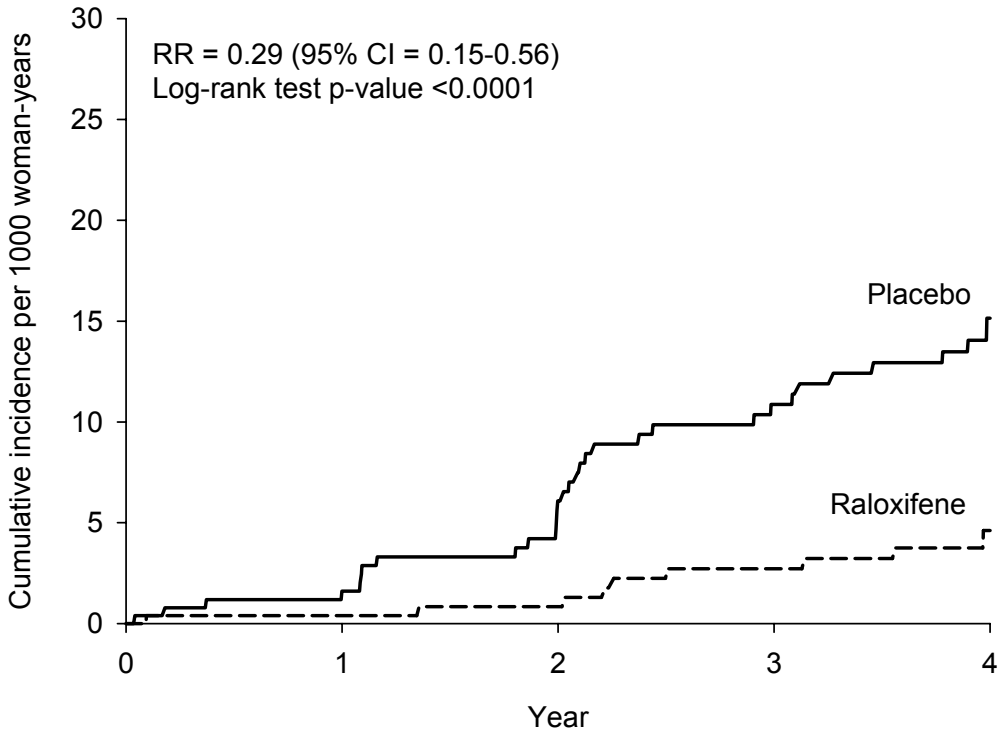


Figure 4. **Effect of raloxifene on invasive breast cancer incidence in MORE.**

Table 1. Invasive Breast Cancer Results for MORE

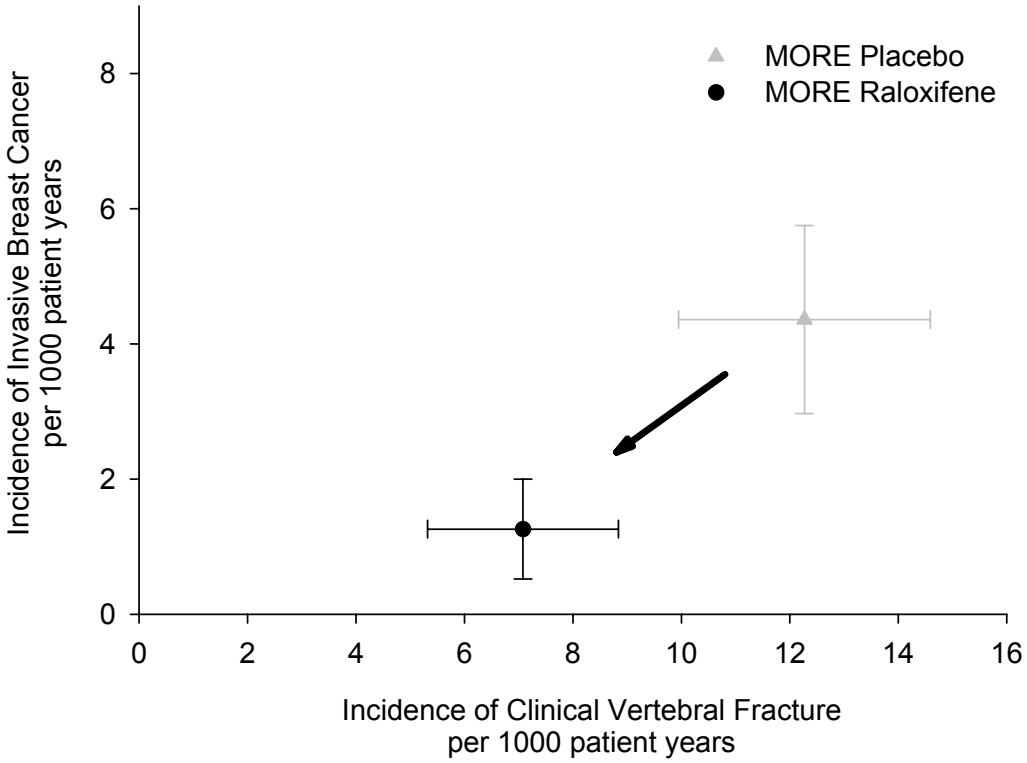
	MORE (N=5133)[a]					
Breast Cancer	**Placebo N=2576**		**Raloxifene N=2557**			
Category	**n**	**IR**	**n**	**IR**	**HR (95% CI)**	**p-value**
Invasive	38	4.36	11	1.26	0.29 (0.15, 0.56)	<0.001
ER- positive	29	3.33	6	0.69	0.20 (0.08, 0.49)	<0.001
ER- negative	4	0.46	5	0.57	1.23 (0.33, 4.60)	0.752
ER unknown	5	0.57	0	0	N/A	N/A

Abbreviations: CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; IR = incidence rate per 1000 patient-years; n = number of patients with breast cancer events; N = number of patients analyzed; N/A= Not Applicable;

[a] Patients randomized in MORE to either placebo or raloxifene HCl 60 mg/day. Breast cancers reported from randomization in MORE to end of MORE (48 months) are presented.

Of 61 total breast cancers reported in MORE, 8 (13%) were classified as noninvasive. Of these 8 cases (all of which were DCIS), 5 and 3 occurred within the placebo and raloxifene groups, respectively. Invasiveness status could not be ascertained for 4 of the 61 adjudicated breast cancers (placebo, 1; raloxifene, 3).

Figure 5 shows the significant effect of raloxifene in reducing both the incidence of invasive breast cancer and clinical vertebral fractures in the MORE population of postmenopausal women with osteoporosis.



Note: Error bars on the point estimates of the rates are 95% confidence intervals. The arrow indicates the effect of treatment. Results shown are for the raloxifene HCl 60 mg/day dose.

Figure 5. **Incidence rates of invasive breast cancer and clinical vertebral fracture per 1000 patient-years in MORE.**

3.2.2. The CORE Study

Postmenopausal women with osteoporosis (median age, 71.0 years), who had been randomized in MORE, participated in CORE. Per the CORE protocol, enrollees had to remain on the same therapy they had received in MORE. Accordingly, of the 4011 CORE enrollees, approximately twice as many were assigned to treatment with raloxifene HCl 60 mg/day (N=2725) as placebo (N=1286).

Of the 4011 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 protocol-specified criteria (diagnosis of an estrogen-dependent malignancy, had a history of venous thromboembolic event (VTE), or had a safety concern during MORE that necessitated unblinding of their treatment assignment) or because they chose not to. All were included in the dataset for the analysis of breast cancer endpoints. In CORE, 55% of patients were treatment compliant (defined as ≥80% of study drug taken).

The incidence of invasive breast cancer was determined from baseline (Visit 1) in CORE to the end of CORE. Of the 4011 women who enrolled in CORE, 21 (12 in the placebo

group and 9 in the raloxifene group) developed breast cancer during their participation in MORE prior to Visit 1 of CORE. These 21 cases were included in the MORE breast cancer analysis and, accordingly, excluded from the dataset for the analysis of breast cancer endpoints in CORE.

The CORE treatment groups were balanced with regard to breast cancer risk assessment characteristics. The mean baseline Gail model-based 5-year predicted risk of invasive breast cancer was 1.94% in both treatment groups. Approximately 54% of patients in each treatment group had a 5-year predicted invasive breast cancer risk of greater than or equal to 1.66%.

Compared with placebo, raloxifene showed a statistically significant 56% decrease in the incidence of invasive breast cancer (Table 2) and a statistically significant 63% decrease in the incidence of ER-positive invasive breast cancer (Table 2).

No significant difference in the incidence of ER-negative invasive breast cancer (Table 2) was observed between treatment groups.

Table 2. Invasive Breast Cancer Results for CORE

	CORE (N=3990)[a]					
Breast Cancer	**Placebo N=1274**		**Raloxifene N=2716**		**HR**	
Category	**n**	**IR**	**n**	**IR**	**(95% CI)**	**p-value**
Invasive	20	5.41	19	2.43	0.44 (0.24, 0.83)	0.009
ER-positive	15	4.05	12	1.54	0.37 (0.17, 0.79)	0.007
ER-negative	3	0.81	6	0.77	0.95 (0.24, 3.79)	0.941
ER unknown	2	0.54	1	0.13	N/A	N/A

Abbreviations: CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; IR = incidence rate per 1000 patient-years; n = number of patients with breast cancer events; N = number of patients analyzed; N/A= Not Applicable;

[a] A total of 4011 patients enrolled in CORE. This analysis includes only those patients enrolled in CORE who had not been diagnosed with breast cancer prior to enrollment (N=3990). The raloxifene group includes 1352 patients who were originally assigned to raloxifene HCl 60 mg/day in MORE and 1364 patients who were originally assigned to raloxifene HCl 120 mg/day in MORE. Breast cancers reported from CORE baseline (Visit 1) to the end of CORE are presented.

Of 46 total breast cancers reported during the 4-year treatment period of CORE, 7 (15%) were classified as noninvasive. Of these 7 cases (all of which were DCIS), 2 occurred among 1274 placebo-assigned patients and 5 occurred among 2716 raloxifene-assigned patients.

3.2.3. Combined MORE and CORE Data Analyses

Only those patients who had been randomized to raloxifene HCl 60 mg/day or to placebo in MORE, and who then continued in CORE, were included in the 8-year combined MORE/CORE analysis (raloxifene, N=1355; placebo, N=1286).

In the combined MORE/CORE analysis, raloxifene, compared with placebo, showed a statistically significant 60% decrease (HR 0.40; 95% CI 0.21-0.77) in the incidence of invasive breast cancer (raloxifene: n=13 cases, incidence rate [IR]=1.24 per 1000 patient-years; placebo: n=32 cases, IR=3.19 per 1000 patient-years).

Raloxifene versus placebo showed a statistically significant 65% decrease (HR 0.35, 95% CI 0.17-0.76) in the incidence of ER-positive invasive breast cancer (raloxifene: n=9 cases, IR=0.86 per 1000 patient-years; placebo: n=25 cases, IR=2.49 per 1000 patient-years).

No significant difference was observed in the incidences of invasive ER-negative breast cancer (n=3 cases per treatment group; HR 1.03, 95% CI 0.21-5.12) or noninvasive breast cancer (n=4 cases [raloxifene], n=2 cases [placebo]; HR 2.05, 95% CI 0.37-11.25) between treatment groups.

3.2.4. MORE and CORE Efficacy Conclusions

Efficacy results for the MORE, CORE, and the combined MORE/CORE analyses are only those for the raloxifene HCl 60 mg/day dose group versus the placebo group, as randomized in MORE.

In MORE, over 4 years of observation, raloxifene HCl 60 mg/day versus placebo showed a statistically significant 71% decrease in the incidence of invasive breast cancer in postmenopausal women with osteoporosis.

In CORE, raloxifene HCl 60 mg/day versus placebo demonstrated a statistically significant 56% decrease in the incidence of invasive breast cancer in a subset of patients from MORE, who were followed for up to an additional 4 years beyond their completion of MORE.

Overall, when the results from CORE are considered together with the results from MORE, CORE provides support that the treatment effect of raloxifene on invasive breast cancer persists beyond 4 years. Further support for a persistent treatment effect is provided by the combined MORE/CORE analysis, in which patients who had received only the raloxifene HCl 60 mg/day dose for up to 8 years throughout both studies, had a statistically significant 60% decrease in the incidence of invasive breast cancer, compared with placebo.

3.3. Efficacy of Raloxifene in Postmenopausal Women at Risk for Major Coronary Events (RUTH study)

In RUTH, 10,101 women at risk for major coronary events (median age 67.6 years) were randomly assigned to treatment with placebo (N=5057) or raloxifene HCl 60 mg/day (N=5044). The median duration of follow-up for both treatment groups was 5.6 years. Approximately 84% of all randomized patients (n=8523) were followed for at least 5 years and 45% (n=4517) were followed for at least 6 years. The median study drug

exposure was 5.1 years for both treatment groups. In RUTH, 70.7% of patients were treatment compliant (defined as ≥70% of study drug taken).

The RUTH placebo and raloxifene groups had similar baseline characteristics. The mean baseline Gail model-based 5-year predicted risk of invasive breast cancer was 1.73% for both treatment groups. Approximately 41% of patients in both treatment groups had 5-year predicted risks greater than or equal to 1.66%.

Raloxifene showed a statistically significant 44% decrease in the incidence of invasive breast cancer compared with placebo (Table 3). Raloxifene significantly decreased ER-positive invasive breast cancer compared with placebo but showed no significant difference versus placebo on the incidences of ER-negative invasive breast cancer or ER-unknown invasive breast cancer (Table 3).

Table 3. Invasive Breast Cancer Results for RUTH

	RUTH (N=10,101)					
Breast Cancer Category	**Placebo N=5057**		**Raloxifene N=5044**		**HR (95% CI)**	**p-value**
	n	**IR**	**n**	**IR**		
Invasive	70	2.66	40	1.50	0.56 (0.38, 0.83)	0.003
ER-positive	55	2.09	25	0.94	0.45 (0.28, 0.72)	<0.001
ER-negative	9	0.34	13	0.49	1.44 (0.61, 3.36)	0.400
ER unknown	6	0.23	2	0.07	0.33 (0.07, 1.63)	0.151

Abbreviations: CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; IR = incidence rate per 1000 patient-years; N = number of patients analyzed; n = number of patients with breast cancer events.

Note: Breast cancer analyses were based on the 128 patients who had at least one adjudicated breast cancer. Invasiveness status could not be ascertained for 2 of the 128 adjudicated breast cancers (placebo, 1; raloxifene, 1).

Raloxifene demonstrated similar effects (all interaction p-values >0.34) on the incidence of invasive breast cancer regardless of age (≤65 or >65 years old), 5-year predicted risk of invasive breast cancer (<1.66% or ≥1.66%), and family history of breast cancer.

Figure 6 shows the cumulative incidence per 1000 patient-years of invasive breast cancer through more than 6 years of treatment in RUTH.

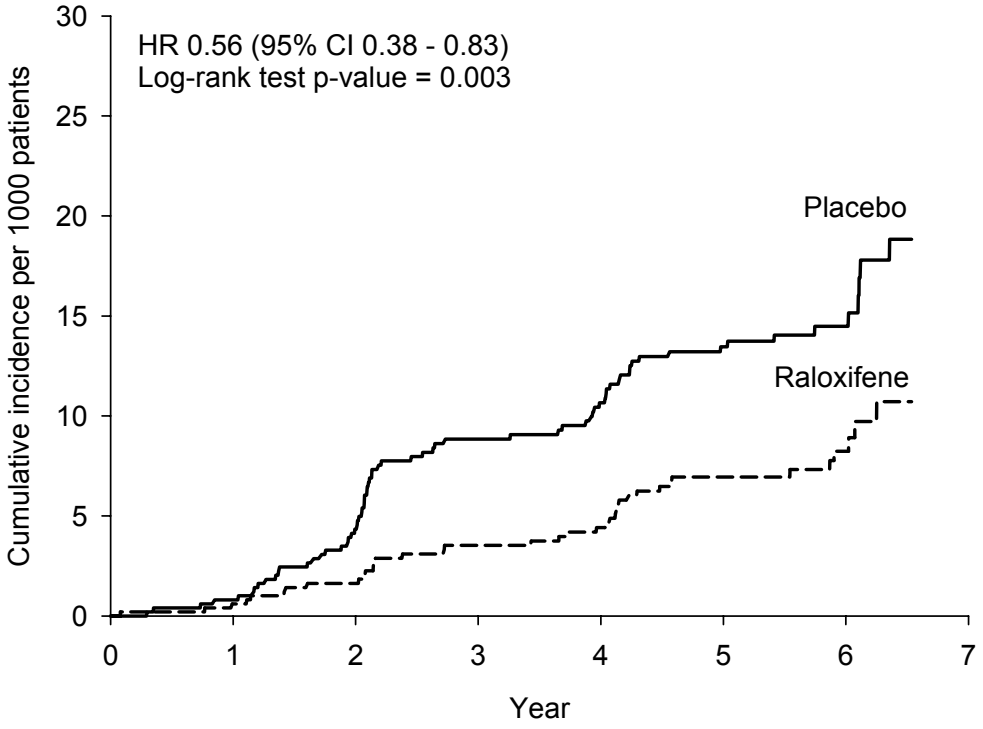
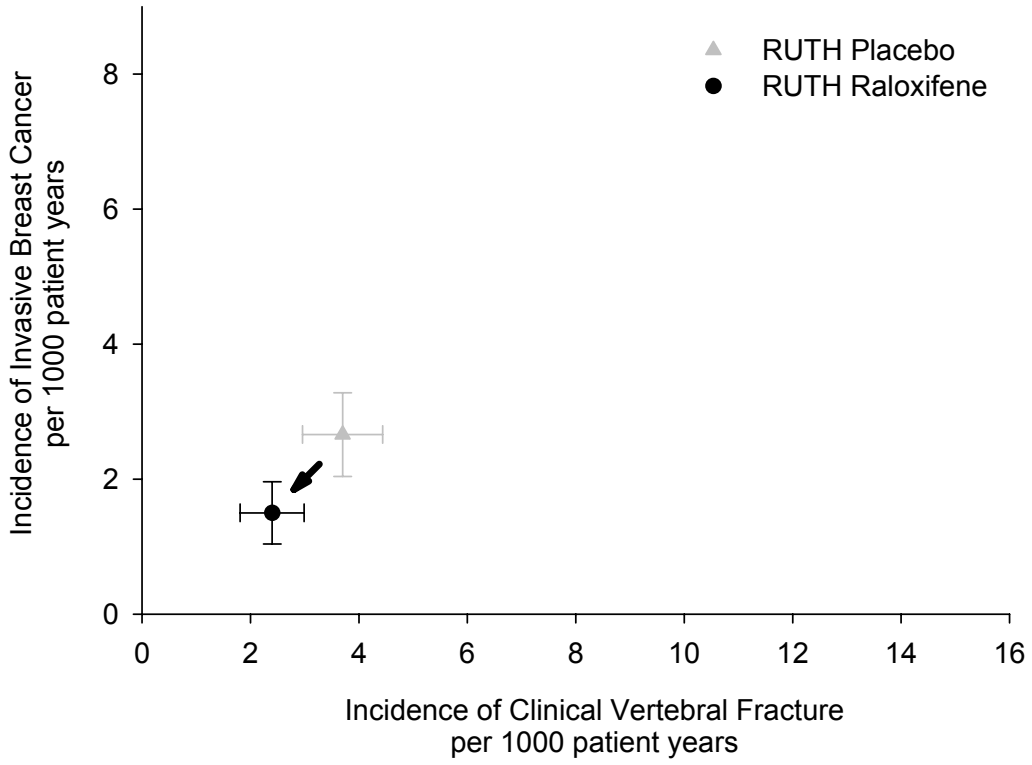


Figure 6. **Effect of raloxifene on invasive breast cancer incidence in RUTH.**

Of 128 total breast cancers reported during RUTH, 16 (12.5%) were classified as noninvasive. Of these 16 cases (all of which were DCIS), 5 and 11 occurred within the placebo and raloxifene groups, respectively.

Figure 7 shows the effect of raloxifene in reducing both the incidence of invasive breast cancer and clinical vertebral fractures in the RUTH population of postmenopausal women at risk for major coronary events. Although the treatment effect on both endpoints is of a lesser magnitude than that observed in MORE (Figure 5), it is nonetheless substantial and clinically relevant for a population at lower risk for both invasive breast cancer and clinical vertebral fractures than the MORE population.



Note: Error bars on the point estimates of the rates are 95% confidence intervals. The arrow indicates the effect of treatment.

Figure 7. **Incidence rates of invasive breast cancer and clinical vertebral fracture per 1000 patient-years in RUTH.**

3.3.1. RUTH Efficacy Conclusions

Raloxifene versus placebo demonstrated a statistically significant 44% decrease in the incidence of invasive breast cancer in postmenopausal women at risk for major coronary events (HR 0.56, 95% CI 0.38-0.83).

3.4. Efficacy of Raloxifene in Postmenopausal Women at Increased Risk of Invasive Breast Cancer (the STAR Study)

The STAR study enrolled postmenopausal women at increased risk of developing invasive breast cancer, defined as a Gail model-based (Costantino et al. 1999) predicted 5-year breast cancer risk greater than or equal to 1.66% or a history of LCIS treated by local excision alone.

3.4.1. STAR Efficacy Analyses

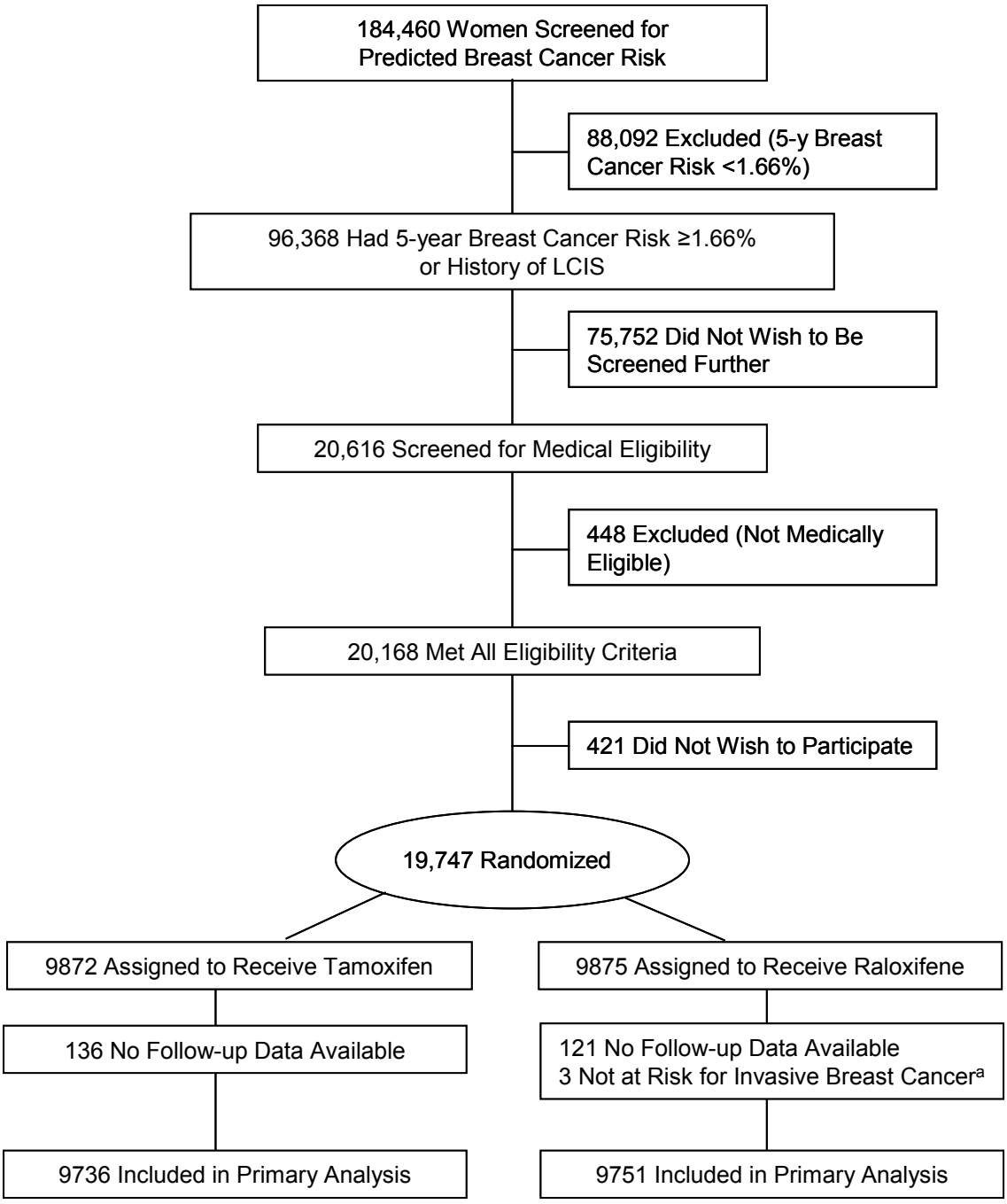
The primary endpoint was invasive breast cancer. Noninvasive breast cancer was a secondary endpoint. Analyses were performed using time-to-first event including all

randomized patients who had at least one postbaseline visit. Analyses are based on follow-up data reported as occurring on or before 31 December 2005 (Section 2.1.2).

3.4.2. STAR Patient Disposition

STAR randomized 19,747 women to treatment: 9872 to tamoxifen 20 mg/day and 9875 to raloxifene HCl 60 mg/day. The primary analysis dataset population comprised 19,487 women who had at least one postbaseline visit, of whom 9736 were assigned to treatment with tamoxifen and 9751 were assigned to treatment with raloxifene (Figure 8).

The median duration of study follow-up was 4.32 (mean 4.06) years for all patients in the primary analysis dataset (Table APP.4 [Appendix 1.2]) and the mean duration of treatment was 3.1 and 3.2 years for the tamoxifen and raloxifene groups, respectively (Table APP.5 [Appendix 1.2]).



[a] 3 patients with follow-up data were excluded from analysis; 2 because of a history of bilateral mastectomy and 1 because of a prior history of invasive breast cancer.

Figure 8. Patient disposition in STAR.

3.4.3. STAR Patient Demographics

Differences in patient demographics and baseline characteristics between treatment groups in STAR were small and not deemed to be clinically relevant (Table 4). The mean age was 58.5 years with a mean predicted 5-year breast cancer risk of 4.03% (SD

2.17%). Both treatment groups had comparable percentages of patients with a history of LCIS and a history of breast atypical hyperplasia (Table 4).

Table 4. Patient Baseline Characteristics in STAR

Patient Characteristic	Tamoxifen (N=9736)		Raloxifene (N=9751)	
	n	%	n	%
Age (years)				
≤49	884	9.1	878	9.0
50-59	4856	49.9	4852	49.8
60-69	3136	32.2	3174	32.6
≥70	860	8.8	847	8.7
Race/ethnicity				
Caucasian	9105	93.5	9112	93.4
African American	233	2.4	243	2.5
Hispanic	192	2.0	193	2.0
Other	206	2.1	203	2.1
No. of first-degree relatives with breast cancer				
0	2838	29.1	2791	28.6
1	5046	51.8	5132	52.6
2	1532	15.7	1561	16.0
≥3	320	3.3	267	2.7
History of hysterectomy				
No	4739	48.7	4715	48.4
Yes	4997	51.3	5036	51.6
History of lobular carcinoma in situ				
No	8845	90.8	8859	90.9
Yes	891	9.2	892	9.1
History of breast atypical hyperplasia				
No	7546	77.5	7512	77.0
Yes	2190	22.5	2239	23.0
5-year predicted breast cancer risk (%)				
≤2.00	1055	10.8	1101	11.3
2.01-3.00	2993	30.7	2892	29.7
3.01-5.00	3042	31.2	3085	31.6
≥5.01	2646	27.2	2673	27.4
History of bilateral oophorectomy				
Yes	2923	30.0	2964	30.4
No	6813	70.0	6787	69.6
History of cataracts				
Yes	1394	14.3	1418	14.5
No	8342	85.7	8333	85.5

Abbreviation: N = patients comprising the primary analysis dataset; n = number of patients; No. = number.

3.4.4. STAR Treatment Adherence

Overall treatment adherence was 74.4%. The greater adherence to treatment in the raloxifene group (76.3%) than the tamoxifen group (72.7%) had no significant impact on the interpretation of study data. Among those categorized as adherent to therapy, significantly ($p<0.001$) more patients in the raloxifene than the tamoxifen group continued study therapy throughout the period of follow-up. Among those categorized as nonadherent to treatment, significantly more patients in the tamoxifen than the raloxifene group stopped therapy for reasons other than those specified in the protocol.

3.4.5. STAR Efficacy Results

3.4.5.1. Invasive Breast Cancer (Primary Endpoint)

Table 5 summarizes the invasive breast cancer results for the tamoxifen and raloxifene groups in STAR. There were 168 and 173 cases of invasive breast cancer reported within the tamoxifen and raloxifene treatment groups, respectively. The corresponding incidence rates of invasive breast cancer were not significantly different for tamoxifen (4.30 per 1000 patient-years) and raloxifene (4.40 per 1000 patient-years). No statistically significant difference in incidence of invasive breast cancer was observed between the treatment groups (primary analysis stratified log-rank p-value=0.99).

Table 5. Invasive Breast Cancer Results STAR Primary Analysis Dataset

Category	Number of Events		Incidence Rate per 1000 Patient-Years			RR (95% CI)
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference[a]	
Invasive	168	173	4.30	4.40	-0.10	1.02 (0.82, 1.27)

Abbreviations: CI = confidence interval; RR = risk ratio for patients in the raloxifene group compared to patients in the tamoxifen group.

Note: Primary analysis dataset included 9736 tamoxifen-assigned patients and 9751 raloxifene-assigned patients.

[a] Rate in the tamoxifen group minus the rate in the raloxifene group.

Two methods, a Gail model-based calculation of the expected invasive breast cancer incidence rate for an untreated group and Rothmann's method (refer to Section 3.4.5.2 and Appendix 1.1), were used to assess the estimated effect of raloxifene relative to a putative placebo. Based on a mean predicted 5-year breast cancer risk of 4.03% for the STAR population, the expected incidence rate for an untreated group, had one been included in the study, was estimated to be 8.2 per 1000 patient-years (Appendix 1.1 provides detailed description of calculation). Tamoxifen and raloxifene reduced the estimated incidence rate by nearly half (tamoxifen; IR 4.30 per 1000 patient-years and raloxifene; IR 4.40 per 1000 patient-years).

Figure 9 shows the cumulative incidence curve for invasive breast cancer over 6 years of study follow-up. The overall cumulative incidence of invasive breast cancer through

72 months was 25.1 and 24.4 per 1000 patients for the tamoxifen and raloxifene groups, respectively.

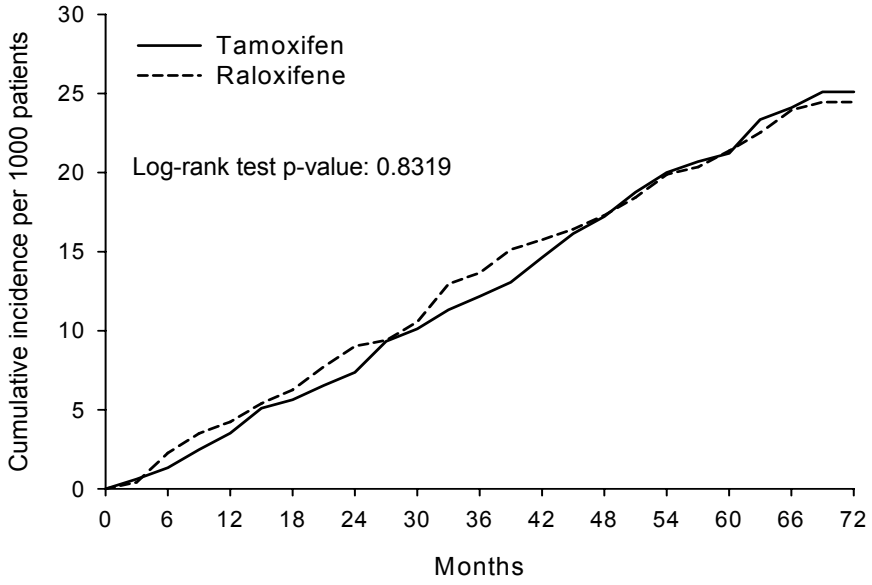


Figure 9. Cumulative incidence of invasive breast cancer in STAR.

3.4.5.2. Analysis Quantifying Relative Effect of Raloxifene and Tamoxifen on the Incidence of Invasive Breast Cancer

A key assumption in the design of STAR was that both raloxifene and tamoxifen are efficacious in decreasing the risk of invasive breast cancer in postmenopausal women at increased risk for breast cancer. If superiority of either treatment was not demonstrated, the protocol specified that "the choice of therapy should be based on benefit/risk considerations." Thus, Lilly believed that further quantification of the relative efficacy of raloxifene compared with tamoxifen was warranted. Since STAR was not designed or powered as a noninferiority study, Lilly performed a prospectively defined analysis using Rothmann's method (Rothmann et al. 2003) to evaluate the proportion of tamoxifen effect retained by raloxifene and the corresponding 95% CI. Since STAR did not include a placebo arm, raloxifene and placebo could not be compared directly. Rothmann's approach allowed for the indirect comparison of the relative risk of raloxifene with a putative placebo, had a placebo group been included in the study. Appendix 1.1 provides the details of this analysis.

One key component of Rothmann's method is the appropriate use of historical data characterizing the comparator's effect. Historical data should be obtained from well-designed clinical studies showing a consistent ability to demonstrate superiority of the active control to placebo. These clinical studies should be similar to the present study with respect to important design characteristics (eg, patient selection, study endpoints, duration, dose of active control, concomitant therapy). Four tamoxifen breast cancer prevention trials have evaluated the effect of tamoxifen on the risk reduction of breast

cancer for women. Table APP.3 (Appendix 1.1) summarizes the study design information for these four trials.

Of these four studies, Lilly chose, for the analysis, to use the P-1 study results for women age 50 years or older (Section 2.1.2) as the historical effect of tamoxifen compared with placebo on invasive breast cancer. Lilly concluded that this population was the most relevant to the STAR population for the following reasons: 1) P-1 was a well-designed, randomized, clinical study with a large sample size; 2) both studies enrolled only North American populations and, therefore, had the same procedures for breast cancer assessment (eg, frequency and quality of breast exams and mammographic screening); 3) neither study allowed the use of estrogen replacement therapy; and 4) enrollment in both studies was based primarily on the 5-year predicted risk of invasive breast cancer. In contrast, the other three studies differed with regard to patient profiles, study durations, endpoint assessments, and the use of estrogen replacement therapies during the study periods (Table APP.3 [Appendix 1.1]).

The analysis indicated that raloxifene maintained at least 65% of the effect of tamoxifen on invasive breast cancer (point estimate of the proportion of effect maintained is 97%, 95% CI 65%-128%). Had a placebo group been included in STAR, raloxifene would have demonstrated a 52% reduction in risk of invasive breast cancer compared with the putative placebo (HR=0.48, 95% CI 0.32-0.72).

3.4.5.3. Tumor Characteristics of Invasive Breast Cancer Events

Submitted pathology reports served as the source documents for characterizing tumor histology, ER status, size, nodal status, and stage; the NSABP did not centrally review pathology slides.

Based on histology, ER status, size, nodal status, and stage of invasive breast cancer, no statistically significant differences in tumor characteristics were observed between tamoxifen and raloxifene treatment groups (Table APP.2 [Appendix 1.1]). Approximately 76% of invasive breast cancers were infiltrating ductal, 68% were ER-positive, 74% were node-negative, 66% were Stage I, and 89% were ≤3.0 cm in size.

3.4.5.4. Analyses of Invasive Breast Cancer by Patient Baseline Characteristics

The study compared the effects of tamoxifen and raloxifene by the patient baseline characteristics of age, history of LCIS, history of atypical hyperplasia, Gail model-based (Costantino et al. 1999) 5-year predicted risk of breast cancer, and number of relatives with a history of breast cancer.

Raloxifene and tamoxifen demonstrated comparable efficacy among women with different baseline characteristics (Table 6). Women who enrolled in the study with a history of LCIS had the highest incidence rates of invasive breast cancer regardless of therapy (Table 6). Statistical analysis of effect sizes across subgroups showed no significant differences (all p-values ≥0.56).

Table 6. Invasive Breast Cancer by Treatment and Patient Baseline Characteristics STAR Primary Analysis Dataset

	Number of Events		Incidence Rate per 1000 Patient-Years			RR (95% CI) [b]
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference [a]	
Overall	**168**	**173**	**4.30**	**4.40**	**-0.10**	**1.02 (0.82,1.27)**
Age at entry (years)						
≤49	8	8	2.28	2.31	-0.03	1.01 (0.33,3.10)
50-59	84	80	4.30	4.07	0.23	0.95 (0.69,1.30)
≥60	76	85	4.74	5.25	-0.51	1.11 (0.80,1.53)
History of lobular carcinoma in situ						
No	134	138	3.76	3.86	-0.10	1.03 (0.80,1.31)
Yes	34	35	9.81	9.91	-0.10	1.01 (0.61,1.67)
History of atypical hyperplasia						
No	127	126	4.11	4.07	0.04	0.99 (0.77,1.28)
Yes	41	47	5.03	5.62	-0.59	1.12 (0.72,1.74)
5-year predicted breast cancer risk (%)						
≤3.00	33	44	2.03	2.75	-0.72	1.35 (0.84,2.20)
3.01-5.00	63	49	5.19	3.92	1.27	0.75 (0.51,1.11)
≥5.01	72	80	6.73	7.40	-0.67	1.10 (0.79,1.53)
No. of first degree relatives with breast cancer						
0	53	55	4.92	5.19	-0.27	1.06 (0.71,1.57)
1	74	79	3.61	3.74	-0.13	1.04 (0.75,1.44)
≥2	41	39	5.25	5.12	0.13	0.97 (0.61,1.55)

Abbreviations: CI = confidence interval; No. = number; RR = risk ratio.

Note: All p-values for interactions between treatment and any of the baseline characteristics were ≥0.56. Performed by testing the significance of the interaction term in a Cox model including terms for treatment, baseline characteristic, and the interaction between treatment and the baseline characteristic. P-value was determined by the Wald's test.

[a] Rate in the tamoxifen group minus rate in the raloxifene group.

[b] Risk ratio for patients in the raloxifene group compared to patients in the tamoxifen group.

3.4.5.5. Deaths Due to Breast Cancer

A total of 7 deaths due to breast cancer were reported in the STAR primary analysis dataset, 5 and 2 within the tamoxifen and raloxifene groups, respectively.

3.4.5.6. Persistence of Effect

Per the STAR protocol, patients who complete 5 years of active treatment are to be followed until the last patient randomized finishes the 5-year treatment phase. From 01 July 1999 (the date that the first patient was randomized to treatment) through 31 December 2005, the mean duration of study follow-up was 4.1 years (Table APP.4 [Appendix 1.2]). Of the 19,487 women in the STAR primary analysis dataset, NSABP researchers have followed 54% (n=10,592) for at least 4 years, 36% (n=6994) for at least 5 years, and 11% (n=2150) for 6 or more years. Per the STAR protocol, no patient received more than 5 years of active treatment.

Figure 10 shows the invasive breast cancer incidence rate per 1000 patient-years for tamoxifen and raloxifene by yearly interval of follow-up. Raloxifene and tamoxifen had comparable effects on the yearly incidence rate of invasive breast cancer through 6 or more years of study follow-up.

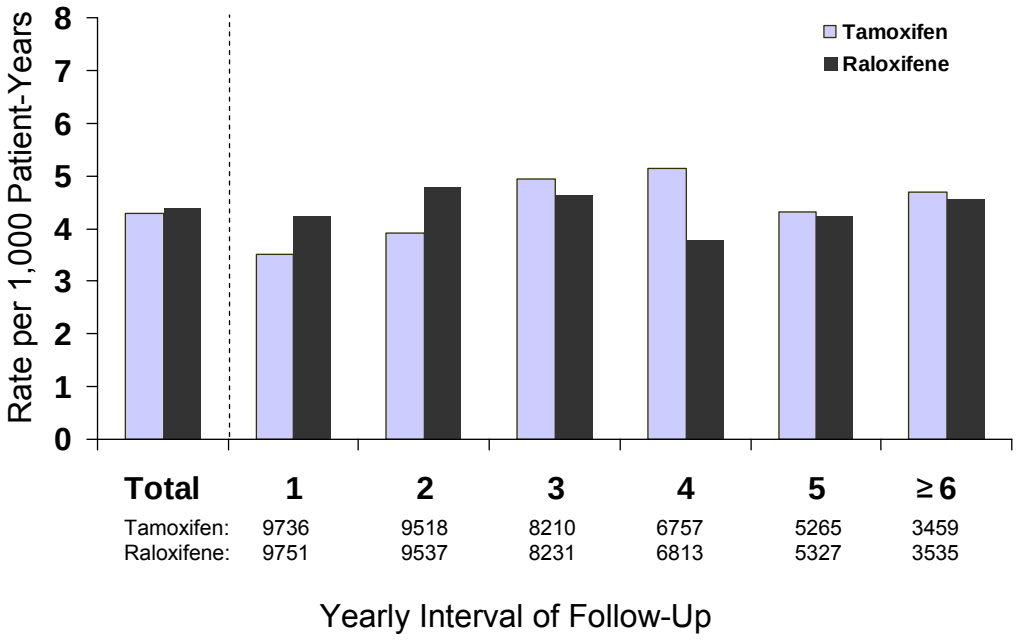


Figure 10. Yearly incidence rate of invasive breast cancer in STAR.

3.4.5.7. Noninvasive Breast Cancer (Secondary Endpoint)

Table 7 summarizes the noninvasive breast cancer results in STAR.

Fewer noninvasive breast cancer events occurred in the tamoxifen than in the raloxifene group (60 versus 83, respectively) but the difference did not reach statistical significance (Table 7).

Table 7. Noninvasive Breast Cancer Results STAR Primary Analysis Dataset

Noninvasive Breast Cancer	Number of Events		Incidence Rate per 1000 Patient-Years			RR [b] (95% CI)
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference[a]	
Overall	**60**	**83**	**1.54**	**2.12**	**-0.58**	**1.38 (0.98,1.95)**
DCIS	32	47	0.82	1.20	-0.38	1.46 (0.91,2.37)
LCIS	23	29	0.59	0.74	-0.15	1.26 (0.70,2.27)
Mixed	5	7	0.13	0.18	-0.05	1.39 (0.38,5.57)

Abbreviations: CI = confidence interval; DCIS =ductal carcinoma in situ; LCIS = lobular carcinoma in situ; RR = risk ratio.

[a] Rate in the tamoxifen group minus rate in the raloxifene group.

[b] Risk ratio for patients in the raloxifene group compared to patients in the tamoxifen group.

Patients in the tamoxifen group of STAR and patients 50 years or older in the tamoxifen group of P-1 had comparable incidence rates of noninvasive breast cancer (1.54 to 1.58 per 1000 patient-years, respectively). In contrast, patients in the raloxifene group of STAR and patients 50 years or older in the placebo group of P-1 had comparable incidence rates of noninvasive breast cancer (2.12 to 2.04 per 1000 patient-years, respectively).

The overall cumulative incidence of noninvasive breast cancer through 72 months was 8.7 and 11.9 per 1000 patients in the tamoxifen and raloxifene groups, respectively (Figure 11).

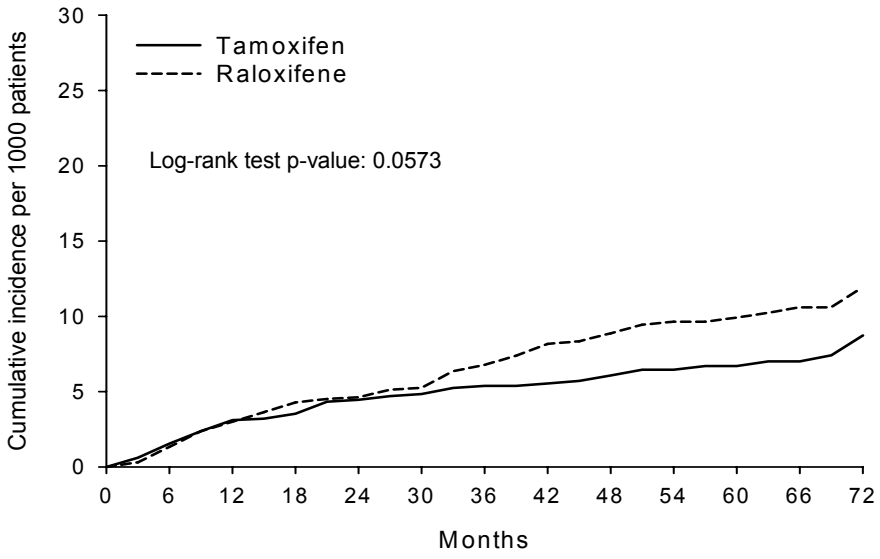


Figure 11. Cumulative incidence of noninvasive breast cancer in STAR.

3.4.6. STAR Efficacy Conclusions

The NSABP designed STAR to assess the effects of raloxifene compared with tamoxifen on the incidence of invasive breast cancer in postmenopausal women at increased risk for the disease. STAR demonstrated that raloxifene reduced the incidence of invasive breast cancer to a comparable extent as tamoxifen by both the protocol-specified analyses provided by the NSABP and the prospectively defined analysis (based on Rothmann's method [Rothmann et al. 2003]) performed by Lilly.

Demographics and Treatment Adherence

No clinically relevant differences were observed in patient demographics and baseline characteristics between treatment groups. Mean overall treatment adherence was 74.4%.

Invasive Breast Cancer – Primary Endpoint

- There were 168 and 173 cases of invasive breast cancer reported within the tamoxifen and raloxifene treatment groups, respectively. The corresponding incidence rates of invasive breast cancer were not significantly different for tamoxifen (4.30 per 1000 patient-years) and raloxifene (4.40 per 1000 patient-years).
- Based on a mean predicted 5-year breast cancer risk of 4.03% for the STAR population, the expected incidence rate for an untreated group, had one been included in the study, was estimated to be 8.2 per 1000 patient-years. Tamoxifen and raloxifene reduced the estimated incidence rate by nearly half (tamoxifen; IR 4.30 per 1000 patient-years and raloxifene; IR 4.40 per 1000 patient-years).

- Based on an analysis using Rothmann's method to quantify the relative efficacy of raloxifene versus tamoxifen, raloxifene was found to maintain at least 65% of the effect of tamoxifen on invasive breast cancer (point estimate of the proportion of effect maintained is 97%, 95% CI 65%-128%). Had a placebo group been included in STAR, raloxifene would have demonstrated a 52% reduction in risk of invasive breast cancer compared with the putative placebo 0.48 (95% CI 0.32-0.72).
- No significant differences in tumor characteristics were observed between the tamoxifen and raloxifene groups.
- No significant differences in the incidence of invasive breast cancer by baseline age, history of atypical hyperplasia, history of LCIS, number of relatives with a history of breast cancer, and predicted 5-year risk of invasive breast cancer were observed between the tamoxifen and raloxifene groups.

Overall, all analyses confirm that raloxifene is comparable to tamoxifen in reducing the incidence of invasive breast cancer in postmenopausal women at increased risk of breast cancer.

Noninvasive Breast Cancer – Secondary Endpoint

- There was a trend for fewer cases of noninvasive breast cancer with tamoxifen than raloxifene. The proportion of women with noninvasive breast cancer was numerically smaller in the tamoxifen (N=60) than raloxifene group (N=83) (RR 1.38, 95% CI 0.98-1.95).
- Patients in the STAR tamoxifen group and patients 50 years or older in the P-1 tamoxifen group had comparable incidence rates of noninvasive breast cancer (1.54 to 1.58 per 1000 patient-years, respectively). In contrast, patients in the STAR raloxifene group and patients 50 years or older in the P-1 placebo group had comparable incidence rates of noninvasive breast cancer (2.12 to 2.04 per 1000 patient-years, respectively). Based on this comparison, tamoxifen reduced the risk of noninvasive breast cancer, while raloxifene appeared to have no effect.

3.5. Overall Efficacy Conclusions

Three randomized clinical studies (MORE, RUTH, and STAR) and one placebo-controlled follow-up study of MORE participants, CORE, examined the efficacy of raloxifene in more than 37,000 postmenopausal women representing three distinct study populations.

MORE demonstrated that raloxifene HCl 60 mg/day versus placebo showed a statistically significant 71% decrease in the incidence of invasive breast cancer in postmenopausal women with osteoporosis. CORE demonstrated that raloxifene HCl 60 mg/day versus placebo showed a statistically significant 56% decrease in the incidence of invasive breast cancer in patients from MORE (N=3990), who were followed for up to an

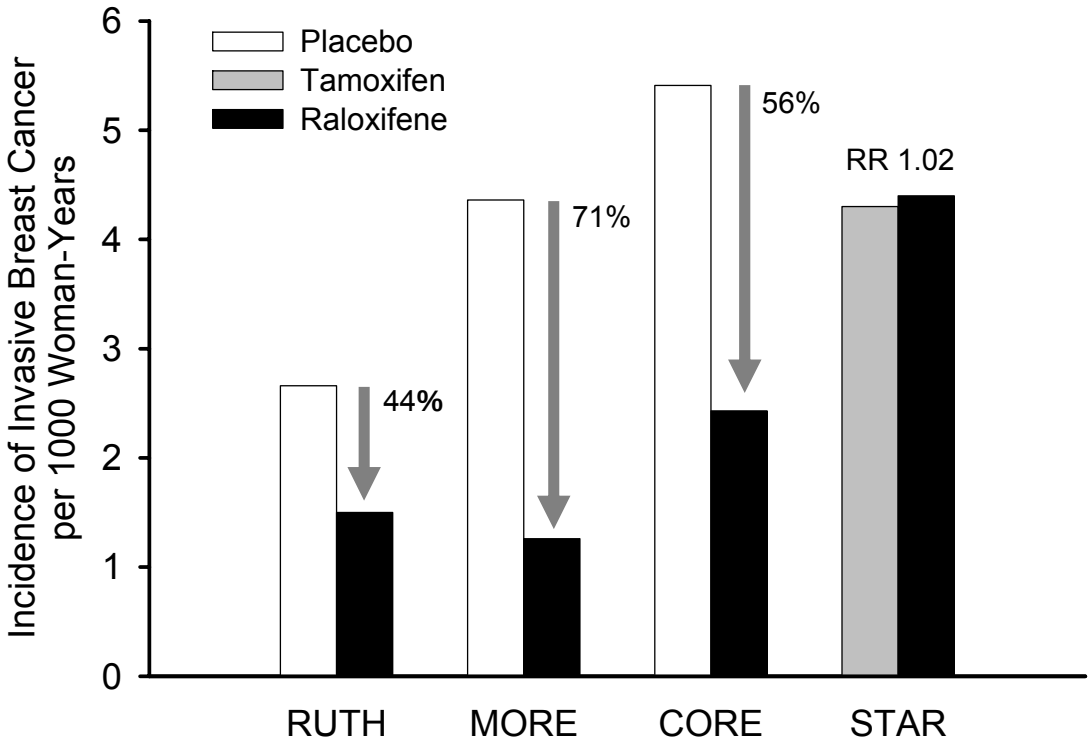
additional 4 years beyond their completion of MORE. The combined MORE/CORE 8-year analysis further demonstrated that raloxifene HCl 60 mg/day versus placebo showed a statistically significant 60% decrease in the incidence of invasive breast cancer in postmenopausal women with osteoporosis who had taken the 60 mg/day dose for up to 8 years of treatment.

Although the RUTH population was enrolled because of their risk for major coronary events, it does provide important confirmatory evidence for the effect of raloxifene to reduce the risk of invasive breast cancer in postmenopausal women. RUTH demonstrated that raloxifene HCl 60 mg/day versus placebo showed a statistically significant 44% decrease in the incidence of invasive breast cancer in postmenopausal women at risk for major coronary events.

STAR demonstrated that raloxifene HCl 60 mg/day is comparable to tamoxifen in reducing the incidence of invasive breast cancer in postmenopausal women at increased risk of invasive breast cancer by both the protocol-specified analyses provided by the NSABP and the prospectively defined analysis (based on Rothmann's method [Rothmann et al. 2003]) performed by Lilly. Raloxifene and tamoxifen were comparable in reducing the risk of invasive breast cancer regardless of age, history of hysterectomy, predicted 5-year risk of invasive breast cancer, family history of breast cancer, history of atypical hyperplasia, or LCIS. There was a trend for fewer cases of noninvasive breast cancer with tamoxifen than raloxifene. The proportion of women with noninvasive breast cancer was numerically smaller in the tamoxifen (N=60) than raloxifene group (N=83) (RR 1.38 95% CI 0.98-1.95).

A small number of cases of noninvasive breast cancer were observed in the randomized placebo-controlled studies, MORE and RUTH, and in the placebo-controlled follow-up study of MORE participants, CORE (all of which were DCIS); the incidences for raloxifene and placebo groups were not significantly different in any of these studies.

Overall, as shown in Figure 12, raloxifene demonstrated significant efficacy in reducing the incidence of invasive breast cancer in postmenopausal women in MORE, CORE, RUTH, and STAR, regardless of their baseline invasive breast cancer risk.



Abbreviation: RR = risk ratio for raloxifene:tamoxifen.
Note: Invasive breast cancer was a secondary endpoint in MORE.

Figure 12. **Effect of raloxifene on the incidence rate of invasive breast cancer in the MORE, CORE, RUTH, and STAR studies.**

4. Safety of Raloxifene

4.1. Individual Studies Assessing Safety

This section summarizes the safety of raloxifene in the randomized placebo-controlled studies MORE and RUTH, the randomized active-comparator controlled study STAR, and the placebo-controlled follow-up study of MORE participants, CORE.

Safety data and conclusions are presented for the placebo-controlled studies (MORE, CORE, and RUTH) followed by the active-comparator controlled study (STAR).

These Phase 3 clinical studies were conducted in postmenopausal women who were enrolled because of their risks for different clinical conditions (eg, osteoporosis, major coronary events, and invasive breast cancer). Hence, patients' baseline risk profiles constitute a key demographic difference among three of these four studies. The only other demographic difference of note among the studies was age. STAR patients were on average approximately 10 years younger (mean age 58.5 years) than patients in MORE (mean age 67 years) and RUTH (mean age 68 years).

Because the studies differed in terms of study design, evaluated three distinct study populations, used different AE coding dictionaries, and solicited AEs differently, Lilly concluded it was inappropriate to pool study safety data. Additionally, the size and the duration of follow-up of STAR and RUTH, in particular, enabled detection of less common AEs, occurring at rates as low as nearly 1 in 10,000 and 1 in 5000 among raloxifene-assigned patients in STAR and RUTH, respectively.

4.2. Extent of Study Drug Exposure in MORE, CORE, RUTH, and STAR

Mean and median study drug exposures were similar between treatment groups in MORE, CORE, RUTH, and STAR (Table APP.5 [Appendix 1.2]). Approximately 75% of MORE patients (N=5682), 47% of CORE patients (N=1502), and 56% of STAR patients (N=10,851) had 3 or more years of study drug exposure, and 54% of RUTH patients (N=5455) had 5 or more years of study drug exposure (Table APP.6 [Appendix 1.2]). For the four studies combined, raloxifene exposure totaled more than 76,000 patient-years.

The extensive study drug exposure for these studies, both in terms of number of patients and length of exposure, provides substantial data to evaluate the safety profile of raloxifene in these patient populations.

4.3. Safety Profile

Sections 4.3.1 and 4.3.2 summarize key safety findings and conclusions, respectively, for the randomized placebo-controlled MORE and RUTH studies and for the placebo-controlled follow-up study of MORE participants, CORE. Sections 4.3.3 and 4.3.4 summarize key safety findings and conclusions, respectively, for the randomized

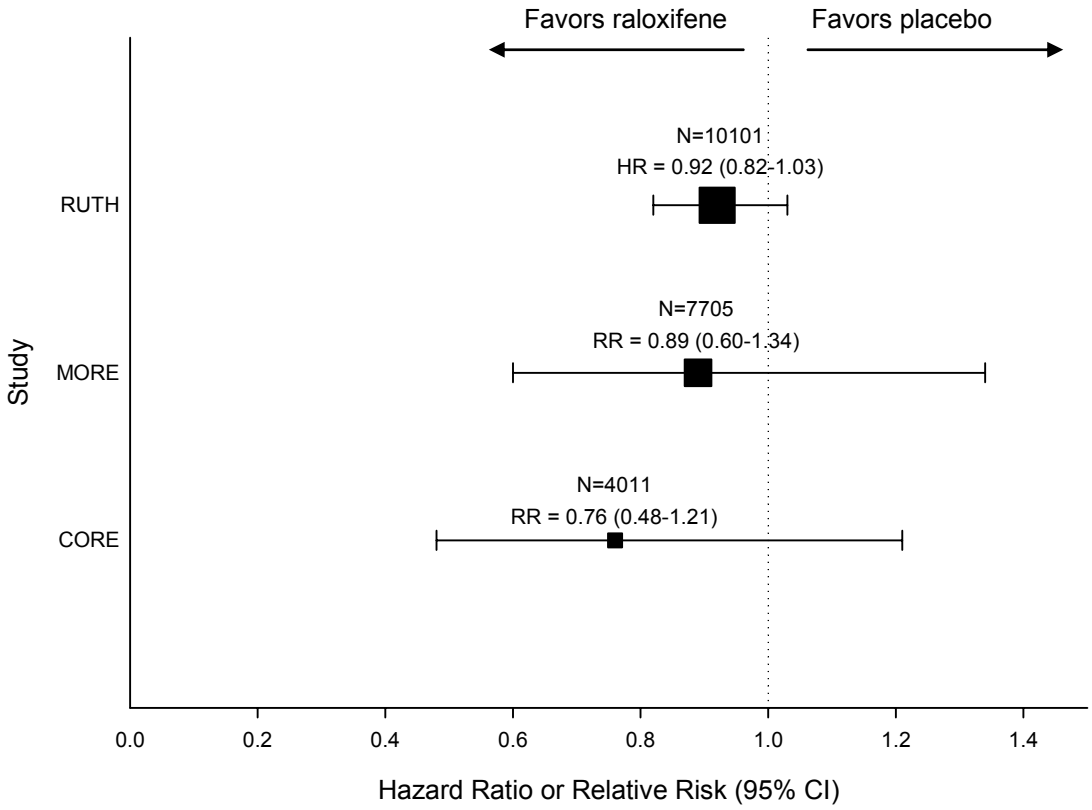
active-comparator controlled STAR study. Safety topics presented for both the placebo-controlled studies and the active-comparator controlled study are mortality, VTEs, cancer events other than breast cancer, cardiovascular (CV) events, and tolerability related events (eg, hot flashes/flushes, leg cramps, peripheral edema, vaginal discharge). Safety topics presented for only the active-comparator controlled study are cataracts and cataract surgery and fracture events.

4.3.1. MORE, CORE, and RUTH – Safety Profile of Raloxifene versus Placebo

The key safety findings and conclusions for the two randomized placebo-controlled studies MORE and RUTH, and the placebo-controlled follow-up study of MORE participants, CORE, are presented below.

4.3.1.1. Mortality

No statistically significant differences in all-cause mortality were noted between placebo and raloxifene treatments in MORE and RUTH, or in the follow-up CORE. However, in all of these analyses, the incidence of all-cause mortality was lower for the raloxifene group than the placebo group (Figure 13).



Abbreviations: CI = confidence interval; HR = hazard ratio; N = patient population (box size is proportional to study size); RR = relative risk.

Figure 13. All-cause mortality hazard ratio or relative risk for all randomized MORE and RUTH patients and all CORE patients.

4.3.1.2. Comparative Safety Profile of Raloxifene versus Placebo

Adverse events in MORE, CORE, and RUTH have been classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA coding dictionary contains the international medical terminology that was developed under the auspices of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

The key safety findings from MORE, CORE and RUTH, summarized in this section, are as follows.

- Venous thromboembolic events
- Hot flushes, leg cramps, peripheral edema, and cholelithiasis
- Cardiovascular events
- Cancer events.

For MORE safety analyses, the raloxifene HCl 60 mg/day and 120 mg/day dose groups were combined so as to provide the greatest opportunity to detect safety signals in the

population studied. The treatment-emergent adverse event (TEAE) baseline for CORE is the first visit in CORE because CORE enrollees had been off study drug for a median of 10.6 months before enrolling in CORE.

4.3.1.2.1. Venous Thromboembolic Events

Venous thromboembolic events (DVT, PE, and other VTEs) are known AEs associated with raloxifene (Evista package insert 2003).

Raloxifene versus placebo showed a statistically significant increase in serious VTEs (DVTs, PEs, plus other VTEs combined) in MORE (89% increase [Table 8]). Though not statistically significant, more VTEs occurred within the raloxifene group than the placebo group in CORE.

Table 8. Venous Thromboembolic Events All Randomized MORE and All CORE Patients

	MORE			CORE[a]		
	Placebo N=2576	Raloxifene N=5129		Placebo N=1286	Raloxifene N=2725	
RSSC	n (%)	n (%)	Relative Risk (95% CI)	n (%)	n (%)	Relative Risk (95% CI)
VTE[b]	17 (0.7)	*64 (1.3)	1.89 (1.11, 3.22)	4 (0.3)	23 (0.8)	2.71 (0.94, 7.83)
PE	4 (0.2)	22 (0.4)	2.76 (0.95, 8.01)	0 (0.0)	9 (0.3)	NA[c]
DVT	8 (0.3)	*44 (0.9)	2.76 (1.30, 5.86)	4 (0.3)	17 (0.6)	2.01 (0.68, 5.95)
RVT	5 (0.2)	5 (0.1)	0.50 (0.15, 1.73)	0 (0.0)	2 (0.1)	NA[c]

Abbreviations: CI = 95% confidence interval, DVT = deep vein thrombosis, n = patients with event, N = patient population, NA = not applicable, PE = pulmonary embolism, RSSC = raloxifene special search category, RVT = retinal vein thrombosis, VTE = venous thromboembolic event.

a VTE was a solicited adverse event in CORE but not MORE.

b VTE was defined as pulmonary embolism, deep vein thrombosis, and other acute serious vein thromboses (including mesenteric and intracerebral vein thromboses). Of these other thromboses, only retinal vein thrombosis was actually reported.

c The pulmonary embolism relative risk and retinal vein thrombosis relative risk could not be calculated for CORE because no events were reported in the placebo treatment group.

* Denotes statistically significant difference based upon Fisher Exact test.

Raloxifene versus placebo showed a statistically significant increase in serious VTEs (DVTs, PEs, plus other VTEs combined) in RUTH (44% increase [Table 9]).

Table 9. Venous Thromboembolic Events All Randomized RUTH Patients

	RUTH		
	Placebo N=5057	Raloxifene N=5044	
Endpoint	**n (%)**	**n (%)**	**Hazard Ratio (95% CI)**
Venous thromboembolic event [a b]	71 (1.40)	*103 (2.04)	1.44 (1.06, 1.95)
Deep vein thrombosis	47 (0.93)	65 (1.29)	1.37 (0.94, 1.99)
Pulmonary embolism	24 (0.47)	36 (0.71)	1.49 (0.89, 2.49)
Intracranial thrombosis	6 (0.12)	8 (0.16)	1.32 (0.46, 3.80)
Other venous thromboembolic event	1 (0.02)	2 (0.04)	NA

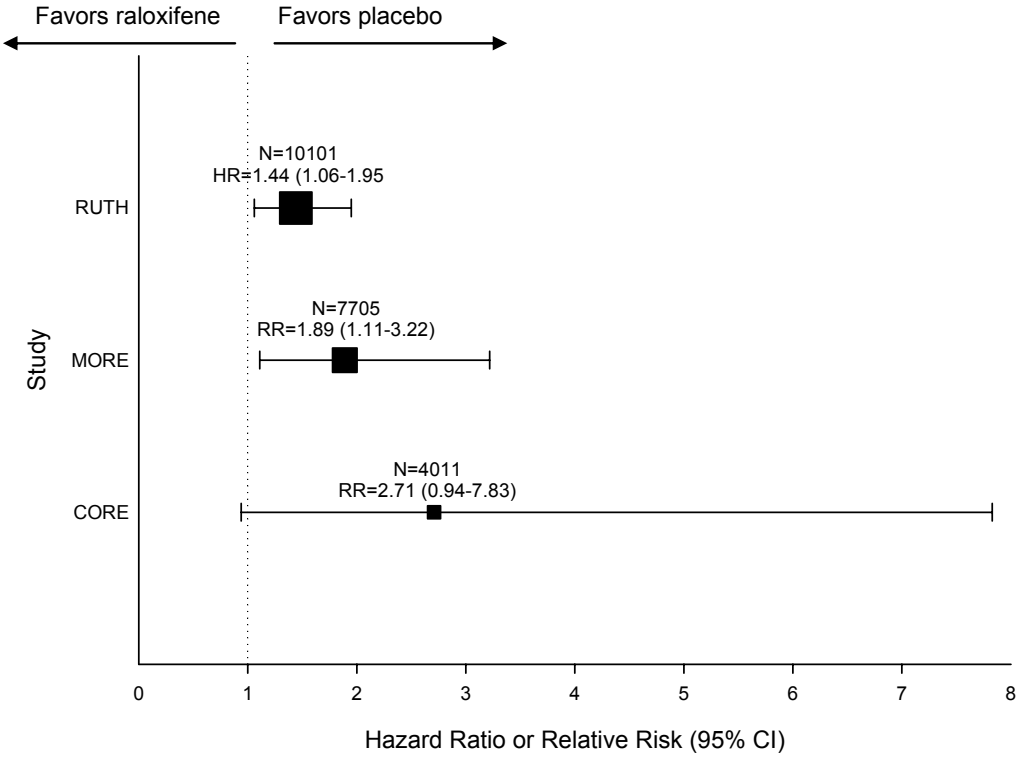
Abbreviations: CI = 95% confidence interval, n = patients with event, N = patient population, NA = not applicable.

a VTE was an adjudicated endpoint in RUTH.

b VTE was defined as pulmonary embolism, deep vein thrombosis, intracranial thrombosis, and other acute serious vein thromboses (including mesenteric and intracerebral vein thromboses).

* Denotes statistically significant difference based upon log-rank test. The statistical test was not performed when the total number of patients was less than 5 in a category.

Figure 14 shows the VTE relative risk for all randomized MORE and RUTH patients and all patients in CORE.



Abbreviations: CI = confidence interval, N = patient population (box size is proportional to study size), HR = hazard ratio, RR = relative risk.

Figure 14. VTE hazard ratio or relative risk for all randomized MORE and RUTH patients and all CORE patients.

4.3.1.2.2. Hot Flushes, Leg Cramps, Peripheral Edema, Cholelithiasis

Hot flushes, leg cramps (muscle spasms), and peripheral edema are known AEs associated with raloxifene (Evista package insert 2003).

Statistically significant increases in the incidences of hot flushes, leg cramps (MedDRA preferred term [PT] = muscle spasms), and peripheral edema were observed in raloxifene-assigned patients compared with placebo-assigned patients in MORE and RUTH but not in CORE (Table 10).

Table 10. Hot Flushes, Leg Cramps, Peripheral Edema
All Randomized RUTH and MORE Patients and All CORE Patients

	RUTH				MORE				CORE			
Event	**RLX N=5044**	**PBO N=5057**	**RLX IR**	**PBO IR**	**RLX N=5129**	**PBO N=2576**	**RLX IR**	**PBO IR**	**RLX N=2725**	**PBO N=1286**	**RLX IR**	**PBO IR**
	n (%)	n (%)			n (%)	n (%)			n (%)	n (%)		
Hot flushes	*397 (7.9)	241 (4.8)	14.82	9.09	*512 (10.0)	151 (5.9)	29.04	17.31	26 (1.0)	11 (0.9)	3.31	2.94
Leg cramps	*483 (9.6)	334 (6.6)	18.03	12.60	*443 (8.6)	150 (5.8)	25.13	17.20	90 (3.3)	36 (2.8)	11.46	9.63
Peripheral edema	*706 (14.0)	583 (11.5)	26.36	22.00	*340 (6.6)	134 (5.2)	19.29	15.36	61 (2.2)	30 (2.3)	7.77	8.03

Abbreviations: ARD = absolute risk difference; IR = incidence rate per 1000 patient-years; n = patients with event, N = patient population, PBO = placebo; RLX = raloxifene.

* Denotes statistically significantly greater incidence than other treatment group within study based upon Cochran-Mantel-Haenszel test ($p<0.05$). For incidence less than 5, p-values were not applicable.

Raloxifene versus placebo showed a statistically significantly greater incidence of cholelithiasis (3.3% versus 2.6%, respectively) in RUTH, but not in MORE or CORE. Raloxifene versus placebo demonstrated no significant difference in the incidences of cholecystitis or cholecystectomy in RUTH, MORE, or CORE.

4.3.1.2.3. Cardiovascular Events

In RUTH, ACS and stroke were study endpoints. For MORE and CORE, special search categories were used to examine MI and stroke.

4.3.1.2.3.1. Acute Coronary Syndrome

MORE and CORE showed no statistically significant difference between treatment groups for TEAEs suggestive of a MI.

One of the primary objectives of RUTH was to assess whether treatment with raloxifene, compared with placebo, reduced the incidence of a combined coronary primary endpoint (defined as coronary death, nonfatal [including silent] MI, or hospitalized ACS other than MI) in postmenopausal women at risk for major coronary events. Raloxifene, compared with placebo, showed no statistically significant difference in the incidence of the combined coronary primary endpoint (HR 0.95, 95% CI 0.84-1.07) (see Figure APP.1 [Appendix 1.2]) or in the incidence of any of the individual events of the coronary primary endpoint.

Thus, raloxifene had no significant effects on the risk of coronary endpoint events.

4.3.1.2.3.2. Cardiac Arrhythmias

Table 11 summarizes TEAE data by special search categories for cardiac arrhythmia across the two randomized placebo-controlled MORE and RUTH studies and the MORE follow-up, CORE.

**Table 11. Cardiac Arrhythmias
All Randomized RUTH and MORE Patients and All CORE Patients**

RSSC Subcategory RSSC	RUTH PBO N=5057 n (%)	 RLX N=5044 n (%)	MORE PBO N=2576 n (%)	 RLX N=5129 n (%)	CORE PBO N=1286 n (%)	 RLX N=2725 n (%)
All Arrhythmias	744 (14.7)	696 (13.8)	178 (6.9)	346 (6.8)	35 (2.7)	94 (3.5)
Supraventricular arrhythmias	441 (8.7)	409 (8.1)	81 (3.1)	158 (3.1)	23 (1.8)	55 (2.0)
Atrial fibrillation	323 (6.4)	309 (6.1)	32 (1.2)	87 (1.7)	15 (1.2)	44 (1.6)
SVAs other than atrial fib	151 (3.0)	127 (2.5)	*56 (2.2)	79 (1.5)	9 (0.7)	13 (0.5)
Cardiac Conduction Disorder	171 (3.4)	162 (3.2)	39 (1.5)	84 (1.6)	1 (0.1)	8 (0.3)
Ventricular Arrhythmias	47 (0.9)	53 (1.1)	13 (0.5)	18 (0.4)	3 (0.2)	10 (0.4)
Other Arrhythmias	186 (3.7)	175 (3.5)	67 (2.6)	127 (2.5)	10 (0.8)	29 (1.1)

Abbreviations: fib = fibrillation; n = patients with event, N = patient population, PBO = placebo, RLX = raloxifene, RSSC = raloxifene special search category; SVA = supraventricular arrhythmias.

* Denotes statistically significantly greater incidence than other treatment group within study based upon Cochran-Mantel-Haenszel test, stratified by country ($p<0.05$). For incidence less than 5, statistical tests were not performed.

The overall pattern of cardiac arrhythmia data in Table 11 does not suggest a causal association between raloxifene and any of the arrhythmia categories.

4.3.1.2.3.3. Stroke

No statistically significant difference in the incidence of treatment-emergent stroke was observed for raloxifene-assigned patients compared with placebo-assigned patients in MORE (RR=0.82, CI 0.59-1.13), CORE (RR=1.65, CI 0.92-2.98) and RUTH (HR=1.10, CI 0.92-1.32).

4.3.1.2.3.4. Death due to Stroke

MORE and CORE showed no statistically significant difference in death due to stroke between raloxifene and placebo treatment. However, RUTH showed a statistically significantly ($p=0.0499$) greater incidence of death due to stroke for raloxifene-assigned patients (2.2 per 1000 patient-years) than placebo-assigned patients (1.5 per 1000 patient-years), representing an absolute risk increase for death due to stroke of 0.7 per 1000 patient-years of raloxifene treatment.

In RUTH, a statistically significant difference ($p=0.029$) in baseline CV risk was observed between the placebo and raloxifene groups, with a higher baseline score for the raloxifene than the placebo group (see Section 2.1.1.2.1 for description of CV risk score). Post hoc analyses in RUTH examined the relationship between stroke and death due to stroke using patient demographics, comorbidities, comedications, and baseline risk factors to identify potential risk factors for death due to stroke. No single risk factor

could statistically identify which patients treated with raloxifene would experience a death due to stroke. Adjusting for baseline risk factors in a multivariate model had a small impact on the statistical significance of the difference in the incidence of death due to stroke between treatment groups (p=0.0571).

Based on clinical judgment, the risk factors of previous stroke, TIA, or atrial fibrillation might have contributed to the increased incidence of death due to stroke observed in the raloxifene-assigned patients in RUTH.

On 12 April 2006, Lilly made public the unblinded clinical study safety findings of death due to stroke from RUTH, and they were published on 13 July 2006 in the New England Journal of Medicine (Barrett-Connor et al. 2006). Subsequent to 12 April 2006, there has been no increase in the reporting rate of death due to stroke in spontaneous reports to Lilly, with only one spontaneous report of fatal stroke with raloxifene as of 01 May 2007.

Compared with placebo, raloxifene had no statistically significant effect on the incidence of death due to CV causes in RUTH. Moreover, raloxifene was associated with a statistically significantly (p=0.0264) decreased incidence of deaths due to non-CV causes compared with placebo. As previously noted, a non-significant decrease in overall mortality was observed with raloxifene compared with placebo (Figure 13) in MORE, CORE, and RUTH.

4.3.1.2.4. Cancer Events

With the exception of statistically significant reductions in breast cancer in each study (and skin cancer in CORE), raloxifene versus placebo showed no statistically significant difference in the incidences of other individual cancers including endometrial cancer, uterine sarcoma, and ovarian cancer in MORE, CORE, and RUTH.

For additional background information, the cancer data from RUTH, which is the larger of the two randomized placebo-controlled studies, are provided. Raloxifene versus placebo in RUTH showed no statistically significant differences in the incidences of all cancers or any specific type of cancer (Table APP.8 [Appendix 1.2]).

4.3.1.2.4.1. Endometrial and Uterine Cancer

No statistically significant difference in the incidences of endometrial and uterine cancer (Figure 15) was observed between the raloxifene and placebo treatment groups in MORE, CORE, and RUTH. For reference, the SEER (Surveillance, Epidemiology, and End Results) age-adjusted rate of uterine cancer for females 50 years of age or older is 0.75 per 1000 patient-years (SEER 2007).

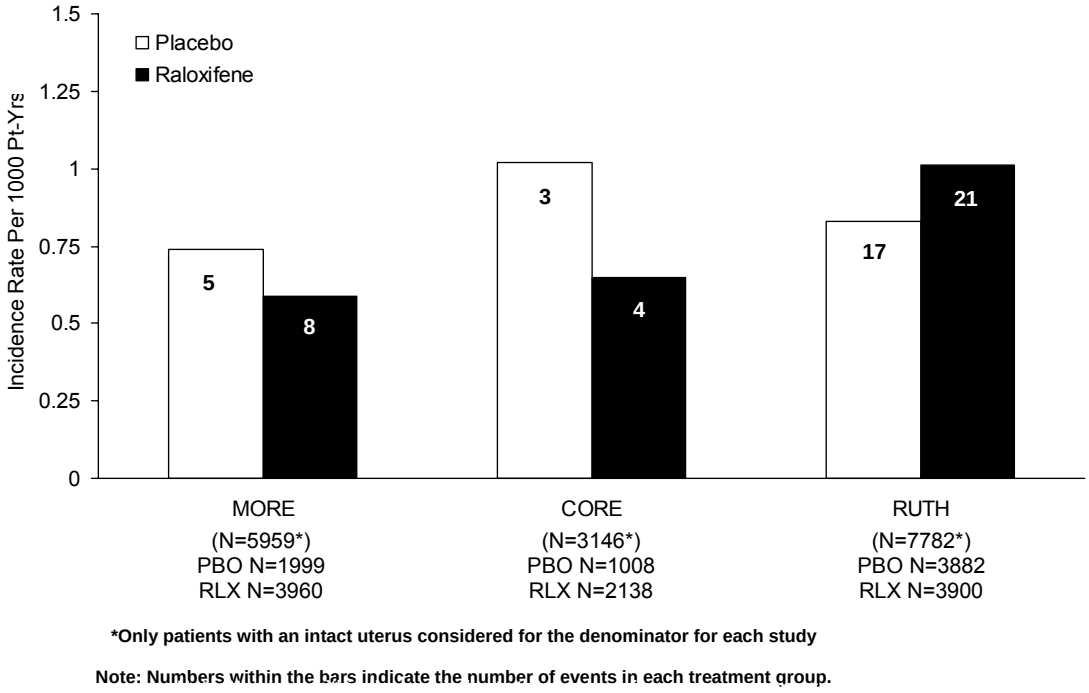


Figure 15. Endometrial and uterine cancer in MORE, CORE, and RUTH.

4.3.1.2.4.2. Ovarian Cancer

MORE, CORE, and RUTH showed no statistically or clinically relevant treatment patterns suggestive of a consistent treatment group difference.

4.3.2. MORE, CORE, and RUTH Safety Conclusions

The two randomized placebo-controlled studies, MORE and RUTH, and one placebo-controlled follow-up study of MORE participants, CORE, examined the safety of raloxifene compared with placebo in postmenopausal women with osteoporosis (MORE and CORE) and postmenopausal women at increased risk for major coronary events (RUTH).

Safety Observations Observed Consistently in MORE, CORE, and RUTH

- **All-Cause Mortality:** No statistically significant differences in the incidence of all-cause mortality were observed in raloxifene-assigned patients compared with placebo-assigned patients in all three studies.
- **Venous thromboembolic event:** MORE and RUTH demonstrated a statistically significant increase in serious VTEs (DVT, PE, and other VTEs combined) for raloxifene compared with placebo. Though not statistically significant, CORE demonstrated a numerical increase in serious VTEs for raloxifene compared with placebo. MORE also showed a statistically significant increase in DVTs for raloxifene compared with placebo.

- **Hot flushes, leg cramps, and peripheral edema:** MORE and RUTH, but not CORE, showed statistically significant increases in the incidences of hot flushes, leg cramps (muscle spasms), and peripheral edema for the raloxifene group compared with the placebo group.
- **Cancer:** No statistically significant differences in the incidence of endometrial cancer, uterine sarcoma, ovarian cancer, or other cancers (except for statistically significant reductions in invasive breast cancer in each study and a significant reduction in skin cancer in CORE) were observed in the raloxifene group compared with the placebo group.

Safety Observations Observed Only in RUTH

The following bullets summarize important safety findings observed only in RUTH in postmenopausal women at increased risk for major coronary events:

- **Death due to stroke:** In patients with CHD or with multiple risks for CHD, RUTH showed a statistically significant (p=0.0499) 49% increase in the incidence of death due to stroke in the raloxifene group compared with placebo group. Raloxifene treatment did not increase the incidence of coronary events, death due to a CV event, or cerebrovascular events, including all strokes in RUTH. Furthermore, raloxifene did not increase the incidence of early CHD events.
    - No single risk factor could statistically identify which patients treated with raloxifene would experience a death due to stroke. Based on clinical judgment, the risk factors of previous stroke, TIA, or atrial fibrillation might have contributed to the increased incidence of death due to stroke observed in the raloxifene group in RUTH.
- **Cholelithiasis:** RUTH showed a statistically significantly greater incidence of cholelithiasis in the raloxifene group than the placebo group (3.3% versus 2.6%). No statistically significant differences in the incidence of cholecystitis or cholecystectomy were observed between the raloxifene group and the placebo group in RUTH.

4.3.3. STAR - Safety Profile of Raloxifene versus Tamoxifen

Safety was assessed through the reporting of toxicities (AEs collected in a nonsolicited manner at every visit and coded to Common Toxicity Criteria [CTC] version 2.0) via the case report form (CRF). Use of the CTC is consistent with oncology study coding. Additional safety assessments included gynecological examinations, ophthalmologic monitoring, and hematology and blood chemistry evaluations.

Section 3 provided STAR data on invasive and noninvasive breast cancer events.

Unless otherwise noted, this section presents analyses of events reported as occurring between 01 July 1999 (the date the first patient in STAR was randomized to treatment) through 31 December 2005 (the data cutoff date for the STAR CSR).

All risk ratios are calculated for the raloxifene group compared with the tamoxifen group.

Safety data collected between 31 December 2005 and 30 September 2006 from the ongoing STAR study were submitted to the FDA in the form of the 4-Month Safety Update. Table APP.7 (Appendix 1.2) provides cumulative safety data through 30 September 2006 for STAR safety endpoints.

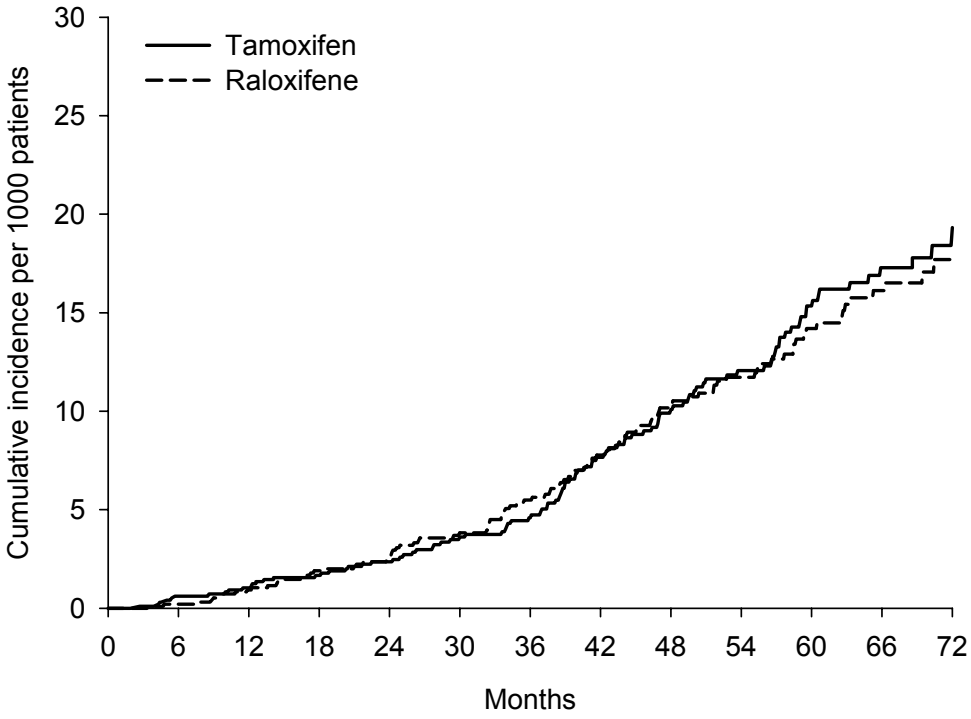
4.3.3.1. Mortality

Among the 19,487 patients comprising the STAR primary analysis dataset, investigators recorded 213 deaths (104 in the raloxifene group and 109 in the tamoxifen group).

Figure 16 shows the cumulative incidence curves for all-cause mortality in STAR. The incidence rates for death were 2.6 and 2.8 per 1000 patient-years for the raloxifene and tamoxifen groups, respectively (RR 0.95, 95% CI 0.72-1.25).

The updated incidence rates for death were 2.7 and 3.1 per 1000 patient-years for the raloxifene and tamoxifen groups, respectively (RR 0.87, 95% CI 0.68-1.13) (Table APP.7 [Deaths; Safety Update]).

No statistically significant differences were noted between raloxifene and tamoxifen in deaths due to cancer (N=52 in both treatment groups), CV disease (N=21 raloxifene; N=25 tamoxifen), or other reason (N=32 in both treatment groups).



Note: Mortality data through 31 December 2005.

Figure 16. Incidence curves for all-cause mortality in STAR.

4.3.3.2. Comparative Safety Profile of Raloxifene versus Tamoxifen

The STAR primary analysis dataset comprises 19,487 postmenopausal women at increased risk for invasive breast cancer whose mean study drug exposure is 3.2 years; thus, the STAR safety database allows for a detailed comparative assessment of the safety profile of raloxifene versus tamoxifen.

This section summarizes the key safety observations from STAR, as follows.

- Venous thromboembolic events
- Cancer events other than breast cancer
- Cardiovascular events
- Cataracts and cataract surgery events
- Hot flash events, vaginal discharge events, and tolerability
- Fracture events.

4.3.3.2.1. Venous Thromboembolic Events

Venous thromboembolic events are known AEs associated with both raloxifene (Evista package insert 2003) and tamoxifen (Nolvadex package insert 2003).

Raloxifene was associated with statistically significantly fewer VTEs (RR 0.69, 95% CI 0.53-0.90) compared with tamoxifen (Table 12). Though not statistically significant, 35% fewer PEs and 28% fewer DVTs were reported in the raloxifene group than the tamoxifen group.

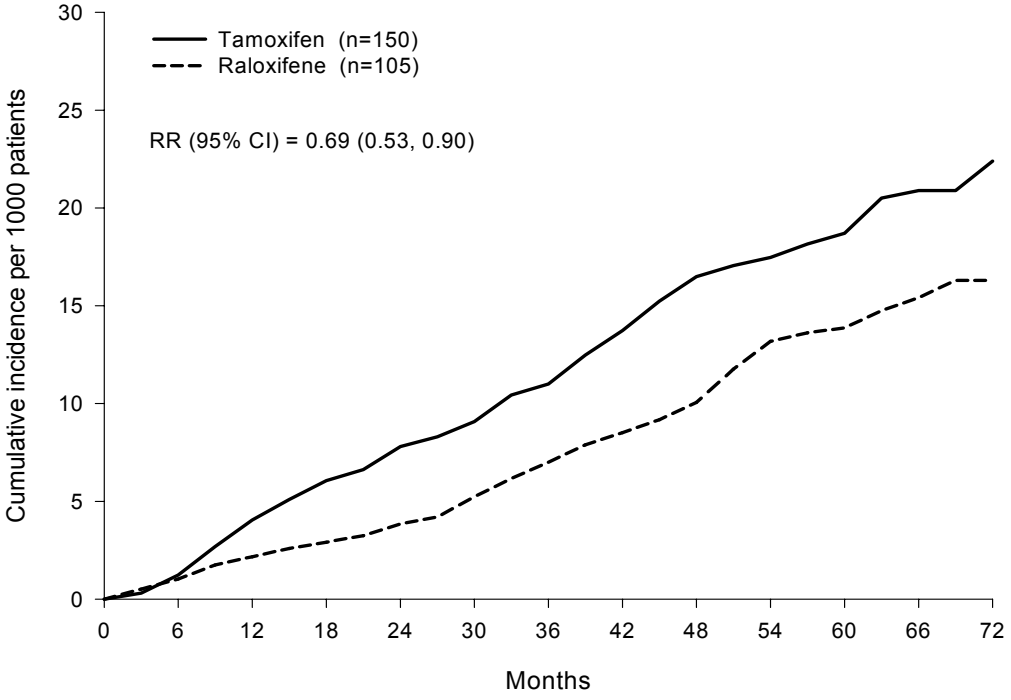
Figure 17 shows the overall cumulative incidence of VTEs through 72 months in STAR.

Table 12. Venous Thromboembolic Events STAR Primary Analysis Dataset

	Tamoxifen N=9736		Raloxifene N=9751		
Event	**n**	**IR**	**n**	**IR**	**RR [a] (95% CI)**
Venous thromboembolism	150	3.83	105	2.66	0.69 (0.53,0.90)
Pulmonary embolism	58	1.47	38	0.96	0.65 (0.42,1.00)
Deep vein thrombosis	92	2.35	67	1.69	0.72 (0.52,1.00)

Abbreviations: CI = 95% confidence interval; IR = incidence rate per 1000 patient-years; n = patients with event, N = patients comprising primary analysis dataset; RR = risk ratio;

[a] Risk ratio for patients in the raloxifene group compared with those in the tamoxifen group.



Note: Includes deep vein thrombosis and pulmonary embolism.

Figure 17. Cumulative incidence curves for venous thromboembolic events in STAR.

4.3.3.2.2. Cancer Events Other Than Breast Cancer

4.3.3.2.2.1. Uterine (Including Endometrial) Cancer, Endometrial Hyperplasia, Hysterectomy, and Vaginal Bleeding

Endometrial hyperplasia, hysterectomy, and vaginal bleeding are not cancer events but, because of their potential association with uterine cancer, are included in this section.

Uterine Cancer

Slightly more than half of the patients in the STAR primary analysis dataset had a baseline history of hysterectomy (raloxifene, 51.6%; tamoxifen, 51.3%). Accordingly, the denominator for uterine cancer incidence, including endometrial cancer, included only those patients with an intact uterus at baseline (raloxifene, 4715 of 9751 patients; tamoxifen, 4739 of 9736 patients). Also, patients who had a hysterectomy during the study were censored at the time of hysterectomy from uterine and gynecological analyses.

Though not statistically significant, 39% fewer uterine (including endometrial) cancers (RR 0.61, 95% CI 0.34-1.05) were reported for raloxifene (23 cases; 1.21 per 1000 patient-years) than for tamoxifen (37 cases; 1.99 per 1000 patient-years).

The overall cumulative incidence of invasive uterine cancer through 72 months of study follow-up was not statistically significantly different between the two treatment groups (Figure 18).

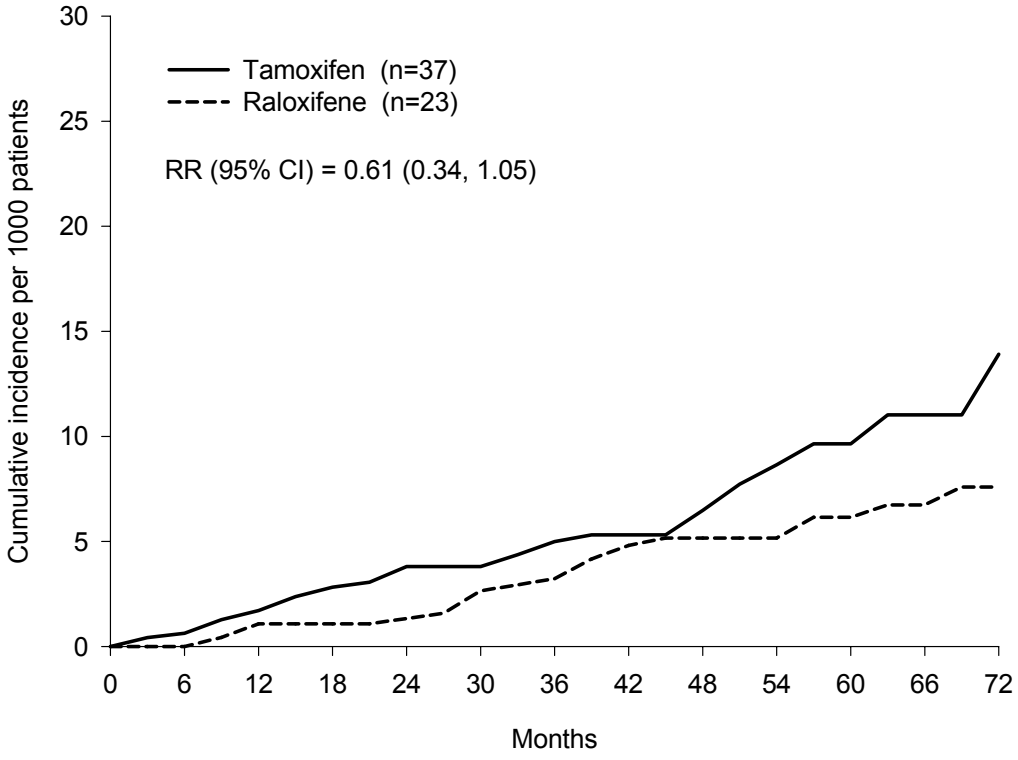


Figure 18. Cumulative incidence curves for invasive uterine cancer in STAR.

Endometrial Hyperplasia

Among patients who did not have a diagnosis of uterine cancer, raloxifene was associated with a statistically significant 83% lower incidence (RR 0.17, 95% CI 0.09-0.28) of endometrial hyperplasia than tamoxifen (Table 13).

Hysterectomy

Statistically significantly fewer postbaseline hysterectomies were performed on patients in the raloxifene than the tamoxifen group, corresponding to a 63% (RR 0.37, 95% CI 0.28-0.47) lower incidence in the raloxifene than the tamoxifen group (Table 13). Thus, through 31 December 2005, 5.2% and 1.9% of patients in the tamoxifen and raloxifene groups, respectively, had hysterectomies.

Because nearly three times as many patients in the tamoxifen than the raloxifene group had hysterectomies during study follow-up, the difference in the relative rate of uterine cancer between the raloxifene and tamoxifen groups (RR 0.61, 95% CI 0.34-1.05; 39%

fewer cases in the raloxifene group) was probably not as substantial as it might otherwise have been.

Table 13. Hysterectomy and Uterine Hyperplasia in STAR

	Raloxifene N=4715 [a]		Tamoxifen N=4739 [a]		RR[b] (95% CI)
Uterine event type	**n**	**IR**	**n**	**IR**	
Hyperplasia	**17**	**0.90**	**100**	**5.42**	**0.17 (0.09,0.28)**
Without atypia	15	0.79	85	4.60	0.17 (0.09,0.30)
With atypia	2	0.11	15	0.81	0.13 (0.01,0.56)
Hysterectomy during follow-up	**92**	**4.84**	**246**	**13.25**	**0.37 (0.28,0.47)**

Abbreviations: CI = 95% confidence interval; IR = incidence rate per 1000 patient-years; n = patients with event, N = patients in the primary analysis dataset with an intact uterus at baseline; RR = risk ratio.

[a] Patients with an intact uterus at baseline (no hysterectomy) were included (tamoxifen, 4739 of 9736; raloxifene, 4715 of 9751). For endometrial hyperplasia rates, time at risk for patients who had a hysterectomy without experiencing an endometrial hyperplasia during follow-up was censored at the time of the hysterectomy. Time at risk for patients who had endometrial cancer without experiencing hyperplasia was censored at the time of diagnosis of endometrial cancer. For hysterectomy rates, time at risk for patients who had endometrial cancer was censored at the time of diagnosis of the endometrial cancer.

[b] Risk ratio for patients in the raloxifene group compared with those in the tamoxifen group.

Vaginal Bleeding

The higher incidence of vaginal bleeding observed within the tamoxifen group (tamoxifen, 909 events, 9%; raloxifene, 484 events, 5%) is consistent with the statistically significantly higher incidence of endometrial hyperplasia, a risk factor for endometrial cancer (Montgomery et al. 2004), and the numerically higher incidence of uterine cancer (see above in this section) observed in the tamoxifen compared to the raloxifene group.

4.3.3.2.2.2. Uterine Sarcoma

Among the total number of uterine cancer events reported in Section 4.3.3.2.2.1, there were two cases of mixed Mullerian uterine sarcoma. Both cases were reported in women assigned to tamoxifen.

4.3.3.2.2.3. Ovarian Cancer

For calculation of ovarian cancer incidence, the denominator only included patients who had at least one intact ovary at baseline (raloxifene, 6787 of 9751 patients; tamoxifen, 6813 of 9736 patients). Patients who had both ovaries removed during their participation in the study were censored at the time of oophorectomy. A total of 32 cases of ovarian cancer were reported in STAR.

The data showed no statistically significant difference in the incidence rate of ovarian cancer between the two treatment groups (Table 14).

Table 14. Ovarian Cancer in STAR

	Raloxifene N=6787		Tamoxifen N=6813		RR [a] (95% CI)
Site of Cancer	n	IR	n	IR	
Ovary	18	0.7	14	0.5	1.27 (0.60,2.76)

Abbreviations: CI = confidence interval; IR = incidence rate per 1000 patient-years; n = patients with event; N = patients comprising primary analysis dataset with at least one intact ovary at baseline; RR = risk ratio.

[a] Risk ratio for patients in the raloxifene group compared with those in the tamoxifen group.

4.3.3.2.2.4. All Invasive Cancers

Raloxifene, compared with tamoxifen, showed no statistically significant difference (p-value=0.448) in the total number of patients developing an invasive cancer other than breast or uterine cancer. A total of 207 (2.12%) invasive cancer events occurred in the raloxifene group and 191 (1.96%) in the tamoxifen group (Table APP.9 [Appendix 1.2]).

4.3.3.2.3. Cardiovascular Events

4.3.3.2.3.1. Ischemic Heart Disease

Raloxifene, compared with tamoxifen, showed no statistically significant difference in the incidence of ischemic heart disease (MI, severe angina, and acute ischemic syndrome, combined) (RR 1.10, CI 0.86-1.41). Moreover, the data showed no statistically significant treatment group difference in incidence when the event types were analyzed individually.

4.3.3.2.3.2. Stroke and Transient Ischemic Attack

Based upon STAR exclusion criteria, patients who had stroke risk factors (history of cerebrovascular accident, TIA, uncontrolled atrial fibrillation, uncontrolled hypertension, and uncontrolled diabetes mellitus) or who were taking coumadin were not eligible to enroll in the study.

Accordingly, the overall incidence of stroke was low, with a total of 110 reported strokes (54 in the raloxifene group and 56 in the tamoxifen group). Raloxifene, compared with tamoxifen, showed no statistically significant difference in the incidences of stroke (RR 0.96, 95% CI 0.65-1.42) or TIA (RR 1.15, 95% CI 0.75-1.77).

4.3.3.2.3.3. Death due to Stroke

Though the number of deaths due to stroke in STAR through 31 December 2005 was low (N=12 deaths due to stroke [0.06%]), the information is provided primarily as a reference for the placebo-controlled RUTH data (Section 4.3.1.2.3.4 [Death due to Stroke]). Of the 12 deaths due to stroke, 5 (0.05%) and 7 (0.07%) occurred within the raloxifene and tamoxifen groups, respectively.

As of 30 September 2006, the cumulative total number of deaths due to stroke is 14, 5 (0.05%) and 9 (0.09%) for the raloxifene and tamoxifen groups, respectively (Table APP.7 [Appendix 1.2]).

4.3.3.2.3.4. Cardiac Arrhythmias

Categories for arrhythmia classification include ventricular arrhythmias, cardiac conduction disorders, supraventricular arrhythmias, and other arrhythmias.

Table 15 summarizes investigator-reported AE data for five cardiac arrhythmia event categories. The most frequently reported category was supraventricular arrhythmia (raloxifene, 50 [0.51%]; tamoxifen 40 [0.41%]).

Table 15. Cardiac Arrhythmia Events by Decreasing Frequency in STAR

	Raloxifene		Tamoxifen	
Arrhythmia Event	**n**	**%**	**n**	**%**
Supraventricular arrhythmia[a]	50	0.5	40	0.4
Arrhythmia other	22	0.2	18	0.2
Ventricular arrhythmia	11	0.1	9	0.1
Nodal junctional arrhythmia/dysrhythmia	9	0.1	4	<0.1
Prolonged QTc interval	1	<0.1	3	<0.1

Abbreviations: n = number of events.

[a] Includes atrial fibrillation (NCI CTC version 2.0).

STAR data collection included a Cardiovascular Event form (CVEVT), which was to be completed for each CV-related inpatient or outpatient procedure. Appendix 1.2 provides a summary of this CV event form review including additional arrhythmia information.

4.3.3.2.4. Cataracts and Cataract Surgery

Of the 16,675 patients in the STAR primary analysis dataset who were cataract-free at baseline, statistically significantly 22% fewer patients developed cataracts in the raloxifene than the tamoxifen group (Table 16).

Similarly, statistically significantly fewer patients had cataract surgery in the raloxifene than the tamoxifen group (Table 16), corresponding to a 19% lower incidence of cataract surgery in the raloxifene group.

Table 16. Cataracts and Cataract Surgery in STAR

Event	Raloxifene N=8333 [a]		Tamoxifen N=8342 [a]		
	n	IR	n	IR	RR [b] (95% CI)
Developed cataracts during follow-up	343	10.34	435	13.19	0.78 (0.68,0.91)
Developed cataracts and had cataract surgery	240	7.17	295	8.85	0.81 (0.68,0.96)

Abbreviations: CI = 95% confidence interval; IR = incidence rate per 1000 patient-years; n = patients with event, N = patients in the primary analysis dataset who were free of cataracts at baseline; RLX = raloxifene; RR = risk ratio; TMX = tamoxifen.

[a] Patients who were free of cataracts at baseline were included (TMX, 8342 of 9736; RLX, 8333 of 9751).

[b] Risk ratio for patients in the raloxifene group compared with those in the tamoxifen group.

4.3.3.2.5. Hot Flashes, Vaginal Discharge, and Tolerability

Tolerability of therapy is an important consideration in any drug meant to be used clinically for risk reduction. Since discontinuations from therapy can indicate tolerability issues, it is worth noting that, hot flashes, the most frequent AE leading to discontinuation of therapy in STAR, led to a significantly higher percentage of discontinuations for patients in the tamoxifen group (646 of 9736 [6.60%]) than the raloxifene group (392 of 9751 [4.00%]; p <0.001).

More patients in the tamoxifen than the raloxifene group discontinued therapy because of vaginal discharge, though the percentage of discontinuations was low for both treatment groups (tamoxifen, 0.31%; raloxifene, 0.11%). In general, more patients in the tamoxifen than raloxifene group (32% versus 20%, respectively) reported vaginal discharge. Increased vaginal discharge is a known AE associated with the use of tamoxifen (Nolvadex package insert 2003), but does not appear to be significantly associated with raloxifene treatment (Martino et al. 2005).

4.3.3.2.6. Fracture Events

Regardless of location, bone fractures were reported for 867 of 9751 (8.9%) patients in the raloxifene group and 941 of 9736 (9.7%) patients in the tamoxifen group (p=0.063).

Hip, spine, and Colles' fractures of the wrist were prespecified as osteoporotic fractures. There was no significant difference between treatment groups in the combined incidence of hip, spine, and Colles' fractures of the wrist (RR 0.97, 95% CI 0.73-1.27) or in the number of fractures at each individual site.

4.3.4. STAR Safety Conclusions

The STAR study examined safety in postmenopausal women at increased risk for invasive breast cancer.

The following bullets summarize the key safety observations from the comparative assessment of raloxifene versus tamoxifen treatment in this patient population:

- **Venous Thromboembolic Events**: Raloxifene was associated with statistically significant 31% fewer VTEs (DVT and PE) than tamoxifen.

- **Uterine cancer:** Though not statistically significant, raloxifene was associated with 39% fewer uterine endometrial cancers than tamoxifen. Approximately 51% of patients in STAR had a history of hysterectomy at baseline (5036 in the raloxifene group and 4997 in the tamoxifen group).
- **Endometrial hyperplasia:** Raloxifene, compared with tamoxifen, demonstrated a statistically significant 83% lower incidence of endometrial hyperplasia (including atypical endometrial hyperplasia, a known clinical precursor of endometrial adenocarcinoma).
- **Hysterectomy**: Raloxifene, compared with tamoxifen, demonstrated statistically significant 63% fewer postbaseline noncancer-related hysterectomies (raloxifene, 92/4715 versus tamoxifen, 246/4739). During the period of study follow-up, 5.2% of patients in the tamoxifen group and 1.9% of patients in the raloxifene group had hysterectomies.
- **Stroke:** Raloxifene, compared with tamoxifen, showed no statistically significant difference in the incidences of stroke or death due to stroke. A total of 12 deaths due to stroke were reported (raloxifene, 5/9751 [0.05%] versus tamoxifen, 7/9736 [0.07%]) tamoxifen.
- **Cataracts and cataract surgery:** Raloxifene, compared with tamoxifen, showed a statistically significantly lower incidence of both cataract development (22% decrease) and cataract surgery (19% decrease).

4.4. Overall Safety Conclusions

STAR, MORE, RUTH, and the follow-up study of MORE participants, CORE, examined the safety of raloxifene in more than 37,000 postmenopausal women representing three distinct populations. Patients in these studies had multiple years of study drug exposure, with more than 8000 patients having had 5 or more years of exposure.

For postmenopausal women at increased risk for invasive breast cancer, STAR data support that raloxifene has a more favorable safety profile than that of tamoxifen.

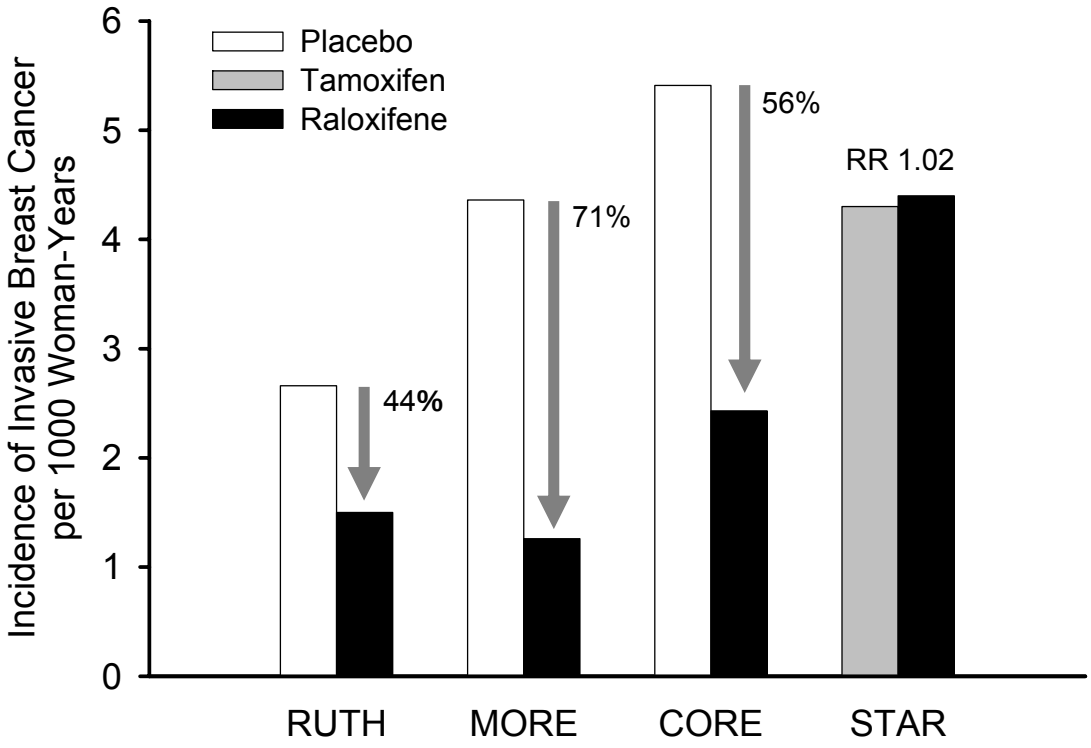
For postmenopausal women with osteoporosis, MORE established the safety profile for raloxifene HCl 60 mg/day. The current US package insert includes the MORE safety data, and these data are supported by the approximately 12 million patient-years (estimated 22 million patients) of worldwide clinical experience with marketed raloxifene.

5. Summary of Benefits and Risks

Raloxifene has been approved to prevent and treat osteoporosis in postmenopausal women since 1997 and 1999, respectively. For these indications, raloxifene has a well established, favorable benefit/risk profile. Since first approval through 30 November 2006, an estimated 22 million patients in 88 countries worldwide have received raloxifene, representing approximately 12 million patient-years of treatment.

MORE was a Phase 3 registration study of 7705 postmenopausal women with osteoporosis that supported the treatment indication in the current raloxifene label. The significantly lower incidence of invasive breast cancer observed in MORE and its follow-up study, CORE, has been confirmed in two additional randomized clinical studies, RUTH and STAR.

Collectively, data from these four clinical studies provide substantial evidence that postmenopausal women who receive raloxifene reduce their risk for invasive breast cancer (Figure 19). MORE and CORE demonstrated that raloxifene, compared with placebo, significantly reduced the risk of invasive breast cancer in postmenopausal women with osteoporosis. STAR demonstrated that raloxifene, comparable to tamoxifen, reduced the risk of invasive breast cancer in postmenopausal women at increased risk of invasive breast cancer. RUTH demonstrated that raloxifene, compared with placebo, significantly reduced the risk of invasive breast cancer in postmenopausal women at risk for major coronary events.



Abbreviation: RR = risk ratio for raloxifene:tamoxifen.
Note: Invasive breast cancer was a secondary endpoint in MORE.

Figure 19. Effect of raloxifene on the incidence rate of invasive breast cancer in the MORE, CORE, STAR, and RUTH studies.

Based on the balance between this consistent clinical benefit and the risk of raloxifene therapy, Lilly is seeking indication language to reflect those women in whom the benefits of raloxifene therapy most clearly outweigh the risks: postmenopausal women with osteoporosis and postmenopausal women at high risk for breast cancer. The benefits and risks of raloxifene therapy in these women will be discussed in the following sections.

Despite the demonstrated benefit of raloxifene to reduce the risk of invasive breast cancer in women at risk for major coronary events, the overall benefit relative to potential risk is only slightly positive in these women. Lilly is not requesting an indication for the use of raloxifene to reduce the risk of invasive breast cancer in this population.

5.1. Summary of Benefits and Risks in Postmenopausal Women with Osteoporosis

The FDA has found raloxifene to be safe and effective for the prevention and treatment of postmenopausal women with osteoporosis (Evista package insert 2003).

Table 17 summarizes IRs and absolute risk differences in terms of fewer versus excess cases (outcomes) associated with raloxifene treatment, compared with placebo, for clinically relevant endpoints in MORE.

Table 17. Efficacy and Important Safety Outcomes in MORE Incidence Rates per 1000 Patient-years and Absolute Risk Difference

	MORE				
Outcome	**Raloxifene IR[a]**	**Placebo IR[b]**	**Fewer Cases[c]**	**Excess Cases[c]**	**p-value∗**
Invasive breast cancer[d]	1.26	4.36	3.10		<0.001
Noninvasive breast cancer[d]	0.34	0.57	0.23		0.466
Death	3.63	4.13	0.50		0.522
Death due to stroke	0.51	0.69	0.18		0.522
Stroke	5.16	6.42	1.26		0.191
Clinical vertebral fracture[d]	7.08	12.27	5.19		<0.001
Deep vein thrombosis	2.50	0.92		1.58	0.006
Pulmonary embolism	1.25	0.46		0.79	0.053
Endometrial cancer[e]	0.59	0.74	0.15		0.528
Ovarian cancer	0.34	0.69	0.35		0.201

Abbreviations: IR = incidence rate per 1000 patient-years.

[a] The number of observed events per 1000 treated patients per year.

[b] The number of observed events per 1000 untreated patients per year.

[c] Per 1000 patients treated with raloxifene versus placebo per year.

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

[e] Only patients with an intact uterus were considered for the denominator (raloxifene denominator = 3960; placebo denominator = 1999).

∗ Obtained from log-rank test.

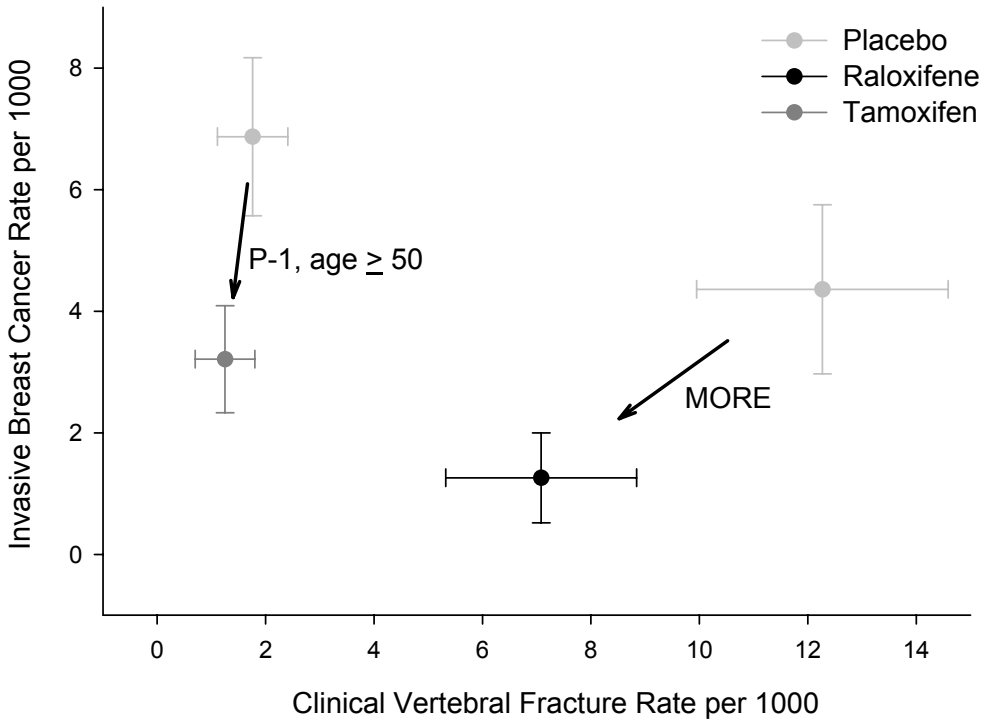
Raloxifene treatment was associated with 3.1 fewer cases of invasive breast cancer per 1000 treated-women per year, compared with placebo.

Figure 20 graphically demonstrates the effect of raloxifene treatment to significantly reduce the risk of both invasive breast cancer and clinical vertebral fracture in the MORE population of postmenopausal women with osteoporosis. For reference, the diagram also demonstrates the effect of tamoxifen treatment to reduce the risk of both invasive breast cancer and clinical vertebral fractures for women 50 years of age or older, at high risk for breast cancer, in the P-1 study of tamoxifen.

As shown in both Table 17 and Figure 20, the magnitude of the effect of raloxifene on invasive breast cancer in postmenopausal women with osteoporosis (MORE) is substantial and comparable to the effect seen in P-1 for women, 50 years of age or older,

at high risk for breast cancer, where tamoxifen was shown to decrease the risk of invasive breast cancer by 3.59 cases per 1000 women per year (Table 18).

Notably, this clinically important reduction in risk of invasive breast cancer adds further benefit to the established favorable benefit/risk profile of raloxifene to reduce vertebral fracture risk in postmenopausal women with osteoporosis.



Note: Error bars on the point estimates of the rates are 95% confidence intervals. Arrows indicate the effect of treatment. For MORE, results are shown for the raloxifene HCl 60 mg/day only.

Figure 20. Incidence rates of invasive breast cancer and clinical vertebral fracture per 1000 women-years for P-1 (age ≥50) and MORE.

The safety profile of raloxifene in postmenopausal women with osteoporosis is well established and is reflected in current labeling. No additional safety findings were identified in the long-term MORE follow-up study, CORE. The observations of cholelithiasis and an increased risk of death due to stroke seen in the RUTH population of postmenopausal women at risk for major coronary events have been disclosed (Section 4.3.1.2.3.4).

The effect of raloxifene to reduce the incidence of invasive breast cancer first observed in MORE has now been confirmed in RUTH, STAR, and the long-term MORE follow-up study, CORE. This additional benefit improves the established favorable benefit/risk

profile of raloxifene in postmenopausal women with osteoporosis. It is essential that the product label reflects this important information to inform the postmenopausal woman weighing the benefits and risks of raloxifene therapy to reduce her risk of vertebral fracture.

5.2. Summary of Benefits and Risks in Postmenopausal Women at Increased Risk of Breast Cancer

STAR convincingly demonstrated that raloxifene is comparable to tamoxifen and is, therefore, effective in reducing the risk of invasive breast cancer in postmenopausal women at increased risk for the disease (Gail model-based 5 year predicted risk of at least 1.66% or with a history of LCIS). This is further supported by the demonstration that raloxifene reduced the risk of invasive breast cancer relative to placebo in women whose predicted 5-year risk of invasive breast cancer greater than or equal to 1.66% in RUTH.

Raloxifene and tamoxifen were comparable in reducing the risk of invasive breast cancer regardless of age, history of hysterectomy, predicted 5-year risk of invasive breast cancer, family history of breast cancer, history of atypical hyperplasia, or history of LCIS.

The magnitude of the benefit of raloxifene in reducing the risk of invasive breast cancer in high risk women is comparable to tamoxifen (Table 18). For reference, in the P-1 study, for women 50 years of age or older at high risk for breast cancer, tamoxifen decreased the risk of invasive breast cancer by 3.59 cases per 1000 women per year (Table 18).

Importantly, it is particularly impressive that raloxifene, comparable to tamoxifen, reduced the risk of invasive breast cancer in women who were at very high risk, such as those with a 5-year predicted risk of invasive breast cancer greater than 5% and those with a history of LCIS or atypical hyperplasia (Table 6).

Table 18. Efficacy and Important Safety Outcomes in STAR and P-1 Incidence Rates per 1000 Patient-years and Absolute Risk Differences

	STAR				P-1 (age ≥50 years)			
Outcome	**TMX IR[c]**	**RLX IR[c]**	**ARD[a]**	**p-value**	**TMX IR[c]**	**PLB IR[c]**	**ARD[b]**	**p-value**
Invasive breast cancer	4.30	4.40	+0.10	0.832	3.21	6.80	-3.59	<0.001
Noninvasive breast cancer	1.54	2.12	+0.58	0.057	1.58	2.04	-0.46	0.334
Death	2.76	2.62	-0.14	0.678	3.19	3.70	-0.51	0.432
Death due to Stroke	0.18	0.13	-0.05	0.552	0.19	0.13	+0.06	0.656
Stroke	1.42	1.36	-0.06	0.819	2.20	1.26	+0.94	0.044
Clinical vertebral fracture	1.47	1.46	-0.01	0.968	1.25	1.76	-0.51	0.239
Deep vein thrombosis	2.35	1.69	-0.66	0.041	1.51	0.88	+0.63	0.105
Pulmonary embolism	1.47	0.96	-0.51	0.037	1.00	0.31	+0.69	0.016
Endometrial cancer[d]	1.99	1.21	-0.78	0.055	3.05	0.76	+2.29	<0.001
Ovarian Cancer	0.52	0.66	+0.14	0.508	0.64	0.48	+0.16	0.577

Abbreviations: ARD = absolute risk difference; IR = incidence rate per 1000 patient-years; PLB = placebo; RLX = raloxifene; TMX = tamoxifen.

[a] In this column, a negative ARD means that X fewer events per 1000 patients per year, where X = the numerical value of the ARD, are associated with raloxifene versus tamoxifen treatment while a positive ARD means that an excess of X events are associated with raloxifene versus tamoxifen treatment.·

[b] In this column, a negative ARD means that X fewer events per 1000 patients per year, where X = the numerical value of the ARD, are associated with tamoxifen versus placebo treatment while a positive ARD means that an excess of X events are associated with tamoxifen versus placebo treatment.·

[c] The number of observed events per 1000 patients per year.

[d] Only patients with an intact uterus at baseline were used in the denominator (for STAR: tamoxifen, n=4739; raloxifene, n=4715).

Fewer noninvasive breast cancer events occurred in the tamoxifen than the raloxifene group (60 versus 83, respectively) in STAR. Though the difference between treatments did not reach statistical significance (p=0.052) either in the overall or the DCIS categories of noninvasive breast cancer, this distinction may be clinically important for some women considering therapy with a SERM.

The totality of the data from STAR and the placebo-controlled studies suggest that raloxifene has no effect on the incidence rate of noninvasive breast cancer. Invasive breast cancer is much more common than noninvasive breast cancer and, in contrast to DCIS, is not universally curable. Importantly, P-1 demonstrated that the magnitude of the risk reduction for invasive breast cancer with tamoxifen (3.59 fewer cases per 1000 treated-women per year) is much greater than that for noninvasive disease (0.46 fewer cases per 1000 treated-women per year) in postmenopausal women 50 years of age or older (Table 18). The possibility of a difference in treatment effect on noninvasive breast cancer between raloxifene and tamoxifen is of unclear clinical relevance, especially in postmenopausal women.

In STAR, raloxifene had a better safety profile than tamoxifen. The long-term, placebo-controlled clinical studies with raloxifene (MORE and RUTH) have demonstrated that raloxifene has no effect on uterine AEs (MORE results shown in Table 17). In contrast, placebo-controlled studies of tamoxifen have clearly demonstrated that tamoxifen increases the incidence of uterine adverse events, including endometrial cancer and uterine sarcoma (Fisher et al. 1998, Cuzick et al. 2003, Nolvadex package insert 2003). The STAR uterine safety findings are consistent with these placebo-controlled data. The ARDs for endometrial cancer (-0.78), for noncancer related hysterectomy (-8.41 [raloxifene, IR 4.84; tamoxifen, IR 13.25]; Table ES.7), and for endometrial hyperplasia (-4.52 [raloxifene, IR 5.42; tamoxifen, IR 0.90]; Table 15) are three clinically relevant differences between raloxifene and tamoxifen that should factor into the patient's benefit risk decision.

In addition to the effect on uterine safety, other safety benefits favor raloxifene. While raloxifene and tamoxifen both increase the risk of VTEs, STAR showed that raloxifene compared with tamoxifen was associated with statistically significantly fewer VTEs (RR 0.69, CI 0.53-0.90), including DVT and PE. Compared with tamoxifen, raloxifene decreased the incidence of DVT by 0.66 cases and PE by 0.51 cases per 1000 treated-women per year (Table 18). Raloxifene was associated with statistically significantly fewer cataracts and cataract surgery, compared with tamoxifen (Table 18). No statistically significant differences were noted between treatment groups in the incidence of other safety outcomes.

In summary, raloxifene is comparable to tamoxifen in reducing the risk of invasive breast cancer in postmenopausal women at increased risk for the disease. In STAR, the safety profile of raloxifene in women at increased risk of invasive breast cancer was more favorable than tamoxifen, particularly in the area of endometrial safety. Postmenopausal women at increased risk for invasive breast cancer should have raloxifene as an additional therapeutic option.

5.3. Perspective on Risk Reduction in the Context of Other Established Prevention Therapies

One might question if it is reasonable for postmenopausal women to take a therapy which reduces the risk of a serious disease by approximately 3 events per year per 1000 women. Other established prevention therapies can help to provide perspective on the ARD of invasive breast cancer with raloxifene.

For example, the ARD for atorvastatin (Lipitor®), which is approved for reduction of the risk of MI in patients at high risk for CHD, is -3.4 per 1000 patient-years, compared with placebo (Sever et al. 2005). Based on this ARD, 294 at risk patients would have to be treated with atorvastatin for 1 year to prevent one MI. In considering the use of atorvastatin, patients and prescribers must weigh this benefit against the rare but serious AEs of liver failure and rhabdomyolysis associated with atorvastatin.

Table 19 summarizes ARDs for additional examples of prevention therapies. For each therapy and disease condition, the table provides the ARDs per 1000 patient-years and the number of patients needed to treat for 1 year to prevent one disease outcome (NNT). Tamoxifen and raloxifene are included for comparison.

Table 19. Absolute Risk Difference and Numbers Needed to Treat to Prevent One Event

Therapy	Event	ARD	NNT
Atorvastatin[a]	MI and CHD death	-3.4	294
Antihypertensives[b]	Strokes	-2.8	370
	Coronary event	-2.4	417
Aspirin[c]	MI	-1.4	753
Tamoxifen[d]	Invasive breast cancer	-3.3	303
Raloxifene[e]	Invasive breast cancer	-3.1	323
Raloxifene[f]	Invasive breast cancer	-3.0	335
Raloxifene[g]	Invasive breast cancer	-1.2	862

Abbreviations: ARD = absolute risk difference per 1000 patient-years; CHD = coronary heart disease; MI = myocardial infarction; NNT = number of patients needed to treat for 1 year to prevent one outcome.

[a] Sever et al. 2003.

[b] MRC Working Party 1992.

[c] Berger et al. 2006.

[d] Fisher et al. 1998; ARD for all tamoxifen-treated patients in P-1.

[e,f,g] ARDs for raloxifene versus placebo in MORE, CORE, and RUTH, respectively.

The ARDs for raloxifene for invasive breast cancer in postmenopausal women with osteoporosis in MORE and its follow-up study, CORE, were comparable to that of tamoxifen in P-1 and atorvastatin in the ASCOT trial. Further, raloxifene appears to be similarly efficient to the use of antihypertensive medications and aspirin with regard to ARD and NNT to prevent adverse events.

5.4. Conclusions

Based on three randomized clinical studies and one follow-up study that together enrolled more than 37,000 postmenopausal women and included more than 76,000 patient-years of exposure to raloxifene, substantial evidence has been provided in NDA 22-042, and in this document, demonstrating the clinical efficacy of raloxifene in reducing the risk of invasive breast cancer in postmenopausal women. The totality of the evidence demonstrates a favorable balance of benefits versus risks and supports that it is appropriate to use raloxifene to reduce the risk of invasive breast cancer in postmenopausal women at increased risk for invasive breast cancer or with osteoporosis.

Women considering or already taking raloxifene as an osteoporosis therapy should be informed about the potential benefit of raloxifene treatment to reduce their risk of invasive breast cancer. Further, raloxifene, like tamoxifen, should now be considered an option for reducing the risk of invasive breast cancer in postmenopausal women at increased risk for the disease.

6. References

Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, McNabb MA, Wenger NK, for the Raloxifene Use for The Heart (RUTH) Trial Investigators. 2006. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. New Engl J Med 355(2):125-137.

Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. 2006. Aspirin for the primary prevention of cardiovascular events in men and women. JAMA 295:306–13.

Bryant HU, Wilson PK, Adrian MD, Cole HW, Phillips DL, Dodge JA, Grese TA, Sluka JP, Glasebrook AL. 1996. Selective estrogen receptor modulators: pharmacological profile in the rat uterus. J Soc Gynecol Invest 3(2 Suppl 1):152A.

Buzdar AU, Marcus C, Holmes F, Hug V, Hortobagyi G. 1988. Phase II evaluation of LY156758 in metastatic breast cancer. Oncology 45:344-345.

Cancer Facts and Figures 2007. American Cancer Society web page. Available at http://www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf. Accessed 7 February 2007.

Clemens JA, Bennett DR, Black LJ, Jones CD. 1983. Effects of a new antiestrogen, keoxifene (LY156758), on growth of carcinogen-induced mammary tumors and on LH and prolactin levels. Life Sci 32(25):2869-75.

Costantino JP, Gail MH, Pee D, Anderson S, Redmond CK, Benichou J, Wieand HS. 1999. Validation studies for models projecting the risk of invasive and total breast cancer incidence. J Natl Cancer Inst 91(18):1541-1548.

Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, Boyle P. 2003. Overview of the main outcome in breast-cancer prevention trials. The Lancet 361:296-300.

Eastell R, Hannon RA, Cuzick J, Dowsett M, Clack G, Adams JE, on behalf of the ATAC Trialists' group. 2006. Effect of an aromatase inhibitor on BMD and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial (18233230). J Bone Miner Res 21(8):1215-1223.

Evista [package insert]. 2003. Indianapolis, IN: Eli Lilly & Co.

Fisher B, Costantino J, Redmond C, Poisson R, Bowman D, Couture J, Dimitrov NV, Wolmark N, Wickerham DL, Fisher ER, Margolese R, Robidoux A, Shibata H, Terz J, Paterson AHG, Feldman MI, Farrar W, Evans J, Lickley HL, Ketner M, et al. 1989. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N Engl J Med 320:479-484.

Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmack N, and other National Surgical Adjuvant Breast and Bowel Project investigators. 1998. Tamoxifen for prevention of breast cancer: report of the National

Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 90:1371-1388.

Freedman AN, Graubard BI, Rao SR, McCaskill-Stevens W, Ballard-Barbash R, Gail MH. 2003. Estimates of the number of US women who could benefit from tamoxifen for breast cancer chemoprevention. JNCI 95(7):526-532.

Gradishar W. and Cella D. 2006. Selective estrogen receptor modulators and prevention of invasive breast cancer. JAMA 295:2784-2786.

Jones CD, Jevnikar MG, Pike AJ, Peters MK, Black LJ, Thompson AR, Falcone JF, Clemens JA. 1984. Antiestrogens. 2. structure-activity studies in a series of 3-aroyl-2-arylbenzo[b]thiophene derivatives leading to [6-hydroxy-2-(4-hydroxyphenyl)benzo[b] thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl]methanone hydrochloride (LY156758), a remarkably effective estrogen antagonist with only minimal intrinsic estrogenicity. J Med Chem 27(8):1057-1066.

Jones PS, Parrott E, White INH. 1999. Activation of transcription by estrogen receptor alpha and beta is cell type- and promoter-dependent. J Biol Chem 274:32008-32014.

Kauffman RF, Bryant HU. 1995. Selective estrogen receptor modulators. Drug News Perspect 8:531-539.

Kelloff GJ, Lippman SM, Dannenberg AJ, Sigman CC, Pearce HL, Reid BJ, Szabo E, Jordan VC, Spitz MR, Mills GB, Papadimitrakopoulou VA, Lotan R, Aggarwal BB, Bresalier RS, Kim J, Arun B, Lu KH, Thomas ME, Rhodes HE, Brewer MA, Follen M, Shin DM, Parnes HL, Siegfried JM, Evans AA, Blot WJ, Chow WH, Blount PL, Maley CC, Wang KK, Lam S, Lee JJ, Dubinett SM, Engstrom PF, Meyskens FL Jr, O'Shaughnessy J, Hawk ET, Levin B, Nelson WG, Hong WK, for the AACR Task Force on Cancer Prevention. 2006. Progress in chemoprevention drug development: the promise of molecular biomarkers for prevention of intraepithelial neoplasia and cancer--a plan to move forward. Clin Cancer Res 12(12):3661-3697.

Land SR, Wickerham DL, Costantino JP, Ritter MW, Vogel VG, Lee M, Pajon ER, III Wade JL, Dakhil S, Lockhart JB, Wolmark N, Ganz PA. 2006. Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention. The NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA 295:2742-2751.

Martino S, Costantino J, McNabb M, Mershon J, Bryant K, Powles T, Secrest RJ. 2004. The role of selective estrogen receptor modulators in the prevention of breast cancer: Comparison of the clinical trials. The Oncologist 9:116-125.

Martino S, Disch D, Dowsett SA, Keech CA, Mershon JL. 2005. Safety assessment of raloxifene over eight years in a clinical trial setting. Curr Med Res Opin 21(9):1441-1452.

Montano MM, Ekena K, Delage-Mourroux R, Chang W, Martini P, Katzenellenbogen BS. 1999. An estrogen receptor-selective coregulator that potentiates the effectiveness of antiestrogens and represses the activity of estrogens. Proc Natl Acad Sci USA 96:6947-6952.

Montgomery BE, Daum GS, Dunton CJ. 2004. Endometrial hyperplasia: a review. Obstet Gynecol Surv 59(5):368-378.

Mosca L, Barrett-Connor E, Wenger NK, Collins P, Grady D, Kornitzer M, Moscarelli E, Paul S, Wright TJ, Helterbrand JD, Anderson PW. 2001. Design and methods of the raloxifene use for the heart (RUTH) study. Am J Cardiol88:392-395.

MRC Working Party. 1992. Medical Research Council trial of treatment of hypertension in older adults: principle results. Br Med J 304:405-412.

Nolvadex [package insert]. 2003. Wilmington, DE: AstraZeneca Pharmaceuticals LP.

Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowsi RT, Feuer EJ, Edwards BK, and Berry D. 2007. The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med 356(16) :1670-1674.

Rothmann M, Li N, Chen G, Chi G, Temple R, Tsou HH. 2003. Design and analysis of non-inferiority mortality trials in oncology. Statistics in Medicine 22:239-264.

[SEER] Surveillance, Epidemiology, and End Results (SEER) Program page. SEER*Stat Databases. [NCI] National Cancer Institute web site. Available at: http://www.seer.cancer.gov. Accessed 18 June 2007.

Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. 2003. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. The Lancet 361:1149-1158.

Sever PS, Poulter NR, Dahlof B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. 2005. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA). Diabetes Care 28(5):1151-1157.

Sporn MB, Dowsett SA, Mershon J, Bryant HU. 2004. Role of raloxifene in breast cancer prevention in postmenopausal women: clinical evidence and potential mechanisms of action. Clinical Therapeutics 26:830-840.

Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, Bevers TB, Fehrenbacher L, Pajon ER Jr, Wade JL 3rd, Robidoux A, Margolese RG, James J, Lippman SM, Runowicz CD, Ganz PA, Reis SE, McCaskill-Stevens W, Ford LG, Jordan VC, Wolmark N, for the National Surgical Adjuvant Breast and Bowel Project (NSABP). 2006. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 295(23):2727-2741.

[WHO] World Health Organization. 1996. Research on the menopause in the 1990s: report of a WHO Scientific Group. Geneva: World Health Organization. WHO Technical Report Series 866. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_866.pdf. Accessed 12 October 2006.

Appendix 1. Supplementary Clinical Study Information

Table APP.1. Summary of Key Features of the STAR, MORE, CORE, and RUTH Studies

Study ID	Study Dates	Study Design Treatment Regimen	Patient Population	Study Objectives Primary	Study Objectives Secondary
STAR	July 1999 - Dec 2005	Phase 3 randomized, double-blind, active-controlled, multicenter (United States, Puerto Rico, and Canada) tamoxifen CT 20 mg/day **OR** raloxifene HCl 60 mg/day	Postmenopausal women at increased risk for breast cancer[a] Enrolled: 19,747 Mean Age: 58.5 yrs.	**Compared** to tamoxifen, raloxifene significantly reduces the incidence rate of invasive breast cancer; **Compared** to raloxifene, tamoxifen significantly reduces the incidence rate of invasive breast cancer; **OR** **The** statistical superiority of one of the treatments cannot be demonstrated and the choice of therapy should be based on benefit/risk considerations.	Evaluate the effect of each treatment on: the incidences of DCIS; LCIS; endometrial cancer; ischemic heart disease; fractures of the hip, spine, or Colles' fractures of the wrist; and patients' quality of life. Assess the toxicity and side effects of each treatment.
MORE	Dec 1994 - Aug 1999	Phase 3 randomized, double-blind, placebo-controlled, global, multicenter placebo **OR** raloxifene HCl 60 mg/day **OR** raloxifene HCl 120 mg/day	Postmenopausal women with osteoporosis Enrolled: 7705 Mean Age: 67 yrs.	Compare the effect of raloxifene versus placebo on: **rate** of new vertebral fractures; **lumbar** spine and femoral neck bone mineral density (BMD).	Compare the effect of raloxifene versus placebo on: **risks** of breast and endometrial cancers; CV disease; **cognitive** and neuropsycho-motor function, dementia, Alzheimer's disease; **total** body BMC and radial BMD; rates of new nonvertebral fractures alone and combined with vertebral fractures; biochemical markers of bone metabolism.

continued

Table APP.1. Summary of Key Features of the STAR, MORE, CORE, and RUTH Studies (concluded)

Study ID	Study Dates	Study Design Treatment Regimen	Patient Population	Study Objectives Primary	Study Objectives Secondary
CORE	Oct 1999 - Aug 2003	Phase 3, nonrandomized[b], double-blind, placebo-controlled, global, multicenter Placebo **OR** raloxifene HCl 60 mg/day	MORE enrollees Enrolled: 4011 Mean age: 71 yrs.	Compare long-term effects of raloxifene versus placebo on: **incidence** of invasive breast cancer.	Compare long-term effects of raloxifene versus placebo on the incidences of: **invasive**, ER+ breast cancer; and **nonvertebral** fractures.
RUTH	June 1998 - Nov 2005	Phase 3, randomized, double-blind, global, multicenter. Placebo **OR** raloxifene HCl 60 mg/day	Postmenopausal women at risk for major coronary events Enrolled: 10,101 Mean age: 68 yrs.	Assess whether raloxifene versus placebo reduced the incidences of: **the** combined coronary endpoint of coronary death, nonfatal (including silent) MI, or hospitalized ACS other than MI; **invasive** breast cancer.	Assess whether raloxifene versus placebo changed the incidences of: **CV** death, nonfatal MI, hospitalized ACS other than MI, myocardial revascularization, or stroke; separately and as a combined endpoint: **Coronary** death, all-cause mortality, hospitalized ACS, all-cause hospitalization, noncoronary arterial revascularization or nontraumatic lower extremity amputation: **All** breast cancer; **Fractures;** **VTEs**.

Abbreviations: ACS = acute coronary syndrome; BMC = bone mineral content; CV = cardiovascular; DCIS = ductal carcinoma in situ; ER+ = Estrogen-receptor positive; LCIS = lobular carcinoma in situ; VTEs = venous thromboembolic events; Yrs = years.

[a] Defined in the STAR protocol as age ≥35 years, with a histology diagnosis of LCIS treated by local incision only, or a minimum projected 5-year probability of invasive breast cancer of at least 1.66%, as determined from the breast cancer risk assessment profile generated by the NSABP (Costantino et al. 1999).

[b] Patients maintained their group assignment from MORE and were not rerandomized.

Appendix 1.1. Efficacy Information

Estimation of Number of Invasive Breast Cancer Cases if there was an Untreated Arm in STAR

Given that the total number of person years of follow-up (PYF) for invasive breast cancer for both treatment groups is 79,173, then the expected PYF in one treatment group is 79,173 ÷ 2 =39,586.5.

Given that the average 5-year Gail probability of getting breast cancer is 4.03% or 0.0403, then the expected annual average rate of invasive breast cancer, λ, in an untreated population can be found by solving for λ in the equation: $0.0403 = 1\text{-}e^{-\lambda t}$; where t is 5 years. Thus, from this equation $\lambda = 0.0082$.

Then, the expected number of invasive breast cancer cases (EC) among an untreated population can be found by solving the equation: EC = PYR x λ; where PYR = 39586.5 and $\lambda = 0.0082$. Thus, EC = 39586.5 x 0.0082 = 324.6, which rounds to 325.

This estimate is based on the Gail model projection of risk and it does not involve any assumptions about an effect of tamoxifen.

Table APP.2. Tumor Characteristics of Invasive Breast Cancers by Treatment Group in STAR

Tumor Characteristic	Number of Events (%[a])		Incidence Rate per 1000 Patient-Years			RR (95% CI)[c]
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference[b]	
Histology						
Infiltrating ductal	129 (76.8)	133 (76.9)	3.30	3.38	-0.08	1.02 (0.80-1.32)
Infiltrating lobular	21 (12.5)	14 (8.1)	0.54	0.36	0.18	0.66 (0.31-1.37)
Infiltrating ductal & lobular	2 (1.2)	6 (3.5)	0.05	0.15	-0.10	2.98 (0.53-30.21)
Infiltrating ductal & other	1 (0.6)	1 (0.6)	0.03	0.03	0.00	0.99 (0.01-78.03)
Infiltrating lobular & other	1 (0.6)	1 (0.6)	0.03	0.03	0.00	0.99 (0.01-78.03)
Other	13 (7.7)	16 (9.3)	0.33	0.41	-0.07	1.22 (0.55-2.76)
Unknown	1 (0.6)	2 (1.2)	0.03	0.05	-0.03	1.99 (0.10-117.30)
ER status						
Positive	120	115	3.07	2.93	0.14	0.95 (0.73, 1.24)
Negative	46	52	1.18	1.32	-0.14	1.12 (0.74,1.71)
Unknown	2	6	0.05	0.15	-0.10	2.98 (0.53, 30.21)
Size (cm)						
≤ 1.0	47 (28.7)	66 (38.6)	1.20	1.68	-0.48	1.40 (0.95-2.07)
1.1-3.0	100 (61.0)	92 (53.8)	2.56	2.34	0.22	0.91 (0.68-1.23)
≥ 3.1	17 (10.4)	13 (7.6)	0.44	0.33	0.11	0.76 (0.34-1.66)
Unknown	4 (2.4)	2 (1.2)	0.10	0.05	0.05	0.50 (0.04-3.47)
Nodal status						
Negative	119 (73.9)	135 (79.9)	3.05	3.43	-0.38	1.13 (0.87-1.46)
Positive	42 (26.1)	34 (20.1)	1.07	0.86	0.21	0.80 (0.50-1.30)
Unknown	7 (4.2)	4 (2.3)	0.18	0.10	0.08	0.57 (0.12-2.23)

continued

Table APP.2. Tumor Characteristics of Invasive Breast Cancers by Treatment Group in STAR (concluded)

Tumor Characteristic	Number of Events (%[a])		Incidence Rate per 1000 Patient-Years			RR (95% CI)[c]
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference[b]	
Stage						
I	106 (63.1)	119 (68.8)	2.71	3.02	0.31	1.12 (0.85-1.46)
II	4 (2.4)	5 (2.9)	0.1	0.13	0.03	1.24 (0.27-6.26)
IIA	35 (20.8)	30 (17.3)	0.9	0.76	-0.14	0.85 (0.51-1.43)
IIB	15 (8.9)	12 (6.9)	0.38	0.3	-0.08	0.80 (0.34-1.82)
IIIA	3 (1.8)	4 (2.3)	0.08	0.1	0.02	1.33 (0.22-9.05)
IIIB	1 (0.6)	1 (0.6)	0.03	0.03	0.00	0.99 (0.01-78.03)
IV	3 (1.8)	0 (0.0)	0.08	0	-0.08	0.00
Unknown	1 (0.6)	2 (1.2)	0.03	0.05	0.02	1.99 (0.10-117.3)

Abbreviations: CI = confidence interval; ER = estrogen receptor; RR = risk ratio.

[a] Percent of women with an invasive breast cancer; N=168 for tamoxifen and N=173 for raloxifene.

[b] Rate in the tamoxifen group minus rate in the raloxifene group.

[c] Risk ratio for patients in the raloxifene group compared to patients in the tamoxifen group.

Analysis Quantifying the Relative Effect of Raloxifene and Tamoxifen on the Incidence of Invasive Breast Cancer

Background Information

STAR was designed and powered to answer important clinical questions regarding the effects of raloxifene and tamoxifen in postmenopausal women at increased risk of breast cancer; quoting from the protocol: "1) that the superiority of one treatment for its effectiveness in reducing breast cancer incidence is sufficient to make it the preferred treatment for women eligible for the trial, or 2) that neither treatment has met this criteria and that other factors may result in each treatment being recommended for certain subsets of participants." As designed, the study had 85% power to detect a 1/3 risk reduction of raloxifene compared with tamoxifen and, quoting again from the protocol, had 95% power "to assure that we would not conclude that the two treatments were equivalent if the overall increase in annual incidence rate associated with raloxifene (vs. tamoxifen) would negate half the gain obtained from tamoxifen vs. placebo. This would occur if the incidence in the rate of invasive breast cancer in those receiving raloxifene increases (relative to those receiving tamoxifen) by 56%." When superiority of either treatment was not demonstrated, the protocol specified that "the choice of therapy should be based on benefit/risk considerations." Thus, further quantification of the relative efficacy of raloxifene compared with tamoxifen was warranted. Since STAR was not designed or powered as a noninferiority study, Lilly performed a prospectively designed analysis using Rothmann's method (Rothmann et al. 2003) to evaluate the proportion of tamoxifen effect retained by raloxifene and the corresponding 95% CI and the relative risk of raloxifene compared with a putative placebo. The detail of the analysis method and key assumptions was included in a document submitted to the FDA on 30 January 2006 (IND 57,137, serial number: 064).

At the time this document was submitted, Lilly remained blinded to the study data. Lilly developed this plan without the participation of NSABP or NCI, so that no unblinded individual might have influenced the proposed framework. The document included a framework that outlined the possible outcomes of invasive breast cancers in each treatment group and proposed interpretations based on expected 327 invasive breast cancers.

Statistics method:

Historical effect of tamoxifen

Historically, four tamoxifen prevention trials aimed to evaluate the effect of tamoxifen on the risk reduction of breast cancer for women (ie, Royal Marsden, Italian, P-1, and IBIS-1). Table APP.3 summarizes study design information for these four trials. P-1 differs from the other three European trials with regard to patient profiles, study duration, endpoint assessments and the use of estrogen replacement therapy during the study periods.

The P-1 population of women age 50 years or older was considered the most relevant to the STAR population for the following reasons: 1) P-1 was a well-designed, randomized, clinical study with a large sample size; 2) both studies enrolled only North American populations and, therefore, had the same procedures for breast cancer assessment (eg, frequency and quality of breast exams and mammographic screening); 3) neither study allowed the use of estrogen replacement therapy; and 4) enrollment in both studies was based primarily on the 5-year predicted risk of invasive breast cancer.

Table APP.3. Summary of Tamoxifen Breast Cancer Prevention Trials [a]

Trial	Study Population/Duration	Primary Endpoint	Enrollment Criteria	Use of ET During the Study
Royal Marsden	N=2471 1986-1996 European Trial	Occurrence of breast cancer	High risk and family history of breast cancer	Yes
Italian	N=5408 1992-1997 European Trial	Occurrence of breast cancer and deaths from breast cancer	Normal risk and hysterectomy	Yes
P-1	N=13388 N=7998 for age >= 50 1992-1997 North American Trial	Occurrence of invasive breast cancer	5 year risk of invasive breast cancer ≥1.66% estimated from Gail model	No
IBIS-1	N=7139 1992-2001 European Trial	Occurrence of breast cancer including DCIS	>2-fold relative risk	Yes

Abbreviations: DCIS = ductal carcinoma in situ; ET = estrogen therapy.

[a] Cuzick et al. 2003; Martino et al. 2004.

Rothmann's Method

The Z statistic, as described in Section 3.6 of Rothmann's paper, is used to derive the point estimate for the proportion of tamoxifen effect retained by raloxifene and the corresponding 95% confidence interval.

$$Z^* = \frac{\log(\hat{HR}(T/C2)) - (1-\delta_0)\log(\hat{HR}(P1/C1))}{\sqrt{(s_1^2 + (1-\delta_0)^2 s_2^2)}}$$

Where as $s_1 = \hat{SE}(\log(\hat{HR}(T/C2)))$ and $s_2 = \hat{SE}(\log(\hat{HR}(P1/C1)))$

T represents the test treatment, C represents the control treatment, and P represents placebo. C2 represents the control treatment in the active control trial, and C1 represents the control treatment in the historical placebo controlled trial. HR represents the hazard ratio and δ_0 represent the proportion of C2's effect that T retained in the active control trial.

The effect of test treatment relative to a putative placebo can be calculated by setting $\delta_0 = 0$.

Assumptions:

- Constancy of the control treatment effect: the relative efficacy of the control treatment versus placebo (*P1*) in the historical trial is the same as in the current active control trail had a placebo arm (*P2*) been included in the current active control, ie, *HR (P2/C2) =HR (P1/C1).*
- Control treatment effect: based on data from women age 50 years or older in P-1 study, tamoxifen demonstrated a 53% risk reduction on invasive breast cancer for postmenopausal women at high risk for the disease, ie, $\hat{HR}$ *(C1/P1) = 0.47 (0.33, 0.66).* Assume that *log* $(\hat{HR})$ is normally distributed, then s_2 *= (log (0.66)-log (0.33)) / (2*1.96) =0.1768*.
- Assay validation of the current active control trial: STAR was a well designed, large sample size clinical trial. The estimate of the variability of the log of the hazard ratio of raloxifene versus tamoxifen, as described in section 3.8 of Rothmann's paper, is, $s_1^2 = \hat{VAR}$ *(log* $(\hat{HR}$ *(T/C2))) = 4/341,* where *341* is the observed number of women who developed invasive breast cancers in STAR.
- Estimate of test treatment effect in the active control trial: used the observed hazard ratio of raloxifene compared with tamoxifen in STAR, ie, $\hat{HR}$ *(T/C2) =1.02.*

Appendix 1.2. Safety Information

Table APP.4. Total Patient-Years of Study Follow Up in STAR

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

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

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

Table APP.5. Exposure to Study Drug: Mean and Median Time in Years for STAR, MORE, CORE and RUTH Patients

	STAR			MORE		CORE[a]		RUTH	
Variable	**Tamoxifen (N=9736)**	**Raloxifene (N=9751)**	**Total (N=19,487)**	**Placebo (N=2576)**	**Raloxifene (N=5129)**	**Placebo (N=1018)**	**Raloxifene (N=2182)**	**Placebo (N=5057)**	**Raloxifene (N=5044)**
Mean	3.13	3.24	3.19	3.24	*3.30	2.68	2.66	4.31	4.32
Median	3.31	3.53	3.43	3.94	3.95	2.98	2.99	5.05	5.06
Standard Deviation	1.66	1.64	1.65	1.29	1.29	0.83	0.88	2.06	2.06
Total patient-years of exposure	30,471	31,603	62,075	8346	16,946	2728	5804	21,777	21,803

Abbreviations: ANOVA = analysis of variance; N = Number of patients.

[a] For CORE, some patients not willing or not able to take study drug were still allowed to participate in the study. Of the 4011 patients enrolled in CORE, 3200 resumed study drug (placebo, 1018; raloxifene, 2182) and this number was used to calculate exposure.

* Denotes statistically significant treatment group difference within study (ANOVA, $p<0.05$).

Table APP.6. Exposure to Study Drug by Year for STAR, MORE, CORE and RUTH Patients

	STAR			MORE		CORE[a]		RUTH	
	Tamoxifen (N=9736)	**Raloxifene (N=9751)**	**Total (N=19,487)**	**Placebo (N=2576)**	**Raloxifene (N=5129)**	**Placebo (N=1018)**	**Raloxifene (N=2182)**	**Placebo (N=5057)**	**Raloxifene (N=5044)**
Variable	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥1 year	8399 (86.3)	8592 (88.1)	16991 (87.2)	2295 (89.1)	4520 (88.1)	917 (90.1)	1935 (88.7)	4444 (87.9)	4416 (87.6)
≥2 years	6756 (69.4)	6989 (71.7)	13745 (70.5)	2043 (79.3)	*4165 (81.2)	837 (82.2)	1756 (80.5)	4033 (79.8)	4030 (79.9)
≥3 years	5269 (54.1)	5582 (57.2)	10851 (55.7)	1848 (71.7)	*3834 (74.8)	475 (46.7)	1027 (47.1)	3678 (72.7)	3713 (73.6)
≥4 years	3964 (40.7)	4221 (43.3)	8185 (42.0)	601 (23.3)	*1323 (25.8)	NA [b]	NA [b]	3360 (66.4)	3390 (67.2)
≥5 years	2565 (26.3)	2740 (28.1)	5305 (27.2)	NA [b]	NA [b]	NA [b]	NA [b]	2722 (53.8)	2723 (54.0)

Abbreviations: n = patients with event; N = patient population; NA = not applicable.

[a] For CORE, some patients not willing or not able to take study drug were still allowed to participate in the study. Of the 4011 patients enrolled in CORE, 3200 resumed study drug (placebo, 1018; raloxifene, 2182) and this number was used to calculate exposure.

[b] Some MORE patients were exposed nearly 5 years , and some CORE patients were exposed nearly 4 years.

* Denotes statistically significant treatment group difference within study (Chi Square, $p<0.05$).

Table APP.7. STAR Efficacy and Safety Endpoint Data Reported in JAMA (Vogel et al. 2006), STAR Clinical Study Report, and 4-Month Safety Update

Endpoint	Source	Tamox Events	Ralox Events	Tamox Rate	Ralox Rate	RR (95% CI)
Invasive BrCa	JAMA	163	168	4.3	4.41	1.02 (0.82-1.28)
	STAR CSR	168	173	4.3	4.4	1.02 (0.82-1.27)
	Safety Update	181	196	4.25	4.57	1.08 (0.87-1.32)
Non-Inv BrCa	JAMA	57	80	1.51	2.11	1.4 (0.98-2.00)
	STAR CSR	60	83	1.54	2.12	1.38 (0.98-1.95)
	Safety Update	70	90	1.65	2.11	1.28 (0.93-1.77)
Invasive Uterine Cancer	JAMA	36	23	2	1.25	0.62 (0.35-1.08)
	STAR CSR	37	23	1.99	1.21	0.61 (0.34-1.05)
	Safety Update	41	27	2.02	1.3	0.64 (0.38-1.07)
Uterine Hyperplasia	JAMA	84	14	4.69	0.76	0.16 (0.09-0.29)
	STAR CSR	100	17	5.42	0.9	0.17 (0.09-0.28)
	Safety Update	108	17	5.36	0.82	0.15 (0.09-0.26)
Hysterectomy	JAMA	244	111	13.57	6.04	0.44 (0.35-0.56)
	STAR CSR	246	92	13.25	4.84	0.37 (0.28-0.47)
	Safety Update	270	102	13.33	4.91	0.37 (0.29-0.46)
Ischemic Heart Disease	JAMA	114	126	3	3.29	1.1 (0.85-1.43)
	STAR CSR	125	138	3.19	3.5	1.1 (0.86-1.41)
	Safety Update	135	144	3.16	3.35	1.06 (0.83-1.35)
Stroke	JAMA	53	51	1.39	1.33	0.96 (0.64-1.43)
	STAR CSR	56	54	1.42	1.36	0.96 (0.65-1.42)
	Safety Update	59	58	1.37	1.34	0.98 (0.67-1.43)
Thromboembolic Events	JAMA	141	100	3.71	2.61	0.7 (0.54-0.91)
	STAR CSR	150	105	3.83	2.66	0.69 (0.53-0.90)
	Safety Update	161	114	3.77	2.64	0.7 (0.55-0.90)
PE	JAMA	54	35	1.41	0.91	0.64 (0.41-1.00)
	STAR CSR	58	38	1.47	0.96	0.65 (0.42-1.00)
	Safety Update	64	43	1.49	0.99	0.67 (0.44-1.00)
Deep Vein Thrombosis	JAMA	87	65	2.29	1.69	0.74 (0.53-1.03)
	STAR CSR	92	67	2.35	1.69	0.72 (0.52-1.00)
	Safety Update	97	71	2.27	1.64	0.72 (0.53-0.99)
Total Osteo Frx	JAMA	104	96	2.73	2.51	0.92 (0.69-1.22)
	STAR CSR	111	108	2.83	2.74	0.97 (0.73-1.27)
	Safety Update	119	121	2.78	2.81	1.01 (0.78-1.31)
Spine Frx	JAMA	53	52	1.39	1.35	0.98 (0.65-1.46)
	STAR CSR	58	58	1.47	1.46	0.99 (0.68-1.46)
	Safety Update	61	64	1.42	1.48	1.04 (0.72-1.50)
Hip Frx	JAMA	26	23	0.68	0.6	0.88 (0.48-1.60)
	STAR CSR	28	26	0.71	0.66	0.92 (0.52-1.63)
	Safety Update	30	32	0.7	0.74	1.06 (0.62-1.80)

(continued)

Table APP.7. STAR Efficacy and Safety Endpoint Data Reported in JAMA (Vogel et al. 2006), STAR Clinical Study Report, and 4-Month Safety Update (concluded)

Endpoint	Source	Tamox Events	Ralox Events	Tamox Rate	Ralox Rate	RR (95% CI)
Colles Frx	JAMA	27	23	0.71	0.6	0.85 (0.46-1.53)
	STAR CSR	27	27	0.69	0.68	0.99 (0.56-1.76)
	Safety Update	30	28	0.7	0.65	0.93 (0.53-1.60)
Cataract with Surgery	JAMA	260	215	8.03	6.62	0.82 (0.68-0.99)
	STAR CSR	295	240	8.85	7.17	0.81 (0.68-0.96)
	Safety Update	337	269	9.29	7.37	0.79 (0.67-0.93)
Deaths	JAMA	101	96	2.64	2.49	0.94 (0.71-1.26)
	STAR CSR	109	104	2.76	2.62	0.95 (0.72-1.25)
	Safety Update	135	119	3.13	2.74	0.87 (0.68-1.13)

Abbreviations: BrCa = breast cancer; CI = confidence interval; Frx = fractures; JAMA = The Journal of the American Medical Association; Non-Inv = noninvasive; PE = pulmonary embolism; Ralox = raloxifene; RR = risk ratio; Tamox = tamoxifen.

Note: Safety Update comprised of STAR data collected through 30 September 2006.

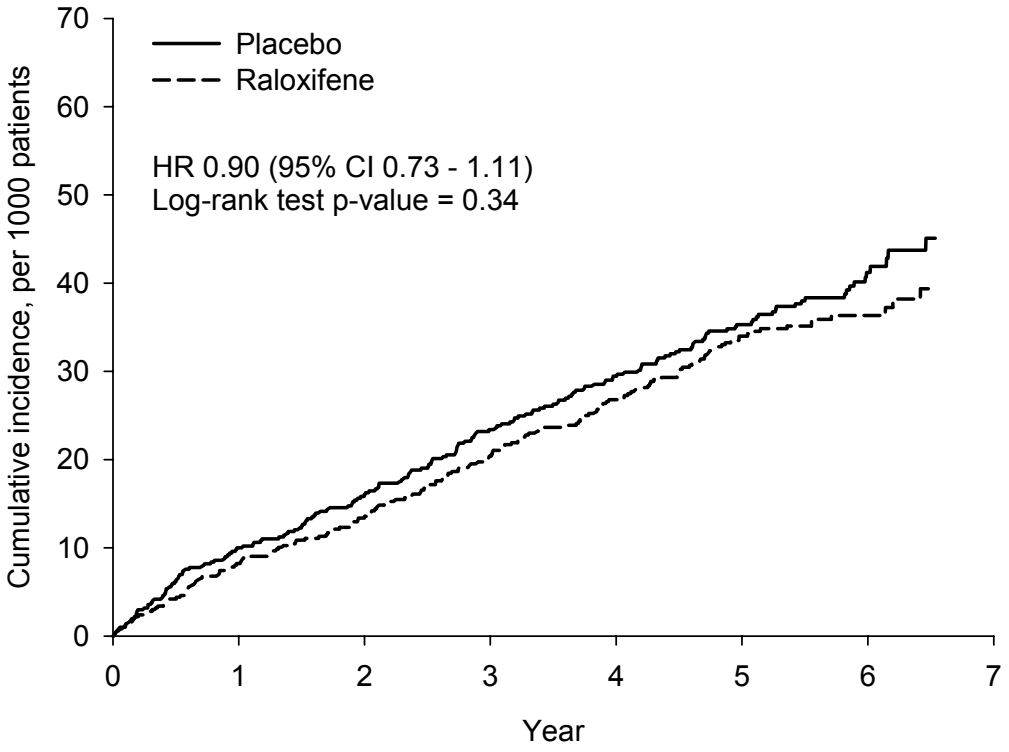


Figure APP.1. Kaplan-Meier curves for the combined coronary primary endpoint (coronary death, nonfatal [including silent] MI, or hospitalized ACS) in RUTH.

Table APP.8. Adverse Events: All Cancer Other than Breast Cancer All Randomized Patients in RUTH

SSC: Special Search Category	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10,101) n (%)	p-value *
Cancer	281 (5.6)	286 (5.7)	567 (5.6)	0.790
Endocrine cancer	8 (0.16)	3 (0.06)	11 (0.11)	0.135
Thyroid cancer	8 (0.16)	3 (0.06)	11 (0.11)	0.135
Other endocrine cancer	0 (0.00)	0 (0.00)	0 (0.00)	N/A
Gastrointestinal cancer	61 (1.21)	61 (1.21)	122 (1.21)	0.977
Anal cancer	2 (0.04)	1 (0.02)	3 (0.03)	N/A
Colon cancer	25 (0.49)	25 (0.50)	50 (0.50)	0.985
Colorectal cancer	1 (0.02)	2 (0.04)	3 (0.03)	N/A
Gastric cancer	8 (0.16)	10 (0.20)	18 (0.18)	0.636
Esophageal cancer	3 (0.06)	3 (0.06)	6 (0.06)	0.992
Pancreas cancer	11 (0.22)	10 (0.20)	21 (0.21)	0.839
Rectal cancer	8 (0.16)	5 (0.10)	13 (0.13)	0.410
Small intestine cancer	0 (0.00)	0 (0.00)	0 (0.00)	N/A
Lip and oral cavity cancer	1 (0.02)	4 (0.08)	5 (0.05)	0.176
Salivary gland cancer	1 (0.02)	1 (0.02)	2 (0.02)	N/A
Other gastrointestinal cancer	1 (0.02)	0 (0.00)	1 (0.01)	N/A
Hematopoietic cancer	1 (0.02)	1 (0.02)	2 (0.02)	N/A
Hepatic and biliary cancer	13 (0.26)	11 (0.22)	24 (0.24)	0.696
Bile duct cancer	2 (0.04)	4 (0.08)	6 (0.06)	0.409
Bladder cancer	4 (0.08)	10 (0.20)	14 (0.14)	0.109
Hepatic cancer	7 (0.14)	2 (0.04)	9 (0.09)	0.096
Other hepatic and biliary cancer	1 (0.02)	0 (0.00)	1 (0.01)	N/A
Leukemias	12 (0.24)	15 (0.30)	27 (0.27)	0.560
Acute myeloid leukemia	3 (0.06)	1 (0.02)	4 (0.04)	N/A
Acute lymphocytic leukemia	0 (0.00)	1 (0.02)	1 (0.01)	N/A
Chronic myeloid leukemia	1 (0.02)	2 (0.04)	3 (0.03)	N/A
Chronic lymphocytic leukemia	4 (0.08)	6 (0.12)	10 (0.10)	0.518
Myelodysplastic syndrome	2 (0.04)	5 (0.10)	7 (0.07)	0.255
Other leukemias	2 (0.04)	0 (0.00)	2 (0.02)	N/A
Lymphomas	13 (0.26)	12 (0.24)	25 (0.25)	0.843
Hodgkin's disease	1 (0.02)	0 (0.00)	1 (0.01)	N/A
Non-Hodgkin's B-cell	4 (0.08)	4 (0.08)	8 (0.08)	0.998
Non-Hodgkin's T-cell	1 (0.02)	0 (0.00)	1 (0.01)	N/A
Non-Hodgkin's lymphomas	6 (0.12)	7 (0.14)	13 (0.13)	0.779
Other lymphomas	1 (0.02)	1 (0.02)	2 (0.02)	N/A
Nervous system (malignant)	10 (0.20)	7 (0.14)	17 (0.17)	0.465
Ocular cancer	2 (0.04)	0 (0.00)	2 (0.02)	N/A

(continued)

Table APP.8. Adverse Events: All Cancer Other than Breast Cancer All Randomized Patients in RUTH (concluded)

SSC: Special Search Category	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10,101) n (%)	p-value *
Plasma cell neoplasm malignant	4 (0.08)	5 (0.10)	9 (0.09)	0.734
Plasma cell cancer	1 (0.02)	2 (0.04)	3 (0.03)	N/A
Multiple myeloma	3 (0.06)	4 (0.08)	7 (0.07)	0.702
Renal and urinary tract cancer	16 (0.32)	24 (0.48)	40 (0.40)	0.205
Bladder cancer	4 (0.08)	10 (0.20)	14 (0.14)	0.109
Non renal cell kidney cancer	0 (0.00)	0 (0.00)	0 (0.00)	N/A
Renal cell kidney cancer	10 (0.20)	14 (0.28)	24 (0.24)	0.408
Renal pelvis and ureter cancer	2 (0.04)	0 (0.00)	2 (0.02)	N/A
Urinary tract cancer	0 (0.00)	0 (0.00)	0 (0.00)	N/A
Reproductive cancer	35 (0.69)	43 (0.85)	78 (0.77)	0.364
Respiratory and mediastinal cancer	41 (0.81)	34 (0.67)	75 (0.74)	0.428
Mesothelioma	0 (0.00)	0 (0.00)	0 (0.00)	N/A
Small cell lung cancer	2 (0.04)	5 (0.10)	7 (0.07)	0.260
Non-small cell lung cancer	11 (0.22)	12 (0.24)	23 (0.23)	0.828
Other respiratory cancer	28 (0.55)	17 (0.34)	45 (0.45)	0.105
Skeletal cancer	1 (0.02)	0 (0.00)	1 (0.01)	N/A
Skin cancer	67 (1.32)	69 (1.37)	136 (1.35)	0.836
Melanoma	10 (0.20)	8 (0.16)	18 (0.18)	0.645
Basal cell skin carcinoma	55 (1.09)	54 (1.07)	109 (1.08)	0.945
Squamous cell skin cancer	5 (0.10)	3 (0.06)	8 (0.08)	0.488
Other skin cancer	2 (0.04)	8 (0.16)	10 (0.10)	0.056
Soft tissue cancer	0 (0.00)	1 (0.02)	1 (0.01)	N/A
Sarcoma (other than bone and uterine)	0 (0.00)	1 (0.02)	1 (0.01)	N/A
Miscellaneous / site unknown cancer	16 (0.32)	16 (0.32)	32 (0.32)	0.984

Note: p-Value is obtained from a Cochran-Mantel-Haenszel (CMH) test, stratified by country. Statistical test is not performed when the total number of patients in a category is less than 5.

STAR Primary Analysis Dataset

Table APP.9. Invasive Breast Cancer Cases Other than Breast and Uterine STAR Primary Analysis Dataset

	Number of Events		
	TMX N=9736	RLX N=9751	
Site of Cancer	n	n	Risk Ratio (95% CI) [b]
Buccal cavity and pharynx	4	3	0.75 (0.11-4.40)
Esophagus	2	0	NA
Stomach	3	1	0.33 (0.01-4.12)
Colorectal	32	30	0.93 (0.55-1.58)
Liver	4	1	0.25 (0.01-2.51)
Gallbladder	3	1	0.33 (0.01-4.12)
Pancreas	7	5	0.71 (0.18-2.60)
Retroperitoneum	5	1	0.20 (0.004-1.78)
Spleen	0	1	NA
Nasal/middle ear/sinuses	1	1	0.99 (0.01-77.99)
Lung/trachea/bronchus	30	40	1.32 (0.80-2.20)
Bone/cartilage/connective tissue	3	3	0.99 (0.13-7.42)
Skin	14	13	0.92 (0.40-2.12)
Gynecologic - cervix	1	0	NA
Gynecologic - ovary	14	18	1.27 (0.60-2.76)
Gynecologic - other	1	2	1.99 (0.10-117.33)
Urinary bladder	8	6	0.75 (0.21-2.45)
Kidney	9	13	1.44 (0.57-3.80)
Eye	0	1	NA
Nervous system	6	9	1.49 (0.47-5.09)
Thyroid gland	9	18	1.99 (0.85-5.02)
Leukemia or other lymphatic/hematopoietic	33	29	0.87 (0.51-1.48)
Site unspecified	5	12	2.38 (0.78-8.64)
Secondary/uncertain	4	1	0.25 (0.01-2.51)

Abbreviations: CI = confidence interval; n = number of patients; N = patients comprising primary analysis dataset; NA = analysis not performed if zero events occurred in either treatment group; RLX = raloxifene; TMX = tamoxifen.

Note: A single patient could have had more than 1 event.

[a] Rate in the tamoxifen group minus rate in the raloxifene group.

[b] Risk ratio for patients in the raloxifene group compared with those in the tamoxifen group.

Review of Cardiovascular Event Form – STAR

Routine ECGs were not required by the protocol. STAR data collection included a cardiovascular event form (CVEVT). Instructions on the form noted that the form was to be completed for each cardiovascular-related or stroke-related inpatient or outpatient procedure. All procedures were to be reported and all related supporting medical documentation were to be submitted so the NSABP medical reviewer could confirm if the findings from the procedure were positive or negative. Documentation to be provided included in-patient and out-patient medical records including hospital discharge summaries, ECG tracings, reports of MRI, CT or VQ scans, operative reports, and any other available supporting documentation related to the procedure.

Subsequent STAR medical review confirmed if one or more specified vascular events were documented. Atrial fibrillation was not one of the vascular events specified on Form CVEVT to generate a medical review.

Nonetheless, the NSABP medical review Form P2VAS did include a checklist (no/yes) for atrial fibrillation. The NSABP medical reviewer was not asked to record any additional information about the atrial fibrillation and did not determine whether the atrial fibrillation was a new event or was pre-existing.

Results of NSABP Medical Review

Across all P2VAS forms, there were 177 patients with atrial fibrillation checked as "yes."

Of the 177 patients, 43 were confirmed by the NSABP reviewer as having a specified vascular event (Table APP.10).

Table APP.10. Atrial Fibrillation Identified with a Specified Vascular Event in STAR

Confirmed Vascular Events	Tamoxifen n	Raloxifene n	Total n
Nonfatal myocardial infarction	2	3	5
Acute ischemic syndromes	6	9	15
Stroke	4	3	7
Transient ischemic attack	4	1	5
Pulmonary embolism	1	1	2
Deep vein thrombosis	1	3	4
Peripheral vascular disease	0	1	1
Other vascular event	4	6	10
Total [a]	21	22	43

[a] Unique patients.

For the categories of confirmed vascular events in Table APP.10, the cases of atrial fibrillation were evenly distributed among the different events, and were balanced between treatment groups.

For the 177 patients with atrial fibrillation checked as “yes”, 101 were in the raloxifene group and 76 in the tamoxifen group. When using the entire STAR primary analysis dataset (9736 tamoxifen patients; 9751 raloxifene patients) as denominators for the statistical comparison, the p-value was 0.060. The clinical interpretation of these data is limited based on the possible confounding factors noted above.

For investigator reported cases of cardiac arrhythmia events in STAR, refer to Section 4.3.3.2.3.4.

It is important to note that data from placebo-controlled studies do not suggest a pattern of causal association between raloxifene and atrial fibrillation (refer to Section 4.3.1.2.3.2).