CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-541/S-010

Medical Review(s)

CLINICAL REVIEW

ARIMIDEX® (anastrozole), ZD1033
Efficacy Supplement Clinical Review

NDA Number: 20,541
Rolling Submission
First Date of submission: December 21, 2001
Completed submission: March 4, 2001
Completion Date: August 28, 2002

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CLINICAL REVIEW

Table of Contents

Table of Tables

Table of Figures

Clinical Review for NDA 20541

Executive Summary

This multidisciplinary medical-statistical review addresses an efficacy supplement to NDA 20-541 for use of Arimidex® (anastrozole) for the adjuvant treatment of early breast cancer in postmenopausal women. The original NDA for Arimidex, was approved on October 16, 1995 for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. On September 1, 2000, the FDA approved a supplemental NDA for the first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer. The current supplement presents the results of a randomized, double blind trial comparing Arimidex alone with Novaldex alone with Arimidex and Novaldex in combination, as adjuvant treatment in postmenopausal women with breast cancer.

I. Recommendations

A. Recommendation on Approvability

The efficacy claims in support of this application are based on the results of a single large randomized well controlled trial (ATAC) entitled, "A randomized, double-blind trial comparing Arimidex ™ alone with Novaldex ™ alone with Arimidex and Novaldex in combination, as adjuvant treatment in postmenopausal women with breast cancer." The protocol-specified primary endpoint was time-to-recurrence of breast cancer; secondary endpoints were time to distant recurrence, survival and incidence in new breast primaries. At 33 months of follow-up, the Arimidex arm demonstrated prolongation of disease free survival and a trend toward prolongation of time to distant recurrence compared to the Tamoxifen arm. Follow-up was too short for an adequate comparison of survival. We recommend accelerated approval, rather than regular approval, of Arimidex under subpart H (CFR 314.500) for the adjuvant treatment of breast cancer in postmenopausal women because the median follow-up is only 33 months. Assessment of the ultimate safety and efficacy outcomes will require additional follow-up of the ATAC trial. We do not recommend approval of the sponsor's additional proposed indication,

Although there is a decrease in the contralateral breast cancers on the Arimidex arm, the data do not provide sufficient evidence to support this additional indication.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

We recommend the following commitments under subpart H, fulfillment of which may allow full approval in the future:

1. To submit a complete report of the updated ATAC data during 2004 to verify the safety and efficacy of Arimidex in the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer. The report will include an analysis of efficacy in the subgroup of patients who have received chemotherapy.
   Rationale:
   Arimidex preliminary significant improvement in disease-free survival at a median follow-up of 33 months should be confirmed since the known benefits of the tamoxifen arm require 5 years of treatment. Mature survival data also need to be evaluated since there is a known significant survival advantage with 5 years of tamoxifen therapy. At the current time, neither the efficacy nor the toxicity of a 5-year course of Arimidex for adjuvant treatment of breast cancer has been fully evaluated.

2. To conduct a double-blind, randomized, comparison trial using Arimidex with and without bisphosphonate therapy in early breast cancer patients. The design of this trial will be finalized in consultation with the Agency by November 1, 2002.

3. To submit a subprotocol and conduct a study to evaluate the development of hyperlipidemia and control of hyperlipidemia in patients on the ATAC trial.

4. Final study reports should be submitted to this NDA as a supplemental application. For administrative purposes, all submissions relating to this post marketing commitment must be clearly designated "Subpart H Post Marketing Commitments."

In addition, the following are postmarketing commitments that are not a condition of the accelerated approval. These commitments, along with any completion dates agreed upon, include:

1. In the NDA Annual Progress Reports provide information regarding the incidence of the pre-specified safety events and hypercholesterolemia for the treatment arms of the ATAC trial.

2. Continue to collect data in the ATAC trial on SAEs including fractures and those associated with hypercholesterolemia (i.e., cardiovascular and cerebrovascular adverse events) for an additional five years following discontinuation of treatment. Submit the safety report summarizing these data by January 1, 2011.

3. To submit a complete report of the updated ATAC data to verify the safety and efficacy of Arimidex in the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer when all patients on the ATAC trial have completed five years of treatment (approximately June 2007). The report will include an analysis of efficacy in the subgroup of patients who have received chemotherapy

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Arimidex is a non-steroidal aromatase inhibitor. It was approved for the second-line treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy in December 1995. Arimidex was approved for the first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer in September 2000. The ATAC trial, the subject of this review, was submitted as a rolling submission from December 21, 2001 to March 4,2002, to support the approval in the adjuvant treatment of postmenopausal women with breast cancer.

B. Efficacy

The ATAC trial was a Phase III, multicenter, multinational, randomized, double-blind study comparing the efficacy and safety of Novaldex alone, Arimidex alone and Arimidex in combination with Novaldex as adjuvant treatment for breast cancer in post-menopausal women. A total of 9366 patients were randomized from 381 centers worldwide.

The median follow-up of the study was 33 months. The treatment arms were well balanced with respect to previous treatment received for breast cancer. Only 21 % of the population had adjuvant chemotherapy, which appears to be low. The tumor characteristics were also balanced among treatment arms. Eighty-three percent of the patients in each arm were ER and or PgR positive. Time to disease recurrence was the primary endpoint; time to distant recurrence, survival and incidence of new contralateral breast cancers were secondary endpoints. At 33 months of follow-up, the Arimidex arm had a statistically significant improvement in time to disease recurrence compared to the tamoxifen arm (p=0.0144 compared to 0.024 level, adjusting for multiple hypotheses testing as specified by the sponsor; Hazard Ratio: 0.83; 2-sided 95.2% C.I.: 0.71-0.96). Arimidex appears to be associated with a reduction in distance recurrence when compared to Tamoxifen, however, the difference did not reach statistical significance (p=0.22; Hazard Ratio=0.88; 2-sided 95.2% C.I.: 0.71-1.08). There are fewer events for this important endpoint and further follow-up will be required to determine whether Arimidex is superior to Tamoxifen. There was a statistically significant decrease in the number of contralateral breast cancers in the Arimidex arm compared to the tamoxifen arm (p=0.0068). However, since this is the initial demonstration of this finding for this class of drugs, it does not justify a separate efficacy claim.

Treatment with the combination of anastrozole plus tamoxifen did not result in an efficacy advantage compared to tamoxifen alone. No difference was seen when comparing these 2 groups in terms of time to disease recurrence (p = 0.77; Hazard Ratio=1.02; 2-sided 95.2% C.I.: 0.89-1.18).

C. Safety

See Safety Review by Dr. Ann Farrell for details.
Women receiving Arimidex had an increase in musculoskeletal events and fractures (including fractures of spine, hip and wrist), and hypercholesterolemia compared with those receiving tamoxifen. Women receiving Arimidex had a decrease in hot flashes, vaginal bleeding, vaginal discharge, endometrial cancer, venous thromboembolic events (including deep venous thrombosis) and ischemic cerebrovascular events compared with those receiving tamoxifen. In the ATAC Bone substudy, women receiving Arimidex had a mean decrease in both lumbar spine and total hip bone mineral density (BMD) compared to baseline. Women receiving tamoxifen had a mean increase in both lumbar spine and total hip BMD compared to baseline.

D. Dosing

The recommended dose of Arimidex is 1 mg tablet taken daily. For adjuvant treatment of early breast cancer in post-menopausal women, the optimal duration of therapy is unknown. Clinical and pharmacokinetic results suggest that tamoxifen should not be administered with Arimidex. Estrogen-containing therapies should not be used with Arimidex.

E. Special Populations

The ATAC trial was conducted solely in females since it targeted breast cancer. This study was conducted exclusively in the postmenopausal population. On December 21, 2001 the sponsor applied for a waiver for pediatric study requirements. The Agency granted a waiver for pediatric studies for breast cancer.

Clinical Review

I Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Drug Name:
Established: Anastrozole (ZD1033)
Trade Name: Arimidex ™
Chemical Name: 1,3-Benzenediacetonitrile, a, a, a', a'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl).

Applicant
AstraZeneca UK Limited
Alderly Park, Macclesfield, UK
US Agent: AstraZeneca Pharmaceuticals LP
Wilmington, DE 19803

Pharmacologic Category
non-steroidal aromatase inhibitor

Sponsor's Proposed Indication
"ARIMIDEX is indicated for adjuvant treatment in postmenopausal women with early breast cancer.

Dosage Form and Route of Administration
"The recommended dose of Arimidex is 1 mg tablet once a day for five years or until recurrence of the disease. Optimal duration of therapy is unknown."

How Supplied:
Arimidex is supplied as white, biconvex, film-coated tablets containing 1 mg of anastrozole. The tablets are impressed on one side with a logo consisting of a letter "A" with an arrowhead attached to the foot of the extended right leg of the "A" and on the reverse with the tablet strength marking "Adx 1". These tablets are supplied in bottles of 30 tablets.

B. State of Armamentarium for Indication(s)

Novaldex (tamoxifen) is the standard adjuvant hormonal treatment for postmenopausal women with breast cancer following total or segmental mastectomy, axillary dissection and breast irradiation. Novaldex also reduces the occurrence of contralateral breast cancer in patients receiving adjuvant therapy. Data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which conducted worldwide overviews of systemic adjuvant therapy for early breast cancer in 1985, 1990, 1995 and 1998 in 36,689 women from 55 randomized trials of adjuvant Novaldex showed increased recurrence free rates and decreased mortality. Among women with ER positive or unknown breast cancer and positive nodes who received 5 years of Novaldex treatment, overall survival at 10 years was 61.4% versus 50.5% for the control. The recurrence free rate at 10 years was 59.7% for Novaldex versus 44.5% for the control. Among women with ER positive or unknown breast cancer and negative nodes who received 5 years of Novaldex treatment, overall survival at 10 years was 78.9% versus 73% for the control. The recurrence free rate at 10 years was 79.2% for Novaldex versus 64.3% for the control.

C. Important Milestones in Product Development

- Previous approvals: Arimidex was approved on December 1995, for the second line treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. On September 2000, Arimidex was approved for the first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.
- May 15 1996: The ATAC trial original version was written.
- On January 16, 1997, the ATAC trial entitled, "A randomized, double-blind trial comparing Arimidex alone with Novaldex alone with Arimidex and Novaldex in combination, as adjuvant treatment in post-menopausal women with breast cancer" was submitted to the IND.
- March 20, 1997: End of Phase II meeting to propose that the Phase III ATAC trial supports the adjuvant breast cancer indication. The Agency agreed that if the proposed 6000 patients single trial achieved its goal it could support approval for an adjuvant indication (without the requirement for additional studies). The Agency also agreed that the inclusion of ER-negative patients in the study would not necessarily lead to the inclusion of this patient population in the labeling and that this would depend on the study results. The Agency stated that unless there is a strong treatment effect in this subset, the number of ER-negative patients enrolled is likely to be insufficient to statistically establish the effectiveness of Arimidex in this subpopulation.
- October 9, 1997: The sponsor submitted three subprotocols to the IND trial, the endometrial, bone density and quality of life.
- March 19, 1998: The blood lipids and clotting factors subprotocol was submitted to the IND.
- May 10, 1999: The sponsor submitted a protocol amendment to adjust the targeted total number of enrolled patients for the clinical trial from 6000 to approximately 9500 patients. The sponsor based the amendment on the EBCTCG update published in Lancet, 1998 and found that recurrence rate for the protocol population was lower than originally predicted. The sample size amendment was acceptable to the Agency.

- September 27, 2000: Industry telephone conference to discuss several issues related to the ATAC trial and the future NDA submission. The Agency stated that the proposed statistical analysis for non-inferiority is not acceptable under current standards and that the sponsor should submit a detailed statistical analysis plan for the non-inferiority analysis. In the analysis plan, the Novaldex effect relative to placebo should be evaluated based on historical data (meta analysis), using the upper bound of the 95% CI for the tamoxifen: placebo hazard ratio, and the non-inferiority margin should preserve a clinically appropriate percentage of Novaldex effect. In addition, an adjustment for the type I error rate will be necessary if the Sponsor intent is to claim the treatment effect based on winning on one of the two comparisons.
- April 20,2001: The Sponsor submitted a proposed bioequivalence study to support the use of a newly formulated combination tablet of 1 mg Arimidex and 20 mg Novaldex for the adjuvant treatment of breast cancer. The Agency agreed with the study design.
- April 25, 2001: The Sponsor submitted a proposed food effect study protocol to support the use of the combination tablet. The Agency agreed with the study design.
- July and August 2001: The Statistical Analysis Plan to the ATAC trial was submitted for review. The final analysis is planned when approximately a total of 1056 (352-x3 arms) patients have had a breast cancer recurrence. Due to the interim analysis, the sponsor proposed an adjustment of the nominal significance level to 0.048 for the primary endpoint, time to disease recurrence. The Agency agreed with this adjustment. The proposed margin for the non-inferiority analysis was not acceptable. As presented by the sponsor, cut-off criteria of 1.25 ensure preservation of only 59% effect of Novaldex by Arimidex. Given that the study population under consideration is disease-free, this is unlikely to be acceptable. The sponsor pointed out that the estimate of the control effect from the EBCTG metanalysis includes pre and postmenopausal patients ER/PR status +, - or unknown who received a different duration of tamoxifen treatment. The Agency stated that the sponsor should do the best attempt to estimate the control effect by including studies with post-menopausal patients who had received 5 years of treatment. It was also stated that it is important to conduct a per protocol analysis with ER/PR + patients only, since ER – patients do not respond to tamoxifen.
- October 15, 2001: A pre-NDA meeting took place. Several issues were discussed including details of future NDA submission and the comments from the review of the SAP.
- November 5, 2001: The sponsor made the following changes to the SAP in response to the FDA comments:
  - The sponsor removed the time to death analysis from the major analysis since this endpoint was not formally analyzed at the time of the major analysis.
  - The sponsor agreed to make a comparison between Arimidex + Novaldex and Arimidex. However, the analysis will be exploratory and will not be used in making a claim.
  - The proportion of Novaldex effect preserved by Arimidex will be based on a comparison with the EBCTCG overview results from the postmenopausal women (rather than the overall estimate from the overview) to provide a better estimate of the control effect. The estimated rate of recurrence for postmenopausal patients receiving about 5 years of tamoxifen treatment was 52.5% of the control with the upper limit of the 95% CI being 57.8%. The proposed cut-off criterion of hazard ratio of 1.25 ensures preservation of 65.6% effect of Novaldex by

Arimidex. The Agency re-emphasized that the margin and preservation of active control effect are review issues.

- December 3 and 18, 2001: The sponsor send preliminary result of the ATAC trial that showed superiority of the Arimidex arm and requested a priority review of the coming NDA. The Agency ask the sponsor to formally request a Fast Track Designation to allow a rolling submission and stated that the User Fee Goal Clock will start once the final piece of the sNDA is submitted.
- December 21, 2001: The application was granted Fast Track Designation.
- March 4, 2002: The final piece of the rolling NDA was submitted and the User Fee Goal Clock was started.

D. Other Relevant Information

Arimidex has been approved in several countries, including the US, Canada and Europe, the second-line and later for the first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.

E. Important Issues with Pharmacologically Related Agents

Anastrozole is a potent and selective non-steroidal aromatase inhibitor. It significantly lowers serum estradiol concentrations and has no detectable effect on formation of adrenal corticosteroids or aldosterone. Safety profile is well described from two controlled studies in the first line and second line treatment of postmenopausal women with metastatic breast cancer. Main adverse events described in this setting are gastrointestinal, nausea and vomiting , and hot flashes. In these studies there was no increase in myocardial infarction or fracture when compared with tamoxifen.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Arimidex is a marketed drug; the clinical pharmacology and mechanisms of action have been previously reviewed and described in the label. See current pharmacokinetics reviews by John Zongyi Duan. The sponsor adequately characterized the pharmacokinetics of Arimidex in

healthy volunteers, in hepatically impaired patients, and in renally impaired patients in NDA 20-541. Since the current submission proposes to use the same formulation with same dose as in NDA 20-541, previous pharmacokinetic data of Arimidex will be taken into consideration for this submission.

The studies in the current submission showed that anastrozole had no effect on the pharmacokinetics of tamoxifen. Co-administration of anastrozole 1 mg with tamoxifen 20 mg resulted in an estimated 27% decrease in anastrozole levels. The clinical significance of the reduction of the levels of anastrozole could not be concluded through the current studies.

B. Pharmacodynamics

Arimidex is a marketed drug; the clinical pharmacology has been previously reviewed by John Zongyi Duan Ph. D. and described in the label.

IV. Description of Clinical Data and Sources

A. Overall Data

The rolling sNDA consisted entirely of an electronic submission. The NDA submission consisted of the primary clinical data from one principal study.

Trial number: 1033IL/0029:
"A Randomized, Double-blind Trial Comparing arimidex alone with Novaldex alone with arimidex and Novaldex in Combination, as Adjuvant Treatment in Postmenopausal Women with Breast Cancer"

NDA report item

Detailed index to the application
Labeling
Application Summary:
Human Pharmacokinetic and Bioavailability
Clinical and Statistical
Case Report Tabulations and Datasets
Patient Case Report Forms

B. Tables Listing the Clinical Trials

The only trial submitted with this NDA is Phase III trial (Trial 1033IL/0029):

- Arimidex Arm
- Tamoxifen Arm
- Combination Arimidex and Tamoxifen Arm

C. Postmarketing Experience

No post marketing experience data was sent with the supplement.

V. Clinical Review Methods

A. How the Review was Conducted

There was only one trial, Protocol 1033IL/0029 submitted with this sNDA. The medical review of sNDA 20541 included:

- Regulatory history of the application.
- Initial submission of Protocol 1033IL/0029 to IND.
- Protocol 1033IL/0029 amendments.
- Annual report for IND.
- The following from the NDA electronic submission:
  Index
  Labeling
  Application Summary
  Pharmacokinetics Summary
  Clinical and Statistical
- Case report forms (electronic) from Protocol 1033IL/0029.
- Patients listings (electronic) which were subject of queries in JUMP and MS Access.
- Safety update.
- Statistical review included analyses on the SAS datasets.

B. Overview of Materials Consulted in Review

The review of sNDA 20541 included regulatory history of the application, labeling, and correspondence from end of phase 2 meetings and Pre-NDA meetings.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

There are two reasons why DSI audit was not conducted:
1. This application is a supplement.
2. Disease free survival is the primary endpoint of interest.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The study was conducted under US IND [redacted] in full compliance with the principles of the Declaration of Helsinki, including all current amendments, or with the laws and regulations of the country in which the study was conducted. Prior to initiation of the study, the protocol, and the patient informed consent were reviewed and approved by the ethics committees or institutional review boards of the centers involved in the study. Subsequent protocol amendments were also submitted, reviewed and approved before implementation.

E. Evaluation of Financial Disclosure

Requirements for Financial Disclosure were discussed with the applicant during the pre-NDA meeting on 12/18/01. The study was completed after 2/2/99 and therefore was subject to the financial disclosure requirements.

Disclosures
Form 3454 was submitted with the application.
- Compensation affected by the outcome of the clinical studies
  None stated or apparent
- Proprietary interest in the tested product (patent, trademark, copyright, licensing agreement)
  None stated or apparent

Reviewer's assessment
- Analysis and publication of the results and submission of an application are based on the completion date. Although follow-up continues, patient accrual is complete.
- The submitted information seems to be adequate and the reviewer believes it to be in compliance with financial disclosure requirements.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The ATAC trial was a multicenter, double blind, randomized, phase III comparative three-arm trial of arimidex versus tamoxifen versus arimidex + tamoxifen as an adjuvant therapy in 9366 postmenopausal patients with breast cancer. Treatment was to be administered daily for 5 years or until disease recurrence, or discontinuation of trial therapy. The trial allowed prior therapy such as surgery, chemotherapy and or radiotherapy at the discretion of the investigator. A total of 381 centers from 21 countries worldwide participated in this study. The trial allowed the inclusion of ER-negative patients, however, over 83% of the patient population had positive hormone receptors. The trial lacked prospective stratification for important prognostic factors. The study treatment arms were well balanced. Only 21% of the population had adjuvant chemotherapy. Time to disease recurrence was the primary efficacy endpoint; time to distant recurrence, time to death, incidence of new breast primaries (contralateral breast cancer) and adverse events were the secondary endpoints. Recurrence was defined as the earliest of loco-regional or distant recurrence, new primary (contralateral) breast cancer, or deaths (as first event related or unrelated to breast cancer). DCIS was also considered as an event.

The median follow-up at the time of data cut-off date was 33 months; less than 3 % of patients had received 4 to 5 years of treatment and approximately 25% of patients had withdrawn from the study before completing 5 years of treatment. Five years of treatment with tamoxifen has been shown to be the optimal duration of therapy (The Lancet, 351: 1451-1467, 1998). Therefore, the current analysis of the ATAC trial is probably comparing to a suboptimal active control.

The sponsor claims that arimidex provides significant clinical benefit over tamoxifen with a 17% reduction in the risk of disease recurrence. The reviewer agrees that at 33 months of follow-up, the Arimidex arm demonstrated prolongation of disease free survival and a trend toward prolongation of time to distant recurrence compared to the Tamoxifen arm. However, assessment of the ultimate efficacy outcomes will require additional follow-up of the ATAC trial. Follow-up was too short for an adequate comparison of survival. The sponsor's additional proposed indication, ——— will not be granted. Although there is a decrease in the contralateral breast cancers on the Arimidex arm, the data does not provide sufficient evidence to support this additional indication.

B. General Approach to Review of the Efficacy of the Drug

The review of the Arimidex supplement consisted of a single randomized well-controlled trial, Protocol 10331L/0029. Detailed efficacy review is described in the next section.

C. Detailed Review of Protocol 10331L/0029

"A randomized, double-blind trial comparing Arimidex ™ alone with Novaldex ™ alone with Arimidex and Novaldex in combination, as adjuvant treatment in postmenopausal women with breast cancer."

Principal Investigators

Professor M Baum, University College London Medical School, The Middlesex Hospital, Mortimer Street, London, W1N 8AA, United Kingdom (Centre 0001).

Protocol Milestones:

Milestone	Dates	# Patients Entered
Protocol Version 1 Submission	May 15, 1996	0
Protocol Version 2 Submission	December 2, 1996	22
Protocol Version 3 Submission	September 1, 1997	1242
Protocol Version 4 Submission	June 1, 1998	4952
Protocol Version 5 Submission	January 12, 1999	8350
Protocol Version 6 Submission	April 28, 2000	9366
First Patient recruited	July 12, 1996	1
Last Patient recruited	March 24, 2000	
Data Cutoff	June 29, 2001	
Start NDA Rolling Submission	December 21, 2001	
End NDA Rolling Submission	March 4, 2002	

Objectives:

Primary: "The primary objectives of this trial are to compare the equivalence of Novaldex (20 mg) and Arimidex (1mg) and to compare the differences between Novaldex (20 mg) and the combination of Arimidex (1 mg) plus Novaldex (20 mg) as adjuvant treatment in terms of:

a) Time to recurrence of breast cancer;
b) Safety and side effects."

Secondary:
"The secondary objectives of this trial are to compare the equivalence of Novaldex and Arimidex and to compare the difference between Novaldex and the combination of Arimidex plus Novaldex as adjuvant treatment in terms of:

a) time to distant recurrence;
b) survival;
c) incidence in new breast primaries."

In addition, some patients from the main trial were to be included in separate sub-protocols that were to address the following objectives:

a) pharmacodynamic and pharmacokinetic interactions
b) modulation of lipoprotein profiles
c) endometrial status
d) bone mineral metabolism
e) quality of life

The review of the subprotocols will be separate from the main trial.

Overall Study Design:

The protocol design was a Phase III, multicenter, multinational, randomized, double-blind study comparing the efficacy and safety of Novaldex alone, Arimidex alone and Arimidex in combination with Novaldex as adjuvant treatment for breast cancer in post-menopausal women. The study is a collaborative trial designed in conjunction with the Cancer Research Campaign, London and conducted in association with investigators from 21 countries. The following breast cancer organizations were involved in the conduction of this study: Australian and New Zealand Breast Cancer Trials Group, Conzorzio Mario Negri Sud, Cancer Research Campaign, North-West Breast Group, North Yorkshire Clinical Trials' Research Unit and Scottish Cancer Therapy Network. Target accrual was approximately 6000 patients from 150 participating sites worldwide. Patients were to be randomized on a 1:1:1 basis into one of three treatment arms:

a) Active Arimidex + Novaldex placebo
b) Active Novaldex + Arimidex placebo
c) Active Arimidex + active Novaldex

Patients were to complete surgery, chemotherapy and radiotherapy according to local practice. Randomization was to take place at regional randomization centers and determined by a randomization scheme prepared by Zeneca Biometrics Group. Patients were to be assessed for tumor recurrence at entry, 3 months, and 6 months; thereafter at 6-month intervals up to 5 years, and annually up to 10 years. Trial treatment was initially intended to be for a minimum of 2 years; in December 1996, the protocol was amended on the basis of interim data from 2 published trials indicating that 5 years of adjuvant tamoxifen therapy was more beneficial than treatment for a 2–year period. If patients were to have disease recurrence, the investigator was to contact the randomization center to be informed of the randomized treatment so decisions could be made for future treatment.

Reviewers Comments:
This Phase III trial is a randomized, large, multicenter study whose intent is to be used as a registration trial to support the adjuvant indication. The following are some concerns with the ATAC protocol design:

a) The protocol allows the inclusion of ER negative patients. This could be problematic because this patient population does not respond to hormonal therapy and therefore the treatment effect could be diluted (EBCTG overview).
b) The duration of the trial was amended after the EBCTG overview was published stating the superiority of 5 year treatment over 2 year treatment.
c) There is a potential imbalance of Stage I, II and III patients.
d) There is a lack of prospective stratification for important prognostic factors.
e) The use of prior adjuvant chemotherapy and radiotherapy at the discretion of the investigator is problematic. This lack of control over the prior therapy may result in treatment arm imbalances if patients receive suboptimal therapies. Since there is no control over the therapies given, the trial should be stratified to account for the survival benefit of the chemotherapy and local control of the radiation therapy.

Protocol Amendments:

The protocol was amended six times.
First amendment submitted June 2, 1996, included the following:

- A modification of the treatment duration from 2 years to 5 years as the EBCTG overview supported 5 years treatment duration.
- The definition of serious adverse events was revised to conform with ICH guidelines.
- Clarification of the serious adverse events occurring after stopping trial treatment but before recurrence, was to be reported.

Reviewer's comments:
At the time of the protocol amendment there were no patients accrued. The Agency agreed with the amendments.

Second amendment submitted on April 15, 1997 included the following clarification of the exclusion criteria:

- Any prior treatment with Tamoxifen must have been pre-surgery.
- Patients with previous history of invasive breast cancer were to be excluded.

Third amendment submitted September 1, 1997, included the following:

- Changes to inclusion criteria: definition of postmenopausal status.
- Log-rank test was introduced to check the robustness of the conclusions from both the interim and the main analysis. Cox model for pre-specified set of covariates were defined.

Reviewer's comments:
At the time of the protocol amendment there were 1242 patients accrued. Concerns about baseline imbalances of prognostic factors were raised by the Agency since the study is not stratified. Zeneca amended the protocol to account for any imbalances retrospectively, using covariates, since the study was not prospectively stratified.

Fourth amendment submitted June 1, 1998, included the following:

- Patient recruitment increased to 7500 and number of participating centers increased to approximately 300.

Reviewer's comments:
At the time of the protocol amendment there were 4952 patients accrued.

Fifth amendment submitted January 12, 1999, included the following:

- Patient recruitment increased to 9500. The sponsor adjusted the number of patients based on the EBCTG meta-analysis update that showed a lower recurrence rate than originally predicted. Based on the revised event rates and the recruitment observed in the trial, patient recruitment was increased in order that 352 events per arm will occurred after 5 years of follow-up.

Reviewer's comments:
At the time of the protocol amendment there were 8350 patients accrued. The Agency accepted the sample size amendment.

Sixth amendment submitted April 28, 2000, included the following:

- Subprotocol to evaluate lipoprotein profiles was no longer required.
- A statistical test was introduced to detect superiority of Arimidex over Novaldex in terms of efficacy.
- The primary endpoint, time to recurrence of breast cancer, was defined as: "the earliest of local or distant recurrence, new primary breast cancer, or death."
- New primary breast cancers were regarded as disease recurrence events to ensure consistency with previous adjuvant trials.
- A subgroup analysis was introduced for hormone receptor status using the log-rank test and Cox proportional hazards model.
- Modification of the interim analysis plan and statistical methods. For the primary endpoint the protocol states: "Evidence of equivalence being defined as the ruling out of the hazard ratio (Arimidex/Novaldex being greater than 1.25. Thus equivalence will be concluded if the upper limit of the 2-sided 90% confidence interval for the hazard ratio does not exceed 1.25. This is effectively performing a 5% significance 1-tailed test at the upper bound".

Reviewer's comments:
At the time of the protocol amendment there were 9366 patients accrued.

- The definition of time to recurrence of breast cancer is not adequate because it is a composite endpoint that includes in-breast recurrence after breast-conserving surgery and any type of

second breast cancer. Although these endpoints are important, these events are separate from the distant recurrence of an already-diagnosed breast cancer and therefore have a different prognosis. Distant recurrence should be reported separately as the primary endpoint.

- The Agency did not accept the statistical analysis for non-inferiority. A detailed statistical analysis plan was requested. In the analysis plan, the Novaldex effect relative to the placebo was to be evaluated based on the historical data from the EBCTG meta-analysis, using the upper bound of a two-sided 95% confidence interval for the hazard ratio of Novaldex to placebo. The non-inferiority margin should preserve a clinically significant percentage of the Novaldex effect.
- The primary statistical method for the analysis of the primary endpoint should be the logrank test and the Cox regression model adjusting for baseline covariates should be considered supportive and exploratory.

Eligibility Criteria

Inclusion Criteria:

- Patients with histologically proven operable invasive breast cancer.
- Patients who have completed all primary surgery and chemotherapy (if given) and are candidates to receive hormonal adjuvant therapy.
- Women defined as postmenopausal according to one or more of the following:
  - over the age of 60
  - age 45-59 years and satisfying one or more of the following criteria:

    amenorrhea for at least 12 months and intact uterus

    amenorrhea for less than 12 months and FSH within the post-menopausal range including patients who had a hysterectomy

    Patients who have received HRT

    Patients rendered amenorrheic by adjuvant chemotherapy must have FSH measured at least 6 weeks after stopping chemotherapy

    Bilateral oophorectomy

Exclusion Criteria:

- Patient in whom there is any clinical evidence of metastatic disease.
- Patients whose chemotherapy was started more than 8 weeks after completion of primary surgery or whose chemotherapy was completed more than 8 weeks before starting randomized treatment. Patients who received neo-adjuvant chemotherapy were ineligible.
- Patients who have not received chemotherapy and whose primary surgery was completed more than 8 weeks before randomized treatment.
- Patients who have received previous hormonal therapy as adjuvant treatment for breast cancer unless:

- tamoxifen started prior to first surgical procedure and received for less than 29 days or
- hormonal therapy was received in the context of a formal trial approved by the Steering Committee.

- Patients who have received tamoxifen as part of any breast cancer prevention trials.
- Patients unwilling to stop taking any drug known to affect sex hormonal status including HRT, or in whom it would be inappropriate to stop.
- Patients with previous history of invasive breast cancer at any time or other invasive malignancy within the last 10 years, other than squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix, adequately cone biopsied.
- Patients with any severe concomitant disease or strong family history of osteoporosis, severe renal or hepatic impairment.
- Patients treated with experimental drug during the 3 months before randomization.

Reviewer's comments:
The following are concerns with the inclusion criteria:
- Uncontrolled therapy prior to randomization
- The protocol does not mention eligibility of patients with prior use of other aromatase inhibitors
- The protocol does not mention eligibility of patients with prior or concomitant use of biphosphonates

Study therapy

Formulation
This double blind trial was to use both active and placebo Arimidex and Novaldex tablets, in order to maintain blindness of the trial. Arimidex 1 mg and matching Arimidex placebo were to be supplied as white, film-coated tablets. Novaldex 20 mg active tablets and matching Novaldex placebo were to be supplied as white, round, biconvex tablets.

Dosage schedule
Patients were to be randomized to receive one of the three following oral regimens:

- Arimidex arm:
  - Arimidex was to be administered orally 1 mg daily.
  - Novaldex was to be administered as placebo.
- Novaldex arm:
  - Novaldex was to be administered orally 20 mg daily.
  - Arimidex was to be administered as placebo.
- Arimidex and Novaldex combination arm:
  - Novaldex was to be administered orally 20 mg daily.

- Arimidex was to be administered orally 1 mg daily.

Therapy was to be started after randomization, no more than 8 weeks after completion of surgery and chemotherapy. Patients could start trial therapy while receiving radiotherapy. The duration of the trial therapy was to be 5 years. Therapy was to be stopped before 5 years if the patient had confirmed disease recurrence, refuses to continue, the investigator recommends early stopping or on recommendation of the Steering Committee.

Patient Evaluations

Patient monitoring is summarized in the following table.

Table 1 Schedule of assessments

Year	0			1		2		3		4		5	5-10
Month	**0**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**72-120**
History [1]	X												
Physical Examination	X												
Co-medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology [2]	X												
Biochemical Profile [3]	X												
Toxicity Assessment [4]		X	X	X	X	X	X	X	X	X	X	X	X
Medication compliance [5]		X	X	X	X	X	X	X	X	X	X	X	
Recurrence of Disease [6]													

[1] Includes full medical and breast cancer history. Breast history includes: surgical procedure, date of surgery, size and grade of primary tumor, nodal status, ER and PR status, details of radiotherapy, chemotherapy and pre-surgical tamoxifen if received. Retrospective histological assessment using paraffin blocks of ER status may be carried out.

[2] Includes hemoglobin, platelet count and leukocytes. Laboratory is to be done at baseline and further testing only if indicated.

[3] Includes creatinine, total bilirubin, alkaline phosphatase, transaminases, sodium, potassium and urea.

[4] Adverse events will be assessed at each follow-up.

[5] In order to assess compliance, patients will be asked to return all unused tablets at each visit.

[6] Patients will be reviewed for recurrence of breast cancer at all follow-up visits. See section on criteria for efficacy assessment for details.

Reviewer's Comments:

- The protocol does not clarify how often the patients will have a physical examination.
- The protocol does not specify how the adverse event data will be collected such as side effects questionnaire etc...
- The protocol does not specify the frequency of follow-up radiologic assessments and mammography.
- The protocol is not clear about the methods that will be used for surveillance and the frequency of the diagnostic tests that will eventually be used.
- The protocol does not specify the frequency of the survival census.

Criteria for Efficacy Assessment

Per protocol the following defines the rules for efficacy evaluation:
Disease Recurrence
The protocol states: "Disease recurrence is the earliest of local or distant recurrence, new primary breast cancer (contralateral or ipsilateral) or death".

The following method of confirmation will be used:
Histology or cytology for *Locoregional recurrence:*

- Ipsilateral breast including DCIS
- Chest wall
- Axillary lymph nodes
- Other regional lymph nodes

Distant recurrence:

- Skeletal: CT or bone scan with X-rays for hot spots. Biopsy may be necessary in the case of a single lesion.
- Pulmonary: Chest X-ray
- Hepatic: CT scan or ultrasound
- Other distant: Imaging or biopsy.

New breast primaries will be regarded as disease recurrence events.

Reviewer's Comments:

- The protocol did not have a definition of disease recurrence until April 2000 when it was submitted as a protocol amendment. FDA reviewer does not agree with the protocol definitions of the efficacy parameters. Disease recurrence should be defined as the appearance of loco-regional recurrence (in a patient with mastectomy) or distant metastases at any site. Ipsilateral recurrence in a patient treated by lumpectomy or contralateral new breast cancers should not be considered as relapses. These events are separate from the distant recurrence of an already-diagnosed breast cancer and therefore have a different prognosis.
- New breast primaries should be reported separately from the primary endpoint. The protocol should report data separately on ipsilateral and contralateral, invasive and non-invasive

second breast cancers. Non-invasive breast cancer should be reported separately as DCIS and LCIS.

Criteria for Safety Assessment

Safety was to be evaluated as adverse event defined in the protocol as "the development of a new medical condition or the deterioration of a pre-existing condition following or during exposure to a medicine." Adverse events are to be reported at the beginning of the randomized treatment, up to 14 days after the randomized treatment is stopped. Off trial adverse events are to be reported providing they occur more than 14 days after stopping the randomized treatment, within 10 years of starting randomized treatment and before recurrence. All adverse events are to be followed until resolution.

Reviewer's Comments:

- The protocol does not specify if adverse events are to be graded according to the NCIC Common Toxicity Criteria grading system.

Serious Adverse Event

Defined in the protocol as any experience that was fatal, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization resulting in persistent or significant disability/incapacity.

Endpoints/Statistical Considerations

Endpoints:

Primary Endpoint:

The primary endpoint for this study was time to disease recurrence. Time to disease recurrence was defined as: "the time between randomization and the earliest occurrence of loco-regional recurrence [including ipsilateral new breast cancer], distant recurrence, contralateral new breast cancer or death."

The date of loco-regional recurrence, distant recurrence or new breast cancer is defined as: "the date of confirmation of the specific recurrence, which is the date of the procedure or physical examination finding which indicated recurrence".

Patients who have not had a disease recurrence will be right-censored at the date of their last assessment.

Secondary Endpoints:

- Time to distant recurrence
- Time to death
- Incidence of new breast primaries (contralateral breast cancer)
- Adverse Events

Time to distant recurrence
This is defined as the time between randomization and the earliest occurrence of distant recurrence or death. The date of distant recurrence is defined as the date of confirmation of distant recurrence. In cases where it was medically unclear whether the patient had a new (non-breast) primary cancer or a distant recurrence, a distant recurrence was recorded if the patient stopped trial therapy at or before the time of this event. Patients who have not had the event will be censored at the date of their last assessment (for patients with follow-up visits, using the last date of assessment for the recurrence follow-up and for patients who only have a baseline visit using the date of randomization.)

Time to death
This is defined as the time between randomization and death. Patients who have not died will be censored at the last date when they were known to be alive.

Incidence of new breast primaries (contralateral breast cancer)
This is defined as the proportion of patients experiencing a **contralateral** new breast primary during the trial prior to recurrence. Any new breast primaries which occur after a loco-regional or distant recurrence will not be included in this endpoint.

Adverse Events
The incidence of the following pre-defined adverse events will be subject to formal statistical analysis:-.

- hot flushes (COSTART term: Vasodilatation),
- nausea and vomiting (COSTART terms: Nausea, Vomiting),
- asthenia (COSTART term: Asthenia),
- mood disturbances (COSTART terms: Agitation, Anxiety, Apathy, Depersonalization, Depression, Emotional lability, Hysteria and Nervousness),
- musculo-skeletal disorders (COSTART terms: Arthralgia, Arthritis, Arthrosis, Joint Disorder),
- vaginal bleeding vaginal
- fractures of the spine, hip, wrist/colles including all events with COSTART term of pathological or Osteoporosis fracture.
- ischemic cerebrovascular events
- venous thromboembolic including deep venous thromboembolic events

Subprotocols

- pharmacodynamic and pharmacokinetic interactions
- modulation of lipoprotein profiles
- endometrial status
- bone mineral metabolism
- quality of life

Details of these subprotocols will be provided in the appendix, separate from the main trial review.

Statistical Considerations:

Sample Size:
The protocol was to target a sample size of 6000 patients. Power calculations were based on the primary analysis for time to disease recurrence. The sample size was determined by estimating the event rate (per year per 100 patients) of disease recurrence for patients diagnosed as having stage I or stage II disease on Novaldex based on the Breast Cancer Overview (1992) performed by Peto et al. Based on this event rate, after three years of recruitment at a uniform rate of 2000 patients per year and a minimum of 2 years follow-up, the following events were expected:

Disease Stage	Event rate per 100 patients
Stage I	11.8
Stage II	32.3

Based on these event rates, will lead to 442 expected events per arm after 5 years.

The protocol was amended on January 1999 and the sponsor adjusted the sample size to 9500 patients because the protocol recruitment did not hold over the first 12 months of the trial. In addition, an update of the EBCTCG overview showed a lower recurrence rate for the protocol population than originally predicted. Based on the revised event rates and the recruitment observed in the trial to date, the sponsor stated that approximately 9500 patients were to be recruited in order that 352 events per arm will have occurred 5 years after the start of recruitment.

Analysis Populations:
The primary statistical analysis for each of the efficacy endpoints was to include all randomized patients (intent to treat population).
A secondary per protocol analysis was to be performed, for each of the efficacy endpoints and was to exclude patients with major protocol violations and deviations. Patients with the following protocol violations were to be excluded from the per protocol analyses:

- no histologically proven operable invasive breast cancer
- not candidates to receive hormonal adjuvant therapy
- not post-menopausal according to protocol criteria
- clinical evidence of metastatic disease
- receiving any drug known to affect sex hormone status at time of randomization.
- previous history of invasive breast cancer at any time or other invasive malignancy within the last 10 years.
- received treatment with a non-approved or experimental drug during the 3 months before randomization

Patients with the following deviations were to be excluded from the per protocol analyses:

- prior to confirmation of disease recurrence, continuous interruption of trial treatment for > 3 months

- prior to confirmation of disease recurrence and while receiving trial therapy, starting of drugs which affect sex hormone status or prevent recurrence of disease e.g.: cytotoxic chemotherapy, oral (systemic) administration of ketoconazole (antifungal) or related compounds, other hormonal treatments for breast cancer

The following concomitant medications were to be considered as major deviations:

- Anabolic steroids, androstan derivatives
- SERMS (selective estrogen receptor modulators).
- chemotherapeutic agents except when used for non cancer indications, e.g., psoriasis or other skin lesions
- endocrine therapy, anti-estrogens except the use of tamoxifen for a limited time of less than 2 months

The protocol states that the intent to treat analysis will be the main emphasis for a conclusion of superiority and for a conclusion of non-inferiority, the intent to treat and per protocol analyses will both be considered in the interpretation.
A secondary subgroup analysis was to be undertaken using the intent to treat and per-protocol populations for the following 3 subgroups: estrogen receptor positive and/or progesterone receptor positive patients, estrogen receptor negative and progesterone receptor negative patients and all other patients.

Interim analysis
One interim analysis was to be conducted when approximately half the expected number of events (352/2=176) occur in any arm. The only variable to be formally analyzed is time to disease recurrence. The analysis was to be done in all randomized patients without adjusting for prognostic factors. The O'Brien-Fleming procedure was to be used to adjust for the interim analysis with a nominal significance level set to 0.005 to ensure Type I error of 5%. Estimates of the treatment effects were to be presented as hazard ratios and the associated 95.5% confidence intervals and p-values.

The final or 'major' analysis was planned when a total of approximately 1056 (352 x 3) patients have had breast cancer recurrences across all 3 arms.

Analysis Methods
The primary analysis for the primary endpoint is going to be the log-rank test in the ITT population.

Nominal Significance Level:
For the analysis of time to disease recurrence the nominal significance level will be 0.048 and the confidence interval for the assessment of non-inferiority will be the two-sided 95.2% confidence interval. The significance has been adjusted due to the interim analysis of this endpoint in order to maintain the overall significance at 5%.

The secondary endpoints will be analyzed with a nominal significance level of 5% and the confidence interval for the assessment of non-inferiority will be the two-sided 95% confidence interval.

Testing H_{0e} and H_{0d}:
The protocol states that if the upper two-sided 95.2% confidence limit (95% confidence interval adjusted for the interim analysis) for the hazard ratio is less than 1.00 the conclusion will be that Arimidex is *superior* to Nolvadex. If the upper two-sided 95.2% confidence limit for the hazard ratio is greater than or equal to 1.0 but less than or equal to the pre-defined criteria for non-inferiority of 1.25, the conclusion will be *non-inferiority* of Arimidex compared to Nolvadex. If the lower two-sided 95.2% confidence limit is greater than one and the upper two-sided 95.2% confidence limit is greater than 1.25 the conclusion will be that Arimidex is inferior to Nolvadex. Otherwise, the result of the Arimidex versus Nolvadex comparison will be considered to be inconclusive.

Protocol pre-defined criteria of 1.25 for non-inferiority:
To estimate the Nolvadex effect, the sponsor used data from the EBCTCG overview (Lancet 1998). In this overview, the estimated rate of recurrence for patients receiving about 5 years treatment with tamoxifen was 57% of that of the control with upper limit of the 95% confidence interval indicating that the rate of recurrence for tamoxifen was no worse than 62% of that of the control. Assuming the effect of tamoxifen in the EBCTCG overview would be similar to the effect of Nolvadex in the ATAC study population, it is possible to calculate a crude estimate of the hazard ration (HR1) for women receiving Arimidex compared to the control group of women for the overview who received no tamoxifen. This estimated hazard ratio could in turn be used to estimate the proportion of the effect of Nolvadex, which is preserved by Arimidex (EP1). By this calculation, if the upper limit for the hazard ratio of Arimidex/Nolvadex is 1.25 (the predefined criteria for non-inferiority), then the estimated hazard ratio for Arimidex/control would be no higher than 0.775 and the estimated proportion of the effect of Nolvadex which is preserved by Arimidex would be 59%.

Reviewer's Comments:

- The study was powered to detect non-inferiority of Arimidex to Novaldex.
- The sample size amendment was appropriate.
- The Agency has previously sent comments to the sponsor regarding the pre-defined criteria for non-inferiority, which are not acceptable. Non-inferiority was defined as the upper limit of the 2-sided 90% confidence interval for the hazard ratio does not exceed 1.25. The Agency asked the sponsor to submit a detailed statistical analysis plan of the non-inferiority analysis. In the analysis plan, the Novaldex effect relative to the placebo should be evaluated based on historical data from the EBCTCG meta-analysis, using the upper bound of a two-sided 95% confidence interval for the hazard ratio of Novaldex to placebo. The non-inferiority margin should preserve a clinically significant percentage of the Novaldex effect.

- The Agency did not agree with the statistical analysis plan for non-inferiority. A cut-off criteria of 1.25 preserves only 59% of the effect of Novaldex by Arimidex. Since the study population is a disease free population, the acceptable non-inferiority margin is around 75%.
- The estimate of the control effect from the EBCTCG overview includes patients pre- and post-menopausal, all ER/PR status (+, -, or unknown), and differing duration of tamoxifen treatment. . Therefore, it is possible that the ATAC population may be different from the 'Overview' population in all or some of these characteristics.
- A per protocol analysis for non-inferiority comparison in ER/PR + patients only is important since this is the population of interest.

Criteria For Exclusion of Patients from Analyses

The following criteria for discontinuation of study were to be used:

- Voluntary discontinuation
- Serious adverse effect: the investigator was to decide if the patient was to be withdrawn from the study.
- Non-compliance with the protocol.
- Breast cancer recurrence

D. Study Results

Patient Demographics/Disposition

Patient Demographics

The following results are from the sponsor's analyses and tables:

Enrollment:

Nine thousand three hundred sixty six patients from 381 centers worldwide were enrolled in the study, 3125 on anastrozole, 3116 on tamoxifen and 3125 on the combination of anastrozole and tamoxifen. As of the data cut-off (June 29,2001), the median duration of follow-up time is 33.3 months which was similar for all 3 treatment arms.

Table 2 Distribution of patients randomized by treatment and length of follow-up.

Length of Follow-up (months)	Arimidex Arm	Tamoxifen Arm	Combination Arm	All Patients (n)
< 12	142 (4.5)	140 (4.5)	153 (4.9)	435 (4.6)
12-to <18	113 (3.6)	139 (4.5)	143 (4.6)	395 (4.2)
18- to <24	222 (7.1)	230 (7.4)	236 (7.6)	688 (7.3)
24- to <30	616 (19.7)	623 (20.0)	634 (20.3)	1873 (20.0)
30 to <36	869 (27.8)	831 (26.7)	841 (26.9)	2541 (27.1)
36 to <42	707 (22.6)	707 (22.6)	705 (22.6)	2119 (22.6)
42 to <48	370 (11.8)	353 (11.3)	331 (10.6)	1054 (11.3)
48 to <54	80 (2.6)	89 (2.9)	79 (2.5)	248 (2.6)
54 to <60	6 (0.2)	4 (0.1)	3 (0.1)	13 (0.1)

Reviewer's Comments:
Detailed information on the length of follow-up was not included in the submission. As per FDA request, on May 29 2002, the sponsor submitted complete information on the length of follow-up (see table above). Most of the patients (63%) have been followed for less than 3 years. No patients were followed for 5 years, which is the optimal duration of the control arm (tamoxifen) treatment.

The following table summarizes all countries and the number of patients enrolled. Sixty-five percent of the patient population was from European countries and twenty-four percent from the US.

Table 3 Clinical Sites Information

Country	Study Sites (n)	Patients Enrolled (n)
UK	95	3228
United States	89	2222
Italy	37	654
Canada	28	640
Netherlands	22	195
Spain	20	417
France	17	366
Sweden	11	291
Australia	10	160
Hungary	7	243
South Africa	7	201
Portugal	7	74
Belgium	5	192
Poland	5	107
Germany	5	121
Argentina	5	30
Czech Republic	3	84
Ireland	3	41
Slovakia	2	33
Turkey	2	53
New Zealand	1	14
Total	**381**	**9366**

The primary analysis of efficacy included the ITT population. The table below shows the number of patients included in the ITT, safety and per-protocol populations.

Table 4 Analysis Populations

Patient (n)	Arimidex Arm	Tamoxifen Arm	Combination Arm	All Patients (n)
ITT Population (patients randomized)	**3125**	**3116**	**3125**	**9366**
Did not start therapy Start wrong therapy	**33** 8 (5T, 3A+T)	**23** 7 (4A, 3A+T)	**27** 7 (4A, 3T)	**83** 22
Safety Population (patients who received study drug)	**3092**	**3094**	**3097**	**9283**
Major violations, deviations	89	78	83	250
Per-Protocol Population	**3003**	**3016**	**3014**	**9033**

Patient Disposition

Protocol violations:
A protocol violation was defined as any infringement of the protocol selection criteria. Patients with major protocol violations were excluded from the secondary per-protocol analysis. The table below summarizes the major protocol violations.

Table 5 Major protocol violations and deviations (Modified from sponsor's Study Report, Table 11 and 12 page 44 and 47)

	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)	All Patients N (%)
ITT Population (patients randomized)	**3125**	**3116**	**3125**	**9366**
Violation				
Patients with a major violation	49	35	41	125
Not postmenopausal	31	19	20	70
Prior history of invasive breast cancer or other invasive malignancy	8	8	8	24
Received treatment with experimental drug within 3 months before randomization	8	5	7	20
No histologically proven operable invasive breast cancer	1	4	2	7
Received drug known to affect sex hormone status at time of randomization	0	0	3	3
Clinical evidence of metastatic disease	1	0	1	2
Deviations				
Patients with a major deviation	44	47	45	136
Prior to disease recurrence start therapy known to affect sex hormone status or prevent recurrence	34	35	28	97
Interruption of trial treatment > 3 months	8	5	9	22
Received a different trial treatment prior to disease recurrence	6	7	8	21

A review of the submitted CRFs showed the following non-allowed therapies were received prior to disease recurrence:

Table 6 During trial and prior to recurrence start non-allowed therapy known to affect sex hormone status or prevent recurrence (Reviewer's table from CRFs)

	Arimidex Arm 34	Tamoxifen Arm 35	Combination Arm 28
Tamoxifen or Anastrozole	0049/0060, 0049/0065, 0049/0070, 0053/0045, 0066/0031, 0011/0002, 0030/0031, 0030/0071, 0093/0015, 0467/0008	0072/0016, 0216/0004, 0489/0041, 0031/0057, 0032/0019, 0113/0004, 0494/0005	0005/0017, 0025/0018, 0030/0095, 0049/0059, 0132/0104, 0240/0007, 0437/0005, 0219/0002, 0433/0035, 0093/0033, 0438/0024
SERMS	0146/0009, 0306/0008, 0415/0012, 0426/0004, 0426/0111, 0449/0013, 0496/0002, 0516/0013: raloxifene for osteoporosis	0003/0025, 0416/0080, 0408/0013, 0436/0085 0486/0081, 0489/0055 raloxifene for osteoporosis	0323/0046, 0416/0024, 0450/0001, 0489/0009, 0512/0001: raloxifene for osteoporosis
Hormones		0413/0016 fludrocortisone for hypoaldosteronism	0436/0073:androstenedione for hot flashes, 0526/0021 megace for hot flashes 0069/0002 fludrocortisone for hypotension
Chemotherapy	0005/0004, 0006/0004, 0040/0013, 0167/0022, 0179/0001: colo-rectal cancer 0012/0021, 0057/0063: adjuvant breast 0030/0066 head and neck cancer 0033/0020, 0144/0010: lung cancer 0099/0014, hydrea for thrombocythosis 0172/0026 ovarian cancer 0426/0031 leukemia (AML) 0509/0018 thymoma 0316/0003 Vincamine for senility 0479/0009 for skin lesion	0010/0008, 0159/0012: lymphoma 0010/0144, 0406/0011, 0470/0011: lung cancer 0011/0016, 0191/0001: ovarian cancer 0014/0017, 0019/0010, 0029/0034, 0021/0011, 0116/0011, 0166/0028, 0216/0004: adjuvant breast 0153/0012, 0182/0019, 0314/0014, 0027/0033: colo-rectal cancer 0257/0028 bladder cancer 0409/0046 leukemia (AML) 0433/0020 myeloma	0008/0012 lymphoma 0059/0001 bladder cancer 0065/0001 myeloma 0141/0002, 0324/0036: ovarian cancer 0003/0058, 0117/0001: adjuvant breast 0488/0003: hydrea for thrombocytosis 0526/0021 for chronic ITP

Reviewer's Comments:
The reviewer retrieved some information from the CRFs and requested the sponsor to complete the non-allowed medication/therapy information including reason and duration of therapy (see table above). A review of the submitted datasets showed the following reasons why patients in the three arms received non-allowed hormonal treatment before disease recurrence.

Arimidex Arm:
Crossover to tamoxifen after withdrawing for adverse event: 0049/0060, 0049/0065, 0049/0070
Received open-label Tam + arimidex for 2 days while hospitalized for hip dislocation: 0053/0045
Open-label tamoxifen after withdrawal for refusing to continue on trial: 0066/0031, 0011/0002, 0030/0031, 0030/0071, 0467/0008
Received open-label anastrozole after withdrawing for adverse event: 093/0015

Tamoxifen Arm:
Received open-label tamoxifen + anastrozole for 2 days: 0072/0016
Open-label tamoxifen after withdrawal for refusing to continue on trial: 0216/0004, 0031/0057, 0032/0019, 0113/0004
Open-label anastrozole for 2 days: 0489/0041
Open-label tamoxifen after withdrawal, at investigator's recommendation: 0494/0005

Combination Arm:
Open-label tamoxifen for unknown reason: 0005/0017, 0433/0035, 0219/0002
Open-label anastrozole after withdrawal for adverse event: 0025/0018
Open-label tamoxifen after withdrawal for adverse event: 0030/0095, 0049/0059, 0240/0007, 0093/0033, 0437/0005, 0438/0024
Open-label tamoxifen after withdrawal, patient refuses to continue on trial: 0132/0104

- In summary, eight patients in the Arimidex Arm, crossover to tamoxifen; eight patients in the combination arm received only tamoxifen, 1 patient only Arimidex and 1 patients received open-label Arimidex and Tamoxifen. No patients in the Tamoxifen arm crossover to Arimidex.
- Overall the protocol violations are unlikely to have affected the study outcome because of the small number compared to the total number of patients involved.

The table below summarizes the protocol violations that did not result in patient exclusion from the analysis.

Table 7 Minor protocol violations (Modified from sponsor's Table 13 page 48 of Study Report)

	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)	All Patients N (%)
ITT Population (patients randomized)	**3125**	**3116**	**3125**	**9366**
Primary surgery > 8 weeks before randomization in patients with no chemotherapy	33	24	26	83
Chemotherapy started > 8 weeks before randomization or > 8 weeks before surgery	21	22	29	72
Lack of written consent	13	14	16	43
Previous hormonal adjuvant therapy	11	8	12	31
Received neoadjuvant therapy	5	0	4	9
Not completed primary surgery and chemotherapy	1	1	3	5

Removal from study:

Twenty-five percent of the patients withdrew from the study (see table below). A higher percentage of patients in the Tamoxifen and combination arm withdrew due to adverse events and disease recurrence. The sponsor reported a large variety of adverse events leading to patient withdrawal. Most of the adverse events frequencies were low with no apparent trends except for the vascular events which were less common in the Arimidex arm, musculoskeletal events that were more common in the Arimidex arm and sweating which was more common in the tamoxifen arm. The most frequent adverse events leading to withdrawal were vascular, nausea, musculoskeletal and skin reactions (see table below). Two patients (0131/0010, 0453/0007), one in the Arimidex arm and one in the combination arm, were withdrawn from treatment due to fractures.

Table 8 Reason for withdrawal (modified from sponsor's Table 10, T4.2 and G4.1)

Safety Population (patients who received study drug)	Arimidex Arm 3092 (100%)	Tamoxifen Arm 3094 (100%)	Combination Arm 3097 (100%)	All Patients 9283 (100%)
Safety-Related				
Adverse Event	246 (8)	330 (11)	332 (11)	908 (10)
Efficacy-Related				
Disease recurrence	195 (6)	229 (7)	240 (8)	664 (7)
Death irrespective of cause	29 (1)	50 (2)	34 (1)	113 (1)
Administrative				
Withdrawn Consent	143 (5)	110 (4)	141 (5)	394 (4)
Investigator's Recommendation	63 (2)	83 (3)	72 (2)	218 (2)
Unknown	0	1	0	1
Total	676 (22)	803 (26)	819 (26)	2298 (25)

Table 9 Important adverse events leading to patient withdrawal (modified from sponsor's table 58 of the study report)

Safety Population (patients who received study drug)	Arimidex Arm 3092 (100%)		Tamoxifen Arm 3094 (100%)		Combination Arm 3097 (100%)	
Vascular-Events						
Vasodilatation	32	(1.0)	43	(1.4)	52	(1.7)
Deep thrombophlebitis	5	(0.2)	17	(0.5)	19	(0.6)
Thrombophlebitis	3	(<0.1)	11	(0.4)	9	(0.3)
Pulmonary embolus	6	(0.2)	4	(0.1)	9	(0.3)
Myocardial infarct	3	(<0.1)	6	(0.2)	4	(0.1)
Cerebrovascular accident	3	(<0.1)	6	(0.2)	2	(<0.1)
Gastrointestinal Events						
Nausea and vomiting	29	(0.9)	25	(0.8)	27	(0.9)
Musculoskeletal Events						
Fractures	1	(<0.1)		0	1	(<0.1)
Arthralgia	13	(0.4)	4	(0.1)	4	(0.1)
Arthritis	7	(0.2)	4	(0.1)	3	(<0.1)
Nervous System Events						
Depression	10	(0.3)	11	(0.4)	15	(0.5)
Metabolic						
Peripheral edema	4	(0.1)	6	(0.2)	10	(0.3)
Weight gain	3	(<0.1)	10	(0.3)	6	(0.2)
Skin Events						
Rash, urticaria, pruritus	20	(0.6)	26	(0.8)	21	(0.7)
sweating	4	(0.1)	12	(0.4)	5	(0.2)
Gynecologic Events						
Vulvovaginitis	9	(0.3)	3	(<0.1)	2	(<0.1)
Ovarian carcinoma	4	(0.1)	6	(0.2)	2	(<0.1)
Endometrial carcinoma	2	(<0.1)	6	(0.2)	5	(0.2)
Endometrial hyperplasia	1	(<0.1)	6	(0.2)	2	(<0.1)
Vaginal hemorrhage	2	(<0.1)		0	5	(0.2)

Protocol unblindings:
Unblinding was allowed by protocol when the randomized treatment was stopped or if knowledge of the randomized treatment was needed to optimize the clinical management of the patient. Unblinding treatment occurred in 319 patients in the Arimidex arm, 402 in the Tamoxifen arm and 408 in the combination arm.

Reviewer's Comments:
The sponsor provided unblinding information at FDA request on May 9, 2002. Imbalances in unblindings followed the events. However, the number of unblindings was balanced therefore it is unlikely that it will influence the outcome of the study.

Table 10 Reasons for unblinding

Reasons for Code Break	Arimidex Arm 3125 (100%)	Tamoxifen Arm 3116 (100%)	Combination Arm 3125 (100%)
Adverse Events	119 (3.8)	191 (6.1)	178 (5.7)
Gastrointestinal			
Nausea/Vomiting	10	9	5
Abdominal pain	4	6	8
Diarrhea	2	2	2
Elevated liver enzymes	4	2	3
Vascular			
Cerebrovascular accident	1	7	6
DVT	1	13	14
Pulmonary embolism	3	1	2
Myocardial infarction	2	3	1
Headaches	4	8	5
Thrombophlebitis	0	6	6
Musculo-skeletal			
Osteoporosis	3	0	1
Myalgias/Arthralgias	19	6	8
Breast Cancer	7	24	15
Other tumors	6	8	2
Genitourinary			
Vaginal bleeding	3	2	6
Endometrial hyperplasia	0	3	0
Endometrial polyp	0	3	2
Endometrial cancer	0	3	1
Menopausal symptoms			
Hot flashes	12	21	28
Sweats	5	2	1
Edema	1	9	7
Depression	4	6	10
Vaginal dryness	4	2	0
Skin			
Rash	12	12	13
Others	12	33	31
Death	1 (0)	0	1 (0)
Error	1 (0)	1 (0)	1 (0)
Investigator recommendation/Other	26 (0.8)	18 (0.6)	22 (0.7)
Patient moved	8	1	2
Patient non compliant	5	2	5
Disallowed medication	4	0	2
Patient ineligible	3	2	2
Adverse events	2	2	3
Patient withdrew consent	0	2	2
Suspected recurrence	1	0	1
Others	3	9	5
Patient refuse to continue	24 (0.8)	24 (0.8)	30 (1.0)
Recurrence	148 (4.7)	168 (5.4)	176 (5.6)
Total	319 (10)	402 (13)	408 (13)

Patient characteristics:

The demographics characteristics of the intent-to-treat population are shown in the table below. There were no significant differences between the treatment groups. The majority of the patients (96%) were Caucasian. There were no differences between groups in the proportion of patients who at entry had undergone hysterectomy or had received HRT.

Table 11 Summary of patient's characteristics

Characteristics	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)
ITT Population (patients randomized)	**3125**	**3116**	**3125**
Age (median)	64	64	64
Age Distribution			
< 60	1104 (35.3)	1104 (35.4)	1095 (35)
≥ 60 ≤ 70	1188 (38)	1157 (37.1)	1177 (37.7)
> 70	833 (26.7)	855 (27.4)	853 (27.3)
Race (%)			
Caucasian	3006 (96.2)	2997 (96.2)	2994 (95.8)
Black	37 (1.2)	44 (1.4)	47 (1.5)
Asian	19 (0.6)	17 (0.5)	19 (0.6)
Hispanic	18 (0.6)	15 (0.5)	17 (0.5)
Other	33 (1.1)	30 (1.0)	34 (1.1)
Hysterectomy	876 (28)	864 (28)	862 (28)
Hormone replacement therapy	1114 (36)	1103 (35)	1103 (35)

Reviewer's Comments:

- Sixty-two percent of the patient population en each arm had an intact uterus and was therefore at risk for hormone-induced endometrial cancer at the start of the trial.
- There is no information of patients who had hysterectomy during the course of the trial.
- Cardiovascular risk factors are not known.
- A review of the datasets showed 23 patients in the Arimidex arm, 12 in the Tamoxifen arm and 16 in the combination arm were less than age 45. From this subgroup of patients 17/23, 11/122 and 13/16 in each arm had adjuvant chemotherapy.

Previous breast cancer treatment:

The proportion of patients, who had previous mastectomy, breast conservation, axillary lymph node surgery, radiation therapy and adjuvant chemotherapy was comparable between the three treatment groups.

Table 12 Previous breast cancer treatment (From sponsor's table 6 page 37 of Study Report)

Characteristics	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)
ITT Population (patients randomized)	**3125**	**3116**	**3125**
Surgical procedure			
Mastectomy	1494 (47.8)	1474 (47.3)	1502 (48.1)
Breast conservation	1630 (52.2)	1642 (52.7)	1623 (51.9)
Not recorded	1 (<0.1)	0	0
Axillary Surgery			
Yes			
Clearance	1993 (63.8)	1921 (61.6)	1962 (62.8)
Sampling	991 (31.7)	1062 (34.1)	1013 (32.4)
Not recorded	0	0	1 (<0.1)
Not performed	140 (4.5)	133 (4.3)	149 (4.8)
Not recorded	1 (<0.1)	0	0
Radiotherapy			
Yes	1978 (63.3)	1946 (62.5)	1936 (62)
No	1146 (36.7)	1170 (37.5)	1189 (38)
Not recorded	1 (<0.1)	0	0
Adjuvant chemotherapy			
Yes	698 (22.3)	647 (20.8)	651 (20.8)
No	2426 (77.6)	2469 (79.2)	2474 (79.2)
Not recorded	1 (<0.1)	0	0
Tamoxifen before first surgical procedure			
Yes	50 (1.6)	51 (1.6)	53 (1.7)
No	3074 (98.4)	3065 (98.4)	3072 (98.3)
Not recorded	1 (<0.1)	0	0

Reviewer's Comments:

The treatment groups were well balanced with respect to previous treatment received for breast cancer. Less than 2% of the patients received neoadjuvant treatment with tamoxifen. The proportion of patients who had neoadjuvant hormonal therapy was similar in the three groups as well as the respective median duration of the treatments (anastrozole: 24 days, tamoxifen: 23 days and combination: 22 days. Ninety-five percent of the patients who had breast conserving surgery had radiotherapy. Only 21% of the population had adjuvant chemotherapy, which is considered low. However, there were no differences between treatment arms.

Tumor Characteristics:

Most of the tumors were moderately differentiated. Poorly differentiated or undifferentiated tumors were evenly distributed among the three arms. For the majority of patients in all treatment arms the primary tumor size was equal or less than 2 cm. Sixty percent of the patients have no axillary lymph node involvement. Estrogen-receptor status was comparable between both treatment arms. Eighty-three percent of the patients were estrogen receptor positive or estrogen receptor negative/progesterone positive, 10% were estrogen receptor negative and 8% unknown.

Table 13 Tumor characteristics

Tumor Characteristics	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)
ITT Population (patients randomized)	**3125**	**3116**	**3125**
Tumor dimension			
≤2	1996 (63.9)	1959 (62.9)	2004 (64.1)
2≤5	1018 (32.6)	1066 (34.2)	1027 (32.9)
>5	85 (2.7)	69 (2.2)	73 (2.3)
Not recorded	1 (< 0.1)	0	0
Nodal Status			
Positive	1092 (34.9)	1047 (33.6)	1046 (33.5)
Negative	1876 (60)	1915 (61.5)	1904 (60.9)
Unknown	157 (5)	154 (4.9)	175 (5.6)
Tumor grade			
Well differentiated	651 (20.8)	638 (20.5)	663 (21.2)
Moderately differentiated	1463 (46.8)	1488 (47.8)	1455 (46.6)
Poorly differentiated/undifferentiated	740 (23.7)	727 (23.3)	741 (23.7)
Not assessed/Not recorded	271 (8.7)	263 (8.4)	266 (8.5)
Hormone receptor status			
ER (+)	2546 (81.5)	2514 (80.7)	2537 (81.2)
ER (-)	321 (10.3)	348 (11.2)	319 (10.2)
Unknown	257 (8.2)	254 (8.2)	269 (8.6)
Not recorded	1 (<0.1)	0	0
ER (-) PR (+)	63 (2.0)	76 (2.4)	81 (2.6)
ER (+) PR (+)	1927 (61.7)	1903 (61.1)	1874 (60)

Reviewer's Comment:
The tumor characteristics were also balanced among treatment groups. Her2/neu status was not reported in this study. Hormone-receptor status was evenly balanced across the three treatment groups, with approximately 83% of the patients with ER and or PR positive tumors. Only 8% of the patients had unknown hormonal status. There was no information provided on history of breast biopsies, presence of DCIS, AH or presence of LCIS prior to randomization. FDA reviewer requested the sponsor on June 7,2002, to provide information on history of previous breast biopsies and diagnosis. The sponsor responded that this information was not specifically requested on the CRFs and therefore was not collected. Only 149 patients had information on history of previous breast biopsy, which was recorded in the previous medical history.

Treatment Delivered

Compliance was evaluated on a prospectively defined schedule. A dispensing record identifies the person to whom the drug is dispensed, the quantity of drug dispensed, and the date of dispensing. Patients were asked to return bottles with any remaining tablets at each visit for assessment of compliance. At the termination of the trial, all returned medication is reconciled with the delivery
Nine thousand two hundred eighty three patients received trial treatment, 3092 (33.3%) were treated with anastrozole, 3094 (33.3%) were treated with tamoxifen, and 3097 (33.4%) were treated with the combination of anastrozole plus tamoxifen. The median duration of treatment for the three arms was 33 months. Eighty-three patients in the three arms did not start therapy, 33 in the arimidex arm, 23 in the tamoxifen arm and 27 in the combination arm (see table 4 analysis population). Twenty-three patients in the whole trial started the wrong therapy, eight patients in the arimidex arm (5T, 3 A+T), seven in the tamoxifen arm (4A, 3 A+T) and seven in the combination arm (4A, 3T).

Table 14 Status of treatment as of data cut-off (modified from sponsor's table 9 page 68)

Treatment status	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)
Patients randomized	3125 (100)	3116 (100)	3125 (100)
Treatment not started	33 (1.1)	23 (0.7)	27 (0.9)
Treatment misallocation	8 (0.3)	7 (0.2)	7 (0.2)
Treatment started	3092 (98.9)	3094 (99.3)	3097 (99.1)
Continuing treatment	2414 (77)	2291 (73)	2273 (73)
Treatment withdrawn	676 (21.6)	803 (25.7)	819 (26.2)
Patients died	195 (6.2)	203 (6.5)	214 (6.8)

Subsequent therapy

The sponsor did not submit information on post-study therapy. FDA requested the sponsor to complete this information and on June 13, 2002 FDA was informed that post-study therapy information is not available. After withdrawal from trial treatment, detailed information on post-study treatment was not collected regularly. For patients who had disease recurrence, details of the first therapy received after recurrence is provided in the table below.

Table 15 Treatment after first recurrence

Tumor Characteristics	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)
ITT Population (patients randomized)	**3125**	**3116**	**3125**
Patients who recurred	224	264	283
Chemotherapy	75 (33)	95 (36)	104 (37)
Hormone Therapy	87 (39)	101 (38)	73 (26)
Radiotherapy	54 (24)	59 (22)	93 (33)
Surgery	27 (12)	42 (16)	50 (18)
Other	22 (10)	28 (11)	38 (13)

Rows are not mutually exclusive: patients may appear in more than one row

Information on non-allowed therapy prior to recurrence was supplied on table 6 from the Protocol Violation Section.

Reviewer Comment:
There is no information on post-study treatment before disease recurrence. If there is an imbalance could impact the validity of the primary endpoint of time to recurrence. Patients who withdrew consent or withdrew for adverse events were followed until the time they recurred or were censored at cut-off date. Since there is no information on post-study therapy, these patients should be censored at time of withdrawal.

Biphosphonates therapy

The protocol did not prohibit the concomitant use of biphosphonates. The sponsor was asked on May 30,2002, to provide information on biphosphonates use. A small percentage of patients received biphosphonates, mostly after randomization.

Table 16 Bisphosphanate use

	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)
ITT Population (patients randomized)	**3125**	**3116**	**3125**
Bisphosphonate use	185 (6)	126 (4)	139 (4)
Bisphosphonates started after randomization	152 (5)	105 (3)	112 (3)

Reviewer's Comments:
The potential role of biphosphonates in the adjuvant setting is not well defined. Biphosphonates use was reported on a higher percent of patients on the Arimidex arm. Since this is a relatively small numbers of patients, the difference is insignificant.

E. Efficacy Conclusions

For reporting the efficacy parameters, the intent-to-treat population was used. At the data cut-off, the median duration of follow-up was 33.3 months. The analysis for the primary endpoint was done once a pre-specified number of events had occurred. As of the data cut-off, only 6.6% of patients had died. The sponsor did not conduct a survival analysis because at the time of data cut-off date too few events had occurred, 200 deaths in arimidex arm, 203 deaths in tamoxifen arm and 214 deaths in the tamoxifen + arimidex arm. The survival analysis was planned once 1056 deaths have occurred.

Sponsor's Efficacy Conclusions:
Analysis of the primary endpoint, time to disease recurrence, showed a 17% reduction in the risk of disease recurrence in favor of anastrozole treatment arm compared with tamoxifen (HR 0.83, 95.2% CI 0.71 to 0.96). This result was statistically significant (p = 0.0144). The reduction in the risk of disease recurrence was higher (22%) in the subgroup of patients with hormone-receptor positive tumors, in favor of anastrozole treatment arm, compared with tamoxifen (HR 0.78, 95.2% CI 0.65 to 0.93). This result was also statistically significant (p = 0.0063). Anastrozole was numerically superior to tamoxifen in terms of time to distant recurrence (HR 0.89, 95% CI 0.75 to 1.05); however, the difference was not statistical significant (p = 0.1663).

Anastrozole was also associated with a 58% reduction in the odds of experiencing a new primary (contralateral) breast cancer compared to tamoxifen (OR 0.42, 95% CI 0.22 to 0.79). This result was statistically significant (p = 0.0068).

Treatment with the combination of anastrozole plus tamoxifen did not result in an efficacy advantage compared to tamoxifen alone. No difference was seen when comparing these 2 groups in terms of time to disease recurrence (HR 1.02, 95.2% CI 0.89 to 1.18, p = 0.77).

FDA's Efficacy Conclusions:
At 33 months of follow-up, the Arimidex arm demonstrated prolongation of disease free survival and a trend toward prolongation of time to distant recurrence compared to the Tamoxifen arm. Follow-up was too short, less than 3 % of patients had received 4 to 5 years of treatment and approximately 25% of patients had withdrawn from the study before completing 5 years of treatment. Follow-up was short for an adequate comparison of survival. Although there is a decrease in the contralateral breast cancers on the Arimidex arm, the data does not provide sufficient evidence to support this additional indication. Assessment of the ultimate efficacy outcomes will require additional follow-up of the ATAC trial.

Sponsor's Analysis of time to disease recurrence:
At data cut-off (June 29, 2001), a total of 1080 patients (11.5%) had disease recurrence (including death from any cause). Three hundred eighteen of the 3125 patients in the Arimidex arm had disease recurrence (10%) compared to 379 of the 3125 patients in the Tamoxifen arm (12%) and 383 of the 3125 patients in the combination arm (12%). This difference is equivalent to a 2% reduction in the risk of disease recurrence for Arimidex arm patients (hazard ratio 0.83, p=0.0147). The table below summarizes the recurrence status according to first confirmed event.

Table 17 Sponsor's data on recurrence status according to first confirmed event (From sponsor's Study Report, Table 17, page 54)

Recurrence Status (first confirmed event)	Arimidex Arm N (%)		Tamoxifen Arm N (%)		Combination Arm N (%)	
Randomized patients	**3125**		**3116**		**3125**	
Total number of events	318	(10.2)	379	(12.2)	383	(12.3)
Loco-regional recurrence [1]	67	(2.1)	83	(2.7)	81	(2.6)
Distant recurrence	157	(5.0)	181	(5.8)	202	(6.5)
Death	80	(2.6)	82	(2.6)	72	(2.3)
Related to breast cancer [2]	2	(<0.1)	1	(<0.1)	2	(<0.1)
Unrelated to breast cancer	78	(2.5)	81	(2.6)	70	(2.2)
New primary (contralateral)	14	(0.4)	33	(1.1)	28	(0.9)
Invasive	9	(0.3)	30	(1.0)	23	(0.7)
DCIS	5	(0.2)	3	(<0.1)	5	(0.2)

[1] Includes new primary ipsilateral breast cancer

[2] Includes patients whose death were recorded as breast cancer but did not have ante-mortem proof of recurrence.

The sites of loco-regional failure are illustrated in the table below. Ipsilateral breast cancer recurrence included DCIS.

Table 18 Site of loco-regional recurrence (FDA table modified from Sponsor's table 36 from Study report)

Site of loco-regional recurrence	Arimidex Arm 3125		Tamoxifen Arm 3116		Combination Arm 3125	
Total number of patients with loco-regional recurrence	**67**		**82**		**81**	
Chest wall	27	(0.9)	24	(0.8)	39	(1.3)
Ipsilateral breast [1]	18	(0.6)	28	(0.9)	16	(0.5)
Other regional lymph nodes	15	(0.5)	20	(0.6)	17	(0.5)
Axillary lymph nodes	7	(0.2)	10	(0.3)	9	(0.3)

[1] Includes DCIS

Reviewer's Comments:

- FDA reviewer asked the sponsor to submit all the pathology reports for all the patients who relapsed in the ipsilateral breast. The following patients had only DCIS with no evidence of invasive breast cancer:
  Arimidex arm:
  Patient 0185/0014: Pathology report states: Paget's DCIS group 3
  Patient 0307/0066: DCIS
  Tamoxifen arm:
  Patient 0171/0022: DCIS
  Patient 0441/0009: DCIS
  Combination Arm:
  Patient 0502/0010: DCIS
- Radiation has been shown to reduce the incidence of local recurrence (NEJM, 328 (22):1581-1586 and NEJM 328 (22): 1587-1590, 1993). Therefore, local recurrence in patients who had breast conservation surgery without radiation (5 in the Arimidex arm, 5 in the Tamoxifen arm and 4 in the combination arm) reflects the expected local failure due to inadequate therapy and should not be considered a true disease recurrence.

Table 19 Breast cancer treatment in patients who had loco-regional failure

Loco-regional recurrence	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)
Total number of local recurrence	**67**	**82**	**81**
Chest	**27**	**24**	**39**
Mastectomy	24	22	38
Breast conservation	2	2	1
Mastectomy + XRT	7/24	3/22	9/38
Breast conservation + XRT	2/2	2/2	1/1
Ipsilateral	**18**	**28**	**16**
Mastectomy	4	7	7
Breast conservation	14	21	9
Mastectomy + XRT	2/14	0/7	0/7
Breast conservation + XRT	12/14	17/21	7/9
Axillary	**7**	**10**	**9**
Mastectomy	3	5	5
Breast conservation	4	5	4
Mastectomy + XRT	1/3	2/5	2/5
Breast conservation + XRT	4/4	4/5	2/4
Other lymph nodes	**15**	**20**	**17**
Mastectomy	9	15	9
Breast conservation	6	5	8
Mastectomy + XRT	3/9	9/15	2/9
Breast conservation + XRT	6/6	5/5	8/8

- The table below illustrate the patients that the FDA reviewer consider should not be counted as treatment failure since they had DCIS which can be cured by surgery and does not have the same prognosis as patients who have an invasive cancer and those who had suboptimal therapy such as breast conservation without radiotherapy.

Table 20 Patients who are not considered to have local failure (FDA table)

Loco-regional Breast Cancer Recurrence	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)
DCIS with no invasion	0185/0014 0307/0066	0171/0022 0441/0009	0502/0010
Suboptimal therapy (breast conserving therapy without radiation)	0307/0008 0307/0066	0013/0015 0491/0003 0122/0007 0171/0022 0486/0063	0307/0002 0012/0014 0474/0012 0321/0009

The reduction in disease recurrence was also seen in the subgroup of patients with hormone receptor positive tumors, in favor of the Arimidex arm (see table below).

Table 21 Recurrence status as of data cut-off for hormone receptor positive patients.

Recurrence Status (first confirmed event)	Arimidex Arm N (%)		Tamoxifen Arm N (%)		Combination Arm N (%)	
Randomized patients	**2617**		**2598**		**2624**	
Total number of events	217	(8.3)	272	(10.5)	278	(10.6)
Loco-regional recurrence [1]	35	(1.3)	48	(1.8)	56	(2.1)
Distant recurrence	105	(4.0)	125	(4.8)	140	(5.3)
Death	66	(2.5)	69	(2.7)	57	(2.2)
Related to breast cancer [2]	2	(<0.1)	1	(<0.1)	1	(<0.1)
Unrelated to breast cancer	64	(2.4)	68	(2.6)	56	(2.1)
New primary (contralateral)	11	(0.4)	30	(1.2)	25	(1.0)
Invasive	8	(0.3)	27	(1.0)	20	(0.8)
DCIS	3	(<0.1)	3	(<0.1)	5	(0.2)

Table 22 Recurrence status in patients who received adjuvant chemotherapy

Recurrence Status (first confirmed event)	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)
Patients who received adjuvant chemotherapy	**698**	**647**	**651**
Total number of events	104 (14.9)	87 (13.4)	104 (16)
Loco-regional recurrence [1]	25 (3.6)	23 (3.6)	25 (3.8)
Distant recurrence	61 (8.7)	50 (7.7)	62 (9.5)
New primary (contralateral)	7 (1.0)	6 (0.9)	7 (1.1)
Invasive	3 (0.4)	6 (0.9)	7 (1.1)
DCIS	4 (0.6)	0	0
Death	11 (1.6)	8 (1.2)	10 (1.5)

Reviewer's Comments:
The additional benefit of Arimidex compared to Tamoxifen is not seen in the subgroup of patients who received chemotherapy. This is a small subgroup analysis and exploratory in nature and we can not form any strong inferences. However, if at the time the study is completed, the data still shows lack of beneficial effect in the Arimidex arm in these chemotherapy subgroup, these results will merit further investigation.

FDA's Analysis of time to disease recurrence:

T
he analysis of the data using the sponsor's definition of disease free survival showed that treatment with Arimidex resulted in a significantly longer disease free survival (p= 0.0147). The relative significance of the clinical benefit is unknown since the median follow-up is only 33 months and the control arm, has not completed 5 years of treatment which is the optimal length of therapy to see the benefit of tamoxifen.

Table 23 FDA's Analysis from sponsor's definition of disease recurrence

Disease Recurrence	Arimidex Arm 3125	Tamoxifen Arm 3116
All events 697	318 (10.2)	379 (12.2)
Loco-regional recurrence including DCIS	67 (2.1)	83 (2.7)
Distant recurrence Includes deaths due to breast cancer	157 (5.0)	181 (5.8)
Deaths unrelated to breast cancer	80 (2.6)	82 (2.6)
New contralateral breast cancer	14 (0.4)	33 (1.1)
Hazard Ratio	0.83	
C.I.	(0.72, 0.96)	
P-value	0.0147*	

* p-value compared to 0.025 because of multiple hypothesis (specified by the sponsor)

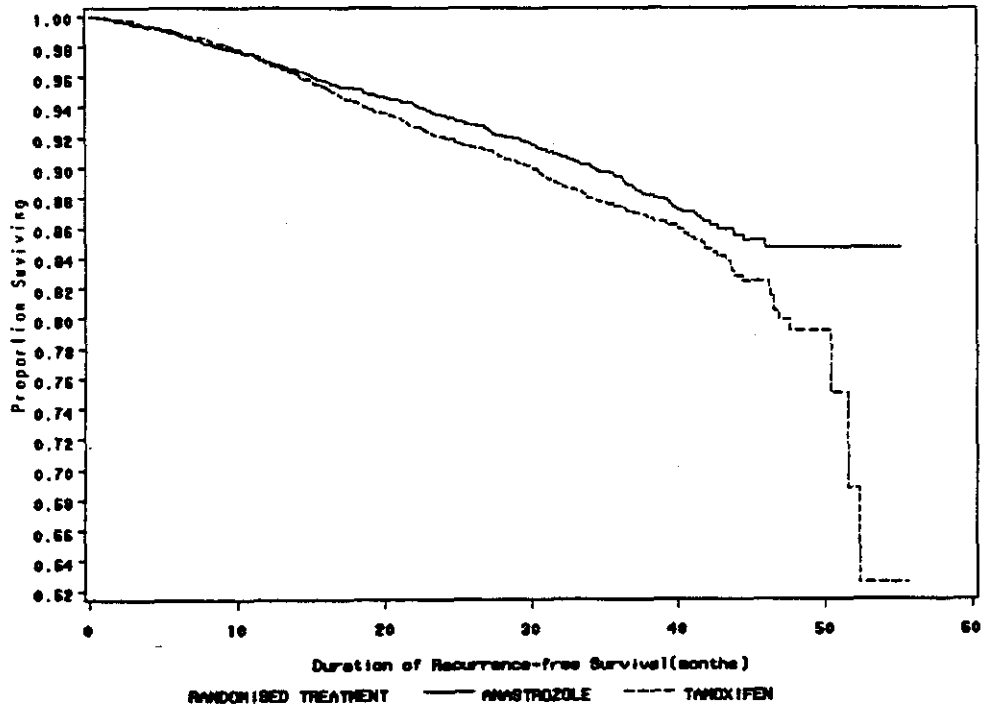

Figure 1 Kaplan-Meier Plot of Recurrence-free Survival of Arimidex versus Tamoxifen (Sponsor defined disease recurrence)

The primary endpoint time to disease recurrence was defined by the sponsor at the time amendment 6 was submitted, April 2000, after all patients were accrued. This is a composite endpoint with each component having a different prognosis. Loco-regional recurrences including DCIS, distant recurrences, new primary contralateral breast cancer including DCIS and all cause mortality as first event were considered as recurrences by the sponsor.

Currently there is no standard definition of disease free survival. The few breast cancer applications in the adjuvant setting had different definitions of this endpoint. Different components of this composite endpoint included local recurrence, distal recurrence, contralateral breast new primaries and unrelated deaths. Most of the applications had not included unrelated deaths as events and patients had been censored if they died without disease recurrence. The FDA reviewers had done three exploratory analyses of the data considering different components of disease free survival. Depending on how the recurrence event is defined, the required level of significance was not reached (see tables and figures below).

The first exploratory analysis documents disease recurrence censoring unrelated deaths and contralateral new primary breast cancers which are considered a separate event from an already-diagnosed breast cancer and therefore have a different prognosis. The local and distant failures were higher in the tamoxifen group but the difference is not statistically significant (see table below).

Table 24 FDA Definition 1 (censoring unrelated deaths and contralateral new primary breast cancers)

Disease Recurrence	Arimidex Arm 3125	Tamoxifen Arm 3116
All events 488	**224**	**264**
Loco-regional recurrence including DCIS	67 (2.1)	83 (2.7)
Distant recurrence Includes deaths due to breast cancer [1]	161 (5.1)	182 (5.8)
Hazard Ratio	0.85	
C.I.	(0.714, 1.017)	
P-value	0.0758*	

* p-value compared to 0.025 because of multiple hypothesis (specified by the sponsor)

[1] 4/80 deaths in A and 1/ 82in T were due to breast cancer and were counted as recurrence events

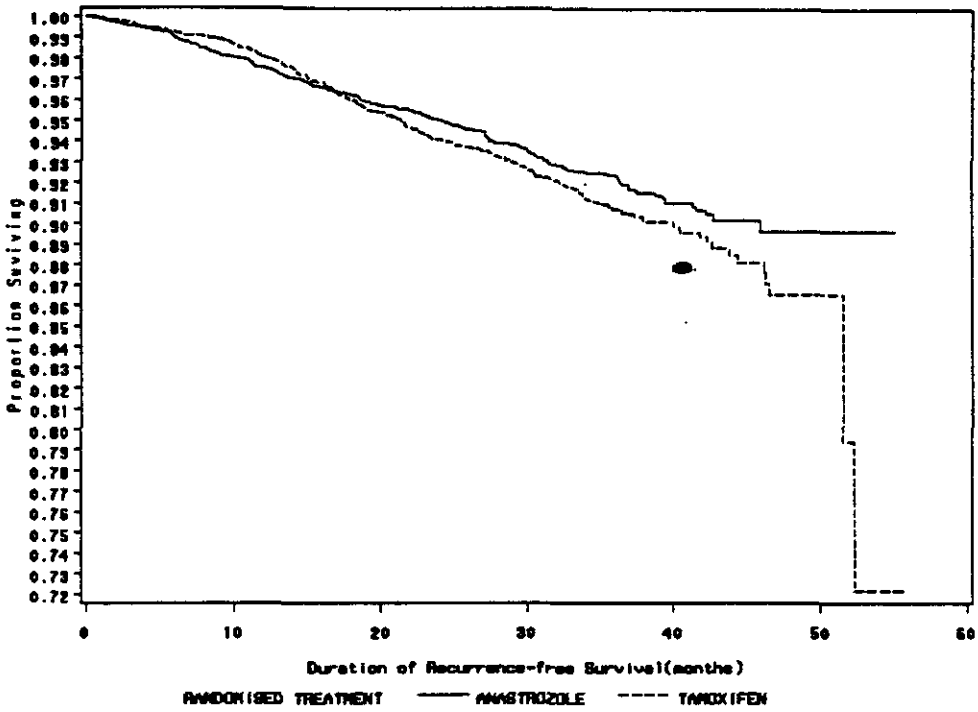

Figure 2 Kaplan-Meier Plot of Recurrence-free Survival of Arimidex versus Tamoxifen (FDA definition 1 of disease recurrence)

The second exploratory analysis of DFS is a more conservative approach which censored unrelated deaths, new contralateral tumors, loco-regional failures which pathology report consisted only of DCIS and loco-regional failures who had suboptimal therapy such as breast conserving surgery without radiotherapy. Although the number of events were higher in the tamoxifen group, the difference was not statistically different.

Table 25 FDA Definition 2 (censoring unrelated deaths, new contralateral breast cancers and loco-regional recurrences which are DCIS with no invasion or where the treatment was suboptimal

Disease Recurrence	Arimidex Arm 3125	Tamoxifen Arm 3116
All events 480	**221**	**259**
Loco-regional recurrence excluding DCIS and suboptimal therapy	64 (2.04)	78 (2.5)
Distant recurrence Includes deaths due to breast cancer	161 (5.1)	182 (5.8)
Hazard Ratio	0.86	
C.I.	(0.717, 1.024)	
P-value	0.0895*	

* p-value compared to 0.025 because of multiple hypothesis (specified by the sponsor)

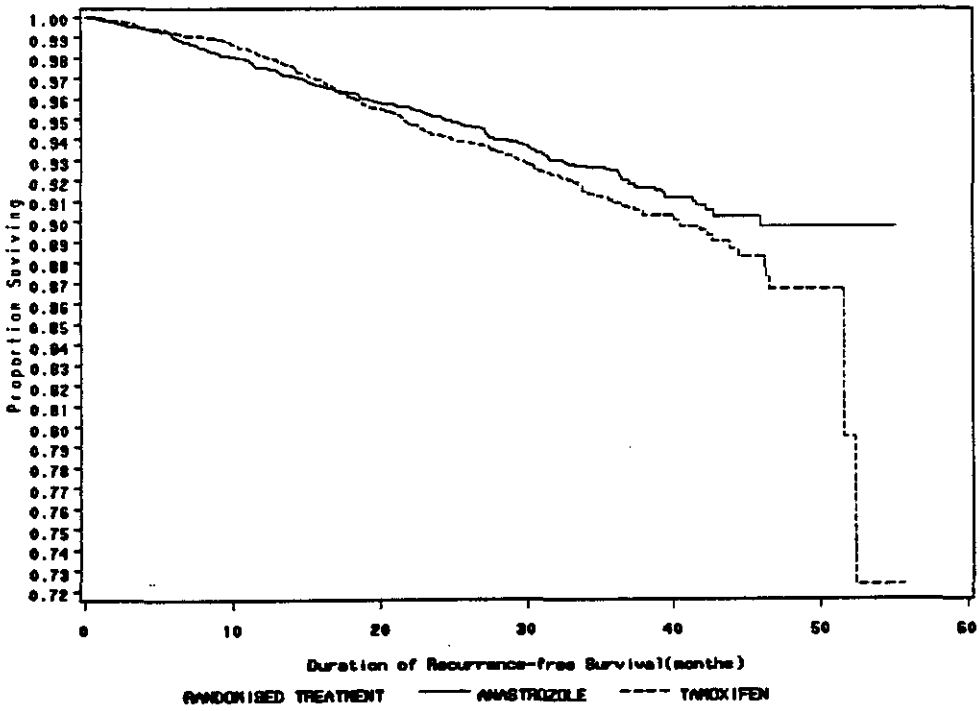

Figure 3 Kaplan-Meier Plot of Recurrence-free Survival of Arimidex versus Tamoxifen (FDA definition 2 of disease recurrence)

The third exploratory analysis was the most conservative of all. In this setting, the following patients were censored: unrelated deaths, contralateral new primaries, loco-regional DCIS with no invasion or where the treatment was suboptimal and patients who received therapy known to affect hormonal status or prevent disease recurrence (from Table 6 of clinical review). In this analysis there are fewer number of events which will require further follow-up.

Table 26 FDA Definition 3 (censoring unrelated deaths, new contralateral breast cancer, loco-regional recurrences which are DCIS with no invasion or where the treatment was suboptimal and patients who received treatment affecting the primary endpoint

Disease Recurrence	Arimidex Arm 3125	Tamoxifen Arm 3116
All events 475	**220**	**255**
Loco-regional recurrence excluding DCIS and suboptimal therapy	63 (2.04)	78 (2.5)
Distant recurrence Includes deaths due to breast cancer	161 (5.1)	178 (5.7)
Hazard Ratio	0.866	
C.I.	(0.724, 1.036)	
P-value	0.1166*	

* p-value compared to 0.025 because of multiple hypothesis (specified by the sponsor)

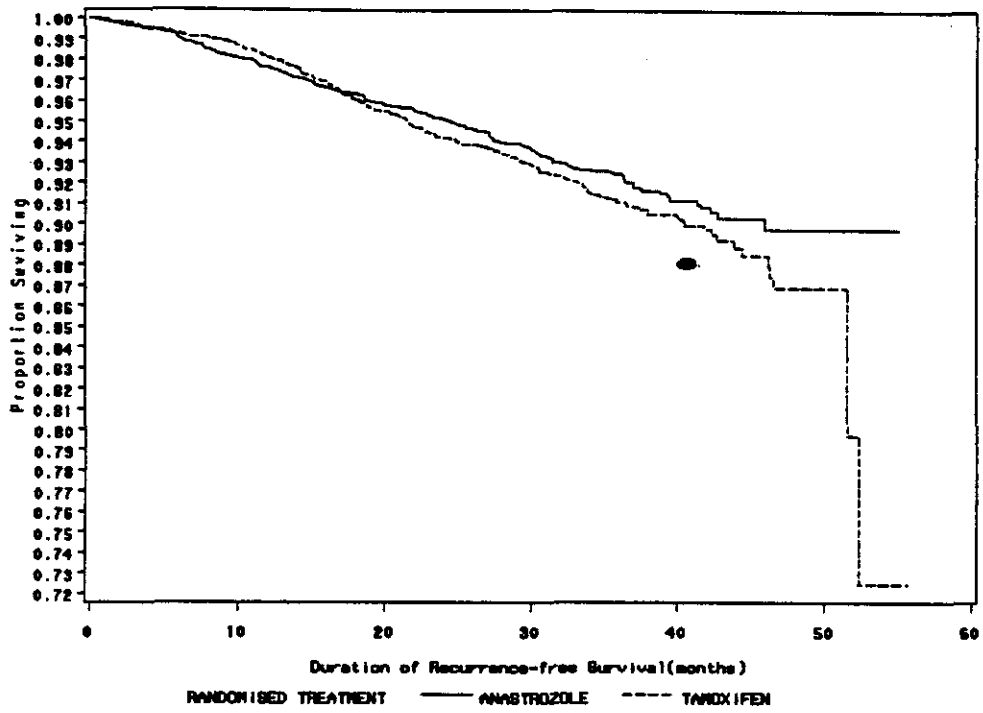

Figure 4 Kaplan-Meier Plot of Recurrence-free Survival of Arimidex versus Tamoxifen (FDA definition 3 of disease recurrence)

Time to Distant Recurrence:

The table below summarizes the distance recurrence status for all randomized patients at the time of the data cut off, June 29,2001.

Table 27 Distant recurrence (From sponsor's data, Table 31 of study report)

Distant Recurrence Status (first confirmed event)	Arimidex Arm 3125	Tamoxifen Arm 3116	Combination Arm 3125
Distant recurrence Includes deaths due to breast cancer	161 (5.1) 99/158	182 (5.8) 97/182	202 (6.5) 113/203
Hazard Ratio	0.88		
2-sided 95% CI	0.708 – 1.083		
p-value	0.2199 *		

* not adjusted for multiple analysis

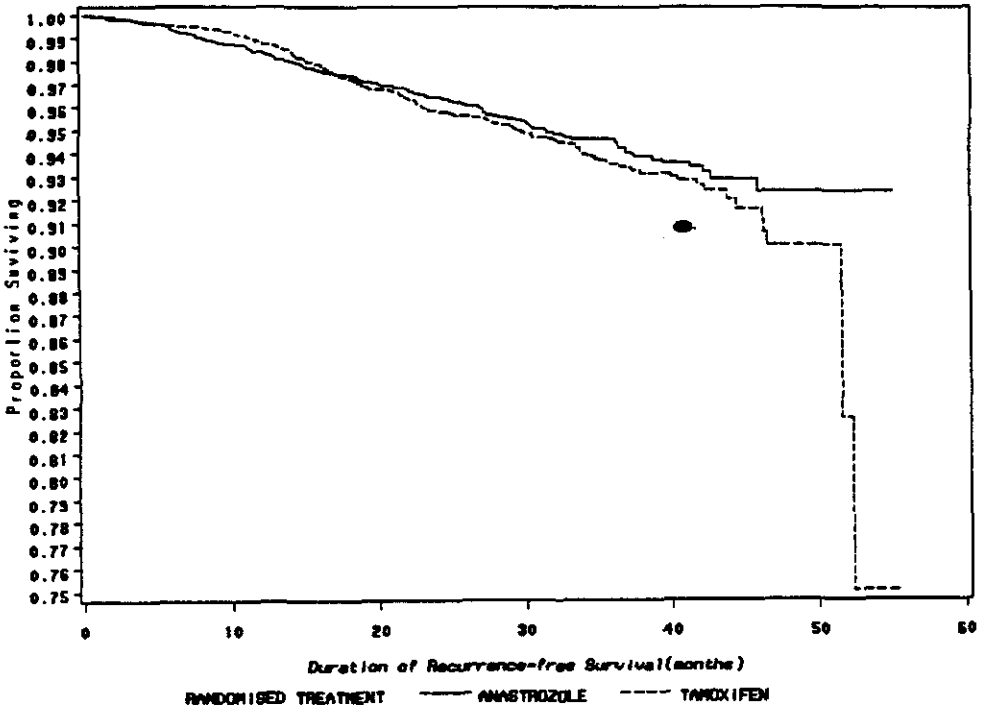

Figure 5 Kaplan-Meier Plot of Distant Recurrence-free Survival of Arimidex versus Tamoxifen (FDA Analysis)

Reviewer's Comments:
Arimidex appears to be associated with a reduction in distance recurrence when compared to Tamoxifen, however, the difference did not reach statistical significance. This result might be a reflection of fewer numbers of events and require further follow-up to see whether a beneficial effect is seen for this endpoint.

Survival:

At the time of data base closure 618 patients had died in the study (see table below). According to the Statistical Analysis Plan, no formal analysis was planned until 1056 have occurred across arms.

Table 28 Survival status (from sponsor's table 33 o f study report)

Survival Status	Arimidex Arm 3125	Tamoxifen Arm 3116	Combination Arm 3125
Alive	2925 (93.6)	2913 (93.5)	2910 (93.1)
Dead	200 (6.4)	203 (6.5)	215 (6.9)
Breast cancer	117 (3.7)	120 (3.9)	136 (4.4)
Other reasons	83 (2.7)	83 (2.7)	79 (2.5)

Table 29 FDA's Analysis of Survival Status

Survival Status	Arimidex Arm 3125	Tamoxifen Arm 3116	Combination Arm 3125
Alive	2925 (93.6)	2913 (93.5)	2910 (93.1)
Total deaths	200 (6.4)	203 (6.5)	214 (6.9)
1st event distant recurrence followed by death	99 (3.2)	97 (3.1)	113 (3.6)
1st event local recurrence followed by death	19 (0.6)	22 (0.7)	28 (0.9)
New primary followed by death	2 (0.1)	2 (0.1)	1 (<0.1)
Unrelated to breast cancer	76 (2.6)	81 (2.6)	72 (2.3)
1st event breast cancer death	4 (0.1)	1 (<0.1)	0

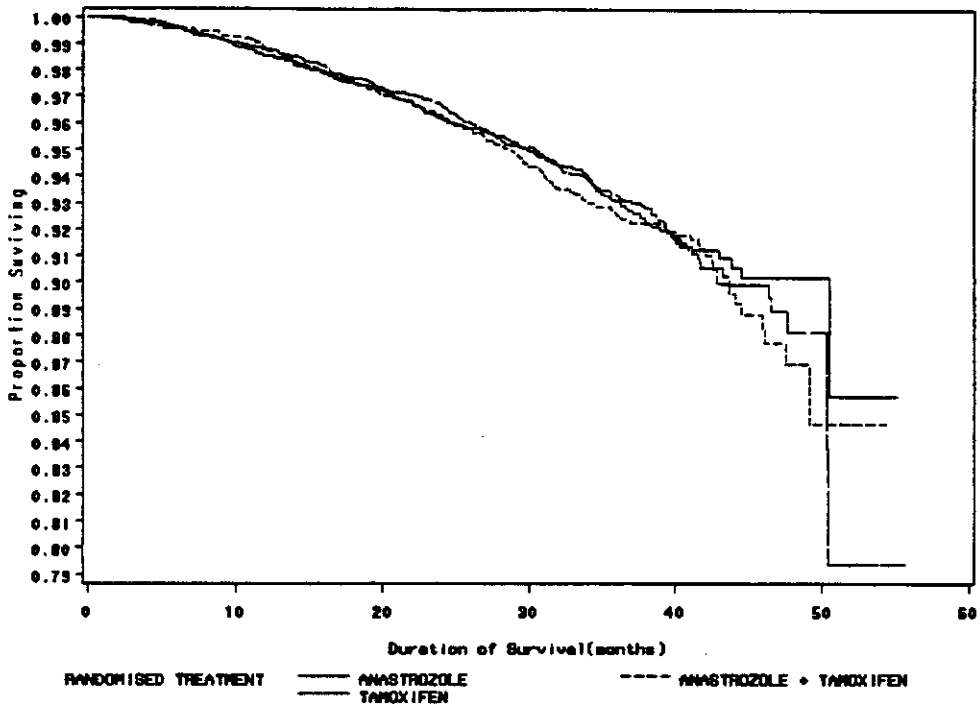

Figure 6 Kaplan-Meier Plot of Overall Survival (FDA Analysis)

Reviewer's Comments:

- This survival data are not mature. The sponsor should submit follow-up data at the time of study completion and when survival data matures.
- The incidence of all deaths was slightly higher in the combination arm. A majority of deaths in all treatment groups were considered by the investigators to be due to progressive disease. The following table summarizes the causes of death :

Table 30 Deaths not related to breast cancer

	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)
Patients were death was unrelated to breast cancer	76	81	72
Leukemia/ lymphoma	0001/0031, 0009/0030 0292/0017, 0426/0031 0436/0030	0010/0008, 0080/0074 0113/0005, 0213/0018 0292/0002, 0409/0046	0183/0024
Myeloma			0065/0001, 0438/0014 0511/0032
Cancer Colo-rectal	0018/0023, 0027/0055 0041/0005, 0058/0004 0080/0062, 0179/0001 0030/0066, 0449/0011	0027/0033, 0153/0012 0226/0014, 0301/0009 0402/0016	0248/0001
Esophageal/Gastric	0050/0009	0072/0016	0009/0053, 0066/0025 0223/0009, 0228/0008 0434/0028
Pancreatic	0409/0019	0014/0043	
Liver, biliary tract	0469/0004, 0521/0025		0433/0035
Head and neck	0031/0027		
Lung	0033/0020, 0144/0010 0034/0015, 0329/0005 0467/0005	0010/0144, 0406/0011 0470/0011, 0478/0017	0429/0003
Renal	0318/0004		0273/0001
Glioblastoma	0438/0007	0436/0001, 0477/0002	

	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)
Ovarian	0064/0015	0009/0010, 0025/0015 0049/0088	0018/0081, 0030/0047
Endometrial	0460/0002		0056/0036
Peritoneal carcinomatosis		0132/0072	
Infections	0004/0024, 0212/0037 0479/0003, 0080/0040 0409/0055	0032/0003, 0032/0007 0135/0005, 0166/0033 0435/0100, 0519/0001	0014/0035, 0026/0001 0032/0008, 0405/0008 0050/0015, 0450/0043 0091/0002, 0134/0026
Gastric/duodenal ulcer		0012/0020	0010/0025
Pyloric stenosis			0022/0008
Pancreatitis			0216/0002
CAD	0008/0042	0526/0017	
Infarct	0049/0004, 0049/0091 0053/0045, 0093/0005 0212/0042, 0284/0003 0416/0050, 0441/0010	0008/0005, 0014/0004 **0029/0037, 0030/0097** 0041/0008, 0121/0053 0203/0002, 0276/0014	0040/0003, 0014/0090 0045/0010, 0089/0012 0119/0013, 0307/0009 0325/0008, 0406/0027 0472/0008
Cardiac surgery		0133/0011	
LV Failure	0020/0007, 0257/0018	0075/0009, 0211/0062	0307/0031
CHF	0032/0010, 0283/0018	0408/0002, 0412/0001	0152/0003, 0490/0018 0301/0021, 0493/0011
Cardiac arrest	0056/0045, 0258/0001 0428/0032	0010/0059, 0030/0064 0527/0013	0414/0010, 0418/0023 0439/0001
Arrhythmia		0438/0016	
Cardiomyopathy	0428/0002		
Cardiogenic shock	0527/0010		
Cerebro vascular accident	0213/0004, 0415/0022 **0445/0004, 0512/0046** 0526/0007	0022/0004, 0027/0076 **0044/0019, 0195/0001** 0212/0005, 0212/0069 0301/0003, 0309/0001 0409/0008, 0415/0015 0416/0016, 0435/0080 0502/0028, 0508/0002	0022/0003, 0302/0009 0402/0017, 0426/0239 0436/0019, 0477/0014 0502/0001
Ischemic vascular disease		0066/0011, 0409/0016	
Ischemic bowel			0491/0008
Aneurysm	0418/0064	0056/0024	
Parkinson's	0526/0015	0438/0008	
Renal failure		0408/0036, 0492/0025	

	Arimidex Arm N (%)	Tamoxifen Arm N (%)	Combination Arm N (%)
Mesenteric vein thrombosis	0292/0011, 0509/0018		
Pulmonary Embolism	0133/0002, 0153/0004 0212/0006, 0280/0007	0010/0002, 0166/0002 0307/0005	0479/0007, 0519/0003
Asthma	0526/0006		0025/0036
COPD	0426/0003	0434/0009, 0469/0006	
Pulmonary edema		0029/0016, 0167/0016	0167/0023, 0253/0009
Alcohol Abuse	0049/0015		
Cirrhosis	0283/0027, 0403/0009 0505/0009		
Respiratory Failure			0491/0005, 0409/0042 0283/0011, 0408/0004
Suicide	0167/0004, 0250/0028		0005/0036, 0056/0003
Sudden death	0436/0012, 0450/0023 0450/0026	0232/0007, 0410/0004 0475/0029	
Unknown	0257/0038, 0283/0047		0438/0011, 0301/0044 0283/0004, 0283/0015 0424/0006, 0435/0037
Fatal stabbing		0144/0009	
Accidents		0425/0003, 0470/0004	0009/0007, 0132/0005

VII. Integrated Review of Safety

Please refer to a separate Safety Review by Ann Far

VIII. Dosing, Regimen, and Administration Issues

The recommended dose of Arimidex is 1 mg tablet taken daily. For adjuvant treatment of early breast cancer in post-menopausal women, the optimal duration of therapy is unknown. Clinical and pharmacokinetic results suggest that tamoxifen should not be administered with Arimidex. Estrogen-containing therapies should not be used with Arimidex.

X. Conclusions and Recommendations

A. Conclusions

This review addresses an efficacy supplement to NDA 20-541 for use of Arimidex® (anastrozole) for the adjuvant treatment of early breast cancer in postmenopausal women. The original NDA for Arimidex, was approved on October 16, 1995 for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. On September 1, 2000, the FDA approved a supplemental NDA for the first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer. The current supplement presents the results of a randomized, double blind trial comparing Arimidex alone with Novaldex alone with Arimidex and Novaldex in combination, as adjuvant treatment in postmenopausal women with breast cancer.

The efficacy claims in support of this application are based on the results of a single large randomized well controlled trial (ATAC) entitled, "A randomized, double-blind trial comparing Arimidex ™ alone with Novaldex ™ alone with Arimidex and Novaldex in combination, as adjuvant treatment in postmenopausal women with breast cancer." The protocol-specified primary endpoint was time-to-recurrence of breast cancer; secondary endpoints were time to distant recurrence, survival and incidence in new breast primaries. At 33 months of follow-up, the Arimidex arm demonstrated prolongation of disease free survival and a trend toward prolongation of time to distant recurrence compared to the Tamoxifen arm. Follow-up was too short for an adequate comparison of survival.

B. Recommendations

We recommend accelerated approval, rather than regular approval, of Arimidex under subpart H (CFR 314.500) for the adjuvant treatment of breast cancer in postmenopausal women because the median follow-up is only 33 months. Assessment of the ultimate safety and efficacy outcomes will require additional follow-up of the ATAC trial. We do not recommend approval of the sponsor's additional proposed indication, [redacted] will not be granted. Although there is a decrease in the contralateral breast cancers on the Arimidex arm, the data do not provide sufficient evidence to support this additional indication.

Post-marketing commitments are recommended under subpart H, fulfillment of which may allow full approval in the future (see Section I.B. for details).

Arimidex preliminary significant improvement in disease-free survival at a median follow-up of 33 months should be confirmed since the known benefits of the tamoxifen arm require 5 years of treatment. Mature survival data also need to be evaluated since there is a known significant survival advantage with 5 years of tamoxifen therapy. At the current time, neither the efficacy nor the toxicity of a 5-year course of Arimidex for adjuvant treatment of breast cancer has been fully evaluated.

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/s/

Patricia Cortazar
9/5/02 10:50:30 AM
MEDICAL OFFICER

Grant Williams
9/5/02 01:48:19 PM
MEDICAL OFFICER

Safety Medical Review of NDA 20541 S-010 ARIMIDEX® (anastrozole)

Division of Oncology Drug Products:
Safety Medical Reviewer- Ann T. Farrell, M.D.
Efficacy Medical Reviewer: Patricia Cortazar, M.D.
Team Leader and Deputy Director: Alison Martin, M.D. and Grant Williams, M.D.

Division of Biometrics:
Statistical Reviewer: Rajeshwari Sridhara, Ph.D
Statistical Team Leader: Gang Chen, Ph.D
Date- September 5, 2002

CLINICAL REVIEW

CLINICAL REVIEW

Table of Contents

Table of Tables in Review

Clinical Review for NDA 20451-10

Executive Summary

The sponsor submitted this New Drug Application (NDA) supplement for ARIMIDEX®, anastrozole, an oral non-steroid aromatase inhibitor, to support the following indications: 1) ARIMIDEX is indicated for adjuvant treatment in postmenopausal women with early breast cancer 2) .

The submission contained preliminary results from one large, international, multicenter, double-blinded, randomized phase 3 trial, A Randomized, Double-blind Trial Comparing ARIMIDEX® Alone with NOLVADEX® (tamoxifen) Alone with ARIMIDEX® and NOLVADEX® in Combination, as Adjuvant Treatment in Postmenopausal Women with Breast Cancer (ATAC). Final ATAC trial results will be available after the last patient has completed five years of trial therapy. The median duration of follow up for the submitted ATAC trial is 33 months. The primary treatment comparison is between the tamoxifen alone-treated patients and the Arimidex alone-treated patients. The primary efficacy analysis in the ongoing ATAC trial is recurrence-free survival. The primary endpoint is time to disease recurrence, a composite endpoint defined as recurrence (locoregional or distant), new contralateral primary or death. The preliminary efficacy results support the sponsor's first proposed indication that Arimidex is effective for the adjuvant treatment of early breast cancer in postmenopausal women. The preliminary efficacy results do not provide sufficient support for the sponsor's second proposed indication.

The major safety concerns of Arimidex use are increased in fractures, musculoskeletal adverse events and hypercholesterolemia. The safety information collected to date is satisfactory; however because of the concerns about long term use (5 years) and the adverse event profile (musculoskeletal adverse events and hypercholesterolemia), additional long term data is important. Reducing fracture risk associated with Arimidex may be possible with concomitant use of bisphosphonate therapy; therefore, as a subpart H commitment, the sponsor will conduct a double-blind, randomized, comparison trial using Arimidex with and without bisphosphonate therapy in early breast cancer patients.

The NDA supplement review is split into separate efficacy and safety reviews. Dr. Patricia Cortazar reviewed the efficacy portion. This safety review discusses the preliminary ATAC safety results and the subprotocol studies.

I. Recommendations

A. Recommendation on Approvability

For Arimidex, the benefit to risk analysis compares the benefits of the reduction in breast cancer recurrence, new contralateral primary, or death for postmenopausal women with early breast cancer and the major safety risks. The ATAC trial results demonstrated a reduction in recurrence, new contralateral primary, or death for postmenopausal women with early breast cancer compared with tamoxifen. The risks of Arimidex use compared with tamoxifen use include an increase in fractures, musculoskeletal adverse events and hypercholesterolemia. Potential safety benefits of Arimidex use compared with tamoxifen use include a decrease in ischemic cerebrovascular events, venous thromboembolic events, endometrial cancer, hot flashes, vaginal discharge, and vaginal bleeding.

The benefit risk assessment from the submitted ATAC trial results is preliminary because the trial is ongoing; thus, the approval recommendation is accelerated approval under subpart H (21 Code of Federal Regulations 314.500) for the following indication: adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The following subpart H commitments/studies should be completed prior to full approval.

1) The sponsor should complete the main ATAC trial and report study results to the Agency.
2) The sponsor should complete all ongoing subprotocol studies and report subprotocol study results to the Agency.
3) The sponsor should conduct a double-blind, randomized, comparison trial using Arimidex with and without bisphosphonate therapy in early breast cancer patients.
4) The sponsor should submit a subprotocol and conduct a study to evaluate the development of hyperlipidemia and control of hyperlipidemia in patients on the ATAC trial.

The following Phase 4 commitments should be completed prior to full approval.

1) The sponsor should provide annual safety updates on the ATAC trial until completion of the trial.
2) The sponsor should follow participants in the ATAC trial for an additional five years following completion of the trial for musculoskeletal adverse events

and for adverse events associated with hypercholesterolemia (i.e., cardiovascular and cerebrovascular adverse events).

Additional Risk Management Steps

The tamoxifen labeling should be revised to include information about coadministration of Arimidex and tamoxifen resulting in lower C_{min} anastrozole levels compared with C_{min} anastrozole levels resulting from administration of anastrozole alone.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The effectiveness of Arimidex®, anastrozole, an oral non-steroidal aromatase inhibitor, for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer is shown in the preliminary results of the ongoing ATAC trial. The ATAC trial is a large, international, multicenter, double-blinded, randomized trial involving 9,366 postmenopausal women. The final ATAC trial results will be available after the last patient has completed 5 years of trial treatment. The preliminary ATAC results submitted in this application are based on a median follow-up of 33 months (median duration of drug exposure 31 months).

Arimidex's effectiveness in adjuvant breast cancer is supported by previous results from trials, which established the safe, and effective use of Arimidex for either first or second line advanced breast cancer. For details, see previous medical officer reviews of NDA 20541.

B. Efficacy

The submission contained preliminary results from one large, international, multicenter, double-blinded, randomized phase 3 trial, A Randomized, Double-blind Trial Comparing ARIMIDEX® Alone with NOLVADEX® (tamoxifen) Alone with ARIMIDEX® and NOLVADEX® in Combination, as Adjuvant Treatment in Postmenopausal Women with Breast Cancer (ATAC) involving 9,366 patients. The final ATAC trial results will be available after the last patient has completed five years of trial therapy. The submitted ATAC trial preliminary results have a median duration of follow up of 33 months. The primary treatment comparison for this submission is between the tamoxifen alone-treated patients and the Arimidex alone-treated patients. The original trial planned for two primary comparisons: 1) between the tamoxifen-alone treated group and the anastrozole-alone treated group and 2) between the tamoxifen-alone treated and the combination group (Arimidex and tamoxifen).

The primary efficacy endpoint in the ongoing ATAC trial is time to disease recurrence, a composite endpoint defined as recurrence (locoregional or distant), new contralateral primaries

or death. The preliminary recurrence-free survival analysis shows that anastrozole alone results in a statistically significant improvement over tamoxifen alone in (Hazard ratio 0.83, 95.2% Confidence Interval (0.71 to 0.96) p=0.014). The table below shows the results for each components of the composite endpoint.

Table 1 ATAC Trial Components of Composite Endpoint

Recurrence-Free Survival	Anastrozole alone (N=3125)	Tamoxifen alone (N=3116)	Combination (N= 3125)
First Event (n,%)	318 (10.2)	379 (12.2)	383 (12.3)
Recurrence			
Locoregional Recurrence[1]	67 (2.1)	83 (2.7)	81 (2.6)
Distant Recurrence	157 (5.0)	181 (5.8)	202 (6.5)
New Contralateral Primary	14 (0.4)	33 (1.1)	28 (0.9)
Invasive	9 (0.3)	30 (1.0)	23 (0.7)
Ductal carcinoma in situ (DCIS)	5 (0.2)	3 (<0.1)	5 (0.2)
Deaths			
Death (breast cancer-related)	4 (0.1)	1 (0)	0(0)
Death (non-breast cancer related)	76 (2.4)	81(2.6)	72 (2.3)

1 Includes DCIS, Ipsilateral Breast Recurrence, axillary recurrence, chest wall recurrence, and other regional lymph nodes

Reviewer's Table

The preliminary efficacy results support the sponsor's first proposed indication that Arimidex is effective for the adjuvant treatment of early breast cancer in postmenopausal women.

For further details concerning the efficacy analysis of this application, see Dr. Patricia Cortazar's efficacy review of this NDA supplement.

C. Safety

The sponsor has provided safety information for the use of Arimidex in early breast cancer from a preliminary analysis of the large adequate and well-conducted ATAC trial, which involves 9366 patients of whom 3092 have received anastrozole alone. The submitted safety update information includes safety information for the trial with median exposure duration of 3.1 years. As of January 25, 2002, approximately 55% of patients have received 3 years of therapy and 14 % of patients have received more than 4 years of trial therapy. Less than 1% of patients have received 5 years or 60 months of trial therapy.

Previously the sponsor submitted sufficient safety information for the labeling of Arimidex for use in the first and second line treatment of postmenopausal women with locally advanced/metastatic breast cancer. The sponsor estimates that worldwide exposure to date is approximately 550,000 patient-years.

The major ATAC trial safety findings included a statistically significant increase in fractures, musculoskeletal adverse events, and hypercholesterolemia compared with tamoxifen. Tamoxifen has been shown in randomized studies to reduce the incidence of fractures of the hip, spine, and wrist and reduce cholesterol levels. As of January 25, 2002, the Arimidex incidence rate for fracture is 7.1% and the Arimidex incidence rate for hypercholesterolemia is 6.8%. Approximately 2.5% of all fractures were serious adverse events. The majority of serious fractures did not result in discontinuation of trial therapy. Although hypercholesterolemia was an adverse event, it was not reported as a serious adverse event. There was a slight increase in cardiovascular adverse events for Arimidex compared with tamoxifen; however, the incidence of myocardial infarction is the same for the two groups. This reviewer recommends that safety information continue to be collected in the ongoing ATAC trial and for five additional years following trial completion, and that the sponsor should conduct a double-blind, randomized, comparison trial using Arimidex with and without bisphosphonate therapy in early breast cancer patients with normal bone mineral density at trial entry.

The pharmacokinetic substudy results showed that concomitant administration of anastrozole and tamoxifen resulted in decreased C_{min} anastrozole levels compared with C_{min} anastrozole levels obtained when anastrozole was administered alone. Interim results from the Bone substudy demonstrated that the Arimidex patients had the greatest decrease in bone mineral density (BMD) compared with the other treatment groups. The quality of life substudy noted a statistically significant increase in reports of loss of interest in sex, vaginal dryness, and pain or discomfort with sex.

D. Dosing

The recommended dose of Arimidex is 1 mg daily. The ATAC trial is ongoing; thus, the optimal duration of treatment is not known for the early breast cancer indication. There are no other unresolved dosing issues. The current labeling based on previous NDA submissions states that

the optimal duration of Arimidex therapy in the first or second line locally advanced/metastatic breast cancer treatment is until recurrence. For details concerning how the dose was determined, dose-toxicity, dose-response relationships, and study information that supported the labeling recommendations for renally impaired or hepatically impaired or elderly patients, see the original Pharmacology and Toxicology, Biopharmaceutics, and Medical Officer reviews of NDA 20-541.

E. Special Populations

This submission contained interim results from the 5-year ATAC trial, an adequate and well-controlled ongoing study, which has demonstrated Arimidex's treatment effect in postmenopausal women with early breast cancer.

Gender
The ATAC trial included only postmenopausal women with early breast cancer. No men were included in this study. Gender assessment of safety and efficacy from the ATAC trial could not be performed.

Ethnicity
Ninety-six percent of ATAC participants were Caucasian. Because few participants were non-Caucasian an ethnicity analysis was not performed. Ideally more non-Caucasian participants should have been enrolled.

The original NDA submission and other supplements have adequately demonstrated that dosing adjustments are not necessary for the renally impaired, hepatically impaired, or elderly patients. For details, see the original Pharmacology and Toxicology, Biopharmaceutics, and Medical Officer reviews of NDA 20-541. In the current submission, most adverse events seen with elderly patients in the ATAC trial are similar to those seen in the elderly population.

Because aromatase activity is not an important mechanism of estrogen generation in premenopausal women, studies in pregnant women with breast cancer are not necessary. The proposed indication is for postmenopausal women with breast cancer; therefore pediatric studies are not needed.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Trade name: Arimidex
Drug name: anastrozole

Drug Class: hormone therapy, aromatase inhibitor

Arimidex has been previously approved for first and second line hormonal therapy in postmenopausal women with advanced breast cancer.

Sponsor's Proposed indications:

1) ARIMIDEX is indicated for adjuvant treatment in postmenopausal women with early breast cancer.

Dose: 1 mg daily

Patient Population: Postmenopausal women with breast cancer

B. State of Armamentarium for Indication(s)

Tamoxifen is the only other hormone treatment approved for the adjuvant treatment of breast cancer.

C. Important Milestones in Product Development

For details, see Dr. Patricia Cortazar's efficacy review of this supplement.

D. Other Relevant Information

Arimidex is not approved as adjuvant therapy in postmenopausal women with hormone receptor positive early breast cancer. Arimidex is approved in other countries for the treatment of advanced breast cancer in postmenopausal women.

E. Important Issues with Pharmacologically Related Agents

Tamoxifen is the only hormonal therapy approved for the adjuvant treatment of early breast cancer. Tamoxifen effectiveness has been established by randomized trials comparing tamoxifen with placebo. Safety concerns with the use of tamoxifen include risk of endometrial cancer, stroke, thromboembolic events, and the development of cataracts.

There are no aromatase inhibitors approved for this indication. Letrozole, an aromatase inhibitor is approved in for use in patients with metastatic breast cancer. The letrozole label notes that fractures have been observed with letrozole use in metastatic breast cancer.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The application contained the following preclinical studies:

1) reproductive toxicology (fertility study)
2) propensity of Arimidex to form hepatic adducts and alone and in the presence of tamoxifen
3) studies on the mechanism of tumor formation

The Pharmacology and Toxicology Review of this supplement recommended a revision of the Precautions section of the label to include information from the completed reproductive toxicology study.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

This submission contained a completed pharmacokinetic substudy. Substudy results demonstrated that coadministration of anastrozole and tamoxifen resulted in decreased C_{min} anastrozole levels compared with C_{min} anastrozole levels obtained when anastrozole was administered alone. Coadministration did not effect Tamoxifen and desmethyltamoxifen levels compared with levels obtained when tamoxifen was administered alone. The sponsor performed an exploratory analysis in substudy patients who also participated in the Bone substudy. The exploratory analysis suggested that estradiol level suppression was similar between the anastrozole alone patients and the tamoxifen alone patients. The Biopharmaceutics reviewer requested studies to conduct the characterization of enzymes responsible for the N-dealkylation and hydroxylation of anastrozole and had additional comments for the Arimidex labeling.

B. Pharmacodynamics

This submission contained no pharmacodynamic data or studies.

IV. Description of Clinical Data and Sources

A. Overall Data

The primary data source for this submission is the preliminary data from the ATAC trial and its substudies (endometrial, bone and quality of life).

B. Tables Listing the Clinical Trials

This section is not applicable because the submission contained only one trial.

C. Postmarketing Experience

The sponsor estimates that the worldwide exposure is approximately 550000 patient-years. The sponsor provides periodic safety updates to the NDA and plans to provide the next update at the end of 2002. The sponsor did not provide specific post-marketing information in this submission.

D. Literature Review

The sponsor provided published abstracts and literature in the about the use of Arimidex in the locally advanced/metastatic breast cancer settings. The sponsor also included the Early Breast Cancer Trialist's Cooperative Group's meta-analysis of the tamoxifen efficacy data. The sponsor also provided the published literature on the tamoxifen prevention trial.

V. Clinical Review Methods

A. How the Review was Conducted

The database for this submission is the ATAC trial. Information from the ATAC substudies is presented in the appendix. Dr. Patricia Cortazar reviewed the efficacy portion of this submission. Dr. Ann Farrell reviewed the safety portion of this submission.

B. Overview of Materials Consulted in Review

The materials consulted in this review include the regulatory history of the Investigational New Drug (IND) application, ATAC database, Medical Officer's reviews for tamoxifen and Arimidex, and published literature.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

For details, see Dr. Patricia Cortazar's efficacy review of this supplement.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

For details, see Dr. Patricia Cortazar's efficacy review of this supplement.

E. Evaluation of Financial Disclosure

For details, see Dr. Patricia Cortazar's efficacy review of this supplement.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

For details, see Dr. Patricia Cortazar's efficacy review of this supplement.

B. General Approach to Review of the Efficacy of the Drug

For details, see Dr. Patricia Cortazar's efficacy review of this supplement.

C. Detailed Review of Trials by Indication

For details, see Dr. Patricia Cortazar's efficacy review of this supplement.

D. Efficacy Conclusions

For details, see Dr. Patricia Cortazar's efficacy review of this supplement.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The ATAC safety database, consisting of the ATAC trial safety data and the subprotocol studies data is the safety database for this application. The cut-off date for the original submission is June 29, 2001. The cut off date for the safety update is January 25, 2002. The safety update includes an additional seven months of data. The sponsor did not submit safety data from other ongoing trials because the trials did not involve the use of Arimidex as adjuvant therapy in early breast cancer. The sponsor did not submit post-marketing surveillance data in this application because the sponsor continues to provide Periodic Safety Update Reviews (PSURs) to the FDA. The major limitation of the safety database is the median study drug exposure of 3.1 years as of January 25, 2002. As of January 25, 2002, approximately 55% of patients have received 3 years of therapy and 14 % of patients have received more than 4 years of trial therapy. Less than 1% of patients have received 5 years or 60 months of trial therapy. Collected adverse event data from the ATAC trial demonstrated a statistically significantly higher rate of musculoskeletal adverse events (arthralgia, arthritis, arthrosis, bone pain, fracture, osteoporosis, and joint disorder), fractures, fractures of the hip, spine, and wrist /Colles, and hypercholesterolemia than the tamoxifen alone treated group. Additional adverse events reported more frequently with anastrozole than the other treatment groups include: Body as a whole (asthenia, pain, headache, chest pain), Cardiovascular (hypertension), Digestive (diarrhea, dyspepsia), Nervous System (insomnia, anxiety, paresthesia), Respiratory (pharyngitis), and Urogenital (breast pain,

vulvovaginitis). Chest pain was reported more frequently in the anastrozole alone treatment group than the tamoxifen alone treatment groups (1.7% vs.1.0%); however, myocardial infarction was not (0.8% vs. 0.8%). Serious adverse events associated more frequently with anastrozole alone compared with tamoxifen alone include: fractures, cataracts, and arthritis.

Subprotocol studies' safety data are reported with the ATAC trial. The pharmacokinetic substudy results demonstrated that coadministration of anastrozole and tamoxifen resulted in a statistically significant decrease in anastrozole levels compared with anastrozole levels seen with the administration of anastrozole alone. The lipoprotein and clotting factors substudy and the endometrial substudy did not accrue adequate numbers of patients to allow conclusions from the data. Interim results from the bone substudy demonstrate that the tamoxifen alone treatment group had the greatest increase in radiological bone density and that the anastrozole alone treatment group had the greatest decrease in radiological bone density. The quality of life substudy results did not demonstrate a statistically significant difference in the Functional Assessment of Cancer Therapy- Breast (FACT-B) Total Outcome Index (TOI) between the anastrozole alone treatment group and the tamoxifen alone treatment group. No statistically significant differences were noted between the anastrozole alone and the tamoxifen alone treatment groups for the FACT-B subscale analyses. Statistically significant differences were noted between the two treatment groups for several responses on the most bothersome endocrine symptoms question against anastrozole for the following symptoms: vaginal dryness, pain/discomfort with intercourse, loss of interest in sex, and diarrhea.

The ATAC trial excluded men from participation; therefore gender analysis cannot be performed. Less than 4% of ATAC participants were non-Caucasian, therefore an ethnicity analysis could not be performed. No age related treatment differences were found between treatment groups.

B. Description of Patient Exposure

The submission safety database includes the subprotocol study data, the original ATAC submission with a safety cut-off date of June 29, 2001 and the safety update with a cut-off date of January 25, 2002. The safety update includes an additional seven months of data. Safety data from the original supplement submission and the safety update submission will be presented with appropriate identification.

The following table shows the numbers of randomized patients and treatment they received.

Table 2 Numbers of Patients by Randomized Treatment and Treatment Received (cut off date - June 29, 2001)

Randomized treatment	Treatment Patients Actually Received			
	Anastrozole	Tamoxifen	Combination	No treatment
Anastrozole	3084	5	3	33

Tamoxifen	4	3086	3	23
Combination	4	3	3091	27
Total Patients	3092[a]	3094[b]	3097[c]	83

[a]This number is the safety analysis denominator for the anastrozole alone treated group.
[b]This number is the safety analysis denominator for the tamoxifen alone treated group.
[c]This number is the safety analysis denominator for the combination treated group.
Reviewer's Table

Since the original sNDA submission, the sponsor determined that Patient #0425/0008 who was randomized to tamoxifen was actually dispensed the medication for Patient #0425/0011 (combination treatment). Thus the safety update treatment denominators are anastrozole 3092, tamoxifen 3093 and combination 3098. In addition, the sponsor noted that ten patients at sites 0432 and 0434 may have received incorrect medication for 6 months due to a shipping error.

Reviewer's Comment: The denominator corrections and the ten patients who may have received the wrong medication for 6 months are unlikely to significantly effect safety results and conclusions.

The following table shows the exposure duration as of January 25, 2002 cut off date. The duration of trial treatment is defined as the time from the date of first dose until the date of the last known dose. The last date of contact prior to the data cut-off was assigned for any patient who had not withdrawn from trial treatment.

Reviewer's Comment: Approximately 55% of patients have completed 3 years of trial therapy and 14% patients have been completed 4 years of trial therapy. Less than 1% have completed 5 years.

Table 3 ATAC Exposure Duration (January 25, 2002)

	Anastrozole (N=3092)	Tamoxifen (N=3093)	Combination (N=3098)
Duration			
1 day to < 12 months	318 (10.3%)	360 (11.6%)	376 (12.1%)
≥ 1 year to < 2 years	245 (7.9%)	288 (9.3%)	286 (9.2%)
≥ 2 year to < 3 years	699 (22.6%)	678 (21.9%)	731 (23.6%)
≥ 3 year to < 4 years	1391 (45%)	1322 (42.7%)	1292 (41.7%)
≥ 4 year to < 5 years	432 (14%)	436 (14.1%)	410 (13.2%)
5 years	7 (0.2%)	9 (0.3%)	3 (0.1%)
Median (months)	37.3	36.9	36.5
Range (months)			

Reviewer's Table

C. Methods and Specific Findings of Safety Review

Adverse Event (AE) Collection
All adverse event information was collected at clinic visits and recorded on Case Report Forms (CRFs). The trial used two sets of CRFs (one- United States and one non-United States). Minor differences exist between CRFs sets; however, the both CRF sets collected the same basic information. The Adverse Event form (#1438) included a separate line for description of the adverse event and several questions about:

Onset and resolution

Event Intensity

Seriousness

Outcome

Causality Assessment

Further Assessments/Therapy (whether treatment was discontinued due to this AE)

The Adverse Event form for **Vaginal Bleeding** and Discharge (#1614) included several questions about:

Investigations Performed (such as ultrasound)

Diagnosis

Further Management

The Statement of Death form (#1094) included questions about the date of death, main cause of death and whether post-mortem was performed.

Reviewer's Comment: The information collected on the CRFs was minimal.

Adverse Event Definitions, Collection and Analysis

The trial adverse event defined adverse events as the development of a new medical condition or the deterioration of a pre-existing condition either during trial treatment or during the 14 days following cessation of trial treatment. The medical condition could be a symptom, a sign, or an abnormal result on investigation. All adverse events (serious and non-serious) were followed to resolution.

The following new or deteriorating medical conditions were excluded from the adverse event reporting:

1) any which occurred as a direct result of recurrence of breast cancer
2) any which were definitely related to chemotherapy or radiotherapy
3) any which were definitely related to withdrawal of HRT at the time of randomization

Serious Adverse Events (SAE)

Serious adverse events were:

1) any fatality
2) any life-threatening event
3) any event that caused or prolonged hospitalization
4) any event that caused disability or incapacity
5) any event that required medical intervention to prevent permanent impairment or damage

Adverse Events Following Withdrawal of Trial Treatment

An adverse event following withdrawal of trial treatment was defined as an adverse event, which met all of the following conditions:

1) occurred more than 14 days after stopping trial treatment
2) occurred within 10 years of starting trial treatment
3) occurred before confirmation of recurrence of breast cancer
4) satisfied one or more of the following criteria:
   a) fatal
   b) life-threatening
   c) caused or prolonged hospitalization
   d) caused disability or incapacity
   e) required medical intervention to prevent permanent impairment or damage

Reviewer's Comment: Thus, the only adverse events reported more than 14 days following withdrawal were serious adverse events.

Protocol "Prespecified" Adverse Events

The protocol identified "prespecified" adverse events of interest. The protocol specified that treatment comparisons would be performed for these adverse events. The "prespecified" adverse events were:

1) hot flushes (COSTART term: vasodilatation)
2) nausea and vomiting (COSTART terms: nausea and vomiting)

3) fatigue/asthenia (COSTART term: asthenia)
4) mood disturbances (COSTART terms: agitation, anxiety, apathy, depersonalization, depression, emotional lability, hysteria, and nervousness)
5) musculoskeletal disorders (COSTART terms: arthralgia, arthritis, arthrosis, and joint disorder)
6) vaginal bleeding (events obtained from CRF # 1614 which concerned vaginal bleeding and/or discharge and included episodes of spotting or hemorrhaging)
7) vaginal discharge (events obtained from CRF #1614 which concerned vaginal bleeding and/or discharge and included patients with discharge)
8) endometrial cancer (COSTART term: endometrial carcinoma)
9) fractures (COSTART term: fracture)
10) cataracts (COSTART term: cataract specified)
11) venous thromboembolic events (COSTART terms: deep thrombophlebitis, pulmonary embolus, retinal vein thrombosis, thrombophlebitis, and thrombosis)
12) ischemic cardiovascular disease (COSTART terms: angina pectoris, coronary artery disorder, myocardial infarct, myocardial ischemia)

The Steering Committee also requested that the following 3 additional categories (defined prior to unblinding the data) be subjected to formal statistical analysis:

1) ischemic cerebrovascular events (COSTART terms: cerebral embolism, cerebral infarct, cerebral ischemia, and cerebrovascular accident)
2) deep venous thromboembolic events (COSTART terms: deep thrombophlebitis, pulmonary embolus, and retinal vein thrombosis)
3) fractures of the spine, hip, or wrist/Colles (identified following a blinded review of all events with a COSTART term of fracture)

Adverse event treatment comparisons were performed using logistic regression with treatment group as a factor. No statistical corrections were performed for the multiple comparisons.

The main ATAC trial did not collect laboratory data as part of the study.

Results

The treatment groups were well balanced with respect to demographic characteristics and past medical history. For details, see the efficacy section of this review. The groups were well balanced with respect to history of osteoporosis and prior musculoskeletal events as shown in the table below.

Table 4 Musculoskeletal Illness at Trial Entry

Musculoskeletal Illness at Trial Entry	Anastrozole (N=3125)	Tamoxifen (N=3116)	Combination (N=3125)
Total Patients	919 (29.4%)	873 (28%)	866 (27.7%)

Arthralgia	49 (1.6%)	32 (1%)	46 (1.5%)
Arthritis	649 (20.8%)	616 (19.8%)	619 (19.8%)
Arthrosis	98 (3.1%)	102 (3.3%)	83 (2.7%)
Joint Disorder	115 (3.7%)	115 (3.7%)	112 (3.6%)
Osteoporosis	144 (4.6%)	120 (3.9%)	127 (4.1%)

Reviewer's Table

Patient Status

The following table shows the status of patients as of the January 25, 2002 cut off date.

Reviewer's Comment: More anastrozole patients remain on trial therapy than the other two treatment group patients. Since the original submission cut off date- June 29, 2001, 75 anastrozole patients (2.4%), 84 tamoxifen patients (2.7%), and 91 combination patients (2.9%) have discontinued trial treatment.

Table 5

Updated ATAC Patient Status as of January 25, 2002 (Number of Patients)

	Anastrozole (N, %)	Tamoxifen (N,%)	Combination (N,%)
Randomized	3125 (100)	3116 (100)	3125 (100)
Correct Treatment Received	3092 (100)	3093 (100)	3098 (100)
Completed protocol therapy	9 (0.3)	12 (0.4)	6 (0.2)
Treatment Withdrawn to date	744 (24.1)	874 (28.3)	910 (29.4)
Patients died	231 (7.5)	245 (7.9)	270 (8.7)
Continuing on Treatment	2339 (75.6)	2207 (71.4)	2182 (70.4)
Missing Information	0	0	0

Reviewer's Table

The following tables show the reasons for withdrawal from trial therapy.

Reviewer's Comment: More than half of the patients who withdraw from trial treatment do so because of an adverse event or disease recurrence. Similar results were seen for the original submission with the June 29, 2001 cut off date. Withdrawals due to confirmed disease recurrence as of June 29, 2001 were: anastrozole alone – 195 (6.3%), tamoxifen alone –229 (7.4%), and combination – 240 (7.7%).

Table 6

Reasons for Withdrawal from Trial Treatment (January 25, 2002)

	Anastrozole (N, %)	Tamoxifen (N,%)	Combination (N,%)
Randomized	3125 (100)	3116 (100)	3125 (100)
Correct Treatment Received	3092 (100)	3093 (100)	3098 (100)

Treatment Withdrawn to date	744 (24.1)	874 (28.3)	910 (29.4)
Died (not included in other categories)	40 (1.3)	57 (1.8)	41 (1.3)
Confirmed Disease Recurrence	215 (7)	256 (8.3)	266 (8.6)
Adverse event	264 (8.5)	358 (11.6)	370 (11.9)
Patient refusal to continue	151 (4.9)	117 (3.8)	155 (5.0)
Investigator Recommendation/Other	74 (2.4)	86 (2.8)	78 (2.5)

Reviewer's Table

Adverse Events

The following table lists the overall and general categories of adverse events.

Reviewer's Comment: The anastrozole alone treatment group reported fewer drug-related adverse events than the other groups. The anastrozole alone treatment group reported statistically significantly fewer adverse events leading to withdrawal compared with the tamoxifen alone treated group (OR 0.68, 95% CI 0.57 to 0.81, p < 0.001). The safety update results are similar to those reported in the table below.

Table 7

Overview of adverse events (June 29, 2001)

Category [a]	Number (%) of patients					
	Anastrozole 1 mg (N = 3092)		Tamoxifen 20 mg (N = 3094)		Anastrozole 1 mg plus tamoxifen 20 mg (N = 3097)	
All adverse events [b]	2821	(91.2)	2845	(92.0)	2845	(91.9)
Drug-related adverse events [b]	1734	(56.1)	1962	(63.4)	1979	(63.9)
All serious adverse events	740	(23.9)	805	(26.0)	800	(25.8)
During treatment [b]	685	(22.2)	755	(24.4)	753	(24.3)
Drug-related serious adverse Events	83	(2.7)	178	(5.8)	152	(4.9)
Following withdrawal of trial Treatment	97	(3.1)	83	(2.7)	85	(2.7)
Adverse events leading to Withdrawal	241	(7.8)	342	(11.1)	337	(10.9)
Drug-related adverse events leading to withdrawal	159	(5.1)	223	(7.2)	228	(7.4)
Adverse events leading to death [c]	76	(2.5)	82	(2.7)	72	(2.3)
During treatment [b]	44	(1.4)	73	(2.4)	58	(1.9)
Drug-related adverse event leading to death	1	(<0.1)	6	(0.2)	5	(0.2)
Following withdrawal of trial Treatment	32	(1.0)	11	(0.4)	20	(0.6)

[a] Patients may be included in more than 1 category in this table.

[b] Includes events occurring within 14 days of stopping trial treatment.
[c] Information derived from the adverse event form 1438.
N Number of patients treated.
Reviewer's table

The table below shows all adverse events with greater than 5% incidence.

Reviewer's Comment: Collected adverse event data demonstrate a statistically significantly higher rate of musculoskeletal adverse events (arthralgia, arthritis, arthrosis and joint disorder), fractures, and fractures of the hip, spine, and wrist /Colles, and hypercholesterolemia than the tamoxifen alone treated group. Additional adverse events reported more frequently with anastrozole than the other treatment groups include: Body as a whole (asthenia, pain, headache, chest pain), Cardiovascular (hypertension), Digestive (diarrhea, dyspepsia), Musculoskeletal (osteoporosis, bone pain), Nervous System (insomnia, anxiety, paresthesia), Respiratory (pharyngitis), and Urogenital (breast pain, vulvovaginits). Chest pain was reported more frequently in the anastrozole treatment group than the tamoxifen treatment groups (1.7% vs.1.0%); however, myocardial infarction was not (0.8% vs. 0.8%). The safety update results in the table below are similar to the results when the supplement was originally submitted.

Table 8 Adverse Events with a Greater than 5% Incidence (January 25, 2002)

Adverse Event	Anastrozole N=3092 (%)	Tamoxifen N=3093 (%)	Combination N=3097 (%)
Body as a Whole			
Asthenia	512 (16.6)	491 (15.9)	468 (15.1)
Pain	461 (14.9)	435 (14.1)	407 (13.1)
Back Pain	256 (8.3)	255 (8.2)	258 (8.3)
Headache	277 (9.0)	216 (7.0)	214 (6.9)
Abdominal Pain	227 (7.3)	228 (7.4)	219 (7.1)
Infection	223 (7.2)	225 (7.3)	211 (6.8)
Accidental Injury	221 (7.1)	221 (7.1)	226 (7.3)
Flu Syndrome	154 (5.0)	170 (5.5)	170 (5.5)
Chest Pain	164 (5.3)	122 (3.9)	152 (4.9)
Cardiovascular			
Vasodilitation	1082 (35.0)	1246 (40.3)	1261 (40.7)
Hypertension	292 (9.4)	252 (8.1)	270 (8.7)

Digestive			
Nausea	307 (9.9)	298 (9.6)	324 (10.5)
Constipation	201 (6.5)	214 (6.9)	232 (7.5)
Diarrhea	227 (7.3)	186 (6)	193 (6.2)
Dyspepsia	166 (5.4)	137 (4.4)	156 (5)
Gastrointestinal Disorder	155 (5)	122 (3.9)	127 (4.1)
Heme and Lymphatic			
Lymphedema	267 (8.6)	299 (9.7)	296 (9.6)
Metabolic and Nutritional			
Peripheral Edema	255 (8.2)	275 (8.9)	281 (9.1)
Weight Gain	253 (8.2)	250 (8.1)	264 (8.5)
Hypercholesterolemia	210 (6.8)	79 (2.6)	72 (2.3)
Musculoskeletal			
Arthritis	431 (13.9)	344 (11.1)	364 (11.7)
Arthralgia	390 (12.6)	251 (8.1)	265 (8.6)
Osteoporosis	229 (7.4)	161 (5.2)	174 (5.6)
Fracture	219 (7.1)	137 (4.4)	178 (5.7)
Bone Pain	165 (5.3)	149 (4.8)	143 (4.6)
Arthrosis	179 (5.8)	136 (4.4)	119 (3.8)
Nervous System			
Depression	348 (11)	341 (11)	342 (11)
Insomnia	266 (8.6)	245 (7.9)	227 (7.3)
Dizziness	198 (6.4)	207 (6.7)	190 (6.1)
Anxiety	168 (5.4)	157 (5.1)	140 (4.5)
Paresthesia	195 (6.3)	116 (3.8)	120 (3.9)
Respiratory			
Pharyngitis	376 (12.2)	359 (11.6)	350 (11.3)
Cough Increased	212 (6.9)	237 (7.7)	203 (6.6)

Dyspnea	186 (6)	185 (6)	175 (5.6)
Skin and Appendages			
Rash	300 (9.7)	331 (10.7)	326 (10.5)
Sweating	121 (3.9)	165 (5.3)	142 (4.6)
Urogenital			
Leukorrhea	75 (2.4)	265 (8.6)	277 (8.9)
Urinary Tract Infection	192 (6.2)	252 (8.1)	228 (7.4)
Breast Pain	205 (6.6)	136 (4.4)	182 (5.9)
Vulvovaginitis	180 (5.8)	134 (4.3)	134 (4.3)

Reviewer's Table

The sponsor collected information on the investigator's severity assessment of the adverse event. The following table shows the adverse events where greater than 1% of the adverse events were categorized as severe in intensity.

Reviewer's Comment: No significant differences were noted for severe adverse events.

Table 9 Investigator Determined Severe Adverse Events with Greater than 1% Incidence (June 29, 2001)

Adverse Event	Anastrozole N=3092 (%)	Tamoxifen N=3093 (%)	Combination N=3097 (%)
Cardiovascular			
Vasodilitation	67 (2.2)	103 (3.3)	116 (3.7)
Musculoskeletal			
Arthritis	46 (1.5)	27 (0.9)	28 (0.9)
Fracture	34 (1.1)	29 (0.9)	26 (0.8)

Reviewer's table

The following table shows the incidence of protocol "pre-specified" adverse events and the Odds Ratios for the comparison of the anastrozole alone and tamoxifen alone treatment groups.

Reviewer's Comment: In the table below, bolded adverse events highlight those adverse events associated with a statistically significantly higher rate in the anastrozole alone treatment group.

Musculoskeletal disorders, fatigue/asthenia, fractures, fractures of the spine, hip and wrist, ischemic cardiovascular events were reported more frequently for the anastrozole alone treated group. The anastrozole alone treatment group was associated with a statistically significantly higher rate of musculoskeletal adverse events, fractures, and fractures of the hip, spine, and wrist /Colles than the tamoxifen alone treatment group and is bolded below. The tamoxifen alone treatment group was associated with a statistically significantly higher rate of hot flushes, vaginal discharge, vaginal bleeding, venous thromboembolic events, deep venous thromboembolic events, ischemic cerebrovascular events and endometrial cancer than the anastrozole alone treatment group.

Table 10 Numbers of Patients with Pre-specified Adverse Events by Treatment Group during or within 14 days of the end of treatment and Odds Ratios Comparison (June 29,2001)

Adverse Event	Anastrozole N=3092	Tamoxifen N=3094	Combination N=3097	Odds Ratio	P-value
Hot flushes	1060 (34.3%)	1229 (39.7%)	1243 (40.1%)	0.79 (0.71,0.88)	<0.0001
Musculoskeletal Disorders[a]	860 (27.8%)	660 (21.3%)	685 (22.1%)	1.42 (1.26, 1.60)	<0.0001
Mood disturbances	480 (15.5%)	469 (15.2%)	482 (15.2%)	1.03 (0.90,1.18)	0.6900
Fatigue/Asthenia	483 (15.6%)	466 (15.1%)	435 (14.0%)	1.04 (0.91,1.20)	0.5415
Nausea and Vomiting	324 (10.5%)	315 (10.2%)	363 (11.7%)	1.03 (0.88,1.22)	0.7005
Vaginal Discharge	86 (2.8%)	354 (11.4%)	357 (11.5%)	0.22 (0.17,0.28)	<0.0001
Vaginal Bleeding	138 (4.5%)	253 (8.2%)	238 (7.7%)	0.52 (0.42,0.65)	<0.0001
Fractures	183 (5.9%)	115 (3.7%)	142 (4.6%)	1.63 (1.28,2.07)	<0.0001
Fractures of the spine, hip, or wrist/Colles	68 (2.2%)	45 (1.5%)	50 (1.6%)	1.52 (1.04,2.23)	0.0299
Cataracts	107 (3.5%)	116 (3.7%)	105 (3.4%)	0.92 (0.70,1.20)	0.5427
Venous thromboembolic events[b]	64 (2.1%)	109 (3.5%)	124 (4%)	0.58 (0.42,0.79)	0.0006
Deep thromboembolic events[c]	32 (1%)	54 (1.7%)	63 (2%)	0.59 (0.38,0.91)	0.0183
Ischemic Cardiovascular	76 (2.5%)	59 (1.9%)	68 (2.2%)	1.30 (0.92,1.83)	0.1391