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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
17-970/S-046

Medical Review(s)

Medical Teamleader Comments and Final Recommendations
NDA 17-970/SE1-046
Nolvadex® (Tamoxifen Citrate) after Surgery and Radiotherapy for Ductal Carcinoma in situ of the Breast (DCIS)

Please refer to the medical/statistical review of the submission by Drs. Honig and Sridhara. I am in complete agreement with their findings and recommendations.

Tamoxifen has been previously approved for several breast cancer indications, including for treatment of metastatic breast cancer, for adjuvant treatment of breast cancer after surgery, and for reducing the risk of breast cancer in patients at high risk. This efficacy supplement seeks approval for "treatment of DCIS in women following breast surgery and radiation." As Dr. Honig notes in her review, the indication proposed by the applicant does not accurately reflect the treatment described in the submitted clinical study; DCIS was not directly treated, rather patients were treated after adequate surgical and radiation treatment of DCIS. The review team recommended the following wording for the indication:

Draft

This wording is similar to that approved for the indication of tamoxifen for treating patients at high risk of breast cancer. This similarity reflects the fact that the women treated under each indication are similar (i.e., they are women at a higher risk of breast cancer) and that for both, tamoxifen acts to decrease that risk. I recommend a slight rewording of the indication as follows:

Draft

This rewording is intended to prevent the possible misconception that tamoxifen is indicated only if persistent DCIS is present after surgery and radiation.

The supplement contains results from one large randomized, double-blind, placebo-controlled trial demonstrating efficacy for this indication and demonstrating a safety profile that is consistent with data from previous submissions. NSABP B-24 compared tamoxifen 20 mg/day to placebo in 1804 women with DCIS who had undergone "lumpectomy" and breast irradiation. The primary endpoint of the trial was the incidence of invasive breast cancer. Secondary protocol endpoints included the incidences of non-invasive breast cancer, ipsilateral breast cancer, and contralateral breast cancer. The following results from Dr. Honig's review are based upon her verification of the individual operative reports:

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

Tamoxifen therapy was associated with a significantly lower rate of invasive breast cancer [44/902 versus 74/902, HR 0.57 (0.39, 0.84)]. Compared to the NSABP P-1 trial that evaluated efficacy in women at high risk of breast cancer, the rate ratio is almost exactly the same (0.57 compared to 0.56 in P-1). The absolute benefit is much greater in this population, however, since the risk of recurrence in the placebo arm is much higher in this DCIS trial than in the P-1 trial, 16.7 versus 6.5 respectively. Given a similar toxicity profile, the benefit in this indication is clearly worth the risk.

One might question whether evidence from one trial should suffice for approval of this indication. I believe the answer in this case is clearly 'yes.' First, the study was well-designed and well-conducted by a respected cancer cooperative group, the NSABP. Second, the results are statistically compelling, with p = 0.004. Lastly, the results are supported by equally compelling and almost identical results from study P-1 in a similar group of women at high risk of breast cancer.

The pharmacology/toxicology and biopharmaceutics reviewers have identified several issues unrelated to this efficacy supplement that need to be addressed in the labeling. Similarly, the clinical review team notes that the geriatrics section of the labeling should be updated. I recommend that the Applicant agree to address these as a phase IV commitment, i.e., to submit a labeling supplement addressing these issues within 3 months of supplement approval. This will allow time for full review and discussion of these issues and will not delay approval of this new indication. Given agreement on this commitment, I recommend approval of this supplement.

/S/ MD 6/28/00

Grant A. Williams, MD
Medical Team Leader
DODP

Medical Officer sNDA Review: Nolvadex® (tamoxifen citrate)
Medical Officer: Susan Flamm Honig, M.D.

1.0 General Information

1.1 NDA Information

1.1.1 NDA number NDA 17-970/SE1-046
1.1.2 Submission date: December 28, 1999
1.1.3 Completion Date:

1.2 Drug Name

1.2.1 Generic Name: Tamoxifen citrate; ICI 46, 474
1.2.2 Trade Name: Nolvadex®
1.2.3 Chemical Name: (Z)-2-[-4-[p-(1,2-diphenyl-1-butenyl) phenoxy]-N,N-dimethylethylamine citrate (1:1)

1.3 Applicant: Zeneca Pharmaceuticals

1.4 Pharmacologic Category: Antiestrogen

1.5 Proposed Indication: "Nolvadex is indicated for the treatment of DCIS in women following breast surgery and radiation"

1.6 Dosage Form and Route of Administration: 10- or 20-mg tablets; oral

1.7 NDA Drug Classification: Priority

1.8 Related INDs and NDAs: NDA 17-970
IND[ ] IND[ ]

1.9 Foreign Marketing: Not applicable to this application

2.0 Table of Contents

3.0 Material Reviewed/Clinical Data sources/Administrative Review

3.1 Sources

The NDA was submitted in 173 volumes and included an electronic dataset. Volumes 9-173 consisted of case report forms. Submitted clinical material included the NSABP B-24 protocol, a list of investigative sites (alphabetically and by accrual), a list of investigators, Financial Disclosure information, proposed labeling, a copy of the published report of the trial in the Lancet, and a "Clinical Road Map."

The protocol for the UK trial of tamoxifen in DCIS and a copy of the NSABP B-24 protocol document with amendments were pre-submitted to IND[ ]

3.2 Administrative review

3.2.1 Submissions to IND[ ]prior to sNDA submission

May 27, 1999

The applicant submitted a pre-NDA briefing document, in which the applicant proposed to submit a draft label, the B-24 protocol document, and a draft publication of the B-24 trial results as the definitive contents of an sNDA for tamoxifen in the treatment of DCIS.

July 15, 1999: pre-NDA teleconference

The Agency stated that primary data must be submitted in order to verify the safety and efficacy of tamoxifen for the proposed indication, as well as a study report that describes the conduct of the study, a complete statistical section with methodology, the original protocol document with amendments, a list of study sites and accrual, appropriate case report forms, and any available information about the UK DCIS trial.

The Agency stated that 21 CFR 54 requires financial disclosure from all investigators in trials submitted in an NDA or sNDA after 2/2/99, even if trials were completed prior to this date. The regulation does not provide for waivers.

July 22, 1999

The applicant submitted Zeneca's version of the meeting minutes from the July 15 teleconference.

August 1999

The applicant held a teleconference with Linda Carter, Associate Director of Regulatory Affairs, ODE I, CDER, FDA about financial disclosure requirements.

August 9, 1999: General Correspondence

The applicant provided a copy of "Protocol of the UK randomised trial for the management of screen-detected DCIS".

September 2, 1999

The applicant submitted a list of patients who withdrew due to adverse events for case report form selection for submission.

September 30, 1999: Response to FDA request for information (RFRI)

The applicant submitted a statistical guidance document and additional details of the planned submission, including proposed data elements.

October 13, 1999

The DODP responded to the 9/30/99 submission.

November 11, 1999

The applicant noted that Radiation Therapy reports were missing for 65 of the 377 patients whose CRFs are to be submitted in the sNDA. They proposed submitting the missing reports when they were located, after sNDA submission.

A second submission 11/11/99 contained additional information about data elements to be included in the sNDA and a copy of the published results of B-24.

November 18, 1999

The DODP responded to the two submissions of 11/11/99. The Division agreed that the missing Radiation Therapy Reports could be submitted on a rolling basis.

November 30, 1999 N 075

The applicant submitted a copy of the NSABP B-24 protocol and the protocol amendments, at the reviewer's request.

December 2, 1999 N 076

The applicant submitted a sample dataset for review. Comments were conveyed to the applicant.

December 21, 1999 N 077

The applicant indicated that detailed records of drug compliance were not required. Limited information regarding actions taken with regard to adverse events or duration of the adverse events observed in NSABP B-24 is available.

December 23, 1999 Facsimile

The applicant responded to comments sent regarding submission 076.

3.2.2 sNDA submission

The sNDA was submitted on December 28, 1999.

3.2.3 Submissions to the supplement

January 14, 2000

The applicant submitted the radiation therapy forms that were missing for 41 patients.

The following represent responses to FDA requests for information during the course of the review:

February 28, 2000
March 20, 2000
April 3, 2000
April 14, 2000
April 27, 2000
May 18, 2000
June 1, 2000
June 14, 2000
June 17, 2000
June 19, 2000
June 20, 2000

3.3 Key volume numbers

Table 1. Key volume numbers

Item	Volume
Table of contents for CRF	140.1
Financial Disclosure	140.1
Proposed labeling	140.1
List of investigators	140.1
List of centers	140.2
NSABP B-24 protocol	140.2
UK protocol	140.2
Lancet publication	140.2
Clinical road map	140.2

3.4 Review of Financial Disclosure information

3.4.1 Background

The Financial Disclosure Rule states that for NDAs or sNDAs submitted on or after February 2, 1999, the applicant must disclose whether the following financial arrangements were made with the investigators:

- Compensation affected by the outcome of the clinical studies
- Significant equity interest in the applicant of a covered study (exceeds $50,000 during the time the investigator conducts the study and for 1 year following completion)
- Proprietary interest in the tested product (patent, trademark, copyright, licensing agreement)
- Significant payments of other sorts (payments to the investigator or the institution of > $25,000, exclusive of study costs during the time the investigator conducts the study and for 1 year following completion)

If these arrangements have been made, the applicant must disclose the arrangements and state what has been done to minimize the potential for bias.

The Final Rule, published 12/31/98, states that for studies completed prior to 2/2/99, applicants are not required to collect information on significant equity interests

and must submit information on significant payments of other sorts only if the payments were made on or after 2/2/99.

Requirements for Financial Disclosure were discussed with the applicant during the pre-sNDA teleconference on 7/15/99. To further clarify the requirements, the applicant held a teleconference with Linda Carter, Associate Director of Regulatory Affairs, ODE I, CDER, FDA.

For the purposes of the Financial Disclosure Rule, "sponsor" refers to NCI/NIH, who funded the study, and to AstraZeneca, who provided drug for the study.

3.4.2 Disclosures

- Compensation affected by the outcome of the clinical studies

  AstraZeneca did not provide compensation of any kind to investigators.

4.0 Chemistry/Manufacturing Controls

Tamoxifen is a marketed drug; this information has been previously reviewed. No new information in this category was submitted.

5.0 Animal Pharmacology/Toxicology

Tamoxifen is a marketed drug; this information has been previously reviewed. No new information in this category was submitted.

6.0 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

Tamoxifen is a marketed drug; this information has been previously reviewed. No new information in this category was submitted.

7.0 Relevant Human Experience/Literature Review

The published literature on tamoxifen is extensive and will not be reviewed in this document.

Published literature on ductal carcinoma in situ includes pathologic classification and description of this entity, molecular biologic findings, and a wealth of information on different treatment approaches and the potential validity of a variety of prognostic factors. Therapy has traditionally consisted of mastectomy, usually performed without an axillary nodal dissection. Simple mastectomy has resulted in long-term disease-free survival rates of 98%, although women with treated DCIS remain at risk for a second breast cancer.

Given that at least 6 prospective randomized published trials demonstrated the effectiveness of lumpectomy followed by radiation therapy for local control of invasive breast cancer, the NSABP considered whether breast-conserving surgery could provide adequate treatment for women with non-invasive ductal cancer. The NSABP B-17 trial was designed to evaluate this hypothesis (Fisher B, Costantino J, Redmond C, et al. N Engl J Med 1993 Jun 3; 328 [22]: 1581-6). In this trial 818 women with DCIS were randomized to undergo lumpectomy or lumpectomy followed by breast irradiation. After 8 years of follow-up, Fisher and colleagues reported that in-breast recurrence occurred in 31% of women treated with surgery alone, compared to 13% in women treated with

surgery and radiotherapy (p=0.0001) (Fisher ER, Dignam J, Tan-Chiu E, et al. Cancer 1999 Aug 1; 86 [3]: 429-38). Overall mortality was 1.6% at 8 years regardless of treatment assignment. Of a number of pathologic features examined in exploratory analyses, only moderate-to-marked comedo necrosis was an independent risk factor for recurrence. It should be noted that free margins were not required for study entry. Subsequent reports from NSABP have suggested that the adequacy of the resection margin, rather than comedo necrosis itself, is a better predictor of local recurrence.

The EORTC, the Norwegian Breast Cancer Group, the Danish Breast Cancer group, a group of Swedish investigators, and the German Breast Cancer Study Group are continuing randomized trials evaluating the addition of radiotherapy to breast-conserving surgery for women with DCIS.

A limited number of papers in the literature address the use of tamoxifen as treatment for DCIS. Most represent case reports or theoretical discussions of the value of this approach. The trial submitted in this sNDA (NSABP B-24) is the only completed prospective randomized clinical trial of tamoxifen versus placebo/no therapy for the adjuvant treatment of DCIS. A UK study is in progress, but no results have been reported. The protocol for the UK trial is discussed in section 12.0 and is compared to and contrasted with the submitted NSABP study.

8.0 Summary of Clinical Study

Title: NSABP B-24: A clinical trial to evaluate the worth of tamoxifen in conjunction with lumpectomy and breast irradiation for the treatment of noninvasive intraductal carcinoma (DCIS) of the breast

Accrual dates: May 1991 through April 1994
Data lock date: December 31, 1998 for efficacy
February 28, 1999 for safety

8.1 Rationale and objectives

8.1.1 Rationale

Tamoxifen was approved by FDA in 1977; many efficacy supplements have subsequently been submitted and approved. Tamoxifen has been shown to be effective in metastatic breast cancer and to reduce recurrence and improve survival (OS) when given adjuvantly to node positive and node negative ER(+) breast cancer patients. Tamoxifen is indicated to reduce the occurrence of contralateral breast cancer in women with breast cancer. More recently, tamoxifen was approved to reduce the incidence of breast cancer in women at high risk for disease, after the NSABP P-1 study demonstrated a 49% reduction in breast cancer in women treated with tamoxifen.

Given the effectiveness of tamoxifen in the adjuvant setting and its ability to decrease breast cancer in high-risk women and women with a history of a prior cancer, the NSABP evaluated the effect of this agent in women with DCIS. The NSABP B-17 study, as previously described, demonstrated the value of radiation therapy in addition to breast-conserving surgery in women with DCIS, and is the only completed prospective randomized controlled trial in this disease. NSABP B-24 was designed to evaluate whether the addition of tamoxifen to lumpectomy and radiation therapy could improve

the outcome of women with DCIS. The eligibility criteria for B-24 were designed to broaden study entry compared to those of B-17, so that study results might support the use of breast conservation in a higher percentage of women with non-invasive breast cancer. Reduction in the incidence of invasive cancer (ipsilateral and contralateral) was the prospectively-defined primary endpoint.

8.2.2 Objectives

8.2.2.a Protocol-specified

Primary objective:

- To determine whether lumpectomy, RT, and tamoxifen is more effective than lumpectomy and RT in preventing occurrence of ipsilateral and contralateral invasive breast carcinoma

Secondary objectives:

To determine whether lumpectomy, RT, and tamoxifen is more effective than lumpectomy and RT in preventing:

- Occurrence of non-invasive cancer (DCIS or LCIS in the ipsilateral or contralateral breast)
- Occurrence of invasive and non-invasive cancer (DCIS or LCIS) in the ipsilateral breast
- Occurrence of invasive and non-invasive cancer (DCIS or LCIS) in the contralateral breast

"Endpoints for statistical analysis":

The protocol listed the following endpoints (in addition to those named in the objectives) for statistical analysis:

- Disease-free survival (DFS), distant disease-free survival, and survival
- Deaths from causes other than breast cancer
- Second primary malignancies

Reviewer Comment:

1. Although the protocol specified both DCIS and LCIS as components of non-invasive disease, the Agency considers them to represent distinct pathologic entities, with different implications for treatment and prognosis. As in the review of NSABP P-1, LCIS will be considered separately from DCIS in the assessment of second non-invasive cancers.

2. Patients with DCIS have a 98% long-term overall survival, as reported in the literature. It is appropriate to consider DFS and OS as tertiary endpoints, primarily for safety reasons.

8.2.2.b As reported in the Lancet

The primary endpoint was an analysis of all ipsilateral breast events, invasive and non-invasive. The NSABP did not consider the alteration of the endpoint to represent a substantial difference, and gave the following justifications for the change:

- The results of the NSABP P-1 trial have shifted interest to all breast cancer events.
- Genetic analysis suggests that DCIS may be a direct precursor to invasive disease. Thus prevention of non-invasive cancers may be clinically more important than previously recognized.
- Both invasive and non-invasive cancers were subject to similar clinical management (mastectomy). The use of tamoxifen in this setting may decrease the need for mastectomy.
- There is often debate among pathologists regarding the classification of tumors as invasive or non-invasive. Assessment of the total impact of tamoxifen on breast tumors of any type is appropriate.

The applicant (Zeneca) notes that power calculations were performed for both the invasive and non-invasive endpoints and the sample size was set accordingly. The applicant states that the protocol-specified endpoints were utilized in this sNDA submission.

Reviewer Comment:

1. The reviewer disagrees with the NSABP's change in the primary endpoint.

- A change in the primary endpoint can result from bias.
- DCIS and invasive cancer may be treated with similar local therapies, but systemic management and prognosis of these entities differs.
- The debate among pathologists regarding tumor classification as invasive or non-invasive generally occurs in the setting of small tumors that are smaller than 0.5 cm.
- Whether DCIS is an obligate precursor to the development of invasive disease remains a question of intense scientific debate.

The reviewer agrees with Zeneca's intention to maintain the protocol-specified primary endpoints.

2. An additional secondary endpoint that is clinically relevant is the incidence of ipsilateral invasive cancer. Women with DCIS who develop an ipsilateral non-invasive recurrence/second primary can be treated with a mastectomy; survival is comparable to that observed in women treated with mastectomy at initial presentation. Of concern is the possibility that women with DCIS might be treated with tamoxifen, radiation therapy, and tamoxifen in place of mastectomy, and that survival after an invasive ipsilateral recurrence might be compromised by this approach. The reviewers will perform an exploratory analysis of this endpoint (see Results).

8.2 Design

NSABP B-24 was a prospective randomized double-blind placebo-controlled trial performed in 1804 women with DCIS treated with lumpectomy and breast irradiation. Following lumpectomy, women were randomized to receive either tamoxifen 10 mg PO BID or placebo 2 pills daily for 5 years, started concomitantly with radiotherapy. Randomized study drug and radiotherapy were to begin within 56 days of lumpectomy.

The protocol included guidelines for the administration of radiation therapy.

Randomization as stated in the protocol was stratified by age (≤ 49 versus ≥ 50) and by method of detection (mammography, clinical examination, or both) and was performed centrally through the NSABP Biostatistical Center. The Lancet publication indicated that randomization was also stratified by tumor type (DCIS or DCIS plus LCIS) in addition to the factors mentioned above.

Patients with an invasive local recurrence in the ipsilateral breast were treated with surgery, radiotherapy, and/or systemic therapy at the discretion of the investigator. If the recurrence was non-invasive, local therapy (surgery, RT) was at the discretion of the investigator, but the patient remained on study and continued to take blinded study drug. Similar guidelines were used for invasive and non-invasive contralateral events.

No specific guidelines for unblinding were included in the protocol. The protocol stated only that patients with non-invasive breast cancer, either ipsilateral or contralateral, were to remain on study medication without unblinding.

Pathology reports, slides, and blocks for the original lesion were to be sent to the NSABP. Reports of all biopsy results, benign or malignant, were to be sent to the NSABP. Although further treatment was at the discretion of the investigator, all additional therapy for local, regional, distant, or ipsilateral breast tumor recurrence was to be reported to the NSABP Biostatistical Center on a follow-up form.

On-study evaluations are summarized in Appendix A.

Reviewer Comment:

1. The applicant was asked to clarify whether randomization was stratified by tumor type. If so, the applicant was asked to provide information about the date of this change and how many patients were entered on study prior to this change.

The applicant responded on 2/28/00 that because of "an error on the part of the NSABP", age was the only stratification variable used during randomization. Information on method of detection and tumor type was prospectively collected, but not used in the randomization algorithm.

The reviewer used the electronic database to assess whether omission of the two stratification variables had resulted in imbalanced patient allocation.

- Ninety-eight patients (5% of the randomized population) presented with mixed DCIS/LCIS lesions, 57 on placebo and 41 on tamoxifen. LCIS has not been reported to increase local recurrence in DCIS patients treated with breast conservation. It is unlikely that this small difference affected the observed outcome of the trial.
- The distribution of the method of detection is listed in Table 9. A slightly higher percentage of patients randomized to tamoxifen had lesions detected by clinical exam or with a combination of mammogram and clinical examination, rather than with mammogram alone, compared to patients randomized to placebo. This factor would obscure a benefit from tamoxifen, but it is unlikely that these small differences affected the observed outcome of the study.

2. The NSABP stated in pre-sNDA meetings that they do not have information regarding the size and prognostic characteristics of the second malignancies. This statement is not consistent with the statement in the protocol requiring submission of all pathology reports and records of additional therapy to the NSABP, and with the June 1994 amendment (see section 8.6). The applicant was asked during the course of the

review to provide this information; the applicant responded and noted that the requested information was not entered into the electronic database.

8.3 Eligibility

8.3.1 Entry criteria

- Patients with noninvasive DCIS
  - Women with mixed DCIS and LCIS are eligible
  - See "Specific Notes on DCIS-related eligibility" below
- Histologic assessment of specimen margins and documentation of the status (free or involved)
- Nodal dissection not required, but if performed it must be negative
- Interval between definitive operation and randomization $\leq$ 56 days
- Adequate hematologic and hepatic function
- Life expectancy $\geq$ 10 years

Specific Notes on DCIS-related eligibility:

- Women with scattered residual microcalcifications are eligible
  - Eligible if read radiographically as benign or indeterminant
  - Eligible if suspicious and associated with DCIS-related calcifications or a mass
    - Biopsy is optional; if performed, must be negative or non-invasive disease
  - Eligible if suspicious but no clusters or mass and a biopsy shows DCIS
- Women with microscopic margin involvement by DCIS or LCIS are eligible
- Women with calcifications/masses in more than one quadrant are eligible if all abnormalities can be excised with grossly free margins and an acceptable cosmetic result

8.3.2 Exclusion criteria

- Breast tumor other than DCIS
- Bilateral malignancy
- Positive nodes on histopathologic exam
- Suspicious palpable nodes in the axilla, supra- or infraclavicular area
- Grossly involved specimen margins after excision or re-excision
- Prior malignancy other than cervical CIS or non-melanoma skin cancer
- Pregnancy at the time of randomization
- Patients with excised DCIS and residual suspicious microcalcifications with a biopsy that demonstrates invasive cancer.

Reviewer Comments:

1. The NSABP tried to include a broad spectrum of patients, including those with potentially more extensive DCIS than clinically recognized. The data will be reviewed to see whether they achieved this aim and whether the results of this trial can be applied to a general population of DCIS patients.

2. Investigators were encouraged to enter patients with pathologically free resection margins, but were not required to do so. The reviewer will assess the number of

patients with microscopically involved margins and whether the reported benefit varied by margin status.

3. It would be of interest to evaluate outcome in women with masses or calcifications in different quadrants, a group generally treated with mastectomy. However, this information was not included in the electronic database.

4. It will be of interest to evaluate other parameters associated with recurrence, such as the presence or absence of comedo necrosis.

5. Additional eligibility criteria were consistent with those generally used in clinical trials. Exclusion criteria were appropriately designed to exclude patients with invasive disease.

8.4 Endpoints

8.4.1 Breast outcome measures

The following definitions were provided in the protocol for breast cancer events.

Local/regional recurrence:	Positive cytology or biopsy required; visible/palpable lesions or abnormal mammogram were categorized as suspicious
Distant sites:	
Contralateral breast, Skin, LN:	Positive cytology, aspirate, or biopsy Suspicious: Visible/palpable lesions or abnormal mammogram
Bone marrow:	Positive cytology, aspirate, or biopsy Suspicious: Unexplained depression of peripheral counts and/or erythroblastic blood picture
Lung:	Positive cytology, aspirate, or biopsy, OR Presence of multiple pulmonary nodules felt to be consistent with pulmonary metastases Solitary pulmonary nodule required biopsy or FNA
Skeletal:	X-ray evidence of lytic, blastic, or mixed lytic/blastic lesions on plain films with or without bone scan confirmation; OR Biopsy proof of bone metastases Bone scan consistent with bone metastases in patients with bone pain, OR Progressive bone scan changes over at least a 4-week period in an asymptomatic patient with bone scan-only evidence of disease
Liver:	Liver enlargement, especially if nodular, with confirmation by an abnormal liver scan and/or abnormal chemistries OR Liver biopsy confirmation of metastatic disease

CNS:	Positive CT scan or MRI with 2 or more lesions OR Biopsy or cytology
Second primary:	Requires confirmation histologically wherever possible. Submit slides to NSABP for review.
Postmortem:	Should be secured whenever possible and reports sent to NSABP. Submit all death certificates to NSABP.

Reviewer Comment:

1. The endpoints were appropriately designed to require pathologic confirmation of recurrence or overwhelming clinical evidence of metastatic disease.

2. As in the P-1 study, death certificates were required for all patients who died with supportive documentation of cause of death, if available.

8.4.2 Statistical endpoints

The primary endpoint was defined as the occurrence of ipsilateral or contralateral invasive breast cancer.

The secondary endpoints were defined as non-invasive cancer of the ipsilateral or contralateral breast, any cancer (invasive or non-invasive) of the ipsilateral breast, and any cancer of the contralateral breast.

The definition of these endpoints was based on the rate of each event as a first event within the trial. Patients diagnosed with non-invasive breast cancer who then had a subsequent invasive cancer were analyzed only in the non-invasive event group.

The rationale for this method, as presented in the "Clinical Road Map" was that the blind was broken at the time of the first breast event, introducing an element of bias for detection of subsequent events.

Reviewer Comment:

1. The protocol specifies that patients with non-invasive events were to continue on blinded study drug. As detailed in Table 5 by the applicant, few patients were unblinded during the trial.

2. A sensitivity analysis of all invasive events and all non-invasive events is of interest to substantiate the magnitude of the effect of tamoxifen, regardless of whether it was a first or second event.

3. As agreed upon by Zeneca and the reviewer, analysis of the protocol-specified primary endpoint will constitute the primary analysis for regulatory purposes.

8.5 Statistical considerations

8.5.1 Sample size calculation

The sample size was calculated based on the assumption that treatment with tamoxifen will reduce the incidence of invasive cancer of the ipsilateral or contralateral

breast by at least 50% on an annual basis, with a one-sided significance level of 5% and 80% power. This decrease is comparable to a 2.9% increase in 5-year DFS. The expected failure rate was assumed to be 0.012 per year, based on data from NSABP B-17. A minimum of 72 events (ipsilateral or contralateral breast cancer, or metastases) was required prior to analysis. The resultant sample size was 1800 patients, 900 per group, with 87% power to detect a 50% reduction in the failure rate at year 7 (5 years of accrual plus 2 years of follow-up).

For non-invasive cancer, the occurrence rate was assumed to be 0.016 per year. A sample size of 1800 women would result in 80% power to detect a 40% decrease in the rate of failure at year 7 (3.0% increase in 5-year event-free survival).

The anticipated rate of all forms of ipsilateral breast cancer was estimated at 0.023 per year. The trial would have 90% power to detect a 40% decrease in the rate of all ipsilateral events at year 7 with the stated sample size.

For all forms of contralateral breast cancer, the anticipated occurrence rate was 0.005 per year. The trial would have 80% power to detect a 50% reduction in the rate of all contralateral breast cancer events at year 11 with randomization of 1800 patients.

Reviewer Comment:

1. The study was adequately powered to detect a decrease in breast cancer events, considered separately or together.

2. The estimated occurrence rates for breast cancer events were based on the best available data.

8.5.2 Interim analysis

8.5.2.a Protocol-specified

Toxicity and accrual were to be monitored quarterly during the trial. Primary endpoints were to be analyzed annually, beginning at the end of the 5th year of the protocol. The two interim tests were planned at reduced alpha levels using O'Brien-Fleming methods.

The alpha levels for the two interim and final analyses were prospectively specified at 0.0025, 0.0030, and 0.0483 respectively.

8.5.2.b As performed during the trial

The trial accrued faster than expected, resulting in an increased number of events prior to the original specified 5-year timepoint. In addition, an NSABP Independent Data Monitoring Committee (DMC) was convened. The interim analysis plan was therefore converted to a rule based on number of events. This change was not incorporated as a protocol amendment. The stopping rules for the study were not altered. Results of the interim analyses were presented to and evaluated by the DMC.

Three interim analyses were performed and did not result in early termination of the trial.

Reviewer Comment:

1. It is preferable to perform interim analyses based on the number of events rather than on a time period. Although this method was not protocol-specified, it is acceptable.

8.5.3 Final analysis plan

8.5.3.a Protocol-specified

The prospectively defined analysis plan called for standard life-table methods and Cox proportional hazards modeling. Statistical adjustments were planned for any prognostic or risk factor that was imbalanced between treatment groups and to account for interactive effects between treatment and a covariate.

A Cox regression model was planned as the primary tool for examining covariates. Log-minus-log survival plots were to be used to check the proportionality assumption of the model. Terms for the stratification variables and treatments were to be included in the model first. If the global likelihood ratio test for all interactions of covariates with treatments was significant, individual interactions were to be tested using the Gail and Simon procedure. If the effect of a covariate was significant in the Cox model and its distribution between treatments was unbalanced, then it was to be considered a confounder, and end results were to be reported both unadjusted and adjusted for the confounder.

8.5.3.b As reported in the Lancet

The Lancet publication noted that cause-specific hazards of failure and hazard rate ratios for various endpoints were computed with exact binomial methods used to test for differences in rates by treatment group. The Cox proportional hazards model was used to compute relative risks of failure according to prognostic covariates and treatment simultaneously, and to evaluate whether response to therapy varied by characteristics (treatment-covariate interactions).

Cumulative probability of the various events were computed using cumulative incidence curves, which account for competing risks. Kaplan-Meier methods were used to evaluate event-free survival and OS, with 95% CI.

Interim analyses were performed without early termination of the study. The adjusted significance criterion for the definitive analysis was 0.0483 according to the Fleming, Harrington, and O'Brien method.

The original protocol specified one-sided p-values. The current analysis used two-sided p-values.

The NSABP defined the endpoint as the rate of the corresponding event over time. The event rate for each endpoint was specified as the number of first events of that type in the treatment group divided by the total person-years of follow-up in that treatment group. Treatment groups were compared using the rate ratio, defined as the event rate in the tamoxifen group divided by the event rate in the placebo group.

8.5.3.c As described in volume 140.2, sNDA submission

8.5.3.c.i Primary analysis

The primary statistical analysis was an exact binomial comparison between tamoxifen and placebo of event rates, unadjusted for baseline or prognostic covariates, using an intent-to-treat analysis. "Intent-to-treat" was defined as all randomized patients with follow-up, analyzed by randomized treatment. Six patients, 3 on each arm, were excluded because of lack of follow-up data for an n of 1798. The binomial comparison

was used instead of the log-rank test because there were few events for some endpoints. In the setting of few events, the exact test is more appropriate. To provide consistency across analyses, the exact test was used for all endpoints. O'Brien-Fleming adjustments were used to account for the interim analyses. No adjustments were made for analysis of multiple secondary endpoints. In addition, the cumulative incidence of each event was calculated through 5 years of follow-up, based on the cumulative incidence function for the event. This function was adjusted for the presence of competing risks of other events.

8.5.3.c.ii Secondary analyses

The secondary analyses were performed to ensure robustness of the results of the primary analysis as follows.

- The stratified logrank test was used for each endpoint, with allowance for the stratification factors, in an intent-to-treat analysis. For both the primary and secondary endpoints, the results of the stratified logrank test and the primary analysis were nearly identical.
- Cox's proportional hazards model was used to compare treatment groups after adjustment for baseline and prognostic covariates in an intent-to-treat analysis. The covariates included age group, race, tumor size, tumor type, method of detection of DCIS, margin status and comedonecrosis. The results of this analysis were similar to those of the primary analysis, expected since the treatment groups were well-balanced. No evidence of treatment-by-covariate interactions was found.
- A per protocol analysis was performed using only those patients who met the eligibility criteria. In addition to the patients excluded because of lack of follow-up, 11 patients on placebo and 18 on tamoxifen were excluded. The most common reason for exclusion was breast tumor other than DCIS. This analysis gave results similar to those of the primary analysis.

Because the results of the secondary analyses were similar to those of the primary analysis, the results were not reported in the publication of this trial.

8.5.3.c.iii Survival

Kaplan-Meier curves were used to summarize 5-year overall survival, and treatment groups were compared using the logrank test in an intent-to-treat, unadjusted analysis.

8.5.3.c.iv Safety data

Safety data were summarized without a formal statistical analysis. Information on the incidence of stroke was not included in the B-24 publication because this information was not found until further review of the data by the NSABP. An erratum to the publication was prepared and submitted to the journal. Data on stroke were contained in the electronic database in this sNDA.

Reviewer Comments:

1. The FDA usually prefers to see an unadjusted intent-to-treat analysis as the primary analysis. Although use of the Cox model was prospectively specified in the protocol, potential covariates were not identified in advance of trial initiation.

2. Some statisticians might perform an analysis using the prospectively specified stratification factors. However, the alternative approach is to use stratification to achieve a balanced study population, then perform a non-stratified analysis.

3. The primary analysis as described in the sNDA submission is acceptable (intent-to-treat analysis, excluding patients without follow-up, unadjusted).

4. The applicant's rationale for the use of the binomial comparison instead of the logrank test seems appropriate. The statistical reviewer agrees.

5. The use of two-sided p-values, although not prospectively specified, is appropriate to ensure that tamoxifen did not cause an adverse outcome in this population of patients with an excellent long-term survival.

6. The results of the secondary analyses were not provided in the sNDA. However, the FDA considers the primary analysis as the basis for approval, and documentation of the results of the secondary analyses is not required.

7. The NSABP reported analyses based on first events only. The following clarification was provided by the NSABP and the applicant. While the original intent of the protocol was to maintain blinded protocol treatment for patients with non-invasive breast cancers, it became clear during the study that patients did not wish to remain on blinded therapy after such an event. Furthermore, 2/3 of these patients were treated with a mastectomy and thus were no longer at risk for an ipsilateral event. Because of potential bias in the decision to request unblinding or to undergo additional therapy, the primary analysis was based on first events. Secondary analyses were performed with all events. The reviewer agrees with this rationale.

8.6 Protocol amendments

The protocol amendments are summarized below.

June 28, 1991	The protocol originally required a mammogram within 3 months of randomization. It was amended to require a mammogram within 3 months of breast surgery.
March 16, 1994	Provided information regarding the incidence of uterine cancer on NSABP B-14 and required an annual gynecologic examination and specific questioning/instructions regarding early warning signs of uterine cancer and the need for prompt evaluation. A new form, "NSABP report form for monitoring of gynecologic symptoms and events", was added. Modification of the consent form to reflect the new information.
May 3, 1994	New mechanism for providing trial participants with updated information; "Dear Participant" letter from NCI
June 16, 1994	Protocol and consent form revisions related to tamoxifen toxicity.

	Additional documentation required for "recurrent" disease, including submission of the mammogram reports documenting the recurrence, the mammogram films, pathology slides, blocks, and reports of ER/PR status
February 22, 1996	Clarification of required gynecologic exam policy for women with hysterectomies (mandatory only if ovaries still in place)
July 12, 1996	Changed follow-up forms to eliminate questions about number of tamoxifen pills taken. Instead, the forms capture whether the patient is still taking study drug. If not, the reason for discontinuation and the last date of administration are collected. Also, information on hot flashes, fluid retention, vaginal discharge, and menstrual problems will no longer be collected.
July 12, 1996	Clarification regarding reporting of adverse events (Agency concurrence sent 11/8/96)
August 1, 1996	Implementation of new forms (treatment and OFF forms) referred to in July 12th amendment
March 18, 1997	New information regarding ophthalmic toxicity of tamoxifen (study P-1E in B-14 patients and unblinded eye data from NSABP P-1); instructions regarding patient notification
July 28, 1997	Reminder regarding patient notification of ophthalmic toxicity related to tamoxifen
December 16, 1998	Release to investigators of positive results of B-24; trial unblinded. Further treatment of the placebo group left to the investigator's discretion.

Reviewer Comments:

1. The majority of the protocol amendments were designed to ensure adequate patient informed consent and follow-up for safety considerations. None of the protocol amendments were likely to have significantly affected the outcome of the trial from an efficacy standpoint.

2. The trial was unblinded in December 1998, potentially interfering with the ability to capture late events that could affect the difference between the two treatment arms. The data lock date for this application was December 31, 1998; thus, the results presented here are unlikely to be affected by unblinding.

3. The NSABP stated in the pre-sNDA meeting that investigators were not required to report the details of a breast cancer event. The June 16, 1994 amendment contradicts this statement. Although accrual was complete by this date, information on many breast cancer events should have been captured. The applicant was asked to provide the missing data but stated it was not collected.

8.7 Enrollment

A total of 1804 women were randomized, 902 to each arm of the study. Of these, 1798 were evaluable, 899 in each group. The median follow-up at the time of the analysis reported in this sNDA was 74 months, with a range of 57 to 93 months (page 8, N 064; Lancet publication, page 1996).

Reviewer Comment:

1. A median follow-up of about 6 years represents approximately one year of follow-up after completion of 5 years of drug therapy. This length of follow-up is adequate to detect a reduced number of events, but longer follow-up will be needed to determine the durability of the effect.

2. All patients on NSABP B-24 completed 5 years of drug therapy (personal communication, Jim Dignum, NSABP statistician).

8.8 Removal from study, unblindings, and protocol violations

This section describes all known deviations from protocol therapy. Late assessments were not identified by NSABP during the course of the study and are not included in these tabulations of protocol violations.

8.8.1 Patients without follow-up data

Six patients, 3 on each arm, did not have follow-up data and were excluded from the primary analysis. These patients are described in the following table.

Table 2. Patients without follow-up data (derived from line listings, table T2, volume 140.2, page 271)

Reason	Placebo	Tamoxifen
Consent withdrawal after starting therapy	1	1
No consent or withdrawal of consent prior to start of therapy	1	2[2]
Other[1]	1	0

[1] Withdrew because of new articles about endometrial cancer and tamoxifen

[2] One of these patients is also listed in Table 4.

Reviewer Comment:

1. The number of patients without follow-up is small (0.3% of the randomized population) and is equally distributed between treatment arms.

8.8.2 Patients who did not meet eligibility criteria

Twenty-nine patients were ineligible after randomization, 11 on placebo and 18 on tamoxifen. The reasons for ineligibility are summarized in the following table. These patients were included in the primary, intent-to-treat analysis.

Table 3. Reasons for ineligibility on NSABP B-24 (derived from line listings, Table T1, volume 140.2, page 269)

Reason	Placebo	Tamoxifen
Invasive cancer (not DCIS)	7	9
Radiation prior to randomization	2	4
Dx to surgery > 56 days	1	1
Consent problems	1	1
Hormonal therapy continued after randomization	0	1
Non-allowed surgery	0	1
Prior cancer	0	1
Total	11	18

Reviewer Comment:

1. The reviewer agrees with the inclusion of these patients in an intent-to-treat analysis.

2. The reviewer found two patients who did not have a bilateral mammogram report in the CRF (441408109 and 444023066). It is not possible to determine whether these patients were eligible for study entry.

3. The reviewer noted that the CRF for one patient (442036017) did not contain the pathology report of the original lesion. A physician note mentions that microinvasion was identified on at least one reading by a consultative pathologist. The applicant noted that despite repeated requests by the NSABP, the site did not submit this report. It is not possible to determine the patient's eligibility for study entry.

4. The number of ineligible patients was small and represents 1.2% of patients randomized to placebo and 2.0% of patients randomized to tamoxifen. The effect of including these patients in the analysis, if any, would bias the results against tamoxifen.

8.8.3 Patients who did not start assigned study medication

Patients who did not start their assigned study medication are summarized in the following table. The table includes one patient (440536923) who withdrew consent and did not provide follow-up information. She is included in Table 2 above and in the following table. Except for this patient, all other patients listed in Table 4 were included in the intent-to-treat analysis.

Table 4. Patients who did not start study medication (derived from line listings in Table T3, volume 140.2, page 272)

Comment	Placebo	Tamoxifen
Withdrew consent or unwilling to take study drug/Did not start RT	1	3
Unwilling to take study drug	2	3[1]
Unknown reason	3	0
Miscommunication at institution	1	0
Refused protocol treatment	1	0
Total	8	6

[1]Two patients on tamoxifen specifically cited fear of side effects

Reviewer Comment:

1. The number of patients who did not take study medication was small and represented less than 1% of the patients randomized on each arm.

8.8.4 Patients who were unblinded early

The protocol did not contain guidelines for unblinding. The following table summarizes the patients whose therapy was unblinded (87 reasons in 86 patients). Most unblindings occurred after the trial results were announced to the investigators in April 1998.

Table 5. Non-protocol unblinding (derived from line listings in Table T4, volume 140.2, pages 273-275)

Reason	Placebo	Tamoxifen
Subject insistence	22	24
Subject insistence—news reports, concerns re: endometrial cancer	2	1
M.D. insistence	1	1
Cancer events:		
Invasive breast cancer	1	1
Non-invasive breast cancer	2	2
Supraclavicular adenopathy	1	0
Gyne problems:		
Endometrial cancer	0	1
Endometrial hyper/dysplasia	1	2
Uterine fibroids	0	1
Ovarian cyst	1	0
Cervical polyps	1	0
Vaginal symptoms	0	3[1]
Hypercoagulable events:		
Deep vein thrombosis	0	1
Stroke	0	2
Eye problems:		
Macular degeneration	1	0
Retinal changes	0	1
Hepatitis	2	0
Psychiatric problems:		
Depression	1	1
ER visit: disoriented	1	0
Hallucinations	0	1
Memory loss	1	0
Pregnancy	1	1
Consent withdrawal	1	0
Osteoporosis	2	0
Insurance company refuses to cover subject if randomized to tamoxifen	0	1
Other, not specified	1	0
Total	43	44

[1] This patient is also listed under "retinal changes"; asked for unblinding for two reasons

Reviewer Comment:

1. Approximately 5% of patients on each arm were unblinded. A higher number of patients on the tamoxifen arm were unblinded due to serious toxicity (endometrial cancer, hypercoagulable events) compared to the placebo arm (4 patients and 0 respectively). Other reasons for unblinding were distributed evenly between treatment arms. The effect of unblinding on the trial results, if any, would bias against tamoxifen.

2. Review of the electronic database indicates that 200 patients were unblinded, 113 on placebo and 87 on tamoxifen. The following outlines the results from the database.

Table 6. Unblindings per the electronic database

Reason	Placebo	Tamoxifen
Eligibility issues	1	0
Medical—side effects	0	2
Medical—other	7	4
Event	12	8
Event	0	0
Event	12	14
Event	44	22
Patient death	1	0
Other	36	37
TOTAL	113	87

According to this table, the incidence of unblinding was much higher, around 11%. More patients on placebo (13%) than on tamoxifen (10%) were unblinded. It is likely that this difference resulted from a higher incidence of second cancers on the placebo arm. However, the applicant has been asked to clarify this discrepancy.

In a reply from the NSABP statistician (6/17/00), patients with an invasive breast cancer or with a second primary cancer were unblinded. Patients who died had their treatments unblinded as well. The reasons for unblinding in these circumstances were to develop a treatment plan and for safety considerations. The non-protocol unblinding reported by the applicant includes those patients whose therapy was unblinded because of:

- Eligibility issues: Issues arising after review of patient eligibility, such as the discovery that the patient had invasive cancer at baseline
- Medical-side effects: Side effect, possibly attributable to drug therapy, which led to a request for unblinding
- Medical-other: Other non-treatment-related medical conditions which might require unblinding.
- Other: Requests for unblinding at the patient's insistence

The applicant reiterated that non-invasive breast cancers were not a protocol-specified reason for unblinding, but some patients made this request during the trial.

8.8.5 Patients who received non-allowed medications

The following table summarizes the medications not permitted by protocol that patients on NSABP B-24 received. Most received these medications after the diagnosis of a new breast event. A total of 123 patients were reported to have received one or more unallowed medication or procedure, 61 on placebo and 62 on tamoxifen.

Table 7. Non-allowed study medications (derived from line listings, Table T5, volume 140.2, pages 276-280). [Numbers indicate medications used, not unique patients]

Medication	Comments	Placebo	Tamoxifen
Tamoxifen	Refers to unblinded administration	17	12
Raloxifene		1	1
Estrogen[1] alone or with progestin	See Table 7	19	14
Progestins alone	Simple hyperplasia:2 T Vaginal bleeding: 1 P, 1 T "Postmen. Benefit": 1 T No reason given: 1 P, 3 T Given w/ open-label T: 1 P	3	7
Megace	No reason given: 1 on P, 2 on T For hot flashes: 3 on P, 1 on T For endometrial hyperplasia: 1 on P	5	3
Depot-Lupron	Menorrhagia: 1 P Endometriosis: 1 T	1	1
Other hormones:			
Prednisone	Placebo: Nephrotic syndrome, myasthenia gravis, dermatitis Tamoxifen: arthritis (2), Crohn's disease, dermatitis (2), knee joint aspiration, polymyalgia rheumatica, radiation pneumonitis, ITP, eye infection	3	10
Synthroid		0	1
Depo-testosterone		0	1
Chemotherapy agents:			
CMF	Metastatic breast cancer	0	1
Navelbine	Metastatic breast cancer	0	1
Paclitaxel/carboplatin	Second lung primary	0	1
Hydrea	Decreased megakaryocytes on bone marrow exam	1	0
5-FU/leucovorin	Colon primary	0	1
Combination chemo	Lymphoma	0	1
Fosamax	Osteoporosis	1	0
Procedures for breast events:			
Lumpectomy	DCIS recurrence; 2nd primary; benign lesion	3	0
Mastectomy	Bilat. prophylactic procedures	0	2
Axillary dissection	Not stated; no second breast event	0	1
Breast radiation	Placebo: DCIS recurrence; initial refusal; second primary (2) Tamoxifen: second primary	4	1
Radiation for MBC		0	1
Breast cyst aspiration		0	1
Procedures for other cancers:			
Radiation	Basal cell, thyroid cancer	2	0
Colonic resection	Colovaginal fistula	1	0

Procedures for gyne events:			
Hysterectomy and/or oophorectomy	See Table 8	14	14
Crohn's disease	Medication not specified	0	1

Abbreviations: P=placebo, T=tamoxifen, MBC=metastatic breast cancer
[1] Includes Premarin, Premarin vaginal cream, estrogen with progesterone, Provera, Estrace, estrogen patch, depo-estradiol, Prempro
[2] Includes Provera, Aygestin

The following table summarizes the reasons given for the use of hormonal therapy during the study.

Table 8. Reasons for estrogen use, alone or with a progestin (derived from line listings, Table T5, volume 140.2, pages 276-280).

Reason	Placebo (n=19)	Tamoxifen (n=14)
No reason given	5	8
Hot flashes	6	1
Osteoporosis	2	0
"Postmenopausal benefit"	0	1
Vaginal dryness	3	1
Vaginal spotting	1	0
Vaginitis	1	2
Depression	1	1

The following table presents the reasons given for proceeding with a hysterectomy in patients who had this operation performed during the trial.

Table 9. Reasons for hysterectomy, oophorectomy, or both (derived from line listings, Table T5, volume 140.2, pages 276-280).

Reason	Placebo (n=14)	Tamoxifen (n=14)
Fibroid tumors	4	6
Endometriosis	1	1
Vaginal bleeding	3	0
Endometrial hyperplasia	2	1 (with focal atypia)
Rectocoele and/or cystourethrocoele	3	1
Uterine prolapse	0	1
Benign ovarian fibroma	0	1
Ovarian teratoma	0	1
Ovarian cysts	1	1
BSO/reason not stated	0	1

Reviewer Comments:

1. Less than 2% of patients on the placebo arm received open-label tamoxifen. It is unlikely that crossover therapy affected the observed outcome of the trial.

2. The use of hormone therapy (estrogen/progesterone, either alone or in combination) was similar between treatment arms. Since these hormones are thought to counteract the effect of tamoxifen, this protocol violation might have biased the study results against tamoxifen, if it had any effect at all.

3. The reasons for HRT use were balanced between treatment arms.

4. The reasons given for proceeding with a hysterectomy were balanced between treatment arms. Of note, hysterectomy for endometrial hyperplasia was performed uncommonly and occurred in 2 patients on placebo and 1 on tamoxifen. The number of hysterectomies performed was small, 14 on each arm (1.6% of patients randomized on each arm).

8.8.6 Patients who withdrew from study treatment

The applicant supplied a list of patients who withdrew in volume 140.2 of the sNDA, with the reason for withdrawal listed as either "tox" or "other" without further detail. These data were not submitted in electronic format. The line listings indicate that 285 patients on placebo and 311 on tamoxifen, or a total of 596 patients, withdrew.

The Lancet publication reports that 564 patients, 269 on placebo and 295 on tamoxifen, discontinued treatment because of side effects (98 and 146 respectively), personal reasons (146 and 124 respectively), and unspecified reasons (25 and 25 respectively).

The Analysis for Primary Publication dated 1/6/99, submitted as N 072, indicated that 661 patients who began therapy discontinued treatment prematurely. The most common reason for discontinuation was side effects (98 on placebo and 146 on tamoxifen). Other reasons accounted for withdrawal of 146 patients on placebo and 123 on tamoxifen.

The withdrawal rate on this study was 5% per year, consistent with the rates observed in other placebo-controlled tamoxifen trials, as reported in N 072.

Reviewer Comment:

1. The reviewer believes that the Analysis for Primary Publication, submitted as N 072, was superceded by subsequent analyses with a later data lock date and data that had been cleaned and reviewed. The applicant confirmed the reviewer's assumption.

2. The patient withdrawal data cited in the Lancet are not concordant with the data reported in the sNDA. The applicant was asked to indicate which statement is correct and to explain the discrepancy. The applicant responded that the NSABP's therapy discontinuation file is not closed and saved at scheduled intervals, but is instead updated on a continuous basis. The electronic database represents the most recent dataset at the time of sNDA submission.

3. The data reported in the sNDA indicate that 33% of randomized patients, 32% on placebo and 34% on tamoxifen, withdrew from the study. These data correspond to a withdrawal rate of 5% per year, as the applicant indicates. A loss of about 1/3 of randomized patients is high. However, dropout was similar on both arms and does not

indicate excessive toxicity or lack of tolerability of tamoxifen as the primary reason for withdrawal.

8.9 Patient characteristics

The following table summarizes the baseline characteristics of the women evaluable for analysis (data on the 6 patients without follow-up not provided).

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Table 10. Demographic and prognostic factors (structure of applicant's Table 1, Lancet publication; data derived from electronic database by reviewer)

Characteristic	Placebo (n=902) N (%--rounded)	Tamoxifen (n=902) N(%)
Age		
≤ 49	301 (33)	303 (34)
50-59	275 (31)	266 (29)
≥ 60	326 (36)	333 (37)
Menopausal status		
Pre/peri	318 (35)	322 (36)
Post	569 (63)	574 (64)
Unknown	15 (2)	6 (1)
Ethnic origin		
White	764 (85)	778 (86)
Black	68 (8)	58 (6)
Other	50 (6)	53 (6)
Unknown	20 (2)	13 (1)
Tumor size		
≤ 1 cm	743 (82)	767 (85)
1.1-2.0	104 (12)	83 (9)
> 2.0	37 (4)	41 (5)
Unknown	18 (2)	11 (1)
Tumor type		
DCIS	843 (93)	857 (95)
DCIS + LCIS	57 (6)	41 (5)
Unknown	2 (0.2)	4 (0.4)
Method of detection		
Mammogram	756 (84)	731 (81)
Clinical examination	72 (8)	85 (9)
Both	72 (8)	82 (9)
Unknown	2 (0.2)	4 (0.4)
Tumor palpable?		
Yes	140 (16)	138 (15)
No	737 (82)	752 (83)
Unknown	25 (3)	12 (1)
Margin status		
Negative	675 (75)	667 (74)
Positive	145 (16)	140 (16)
Unknown	82 (9)	95 (11)
Comedo necrosis		
Absent	447 (50)	469 (52)
Present	433 (48)	414 (46)
Unknown	22 (2)	19 (2)

Abbreviations: RT = radiation therapy; LCIS = lobular carcinoma in situ

Reviewer Comments:

1. Patients entered on this trial fit the general profile of DCIS patients in the United States at the present time; more than 80% had lesions less than 1 cm detected mammographically.

2. Approximately 1/3 of the women in this study were less than age 49, 1/3 were between 50 and 59, and about 1/3 were age 60 or older.

3. Menopausal status was determined by patient self-report. This method is acceptable, as tamoxifen's effect is not dependent on menopausal status.

4. The majority of women on this clinical trial were white. In the P-1 trial, tamoxifen reduced the incidence of breast cancers in all subsets except non-white women. The reviewer will examine effect by race in this application.

5. Although women with involved margins were eligible for study entry, approximately 75% had free margins. The results of this trial must be interpreted with caution with regard to women with positive margins or more extensive DCIS.

6. Comedo necrosis is considered by some to represent a risk factor for local recurrence. Others consider it a risk factor only for large or incompletely excised lesions. There was a slight increase in the incidence of comedo necrosis on the placebo arm compared to the tamoxifen arm, but this small difference is not significant.

7. Overall, demographic and baseline tumor characteristics were well-balanced between treatment arms.

9.0 Efficacy review of NSABP B-24

9.1 Introduction

9.1.1 Agency review

The efficacy review of this study was dependent on verification of breast cancer events and classification of these events as invasive or non-invasive as well as ipsilateral or contralateral. The reviewer examined a total of 380 case report forms, or 21% of the patient population. CRFs were submitted on patients with the following events:

- Invasive ipsilateral breast cancer
- Invasive contralateral breast cancer
- Non-invasive ipsilateral breast cancer
- Non-invasive contralateral breast cancer
- Deaths
- Second primary cancer
- Breast cancer recurrence at local/regional/distant sites
- Endometrial cancer
- Stroke
- Phlebitis/thromboembolic events

In addition, the FDA reviewed a list of reasons for withdrawals due to adverse events. Selected CRFs were reviewed as a quality control check to evaluate whether some adverse events were missed. For example, the CRFs of patients who withdrew for hot flashes were not reviewed, but those of patients who withdrew for shortness of breath or leg pain were requested.

As a result, the Agency was able to review CRFs for patients with and without events in order to check reporting validity for the primary efficacy and safety endpoints.

The reviewer was blinded to patient treatment assignment during the CRF review. Unblinding using the electronic database tables was performed only after abstracting relevant information and assessing whether, in the reviewer's opinion, an event occurred.

It should be noted that the applicant submitted information on whether a breast cancer event occurred and whether it was ipsilateral or contralateral. No other information was provided. The protocol specifically stated that all information documenting recurrence, including mammogram reports, films, pathology reports, slides, blocks, and ER/PR status was to be submitted to the NSABP. In a response dated 3/20/00, the applicant states that this information was not entered in the electronic database. As a result, the reviewer extracted information on pathology and stage by hand from the CRFs.

9.1.2 Summary outcomes reported by the applicant

The applicant submitted several sets of data for review: the Briefing Document (submitted to the NSA as N064, 5/27/99), the Technical Report (N 072, submitted to the IND 9/30/99), the Lancet publication (submitted in the sNDA), and the electronic database (submitted in the sNDA). The cited results are similar but not identical. The applicant confirmed that the Lancet publication should be used as the best source of data. The first two documents were based on an earlier data lock date.

The following table summarizes the study outcomes as reported by the applicant in the sNDA.

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Table 11. Site, cumulative incidence, rate, and rate ratios of first events (applicant's Table 2, Lancet publication)

First Event	Placebo (n=899)			Tamoxifen (n=899)			Rate ratio (95% CI)[2]	p
	No. events	Cumul. incidence at 5 yrs (%)	Rate[1]	No. events	Cumul. incidence at 5 yrs (%)	Rate[1]		
Breast and non-breast cancer	169	16.7	38.12	126	12.6	27.50	0.72 (0.57, 0.91)	0.006
All breast cancer								
Total	130	13.4	29.32	84	8.2	18.33	0.63 (0.47, 0.83)	0.0009
Invasive[3]	70	7.2	15.79	41	4.1	8.95	0.57 (0.38, 0.85)	0.004
Non-invasive[4]	60	6.2	13.53	43	4.2	9.39	0.69 (0.46, 1.04)	0.08
Ipsilateral breast cancer								
Total	87	9.3	19.62	63	6.0	13.75	0.70 (0.50, 0.98)	0.04
Invasive	40	4.2	9.02	23	2.1	5.02	0.56 (0.32, 0.95)	0.03
Non-invasive	47	5.1	10.60	40	3.9	8.73	0.82 (0.53, 1.28)	0.43
Contralateral breast cancer								
Total	36	3.4	8.12	18	2.0	3.93	0.48 (0.26, 0.87)	0.01
Invasive	23	2.3	5.19	15	1.8	3.27	0.63 (0.31, 1.26)	0.22
Non-invasive	13	1.1	2.93	3	0.2	0.66	0.22 (0.04, 0.81)	0.02
Breast cancer at regional or distant sites	7	--	1.58	3	--	0.66	0.42 (0.07, 1.82)	0.32
Non-breast cancer								
Total	39	3.3	8.80	42	4.4	9.17	1.04 (0.66, 1.65)	0.94
Second primary cancer other than endometrial	26	--	5.86	25	--	5.46	0.93 (0.52, 1.68)	0.91
Endometrial cancer	2	--	0.45	7	--	1.53	3.39 (0.64, 33.42)	0.20
Deaths, NED	11	--	2.48	10	--	2.18	0.88 (0.33, 2.28)	0.94

[1] Rate per 1000 patients per year

[2] Rate in tamoxifen group divided by rate in placebo group

[3] Includes ipsilateral breast cancer, contralateral breast cancer, and local/regional/distant disease

[4] Includes ipsilateral and contralateral non-invasive tumors

The NSABP noted in the Lancet publication that after 5 years of follow-up, 83.3% of women treated with placebo were event-free (95% CI 80.8, 85.8) compared to 87.4% of women treated with tamoxifen (95% CI 85.1, 89.6). For all breast cancer events, 130 occurred in women treated with placebo compared to 84 in women treated with tamoxifen. The rate ratio for all breast cancer events of 0.63 (see Table 11 for 95% CI and p value) represents 37% fewer events for women treated with tamoxifen.

Reviewer Comment:

1. The majority of women did not have any breast cancer event. While the relative risk reductions reported for this study are similar to those found for tamoxifen for other indications, the absolute benefit from tamoxifen is small. In NSABP B-24, an

absolute difference of 4% was observed after 5 years of follow-up. While small, this difference is consistent with the absolute benefit from adjuvant therapy observed in adjuvant breast cancer clinical trials and in the Overview analysis.

2. Re-running the statistical datasets as submitted by the applicant results in rates that are similar but not identical to the numbers in the above table. For example, for "Breast cancer at regional or distant sites", the rate for tamoxifen is 0.65 rather than 0.66, and the rate ratio is 0.41 rather than 0.42. This difference is due to the fact that the Lancet publication reported on randomized patients with follow-up, and the sNDA submission included all randomized patients.

9.2 Invasive breast cancer (Lancet)

The number of ipsilateral and contralateral invasive breast cancers was the protocol-specified primary endpoint, although it was not reported as such in the Lancet publication. The authors state that women treated with tamoxifen had 43% fewer invasive breast cancer events compared to women treated with placebo.

Reviewer Comments:

1. Case report forms for ***all patients with invasive breast cancer*** (ipsilateral and contralateral) were reviewed. The review was designed to determine whether the reported lesion in fact consisted of an invasive cancer, whether the patient was eligible for the trial, and whether the lesion was pre-existing. While the Division agrees that an intent-to-treat analysis is the appropriate primary analysis, this approach allowed us to verify the primary data and to perform exploratory analyses to evaluate the robustness of the observed results. The results are summarized in the following points.

2. ***Ipsilateral invasive disease***

A. The applicant reported 63 patients with ipsilateral invasive disease, 40 on placebo and 23 on tamoxifen. When these patient numbers were re-analyzed by the statistical reviewer, the following results were obtained.

Table 12. FDA statistician's analysis of applicant's ipsilateral invasive events

Event	Placebo		Tamoxifen		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
Ipsilateral invasive breast cancer	40	9.02	23	5.02	0.56 (0.32, 0.95)	0.0312

These results replicate those of the applicant.

B. The reviewer found 4 additional cases of ipsilateral invasive disease from review of the CRFs:

Placebo

444400277 This patient was diagnosed simultaneously with a contralateral non-invasive and an ipsilateral invasive cancer. The applicant coded this patient as a non-invasive event, because the definitive procedure for the invasive lesion was performed after the bilateral biopsies. The reviewer believes this patient should be classified according to the most serious event, which is the ipsilateral invasive cancer.

441148104 This patient was diagnosed with DCIS with microinvasion. A second pathologist indicated that the reading was a difficult one. Microinvasion could be present, but since the patient was on a study, the NSABP should make the final reading. The protocol stated that the local pathology report should be used; the reviewer has therefore assigned this case as invasive disease.

Tamoxifen

443929926 This patient had DCIS with early stromal invasion. The applicant noted that the pathology report stated "suggestive" of stromal invasion. Because of the lack of certainty, the applicant classified the case as non-invasive. The reviewer noted that the DCIS was multifocal and extensive throughout the breast at mastectomy. The pathology report also stated "early stromal invasion is suspected." The reviewer classified the case as invasive based on the extensive nature of the findings, the suspicion of the pathologist (stronger statement that "suggestive"), and the fact that concern regarding invasion extended to several areas of the specimen rather than to a small unique focus.

440406112 This patient had DCIS with invasive disease and was classified as a non-invasive recurrence by the applicant because the event was first reported as non-invasive breast cancer. The applicant agrees that the event should be considered as an invasive breast cancer (correspondence dated 6/1/00).

C. The total number of FDA ipsilateral invasive cancer cases is 67, 42 on placebo and 25 on tamoxifen. When the statistical analysis was re-run using these corrected numbers, the following results were obtained.

Table 13. FDA statistical analysis: Additional invasive cases identified

Event	Placebo		Tamoxifen		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
Ipsilateral invasive breast cancer	42	9.47	25	5.46	0.58 (0.34, 0.97)	0.0361

The results are similar, with a 42% reduction in the incidence of ipsilateral invasive cases and a statistically significant result.

D. The applicant listed 10 patients with ***regional/local/distant recurrence*** in a separate category. These patients relapsed with invasive disease and should be included in the primary endpoint of all invasive cancers, instead of undergoing separate consideration. In reviewing the CRFs for these patients, it was noted that although many did not have an identifiable breast lesion, most relapsed in the axilla. The development of malignant axillary adenopathy permits assignment as either ipsilateral or contralateral recurrence. The reviewer found a total of 12 patients with regional/local/distant recurrence, and reassigned them to the appropriate category. Two patients died of metastatic disease without evidence of laterality. They will be included in the overall endpoint of all invasive events, but there is insufficient information to assign them to ipsilateral or contralateral categories.

The following describes patients reassigned from "local/regional/distant" to ipsilateral invasive disease. All of these patients were identified by the applicant as having distant metastases.

Placebo

440094946 This patient was diagnosed with simultaneous invasive disease in the ipsilateral breast and suspicious lesions in the liver that were never biopsied. The event occurred in 12/94; a note from 1/13/98 indicates that the patient is "alive and without disease." Although the liver lesions were never biopsied, the patient clearly had ipsilateral invasive breast disease and may have metastatic disease as well. The applicant indicates that no further documentation has been submitted to clarify this issue.

440695290 The patient was simultaneously diagnosed with ipsilateral invasive breast cancer and distant metastases. She subsequently died of metastatic breast cancer.

441598018 The patient was diagnosed with an ipsilateral axillary mass and had 21 of 25 lymph nodes positive for metastatic adenocarcinoma at surgery.

441651022 This patient had invasive disease in ipsilateral axillary nodes with spread into surrounding adipose tissue.

442354073 This patient was diagnosed simultaneously with an invasive ipsilateral breast cancer and a malignant pleural effusion (pathologically confirmed as metastatic).

444526022 This patient recurred in ipsilateral axillary nodes and subsequently died of metastatic breast cancer. Mammograms remained normal.

Tamoxifen

440761225 This patient recurred with a bulky ipsilateral axillary mass. Multiple nodes were involved with metastatic adenocarcinoma (number not given). Paratracheal and precarinal nodes were visible on CT. The tumor was ER(+).

443816104 This patient had a suspicious ipsilateral mammogram soon after study entry, with increasing residual calcifications. A note stated that later mammograms were normal. The patient then developed an enlarged ipsilateral axillary node on mammogram and was found to have metastatic adenocarcinoma in axillary nodes, consistent with breast primary. Vascular and perineural invasion was observed.

441621017 This patient was diagnosed with ipsilateral DCIS as the first event on study, then presented with ipsilateral axillary lymph nodes (biopsy consistent with metastatic breast cancer) and simultaneous bone metastases. This patient was not included as an invasive event by the applicant because the first event was a non-invasive breast cancer. Although the protocol states that only first events will be counted, this serious and life-threatening event should be included.

Adding these patients results in a total of 76 FDA cases, 48 on placebo and 28 on tamoxifen. The following table summarizes the statistical analysis of these cases.

Table 14. FDA statistical analysis: Additional invasive cases + distant/regional/local ipsilateral invasive disease

Event	Placebo		Tamoxifen		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
Ipsilateral invasive breast cancer	48	10.83	28	6.11	0.56 (0.34, 0.92)	0.0197

The results remain statistically and clinically significant with a 44% reduction in ipsilateral invasive events with tamoxifen therapy.

E. Two patients (443735225 randomized to placebo and 440067089 randomized to tamoxifen) had Paget's disease at biopsy, with ***no evidence of invasive disease***. These patients were excluded from the FDA analysis. The applicant agreed that there is no documentation that patient 440067089 had invasive breast cancer. Patient 443735225 had Paget's disease with DCIS in a lactiferous duct. The applicant agreed that these cases might be more appropriately considered noninvasive ipsilateral recurrences (4/3/00).

F. The total number of FDA-verified ipsilateral invasive breast cancer cases is 74, 47 on placebo and 27 on tamoxifen. This value is considered by the FDA reviewer to represent the total number of identified and verified ipsilateral invasive breast cancer cases reported to date on NSABP B-24. The statistical analysis follows.

Table 15. FDA statistical analysis of verified ipsilateral invasive breast cancers

Event	Placebo		Tamoxifen		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
Ipsilateral invasive breast cancer	47	10.61	27	5.90	0.56 (0.33, 0.91)	0.0182

Although ipsilateral invasive events did not comprise the primary endpoint of the trial, the incidence of these events is clinically relevant. An ipsilateral invasive event is potentially life-threatening, and the risk of such an event could be reduced by initial treatment with mastectomy instead of with breast conservation plus tamoxifen therapy. These results demonstrate, however, that tamoxifen was beneficial in reducing the risk of these events by 44%. The result was clinically meaningful, statistically significant, and consistent with results for tamoxifen in reducing the risk of breast cancer in women at high risk for breast cancer.

G. Six patients (440485026, 440490004, 440823905, 442416926, 444037086, and 444101112), all on placebo, in retrospect had invasive disease on the index lesion and were ineligible. This distribution favors the tamoxifen arm.

H. Six patients (5 on placebo, 1 on tamoxifen) were diagnosed with invasive cancer in less than 1 year from study entry, making it likely that they had pre-existing lesions. These patients were:

- 440490004 on placebo (already mentioned in G)
- 442325002 on placebo, diagnosed 4 months after study entry
- 442416926 on placebo: She had residual microcalcifications on mammogram after the initial diagnosis of DCIS. She was placed on study and had a re-excision of the microcalcifications 3 months later, with demonstration of invasive disease. These lesion appeared to be pre-existing. (already mentioned in G)
- 442689060 on placebo, diagnosed 11 months after randomization
- 443236928 on placebo, diagnosed 11 months after randomization
- 441770014 on tamoxifen, diagnosed 7 months after randomization

This distribution favors the tamoxifen arm.

I. ***An exploratory analysis*** was performed in which the patients described in G and H were excluded from analysis. The total number of cases was 64, 38 on placebo and 26 on tamoxifen.

Table 16. FDA statistical analysis, excluding patients with baseline invasive disease

Event	Placebo		Tamoxifen		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
Ipsilateral invasive breast cancer	38	8.61	26	5.68	0.66 (0.38, 1.12)	0.1277

These results should be viewed with caution, as they are exploratory only. Although the results are not statistically significant, the number of cases is consistently lower on the tamoxifen arm, and the rate ratio indicates a 34% reduction with tamoxifen therapy. In the reviewer's opinion, the results are robust and demonstrate that tamoxifen reduced the incidence of ipsilateral invasive events in the studied population.

J. It is important to note that a greater number of patients with microinvasion in the index lesion (determined retrospectively) or with diagnoses in less than one year from study entry were randomized to placebo. The reviewer does not believe that a consistent bias favoring the tamoxifen arm occurred during randomization. Instead, it is likely that similar numbers of these patients were entered on both arms of the study, but that tamoxifen was beneficial in treating microscopic or subclinical disease, consistent with a similar effect observed in other trials.

3. Contralateral invasive breast cancer

A. The ***applicant reported*** 38 cases of invasive contralateral breast cancer, 23 on placebo and 15 on tamoxifen. The FDA statistician verified the applicant's statistical analysis of these events.

B. The reviewer noted a total of 42 cases, 26 on placebo and 16 on tamoxifen. The ***additional cases*** are described below:

Placebo

440941333 This patient was diagnosed with a contralateral invasive cancer on 7/10/98. She was excluded from the applicant's list because she was diagnosed with renal cell cancer on 6/10/93.

443074212 This patient was reported as having a contralateral non-invasive breast cancer. The pathology report noted that 0.9 cm of invasive disease was present in the biopsy. The applicant agrees that this lesion might be better classified as invasive disease.

443223335 The patient had a breast biopsy reported as adenocarcinoma. It was not characterized as invasive or non-invasive. The applicant categorized it as "other second primary cancer." The reviewer believes it is appropriate to assign it as the most serious outcome, invasive disease, and include it in this category because the primary biopsy site was the breast.

Tamoxifen

440870085 This patient was not included in the database because her first event was a non-invasive ipsilateral breast cancer. She was subsequently diagnosed with a contralateral invasive cancer. Per protocol, only the first event was counted. While the reviewer accepts the protocol-specified procedure as the primary analysis, it is important to look at all events. An ipsilateral recurrence, whether invasive or non-invasive, may be related to the adequacy of the initial surgery. A contralateral event is related to the risk associated with a prior diagnosis of breast cancer, and the effects of tamoxifen should be separately evaluated.

The FDA statistician performed the following statistical analysis using these case numbers.

Table 17. FDA statistical analysis, contralateral invasive cases (additional cases)

Event	Placebo		Tamoxifen		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
Contralateral invasive breast cancer	26	5.86	16	3.49	0.60 (0.30, 1.15)	0.1341

C. Local/Regional/Distant recurrence

One patient randomized to tamoxifen (443528337) developed a contralateral enlarged axillary lymph node, mediastinal adenopathy, and ultimately bone metastases. The reviewer categorizes her as having contralateral invasive disease.

D. The addition of these cases brings the FDA numbers of contralateral invasive disease to 43, 26 on placebo and 17 on tamoxifen.

Table 18. FDA statistical analysis, contralateral invasive cases including local/regional/distant

Event	Placebo		Tamoxifen		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
Contralateral invasive breast cancer	26	5.86	17	3.71	0.63 (0.32, 1.21)	0.1838

E. In the course of the review, it was noted that one patient did not have breast cancer:

441765940 This patient, on placebo, had a basal cell carcinoma of the skin overlying the breast. She did not have a diagnosis of breast cancer.

F. The total number of FDA-verified cases of contralateral invasive breast cancer is 42, 25 on placebo and 17 on tamoxifen.

Table 19. FDA-verified contralateral invasive cases

Event	Placebo		Tamoxifen		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
Contralateral invasive breast cancer	**25**	**5.64**	**17**	**3.71**	**0.66 (0.33, 1.27)**	**0.2351**

The rate ratio of 0.66 demonstrates a 34% reduction in the incidence of contralateral invasive events. The lack of statistical significance is most likely due to the small number of events, rather than to a lack of efficacy of tamoxifen in this setting.

G. One patient, also randomized to placebo (443952415), had an abnormality in the contralateral breast at baseline that was not worked up. This abnormality increased in size and led to the diagnosis of contralateral invasive breast cancer. The reviewer judges this lesion to be pre-existing.

H. Two patients, one on placebo (440453946) and one on tamoxifen (444028065), were diagnosed with contralateral invasive disease 5 months and 6 months after randomization respectively. The reviewer judges these lesions to be pre-existing.

I. ***An exploratory analysis*** of contralateral invasive disease, excluding the patients in G and H, was performed. A total of 39 patients, 23 on placebo and 16 on tamoxifen, were included.

Table 20. FDA exploratory analysis, excluding patients with pre-existing lesions

Event	Placebo		Tamoxifen		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
Contralateral invasive breast cancer	23	5.19	16	3.49	0.67 (0.33, 1.33)	0.2870

This analysis should be viewed with caution and is exploratory only. A similar rate ratio is observed, confirming the robustness of the observed result.

4. Patients with ***invasive disease, not otherwise specified***

Two patients, both on placebo, had metastatic breast cancer without evidence of a primary site.

442874118 Died of metastatic breast cancer; no documentation of recurrence provided

443959232 Died of metastatic breast cancer with normal mammograms. Had a diagnosis of endometrial cancer as well. [This patient was not identified by the applicant as having metastatic breast cancer.]

5. ***The protocol-specified primary endpoint*** was the occurrence of all invasive cancer. One hundred eighteen verified invasive breast cancer events were observed, 74 on placebo and 44 on tamoxifen.

Table 21. FDA analysis of all FDA-verified invasive breast cancer events

Event	Placebo		Tamoxifen		Rate Ratio (95% CI)	Exact p
	No. Events	Rate	No. Events	Rate		
All invasive breast cancer	74	16.73	44	9.60	0.57 (0.39, 0.84)	0.0041

These data demonstrate that tamoxifen reduced the incidence of invasive cancer by 43%, a finding that is both statistically significant and clinically meaningful. The reduction in cancer incidence is consistent with that previously identified in breast cancer patients at risk for contralateral breast cancer and in women at high risk for breast cancer.

6. The applicant stated that information on the size and stage of the subsequent invasive tumor was not collected, although the case report forms contained specific pages for this information. The reviewer collated available information from the CRF review. In most cases, staging information was available. Frequently, nodal status was unavailable, as patients had undergone axillary dissection at the time of the treatment of the index lesion. In these cases, the diagnosis of a subsequent T1 lesion was presumed to represent Stage I disease. The following table summarizes ***staging information***.