Table 77. Global Analysis—Part A: Difference in Events (Table 17, ERSMAC report, page 28, volume 109.3)

Type of Event	Placebo (no. cases)	Tamoxifen (no. cases)	Difference
Breast cancer	154	85	69
Heart disease	59	61	-2
Hip fracture	20	9	11
Endometrial cancer	14	33	-19
Colorectal cancer	12	14	-2
Liver cancer	0	0	0
Pulmonary embolism	6	17*	-11*
Stroke	24	34	-10
TIA	21	18	3
DVT	19	30	-11
Other deaths	54	40	14
Total	383	341	42
Weighted number of events	388.5	335.5	53

*Without the 18th identified case; see section 10.4.3

Table 78. Global Analysis—Part B: Percent of all participants with events

Type of Event	Percent of participants with events		Difference	Stand. Diff.
	Placebo	Tamoxifen		
Breast cancer	2.296	1.272	1.024	4.27
Heart disease	0.880	0.913	-0.033	-0.20
Hip fracture	0.298	0.135	0.164	1.94
Endometrial cancer	0.209	0.494	-0.285	-2.66
Colorectal cancer	0.179	0.210	-0.031	-0.38
Liver cancer	0	0	0	0
Pulmonary embolism	0.090	0.254	-0.165	-2.20
Stroke	0.358	0.509	-0.151	-1.27
TIA	0.313	0.269	0.044	0.45
DVT	0.283	0.449	-0.166	-1.51
Other deaths	0.805	0.599	0.206	1.36
Total	5.710	5.104	0.606	1.45

Weighted index= 1.58

Table 79 (Table 19, ERSMAC report, volume 3, page 30). Average annual hazard rates, risk ratios, and 95% CI for events included in the global analysis—1/31/98

Type of event	Average Annual Hazard Rate (per 1,000)		Risk Ratio*	95% CI
	Placebo	Tamoxifen		
Breast cancer	6.493	3.581	0.55	0.42--0.72
Heart disease	2.470	2.567	1.04	0.73--1.49
Hip fracture	0.835	0.377	0.45	0.21—0.99
Endometrial cancer	0.923	2.290	2.48	1.33—4.63
Colorectal cancer	0.501	0.587	1.17	0.54—2.53
Liver cancer	0	0	--	--
Pulmonary embolism	0.250	0.712	2.85	1.12—7.22
Stroke	1.002	1.427	1.42	0.84—2.40
TIA	0.877	0.755	0.86	0.46—1.62
DVT	0.793	1.259	1.59	0.89—2.82
Other deaths	2.251	1.674	0.74	0.49—1.12

*TRT B relative to TRT A

A description of the global analysis was not included, nor how the weighted indices were calculated. The NSABP described these results in the ERSMAC report as consistent with a decreased risk for breast cancer and hip fracture with tamoxifen treatment and an increased risk for endometrial cancer, DVT, and pulmonary embolism with tamoxifen. Overall, there were slightly fewer deaths in women treated with tamoxifen compared to placebo.

In the NSABP P-1 manuscript, the authors state that tamoxifen reduces the risk of invasive and non-invasive breast cancer by almost 50% in all age groups, and is effective regardless of the type of risk associated with P-1 participants. Tamoxifen reduces risk in women with a history of AH and LCIS.

No significant difference in the incidence of cardiovascular disease was observed, despite evidence that tamoxifen can alter lipid profiles. The authors state that tamoxifen reduced the risk of hip, Colles', and spine fractures by 55%, 42%, and 21% in women over age 50.

In terms of adverse events, the authors stated that tamoxifen increased the risk of endometrial cancer in women over age 50. However, the endometrial cancers that were diagnosed had characteristics similar to those seen in the general population, and did not have aggressive features. Regular gynecologic evaluations with additional evaluation for vaginal bleeding were recommended.

An increased rate of vascular events was noted. The authors acknowledged that there was an increase in the average annual rate of stroke in women over age 50, but did

not describe a mechanism for this finding. They also stated that while the risk of PE was increased and 3 women died of PE, "...all were associated with comorbid conditions that could have accounted for those deaths."

An increased rate of cataract formation was found in the tamoxifen-treated group. In the opinion of the authors, the ophthalmic effects of tamoxifen "...are not considered sufficiently great to warrant withholding the drug from women such as those who participated in the P-1 trial."

Whether tamoxifen can prevent the initiation of tumors or whether it inhibits the growth of occult tumors is unknown. The optimal duration of tamoxifen exposure has not been firmly established.

The findings from the two recently published European trials were discussed in the manuscript. The authors felt the results from the Royal Marsden and Italian studies did not change the conclusions drawn from the NSABP P-1 study. They cite the following points:

- The studies are dissimilar with regard to design and study population
- There were few events in the European trials (70 in the British study, 49 in the Italian study, and 319 in the P-1 study)
- The European studies had a smaller sample size, enriched for younger women who were more likely to have ER(-) disease at diagnosis (an entity not prevented by tamoxifen)
- Noncompliance rates were high in the European studies
- HRT was allowed in the European studies; the authors cite the rates as 41% in the British study and 14% in the Italian study

Investigators at the NSABP recommend that tamoxifen be considered for:

- Premenopausal women whose risk for breast cancer is equivalent to that of P-1 participants
- Women with LCIS or atypical hyperplasia, regardless of age
- Women who have had a hysterectomy

The authors listed women who might be candidates for therapy:

- Women with a history of DCIS
- Women with BRCA1/2 mutations

Overall, women and their physicians must weight individual risks and benefits in order to decide whether treatment is advisable. A simple method of adding up the beneficial events and subtracting adverse events is not appropriate, since not all events are equal in terms of morbidity and mortality. Additional tools to guide treatment decisions are under development at the NCI and at NSABP.

14.0 Reviewer's Summary of Safety and Efficacy

14.1 Benefit: Breast cancer endpoints

The NSABP P-1 study is the first randomized double-blind trial of a chemopreventive agent that demonstrates a significant reduction in the incidence of invasive breast cancer. Review of the submitted materials indicates that tamoxifen decreases breast cancer in women:

- Aged 35 or more with a 1.7% risk of developing breast cancer in the next 5 years, regardless of age subgroup and regardless of risk level
- With AH or LCIS
- Regardless of family history of breast cancer, and regardless of the number of affected first-degree relatives
- With a broad spectrum of possible risk factor combinations
- Tamoxifen also decreased the number of cases of DCIS by 34%

However, it is important to also point out the limitations of tamoxifen therapy:

- Tamoxifen reduces but does not eliminate breast cancer risk
  - Women on tamoxifen should have regular breast exams and mammograms
  - Women on tamoxifen should seek prompt medical attention for any new breast lumps that they may detect themselves
- Despite close follow-up in this trial, 23% of the breast cancers women had axillary lymph node involvement, 4% of the breast cancers were inflammatory breast cancer, and 0.8% of the breast cancers were Stage IV at diagnosis
- Tamoxifen does not prevent ER negative breast cancer
- It prevents tumors less than 2 cm in size; little difference between tamoxifen and placebo was observed for larger tumors
- Our review does not demonstrate an effect of tamoxifen on the incidence of LCIS, a marker lesion of risk

The effects of tamoxifen in African-American women and women of other non-Caucasian races is unknown. There were a higher number of breast cancer events on the tamoxifen arm than on the placebo arm in this subset of women, but the absolute number of events was rare.

The sample size was re-calculated during the course of the study, a change that can influence the validity of the study conclusions. In NSABP P-1, the sample size calculation was prospectively defined and was planned to occur after 25% of the patients had been accrued. Based on the original target of 16,000 women, the sample size evaluation should have been performed after accrual of 4000 women, midway through the first year (accrual from 6/92 through 5/93 was 7154, according to the amendment). However, the change in sample size was not made until 9/30/96. The delay was due to the need for prolonged follow-up of the participants to fully evaluate risk levels. Given

the overall results of the trial and the internal consistency within prospectively defined subgroups, it is unlikely that the change in sample size weakened the study results. We find them to be robust.

14.2 Benefit: Cardiovascular and fracture endpoints

The trial anticipated that tamoxifen might reduce the risk of cardiovascular events and fractures.

No benefit for tamoxifen was seen with regard to cardiovascular endpoints. However, the number of women on study aged 50 or older, evaluated by an Access query of the database, was 8127, rather than the 10,000 calculated as the approximate sample size necessary to evaluate cardiovascular events. The failure of tamoxifen to reduce myocardial infarction may be due to power considerations rather than a true lack of effect.

In terms of fracture reduction, the Agency does not consider spine fractures *as defined and evaluated in NSABP P-1* to represent a reproducible measure of efficacy, even though the Agency recognizes that many of these fractures occur yearly in the United States and result in significant pain and debilitation for the patient. There was a reduction in the number of hip fractures and the number of Colles' fractures for women treated with tamoxifen. Benefit was seen for women of all ages, although older women had a greater absolute benefit.

14.3 Risks: Death

Treatment with tamoxifen did not increase mortality compared to placebo. Although few women in the trial died of breast cancer, tamoxifen did not reduce breast cancer mortality, with the follow-up available.

14.4 Risks: Endometrial cancer

Tamoxifen increased the risk of endometrial cancer, with a risk ratio of 2.48. Although the excess risk was confined to postmenopausal women, it should be noted that the premenopausal women in this trial had a higher risk of endometrial cancer than that predicted by SEER data or by the control arm of NSABP B-14, which may mask a tamoxifen effect in the treatment group. We believe that the following points should be discussed with women who are considering chemopreventive therapy with tamoxifen:

- Tamoxifen is associated with an increased risk of endometrial cancer, regardless of age
- Early stage endometrial cancer is treated with a TAH-BSO and may also require pelvic irradiation; these treatments carry both short- and long-term complications
- Obesity increases the risk for endometrial cancer but does not account for all the risk
- Women with endometrial cancer may be asymptomatic.
  - Women on tamoxifen should have regular gynecologic evaluation

- Women on tamoxifen should seek prompt medical attention for any vaginal bleeding or other gynecologic symptom
- Endometrial sampling may detect endometrial cancer in rare instances

14.5 Risks: Stroke, DVT, PE

More strokes were observed on the tamoxifen arm than on the placebo arm, predominantly in postmenopausal women with other risk factors for stroke. The majority of events were thrombotic, consistent with that seen in clinical practice. It is possible that the increased number of events is related to the thrombogenic properties of tamoxifen.

Tamoxifen was associated with an increased risk of both DVT and PE. In our analysis, the risk of DVT was observed in women both under and over the age of 50. Pulmonary emboli were seen almost exclusively in postmenopausal women; three were fatal. We identified the third case of fatal pulmonary embolism during the course of our review. We disagree with the comments in the manuscript that indicate that participants died "*with* a PE rather than *of* a PE." One participant had a history of well-controlled diabetes mellitus; her glucose became difficult to control as a result of her initially asymptomatic pulmonary embolus. Review of the CRF demonstrates PE as the cause of death, not end-stage diabetes mellitus. A second participant had idiopathic pulmonary fibrosis. While she had generally compromised lung function, she was stable and ready for discharge after hospitalization for complications of Imuran therapy, and died suddenly of a PE. The third patient had metastatic pancreatic cancer and most likely would have died shortly from her disease had she not developed a PE. The seriousness of a PE should not be minimized. In a large trial such as NSABP P-1, factors for comorbid illnesses were equally distributed; the observation that there is an increased number of PEs on the tamoxifen arm suggests a causal relationship and should be fully discussed with women considering tamoxifen chemopreventive therapy.

From review of the MedWatch forms for ophthalmic complaints, tamoxifen may also cause retinal vein occlusion.

Factors that are important to mention when counseling women include:

- The risk of thromboembolic disease is increased, regardless of age
  - A number of sites, including brain, lung, legs, and eye, may be affected by the risk of clot formation
- Smoking and obesity may contribute to risk, but do not fully account for risk
- As with any thromboembolic event, a woman remains at increased risk for a second event, because of the underlying disorder that led to the first event (coagulopathies, obesity, tobacco use) in addition to anatomic abnormalities caused by the first event (altered venous architecture)
- There may be complications of an event, such as venous insufficiency or complications of anticoagulation
- Women on tamoxifen with symptoms of leg swelling, tenderness, unexplained shortness of breath, or a change in baseline pulmonary symptoms should seek prompt medical attention, and inform the treating physician that they take tamoxifen
- Women with a history of DVT or PE should not take tamoxifen

14.6 Risks: Cataracts and other eye events

An increased risk of cataract development and cataract surgery was observed in the tamoxifen arm. We agree with the sponsor that this risk by itself does not obviate the use of tamoxifen as a chemopreventive agent, but should be discussed with women considering its use.

Because information on other eye events was not systematically collected and because participants were not required to have annual eye examinations, we believe there is insufficient information to address whether tamoxifen increases the risk of non-cataract ophthalmic events. The ocular study performed on a subset of NSABP B-14 patients, cited by the NSABP, evaluated 303 volunteers: 85 on placebo, 140 who had completed tamoxifen therapy, and 78 on continuous tamoxifen. Only the medical staff were blinded; the patients were not. Since ophthalmic toxicity from tamoxifen appears to be a rare event, it is unlikely that this sample size and the heterogeneous nature of the population provide enough power to address this issue.

The following points should be discussed with women considering tamoxifen therapy:

- Tamoxifen increases the risk of cataract formation and the need for cataract surgery
- Tamoxifen may increase the risk of retinal vein occlusion, leading to visual impairment
- The effect of tamoxifen on other eye events is unknown
- Women on tamoxifen for the chemoprevention of breast cancer should undergo yearly eye exams and inform their eye care provider that they take tamoxifen

14.7 Risks: Depression

The quality of life analyses for this study do not demonstrate an increased incidence of depression with tamoxifen treatment. However, the CES-D scale used frequently did not correlate with clinical psychiatric events described in the CRFs.

- Women considering tamoxifen should be informed that there is insufficient information with which to evaluate the relationship of tamoxifen to depression.

14.8 Risks: General

- The daily side effects of tamoxifen were consistent with those previously reported in the literature and included hot flashes and vaginal discharge.
- The effect of tamoxifen on the fetus is unknown; women should be cautioned to use an effective form of birth control while taking the drug.

14.9 Summary

The benefit of a reduction in breast cancer must be weighed against the toxicities of tamoxifen. Careful consideration is warranted, particularly in light of the fact that the

study was powered to detect a benefit of tamoxifen, but was not powered to detect a detrimental effect of treatment with tamoxifen.

Reporting of events in this trial was complex. First, for most endpoints, the first event per patient was reported, or the worst event of a series of related events. For example, a participant with severe angina and an MI was reported only as an MI; a participant with 2 episodes of severe angina was reported once. In distinction, the sponsor reported each fracture individually, rather than reporting one event per patient as with the other endpoints. Second, many events were reported for participants who had discontinued study drug. While there is a rationale for this approach (tamoxifen has a long half-life, and effects on bone and cardiovascular function may be long-lasting), *the events on and off study drug should be considered separately as well as together.*

The risks and benefits of tamoxifen for chemoprevention, based on review of the submitted materials, can be summarized as follow:

Table 80. Risks and benefits of tamoxifen therapy

BENEFITS	UNKNOWN EFFECT	NO EFFECT	RISKS
Decreases invasive breast cancer	Breast cancer reduction in women of color	Ischemic heart disease	Endometrial cancer
Decreases DCIS	Women with BRCA1/2 mutations	Death from all causes	DVT
Decreases hip and Colles' fractures	Women with known DCIS*	Incidence of other cancers	PE
	Depression	Prevention of LCIS	Stroke
	Non-cataract ophthalmic toxicity		Cataracts, cataract surgery
			Hot flashes, vaginal discharge

*Early reports show benefit; data not published and not submitted to FDA at this time

The findings noted above are based on this trial and are therefore applicable to the type of women entered into this trial—i.e., women who met the eligibility criteria as defined by age, prior history of LCIS, and as predicted by the Gail model, *with the level of risk comparable to the women actually entered on the trial.* In contrast to the authors of the NSABP manuscript, we would like to point out that data describing the effect of tamoxifen on subsequent events in women with DCIS have not been published or reviewed by the Agency. We do not feel there is sufficient information available at this time to consider these women for tamoxifen therapy. Similarly, there are no data that address the efficacy of tamoxifen in women with hereditary breast cancer syndromes, and we do not feel these women should be considered for tamoxifen therapy at this time. Finally, women who have had a hysterectomy should still have the level of risk required

for P-1 study entry to consider tamoxifen therapy. Although these women will not be at risk for endometrial cancer, they remain at risk for other events and should undergo the same risk-benefit discussion as women with other risk characteristics.

We agree with the NSABP authors that not all events carry the same weight with regard to their seriousness or significance. However, different women will weigh events differently, and a detailed risk-benefit discussion with a woman considering therapy is essential. It is also important to point out that the risk-benefit ratio is not constant over the course of therapy: women will become older, and if they become postmenopausal, their personal risk-benefit assessment may change significantly.

Although tamoxifen carries significant risks, this trial demonstrates that it is highly effective in reducing the incidence of breast cancer, the most common cancer among women in North America and a significant health concern, both medically and emotionally, for many women in the United States. It is important to consider the results from other chemoprevention trials with tamoxifen, which will be discussed at ODAC. However, the reviewer believes that the weight of evidence, including published literature that demonstrates a reduction in contralateral breast cancers with tamoxifen, supports the results of the NSABP P-1 trial. The contrasting results of the European studies can be attributed to different levels of risk at entry, compliance, concomitant hormonal therapy, and statistical power to demonstrate a difference between the two treatment arms. While tamoxifen is associated with a number of risks, ranging from bothersome to potentially fatal, the number of invasive breast cancer events prevented in this high-risk population is greater than the number of serious adverse events.

Overall, the reviewer recommends approval of tamoxifen for the chemoprevention of breast cancer, pending discussion by the ODAC members.

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Appendix A. Required on-study evaluations

Appendix B. Review of European breast cancer prevention trials

During the course of the review of this application, 2 European trials of tamoxifen for breast cancer prevention were published. These trials and their potential relevance to the trial results of NSABP P-1 are discussed in this section.

Italian Breast Cancer Prevention Trial

Materials reviewed:

Protocol document: Tamoxifen study: Prevention of breast carcinoma with annual mammograms and the use of an antiestrogen

Publication: Veronesi U, Maisonneuve P, Costa A, et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Lancet 1998; 352: 93-97

The Italian Breast Cancer Prevention trial was a multicenter randomized double-blind placebo-controlled trial of tamoxifen 20 mg daily versus placebo for 5 years. The *protocol document* outlined the following plan of study:

Eligibility included:

- Women between the ages of 35 and 70 who had undergone a hysterectomy for non-malignant indications and who had a normal mammogram and breast exam at entry.
  - Hysterectomy should be confirmed by pelvic ultrasound if necessary

Exclusion criteria included women with:

- Prior diagnosis of cancer (except basal cell skin cancer and CIS of the cervix)
- Endometriosis
- DVT, PE, superficial phlebitis, family history ($\geq$ 2 first-degree relatives) of venous thrombosis
- Prior CVA or TIA
- Carotid vascular murmur
- Claudication
- Cardiac functional class $\geq$ II
- Prosthetic valve
- Raynaud's disease
- Aortic aneurysm
- Current requirement for anticoagulation
- Valvulopathy (mitral or tricuspid)
- Unstable angina
- Uncontrolled hypertension
- Atrial fibrillation
- Prior MI
- Ischemic cardiomyopathy
- Prior prophylactic mastectomy
- Retinopathy or visual impairment

- History of porphyria
- Inadequate hematologic parameters

Women were followed every 6 months with yearly mammography and labwork. Bloodwork included hematocrit, transaminases, total cholesterol, HDL, and LDL. Bone densitometry was performed in a subset of women at baseline, 1, 2, 3, 4, and 5 years with osteocalcin levels. Psychological testing was planned in a subset of women to evaluate cognitive function. Stated events for follow-up included cardiovascular complaints, thromboembolic events, bone fractures, other cancers, hepatic diseases, retinopathies, and visual disorders. Specific symptoms to be evaluated included hot flashes, skin flushing, palpitations, perspiration, and vaginal dryness.

Randomization was performed centrally, stratified by center. Women were to be removed from study for the development of any condition listed in the exclusion criteria. Temporary interruptions of therapy, to evaluate changes in laboratory tests for example, were permitted. All women were to be followed, even if removed from study.

The use of "temporary estrogen treatment" was permitted. This therapy is generally delivered transdermally, by patch, in Italy.

The primary endpoint was reduction in the incidence and mortality rate of breast cancer. Other causes of death were recorded. Death due to MI was of particular importance.

The investigators assumed a risk of breast cancer in the participant population of 1.7 per 1000 per year. In order to demonstrate a 33% reduction in breast cancer risk with a compliance rate of 75%, the power to demonstrate a difference between treatment arms was calculated at 57% after 7 years of follow-up with 20,000 participants. Several other examples were given; a definite sample size for the study was never defined. The data were analyzed on an intent-to-treat basis. The frequency of events in each group was compared using the logrank test. A simulation analysis was done to assess the possible effects of reporting the result before the time specified in the protocol. Analyses were performed for an intent-to-treat population and an intent-to-treat analysis that excluded all participants who were on study for less than 12 months.

The trial was monitored by an International Data Monitoring Committee and by and Adverse Reactions Monitoring Panel.

In the publication, the investigators reported that the trial opened in October 1993 and terminated recruitment July 1997 because of the high drop-out rate. Ninety-one women were entered with a "subtotal hysterectomy" and were excluded from analysis.

Fifty-five centers randomized 5408 women on study. However, 97% of women were entered from Italian centers. The median age was 51. Of these participants, 3837 remain on treatment, 149 completed 5 years of treatment, and 1422 dropped out.

Ninety-eight percent (5287) had undergone a total hysterectomy; 26.3% (1412) had conservation of the ovaries, 48.3% (2595) had a bilateral oophorectomy, 18.6% (998) had a unilateral oophorectomy, and in 5.2% (282) there was no information. Twelve percent of the population had a first-degree relative with breast cancer.

Of the women who withdrew from study, 239 went off study because of an adverse event. Side effects or unwillingness to continue accounted for the withdrawal of 1027 women. Although the authors' statement that most drop-outs occurred in the first year, there was still a significant drop-out rate during years 2-4.

Fifteen deaths occurred, 9 on placebo and 6 on tamoxifen; none were from breast cancer. There was no apparent difference in cause of death between arms.

Thirty-three cases of breast cancer occurred, 19 on placebo and 14 on tamoxifen. An additional 8 cases occurred after study drug was stopped (3 versus 5). Among women with breast cancer, 9 had used HRT at baseline and throughout the trial (8 placebo, 1 tamoxifen). One woman on each arm had used HRT at some point during the trial. A comparable number of ER(+) cases were identified on each arm. Four of the cases represented in situ disease.

Sixty-four thromboembolic events occurred in 56 women (18 on placebo and 38 on tamoxifen). There were 42 cases of superficial thrombophlebitis (9 P, 33 T), 9 cases of DVT (3 P, 6 T), 2 cases of PE (1 on each arm), and 14 CVAs (5 P, 9 T). Hypertriglyceridemia was reported in 2 women on placebo and 15 on tamoxifen; this parameter was not measured as part of the study protocol. Information was obtained from participant self-report.

The investigators concluded that the observed death rate and stroke rate were lower than those expected in the general Italian population. While no difference in the incidence of breast cancer was demonstrated, this population was at low risk for breast cancer and the study had low power to detect a difference (34% power, calculated retrospectively). The authors also stated that tamoxifen protected women on HRT from an increased incidence of breast cancer, which should be evaluated in subsequent studies.

Royal Marsden Hospital trial

Materials reviewed:

Publication: Powles T, Eeles R, Ashley S, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. Lancet 1998; 352: 98-101.

Protocol document unavailable

The Royal Marsden study is a randomized double-blind placebo-controlled trial of tamoxifen 20 mg daily compared to placebo for 8 years. The eligibility requirements for this study are as follows:

- Aged 30-70, without evidence of breast cancer
- Must have:
  - At least 1 first-degree relative under age 50 with breast cancer, or
  - One first-degree relative with bilateral breast cancer, or
  - One affected first-degree relative of any age plus another affected first- or second-degree relative, or