Table 22. Stage of invasive disease, NSABP B-24 trial

Stage	Placebo	Tamoxifen	TOTAL
I	14 +31[1]	4 +20[1]	69
II	10 +3[2]	7 + 1[2]	21
III	3 + 1[3]	3 + 1[3]	8
IV	5	3	8
Unknown	7	5	12

[1] Cases with T1 lesions; N status unknown—prior dissection or no dissection reported
[2] Cases with T2 lesions; N status unknown—prior dissection or no dissection reported
[3] Cases with T3 lesions; N status unknown—prior dissection or no dissection reported

There did not appear to be an excess number of cases diagnosed with advanced disease. Breast cancer occurred more commonly in women randomized to placebo compared to women randomized to tamoxifen. The stage distribution appeared to be similar between treatment arms. However, it is worth noting that even with careful follow-up in the setting of a clinical trial, approximately 7% of patients presented with metastatic disease as the first sign of recurrence.

There was no apparent association between the subsequent development of advanced (stage III or IV disease) and size, margin status, presence or absence of comedo necrosis, or method of detection of the index lesion.

9.3 Non-invasive breast cancer (Lancet)

The number of non-invasive breast cancer events was reduced by 31% in women treated with tamoxifen compared to women treated with placebo.

Non-invasive breast cancers (ipsilateral and contralateral events) were reduced by 18% and 78% respectively in women treated with tamoxifen. The effect of tamoxifen was greater in the contralateral breast.

Reviewer Comment:

1. Because radiation therapy decreases the risk of ipsilateral breast recurrence, one might expect the absolute effect of tamoxifen to be less on this side.

2. The incidence of non-invasive breast cancer, both ipsilateral and contralateral, was the second endpoint of the trial. The applicant reported a total of 103 cases, 87 ipsilateral (47 on placebo, 40 on tamoxifen) and 16 contralateral (13 on placebo, 3 on tamoxifen).

3. The reviewer found a total of 99 unique cases, 58 on placebo and 41 on tamoxifen. Four patients, all on placebo, had two events for a total of 103 cases, 62 on placebo and 41 on tamoxifen. Duplicate entries were used only in assessing ipsilateral versus contralateral events (see next section). Ipsilateral events may be due to residual cancer, while contralateral processes probably result from a combination of risk factors that increases the likelihood of an event that is distinct from the first.

The case numbers differed from those of the applicant as follows.

A. Ipsilateral non-invasive breast cancer:

The following patients were ***removed*** from the applicant's list:

Placebo:

441148104 This patient had microinvasion per the local pathologist. She was reassigned to ipsilateral invasive cancer (see above)

Tamoxifen:

443929926 Had DCIS with stromal invasion. This patient was reassigned as an ipsilateral invasive cancer, as described above

440406112 This patient had invasion in the pathology specimen and was reassigned as an ipsilateral invasive cancer (described above).

441621017 This patient had an ipsilateral DCIS as a first event, then developed ipsilateral adenopathy and distant metastases. Per protocol, only her first event was counted. However, the reviewer believes it is more appropriate to count her most serious event, the metastatic disease and ipsilateral invasive failure, and has deleted her from the non-invasive list.

The following patients were ***added*** to the applicant's list:

Placebo:

443735225 This patient was diagnosed with Paget's disease and was reassigned to ipsilateral non-invasive disease (see above discussion).

Tamoxifen:

440067089 This patient was diagnosed with Paget's disease; the reviewer reassigned her from ipsilateral invasive cancer to ipsilateral non-invasive disease (see above discussion).

These changes result in a total of 101 patients, 60 on placebo and 41 on tamoxifen.

B. Contralateral non-invasive breast cancer:

The following patients were ***removed*** from the applicant's list:

Placebo:

443074212 The biopsy specimen contained DCIS with 0.9 cm of IDC. This patient was reclassified as having contralateral invasive breast cancer.

444400277 Diagnosed with simultaneous contralateral non-invasive and ipsilateral invasive breast cancer. The reviewer categorizes this patient according to the most serious event.

These changes result in a total of 99 patients, 58 on placebo and 41 on tamoxifen.

C. Patients excluded on the basis of pathology

Two patients, both on placebo (443769415 and 444302104) were excluded because their biopsies demonstrated LCIS, not DCIS. LCIS is a premalignant lesion that is associated with an increased risk of bilateral breast cancer. There are no data that demonstrate that a diagnosis of LCIS after a diagnosis of DCIS changes the risk profile of an individual. A subsequent diagnosis of LCIS usually does not lead to a change in patient management. For this reason, these events are excluded.

D. The total number of FDA-verified cases of non-invasive breast cancer is 97, 56 on placebo and 41 on tamoxifen.

Table 23. FDA analysis, FDA-verified non-invasive breast cancers (ipsilateral and contralateral)

Event	Placebo		Tamoxifen		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
All non-invasive cancers	56	12.66	41	8.95	0.71 (0.46, 1.08)	0.1106

While the reduction in non-invasive breast cancers is not statistically significant, fewer events occurred. A 29% reduction in risk was observed.

The following sections refer to additional exclusions for the exploratory analysis.

E. Patients excluded because of pre-existing disease

Three patients, 2 on placebo and 1 on tamoxifen, were excluded because their lesions appeared to be pre-existing:

Placebo:

440821905 This patient was randomized on study in 11/92, then changed her mind and elected to have a mastectomy in 12/92. The pathology of the mastectomy showed DCIS. This finding is unlikely to represent a new event and instead is consistent with residual but not recurrent disease.

444659108 This patient had microinvasive disease at baseline.

Tamoxifen:

442055945 This patient had microinvasive disease at baseline.

F. Patients excluded—second event within 1 year of randomization

The following patients were diagnosed with non-invasive breast cancer in less than a year from randomization, increasing the likelihood that disease was pre-existing:

Placebo:

440776925	8.3 months
440821905	1.8 (already excluded in E for pre-existing disease)
443288055	10
443449416	11.9
444659108	8.6 (already excluded in E for pre-existing disease)
444863134	7.3

Tamoxifen:

441464957	5.5 months
441601940	9.4
442549213	4.5
444209054	4.6
444315019	3.4

In contradistinction to the invasive cancers, the number of non-invasive cancers diagnosed in the first year was similar on both arms.

These changes result in 85 cases for the exploratory analysis, 50 on placebo and 35 on tamoxifen. The results of the exploratory statistical analysis were similar to those of the FDA-verified analysis (rate ratio 0.68 with 95% CI 0.43, 1.06; p=0.0925).

E. Duplicate entries

In order to evaluate in-breast recurrence, 3 patients whose first event was a contralateral non-invasive breast cancer but who had ipsilateral non-invasive breast cancer as a second event were added to the ipsilateral category:

Placebo:

441409441
441062187
440963337

These three patients represent duplicate events but were not counted twice in the endpoint of all non-invasive cancers.

The following patient was added to the applicant's list, only for assessment of contralateral versus ipsilateral events:

Placebo:

444901014 Her first event was an ipsilateral DCIS; she then had a non-invasive contralateral DCIS as a second event.

These duplicate entries will be used for analysis in the next sections.

9.4 Ipsilateral breast cancer (invasive and non-invasive) (Lancet)

The majority of the observed breast cancer events occurred in the ipsilateral breast (150, or 70%). Tamoxifen reduced the incidence of ipsilateral invasive breast cancer (44% reduction), but did not significantly change the rate of ipsilateral non-invasive breast cancer events compared to placebo (18% reduction; p=0.43).

Of the 150 women with an ipsilateral breast cancer event, 64% were treated with mastectomy. Thirty-six percent were treated with a second lumpectomy. When analyzed by treatment arm, 68% of women on placebo with an ipsilateral breast tumor were treated with mastectomy, compared to 59% of those on tamoxifen. Women with an invasive ipsilateral recurrence, regardless of treatment arm, were more likely to have a mastectomy than women with a non-invasive ipsilateral event (75 and 56% respectively, p=0.03).

Reviewer Comments:

1. The applicant reported 150 ipsilateral breast cancer events, 87 on placebo and 63 on tamoxifen.

2. The reviewer noted 161 ipsilateral breast cancer events, 96 on placebo and 65 on tamoxifen. The differences in the patient numbers between these two distributions can be found in the above explanations of the differences in assessment of invasive and non-invasive disease. In addition to the total number of ipsilateral invasive and non-invasive cases described above, 3 patients randomized to placebo who had contralateral non-invasive breast cancer as a first event and who then had ipsilateral non-invasive breast cancer as a second event are included here (see "E. Duplicate entries" above).

The statistical analysis of all ipsilateral breast cancer events is summarized below.

Table 24. FDA analysis of all ipsilateral breast cancer events

Event	Placebo		Tamoxifen		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
All ipsilateral breast events	96	21.70	65	14.19	0.65 (0.47, 0.91)	0.0095

3. Tamoxifen reduced the incidence of ipsilateral breast cancer events by 35% (statistically significant).

4. Given that all women had ipsilateral radiation therapy as part of the initial treatment, it is not surprising that a high percentage of patients were treated with mastectomy for a second ipsilateral event.

9.5 Contralateral breast cancer (invasive and non-invasive) (Lancet)

Fifty-four contralateral breast cancer events were observed, 36 on placebo and 18 on tamoxifen. Among women randomized to placebo, 23 events were invasive and 13 were non-invasive. Among women randomized to tamoxifen, there were 15 invasive cancers and 3 non-invasive cancers. The relative risk of contralateral breast cancer was 0.48, a 52% reduction in the number of events for women treated with tamoxifen. The

cumulative incidence of all contralateral breast cancer occurring as first events at 5 years was 3.4% for placebo and 2.0% for tamoxifen. The reduction in invasive contralateral breast cancers (23 on placebo versus 15 on tamoxifen; 37% reduction) was not significant (p=0.22). The reduction in non-invasive contralateral breast cancers, while large (78%) was derived from a small number of events (13 on placebo versus 3 on tamoxifen; p=0.02). The cumulative incidence of invasive and non-invasive contralateral tumors at 5 years was low: for invasive tumors, it was 2.3% compared to 1.8% (placebo versus tamoxifen) and for non-invasive tumors, 1.1% compared to 0.2% respectively.

In data not shown but reported in the Lancet publication, the NSABP looked at all contralateral breast cancers, whether they represented first or subsequent events. A total of 39 were seen in women on placebo and 23 in women on tamoxifen. The relative risk of contralateral breast cancer was 0.58 (95% CI 0.35, 0.97), a 42% reduction among women randomized to tamoxifen.

Reviewer Comments:

1. The applicant reported 54 contralateral breast cancer events, 36 on placebo and 18 on tamoxifen.

2. The reviewer found 57 contralateral events, 37 on placebo and 20 on tamoxifen. The difference between the applicant's and the reviewer's assessments is described in the sections on invasive and non-invasive disease. In addition, one patient randomized to placebo had ipsilateral DCIS as her first event, then non-invasive contralateral DCIS as the second event. She is included in this tally.

Table 25. FDA analysis of contralateral breast cancer events

Event	Placebo		Tamoxifen		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
All contralateral events	37	8.36	20	4.37	0.52 (0.29, 0.92)	0.0237

3. Tamoxifen was associated with a 48% reduction in the risk of contralateral breast cancer events. This reduction is consistent with the benefit observed with tamoxifen in women treated for early stage breast cancer.

4. The applicant refers to data reported in the Lancet, where a total of 39 contralateral breast cancer events were seen in women on placebo and 23 in women on tamoxifen. These data were sent to the Agency 6/20/00.

9.6 Relationship between baseline factors and second breast events

The relationship between patient age and baseline DCIS characteristics and second ipsilateral breast cancer events is summarized in the following table.

Table 26. Rates and RR of ipsilateral tumors by patient and DCIS characteristics (applicant's table 3, Lancet)

Characteristic	Placebo			Tamoxifen			Relative risk[3]	95% CI
	N	# IBT[1]	Rate[2]	N	# IBT[1]	Rate[2]		
All patients	899	87	19.6	899	63	13.75		
Age group:								
< 50	300	48	33.3	302	32	20.77	1.00	
≥ 50	599	39	13.03	597	31	10.19	0.43	0.31, 0.59
Margins:								
Negative	675	54	16.05	666	42	12.45	1.00	
Positive/unknown	224	33	30.89	233	21	17.37	1.68	1.20, 2.34
Comedo necrosis:								
Absent	446	29	12.78	469	24	9.9	1.00	
Present	433	56	26.69	414	39	18.54	2.01	1.44, 2.81
Detection method:								
Mammographic only	755	67	17.93	733	38	10.10	1.00	
Clinical	144	20	28.71	166	25	30.45	2.17	1.53, 3.08

[1] Ipsilateral breast tumor, including invasive and non-invasive

[2] Rate per 1000 patients per year

[3] Relative risk for patients in given covariate stratum, relative to reference (first) stratum, adjusted for treatment

Age at diagnosis was significantly associated with occurrence of ipsilateral breast tumors; younger patients were at increased risk of invasive disease compared to older patients, regardless of treatment assignment. The annual rate of ipsilateral breast cancer per 1000 women aged ≤ 49 on placebo was 33.3, compared to 13.03 for women aged ≥ 50. Tamoxifen administration resulted in a 38% reduction in ipsilateral breast cancers in women younger than 50 and a 22% reduction in women older than age 50.

Positive tumor margins were significantly associated with ipsilateral breast cancer recurrence, either invasive or non-invasive. Patients with DCIS detected clinically or by physical examination were at higher risk for ipsilateral recurrence than those whose DCIS was detected mammographically. Tamoxifen was effective in reducing the risk of ipsilateral breast cancer regardless of margin status. It reduced the risk by 22% in women with negative margins and by 44% in women with positive or unknown margins.

There were insufficient numbers of events for analysis of subsequent breast cancer events in relation to the size of the index lesion.

Women with comedonecrosis in their original DCIS lesion were twice as likely to develop an ipsilateral breast cancer as women without comedonecrosis. Based on data not shown but reported in the Lancet, the presence of comedonecrosis was more strongly associated with the occurrence of a non-invasive cancer than an invasive cancer. Tamoxifen reduced the rate of ipsilateral breast tumors by 23% in women without comedonecrosis at entry compared to 31% in women with comedonecrosis, indicating a similar degree of effectiveness in both groups of women.

None of the patient or tumor factors examined were associated with a significantly increased risk of contralateral breast cancer. Age was weakly associated with an increased incidence of contralateral tumors, consistent with its well-known status

as a breast cancer risk factor (N 072). However, there was no statistical evidence of a differential treatment benefit by age.

Reviewer Comments:

1. The statistical reviewer verified the calculations in the above table. There were minor differences (usually in the second decimal point), due to updated numbers of events in the electronic database.

2. Women less than age 50 and women with DCIS with positive margins and comedo necrosis had a higher rate of subsequent ipsilateral tumor events that older women or women with more favorable histopathologic features.

3. Rates were also higher in women whose lesions were detected clinically rather than by mammogram alone. Clinical detection may be considered as a surrogate marker for lesion size, consistent with clinical data on the likelihood of in-breast recurrence.

4. The following table summarizes the number of events in the study population based on the size of the initial DCIS lesion.

Table 27. Distribution of all breast cancer events by index lesion size

Tumor size	Placebo (n=902)		Tamoxifen (n=902)	
	No. pts	No. events	No. pts.	No. events
≤ 1.0	743	107	767	74
1.1-2.0 cm	104	12	83	6
>2.1 cm	37	11	41	4
Unknown	18	0	11	0

Most patients had small lesions, and the majority of events occurred in this group of patients. Notably, tamoxifen was effective even in women whose initial DCIS lesions were less than 1 cm in size.

5. The rates of ipsilateral breast cancer were lowered by tamoxifen in all subsets. Based on these data, it is not possible to define a subset of the study population, based on presenting tumor characteristics, who will derive greater benefit from tamoxifen and who might be targeted for therapy.

6. The reviewer looked at women who subsequently developed breast cancer and evaluated the effect of tamoxifen in these subsets.

Table 28. Women with subsequent invasive cancers by baseline characteristics (FDA assigned cases)

Factor (baseline)	Placebo	Tamoxifen	TOTAL
Age:			
≤ 49	34	17	51
≥ 50	40	27	67
Comedo necrosis:			
Present	35	22	57
Absent	39	22	61
Margins:			
Negative	50	31	81
Positive	18	6	24
Unknown	6	7	13
Method of detection:			
Clinical	8	5	13
Mammogram	58	31	89
Both	8	8	16
Axillary node dissection:			
Yes	66	40	106
No	8	4	12
Lesion size:			
≤ 1.0 cm	59	41	100
1.1 – 2.0 cm	9	3	12
≥ 2.0 cm	6	0	6

It does not appear from these data that there were any features of the original lesions that might permit identification of a subset of women at higher risk for developing a subsequent ipsilateral invasive lesion. Similar results were seen when non-invasive events were evaluated.

7. Effect of race

In NSABP P-1, tamoxifen decreased the incidence of subsequent breast cancers in all subgroups examined except women of color. It was not possible to determine whether this finding represented a true lack of effect or a lack of statistical power given the small number of non-white women enrolled in the study.

In NSABP B-24, the following table summarizes the incidence of all breast cancer events by race.

Table 29. Incidence of breast cancer events by race (applicant's numbers)

Race	Placebo (n=902)		Tamoxifen (n=902)		Total
	N rand	N events	N rand	N events	
White	764	104	778	70	174
African-American	68	13	58	10	23
Other	50	11	53	2	13
Unknown	20	0	13	0	0
Total	902	128	902	82	210

The reduction in number of cases of invasive or non-invasive breast cancer in African-American women treated with tamoxifen compared to placebo is somewhat less than that observed in white women. However, the proportion of African-American women in the study population was low, with few events in this cohort. If women of color are considered together, the number of events was halved by the use of tamoxifen.

9.7 Disease-free survival

As shown in Table 11, 7 women on placebo and 3 on tamoxifen developed regional or distant breast cancer. The rate ratio was 0.42, but this reduction is not statistically significant (p=0.32).

Reviewer Comment:

1. The reviewer did not analyze this endpoint for the following reasons:

- Most patients remained disease-free
- In this study, failure to remain disease-free does not have the same poor prognosis associated with treatment failure in the adjuvant or metastatic settings. For example, the occurrence of an ipsilateral non-invasive breast cancer would result in classifying the patient as a treatment failure, yet her long-term survival remains excellent with appropriate local therapy.

9.8 Distant disease-free survival

Although specified as a statistical secondary endpoint in the protocol, an analysis of distant DFS was not performed because few events occurred at the time of data lock.

Reviewer Comments:

1. The reviewer did not analyze distant disease-free survival, given the small number of events and classification difficulties. Instead, overall survival was examined as a better predictor of outcome.

9.9 Overall survival

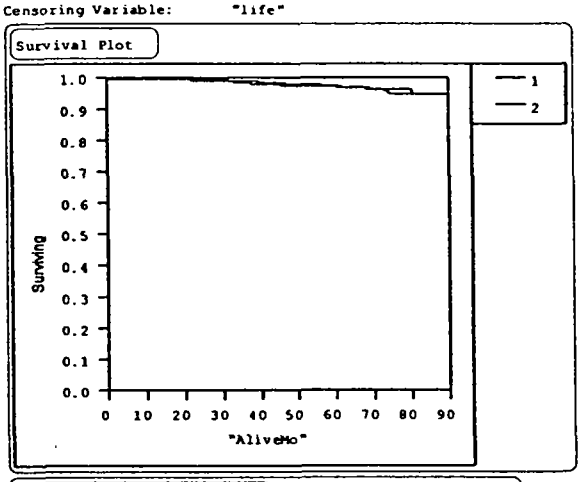
As reported in the Lancet article, at 5 years from study entry, 28 women in the placebo group had died compared to 26 in the tamoxifen group. Among the women randomized to placebo who died, 6 had invasive breast cancer; 2 of the 6 had invasive ipsilateral breast cancer. Among the women randomized to tamoxifen who died, 4 had invasive breast cancer, and 3 of the 4 had invasive ipsilateral disease. One developed a new primary. Overall survival on both arms was 97% at 5 years (Lancet publication; technical document submitted as N 064).

Reviewer Comment:

1. The reviewer identified 60 deaths during the CRF review. The discrepancy is due to the difference between the data lock date and the date the CRFs were copied for submission. This small increase does not alter the overall survival rate, which was high on both arms. The excellent survival is summarized in the following curve:

Figure 1. Overall survival, FDA analysis of NSABP B-24

Product-Limit Survival Estimates
Time Variable: "AliveMo"
Censoring Variable: "life"



Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	0.1115	1	0.7384
Wilcoxon	0.1123	1	0.7375

2. The 97% survival rate implies that tamoxifen, in this setting, does not alter the course of DCIS. Instead, tamoxifen's effect is on second breast cancer events. This trial conceptually is better thought of as an extension of P-1 (hypothesis: tamoxifen reduces the incidence of breast cancer in women at high risk for breast cancer, defined by a prior diagnosis of DCIS) rather than as a treatment trial for DCIS.

9.10 Deaths from causes other than breast cancer

Although specified as a statistical secondary endpoint in the protocol, an analysis of deaths unrelated to breast cancer was not performed because few events had occurred by the data lock date.

Reviewer Comment:

1. The reviewer agrees with this statement. The issue of breast cancer-related mortality is discussed further in the safety review in section 10.1

10.0 Safety review of NSABP B-24

This section summarizes the safety review of the submitted trial. Because of the extensive documentation of the safety profile of tamoxifen in previously submitted supplements, only serious adverse events were reviewed.

The overall incidence of toxicity of any grade in this study is summarized in the following table:

Table 30. Overall toxicity in NSABP B-24 (derived from applicant's Table 4, Lancet)

Overall toxicity[1]	Placebo (n=890)	Tamoxifen (n=891)
None	559 (63%)	509 (57%)
Grade 1	176 (20%)	196 (22%)
Grade 2	114 (13%)	137 (15%)
Grade 3	32 (4%)	41 (5%)
Grade 4	6 (1%)	7 (1%)

[1] Excludes alopecia, irregular menses, hot flashes, fluid retention, vaginal discharge, nadir grades, and weight gain/loss; septic episode classified as grade 4.

Reviewer Comment:

1. The majority of patients tolerated therapy well. Seventy-nine percent of women randomized to tamoxifen reported either no toxicity or grade 1 toxicity, compared to 83% of women randomized to placebo. Ninety-four percent of women randomized to tamoxifen reported events of grade 2 or lesser severity.

10.1 Deaths

The applicant reported a total of 54 deaths in the database, 28 on placebo and 26 on tamoxifen.

Reviewer Comments:

1. The reviewer identified 60 deaths during review of CRFs.

2. The following table (derived from review of CRFs and compared to the cause of death listed by the applicant in the electronic database) summarizes the causes of death among the patients on B-24, as determined by the reviewer.

Table 31. FDA cause of death by treatment arm

Cause of death	Placebo (no.)	Tamoxifen (no.)
Cancer		
Metastatic breast	9[1]	5[2]
Lung	1	4[3]
GI origin, NOS	1	2
Esophageal	1	0
Pancreatic	1	1
Cholangiocarcinoma	1	0
Gastric	0	1
Colon	0	1
Mesothelioma	1	0
Ovarian	1	0
CNS lymphoma	0	1
Hodgkin's disease	1	0
Non-Hodgkin's lymphoma	2	1[5]
Leiomyosarcoma	0	1
Glioblastoma multiforme	0	1
Diabetes mellitus	2	0
COPD	0	2
Pulmonary fibrosis/insufficiency	1	2
MI/ischemic coronary disease	1	3
Sepsis	2	0
Parkinson's	1	0
ALS	0	1
MVA	1[6]	0
Suicide	1	0
Alcoholic liver disease	1	0
Cerebral aneurysm	2[7]	0
Unknown	1	2
Total	**32**	**28**

[1] Applicant coded one of these deaths as due to "metastatic cancer" (442751055). This patient had a mastectomy for an ipsilateral invasive event, developed metastases less than a year later (no biopsy), and died less than a year after radiographic documentation of metastases. While the applicant has adhered to the protocol criteria for documenting recurrence, the reviewer believes the metastases were almost certainly due to recurrent breast cancer. The death of a second patient (44049004) was noted in the review of the case report forms, but it was not included in the applicant's database.

[2] The applicant coded one of these deaths as unknown (443793408). This patient had documented metastatic disease and received chemotherapy. Seven months after her last contact with her NSABP physician, a death notice appeared in the newspaper. No information could be obtained about her death. The applicant appropriately coded her death as unknown, but it is likely that she died of metastatic breast disease. A second patient (443902201) was not included in the applicant's database; she died of metastatic breast cancer.

[3] Pt 440726341 was not included in the applicant's database; died of non-small cell lung cancer

[4] Pts 440963337 and 443322296 were not in the applicant's database; they died of follicular and non-Hodgkin's lymphoma respectively.

[5] Applicant coded this death as congestive heart failure, based on the death certificate. However, the patient was diagnosed with NHL, did not receive treatment at her and her family's request, and died in a nursing home shortly afterwards.

[6] This patient was depressed. The physician's note indicated that she may have deliberately driven her car into a tree, but emphasized that suicide could not be proven or inferred from the event.
[7] Patient 444868091 not included in database; reported to have died of cerebral "pseudo-aneurysm"

3. These attributions differ from those of the applicant as follows:

Placebo

441306333 This patient had a history of pulmonary fibrosis, cor pulmonale and O_2 dependence documented in the note from her terminal hospital admission. She was discharged to home on 1/27/97 with supportive care and died 2/4/97. The applicant determined the COD as unknown; the reviewer assesses it as due to pulmonary fibrosis, cor pulmonale, and respiratory failure.

444255301 This patient had a history of depression. She stopped all her medications and died in an automobile accident (her car hit a tree). The applicant assessed her death as due to a motor vehicle accident. The reviewer agrees, but notes, as did the patient's attending physician, that suicide was a possible cause of death.

Tamoxifen

440157187 This patient had non-Hodgkin's lymphoma and entered a nursing home after a stroke. The death certificate lists the COD as congestive heart failure. While it is appropriate to use the cause listed on the death certificate, the reviewer believes it is likely that she died of lymphoma.

443793408 This patient's cause of death was listed as unknown in 9/95. She had a confirmed diagnosis of metastatic breast cancer, was treated with paclitaxel through 12/94, and had scans in 2/95 demonstrating persistent metastases. It is likely that she died of metastatic breast cancer.

4. The following patients had death reports in the CRF but were not included in the applicant's database because they were reported after the data lock date:

Placebo

444868091 "Pseudo-aneurysm" (after data lock date)
440490004 Metastatic breast cancer (after data lock date)
443322296 Non-Hodgkin's lymphoma
440963337 Follicular lymphoma

Tamoxifen

440726341 Non-small cell lung cancer (after data lock date)
443902201 Metastatic breast cancer

5. One patient, 442650022 (randomized to placebo), was diagnosed with a pelvic malignancy that involved the right ovary, uterine serosa, omentum, and colon. It was

difficult to determine whether she had primary ovarian cancer or metastatic breast cancer. Her physicians treated her as a metastatic breast cancer patient and listed MBC as the cause of death. The applicant coded the death as MBC. The reviewer agrees, but because of the uncertainty of her diagnosis, this patient was not included in the analysis of the primary endpoint of the study.

6. The reviewer and the applicant have minor differences of opinion about the cause of death in this study that do not materially affect the outcome of the trial.

7. The additional deaths noted by the reviewer on the placebo arm do not change the overall survival rate, which is high on both arms. These deaths either occurred after the data cutoff for the electronic database or were reported to the NSABP after this deadline.

8. While not statistically significant because of the small number of events, it is interesting to note that deaths from metastatic breast cancer were almost twice as frequent on placebo as on tamoxifen.

10.2 Endometrial cancer

There were 7 cases (0.8%) of endometrial cancer in the tamoxifen group, compared to 2 cases (0.2%) in the placebo group. The rate ratio (tamoxifen: placebo) was 3.39 (p=0.20) [data derived from submission N 064].

Reviewer Comments:

1. ***Patient characteristics***

The following table summarizes the reviewer's assessment of the 9 patients diagnosed with endometrial cancer during this study.

Table 32. FDA Assessment of endometrial cancer cases on B-24

Characteristic	Placebo N = 2	Tamoxifen N = 7
Patient characteristics and risk factors:		
Age at entry (yrs)	66, 69	38, 46, 62, 66, 69, 72, 76
Menopausal status at entry[1]		
Premenopausal	0	2[2]
Postmenopausal	2	5
Prior estrogen use[3]		
Yes	1	1[4]
No	1	6
Nulliparous:		
Yes	0	2
No	2	5
Weight (kg)	45, 77	59, 61, 65, 75, 78, 81, 81
DM or HTN	1	0
Tumor characteristics and time on study drug:		
FIGO Stage		
I A	1	3
B	1	3
C	0	0
II	0	1
III	0	0
IV	0	0
Postop radiation therapy	1	2
Suspicious signs/symptoms:		
No	1	1
Yes	1	6
Time to diagnosis (mos)[5]	22.3, 24.6	0.8, 19.1, 19.2, 22.3, 25.1, 39.1, 60.3

[1] As determined from the NSABP Patient History Form

[2] Premenopausal at study entry; postmenopausal at time of event

[3] Duration of estrogen use not collected

[4] Remote history of oral contraceptive use

[5] Comparable to time on study drug, within 1-8 days

2. The number of cases is too small to perform significant statistical analyses. There were an excess number of cases of endometrial cancer on the tamoxifen arm compared to placebo, consistent with results from review of other large tamoxifen databases. Most of the cases occurred in postmenopausal women; however, 2 of 7 cases, or 29%, occurred in premenopausal women (as defined from the time of randomization). Note that one premenopausal patient became postmenopausal during the course of the study. She developed endometrial cancer approximately 4.5 years after becoming postmenopausal and after 60 months of drug exposure. Practitioners should be aware of

the potential for menopausal status to change during the 5-year course of drug therapy and should question patients about signs or symptoms of uterine cancer.

3. ***Risk factors for endometrial cancer***

Few women in this study had used prior estrogen therapy by self-report or had other factors reported to increase the risk of uterine cancer, such as diabetes mellitus, hypertension, or nulliparity. Obesity is another risk factor for endometrial cancer. While the reported weights of some of the women meet criteria for obesity based on height, the weights of these women do not appear to differ significantly from weights in the entire study or in the U.S. population.

4. ***Stage at presentation***

Most of the tumors were diagnosed at an early stage; no patient presented with Stage IV disease. However, early stage tumors required surgery, generally with a TAH-BSO and nodal dissection. Two of the 7 patients were treated with abdominopelvic radiation therapy, with the potential for short- and long-term toxicity that should be considered in a risk-benefit discussion of tamoxifen for a DCIS patient.

5. At least one patient subsequently developed metastatic endometrial cancer, despite initial diagnosis at an early stage.

Patient 440763017, randomized to tamoxifen, was diagnosed with FIGO IA endometrial cancer. The CRF indicates that she underwent a therapeutic paracentesis and chemotherapy with paclitaxel and carboplatin. The applicant confirmed after an FDA request for information that this patient developed metastatic endometrial cancer (4/14/00).

A second patient, patient 440664311 randomized to placebo, is receiving paclitaxel and carboplatin for papillary serous adenocarcinoma. The applicant listed this patient as "probably" having recurrence. It is also possible that the patient has a second ovarian cancer primary.

6. ***Presenting symptoms***

Nearly all patients had a clinical sign or symptom that led to work-up and early diagnosis. The symptom was vaginal bleeding in all of these patients. One patient was reported to have had a biopsy for vaginal spotting that revealed complex hyperplasia. A hysterectomy was performed and showed endometrial cancer.

One patient on placebo did not have details of the diagnosis of endometrial cancer documented in the CRF. The toxicity forms coded only a slight increase in vaginal discharge, then no further toxicity. It is unknown whether this lesion was detected on routine screening or because of symptoms that developed between visits. One patient on tamoxifen was diagnosed with endometrial cancer, but no details were provided about antecedent symptoms.

7. ***Time to diagnosis***

In patients with symptoms, the interval between the report of the symptom and the diagnosis of endometrial cancer ranged from 3 month to 1.5 years. It is concerning that despite the national attention tamoxifen has received as a potential cause of endometrial cancer, work-ups are not always undertaken promptly at the time of reported postmenopausal vaginal bleeding (see next comment).

8. In the course of CRF review for other events, several patients were noted to have symptoms but no work-up:

Placebo:

441306333	Office note dated 3/9/94 (volume 29, page 53) indicates that the patient had brownish vaginal discharge. No work-up performed.	
443343114	42 year old with grade 1 spotting on 2 occasions. Had a normal gynecologic examination; no other work-up.	

Tamoxifen:

441982913:	1/5/94 to 8/30/94	Self-report of brown vaginal discharge
	7/15/94	Reported to have vaginal bleeding/spotting. No evaluation performed
440720129	53 year old who developed vaginal spotting within 2 weeks of starting therapy; never returned for follow-up	
440966014	49 year old with intermittent vaginal spotting. Treatment was held and a gynecologic examination was performed. Medication was then re-started. No work-up was performed.	
443678930	72 year old woman with grade 1 vaginal bleeding; refused endometrial biopsy. Persistent anemia 2.5 years later	

9. The following patients had work-ups for abnormalities, but the results were not included in the CRFs.

Placebo

444743357	Scheduled for surgery 4/99 for a "basketball sized pelvic mass". The applicant was asked to provide the pathology report of this procedure. It demonstrated stage IA ovarian cancer with benign fibrovascular tissue.
441008270	This patient had an endometrial biopsy and a separate procedure to perform fibroid resection. The reviewer requested the pathology reports. The pathology reports demonstrated leiomyoma and weakly proliferative endometrium.

Tamoxifen

440296090	This patient had a pelvic examination under anesthesia and a fractional D&C for complaints of pelvic pain and an abnormal pelvic ultrasound. The applicant was asked to provide the pathology report from this procedure. It demonstrated a benign mucosal polyp originating from the lower uterine segment.
443695176	The patient had postmenopausal bleeding prior to study entry. A D&C was recommended. The applicant was asked whether the procedure was performed; if so, the pathology report was requested. She was

subsequently entered on study and then developed uterine cancer, FIGO IB. The applicant was asked to provide information about her treatment. The applicant responded that pathology reports from procedures performed prior to study entry were not required, and that no information was available on the patient's treatment for endometrial cancer.

443802023 42 year old woman with vaginal bleeding; stopped study drug because of "endometrial hyperplasia" by report; no path report. The pathology report was submitted and showed focal cystic dilatation and compact sroma with proliferative endometrium. The presence of mitotic figures raised the possibility of simple hyperplasia.

440846415 This patient was reported to have grade 2 vaginal bleeding with severe cramps. She subsequently was reported to have grade 3 bleeding. Doctor's notes, an operative report, a discharge summary, and biopsy reports were submitted to NSABP but were not included in the CRF. The applicant was asked to provide these documents. Pathology showed a Class I Pap smear and endometrial atrophy

441661247 This postmenopausal patient developed vaginal bleeding and had an endometrial biopsy performed. The pathology report was requested. The report demonstrated sloughing nonsecretory endometrium

444591352 Pathology report from uterine biopsy requested—demonstrated endometriosis.

Submission of these reports does not suggest that events were missed during the study.

10. The time from randomization (or initiation of study drug) to the development of endometrial cancer ranged from 19 to 60 months. One patient on tamoxifen was found to have endometrial cancer after less than 1 month of drug therapy. In the opinion of the reviewer, it is likely that this tumor was present prior to entry into the study. The median time to event, excluding this patient with pre-existing cancer, was about 22 months. Endometrial cancer can occur within 2 years of beginning drug therapy. Women on tamoxifen should report any episode of vaginal bleeding to their physician promptly and undergo an appropriate work-up. Yearly gynecologic examinations are recommended.

10.3 Other cancers

Information on second malignancies was prospectively collected in this trial. According to the applicant, the incidence of second non-uterine malignancies was similar between treatment arms. The following table was submitted in the NDA:

Table 33. Second primary cancers as first events, NSABP B-24 (applicant's table 5, submitted by facsimile 4/3/00)

Site of second primary	Placebo	Tamoxifen	Total
GI:			
Salivary gland	1	0	1
Esophagus	2	0	2
Stomach	2	1	3
Colon	3	5	8
Rectum and recto-sigmoid junction	1	0	1
Gallbladder and bile ducts	1	0	1
Pancreas	1	1	2
Peritoneum and RP tissue	0	2	2
Liver, secondary	1	0	1
TOTAL GI CANCERS	**12**	**9**	**21**
Pulmonary:			
Trachea, bronchus, and lung	1	5	6
Pleura	1	0	1
TOTAL PULMONARY CANCERS	**2**	**5**	**7**
Connective and other soft tissue	0	2	2
Malignant melanoma	0	1	1
Kidney	1	1	2
Brain	0	1	1
Thyroid	1	0	1
Hematologic malignancies:			
Hodgkin's disease	1	0	1
Other lymphoid malignancy	2	3	5
Multiple myeloma	0	1	1
Polycythemia vera	0	1	1
Leukemia	2	0	2
TOTAL HEMATOLOGIC CANCERS	**5**	**5**	**10**
TOTAL NON-BREAST NON-GYNE	**21**	**24**	**45**
Gyne (excluding uterine):			
Ovary, fallopian tube, broad ligament	5	1	6
TOTAL NON-BREAST NON-ENDOMETRIAL CANCERS	**26**	**25**	**51**
Breast	70	41	111
Endometrial	2	7	9
TOTAL CANCERS	**98**	**73**	**171**

Reviewer Comments:

1. The above table was submitted in the sNDA, with a total of 52 second malignancies. The electronic database and the line listings indicate that 51 patients had second primary cancers.

2. The reviewer noted 56 patients with 59 non-breast non-endometrial cancers. The following patients were added:

Placebo

440963337 This patient was noted to have follicular lymphoma (volume 115, page 60). The applicant did not include this patient (confirmed to have follicular lymphoma) because she had a non-invasive contralateral breast cancer as a first event. The reviewer believes that breast cancer events are likely to be independent from the occurrence of other breast cancers, and that all reported second malignancies should be included.

444743357 This patient had a surgical procedure for a "basketball-sized mass" in the pelvis. She was found to have Stage IA ovarian cancer with benign fibrovascular tissue. This case was diagnosed after the data lock date.

Tamoxifen

440601112 Glioblastoma multiforme.

444233243 Non-small cell lung cancer

440340223 Intra-abdominal cancer

3. Two patients had more than one cancer:

Placebo

440941333 TCC of the kidney; SCCA of the larynx and pyriform sinus
This patient subsequently developed a contralateral breast cancer.

441390014 Colon cancer; platelet count > 1,000,000 treated with hydrea; called myelodysplastic syndrome by the investigator

Tamoxifen

440798038: Gastric cancer; anal cancer

4. Four patients had a second non-breast malignancy as well as a second breast cancer.

Placebo

440941333: TCC of the kidney; SCCA of the larynx and pyriform sinus
This patient subsequently developed a contralateral breast cancer.

443223335 CLL; then developed a contralateral breast adenocarcinoma. The diagnosis was made on fine needle aspiration and the subsequent lumpectomy showed no residual disease. It is unclear whether the tumor was invasive or non-invasive.

440963337 This patient had a follicular lymphoma and a non-invasive contralateral breast cancer.

Tamoxifen

440601112 This patient had a glioblastoma multiforme after developing a second DCIS with microinvasion.

5. The distribution of cancers as noted by the reviewer is listed in the following table.

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ON ORIGINAL

Table 34. FDA Assessment of second malignancies

Site of second primary	Placebo	Tamoxifen	Total
GI:			
Salivary gland	1	0	1
Esophagus	2	0	2
Stomach	0	1	1
Colon	3	4	7
Rectum and recto-sigmoid junction	1	0	1
Gallbladder and bile ducts	1	0	1
Pancreas	1	1	2
Non-specified GI	1	1	2
Anal	0	1	1
TOTAL GI CANCERS	**10**	**8**	**18**
Pulmonary:			
Trachea, bronchus, and lung	1	7	8
Pleura (mesothelioma)	1	0	1
TOTAL PULMONARY CANCERS	**2**	**7**	**9**
Head and neck	1	0	1
Malignant melanoma	0	1	1
Non-melanoma skin	0	1[1]	1
Kidney	1	1	2
Brain	0	1	1
Leiomyosarcoma	1 (gastric)	1	2
Carcinoid	1 (gastric)	1 (appendix)	2
Thyroid	1	0	1
Hematologic malignancies:			
Hodgkin's disease	1	0	1
Non-Hodgkin's lymphoma	3	4[2]	7
Other lymphoid malignancy	0	1[3]	1
Multiple myeloma	0	1	1
Myelodysplastic syndrome	1	0	1
Leukemia (CLL)	2	0	2
TOTAL HEMATOLOGIC CANCERS	**7**	**6**	**13**
Gyne (excluding endometrial):			
Ovary, fallopian tube, broad ligament	6	2[4]	6
TOTAL CANCERS	**30**	**29**	**59**

[1] Cutaneous angiosarcoma
[2] Including one patient with CNS lymphoma
[3] Polycythemia vera
[4] Includes one patient with primary peritoneal cancer

6. The differences between the reviewer's and the applicant's assigned pathologic diagnoses are minor.

7. The only apparent imbalance is the presence of 7 cases of lung cancer on the tamoxifen arm, compared to 1 case on placebo. No information about risk factors for lung cancer, such as tobacco use or asbestos/radon exposure, was provided. The number of cases is small (less than 1% of the patients on each arm) and tamoxifen has not been previously reported in large databases to be associated with an increased risk of lung cancer. It is unlikely that an etiologic relationship exists.

10.4 Cardiovascular events

10.4.1 Ischemic heart disease

There was one fatal MI on placebo, compared to one fatal and 3 non-fatal MIs on tamoxifen. There were no significant differences between the two arms in the incidence of angina or ECG changes [data reported in submission N 072].

Reviewer Comment:

1. Information on myocardial infarction was not a prospectively specified endpoint. In the NSABP P-1 study, no difference in the incidence of MI was observed between placebo and tamoxifen.

2. This endpoint was not reviewed apart from the review of CRFs for deaths.

10.4.2 Stroke and TIA

The original Lancet publication did not report any strokes. A subsequent Erratum to the Lancet reported 6 strokes in the study. The case report forms for these events were submitted in the sNDA. No discussion or interpretation of these events was provided by the applicant.

Reviewer Comments:

1. The reviewer found a total of 9 patients with stroke during the course of the trial. The ***characteristics of these patients*** are summarized in the following table.

Table 35. Characteristics of patients with stroke on B-24

Characteristics	Placebo (n=2)	Tamoxifen (n=7)
Age years	53, 64	Range: 58-76 (58, 65, 65, 70, 73, 74, 76)
Hypertension	Yes, No	2
Diabetes mellitus	Yes, No	1
Hyperlipidemia	Yes, No	1
Atrial fibrillation/flutter	Yes, No	1
Smoking history	Yes, No	1 current, 1 past
Prior TIA	Yes, No	1 patient
Symptomatic CAD	Yes, unstable angina; Yes	1 patient
Symptomatic carotid plaques	No, No	None
Hemorrhagic stroke	No, No	1
Time to event	13.2 months, 48.6 months	Mean 26.2 months (range 6.0 – 42.2 mo)

Patients with strokes were in the age range associated with stroke in the general population. While the numbers were small (less than 1% of patients treated) and preclude formal statistical analysis, it is notable that 2 patients on placebo, compared to 7 on tamoxifen, had a stroke during the course of the study.

One placebo patient had multiple risk factors for stroke. The second placebo patient had a history of symptomatic coronary artery disease and was reported to have had a cerebellar stroke.

Four of the 7 stroke patients on the tamoxifen arm had at least one risk factor for stroke: 3 of the 4 had one risk factor and 1 patient had 4 risk factors. Three stroke patients on tamoxifen did not have documented risk factors, although one was on long-term anticoagulation for unspecified reasons.

2. The patients included by FDA but not by the applicant are as follows:

Placebo

444868091 This patient was documented to have a cerebellar stroke.

Tamoxifen

440157187 The applicant agrees that this patient had a stroke. However, the institution did not submit an adverse event form, and thus the event was inadvertently omitted from the database.

442653208 This patient had a stroke documented in the context of a complicated admission for an MI and emergency bypass. The applicant excluded this patient as a stroke event because they considered it to be a pre-terminal event unrelated to protocol therapy. The reviewer included this event, as it was a confirmed stroke that occurred during the study.

3. ***Hemorrhagic versus thrombotic:***

One stroke on the tamoxifen arm was hemorrhagic in nature and is unlikely to be related to tamoxifen therapy. This patient had a history of hyperlipidemia.

4. ***Occurrence on or off drug therapy***:

All strokes except one occurred during study drug therapy. Patient 440157187 (randomized to tamoxifen) stopped study drug on 6/28/94 and had a stroke 3/5/95. She had 4 risk factors for stroke.

5. ***Fatal strokes:***

One stroke, in patient 442653208, occurred at the time of the patient's death. This patient had a complicated medical history. She had an MI and had emergency bypass surgery complicated by thrombocytopenia and cardiogenic shock. A head CT obtained during this admission demonstrated an occipital stroke. She died, probably due to the cardiac events and not from the stroke. [See Reviewer Comment 2]

6. ***Possible events:***

One additional patient randomized to tamoxifen may have suffered a stroke. This 62 year old woman (443539943) had a history of hypertension and diabetes and presented to her physician with a 2-3 day history of left facial numbness and difficulty moving her lips. She reported a history of a right Bell's palsy 35 years earlier. The neurologic examination was recorded as "Does appear to have significant left facial weakness." She was prescribed an ocular lubricant and a patch for her eye at night. Her 6 month visit note did not document a neurologic examination. An exam one year later documented only a lack of ankle jerks as the neurologic examination. The history section of the note stated "No TIAs or claudication." The reviewer believes it is difficult to assess whether this patient had a second Bell's palsy or a TIA. She has significant risk factors for neurologic disease. However, the absence of a documented neurologic examination makes it difficult to reach a definitive conclusion. For this reason, she was not added to the list of stroke patients.

7. Overall, although no formal statistical analysis can be performed, there were an excess number of cases of thrombotic stroke on the tamoxifen arm, consistent with observations in other tamoxifen trials.

10.4.3 Thromboembolic events

There were 2 cases (0.2%) of deep vein thrombosis in the placebo group, compared to 9 cases (1.0%) in the tamoxifen group. Pulmonary embolus was reported in 1 (0.1%) and 2 (0.2%) cases respectively. No deaths from pulmonary emboli occurred. (data from submission N 064; consistent with the data reported in the Lancet)

Table 36. Thromboembolic events on NSABP B-24 (from Table 4, Lancet)

Severity of event	Placebo (n=890)	Tamoxifen (n-891)
None	883 (99.2%)	875 (98.2%)
Superficial vein	4 (0.4%)	5 (0.6%)
Deep vein thrombosis	2 (0.2%)	9 (1.0%)
Pulmonary embolism[1]	1 (0.1%)	2 (0.2%)

[1] All events non-fatal

Reviewer Comments:

1. The applicant reported 14 thromboembolic events in the published account of NSABP B-24 and in the line listings included with the sNDA (3 on placebo, 11 on tamoxifen). The applicant listed 24 cases (8 on placebo and 16 on tamoxifen) in the electronic database. The electronic database includes all grades of events. However, some patients coded as "superficial thrombophlebitis" were included in the line listings (ex: 441747090) and others were not. The applicant was asked to explain these discrepancies.

2. The reviewer found 26 cases of documented or potential thromboembolic disease of any grade documented in CRFs, 8 on placebo and 18 on tamoxifen. The cases added to the line listings are as follows:

Placebo

442033906* DVT—not on the applicant's list because it was reported as a Withdrawal due to Adverse Event and was processed after the list of thromboembolic events was generated. [Note: this patient had been off study drug for approximately 8.5 months at the time of the event]

442734301 The patient presented with lower extremity pain and phlebitis. No work-up was performed. She had a history of prior deep vein thrombosis and venous insufficiency. The drug was discontinued because of the event.

443769415* Thrombosed labial varix. The reviewer included all clots, regardless of likelihood of relationship to study drug, in a blinded review.

443988212 Superficial thrombophlebitis treated with indocin; no work-up performed. The study drug was discontinued because of this event.

444259187 The patient presented with new onset of calf pain and shortness of breath. No work-up or follow-up was reported. The applicant was asked to provide this information to ensure that this event does not represent a missed PE or DVT. The applicant responded that the patient did not have a work-up or treatment for DVT or PE. A follow-up form dated 3/24/99 indicated that she was alive and without recurrence.

Tamoxifen

440163085 Randomized 3/6/92; developed 5 days of left-sided superficial phlebitis. The patient had a prior history of vein stripping with chronic lower extremity edema. She was seen in the emergency room 1/4/94 and was treated with local therapy for superficial thrombophlebitis. No work-up was performed. A follow-up visit on 1/12/94 demonstrated improvement. The patient declined further therapy with study drug. This event may have represented a missed DVT.

440761225* This patient developed recurrent nodal disease with subsequent supraclavicular clot. While the recurrent adenopathy was the proximal cause of the clot, it is difficult to determine whether or not study drug contributed to this event. The reviewer included all documented events in a blinded review to minimize bias. [Note: this patient discontinued study drug 6 months prior to the event.]

441611134 This patient had a prior history of DVT and 5-6 previous episodes of thrombophlebitis. She developed swelling of the left ankle and was clinically considered to have superficial thrombophlebitis. Venograms were negative for DVT. However, because of continued and worsening symptoms, study drug was discontinued.

441807022* The patient presented with 10 days of crampy left leg pain with difficulty walking, erythema, and tenderness. A doppler study demonstrated thrombosis of the greater saphenous vein extending into the upper calf and short saphenous vein. The applicant classified this event as superficial thrombophlebitis and did not include it. The local physician considered it to represent a deep venous thrombosis and treated the patient accordingly. Study drug was discontinued. The applicant agrees that the event is consistent with DVT.

442899058* This patient developed a deep vein thrombosis after colon surgery. The clot is documented in an MD note. The applicant did not include this event because of lack of primary source documentation. The reviewer accepts the treating reviewer's assessment, particularly since he considered the event serious enough to warrant discontinuation of study drug.

443732301 Superficial thrombophlebitis; minimal additional information

444356199* The hospital discharge note for this patient indicates that a V/Q scan was interpreted as high probability for PE. She was treated with heparin and chronic coumadin. The applicant did not include this patient because interpretation of the lung scan was difficult due to the patient's underlying COPD. However, the applicant agrees that because the investigator considered the event to represent a pulmonary embolus, it is reasonable to classify it as such.

* Documented cases of DVT or PE, per FDA reviewer

2. ***If one includes only cases with documented DVT or PE, there are a total of 20 cases, 5 on placebo and 15 on tamoxifen. Of these, 4 were pulmonary emboli, 1 on placebo and 3 on tamoxifen.***

3. The applicant listed the following patients in the electronic database that were not included in the reviewer's list of DVT and PE:

Placebo

440972058 Superficial thrombophlebitis: Mondor's disease

444285935 Superficial thrombophlebitis: no documentation other than a checkmark on a single toxicity form

Tamoxifen

442018201 Superficial thrombophlebitis: no documentation other than a checkmark on a single toxicity form

The CRFs of these patients were reviewed in order to ensure that DVT or PE were not missed.

4. ***The total number of thromboembolic events of any grade is 29, 10 on placebo and 19 on tamoxifen.***

5. As noted above, one event on each arm occurred in a patient who had discontinued study drug. Inclusion of these events does not change the reported outcomes for the study.

6. ***Characteristics of patients with thromboembolic events***

The following table summarizes some of the risk factor information for patients with clots in NSABP B-24. The 3 patients listed in comment 3 were not included. The entire study population was not analyzed, since risk factor information is not available for all randomized patients.

Table 37. Risk factors in patients with thromboembolic events

Factor	Placebo (n=8)	Tamoxifen (n=18)	Total (n=26)
Age range	45-73	39-72	
Mean	61	64	
Weight[1]:			
≤65 kg	2	4	6
>65 kg	6	14	20
Tobacco:			
No	2	8	10
Past/current	1	3	4
Unknown	5	7	12
Menopausal status:			
Post	7	14	21
Peri	1	0	1
Pre	0	4	4
Precipitating event:			
Surgery/general anesthesia	1	1	2
Long trips	1	1	2
Trauma	0	1	1
Underlying predisposing medical disorder:			
Malignancy	1	2	3
Prior history vein stripping	0	2	2
Prior history DVT	0	1	1
Prior history familial DVT	0	1	1

[1] Based on the standard "65-kg woman"

Most patients who developed thromboembolic events were postmenopausal. More events occurred in patients who were overweight on either arm of the study, but events occurred in women of normal weight as well. Detailed risk information was not available for all patients. With the limited information available, there does not appear to be a predisposing factor that identifies a subset of the population at risk.

7. ***Complications of thromboembolic events***

- None of the events was fatal.
- Complications of therapy: Only one complication of therapy was reported. Patient 443959232 had a complicated medical history. She presented with a DVT and was found to have endometrial cancer. After a TAH-BSO and nodal dissection, she developed a postoperative DVT. Scans one month later demonstrated further extension of her clot and necessitated the placement of a Greenfield filter.
- Second events: patient 441747090 had 2 episodes of superficial thrombophlebitis treated conservatively in 5/93 and 7/93. A DVT was diagnosed in 9/93. It is possible that the patient's symptoms represented one event with a delay in diagnosis.

As noted in the review of the P-1 study, patients considering therapy should understand that thromboembolic events may occur, that more than one event may occur in an individual despite cessation of tamoxifen, and that complications of treating the clot may occur.

8. Cessation of study drug

Several patients did not have the study drug discontinued despite documentation of a clot.

Placebo

443959232 Study medication was stopped after the second documentation of DVT.

Tamoxifen

440004014 Drug continued for two months after the clot per treating M.D.; drug stopped by NSABP

444356199 Drug stopped after documentation of PE, then restarted. Subsequently stopped because of patient's complaints of nausea, weight loss

443732301 Study drug was not stopped; however, this patient was reported to have superficial thrombophlebitis and not DVT and was appropriately continued on therapy.

It is concerning that despite the labeled indications for tamoxifen and the publicity regarding thromboembolic events, the drug was not always promptly discontinued after a thrombotic event.

9. Several patients had pre-existing clotting histories. While not an exclusion criteria for entry into this study, such patients should be counseled carefully about potential risks and benefits associated with tamoxifen treatment.

Tamoxifen

441938014 History of a pulmonary embolus and simultaneous deep vein thrombosis two years prior to study entry

444784225 History of superficial thrombophlebitis of the upper arm and past history of a DVT

10. In summary, tamoxifen therapy was associated with an increased risk of all thromboembolic events of any grade, of DVT, and of PE. Patients should be adequately counseled about the signs and symptoms of thromboembolic events and should seek prompt medical attention should these signs develop.

10.5 Adverse events

10.5.1 Hematologic adverse events

Laboratory values were not submitted with the sNDA, as agreed upon in the pre-sNDA meeting. The applicant indicated that while periodic laboratory testing was required on study, the primary data were not collected. A review of the electronic

database for sequelae of abnormal counts (sepsis, infection, hemorrhage, for example) demonstrated few events that were not clinically different in frequency between treatment arms. The hematologic safety profile of tamoxifen has been well-documented in previous studies.

10.5.2 Hepatic toxicity

Primary laboratory data were not entered into the electronic database and were not submitted, as agreed upon in the pre-sNDA meeting. The electronic database does not contain a surrogate term to evaluate hepatic toxicity. This issue has been extensively examined in previous tamoxifen studies, and no definite evidence of tamoxifen-related hepatotoxicity has been demonstrated in humans to date.

Review of the case report forms provided additional, albeit incomplete, information. The case studies are listed below.

Placebo	
442698913	Grade 1 elevation of transaminases after 4 years of drug therapy; patient chose to discontinue study drug.
443703104	52 year old woman with elevated LFTs after 3 years of therapy. GGT 254, PT/OT reported to be elevated, but no levels given. GGT remained high off therapy although transaminases were reported to have normalized. Liver biopsy was non-diagnostic.
Tamoxifen	
440147182	Two years after randomization, this patient developed liver abnormalities consistent with chronic active steatohepatitis and questionable cirrhosis
440033923	Grade 1 elevations of LFTs 3 years after study entry
441189946	She developed grade 2 elevation of LFTs after 1.5 years of drug therapy. Reversible after stopping drug.
441554055	She developed grade 1 LFT elevation 2.5 years after starting study drug. The drug was discontinued for 5 months, then restarted. The grade 2 abnormalities recurred after 1 year of therapy. The drug was discontinued. One year later, ALT remained elevated at 64; AST was normal. Abdominal ultrasound normal
443331311	70 year old woman with rising LFTs first noted 9 months after randomization. Values peaked 2.5 years after randomization with SGOT = 103 and SGPT = 96. All values normalized approximately 6 months after stopping study drug.

Several of these cases suggest a causal relationship between tamoxifen and elevated liver function tests, but there is insufficient information to draw firm conclusions.

It should be noted that no cases of hepatocellular carcinoma were observed on either arm during this trial.

10.5.3 Gynecologic symptoms

The following table presents the most common non-serious adverse events for this trial.

Table 38. Common adverse events (applicant's Table 3 from N064 and from Table 4, Lancet).

Event	Placebo N (%)	Tamoxifen N (%)
Hot flashes	525 (59)	620 (70)
Fluid retention	248 (28)	291 (33)
Vaginal discharge	178 (20)	289 (32)
Menstrual problems	142 (16)	171 (19)

There were no significant differences in the incidence of mood-related toxicities between the two treatment arms, as summarized in the following table.

Table 39. Self-reported mood changes on NSABP B-24 (derived from applicant's Table 4, Lancet)

Severity of mood change	Placebo (n=890)	Tamoxifen (n-891)
Normal	793 (89%)	797 (90%)
Mild	51 (6%)	37 (4%)
Moderate	36 (4%)	45 (5%)
Severe	7 (1%)	11 (1%)
Suicidal	1 (0.1%)	1 (0.1%)
Death from suicide	1 (0.1%)	0

Reviewer Comment:

1. As agreed, the Division did not request primary data to verify the incidence of hot flashes, fluid retention, vaginal discharge, and menstrual problems, as these adverse events have been reviewed in detail in larger, previously submitted, placebo-controlled studies of tamoxifen.

2. The incidences of mood change by severity level reported in the Lancet are similar to those reported in the electronic database. The incidences are identical for severe, suicidal, and death from suicide categories. The "moderate" category differs by one point for the placebo group (37, not 36) and by 3 for the tamoxifen group (48, not 45).

3. No significant difference in the incidence of mood changes was observed between treatment arms in this study.

11.0 Comparison of the submitted clinical trial results with the published results

The submitted clinical trial results differ from the published results in the following way:

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

13.0 Applicant's summary of safety and efficacy (Discussion, Lancet publication)

The applicant stated that women with DCIS treated with lumpectomy and radiation therapy benefited from the addition of tamoxifen therapy. The benefit was primarily due to a decreased rate of invasive ipsilateral breast cancer, although a decrease

was also observed for non-invasive cancers and for the contralateral breast. Regional and distant metastases were decreased as well. The applicant argues that combining all of these events into one endpoint is the best way to assess the benefit of adding tamoxifen.

The authors point out that this trial was performed in the context of optimal local therapy for DCIS, which included both lumpectomy and radiation therapy. The benefit of tamoxifen in treating DCIS after lumpectomy alone is unknown.

The drug was well-tolerated and should be considered in women with a diagnosis of DCIS.

14.0 Reviewer's summary of safety and efficacy

The following table summarizes the FDA review of efficacy for NSABP B-24.

Table 40. FDA summary of efficacy, NSABP B-24

Event	Placebo (n=902)		Tamoxifen (n=902)		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
All invasive breast cancer[1]	74	16.73	44	9.60	0.57 (0.39, 0.84)	0.004
Ipsilateral invasive	47	10.61	27	5.90	0.56 (0.33, 0.91)	0.02
Contralateral invasive	25	5.64	17	3.71	0.66 (0.33, 1.27)	0.24
Invasive, side undetermined	2	--	0	--	--	--
All non-invasive breast cancer	56	12.66	41	8.95	0.71 (0.46, 1.08)	0.11
Ipsilateral non-invasive	46	10.40	38	8.29	0.80 (0.51, 1.25)	0.36
Contralateral non-invasive	10	2.26	3	0.65	0.29 (0.05, 1.13)	0.08
All ipsilateral events	96	21.70	65	14.19	0.65 (0.47, 0.91)	0.01
All contralateral events	37	8.36	20	4.37	0.52 (0.29, 0.92)	0.02
Survival	870	--	874	--	--	--

[1] Includes regional/distant/local recurrences

The following table presents a side-by-side comparison of the applicant's and the FDA's analyses.

Table 41. Comparison of Applicant's and FDA's Efficacy Results

Event	Placebo (n=902)		Tamoxifen (n=902)		Rate Ratio (95% CI): Applicant	Rate Ratio (95% CI): FDA
	No. Events: Applicant	No. Events: FDA	No. Events: Applicant	No. Events: FDA		
All invasive breast cancer[1]	70	74	41	44	0.57 (0.38, 0.85)	0.57 (0.39, 0.84)
Ipsilateral invasive	40	47	23	27	0.56 (0.32, 0.95)	0.56 (0.33, 0.91)
Contralateral invasive	23	25	15	17	0.63 (0.31, 1.26)	0.66 (0.33, 1.27)
Invasive, side undetermined	--	2	--	0	--	--
All non-invasive breast cancer	60	56	43	41	0.69 (0.46, 1.04)	0.71 (0.46, 1.08)
Ipsilateral non-invasive	47	46	40	38	0.82 (0.53, 1.28)	0.80 (0.51, 1.25)
Contralateral non-invasive	13	10	3	3	0.22 (0.04, 0.81)	0.29 (0.05, 1.13)
All ipsilateral events	87	96	63	65	0.70(0.50, 0.98)	0.65 (0.47, 0.91)
All contralateral events	36	37	18	20	0.48 (0.26, 0.87)	0.52 (0.29, 0.92)

The following table summarizes the FDA review of serious adverse events for NSABP B-24.

Table 42. FDA summary of safety, NSABP B-24

Event	Placebo	Tamoxifen
Deaths	32	28
Breast-cancer specific deaths	9	5
Endometrial cancer	2	7
Second cancers (non-breast non-uterine)	30	29
Stroke	2	7
Thromboembolic events	5	15
DVT	4	12
PE	1	3

These results demonstrate a statistically significant reduction in the incidence of invasive but not non-invasive breast cancer per the FDA analysis. The occurrence of all ipsilateral and all contralateral events was significantly decreased as well. Although the analysis of non-invasive events did not yield a significant result, it should be noted that the rate ratios indicated a beneficial effect of tamoxifen. It is likely that the lack of statistical significance results from a lack of power (few events) rather than from a lack of efficacy of tamoxifen.

Reduction in the incidence of invasive cancer is perhaps the most clinically relevant endpoint, as invasive disease has the potential to metastasize. Most of the effect resulted from the reduction in ipsilateral invasive events, as the difference in contralateral invasive events was not significant. While reduction in invasive disease was clinically

meaningful and large by oncologic standards, the absolute difference in invasive breast cancer rates between treatment arms at 5 years was 4%. The subset of patients who benefited from tamoxifen could not be predicted by the baseline characteristics of the tumor or the patient.

It should be noted that overall survival was not affected by the use of tamoxifen. Survival was excellent in both arms. It is likely that tamoxifen has a predominant effect on the incidence of new events, rather than on further treatment of the index lesion. Its effect in this setting is analogous to that observed in the NSABP P-1 study and to its ability to decrease the incidence of contralateral breast cancer in women with a prior diagnosis of invasive disease.

The applicant's statement that regional/local/distant recurrence was decreased by tamoxifen therapy is accurate, and raises the question as to whether tamoxifen might decrease breast cancer-related deaths. Nine breast cancer-related deaths were observed on placebo, compared to 5 on tamoxifen. While it is intriguing that breast cancer-specific deaths may have been decreased by the use of tamoxifen, there are too few events and follow-up is too short to draw any conclusions.

The reviewer agrees with the applicant's note that all patients in this study received optimal local treatment with lumpectomy and radiation therapy. Most pathology specimens had clear margins. This trial does not provide information that supports the use of tamoxifen in place of radiation therapy. Recently reported results from NSABP B-21 demonstrate that tamoxifen cannot substitute for radiation therapy. In B-21, women with node negative breast tumors less than or equal to 1 cm in size were randomized to lumpectomy and radiotherapy plus tamoxifen versus lumpectomy and radiotherapy plus placebo versus lumpectomy and tamoxifen. Analysis of the 2nd and 3rd arms demonstrated a highly significant reduction in the incidence of in-breast tumor recurrence with the use of radiotherapy.

Analysis of the safety data is consistent with the known safety profile of tamoxifen. The small number of events precludes a formal statistical analysis. Tamoxifen was associated with an increased incidence of endometrial cancer, stroke, and thromboembolic disease. An increased incidence of non-breast non-endometrial cancers was not observed. Data on myocardial events and eye events were not prospectively collected.

The reduction in invasive cancer incidence observed in this trial was statistically significant and clinically meaningful. However, patients should be aware that their long-term disease-free and overall survival after a diagnosis of DCIS is excellent, and that tamoxifen's potential benefit will primarily be reflected in a reduction in second breast cancers. Women and their physicians should carefully weigh the risks and benefits, including an assessment of factors that may increase the risk of serious adverse events, before electing to proceed with treatment.

15.0 Reviewer's recommendations

The reviewer recommends approval of tamoxifen to reduce the incidence of second breast cancer events in women with DCIS treated with lumpectomy and radiation therapy.

As part of the Approval, if the Division and Office agree with the recommendation, the applicant should be asked to provide the following information as part of its Phase IV commitments:

- Submit annual follow-up information on the number of invasive, non-invasive, contralateral, and ipsilateral breast cancer events by treatment arm. Evidence of local/regional/distant failure should also be provided. These data will provide information about the durability of effect.
- Submit the results of the central pathology review
- Submit the final results of the UK trial when available

Signatures

/S/

Susan Flamm Honig, M.D.
Medical Reviewer

/S/

Rajeshwari Sridhara, Ph.D.
Statistical Reviewer

/S/

Grant Williams, M.D.
Medical Team Leader

/S/

Gang Chen, Ph.D.
Statistical Team Leader

/S/

Kooros Mahjoob, Ph.D.
Deputy Division Director, Biometrics

Appendix A. Schedule of follow-up evaluations, NSABP B-24

PROTOCOL NO. B-24

TABLE 2: STUDIES REQUIRED DURING YEAR 1

	Year 1		
	All Patients	Remainder of Year 1	
Required Studies	Prior to Randomization	Every 6 mos. all patients	At 12 mos. all patients
History* & Physical Examination	X	X	
Gynecologic examination	X		X
Method of detection of tumor (clinical, mammographic, or both)	X		
Hematologic Studies			
CBC and differential	X	X	
Platelet count	X	X	
Chemistries			
Calcium	X	X	
Bilirubin	X	X	
Alkaline phosphatase	X	X	
SGOT/or SGPT	X	X	
Roentgenologic Exam			
Bilateral mammogram or xeroradiogram	X (performed within 3 months prior to breast surgery)	X (ipsilateral)	X

*Please include family history

PROTOCOL NO. B-24

TABLE 3: STUDIES REQUIRED AFTER YEAR 1

	Years 2 to 5		Year 5+
Required Studies	Every 6 mos.	Every 12 mos.	Every 12 mos.
Physical Examination	X		X
Gynecologic examination		X	X
Hematologic Studies			
CBC and differential	X		X
Platelet count	X		X
Chemistries			
Calcium	X		X
Bilirubin	X		X
Alkaline phosphatase	X		X
SGOT/or SGPT	X		X
Roentgenologic Exam			
Bilateral mammogram or xeroradiogram		X	X

4 pages redacted from this section of the approval package consisted of draft labeling

PR-84-87

Patient Package Insert

Page 31:

- Change the indication in the PPI to match that in the PI

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Signatures

/S/ M.D.
Susan Flamm Honig, M.D.
Medical Reviewer

/S/
Rajeshwari Sridhara, Ph.D.
Statistical Reviewer

/S/ MD
Grant Williams, M.D.
Medical Team Leader

/S/
Gang Chen, Ph.D.
Statistical Team Leader

/S/
Kooros Mahjoob, Ph.D.
Deputy Division Director, Biometrics