- A history of a benign breast biopsy with a first-degree relative with breast cancer

Exclusion criteria included:

- History of cancer
- History of DVT, PE
- Premenopausal women considering pregnancy
- Current oral contraceptive use

Women were permitted to enter the trial on HRT, or to begin HRT at any point during the trial.

Randomization was performed at the Royal Marsden. Menopausal status at randomization was recorded, although it does not appear that the trial was stratified prior to randomization. A data safety monitoring committee periodically reviewed the data.

Women were followed every 6 months with exams and had yearly mammograms. Random blood testing for tamoxifen levels was performed to ensure compliance.

Initially, women with DCIS were permitted to enter the trial. The trial was subsequently amended, and the 22 women with DCIS already on study were excluded from analysis. Eleven participants were found to have administrative errors and were re-randomized. Their data was censored at the time of the second randomization.

The trial was designed to have 90% power to detect a 75% reduction in breast cancer risk in 1996, and a 50% reduction in 1998, using a two-sided alpha of 5%. Interim analyses were planned for these timepoints. This report is for the 1998 results. The primary endpoint was the occurrence of breast cancer. Baseline characteristics and compliance (numbers who stopped prematurely) of the participants were compared using Chi-square tests. Breast cancer-free survival was analyzed using Kaplan-Meier and logrank techniques. These methods were also used to assess compliance by analyzing the time to stopping treatment on each arm. Analyses were adjusted for age, menopausal status, family history of breast and ovarian cancer, and use of HRT with the Cox model.

The trial opened in October 1986 and completed accrual in April 1996. Two thousand four hundred ninety-four women gave consent. Fourteen withdrew consent prior to randomization, leaving 2494 who were randomized, 1250 to tamoxifen and 1244 to placebo. As previously mentioned, 22 women with DCIS (12 on tamoxifen, 10 on placebo) were excluded from analysis, as was 1 participant on placebo found to have invasive breast cancer. Thus, 1238 on tamoxifen and 1233 on placebo were included in the analysis. These participants were matched for age, menopausal status, previous breast biopsy, number of affected first-degree relatives, and use of HRT at study entry (15% on tamoxifen, 16% on placebo). Median follow-up is 70 months; 42% of women are off drug. Of the 1033 women who are off treatment, 6% on each arm completed 8 years of therapy. Fourteen percent on tamoxifen and 16% on placebo discontinued drug for non-medical reasons. Twenty-six percent on tamoxifen compared to 14% on placebo stopped because of medical reasons ($p< 0.0005$), including nausea, hot flashes, menstrual irregularities, and gynecologic problems. Twenty-seven percent on tamoxifen and 25% on placebo began HRT while on study. Eleven percent of the population was lost to follow up.

Breast cancer was diagnosed in 34 women on tamoxifen and 36 on placebo. Eight of these cancers were DCIS, 4 on each arm. Women on HRT had a higher incidence of breast cancer compared to women who did not use these medications; however, the number of breast cancers among HRT users did not differ between treatment arms.

Four endometrial cancers were diagnosed on tamoxifen compared to 1 on placebo. Four DVTs occurred on tamoxifen compared to 2 on placebo; there were 3 and 2 PEs respectively. Four breast cancer-related deaths were observed on the tamoxifen arm compared to 1 on placebo.

Compliance was high as measured by self-reporting, by random blood levels, and by using change in cholesterol levels as a surrogate for biologic effect.

The authors concluded that there was no observed protective effect of tamoxifen. Possible reasons for the differences in results between this trial and P-1 include a random statistical fluke; enrichment for a BRCA1/2-linked history of breast cancer, which may not be affected by hormonal blockade; potential confounding by the use of concomitant HRT; or longer duration of follow-up in the Royal Marsden study. The investigators suggested that the benefit seen in P-1 might disappear with longer follow-up.

Reviewer's Assessment

The following table summarizes the differences between the 3 reported breast cancer prevention trials with tamoxifen.

Table B1. Differences between tamoxifen breast cancer prevention trial design

Factor	Italian	Royal Marsden	NSABP P-1
Eligibility	Hysterectomy only	FHx in 1st-degree relatives; suggestive of hereditary breast cancer syndrome	1.7% risk over the next 5 years (age, LCIS, Gail model)
Exclusion criteria	Substantial list	At risk for known toxicities of tamoxifen; OC	At risk for known toxicities of tamoxifen;OC, HRT
Planned duration of drug therapy	5 years	8 years	5 years
Sample size	5408	2494	13,388
Statistical power	Low (34% power to detect a 33% difference)	90% power to detect a 50% difference	80% power to detect a 40% difference
Age: % < 50	38%	66%	40%
% with affected 1st degree relative	12%	?100%	76%
Prior hysterectomy	94.8%	Not reported	37%
% of women on	14%	41% P, 42% T	< 1% P, < 1% T

HRT			
% off-therapy	27.4% on P, 30.7% on T	30.5% on P; 39.7% on T	29.2% P, 33.8% T
% women completing full Tx course	2.7% P, 2.9% T	6.2% P, 6.3%	26.6% P, 23.9% T
Median follow-up	30.5 months	70 months	50.4 months

Table B2. Differences in tamoxifen breast cancer prevention trial results

Endpoint	Italian study		Royal Marsden		NSABP P-1	
	Placebo	Tamoxifen	Placebo	Tamoxifen	Placebo	Tamoxifen
Breast cancer	22	19	32	30	154	85
DCIS	4; treatment not reported		4	4	35	23
Endometrial cancer	Not applicable		1	4	14	33
DVT	3	6	2	4	19	30
PE	1	1	2	3	6	18
CVA	5	9	Not reported		24	34

The Italian study cannot be considered comparable to NSABP P-1. This trial did not attempt to enroll women at high risk. Any woman was eligible; eligibility and exclusion criteria were designed instead to exclude women who might experience a significant toxicity related to tamoxifen. It did not have a well-designed statistical plan and had low power to detect a difference between treatment arms. Median follow-up is short, and the trial was terminated early because drop-out was considered unacceptable. Although there was no difference in breast cancer incidence between treatment arms, the trial collected information on serious adverse events that show the same pattern and relation to study drug as the results from NSABP P-1.

The Royal Marsden study was designed to capture younger women at high risk of breast cancer by using eligibility criteria based on family history suggestive of a hereditary breast cancer syndrome. Tamoxifen was designed to be given for 8 years. In addition to these differences, the trial differed from NSABP P-1 in that a higher percentage of premenopausal women were entered on study, and concomitant HRT was permitted. At 70 months of follow-up, the Royal Marsden has long-term data not available from the NSABP P-1 trial.

Despite a sample size calculation that would result in 90% power to detect a reduction in breast cancer incidence of the size observed in the P-1 trial, no difference between treatment arms was observed. While fewer serious adverse events occurred, they

followed the same pattern and relation to tamoxifen therapy as those reported from NSABP P-1.

Why might these two trials differ in the primary outcome measurement?

1. Women entered on the Royal Marsden study were at lower risk for breast cancer than were women entered on the NSABP P-1 trial.

Although the investigators intended to enrich their sample for women with hereditary breast cancer syndromes, it is unlikely that their eligibility criteria accomplished this purpose. Frank and colleagues reported that in a series of 335 women at high risk of HBOC (hereditary breast and ovarian cancer), women with breast cancer diagnosed before age 50 who had 1 first-degree relative with breast cancer < age 50 had a 20% incidence of BRCA1/2 mutations (Am.J. Hum.Genet 61[suppl]: abstr. 351, 1997; J. Clin. Oncol. 16: 2417-25, 1998). When women with a personal and/or family history of breast and ovarian cancer were tested, mutations were identified in 33-59% (Am.J.Hum.Genet. 61[Suppl]: abstr. 351, 1997; J. Clin. Oncol. 16: 2417-25, 1998; Proc. AACR 39: abstr. 3232, 1998). Another study tested women who were seen as self-referrals to breast cancer screening clinics (N.Engl.J.Med. 1997; 336: 1409-15). These women were not initially identified as likely to be at high risk for HBOC. Among women with a personal or family history of 1 case of breast cancer diagnosed before age 40, but no family history of ovarian cancer, 3.7% were found to have a mutation of BRCA1. For women with 1 affected relative with bilateral breast cancer, the rate was 33.3%. For women with 2 affected first-degree relatives but no history of ovarian cancer, 18.5% were found to have a mutation in BRCA1.

Overall, it is likely that only about 20% of women in this study were at high risk for breast cancer, and that the study is underpowered to detect a difference because of errors in the assumptions underlying the sample size calculation. In addition, tamoxifen may be ineffective in women with genetic mutations; these cancers may arise by different mechanisms.

2. While the rates of non-compliance appear similar across the studies, only NSABP P-1 took probable annual non-compliance rates into account when powering the study. Thus, the Royal Marsden study power calculations are based on inaccurate assumptions of both baseline breast cancer risk and compliance with therapy.

3. Younger women are more likely to have ER(-) disease; tamoxifen is only effective against ER(+) disease.

Seventy-eight percent of postmenopausal women have been reported to have ER(+) disease, compared to 57% of premenopausal women (Wittliff JL, Day TG, Dean WL, and Allegra JC. Steroid receptors and endocrine responsive cancer. In Prediction of response in cancer therapy. Alan R. Liss, 1988, pages 11-41). This difference might have influenced the results of the Royal Marsden trial.

4. The use of HRT in the Royal Marsden trial is a confounding factor and may have interfered with the ability of tamoxifen to prevent breast cancer.

For a number of possible reasons, the number of events observed in the Royal Marsden trial is substantially lower than the number seen in the NSABP P-1 study. The NSABP was a large, well-controlled study that recorded a sufficiently large number of events, both beneficial and adverse, to demonstrate the effects of tamoxifen in this population. The evidence from P-1 is also consistent with the large body of literature on the use of tamoxifen for prevention of contralateral breast cancer in women who have already had one breast cancer. On the basis of its size and statistical power, the results from this study should carry more weight than those reported in the two European trials.

Appendix C. Summary of ODAC questions and vote September 2, 1998

Questions to the Committee

NDA 17-970/SE1-40: **Nolvadex® (tamoxifen citrate)**
Zeneca Pharmaceuticals
Indication: for the prevention of breast cancer in women at high risk
Submission date: April 30, 1998

NSABP P-1 was a prospective, multicenter, randomized, double-blind, placebo-controlled trial of tamoxifen versus placebo for 5 years in women at increased risk for breast cancer as determined by age, prior history of LCIS, or a 1.7% risk of developing breast cancer in the next 5 years as predicted by the Gail model. Thirteen thousand three hundred eighty-eight women were randomized, 6707 on placebo and 6681 on tamoxifen. The objectives of the trial were to test the ability of tamoxifen to prevent invasive breast cancer, mortality from cardiovascular disease, and bone fractures, and to assess the toxicity and side effects of tamoxifen in this participant population.

The results of the trial, per FDA review, may be summarized as follows. Events have been categorized by age at diagnosis of the event, rather than age at randomization.

Table C1. Summary of Primary Endpoints, FDA Analysis

Event	Number of Events		Risk ratio	95% CI	P value
	Placebo	Tamoxifen			
Invasive breast cancer	**156**	**86**	**0.55**	**0.42-0.72**	**<0.0001**
≤49	59	38	0.65	0.42-0.99	0.04
≥50	97	48	0.49	0.35-0.70	0.0001
DCIS[1]	**35**	**23**	**0.66**	**0.39-1.11**	**0.12**
≤49	14	6	0.43	0.17-1.12	0.08
≥50	21	17	0.81	0.43-1.53	0.51
Hip fractures	**20[2]**	**9[3]**	**0.45**	**0.18-1.04***	**0.05**
≤49	4	0			0.13[4]
≥50	16	9	0.56	0.25-1.27	0.17
Colles' fractures	**12**	**7**	**0.59**	**0.20-1.61***	**0.26**
≤49	3	0			0.25[4]
≥50	9	7	0.78	0.3-2.1	0.62

1 The numbers are for DCIS only. The sponsor reported non-invasive breast cancer events, including LCIS and AH, as 59 on placebo and 31 on tamoxifen
2 One woman also had a Colles' fracture
3 One woman also had a Colles' fracture
4 Fisher's exact two-sided test
*Calculated by the sponsor using exact methods; rest calculated by FDA using approximate methods
N.B. We do not consider spine fractures to be a reliable and reproducible efficacy endpoint.

No reduction in ischemic heart events was observed in the tamoxifen arm compared to placebo.

1. Is NSABP P-1 an adequate and well-controlled trial demonstrating the efficacy of tamoxifen for the prevention of breast cancer in women at increased risk as defined by the study?

The adverse events in the trial, per FDA review, may be summarized as follows.

Table C2. Adverse Events in NSABP P-1, FDA Analysis

Event	Number of Events		Risk Ratio	95% CI	P-value
	Placebo	Tamoxifen			
Invasive endometrial cancer	**14**	**33**	**2.48**	**1.27-4.92[5]**	**0.004**
Age ≤ 49[1]	2	4	2.21	0.4-12.0	0.36
Age ≥ 50	12	29	2.5	1.3-4.9	0.007
DVT	**19**	**30**	**1.59**	**0.86-2.98[5]**	**0.12**
Age ≤ 49	6	9	1.52	0.48-5.19[5]	0.62
Age ≥ 50	13	21	1.62	0.77-3.51[5]	0.11
PE - total	**6**	**18**	**3.01**	**1.15-9.27[5]**	**0.03**
Fatal	0	3			
Age ≤ 49	1	0			1.00[4]
Age ≥ 50	5	18	3.4	1.26-9.24	0.02
Stroke -total	**24**	**34**	**1.42**	**0.82-2.51[5]**	**0.19**
Fatal	3	4			
Age ≤ 49	3	1	0.33	0.03-3.1	0.33
Age ≥ 50	21	33	1.57	0.91-2.7	0.11
Cataract surgery[2]	**129**	**201**	**1.51**	**1.21-1.89[5]**	**<0.0001**
Age ≤ 49	6	8	1.36	0.47-3.9	0.57
Age ≥ 50	123	193	1.58	1.26-1.99	<0.0001
Hot flashes: ≥ grade 1[3]	**4416/6563 (67%)**	**5172/6555 (79%)**	**NA**	**0.10-0.13[6]**	**<0.0001**
Age ≤ 49	1794/2580 (70%)	2135/2574 (83%)	NA	0.11-0.16[6]	<0.0001
Age ≥ 50	2622/3983 (66%)	3037/3981 (76%)	NA	0.09-0.12[6]	<0.0001
Vaginal discharge: ≥ grade 1[3]	**2239/6563 (34%)**	**3533/6555 (54%)**	**NA**	**0.18-0.21[6]**	<0.0001
Age ≤ 49	1170/2580 (45%)	1595/2574 (62%)	NA	0.14-0.19[6]	<0.0001
Age ≥ 50	1069/3983 (27%)	1938/3981 (49%)	NA	0.20-0.24[6]	<0.0001

1 Higher risk than that predicted by SEER data or by the control arm of NSABP B-14
2 Age at randomization
3 Based on 13,118 participants with follow-up
4 Fisher's exact two-sided test
5 Calculated by the sponsor using exact methods; rest calculated by FDA using approximate methods
6 95% CI for hot flashes, vaginal discharge: difference of TAM – PLA proportions

The mortality, breast cancer-related mortality, and occurrence of other cancers were not significantly different between the two arms.

Table C3. Mortality/Other Adverse Events, NSABP P-1

Event	Placebo	Tamoxifen	Total
Mortality	65	53	118
Breast cancer mortality	5	4	9
Other cancers	88	85	173

2. Does NSABP P-1 demonstrate that tamoxifen has a favorable benefit:risk ratio for the prevention of breast cancer in women at increased risk as defined by the study? If the answer is no, can the committee identify a subpopulation in the study for which the benefit:risk ratio is acceptable?

During the course of the review, 2 European trials of tamoxifen for breast cancer prevention were published. Although these trials did not demonstrate a reduction in breast cancer incidence, they differed from the NSABP P-1 design in potentially important ways. In addition, these results are in contrast to the published literature on the efficacy of tamoxifen in reducing contralateral breast cancer in women with a previous diagnosis of breast cancer. The 1995 update of the Early Breast Cancer Trialists' Collaborative Group overview analysis reported a proportional reduction in the incidence of contralateral breast cancer of 47% with 5 years of tamoxifen.

Table C4. Differences in Tamoxifen Breast Cancer Prevention Trial Results

Endpoint	Italian BCPT		Royal Marsden		NSABP P-1	
	Placebo	Tamoxifen	Placebo	Tamoxifen	Placebo	Tamoxifen
Breast cancer	19	14	32	30	154	85
DCIS	4; treatment arm not reported		4	4	35	23
Endometrial cancer	Not applicable		1	4	14	33
DVT	3	6	2	4	19	30
PE	1	1	2	3	6	18
CVA	5	9	Not reported		24	34

Table C5. Differences among Tamoxifen Breast Cancer Prevention Trial Designs

Factor	Italian BCPT	Royal Marsden	NSABP P-1
Eligibility	Hysterectomy only	FHx in 1st-degree relatives; suggestive of hereditary breast cancer syndrome	1.7% risk over the next 5 years (age, LCIS, Gail model)
Exclusion criteria	Substantial list	At risk for known toxicities of tamoxifen; OC	At risk for known toxicities of tamoxifen;OC, HRT
Planned duration of drug therapy	5 years	8 years	5 years
Sample size	5408	2494	13,388
Statistical power	Low	90% power to detect a 50% difference	80% power to detect a 40% difference
Age: % < 50	38%	66%	40%
% with affected 1st degree relative	12%	?100%	76%
Prior hysterectomy	94.8%	Not reported	37%
% of women on HRT	14%	41% P, 42% T	< 1% P, < 1% T
% off-therapy	27.4% on P, 30.7% on T	30.5% on P; 39.7% on T	29.2% P, 33.8% T
% women completing full Tx course	2.7% P, 2.9% T	6.2% P, 6.3%	26.6% P, 23.9% T
Median follow-up	30.5 months	70 months	50.4 months

3. **What effect should the results of the Royal Marsden and Italian tamoxifen breast cancer prevention studies have on the approvability of the indication that the applicant is seeking? If they do not affect approvability, should the results be addressed in the tamoxifen package insert and patient package insert?**

4. **Should tamoxifen be approved for the prevention of breast cancer in women at increased risk as defined in the study or as identified in the answer to question 2?**

In NSABP P-1, participants were required to have a history and physical examination, blood tests (WBC, platelets, liver function tests, and creatinine), and a gynecologic exam (pelvic and Pap smear) at baseline. Women were required to have had a normal mammogram within the past 180 days. After study entry, a physical examination, breast

examination and blood tests were performed at 3 months, 6 months, and then every 6 months. Yearly mammograms and gynecologic evaluation, as defined at baseline, were required.

5. **Does the committee recommend that the package insert and patient package insert should include all of the above protocol-specified monitoring?**

Endometrial sampling at baseline and annually was added as a protocol amendment. Four thousand three hundred forty-five women were screened from 1 to 5 times. Twenty-six of the 47 women with endometrial cancer had at least one endometrial sampling. One comparison that could be made is shown below.

Table C6. Endometrial Cancer Detection Rates (Per Patient)

Endometrial Cancer Status	Endometrial Sampling	No sampling
Number of Endometrial Cancers	26 (0.60%)	21 (0.5%)
Participants without Endometrial Cancer	4345	4182

The detection rate on a per patient basis (not per sampling) was significantly higher with endometrial sampling (Fisher's Exact Test, $p < 0.005$). Twelve women (0.28% of women with sampling) were found to have endometrial cancer only on sampling, 4 were randomized to placebo and 8 were randomized to tamoxifen. Six of these women (0.14% of women with sampling) had no antecedent signs or symptoms and diagnosis of their endometrial cancer might have otherwise been delayed. Four of the 6 were found to have endometrial cancer on routine sampling and the other 2 were found to have complex atypical hyperplasia, which was treated with hysterectomy and endometrial cancer was found incidentally during pathology review.

6. **Based on the information from this study, should the package insert and patient package insert recommend that women who take tamoxifen for the prevention of breast cancer undergo yearly endometrial sampling?**

7. **On NSABP P-1, women on tamoxifen had a higher incidence of cataract formation and a higher rate of cataract surgery (Table 2). Information about non-cataract ophthalmologic toxicity was not collected. Should the package insert and patient package insert recommend that women who take tamoxifen for the prevention of breast cancer undergo yearly eye examinations?**

8. **Does the committee have any other recommendations for monitoring the safety of women taking tamoxifen for breast cancer prevention?**

9. Should FDA ask for a Phase 4 commitment to further study participants

10. Should FDA ask for a Phase 4 commitment to further study women on tamoxifen for non-cataract ophthalmologic toxicity?

Questions 1-4 and 6 were re-worded by the ODAC and the new wording, which was used for voting, is included in this report.

1. (reworded) Is NSABP P-1 an adequate and well-controlled trial demonstrating the efficacy of tamoxifen in reducing the short term incidence of breast cancer in the women entered in the trial?

   Yes - 11 No - 0

2. (original wording) Does NSABP P-1 demonstrate that tamoxifen has a favorable benefit:risk ratio for the prevention of breast cancer in women at increased risk as defined by the study? If the answer is no, can the committee identify a subpopulation in the study for which the benefit:risk ratio is acceptable?

   Yes - 0 No - 11

   (reworded) With the limited follow-up available, does NASBP-1 demonstrate that tamoxifen has a favorable benefit:risk ratio for decreasing the incidence of breast cancer in the patients in the study population?

   Yes - 9 No - 2

3. (reworded) Should the results of the Royal Marsden and Italian tamoxifen breast cancer prevention studies have an effect on the approvability of the risk reduction indication that the applicant is seeking? If they do not affect approvability, should the results be addressed in the tamoxifen package insert and patient package insert?

There was no vote on Question 3. The Committee indicated that the Royal Marsden trial highlights the fact that some women will benefit from tamoxifen and others will not, and that the definition of these populations is not clear. The trials were not part of the NDA and so were not reviewed by the FDA in the same detail as NSABP-1. The Committee did feel that the results of the Royal Marsden and Italian studies should be referenced in the product information.

4. (reworded) Should tamoxifen be approved for the risk reduction of short term incidence of breast cancer in women at increased risk as defined by the study population?

Yes - 9 No - 0 Abstain - 2

5. Does the committee recommend that the package insert and patient package insert should include all of the above protocol-specified monitoring?

The Committee indicated that the medical history, mammogram, and physical and gynecological examinations should all be recommended, but that the blood tests were not necessary.

6. Based on the information from this study, should the package insert and patient package insert recommend that women who take tamoxifen for the short term reduction of breast cancer incidence undergo yearly endometrial sampling?

Yes - 0 No - 9 Abstain - 2

7. On NSABP P-1, women on tamoxifen had a higher incidence of cataract formation and a higher rate of cataract surgery (Table 2). Information about non-cataract ophthalmologic toxicity was not collected. Should the package insert and patient package insert recommend that women who take tamoxifen for the prevention of breast cancer undergo yearly eye examinations?

Yes - 0 No - 10 Abstain - 1

8. Does the committee have any other recommendations for monitoring the safety of women taking tamoxifen for short term breast cancer risk reduction?

The Committee made numerous recommendations throughout the discussion, but strongly emphasized the need for both physician and patient education. Special effort should be made to fully inform primary care physicians and obstetrician/gynecologists or risks and benefits as they would be more likely to prescribe for this indication than oncologists. A pregnancy test should also be completed before the start of treatment.

9. Should FDA ask for a Phase 4 commitment to further study participants with thromboembolic events for possible predisposing factors.

Yes - 11 No - 0

10. Should FDA ask for a Phase 4 commitment to further study women on tamoxifen for non-cataract ophthalmologic toxicity?

Yes - 0 No - 11

Overall, the Committee indicated that the NSABP-1 trial was not large enough or long enough to show a difference in mortality between the two arms. The toxicity profile is a concern as the treatment group will consist of healthy women, who will be put at increased risk of endometrial cancer and serious blood clots. More information is needed on the mechanism of the effects of tamoxifen, and there is a need for an improved formula for determining exactly which women will have a favorable benefit:risk ration for treatment.

Appendix D. Review of absolute risk levels in women aged 60 or greater

The data sent by the NSABP were analyzed to further delineate the risks and benefits in women age 60 or older. Women who were age 60 or older were automatically eligible for NSABP P-1; however, a Gail score was calculated on all these women based on their risk factors. Some women over 60 without additional risk factors had a 5-year predicted risk of breast cancer that was less than 1.66%, because the 1.66% figure represents an *average* risk for women in this age group. The following table presents the risks and benefits of tamoxifen therapy in these women.

Table D1. Women aged 60 or greater, grouped by absolute 5-year predicted risk of breast cancer

Event	< 1.66% (N=580)		1.66-2.00% (N=462)		2.01-3.00% (N=811)		3.01-5.00% (N=1294)		≥ 5.01% (N=869)	
	P (n=297)	T (n=284)	P (n=236)	T (n=226)	P (n=408)	T (n=403)	P (n=652)	T (n=642)	P (n=425)	T (n=444)
IBC	1	3	5	2	7	4	18	9	18	5
DCIS	0	0	1	2	4	3	3	1	3	1
Endometrial cancer	0	4	0	1	1	2	1	2	0	3
Stroke	1	1	3	4	2	4	9*	8	1	2**
PE	0	2#	0	1	0	2	2	1	1	3
DVT	0	2	1	0	2	2	2	6	0	1
Cataracts on study	41	37	36	35	58	70	108	128	75	87
Cataract surgery	12	15	9	18	22	32	33	64	29	36

* 1 fatal
** Both fatal
# 1 fatal

Women over age 60 with a 5-year risk of < 1.66% had no benefit from tamoxifen (1 cancer on placebo compared to 3 on tamoxifen). However, this group experienced serious adverse events, including 4 endometrial cancers, 2 pulmonary emboli (1 fatal), and 2 deep vein thromboses, compared to none on placebo.

For women with risks greater than 1.66%, there was approximately a 50% reduction in breast cancer incidence at each prospectively defined risk strata.

Based on this analysis, the reviewer concludes that only women with a 5-year risk of breast cancer of ≥1.66%, as calculated by the Gail model, should be considered for tamoxifen therapy to decrease the incidence of breast cancer, rather than women aged 35-39 with a 5-year risk of ≥ 1.66% plus all women age 60 and older.